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Tetrahedron

Tetrahedron Vol. 62, No. 2–3, 2006

Tetrahedron Symposium-in-Print Number 116

Organocatalysis in organic synthesis

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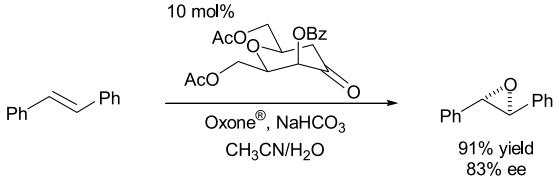
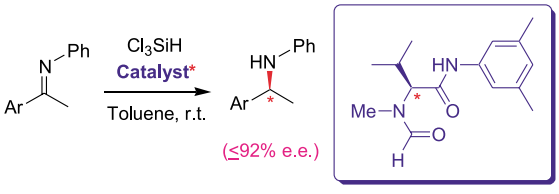
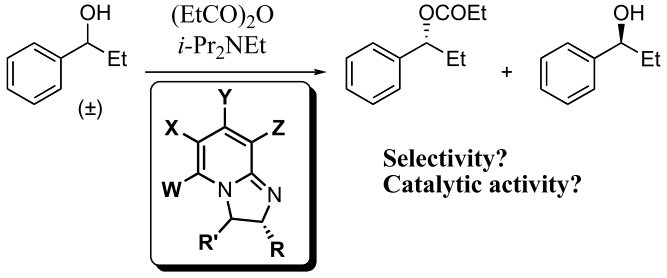
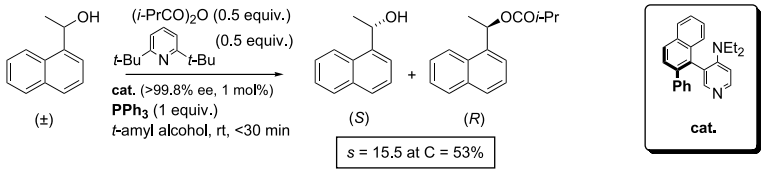
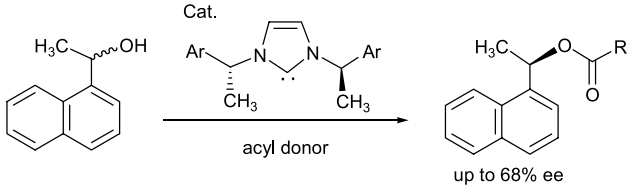
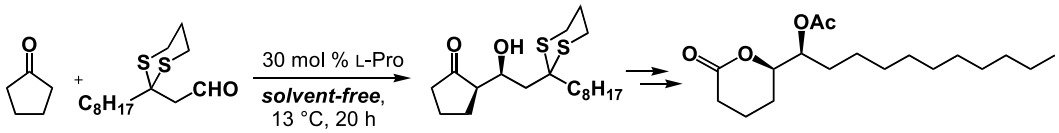


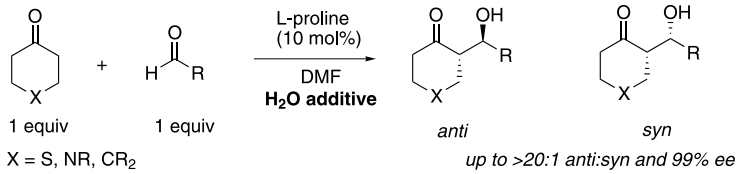


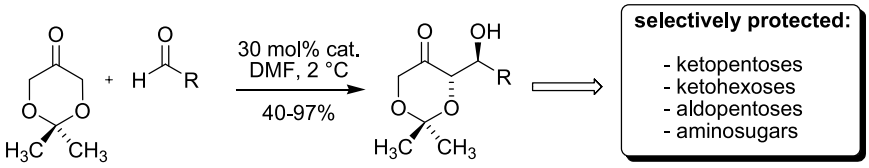


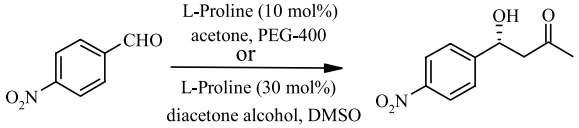


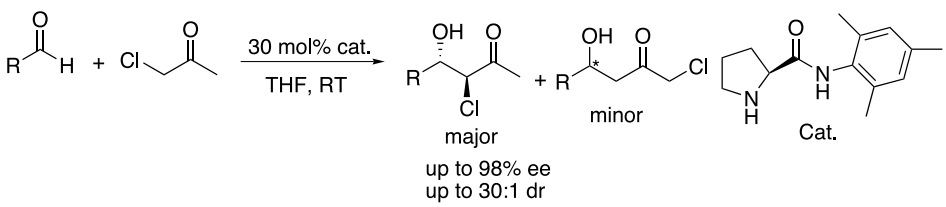


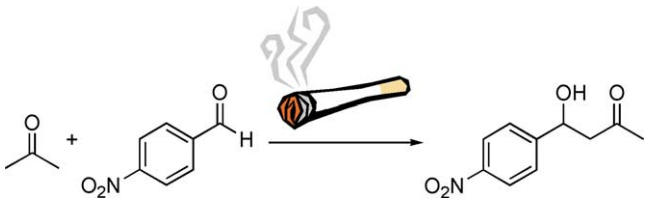


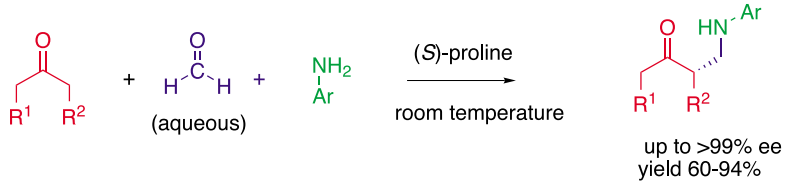


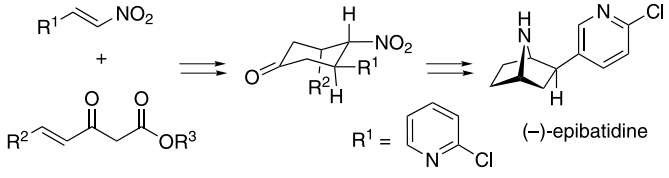


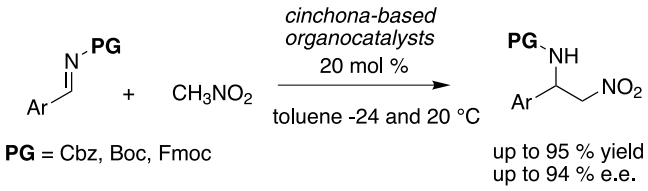


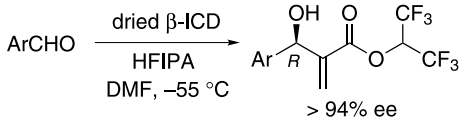


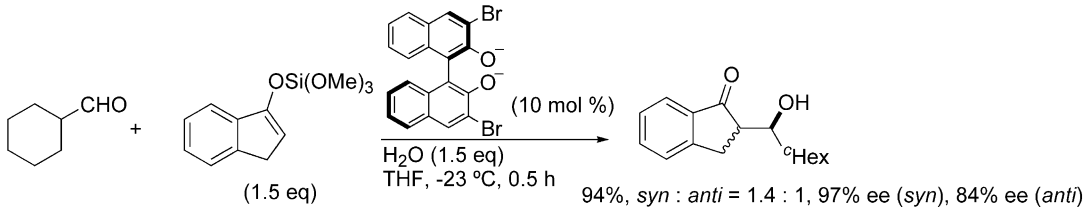


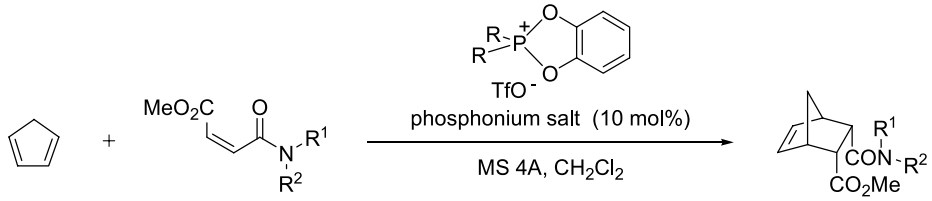


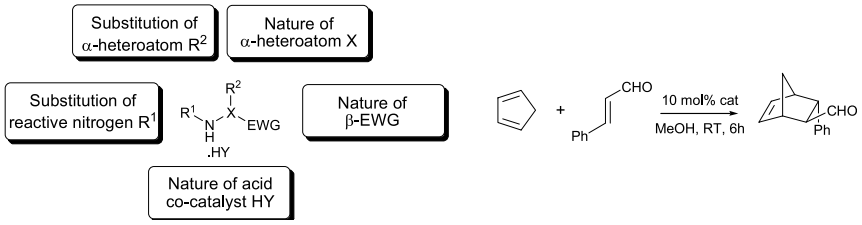


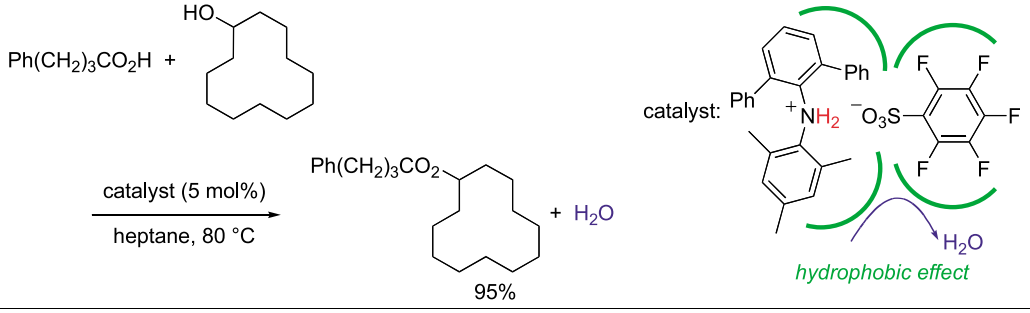


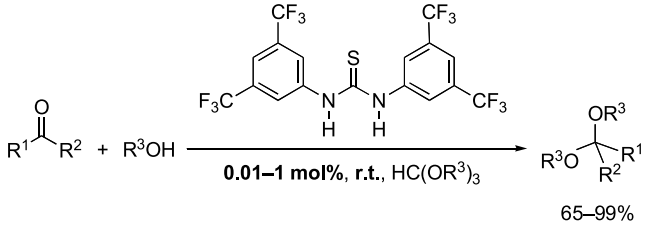


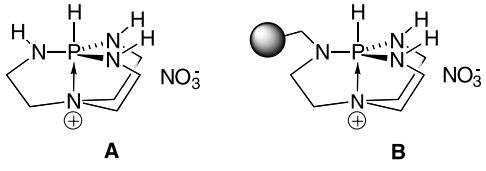






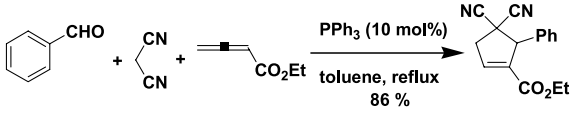


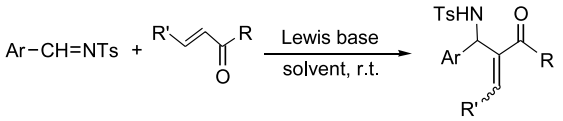


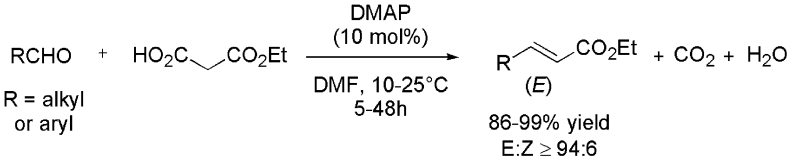


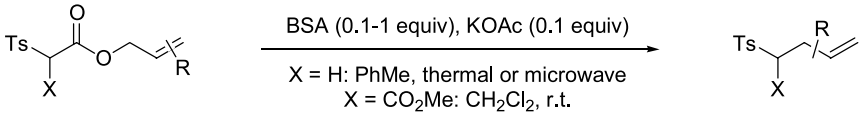
A B

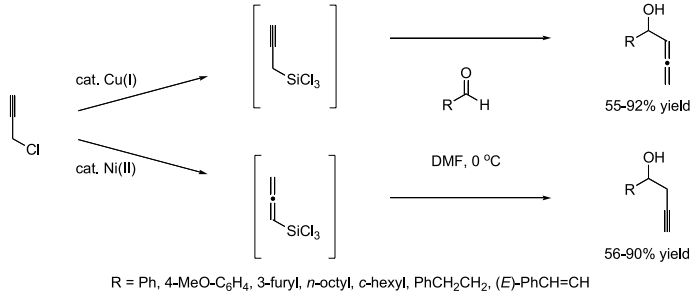
Compound **A** is an efficient homogeneous catalyst for the generally room temperature synthesis of Strecker products and Reissert compounds in three and four-component one-pot transformations, respectively, and also for aza and thia-Michael addition products. Polymer supported **B** is an equally efficient catalyst for these reactions, showing impressive recycling/regeneration capabilities.











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*Corresponding author
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COVER

The cover figure represents a mosaic, derived from selected papers that appear in this Symposium-in-Print. The catalytic reduction of imines with trichlorosilane (Paper 2) is highlighted in the middle and a space-filling model of the catalyst is shown in the bottom-right corner. The top two structures are proline, the most often used organocatalyst (Papers 6-10, and 11), and the CF_3-PIP acylation catalyst (Paper 3). In the bottom, from left, there is a new tetrahydropyran-4-one-derived catalyst for epoxidation (Paper 1), and nornicotine, a catalyst for aldol condensation (Paper 11); the diagram in the top-right corner highlights the mechanistic investigation presented in the latter paper.

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ISSN 0040-4020

Tetrahedron Symposia-in-Print

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Authors who have not already been invited, and who may have obtained recent significant results in the area of the announced symposium, may also submit contributions for Editorial consideration and possible inclusion. Before submitting such papers authors should send an abstract to the Symposium Editor for preliminary evaluation. Firm deadlines for receipt of papers will allow sufficient time for completion and presentation of ongoing work without loss of the freshness and timeliness of the research results.

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Preface

Organocatalysis in organic synthesis

The term 'organocatalysis' was coined a few years ago by MacMillan, who wished to distinguish the new concepts in metal-free catalysis that emanated from the work carried out in the 1990s by several groups. Thus, this 'invention' coincided with the turn of the millennium and can be viewed as the fresh start into the 21st century. However, the topic is not entirely new, since notable examples can be found in the earlier literature. Interestingly, the seminal work by Hajos and Parish and the Wiechert group on proline catalysis in the 1970s laid dormant until recently, as it was apparently regarded (erroneously) as being limited to the synthesis of the Wieland–Miescher ketone. The last decade, and especially the last few years, have witnessed an explosive growth of the field, with new catalysts, methodologies, and mechanistic studies being published practically every day, thereby expanding the portfolio of powerful new approaches with a breath-taking speed.

The present Symposium-in-Print shows some recent developments in organocatalysis. It was not possible to cover all the significant work done in the area; rather, we intended to highlight some important trends and the development of new catalysts. The majority of the contributions deal with enantioselective reactions but there is an important component of those where chirality is not necessarily an issue. The former part highlights novel methods for epoxidation (Armstrong); imine reduction (Malkov–Kočovský); acylation (Birman, Spivey, and Suzuki); synthetic and mechanistic aspects of aldol condensation with proline and its congeners as catalysts (Kotsuki, Pihko, Enders, Chandrasekhar, Gong, and Janda); Mannich-type reaction (Córdova), Michael addition (Takemoto); new phase-transfer processes for the aza-Henry and Baylis–Hillman reaction (Ricci and Hatakeyama); and BINOL-type catalysts for aldol reaction (Nakajima). In the latter part, the following issues are addressed, some of which will be amenable to enantioselection: novel Lewis-acidic catalysts for Diels–Alder reaction (Terada); the α-effect in iminium ion catalysis (Tomkinson); esterification catalyzed by new diarylammonium sulfonates (Ishihara); acetal formation using the urea-type Brønsted-acidic catalysts (Schreiner); Strecker and thio-Michael reaction, catalyzed by azaphosphatrane nitrate (Vederas); triphenylphosphine-catalyzed reactions of allenes (Lu); Lewis base-catalyzed aza-Baylis–Hillman reaction (Shi); new atom-economical alternative to Wittig reaction with DMP as catalyst (List); Claisen rearrangement catalyzed by potassium acetate (Craig); and propargylsilane addition to aldehydes catalyzed by DMF (Kobayashi)

We hope that the present selection of 26 contributions will stimulate further research and provide useful information to those working in synthetic organic chemistry in general.

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doi:10.1016/j.tet.2005.11.012

Available online at www.sciencedirect.com
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Tetrahedron
Tetrahedron 62 (2006) 257–263

A new class of chiral tetrahydropyran-4-one catalyst for asymmetric epoxidation of alkenes

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Received 18 May 2005; revised 6 July 2005; accepted 31 August 2005

Available online 28 September 2005

Dedicated to Professor Steven V. Ley on the occasion of his 60th birthday

Abstract—A new class of chiral α-oxygenated-tetrahydropyran-4-ones for asymmetric epoxidation of alkenes using Oxone® is described, affording epoxides with up to 83% ee.

1. Introduction

Dioxiranes derived from chiral ketone precursors are some of the most promising catalysts for asymmetric epoxidation of alkenes.[1] In particular, excellent results have been achieved with trisubstituted and *E*-alkenes, and encouraging enantioselectivities are also emerging for other alkene substitution patterns.[2] Our own studies have demonstrated that catalysts based on the bicyclo[3.2.1]octanone framework can afford high epoxide enantioselectivities.[3–6] For example, the acetate **4** epoxidises *E*-stilbene with 93% ee at room temperature.[4,5] However, it is currently difficult to prepare **4** in enantiomerically pure form. We have generally employed chiral base desymmetrization of the parent ketones **1** and **3**, and while certain desymmetrized products (for example, the fluoroketone **2**)[3,6] can be recrystallized to enantiomeric purity, this is not the case for acetate **4**. In evaluating alternative routes to enantiomerically pure bicyclo[3.2.1]octanones, we were aware of the diastereoselective [4+3]-cycloaddition developed by Hoffmann (Scheme 1), which affords separable diastereomers **5** and **6**.[7,8] However, these products have the substituent α- to the ketone in an equatorial orientation, and our preliminary attempts to invert this stereocentre were not encouraging. We reasoned that cleavage of the alkene unit in the two-carbon bridge should result in ring flipping to place the α-substituent axial in **7** (Scheme 1).[9] Our TS-models for epoxidation with the bicyclic ketones **2** and **4** have assumed that the two-carbon bridge prevents attack on the *endo*-dioxirane oxygen atom,[3,6] but our computational studies of epoxidation by α-fluorocyclohexanones suggested that the axial electronegative α-substituent serves to steer the olefin to the dioxirane oxygen *syn* to it.[10] Indeed, successful axially-fluorinated monocyclic cyclohexanones have since been developed.[11] Preparation of **7** would provide some novel enantiomerically pure ketone catalysts, and also allow evaluation of whether the bicyclic catalyst framework in our own catalyst family is necessary for enantioselectivity, or if the influence of the axial α-substituent is sufficient. Here we report the results of this study.

2. Results and discussion

We first prepared the diastereomerically and enantiomerically pure ketone **5** according to Hoffmann's procedure[7] (Scheme 1). In order to facilitate handling of later polar polyol intermediates, ketone reduction and TBS-protection to give **8** were next effected (Scheme 2). Subsequent ozonolysis with reductive work up and acetylation of the resultant primary alcohols afforded **9**. The ketone **10** was now regenerated by TBS-deprotection and TPAP oxidation.[12] We were able to effect simultaneous removal of the α-methylbenzyl auxiliary and ester formation by reaction of **10** with an acid anhydride in the presence of $FeCl_3$.[13] This method allowed synthesis of a range of catalysts **11**–**13**, allowing us to probe the effect of the ester substituent on enantioselectivity. The axial orientation of the ester substituent was demonstrated by analysis of ^1H NMR coupling constants. For example in **13**, one of the H5-protons (H_{5ax}) has $J=11.6$ Hz, indicating a trans–diaxial relationship with H6. The acetoxymethyl groups are, therefore, equatorial. J_{H3-H2} is small (ca. 2 Hz), showing that the OR substituent at C3 is axial. We found these ketones to be configurationally stable to the subsequent Oxone epoxidation conditions. However, heating **13** at

Keywords: Epoxidation; Asymmetric; Ketone; Dioxirane.
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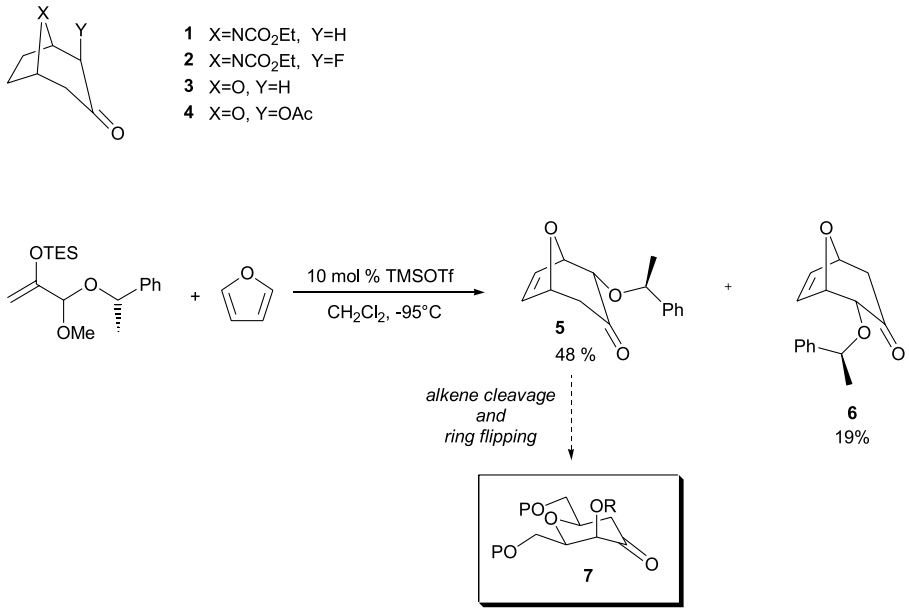
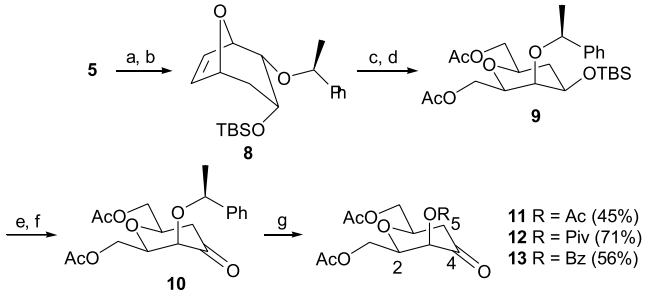
doi:10.1016/j.tet.2005.08.112



Scheme 1.



Scheme 2. (a) $NaBH_4$, methanol, −78 °C; (b) TBSOTf, CH_2Cl_2, 0 °C to rt, 100%; (c) O_3, CH_2Cl_2/MeOH, −78 °C, then $NaBH_4$, 92%; (d) Ac_2O, pyridine, rt, 76%; (e) TBAF, THF, rt, 91%; (f) TPAP, NMO, CH_2Cl_2, rt, 82%; (g) $FeCl_3$ (3 equiv), acid anhydride (3 equiv), CH_2Cl_2, 0 °C to rt, 10 min.

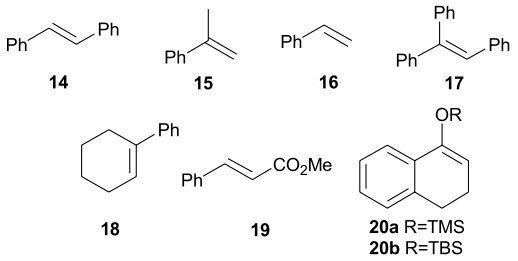
reflux in Et_3N affords the equatorial C3-epimer, which has $J_{H3–H2}=10.4$ Hz, consistent with the expected trans–diaxial relationship between these protons in that compound and further confirming the configuration of **13** itself.

We first tested the acetate **11** under standard Oxone® epoxidation conditions with three alkenes of differing substitution pattern (Table 1): *E*-stilbene **14** (entry 1), α-methylstyrene **15** (entry 2) and styrene **16** (entry 3). *E*-Stilbene was epoxidised with 81% ee, with the (*S*,*S*)-isomer predominating; this sense of enantioselectivity is in accord with the well established spiro-mode of approach[14] on the dioxirane oxygen *syn* to the axial acetoxy substituent. The corresponding bicyclic ketone, acetate **4**, affords 93% ee under similar conditions,[4,5] so removal of the two-carbon bridge does result in lowering of enantioselectivity. Nevertheless, the value obtained with monocyclic ketone catalyst **11** is remarkably high, particularly for such a simple asymmetric environment, and is comparable to the value obtained (76% ee) for *E*-stilbene epoxidation using the fluorotropinone derivative **2**.[3,6] As with most chiral dioxiranes, lower enantioselectivities were obtained for the challenging terminal alkenes (entries 2 and 3). The pivalate ester **12** generally afforded lower enantioselectivities than **11** (entries 4–6). However, the benzoate **13** gave better ee values (entries 7–9), albeit with slightly lower conversions in some cases. This is surprising, since in our studies of the oxabicyclooctanone series, the acetate **4** generally gave better enantioselectivities than did other ester derivatives.[5] We explored the epoxidation of several other informative alkene types with **13** (entries 10–14). As expected, good ee was observed for epoxidation of phenylstilbene (entry 10), 1-phenylcyclohexene (entry 11) and for *E*-methyl cinnamate (entry 12), but conversion was low in the case of this electron-poor substrate. In line with our studies on the fluoroketone **2**,[6] surprisingly low ee values were observed for silyl enol ethers (entries 13 and 14). We have speculated[6] that this is due to the olefinic hydrogen being less electron deficient in an enol ether than in a normal alkene, resulting in decreased TS electrostatic attraction to the electronegative axial substituent α- to the dioxirane.

3. Conclusions

In summary, we have developed a new route to enantiomerically pure tetrahydropyran-4-ones with an axial α-substituent, providing an alternative to chiral base chemistry for the synthesis of such compounds. These novel monocyclic pyranone derivatives have allowed assessment of the need for the two-carbon bridge in our previously reported bicyclooctanone catalysts. Loss of the bicyclic system results in some reduction in epoxide enantioselectivity, but surprisingly good results are still obtained (at least for *E*-alkenes), confirming that an axial heteroatom can be an effective controller. It should be noted that these new ketones all appear to be stable to the reaction conditions, and were employed at the 10 mol% level. In contrast to the bicyclooctanone catalysts,[5] the benzoate derivative can give better ee values than the acetate. This

Table 1. Oxone® epoxidation of alkenes **14–20** catalysed by ketones **11–13**[a]



Entry	Ketone	Alkene	Conversion (%)[b]	Yield (%)	ee (%)
1	**11**	**14**	100	100	81 (*S*,*S*)[c]
2	**11**	**15**	100	93	7 (*S*)[c]
3	**11**	**16**	99	79	19 (*S*)[d]
4	**12**	**14**	52	43	43 (*S*,*S*)[c]
5	**12**	**15**	83	83	3 (*S*)[c]
6	**12**	**16**	99	78	19 (*S*)[d]
7	**13**	**14**	100	91	83 (*S*,*S*)[c]
8	**13**	**15**	100	97	18 (*S*)[c]
9	**13**	**16**	50	43	31 (*S*)[d]
10	**13**	**17**	60	53	82 (*S*)[c]
11	**13**	**18**	100	100	74 (*S*,*S*)[d]
12	**13**	**19**	17	9	67 (2*R*,3*S*)[c]
13[e]	**13**[f]	**20a**	—	100	12[g]
14[e]	**13**[f]	**20b**	—	27	3[g]

[a] Reaction conditions: alkene (1 equiv), ketone (10 mol%), Oxone® (10 equiv of $KHSO_5$), $NaHCO_3$ (15.5 equiv), CH_3CN/aq Na_2EDTA (0.4 mmol dm^{-3} solution) (3:2, 25 mL/mmol), 24 h, rt.
[b] Estimated by integration of the ^1H NMR spectrum of the crude reaction mixture.
[c] Measured by chiral HPLC (Chiracel OD column).
[d] Measured by chiral GC (ChiraPak G-TA column).
[e] The product epoxide was treated with 10% HCl in methanol during work up to obtain the α-hydroxyketone.
[f] Catalyst (30 mol%) was used.
[g] Enantiomeric excess of the α-hydroxyketone, measured by chiral HPLC (ChiraPak AD column).

suggests that preparation of a wider range of aromatic ester derivatives in the ongoing search for improved enantioselectivities, particularly for terminal alkenes, is a worthwhile endeavour.

4. Experimental

4.1. General

All the reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Syringes and needles were oven-dried and allowed to cool in a desiccator over silica gel before use. Solvents were freshly distilled before use from sodium/benzophenone (diethyl ether, THF) or CaH_2 (CH_2Cl_2, CH_3CN and Et_3N). Liquid reagents were distilled prior to use, while other commercial solids were used as supplied unless stated in the relevant text. Solutions of butyl lithium were titrated against diphenylacetic acid before use. Reaction temperatures were recorded as bath temperatures. Analytical thin-layer chromatography was performed on pre-coated Merck silica gel 60 F_{254} glass-backed plates and visualised by UV lamp (254 nm) or potassium permanganate or ceric ammonium nitrate or anisaldehyde stains as appropriate. Flash chromatography was performed silica gel 60 (particle size 40–63 μm) as supplied by Merck. Petrol ether refers to light petroleum ether, which is the fraction with bp 40–60 °C.

Melting points were obtained using a Kofler hot stage apparatus and are quoted as uncorrected. Optical rotations were recorded on an Optical-Activity AA-5 Polarimeter, with a path length of 10 or 5 cm, in chloroform unless stated otherwise. $[\alpha]_D$ values are given in 10^{-1} degrees $cm^2\ g^{-1}$. Concentrations (*c*) are given in grams per 100 mL. Infrared analyses were recorded as a thin-film (produced from evaporation of a dichloromethane solution) on NaCl plates using a Mattson Satellite FTIR spectrometer and absorption maxima are reported in wavenumber (cm^{-1}). ^1H and ^{13}C NMR analyses were performed on a Bruker AC250 MHz or Bruker DRX400 MHz spectrometer in $CDCl_3$. Mass spectrometry was carried out under CI (ammonia reagent gas) using a Micromass Autospec-Q spectrometer at the Imperial College Mass Spectrometry Service.

4.1.1. (−)-(1*R*,2*S*,3*R*,5*R*)-2-((*S*)-1-Phenylethoxy)-3-(*tert*-butyldimethylsilanyloxy)-8-oxabicyclo[3.2.1]oct-6-ene 8. To a solution of (−)-(1*R*,2*S*,5*R*)-2-((*S*)-1-phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one **5**[7] (0.10 g, 0.41 mmol) in methanol (10 mL) at −78 °C was added sodium borohydride (0.17 g, 0.45 mmol). The mixture was stirred under a nitrogen atmosphere for 3 h, before water (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (diethyl ether) afforded the alcohol (0.11 g, 100%) as a white solid, mp 107–108 °C; $[\alpha]_D^{18}$ −51.5 (*c* 0.78, $CHCl_3$); R_f 0.49 (2:8 petroleum ether/diethyl ether); ν_{max}/cm^{-1} 3015, 2978, 2952, 2929, 1603, 1451, 1376, 1215, 1086, 1057; δ_H (250 MHz, $CDCl_3$)

7.40–7.28 (5H, m, Ph), 6.34 (1H, dd, J=6.1, 1.2 Hz, H_7), 6.28 (1H, dd, J=6.1, 1.2 Hz, H_6), 4.64 (1H, br s, H_1), 4.60 (1H, q, J=6.4 Hz, PhC*H*), 4.34 (1H, br d, J=4.3 Hz, H_5), 4.21 (1H, m, H_3), 3.60 (1H, dd, J=5.2, 4.6 Hz, H_2), 2.67 (1H, d, J=2.7 Hz, OH), 2.01 (1H, ddd, J=14.6, 4.9, 4.3 Hz, H_{4ax}), 1.80 (1H, d, J=14.6 Hz, H_{4eq}), 1.44 (3H, d, J=6.4 Hz, CHC*H*$_3$); δ_C (62.5 MHz, $CDCl_3$) 143.1, 136.5, 131.7, 128.6, 128.0, 126.2, 78.8, 78.3, 76.4, 72.4, 65.0, 32.8, 24.3; MS (CI–NH_3): *m*/*z* (%) 264 (100) $[M+NH_4]^+$, 246 (57); calcd for $C_{15}H_{22}NO_3$ $[M+NH_4]^+$: 264.1600; found $[M+NH_4]^+$: 264.1610.

A solution of this alcohol (0.10 g, 0.41 mmol) in CH_2Cl_2 (10 mL) was cooled down to 0 °C under a nitrogen atmosphere. 2,6-Lutidine (0.10 mL, 0.81 mmol) and *tert*-butyldimethylsilyl triflate (0.15 mL, 0.65 mmol) were added to the solution. The reaction temperature was warmed back to room temperature. The reaction was monitored with TLC until complete. The reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8:2 petroleum ether/diethyl ether) to give silyl ether **8** (0.16 g, 100%) as a colourless oil; $[\alpha]_D^{20}$ −20.0 (*c* 1.00, $CHCl_3$); R_f 0.54 (8:2 petroleum ether/diethyl ether); ν_{max}/cm^{-1} 3018, 2954, 2930, 2986, 2857, 1620, 1601, 1471, 1215, 757; δ_H (250 MHz, $CDCl_3$) 7.38–7.27 (5H, m, Ph), 6.18 (1H, dd, J=6.1, 1.5 Hz, H_7), 6.03 (1H, dd, J=6.1, 1.5 Hz, H_6), 4.61–4.56 (1H, m, H_1), 4.52 (1H, q, J=6.4 Hz, PhC*H*), 4.28–4.22 (2H, m, H_3 and H_5), 3.54 (1H, dd, J=4.9, 3.7 Hz, H_2), 2.02 (1H, ddd, J=14.3, 4.9, 4.0 Hz, H_{4ax}), 1.60 (1H, dd, J=14.3, 1.2 Hz, H_{4eq}), 1.41 (3H, d, J=6.4 Hz, CHC*H*$_3$), 0.93–0.91 (9H, s, CC*H*$_3$), 0.05–0.01 (6H, m, $SiCH_2$); δ_C (62.5 MHz, $CDCl_3$) 144.6, 134.4, 132.5, 128.5, 127.5, 126.1, 79.5, 78.2, 76.7, 75.4, 66.9, 35.7, 25.8, 24.6, 18.1, −4.8; MS (CI–NH_3): *m*/*z* (%) 361 (100) $[M+H]^+$, 257 (75), 122 (48), 378 (18) $[M+NH_4]^+$; calcd for $C_{21}H_{33}O_3Si$ $[M+H]^+$: 361.2199; found $[M+H]^+$361.2208.

4.1.2. (−)-(2*R*,3*S*,4*R*,6*R*)-2,6-Bis-acetoxymethyl-3-((*S*)-1-phenylethoxy)-4-(*tert*-butyldimethylsilanyloxy)-tetrahydropyran 9. A solution of **8** (154 mg, 0.43 mmol) in 4:1 mixture of CH_3OH/CH_2Cl_2 (5 mL) was cooled down to −78 °C and treated with a stream of ozone until the colour of the solution turned into blue. The excess ozone was removed by passing through a stream of nitrogen until the colour of the solution became colourless. Sodium borohydride (44 mg, 1.17 mmol) was added to the solution carefully by potion and stirred at room temperature for 1 h. The organic layer was separated by adding water (10 mL) and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate) to yield the diol (156 mg, 92%) as a white solid, mp 119–120 °C; $[\alpha]_D^{21}$ −63.5 (*c* 1.02, $CHCl_3$); R_f 0.33 (ethyl acetate); ν_{max}/cm^{-1} 3426, 2955, 2925, 2889, 2855, 1667, 1463, 1382, 1255, 1083; δ_H (250 MHz, $CDCl_3$) 7.40–7.24 (5H, m, Ph), 4.99 (1H, q, J=6.70 Hz, PhC*H*), 3.89 (1H, br s, OH), 3.78 (1H, dd, J=11.6, 4.6 Hz, H_4), 3.70–3.40 (4H, m, CH_2O), 3.39 (1H, s, H_3), 3.23 (1H, dd, J=7.6, 3.7 Hz, H_2), 3.10 (1H, br s, OH), 3.01–2.92 (1H, m, H_6), 1.89 (1H, apparent q, J=11.9 Hz, H_{5ax}), 1.51–1.40 (4H, m, CH_3, H_{5eq}), 0.95 (9H, s, $SiCCH_3$), 0.13 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$); δ_C (62.5 MHz, $CDCl_3$) 143.4, 128.5, 127.9, 127.1, 79.9, 78.8, 73.4, 72.9, 72.9, 65.5, 63.3, 31.7, 25.8, 23.2, 18.0, −4.8; MS (CI–NH_3): *m*/*z* (%) 310 (97), 414 (100) $[M+NH_4]^+$; calcd for $C_{21}H_{36}O_5Si$ $[M+NH_4]^+$: 414.2676; found $[M+NH_4]^+$ 414.2679.

To a solution of this diol (0.32 g, 0.82 mmol) in pyridine (10 mL), acetic anhydride (0.17 mL, 1.80 mmol) was added at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 24 h and poured unto saturated sodium hydrogen carbonate solution (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (7:3 petroleum ether/diethyl ether) giving **9** (0.30 g, 76%) as a white solid, mp 59–60 °C; $[\alpha]_D^{21}$ −42.9 (*c* 1.03, $CHCl_3$); R_f 0.38 (4:6 diethyl ether/petroleum ether); ν_{max}/cm^{-1} 2953, 2927, 2856, 1741, 1617, 1456, 1369, 1248, 1106, 1083, 1037; δ_H (250 MHz, $CDCl_3$) 7.32–7.20 (5H, m, Ph), 5.10–4.92 (1H, q, J=6.7 Hz, PhC*H*), 4.12–4.08 (2H, m, CH_2O), 3.97 (1H, dd, J=11.3, 6.7 Hz, CH*H*O), 3.78 (1H, ddd, J=11.6, 4.6, 2.7 Hz, H_4), 3.61 (1H, dd, J=11.3, 5.8 Hz, C*H*HO), 3.60–3.51 (1H, m, H_6), 3.41 (1H, br s, H_3), 3.34 (1H, apparent t, J=6.7 Hz, H_2), 2.06 (3H, s, CH_3C=O), 1.94 (1H, apparent q, J=11.9 Hz, H_{5ax}), 1.75 (3H, s, CH_3C=O), 1.54 (1H, dd, J=11.9, 4.6 Hz, H_{5eq}), 1.45 (3H, d, J=6.7 Hz, CH_3), 0.96 (9H, s, $SiCCH_3$), 0.14 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$); δ_C (62.5 MHz, $CDCl_3$) 170.9, 170.4, 143.6, 128.3, 127.7, 127.1, 78.8, 76.0, 73.9, 72.7, 72.5, 66.6, 64.1, 32.1, 25.8, 23.6, 20.9, 20.6, 18.0, −4.6; MS (CI–NH_3): *m*/*z* (%) 498 (100) $[M+NH_4]^+$; calcd for $C_{25}H_{44}NO_7Si$ $[M+NH_4]^+$: 498.2887; found $[M+NH_4]^+$ 498.2887.

4.1.3. (−)-(2*R*,3*R*,6*R*)-2,6-Bis-acetoxymethyl-3-((*S*)-1-phenylethoxy)-tetrahydropyran-4-one 10. To a solution of **9** (0.35 g, 0.76 mmol) in THF (50 mL), tetrabutylammonium fluoride (1 M in THF, 0.80 mL, 0.80 mmol) was added at room temperature under nitrogen atmosphere. The reaction was monitored with TLC until complete and then quenched with water (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (2:8 petroleum ether/diethyl ether) giving the alcohol (0.24 g, 91%) as a white solid, mp 78–79 °C; $[\alpha]_D^{21}$ −26.7 (*c* 1.05, $CHCl_3$); R_f 0.41 (diethyl ether); ν_{max}/cm^{-1} 3481, 2975, 2931, 2904, 1731, 1377, 1230, 1066, 1028; δ_H (250 MHz, $CDCl_3$) 7.35–7.20 (5H, m, Ph), 4.77 (1H, q, J=6.4 Hz, PhC*H*), 4.10 (2H, d, J=5.5 Hz, CH_2O), 3.98 (1H, dd, J=11.3, 7.0 Hz, C*H*HO), 3.83–3.73 (1H, m, H_4), 3.69–3.53 (3H, m, CH*H*O, H_6 and H_3), 3.39 (1H, ddd, J=7.0, 6.4, 5.8 Hz, H_2), 2.19 (1H, br s, OH), 2.06 (3H, s, C=OCH_3), 1.85 (3H, s, $COCH_3$), 1.81–1.71 (2H, m, H_{5ax} and H_{5eq}), 1.50 (3H, d, J=6.4 Hz, CHC*H*$_3$); δ_C (62.5 MHz, $CDCl_3$) 171.0, 170.5, 143.0, 128.4, 127.8, 126.8, 79.3, 76.1, 73.8, 73.1, 70.6, 66.4, 63.8, 32.2, 23.5, 20.9, 20.8; MS (CI–NH_3):

m/z (%) 280 (38), 384 (100) $[M+NH_4]^+$; calcd for $C_{19}H_{26}O_7$ $[M+NH_4]^+$: 384.2022; found $[M+NH_4]^+$ 384.2017.

This alcohol (0.24 g, 0.66 mmol) was dissolved in CH_2Cl_2 (30 mL) containing 4 Å molecular sieves and *N*-methylmorpholine *N*-oxide (0.16 g, 1.37 mmol). After stirring the mixture for 10 min at room temperature, tetra-*n*-propylammonium perruthenate (12.0 mg, 0.034 mmol) was added. The reaction was monitored with TLC until complete. The mixture was diluted with CH_2Cl_2 and then washed with sodium sulfite solution (10 mL), brine (30 mL) and finally saturated copper(II) sulfate solution (3×50 mL). The aqueous layer was extracted with diethyl ether (3× 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated to obtain the crude product. The product was purified by flash column chromatography (1:1 petroleum ether/diethyl ether), giving **10** (0.20 g, 82%) as colourless oil; $[\alpha]_D^{21}$ −65.8 (*c* 1.13, $CHCl_3$); R_f 0.81 (diethyl ether); ν_{max}/cm^{-1} 2978, 1743, 1455, 1372, 1235, 1048; δ_H (250 MHz, $CDCl_3$) 7.31–7.17 (5H, m, Ph), 4.30–4.00 (5H, m, CH_2O, PhC*H*), 3.86–3.75 (1H, m, H_6), 3.63 (1H, td, *J*= 6.4, 1.5 Hz, H_2), 3.33 (1H, s, H_3), 2.90 (1H, dd, *J*=13.1, 12.2 Hz, H_{5ax}), 2.26 (1H, d, *J*=13.1 Hz, H_{5eq}), 2.02 (3H, s, CH_3C=O), 1.79 (3H, s, CH_3C=O), 1.38 (3H, d, *J*=6.4 Hz, CHC*H*$_3$); δ_C (62.5 MHz, $CDCl_3$) 205.4, 170.5, 170.3, 141.3, 128.5, 128.1, 126.8, 77.5, 76.7, 76.7, 75.4, 65.7, 62.1, 41.3, 23.8, 20.7, 20.6; MS (CI–NH_3): *m/z* (%) 278 (22), 382 (100) $[M+NH_4]^+$; calcd for $C_{19}H_{24}O_7$ $[M+NH_4]^+$: 382.1866; found $[M+NH_4]^+$ 382.1852.

4.1.4. (−)-(2*R*,3*S*,6*R*)-2,6-Bis-acetoxymethyl-3-acetoxy-tetrahydropyran-4-one 11. To a stirred solution of acetic anhydride (0.025 mL, 0.26 mmol) in dry CH_2Cl_2 (6 mL) at room temperature under nitrogen atmosphere, anhydrous $FeCl_3$ (36.0 mg, 0.22 mmol) was added and stirred for 15 min at 0 °C. A solution of **10** (30.0 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) was then added then the reaction was stirred for 10 min. The colour of the reaction mixture changed from orange to very dark green. It was quenched by addition of water (10 mL) then extracted with diethyl ether (3× 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (diethyl ether) to afford **11** (11.1 mg, 45%) as colourless oil; $[\alpha]_D^{22}$ −3.80 (*c* 0.79, $CHCl_3$); R_f 0.27 (diethyl ether); ν_{max}/cm^{-1} 2963, 2933, 2899, 1741, 1642, 1434, 1372, 1238, 1045; δ_H (250 MHz, $CDCl_3$) 5.02 (1H, dd, *J*=2.1, 0.9 Hz, H_3), 4.32–4.09 (4H, m, CH_2O), 4.09–3.93 (2H, m, H_2 and H_6), 2.76 (1H, dd, *J*=13.7, 11.6 Hz, H_{5ax}), 2.45 (1H, ddd, *J*=13.7, 2.7, 0.9 Hz, H_{5eq}), 2.16 (3H, s, C=OCH_3), 2.10 (3H, s, C=OCH_3), 2.06 (3H, s, C=OCH_3); δ_C (100 MHz, $CDCl_3$) 200.7 (C, C_4), 170.6, 170.4, 169.5 (C, OC=O), 76.8 (CH, C_2), 75.4 (CH, C_6), 74.1 (CH, C_3), 65.6 (CH_2, OCH_2), 61.7 (CH_2, OCH_2), 41.6 (CH_2, C_5), 20.8, 20.7, 20.5 (CH_3, CH_3); MS (CI–NH_3): *m/z* (%) 320 (100) $[M+NH_4]^+$; calcd for $C_{13}H_{22}NO_8$ $[M+NH_4]^+$: 320.1345; found $[M+NH_4]^+$: 320.1346.

4.1.5. (−)-(2*R*,3*S*,6*R*)-2,6-Bis-acetoxymethyl-3-(2,2-dimethylpropionyloxy)-tetrahydropyran-4-one 12. To a stirred solution of 2,2-dimethylpropionic anhydride (0.05 mL, 0.246 mmol) in dry CH_2Cl_2 (7 mL) at room temperature under nitrogen atmosphere, anhydrous $FeCl_3$ (43.1 mg, 0.266 mmol) was added and stirred for 15 min at 0 °C. A solution of **10** (30.1 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) was then added. The reaction was stirred for 10 min. The colour of the reaction mixture changed from orange to very dark green. It was then quenched by addition of saturated sodium hydrogen carbonate solution (10 mL). The mixture was stirred for 1 min and then extracted with diethyl ether (3×25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (diethyl ether) to afford **12** (20.3 mg, 71%) as colourless oil; $[\alpha]_D^{22}$ −2.10 (*c* 2.37, $CHCl_3$); R_f 0.33 (diethyl ether); ν_{max}/cm^{-1} 2976, 2936, 2910, 1744, 1370, 1238, 1140, 1049; δ_H (250 MHz, $CDCl_3$) 4.93 (1H, dd, *J*= 1.8, 0.9 Hz, H3), 4.31–4.10 (4H, m, CH_2O), 4.06–3.95 (2H, m, H_2 and H_6), 2.73 (1H, dd, *J*=13.4, 11.6 Hz, H_{5ax}), 2.41 (1H, ddd, *J*=13.4, 2.7, 1.2 Hz, H_{5eq}), 2.09 (3H, s, C=OCH_3), 2.06 (3H, s, C=OCH_3), 1.24 (9H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 201.1, 176.9, 170.6, 170.4, 77.0, 75.3, 74.2, 65.6, 61.7, 41.4, 39.0, 27.0, 20.7, 20.6; MS (CI–NH_3): *m/z* (%) 362 (100) $[M+NH_4]^+$; calcd for $C_{16}H_{28}NO_8$ $[M+NH_4]^+$: 362.1815; found $[M+NH_4]^+$: 362.1818.

4.1.6. (+)-(2*R*,3*S*,6*R*)-2,6-Bis-acetoxymethyl-3-benzoyl-oxy-tetrahydropyran-4-one 13. To a stirred solution of benzoic anhydride (92.5 mg, 0.41 mmol) in dry CH_2Cl_2 (7 mL) at temperature under nitrogen atmosphere, anhydrous $FeCl_3$ (59.0 mg, 0.36 mmol) was added and stirred for 15 min at 0 °C. A solution of **10** (49.5 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was then added to the reaction mixture. The reaction was stirred for 10 min. The colour of the reaction mixture changed from orange to very dark green. It was then quenched by addition of saturated sodium hydrogen carbonate solution (10 mL). The mixture was stirred for 1 min and then extracted with diethyl ether (3×25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (diethyl ether) to afford **13** (27.8 mg, 56%) as colourless oil; $[\alpha]_D^{22}$ +6.53 (*c* 1.07, $CHCl_3$); R_f 0.39 (ether); ν_{max}/cm^{-1} 3068, 3018, 2965, 2879, 1735, 1602, 1263, 1113, 1047; δ_H (250 MHz, $CDCl_3$) 8.10–8.04 (2H, m, Ph), 7.67–7.58 (1H, m, Ph), 7.52–7.42 (2H, m, Ph), 5.20 (1H, dd, *J*=1.8, 0.9 Hz, H_3), 4.42 (1H, dd, *J*=11.6, 6.1 Hz, OC*H*H), 4.28 (1H, dd, *J*=11.6, 6.1 Hz, OCH*H*), 4.23 (2H, d, *J*=4.9 Hz, OCH_2), 4.15–4.01 (2H, m, H_2 and H_6), 2.86 (1H, dd, *J*=13.4, 11.6 Hz, H_{5ax}), 2.46 (1H, dd, *J*=13.4, 1.2 Hz, H_{5eq}), 2.10 (3H, s, C=OCH_3), 2.05 (3H, s, C=OCH_3); δ_C (100 MHz, $CDCl_3$) 201.0, 170.6, 170.5, 165.1, 133.9, 130.1, 128.7, 128.5, 77.1, 75.6, 74.9, 65.6, 62.0, 41.6, 20.8, 20.7; MS (CI–NH_3): *m/z* (%) 382 (100) $[M+NH_4]^+$; calcd for $C_{18}H_{24}NO_8$ $[M+NH_4]^+$: 382.1503; found $[M+NH_4]^+$: 382.1502.

4.2. Epoxidation procedure

To a solution of ketone and alkene (0.1 mmol) in acetonitrile (1.5 mL) was added aqueous Na_2EDTA solution (1.0 mL of a 0.4 mM aqueous solution). Oxone® (307 mg, 1.0 mmol $KHSO_5$) and $NaHCO_3$ (130 mg, 1.55 mmol) were added in portions simultaneously over

60 min. The reaction was stirred vigorously at room temperature until completion (monitored by TLC) and for 24 h, then diluted with water (10 mL) and the reaction mixture extracted into petrol ether or diethyl ether as appropriate (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Flash column chromatography on silica, previously washed with 2% Et_3N in petroleum ether, eluting with appropriate proportion of petroleum ether and diethyl ether afforded the relevant epoxide. Epoxide data as described previously.[6]

4.3. Determination of epoxide enantiomeric purity in Table 1

Entries 1, 4 and 7: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd, catalogue number: 14025), 20% *i*PrOH/hexane, 1.0 mL/min, at 30 °C in oven, detecting at 254 nm, as detailed by Shi.[15] Absolute configuration determined by comparison to Shi's results.

Entries 2, 5 and 8: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd, catalogue number: 14025), 5% *i*PrOH/hexane, 0.8 mL/min, at 30 °C in oven, detecting at 254 nm, as detailed by Shi.[15] Absolute configuration determined by comparison to Shi's results.

Entries 3, 6 and 9: chiral GC on Chiraldex G-TA (Advanced Separation Technologies Ltd, catalogue number: 71020), helium head pressure 13 psi, at 75 °C in oven, injection temperature 200 °C, detection by FID at 250 °C, as detailed by Shi.[15] Absolute configuration determined by comparison to Shi's results.

Entry 10: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd, catalogue number: 14025), 20% *i*PrOH/hexane, 1.0 mL/min, at 30 °C in oven, detecting at 254 nm, as detailed by Shi.[15] Absolute configuration determined by comparison to Shi's results.

Entry 11: chiral GC on Chiraldex G-TA (Advanced Separation Technologies Ltd, catalogue number: 71020), helium head pressure 13 psi, at 65 °C in oven, injection temperature 200 °C, detection by FID at 250 °C, retention times 140.22 min (major enantiomer), 154.55 min (minor enantiomer), as detailed by Shi.[15] Absolute configuration determined by comparison to Shi's results.

Entry 12: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd, catalogue number: 14025), 5% *i*PrOH/hexane, 1.0 mL/min, at 30 °C in oven, detecting at 254 nm, retention times 11.85 min (major enantiomer), 17.64 min (minor enantiomer). Absolute configuration of product determined by comparison of sign of optical rotation to the literature value ($[\alpha]_D^{22}-72.3$ (*c* 0.83, $CHCl_3$)); lit.[16] ($[\alpha]_D^{22}-111.8$ (*c* 1.17, $CHCl_3$)) at 92% ee.

Entries 13 and 14: chiral HPLC on Chiracel AD (Diacel Chemical Industries Ltd, catalogue number: 19025), 5% *i*PrOH/hexane, 1.0 mL/min, at 30 °C in oven, detecting at 254 nm, retention times 27.25 min (major enantiomer), 39.19 min (minor enantiomer).

Acknowledgements

We are grateful to Bristol-Myers Squibb, Pfizer, and Merck Sharpe and Dohme for unrestricted support of our research programmes.

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Tetrahedron

Formamides derived from *N*-methyl amino acids serve as new chiral organocatalysts in the enantioselective reduction of aromatic ketimines with trichlorosilane

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Received 1 July 2005; revised 8 August 2005; accepted 31 August 2005

Available online 10 October 2005

Dedicated to Professor Peter Pauson on the occasion of his 80th birthday

Abstract—Asymmetric reduction of *N*-aryl ketimines **1a–k**, **43**, and **45** with trichlorosilane can be catalyzed by new *N*-methyl L-amino acid-derived Lewis-basic organocatalysts, such as the valine-derived bisamide **3d** (10 mol%), in toluene at room temperature with high enantioselectivity ($\leq$92% ee). The structure–reactivity investigation shows that the product configuration is controlled by the nature of the side chain of the catalyst scaffold (e.g., *i*-Pr vs Me, as in **3d** and **6e**), so that catalysts of the same absolute configuration may induce the formation of the opposite enantiomers of the product. Arene–arene interactions between the catalyst and the incoming imine appear to be the prerequisite for asymmetric induction. This metal-free, organocatalytic protocol is competitive with the traditional, metal-catalyzed methodology.

1. Introduction

While asymmetric reduction of ketones (both stoichiometric and catalytic) is now well developed,[1] ketimines seem to be a Cinderella, with only a limited portfolio of acceptably efficient protocols reported to date.[1–3] The currently most successful methods are based on transition metal-catalyzed high-pressure hydrogenation,[1,2] hydrosilylation,[1,3] and transfer hydrogenation.[2j,4] However, this traditional approach to imine reduction (Scheme 1) is tainted by the problems associated with metal leaching and catalyst regeneration, so that development of an organocatalytic[5] alternative appears to be very attractive.

Scheme 1. Asymmetric reduction of ketimines. For R^1 and R^2, see Tables 1 and 2.

Generally, development of any new catalytic protocol includes a delicate balancing of various factors, such as catalyst structure and loading, solvent, temperature, etc. Often, even minor changes in any of these characteristics can produce a dramatic effect on the stereochemical outcome of the reaction.[1,6] Among the approaches aiming at the enhancement of enantioselectivity through structural variations, the chiral relay effect[7] is now gaining recognition as a powerful tool. The philosophy of this approach is based on the behavior of a conformationally flexible group, positioned in such a way that it can effectively convey the chiral information from the scaffold to the reaction center.[7]

As part of another project, focused on the enantioselective, transition metal-catalyzed reactions,[8] we have recently developed new *N*-methylamino acid-derived amidophoshine ligands and demonstrated that the conformational bias, imposed by the tertiary amide group, can lead to high enantioselectivity in the Cu(I)-catalyzed conjugate addition of Et_2Zn to α,β-enones.[9] Interestingly, our ligands derived from *N*-methyl valine proved to be superior to those prepared from proline, showing that the rigid cyclic framework of proline may not always be an advantage.[9] Herein, we demonstrate that these principles can be extended to the realm of organocatalysis and report on a

Keywords: Organocatalysis; Asymmetric reduction; Imines; Hydrosilylation; Lewis bases; Enantiopure amines.
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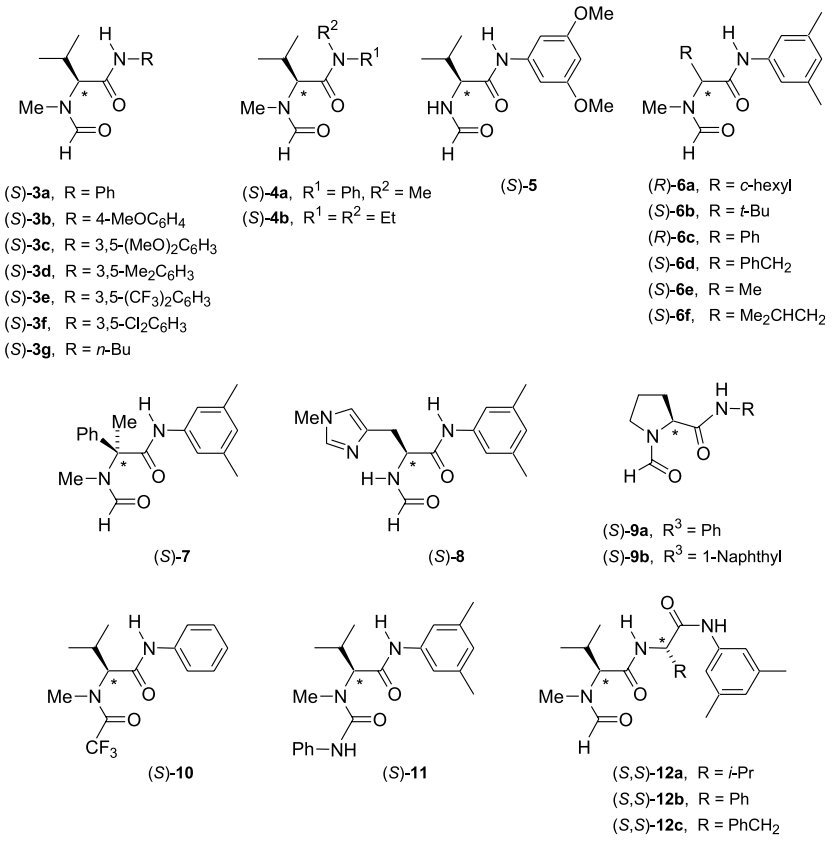
doi:10.1016/j.tet.2005.08.117



Scheme 2. Amino acid-derived organocatalysts.

powerful, organocatalytic reduction of ketimines with trichlorosilane to produce chiral amines.[10]

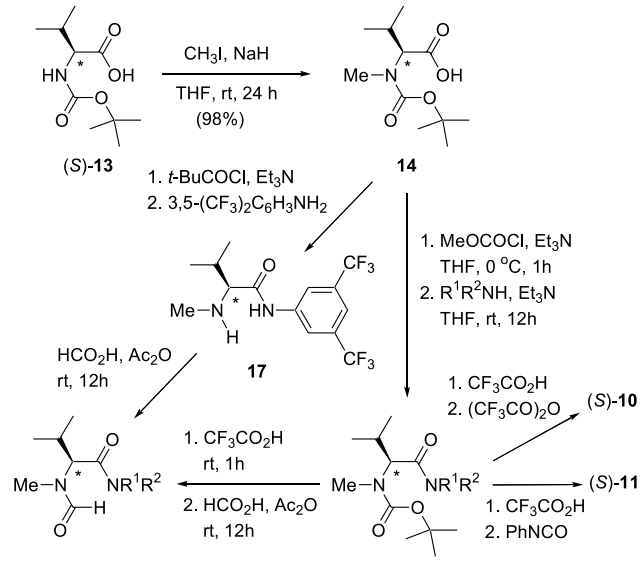
Since Cl_3SiH can be activated by Lewis bases, such as R_3N, DMF, and MeCN, etc., to effect hydrosilylation of imines,[11,12] we set out to design a suitable chiral Lewis-basic catalyst that could be viewed as a chiral analogue of DMF with one of the methyl groups replaced by a chiral moiety (Scheme 2).[12–14]

2. Results and discussion

2.1. Catalyst design and synthesis

The strategy of designing chiral analogues of DMF relied on the use of amino acids as the chiral scaffold, with the α-amino group converted into the *N*-methyl formamide moiety. It was also intended to convert the amino acid carboxyl into another amide group, with either aromatic or aliphatic substituent adjacent to the nitrogen. In our preliminary communication,[10] we have reported on formamides **3**–**5**, derived from valine and the series is now extended to other amino acid scaffolds, namely **6a**–**f**, **7**, and **8**, supplemented by **10** and **11** and by dipeptides **12a**–**c**. While this initial work was in progress, Matsumura reported on the synthesis of the *N*-formyl proline derivatives **9a**,**b** (vide infra).[14]

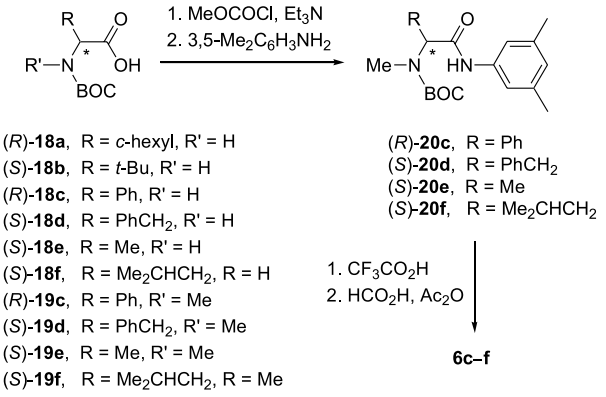
The synthesis of valine-derived formamides commenced with *N*-methylation of the BOC-protected L-valine **13** with MeI in the presence of NaH[15] (Scheme 3), which afforded the BOC-protected *N*-methyl valine[16] **14** (98%). The latter



3a, R^1 = Ph, R^2 = H
3b, R^1 = 4-MeO-C_6H_4, R^2 = H
3c, R^1 = 3,5-$(MeO)_2C_6H_3$, R^2 = H
3d, R^1 = 3,5-$Me_2C_6H_3$, R^2 = H
3e, R^1 = 3,5-$(CF_3)_2C_6H_3$, R^2 = H
3f, R^1 = 3,5-$Cl_2C_6H_3$, R^2 = H
3g, R^1 = *n*-Bu, R^2 = H
4a, R^1 = Ph, R^2 = Me
4b, R^1 = Et, R^2 = Et

15a, R^1 = Ph, R^2 = H
15b, R^1 = 4-MeO-C_6H_4, R^2 = H
15c, R^1 = 3,5-$(MeO)_2C_6H_3$, R^2 = H
15d, R^1 = 3,5-$Me_2C_6H_3$, R^2 = H
15f, R^1 = 3,5-$Cl_2C_6H_3$, R^2 = H
15g, R^1 = *n*-Bu, R^2 = H
16a, R^1 = Ph, R^2 = Me
16b, R^1 = Et, R^2 = Et

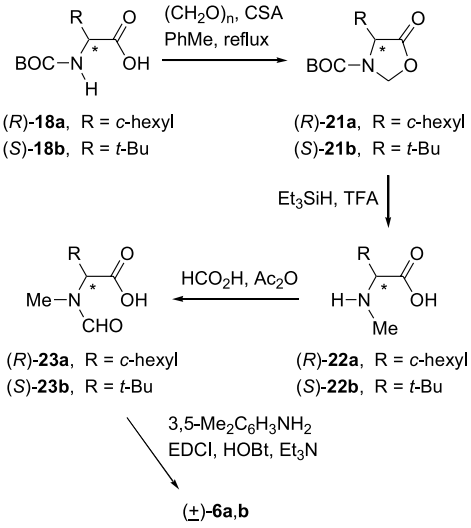
Scheme 3. Catalyst synthesis.



(*R*)-**18a**, R = *c*-hexyl, R' = H
(*S*)-**18b**, R = *t*-Bu, R' = H
(*R*)-**18c**, R = Ph, R' = H
(*S*)-**18d**, R = $PhCH_2$, R' = H
(*S*)-**18e**, R = Me, R' = H
(*S*)-**18f**, R = Me_2CHCH_2, R = H
(*R*)-**19c**, R = Ph, R' = Me
(*S*)-**19d**, R = $PhCH_2$, R' = Me
(*S*)-**19e**, R = Me, R' = Me
(*S*)-**19f**, R = Me_2CHCH_2, R = Me

(*R*)-**20c**, R = Ph
(*S*)-**20d**, R = $PhCH_2$
(*S*)-**20e**, R = Me
(*S*)-**20f**, R = Me_2CHCH_2

Scheme 4. Catalyst synthesis.



(*R*)-**18a**, R = *c*-hexyl
(*S*)-**18b**, R = *t*-Bu

(*R*)-**21a**, R = *c*-hexyl
(*S*)-**21b**, R = *t*-Bu

(*R*)-**23a**, R = *c*-hexyl
(*S*)-**23b**, R = *t*-Bu

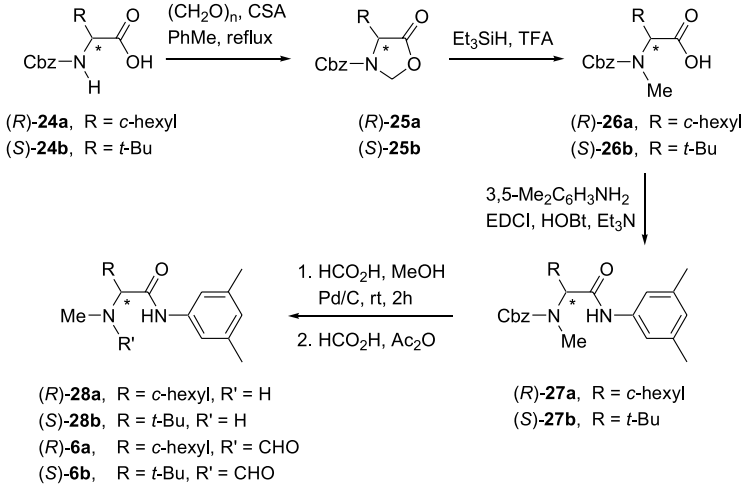
(*R*)-**22a**, R = *c*-hexyl
(*S*)-**22b**, R = *t*-Bu

Scheme 5. Catalyst synthesis.

derivative was then converted into a series of secondary and tertiary amides **15** and **16**, employing the mixed anhydride method (or, as in the case of **16b**, the carbodiimide method). The mixed anhydride was generated in situ from **14** and methyl chloroformate and then reacted with the respective amine to produce **15a–d**, **15f**,**g**, and **16a**. Only in one case this protocol failed, namely for 3,5-bis-(trifluoromethyl)-aniline, reflecting the reduced nucleophilicity of the nitrogen. Therefore, pivalyl chloride was employed here to generate the mixed anhydride,[17] which proved to react efficiently. However, this reaction led to the simultaneous loss of the BOC group, so that the free amine **17** was obtained instead of the expected BOC derivative. BOC-deprotection (with TFA) of each of the amides **15a–d**, **15f**,**g**, and **16a**,**b** was followed by formylation with a mixed anhydride, generated in situ from formic acid and acetic anhydride, to produce the desired *N*-methyl formamides **3a–d**, **3f**,**g**, and **4a**,**b**. The remaining member of this family, formamide **3e**, was obtained by formylation of amine **17**. Trifluoroacetamide **10** was obtained from the BOC-protected amide **15a** via deprotection with trifluoroacetic acid followed by acylation with trifluoroacetic anhydride. Finally, **15d** was converted into the urea derivative **11** via deprotection followed by treatment with phenylisocyanate.

The same strategy was employed for the synthesis of the remaining amino acid-derived amides and proved to work successfully with the BOC-protected phenylglycine, phenylalanine, alanine, and leucine (**18c–f**) as starting materials, to produce formamides **6c–f** in four steps (Scheme 4). However, when applied to the BOC-protected cyclohexylglycine and *t*-leucine (**18a**,**b**), it failed in the first step, as the *N*-methylation turned out to be sluggish. Attempted alkylation of both **18a**,**b** using $(MeO)_2SO_2$ and NaH[18] and the variant utilizing Nosyl- instead of BOC-protected substrate for *N*-alkylation with MeI and Et_3N in MeCN[19] were equally unsuccessful. Therefore, an alternative route had to be sought.

In an alternative approach[20] to *N*-methylation, the BOC-protected **18a**,**b** were first converted into the respective oxazolidinones **21a**,**b** (Scheme 5). Treatment of the latter intermediates with Et_3SiH and CF_3CO_2H in chloroform effected both the desired cleavage of the C–O bond and the loss of the BOC group to produce the *N*-methyl amino acids **22a**,**b**. Subsequent *N*-formylation under standard conditions afforded the *N*-methyl formamides **23a**,**b**,[21] which were then reacted with 3,5-dimethyl aniline using the carbodiimide method. The resulting amides **6a**,**b**, however, turned out to be racemic, as a result of racemization in the last



(*R*)-**24a**, R = *c*-hexyl
(*S*)-**24b**, R = *t*-Bu

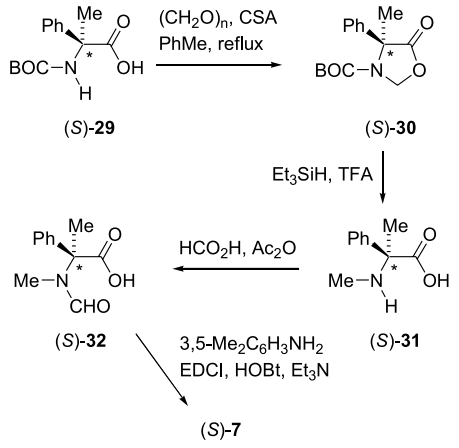
(*R*)-**25a**
(*S*)-**25b**

(*R*)-**26a**, R = *c*-hexyl
(*S*)-**26b**, R = *t*-Bu

(*R*)-**28a**, R = *c*-hexyl, R' = H
(*S*)-**28b**, R = *t*-Bu, R' = H
(*R*)-**6a**, R = *c*-hexyl, R' = CHO
(*S*)-**6b**, R = *t*-Bu, R' = CHO

(*R*)-**27a**, R = *c*-hexyl
(*S*)-**27b**, R = *t*-Bu

Scheme 6. Catalyst synthesis.



Scheme 7. Catalyst synthesis.

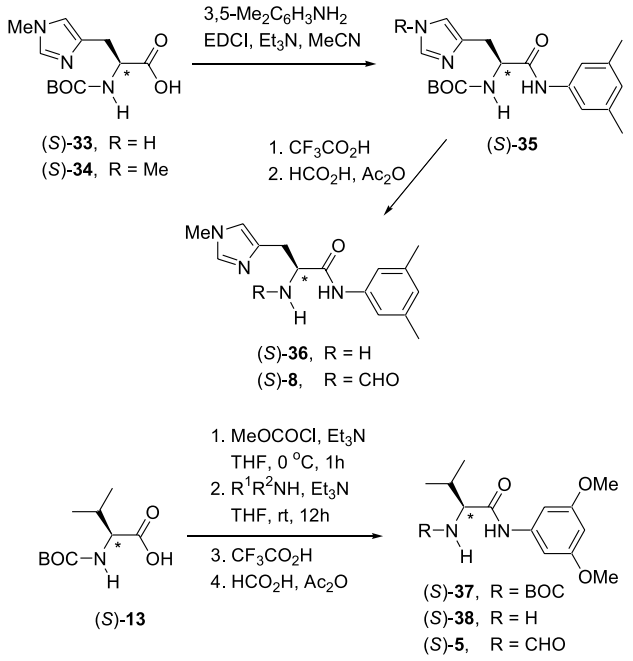
step.[22] Since the mixed anhydride method proved equally fruitless, a further modification of this approach was sought.

The new alternative employed the Cbz protecting group to prevent the loss of *N*-protection in the reduction step (Scheme 6).[23] Thus, the Cbz-protected amino acids **24a**,**b** were converted into the respective oxazolidinones **25a**,**b** in the same way as their BOC counterparts. However, the desired C–O bond cleavage to give the expected *N*-methyl derivatives **26a**,**b** turned out to be sluggish (room temperature, 1 week) and rather low-yielding. Subsequent reaction of **26a** with 3,5-dimethyl aniline, using the carbodiimide method, afforded **27a** in moderate yield (64%), whereas **27b** was isolated as an inseparable mixture with **25b** in low yield. The final reductive deprotection of **27a**,**b**, followed by formylation, proceeded uneventfully, affording **6a**,**b** in good yields.

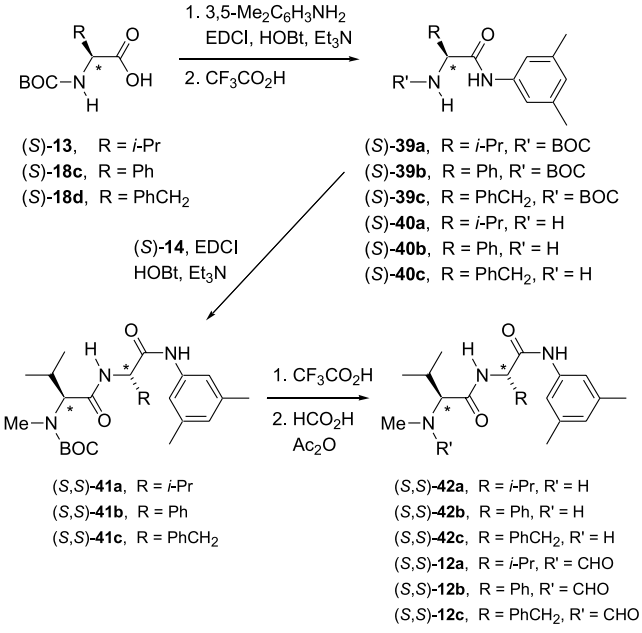
The synthesis of **7** (Scheme 7), starting with the BOC-protected α-methyl phenylglycine **29**, utilized the oxazolidinone-type methylation again and proved to be uneventful, except for the low yielding amide formation step (**32**→**7**), which obviously stems from the steric hindrance in this α,α-disubstituted amino acid derivative.

The synthesis of the histidine-derived candidate catalyst **8** (Scheme 8) commenced with *N*-methylation of the imidazole nitrogen in the BOC-protected histidine (**33**→**34**) using the MeI/NaH method,[24] followed by amidation under the standard carbodiimide conditions. The resulting amide **35**[25] was then deprotected and formylated to produce **8** in good overall yield. The valine-derived formamide **5** was synthesized in the same manner from the BOC-protected valine (*S*)-**13** (Scheme 8).

Finally, dipeptides **12a**–**c** were synthesized from the BOC-protected *N*-methyl valine (*S*)-**14**, which served as the building block for the *N*-terminus, and amides (*S*)-**40a**–**c**, obtained in two steps from the respective BOC-protected amino acids (*S*)-**13** and (*S*)-**18c**,**d** (Scheme 9).[26] The peptide bond was constructed using the carbodiimide method and the resulting products **41a**–**c** were deprotected to afford **42a**–**c**. Subsequent formylation gave rise to the desired formamides (*S*,*S*)-**12a**–**c**.



Scheme 8. Catalyst synthesis.



Scheme 9. Amino acid-derived orgnocatalysts.

2.2. Asymmetric reduction of ketimines with Cl_3SiH catalyzed by chiral formamides

Reduction of imines **1a**–**k** (Scheme 1), catalyzed by formamides **3**–**5** (10 mol%), has been reported in our preliminary communication[10] and the salient features, required for further discussion, are highlighted in Table 1. Herein, we present an orchestration of our earlier efforts by extending the set of catalysts (**6**–**8** and **10**–**12**) and substrates and by reporting the temperature and solvent effects.

Reduction of ketimine **1a** (derived from acetophenone and

Table 1. Reduction of ketimines **1a–j** with trichlorosilane, catalyzed by (*S*)-**3a** and (*S*)-**9a**,**b**[a]

Entry	Imine	R^1, R^2	Catalyst	Solvent	Yield (%)[b]	**2**, % ee[c] (config)[d]
1	**1a**	Ph, Ph	**3a**	CH_2Cl_2	68	79 (*S*)
2	**1a**	Ph, Ph	**3a**	$CHCl_3$	79	86 (*S*)
3[e]	**1a**	Ph, Ph	**3a**	$CHCl_3$	49	92 (*S*)
4	**1a**	Ph, Ph	**3a**	MeCN	65	30 (*S*)
5	**1a**	Ph, Ph	**9a**	CH_2Cl_2	91	55 (*R*)[f]
6	**1a**	Ph, Ph	**9b**	CH_2Cl_2	52	66 (*R*)[f]
7	**1b**	4-$MeOC_6H_4$, Ph	**3a**	$CHCl_3$	57	80 (*S*)
8	**1c**	4-$CF_3C_6H_4$, Ph	**3a**	$CHCl_3$	43	87 (*S*)
9	**1d**	2-Naphth, Ph	**3a**	$CHCl_3$	60	87 (*S*)
10	**1e**	*c*-C_6H_{11}, Ph	**3a**	$CHCl_3$	80	37 (*S*)
11[e]	**1e**	*c*-C_6H_{11}, Ph	**3a**	$CHCl_3$	53	59 (*S*)
12	**1f**	Ph, 4-$MeOC_6H_4$	**3a**	$CHCl_3$	96	85 (*S*)
13	**1g**	Ph, 2-$MeOC_6H_4$	**3a**	CH_2Cl_2	36	22 (*S*)
14	**1h**	Ph, *c*-C_6H_{11}	**3a**	$CHCl_3$	50	<5
15	**1i**	Ph, *n*-Bu	**3a**	$CHCl_3$	60	<5
16	**1j**	Ph, CH_2Ph	**3a**	$CHCl_3$	46	8

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol% of the catalyst at room temperature for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or GC.
[d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Section 4) and/or by HPLC/GC via comparison with authentic samples.
[e] The reaction was carried out at −20 °C.
[f] Ref. 14a.

aniline) with Cl_3SiH in the presence of the L-valine-derived catalyst (*S*)-**3a** (10 mol%), was carried out in CH_2Cl_2 at room temperature, and afforded the corresponding amine (*S*)-**2a** in good yield and with 79% ee (Table 1, entry 1). Changing the solvent to chloroform had a beneficial effect, as both the yield and enantioselectivity had improved (entry 2). Further increase in enantioselectivity (to 92% ee) was attained by lowering the reaction temperature to −20 °C, though at the expense of the reaction rate (entry 3). The use of acetonitrile as solvent led to a dramatic reduction of enantioselectivity (entry 4).[27]

While our initial work was in progress, Matsumura reported on the same reduction catalyzed by the L-proline-derived formamides (*S*)-**9a**,**b** (10–20 mol%) with ≤66% ee (entries 5 and 6);[14a] however, he obtained the opposite enantiomer of the product! The latter results are intriguing and suggest that the enantiodifferentiation mechanisms for valine- and proline-derived catalysts are dramatically different, which warranted a thorough study of the structural effects of both the catalyst and the substrate.

Recently, we have shown that arene-arene interactions have a strong impact on the reactivity and enantioselectivity in organocatalysis,[28] which prompted us to probe the extent of non-covalent interactions involved in this reduction of imines. The solvent effect observed (entries 1–3) is consistent with the involvement of hydrophobic, presumably arene–arene interactions of the catalyst and the substrate[29] but further evidence was required.

In order to shed light on the origin of the asymmetric induction and, in the same time, to probe the scope of this reduction, the aromatic system in the ketimine **1** and in the catalyst **3** was varied. The electronic effect on the conversion and enantioselectivity turned out to be marginal, as demonstrated by comparison of the electron-rich and electron-poor imines **1b** and **1c** (entries 7 and 8, and further entries in Table 2). 2-Naphthyl-imine **1d** reacted in the same way as **1a** (entry 9) but the cyclohexyl analogue **1e** exhibited a significantly reduced enantioselectivity, although in this case the overall result was affected by rather fast, non-catalytic background reaction (entry 10). Here, decreasing the temperature resulted in the increase of enantioselectivity by 22% (entry 11), presumably by suppressing the competing, non-catalytic process.

Variation of the imine *N*-substituent (R^2) had a more dramatic effect. Thus, while *p*-methoxy imine **1f** gave high conversion and enantioselectivity (entry 12), reduction of its *o*-isomer **1g** was much less efficient (entry 13), indicating the influence of the steric effect. By contrast, imines **1h–j**, derived from non-aromatic amines, afforded practically racemic products (entries 14–16), demonstrating the crucial role of the *N*-aryl moiety of the ketimine for asymmetric induction.[30]

The role of the amide functionality in the catalyst, in particular its contribution to aromatic interactions, was elucidated with the aid of amides **3–5**.[31] Catalyst **3b** with a donor group was found to be slightly less efficient with imine **1a**, compared to **3a** (Table 2, entry 1; compare with Table 1, entry 2). Additional methoxy substituent (**3c**) led to a further decrease in selectivity (entries 2–4). 3,5-Dimethylphenylamide **3d** generally gave higher yields and slightly better selectivity than the parent phenylamide **3a** (entries 5–11). By contrast, a significantly reduced efficacy was observed for the electron-poor 3,5-bis(trifluoromethyl)- and 3,5-dichloroanalogues **3e** and **3f** (entries 20–22). No reaction was observed with *n*-butyl amide **3g** (Table 2, entry 23), confirming the importance of the aromatic system in this position. Tertiary amide **4a**, lacking the NH group, proved to be a sluggish catalyst (entry 24), which may suggest that a hydrogen bonding between the NH group of the catalyst and the imine nitrogen plays a role in the transition state. As expected, diethylamide **4b** proved inert (entry 25). Furthermore, removing the *N*-Me group from the formamide part, as in catalyst **5**, proved to be detrimental to

Table 2. Reduction of ketimines **1a–k** with trichlorosilane, catalyzed by (*S*)-**3a–g**, **4a**,**b**, and **5**[a]

Entry	Imine		Catalyst	Solvent	Temperature (°C)	Yield (%)[b]	**2**, % ee[c] (config)[d]
1	**1a**	Ph, Ph	(*S*)-**3b**	$CHCl_3$	Ambient	62	85 (*S*)
2	**1a**	Ph, Ph	(*S*)-**3c**	$CHCl_3$	Ambient	81	82 (*S*)
3	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3c**	$CHCl_3$	Ambient	94	77 (*S*)
4	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**3c**	$CHCl_3$	Ambient	82	79 (S)
5	**1a**	Ph, Ph	(*S*)-**3d**	$CHCl_3$	Ambient	70	89 (*S*)
6	**1a**	Ph, Ph	(*S*)-**3d**	$CHCl_3$	−20	94	92 (*S*)
7	**1b**	4-$MeOC_6H_4$, Ph	(*S*)-**3d**	$CHCl_3$	Ambient	62	87 (*S*)
8	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3d**	$CHCl_3$	Ambient	88	87 (*S*)
9	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3d**	$CHCl_3$	−20	95	89 (*S*)
10	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**3d**	$CHCl_3$	Ambient	79	86 (*S*)
11	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**3d**	$CHCl_3$	−20	85	90 (*S*)
12	**1a**	Ph, Ph	(*S*)-**3d**	Tol	Ambient	81	92 (*S*)
13	**1a**	Ph, Ph	(*S*)-**3d**	Tol	−20	54	92 (*S*)
14	**1b**	4-$MeOC_6H_4$, Ph	(*S*)-**3d**	Tol	Ambient	86	85 (*S*)
15	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3d**	Tol	Ambient	86	89 (*S*)
16	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3d**	Tol	−20	80	89 (*S*)
17	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**3d**	Tol	Ambient	85	91 (*S*)
18	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**3d**	Tol	−20	46	93 (*S*)
19	**1k**	2-MeC_6H_4, Ph	(*S*)-**3d**	Tol	Ambient	90	92 (*S*)[e]
20	**1a**	Ph, Ph	(*S*)-**3e**	$CHCl_3$	Ambient	88	53 (*S*)
21	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**3e**	$CHCl_3$	Ambient	92	69 (*S*)
22	**1a**	Ph, Ph	(*S*)-**3f**	$CHCl_3$	Ambient	35	56 (*S*)
23	**1a**	Ph, Ph	(*S*)-**3g**	$CHCl_3$	Ambient	0	—
24	**1a**	Ph, Ph	(*S*)-**4a**	$CHCl_3$	Ambient	23	7 (*S*)
25	**1a**	Ph, Ph	(*S*)-**4b**	$CHCl_3$	Ambient	0	—
26	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**5**	$CHCl_3$	Ambient	84	35 (*S*)

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol% of the catalyst for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or GC.
[d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Section 4) and/or by HPLC/GC via comparison with authentic samples.
[e] Configuration of **2k** is assumed to be (*S*) in analogy with the rest of the series.

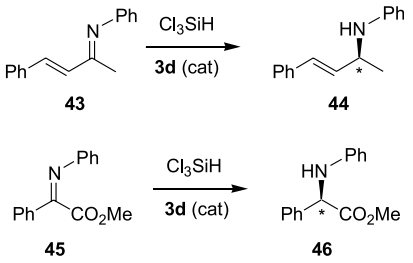
enantioselectivity (entry 26; compare with entry 3), showing the importance of the *N*-Me for the chiral relay.[9]

All the experiments discussed to this point were run in chlorinated solvents, namely CH_2Cl_2 and $CHCl_3$, of which the latter gave somewhat better results. A few experiments with MeCN proved its inferiority, clearly indicating that the reaction requires nonpolar solvents. However, neither CH_2Cl_2 nor $CHCl_3$ are environmentally friendly, so that other non-polar solvents were probed as the next stage and toluene was found to be the solvent-of-choice: in this solvent, the enantioselectivity attained with catalyst **3d** at

Table 3. Reduction of ketimines **1a**,**c**,**f** with trichlorosilane, catalyzed by **6a–f**, **7–11**, and **12a–c**[a]

Entry	Imine	R^1, R^2	Catalyst	Solvent	Yield (%)[b]	**2**, % ee[c] (config)[d]
1	**1c**	4-$CF_3C_6H_4$, Ph	(*R*)-**6a**	Tol	74	89 (*R*)[e]
2	**1f**	Ph, 4-$MeOC_6H_4$	(*R*)-**6a**	Tol	95	82 (*R*)[e]
3	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**6b**	Tol	84	82 (*S*)
4	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**6b**	Tol	95	83 (*S*)
5	**1a**	Ph, Ph	(*R*)-**6c**	Tol	84	0
6	**1c**	4-$CF_3C_6H_4$, Ph	(*R*)-**6c**	Tol	70	0
7	**1f**	Ph, 4-$MeOC_6H_4$	(*R*)-**6c**	Tol	76	0
8	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**6d**	Tol	85	26 (*S*)
9	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**6d**	Tol	84	49 (*S*)
10	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**6e**	Tol	92	38 (*R*)
11	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**6f**	Tol	89	10 (*S*)
12	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**7**	Tol	89	47 (*S*)
13	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**7**	Tol	80	42 (*S*)
14	**1f**	Ph, 4-$MeOC_6H_4$	(*S*)-**8**	Tol	0	—
15	**1a**	Ph, Ph	(*S*)-**10**	CH_2Cl_2	<10	0
16	**1c**	4-$CF_3C_6H_4$, Ph	(*S*)-**11**	Tol	70	0
17	**1c**	4-$CF_3C_6H_4$, Ph	**12a**	Tol	84	17 (*R*)
18	**1f**	Ph, 4-$MeOC_6H_4$	**12a**	Tol	91	10 (*R*)
19	**1f**	Ph, 4-$MeOC_6H_4$	**12b**	Tol	78	7 (*S*)
20	**1f**	Ph, 4-$MeOC_6H_4$	**12c**	Tol	87	0

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol% of the catalyst at room temperature, 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or GC.
[d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Section 4) and/or by HPLC/GC via comparison with authentic samples.
[e] Note the (*R*) configuration of the catalyst.



Scheme 10. Asymmetric reduction of of ketimines.

Table 4. Reduction of ketimines **43** and **45** with trichlorosilane, catalyzed by (*S*)-**3d**[a]

Entry	Imine	Temperature (°C)	Yield (%)[b]	% ee[c] (config)[d]
1	**43**	Ambient	59	74 (*S*)
2	**43**	−20	64	81 (*S*)
3	**45**	Ambient	68	30 (*R*)[e]
4	**45**	−20	69	59 (*R*)[e,f]

[a] The reaction was carried out at 0.5 mmol scale with 1.5 equiv of Cl_3SiH and 10 mol% of the catalyst in toluene for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or GC.
[d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data (see the Section 4) and/or by HPLC/GC via comparison with authentic samples.
[e] Note the change of substituent priorities in the CIP nomenclature.
[f] The reaction was run for 24 h.

room temperature (Table 2, entry 12) matched the result obtained for $CHCl_3$ at −20 °C (Table 1, entry 3) but with much higher yield. Marginal increase in the enantioselectivity was observed for **1f** in toluene at −20 °C (Table 2, entries 17 and 18), whereas **1a** and **1c** showed no further improvement at low temperature (Table 2, entries 12, 13, 15, and 16).

Variation of the side chain of the amino acid scaffold was investigated next (**6–8**, **10–12**; Table 3). The cyclohexyl analogue **6a** exhibited similar enantioselectivity (Table 3, entries 1 and 2) as its isopropyl counterpart derived from valine (Table 2, entries 15 and 17). The *t*-butyl derivative **6b** showed only a marginally reduced efficiency (Table 3, entries 3 and 4), whereas the application of the phenylglycine-derived catalyst **6c** gave rise, surprisingly, to racemic products (Table 3, entries 5–7). Modest to low enantioselectivity was also observed for the phenylalanine-, alanine-, and leucine-derived catalysts **6d–f** (entries 8–11). Interestingly, the alanine-derived catalyst **6e** induced the preferential formation of the opposite enantiomer of the product, though with moderate enantioselectivity (38% ee; entry 10), suggesting that competing transition states play a role in this series. In contrast to the phenylglycine-derived catalyst **6c**, which gave racemic products, its methylated analogue **7** resumed a moderate level of enantioselectivity (entries 12–13). In contrast to the rest of the series, the histidine derivative **8** failed to catalyze the reaction (entry 14), suggesting an interference by the imidazole moiety. The valine-derivative **10**, having the formamide moiety replaced by the much less Lewis-basic trifluoroacetamide group, proved equally inefficient (entry 15), demonstrating the crucial role of the formamide group (compare with Table 1, entry 1). The urea derivative **11** did catalyze the reaction but afforded a racemic product (Table 3, entry 16) and the dipeptides **12a–c** behaved similarly, exhibiting very low enantioselectivity, if any (entries 17–20).

From the efficiency standpoint, 3,5-dimethylphenylamide **3d** is clearly the champion catalyst. Therefore, it was this derivative that was employed to briefly probe the scope of this methodology (Scheme 10). With the chalcone-derived imine **43**, the reduction proceeded well, though with rather reduced enantioselectivity (Table 4, entries 1 and 2). Imine **45**, whose reduction produced the phenylglycine derivative **46**, exhibited good reactivity but rather low enantioselectivity (entry 3). Lowering the temperature resulted in an increase of the asymmetric induction (to 59% ee) but at the expense of the reaction rate (entry 4).

2.3. Mechanistic considerations

Our experiments indicate that for the activation of trichlorosilane, the catalyst is required to posses two amide groups, one of the formamide type, the other as anilide, both of which can be assumed to be available for coordination as donors (Fig. 1). In the ^{13}C NMR spectrum of a 1:1 mixture of **3d** and $HSiCl_3$, shifts of ~0.1 and 0.2 ppm were observed for the corresponding signals of the formamide and anilide carbonyls relative to free **3d**. Furthermore, the methyl groups at the aromatic ring became non-equivalent,[32] suggesting a weak coordination (possibly bidentate) that restricts the rotation about the N–Ar bond.

In the series of catalysts **3a–f**, the Lewis basicity of the

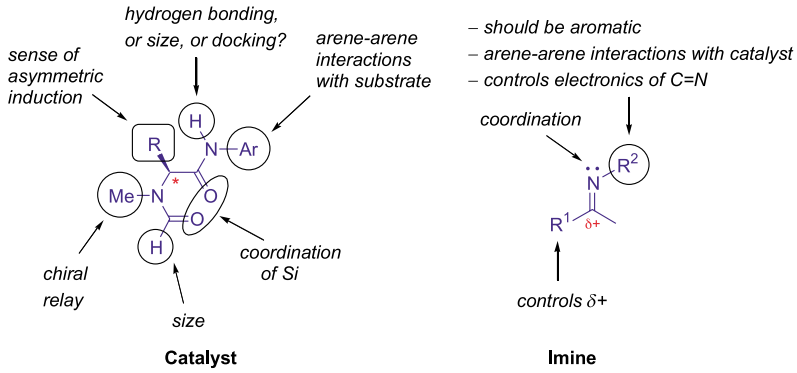


Figure 1. Key features of the catalyst and the substrate.

formamide moiety remained constant while the substituents in the arylamide part were designed to affect its donor properties. Apparently, catalyst **3f**, having electron withdrawing groups at the aromatic ring, is less efficient in coordination, which may account for the decreased enantioselectivity in this instance (Table 2, entry 22). 3,5-Dimethylanilide **3d** appears to represent the right balance of the electronic and steric properties, giving rise to the highest reactivity and enantioselectivity (Fig. 1).

While the secondary anilides **3a–f** were identified as efficient catalysts, the tertiary anilide **4a** proved inert, suggesting that the N–H group plays an important role (Fig. 1), either through hydrogen bonding or by allowing greater flexibility of the amide group (vide infra). Furthermore, the reaction does require an *N*-Ar group to be part of the catalyst (as in **3a–f**, **6a–f**, **7**, and **9**) since the *N*-Bu derivative **3g** fails to catalyze the reaction. This behavior can be best rationalized by the arene-arene interactions between the catalyst and the imine, as an important factor contributing to the facial discrimination of the incoming imine.

The tertiary formamide group (as in **3a–f**, **6a–f**, **7**, **9**, and **12a–c**) is a prerequisite for the catalytic activity (Fig. 1). Here, the carbonyl must be sufficiently Lewis basic (note that **10** is ineffective) and, simultaneously, the group must be sufficiently small (i.e., formamide); note that the bulkier amides, such as the benzamide congener of **6c**, the acetamide counterpart of **9a**,[14a] the BOC derivative **15a**, and the urea analogue **11** are ineffective. The role of the *N*-Me group in the formamide moiety is important for the enantioselectivity, though not crucial for the reaction to occur, as can be seen from the comparison of **3c** with **5** (Table 2, compare entries 3, 4, and 26). It can be hypothesized that the *N*-methyl is responsible for assuming the right conformation of the formamide group that conveys the chiral information from the chiral center.[33]

The side chain of the amino acid scaffold exhibits the most intriguing effect (Fig. 1). Thus, the *i*-Pr group of the valine derived catalysts **3a–f**, *c*-Hex of **6a**, *t*-Bu of **6b**, and $PhCH_2$ of **6d** (Table 1, entries 1–3; Table 2, entries 1–23; Table 3, entries 1–4, 8, and 9) all induce the formation of the amine of the same configuration (the latter analogue with a rather decreased level of selectivity). The alanine derivative with the Me substituent (**6e**) induces formation of the opposite enantiomer with modest enantioselectivity (Table 2, entry 10) and this trend is further increased with the proline-derived formamides **9a**,**b**[14a] (Table 1, entries 5 and 6). The phenylglycine derivative **6c** gives a racemic product (Table 2, entries 5–7), which places this catalyst at the borderline. Apparently, the side chain is responsible for inducing subtle conformational changes[34] of the catalyst, which play a key role in determining the sense of enantiodifferentiation in the transition state.

The structural requirements for the ketimine **1** are as follows (Fig. 1): the R^1 group should preferably be aromatic, as in **1a–d**, to attain high conversion and enantioselectivity (Table 1, entries 1–9); both electron-donating and electron-withdrawing groups are well tolerated, as in **1b**,**c** (compare Table 1, entry 7 vs 8; Table 2, entries 7 vs 8 and 14 vs 15). With a non-aromatic group at this position, such as cyclohexyl (**1e**), the reaction does occur but with a lower degree of asymmetric induction (Table 1, entries 10 and 11), owing partly to the competing, uncatalyzed background reaction. When the conjugation is extended, as in the vinylogue **43**, the reaction reverts to high enantioselectivity (Table 4, entries 1 and 2), demonstrating the beneficial effect of conjugation. Regarding the R^2 group, its aromatic character (**1a–f**) is crucial for attaining high asymmetric induction (Table 1, entries 1–12); the absence of conjugation, as in **1h–j**, does not prevent the reaction but results in the formation of a practically racemic product in good yield (Table 1, entries 14–16). Examination of the phenyl and methoxyphenyl derivatives (**1a**,**f**,**g**) revealed that steric congestion close to the nitrogen (as in the *o*-methoxy derivative **1g**) should be avoided, for it results in a dramatic decrease in the reaction rate and enantioselectivity (Table 1, entry 13). On the other hand, **1a** and **1f** gave comparable result (e.g., Table 1, entries 2 and 12). The good enantioselectivity attained with the *p*-methoxy derivative **1f** is particularly important, since this electron-rich *N*-Aryl group can be removed by oxidative methods,[35] which extends the scope of this methodology to the realm of primary amines.

Another notable feature of this reduction is the linear relationship between the enantiomeric purity of the catalyst and the product, observed for **3d** as the representative catalyst, suggesting that no more than one molecule of the catalyst is involved in the enantiodifferentiating process.

3. Conclusions

The structural features and their implications to the reaction mechanism of this hydrosilylation of ketimines can be summarized, with reference to Fig. 1, as follows: (1) the *N*-methyl formamide moiety of the catalyst is crucial for the enantioselectivity, presumably by controlling the spatial orientation of the formamide group and relaying the chiral information from the chiral center. (2) The anilide part of the catalyst and the *N*-aryl substituent of the substrate imine (R^2) are crucial for the enantiodifferentiating process, suggesting arene–arene interactions. (3) The anilide moiety of the catalyst must constitute a secondary amide, with an NH group. This effect is not clear at present, since it can either be rationalized by a hydrogen bonding to the substrate or attributed to the increased flexibility of the secondary (vs tertiary) amide; docking of the substrate imine by the CONH-R group may also be possible, in light of the recent model calculation of the rather strong attractive interaction between the formamide and benzene molecules.[36] (4) The reagent, Cl_3SiH, is apparently activated by the formamide moiety of the catalyst, in consonance with other investigations.[11b,13] The anilide carbonyl is also capable of coordinating the silicon, as evidenced by the NMR, so that it can be conjectured to take part in the enantiodifferentiation, but more experiments will be required to address this issue. (5) The nature of the amino acid side chain determines the configuration of the resulting product, apparently by controlling the conformation of the transition state; the valine-derived (*S*)-**3d** and the proline-derived

(*S*)-**9b**[14a] represent the extremes, favoring the formation of (*S*)-**2a** (≤92% ee) and (*R*)-**2a** (≤66% ee), respectively.

In conclusion, we have designed new amino acid-derived organocatalysts **3** and **6**, which effect hydrosilylation of *N*-aryl ketimines **1a–k**, **43**, and **45** with Cl_3SiH to afford secondary amines **2a–k**, **44**, and **46**, respectively. The observed enantioselectivity (≤93% ee) of this metal-free protocol matches the level of the transition metal-catalyzed methods,[2] with the L-valine-derived formamide **3d** being the champion catalyst and toluene the solvent of choice. Arene–arene interactions between the anilide moiety of the catalyst and *N*-aryl substituent of the substrate ketimine appear to be the key factor contributing to the enantiodifferentiation process.

4. Experimental

4.1. General methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of $\leq \pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^3 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^1H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for $CHCl_3$ solutions unless otherwise indicated. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware, twice evacuated and filled with inert gas. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride). Petroleum ether refers to the fraction boiling in the range of 60–80 °C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. The imines **1a**,[2j,37] **1b**,[2j] **1d**,[2j] **1e**,[2j,3c] **1f**,[38] **1g**,[38] **1h**,[39] **1i**,[37] **1j**,[2j] **1k**,[3c] and **43**,[40] and **45**[14a] are known compounds and were prepared according to the procedure shown for **1c**, the only new member of this series. Amines **2a**,[41,42] **2b**,[2j,37] **2c**,[42] **2d**,[41,42] **2e**,[3c] **2f**,[42] **2g**,[43] **2h**,[44] **2i**,[37] **2j**,[2j,37] **2k**,[3c,14a] **44**,[40,45] and **46**[46] are all know compounds and their absolute configuration was established in reference to the literature data.

4.1.1. Imine 1c. A mixture of $NaHCO_3$ (2.2 g, 26 mmol), aniline (0.48 mL, 5.3 mmol), *p*-trifluoromethylacetophenone (1.0 g, 5.3 mmol), and activated molecular sieves (4 g, 4 Å) in anhydrous toluene (5 mL) was heated at 80 °C for 12 h under an argon atmosphere. The mixture was filtered through celite and the celite was washed with CH_2Cl_2. The filtrate was evaporated in vacuo and the product was crystallized from petroleum ether at 5 °C to give pure **1c** (0.67 g, 48%): mp 74–77 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 6.71 (d, J=8.0 Hz, 2H), 7.03 (t, J=8.0 Hz, 1H), 7.30 (t, J=8.0 Hz, 2H), 7.61 (d, J=8.2 Hz, 2H), 7.99 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 17.80 (CH_3), 119.57 (CH), 124.04 (CH), 125.72 (CH), 127.92 (CH), 129.44 (CH), 132.31 (CF_3), 143.02 (C), 151.51 (C), 164.69 (C); IR (NaCl) ν 1643 cm^{-1}; MS *m/z* (%) 263 (M^+, 61), 248 (100), 244 (7), 152 (4), 181 (16), 77 (71); HRMS (EI): 263.0922 ($C_{15}H_{12}N_2F_3$ requires 263.0921).

4.2. Protocol A: general procedure for the catalytic hydrosilylation of imines 1a–k, 43, and 45

Trichlorosilane (77 μL, 0.77 mmol) was added dropwise to a stirred solution of the imine **1a–k** (0.51 mmol) and the catalyst (0.051 mmol) in anhydrous CH_2Cl_2 (or $CHCl_3$ or MeCN; see Tables 1 and 2) at 0 °C (or at −20 °C), and the mixture was allowed to stir overnight at room temperature (or at −20 °C) under an argon atmosphere. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the product was extracted with ethyl acetate (100 mL). The extract was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (24/1) afforded the product as an oil. The yields and ee are given in Tables 1–4.

4.2.1. Compound (*S*)-(+)-2a. $[\alpha]_D$ +16.8 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J=7.1 Hz, 3H), 3.94 (br s, 1H), 4.41 (q, J=6.7 Hz, 1H), 6.44 (d, J=8.6 Hz, 2H), 6.57 (t, J=7.3 Hz, 1H), 7.01 (t, J=7.5 Hz, 2H), 7.13 (t, J=6.8 Hz, 1H), 7.27 (t, J=7.3 Hz, 2H), 7.30 (d, J=7.3 Hz, 2H) in agreement with the literature data;[42] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1+0.1% NEt_3, 0.5 mL/min) showed 92% ee (t_S=15.1 min, t_R=17.7 min).[47]

4.2.2. Compound (*S*)-(+)-2b. $[\alpha]_D$ +4.45 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, J=7.2 Hz, 3H), 3.68 (s, 3H), 3.90 (br s, 1H), 4.35 (q, J=6.6 Hz, 1H), 6.41 (d, J=8.5 Hz, 2H), 6.55 (t, J=7.31 Hz, 1H), 6.77 (d, J=7.2 Hz, 2H), 6.97 (t, J=6.5 Hz, 2H), 7.14 (d, J=7.2 Hz, 2H) in agreement with the literature data;[2j,37] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1+0.1% NEt_3 0.5 mL/min) showed 80% ee (t_S=19.3 min, t_R=22.7 min).[47]

4.2.3. Compound (*S*)-(+)-2c. $[\alpha]_D$ +20.0 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, J=7.1 Hz, 3H), 3.97 (br s, 1H), 4.46 (q, J=6.7 Hz, 1H), 6.38 (d, J=7.6 Hz, 2H), 6.59 (t, J=7.4 Hz, 1H), 7.02 (t, J=7.3 Hz, 2H), 7.41 (d, J=8.2 Hz, 2H), 7.51 (d, J=8.2 Hz, 2H) in agreement with the literature data;[42] chiral GC (Supelco β-DEX 120 column, oven: 125 °C for 2 min, then 1 °C/min to 200 °C, 10 min at that temperature) showed ee of 89% (t_S=42.8 min, t_R=43.2 min).

4.2.4. Compound (*S*)-(+)-2d. $[\alpha]_D$ +16.2 (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, J=7.1 Hz, 3H), 4.03

(br s, 1H), 4.54 (q, J=6.7 Hz, 1H), 6.45 (d, J=8.0 Hz, 2H), 6.56 (t, J=7.5 Hz, 1H), 6.98 (t, J=7.6 Hz, 2H), 7.30 (t, J=7.8 Hz, 2H), 7.36 (d, J=7.2 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H), 7.70 (s, 1H) in agreement with the literature data;[41,42] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 15:1+0.1% NEt_3, 0.5 mL/min) showed 88% ee (t_S=18.7 min, t_R=21.2 min).[47]

4.2.5. Compound (*S*)-(+)-2e. $[\alpha]_D$ +6.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91–1.80 (m, 11H), 1.05 (d, J=6.7 Hz, 3H), 3.2 (q, J=8.0 Hz, 1H), 3.38 (br s, 1H), 6.49 (d, J=8.0 Hz, 2H), 6.55 (t, J=8.0 Hz, 1H), 7.07 (t, J=10.0 Hz, 2H) in agreement with the literature data;[3c] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 37% ee (t_R=8.2 min, t_S=8.7 min).

4.2.6. Compound (*S*)-(+)-2f. $[\alpha]_D$ +2.5 (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J=7.0 Hz, 3H), 3.60 (s, 3H), 4.32 (q, J=6.4 Hz, 1H), 6.37 (d, J=8.1 Hz, 2H), 6.61 (d, J=7.6 Hz, 2H), 7.15 (t, J=7.4 Hz, 1H), 7.22 (t, J=7.4 Hz, 2H), 7.28 (d, J=7.6 Hz, 2H) in agreement with the literature data;[42] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 85% ee (t_R=15.5 min, t_S=18.6 min).

4.2.7. Compound (*S*)-(+)-2g. $[\alpha]_D$ +9.2 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, J=7.1 Hz, 3H), 3.80 (s, 3H), 4.38 (q, J=6.8 Hz, 1H), 4.54 (br s, 1H), 6.25 (d, J=8.0 Hz, 1H), 6.52 (t, J=6.9 Hz, 1H), 6.61 (t, J=7.2 Hz, 1H), 6.69 (d, J=7.1 Hz, 1H), 7.12 (t, J=7.5 Hz, 1H), 7.24 (t, J=7.2 Hz, 2H), 7.33 (d, J=7.2 Hz, 2H) in agreement with the literature data;[43] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.75 mL/min) showed 22% ee (t_S=7.1 min, t_R=8.1 min).[47]

4.2.8. Compound (±)-2h. NMR (400 MHz, $CDCl_3$) δ 0.91–2.29 (m, 11H), 1.34 (d, J=6.8 Hz, 3H), 3.93 (q, J=6.8 Hz, 1H), 7.16–7.29 (m, 5H) in agreement with the literature data.[44] The racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).

4.2.9. Compound (±)-2i. NMR (400 MHz, $CDCl_3$) δ 0.79 (t, J=7.3 Hz, 3H), 1.19 (m, 2H), 1.32 (d, J=7.2 Hz, 3H), 1.36 (m, 2H), 2.40 (m, 2H), 3.73 (q, J=6.6 Hz, 1H), 7.1–7.3 (arom, 5H) in agreement with the literature data.[37] The racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).

4.2.10. Compound 2j. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J=7.1 Hz, 3H), 2.13 (br s, 1H), 3.53 (m, 2H), 3.73 (q, J=5.5 Hz, 1H), 7.1–7.3 (arom, 10H) in agreement with the literature data.[2j,37] The almost racemic nature was confirmed by running the NMR spectrum in the presence of mandelic acid (2 equiv).

4.2.11. Compound 2k. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, J=6.6 Hz, 3H), 2.36 (s, 3H), 3.93 (br s, 1H), 4.60 (q, J=6.6 Hz, 1H), 6.36 (d, J=8.6 Hz, 2H), 6.50 (t, J=7.3 Hz, 1H), 6.94–7.46 (m, 6H).[3c] For the ee determination, amine **2k** was converted into the acetyl derivative by heating at reflux with acetyl chloride (3 equiv), triethylamine (3 equiv) and DMAP (cat.) in $CHCl_3$ for 30 min. Aqueous work up followed by purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (2/1) afforded the acetamide derivative as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J=6.7 Hz, 3H), 1.69 (s, 3H), 2.48 (s, 3H), 6.27 (q, J=6.8 Hz, 1H), 6.57 (d, J=8.0 Hz, 1H), 6.82 (t, J=7.6 Hz, 1H), 6.84–7.23 (m, 7H); chiral HPLC (Whelk-O1, hexane/2-propanol 91:9, 1.0 mL/min) showed 92% ee (t_{major}=12.7 min, t_{minor}=14.5 min). The absolute configuration of the prevailing enantiomer is assumed to be (*S*) in analogy with the rest of the series but has not been rigorously proven.

4.2.12. Compound (*S*)-(−)-44. $[\alpha]_D$ −17.4 (*c* 1.0, $CHCl_3$) [lit.[45] gives +4.4 (*c* 1.0, $CHCl_3$) for the (*R*)-enantiomer]; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J=6.6 Hz, 3H), 3.63 (br s, 1H), 4.05 (m, 1H), 6.13 (dd, J=5.8, 16.0 Hz, 1H), 6.50 (d, J=16.0 Hz, 1H), 6.56–7.28 (m, 10H) in agreement with the literature data;[40,45] For the ee determination, amine **44** was converted into the acetyl derivative by heating at reflux with acetyl chloride (3 equiv), triethylamine (3 equiv) and DMAP (cat.) in $CHCl_3$ for 30 min. Aqueous work up followed by purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (2/1) afforded the acetamide derivative as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J=6.5 Hz, 3H), 1.72 (s, 3H), 5.55 (q, J=6.7 Hz, 1H), 6.04 (dd, J=5.8, 15.9 Hz, 1H), 6.40 (d, J=15.9 Hz, 1H) 7.03–7.34 (m, 10H); chiral HPLC (Chiralcel OD-H, hexane/2-propanol 85:15, 1.0 mL/min) showed 74% ee (t_S=17.5 min, t_R=36.8 min).

4.2.13. Compound (*R*)-(−)-46. $[\alpha]_D$ −20.2 (*c* 1.0, $CHCl_3$), −13.2 (*c* 1.0, THF) [lit.[46b] gives +68.3 (*c* 0.32, THF) for the (*S*)-enantiomer]; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 4.87 (br s, 1H), 5.01 (d, J=5.6 Hz, 1H), 6.47 (d, J=8.4 Hz, 2H), 6.62 (t, J=6.8 Hz, 1H), 7.05 (t, J=7.6 Hz, 2H), 7.24–7.31 (m, 3H), 7.43 (d, J=7.6 Hz, 2H) in agreement with the literature data;[46] chiral HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 1 mL/min) showed 30% ee (t_S=19.5 min, t_R=23.1 min).

4.3. Protocol B: general procedure for the synthesis of formamides 3a–g, 4a,b, 5, and 6c–e

The BOC derivative **15a–d**, **15f,g**, **16a,b**, **20c–e**, and **37** (1.03 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 h the reaction mixture was evaporated in vacuo, the residue (the free amine) was dissolved in formic acid (1.5 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.68 mL, 7.21 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight. The volatiles were then removed by reduced pressure. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (2/1) afforded the **3a–d**, **3f,g**, **4a,b**, **5**, and **6c–e**; the yields are give below. Formylation of amine **17** (1.03 mmol) in the same fashion (skipping the deprotection step) furnished **3e**.

4.4. Protocol C: general procedure for the synthesis of dipeptide formamides (*S*,*S*)-12a–c via *N*-BOC deprotection

Trifluoroacetic acid (3 mL) was added dropwise to a solution of (*S*,*S*)-**41a–c** (0.60 mmol) in dichloromethane (3 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The solvent was then removed under reduced pressure and the residue was co-evaporated with toluene (3×5 mL) to afford a TFA salt of the deprotected amide **42a–c** as a colorless solid, which was used in the following step without further purification. The crude amide **42a–c** was dissolved in formic acid (1.7 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (0.86 mL, 9.1 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The traces of acids were removed by co-evaporation with toluene (3×5 mL) and the residue was purified by column chromatography on silica gel to afford (*S*,*S*)-**12a–c**; the yields and chromatography details are give below.

4.5. Protocol D: general procedure for the synthesis of 6a,b via *N*-Cbz deprotection

Pd/C (10%, 334 mg) was added to a solution of (*R*)-**27a** and (*S*)-**27b**, respectively (0.81 mmol) in a mixture of methanol (23.4 mL) and formic acid (1.1 mL) and the mixture was stirred at room temperature for 2 h, then filtered through a Celite pad. The pad was washed with methanol, the combined filtrate was evaporated to dryness, and co-evaporated with toluene (3×10 mL) to afford a formate salt of the deprotected amine (*R*)-**28a** and (*S*)-**28b**, respectively, as a colorless solid. The latter solid was dissolved in formic acid (2.7 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (1.3 mL, 13.8 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature overnight, and then evaporated to dryness. The traces of acids were removed by co-evaporation with toluene (3×5 mL) and the remaining yellowish oil was purified by column chromatography on silica gel to afford (*R*)-**6a** and (*S*)-**6b**; the yields and chromatography details are give below.

4.6. Protocol E: general procedure for the synthesis of *N*-methyl-formamides 23a,b and (*S*)-32 via reduction of oxazolidinones

Triethylsilane (0.5 mL, 3.1 mmol) and trifluoroacetic acid (5 mL) were added dropwise to a stirred solution of (*R*)-**21a**, (*S*)-**21b**, and (*S*)-**30**, respectively (1.00 mmol), in dry chloroform (5 mL) and the mixture was stirred overnight at room temperature. The mixture was then evaporated to dryness and co-evaporated with toluene (3×10 mL) to afford crude **22a**,**b** and **31**, respectively, as a colorless salt (containing two TFA molecules) in quantitative yield, which was used in the following step without further purification. The latter salt was dissolved in formic acid (3 mL) and the resulting solution was cooled to 0 °C. Acetic anhydride (1.5 mL, 15.9 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight, and then evaporated to dryness and co-evaporated with toluene (3×5 mL). The semi-solid crude product was triturated with a petroleum ether–ether mixture (1/1) and filtered to afford the pure product (*R*)-**23a**,(*S*)-**23b**, and (*S*)-**32**, respectively; see below for the characteristics.

4.7. Protocol F: general procedure for the synthesis of formamides (±)-6a,b and (*S*)-7 via amidation

Triethylamine (0.1 mL, 0.75 mmol) was added dropwise to a cooled (0 °C) suspension of (*R*)-**23a**, (*S*)-**23b**, and (*S*)-**32**, respectively (0.50 mmol), in dry dichloromethane (5 mL). After the suspension had dissolved, 3,5-dimethylaniline (0.075 mL, 0.6 mmol) was added, followed by 1-hydroxybenzotriazole hydrate (HOBt; 117 mg, ca. 0.65 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 125 mg, 0.65 mmol). The mixture was stirred at 0 °C for 1 h, and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (25 mL) and washed successively with water (10 mL), cold 0.5 M HCl (2×10 mL), saturated $NaHCO_3$ (2×10 mL), and brine (10 mL) and dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel to afford (±)-**6a**,**b** and (*S*)-**7**, respectively.

4.8. Protocol G: general procedure for the synthesis of *N*-methyl Boc-protected amino acids (*S*)-14, (*R*)-19c, (*S*)-19d, and (*S*)-19e

Sodium hydride (60% dispersion in mineral oil; 3.0 g, 138 mmol) was added in small portions to a stirred solution of the respective BOC-protected amino acid (*S*)-**13**, (*R*)-**18c**, (*S*)-**18d**, and (*S*)-**18e** (13.8 mmol) and methyl iodide (19.6 g, 138 mmol) in anhydrous THF (60 mL) at 0 °C. The mixture was allowed to stir at room temperature for 24 h under an argon atmosphere, the reaction was then quenched with water (15 mL), ethyl acetate (10 mL) was added and the mixture was evaporated in vacuo. The concentrate was diluted with water (300 mL) and washed with ethyl acetate (150 mL). The aqueous solution was acidified to pH 3.5 with a solution of 5% citric acid and extracted with ethyl acetate (200 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the **14** and **19c–d**, respectively; the yields are given below.

4.9. Protocol H: general procedure for the synthesis of amides 15a–d, 15f,g, 16a, 20c–e, and 37

Methyl chloroformate (0.55 mL, 7.15 mmol) was added dropwise to a stirred solution of (*S*)-**14** (1.40 g, 6.05 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C under an argon atmosphere and the mixture was stirred at that temperature for 2 h. The precipitate was removed by suction filtration and the filtrate was added dropwise to a solution of the corresponding amine (8.5 mmol) and triethylamine (1.0 mL, 7.15 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was allowed to stir at room temperature overnight under an argon atmosphere and the solvent was then removed under reduced pressure. The residue was purified using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (4/1) to afford **15a–d**, **15f**,**g**, **16a**, **20c–e**, and **37**; the yields are given below.

4.10. Protocol I: general procedure for the synthesis of the *N*-BOC protected amides (*S*)-39a–c

Triethylamine (1.05 mL, 7.5 mmol) was added to a solution of **13** and **18c**,**d**, respectively (5.00 mmol) in dry dichloromethane (50 mL) at 0 °C. To the resulting clear solution were consecutively added 3,5-dimethylaniline (0.75 mL, 6 mmol), 1-hydroxy-benzotriazole hydrate (HOBt; 1.17 g, ca. 6.5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 1.25 g, 6.5 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (250 mL) and washed successively with water (100 mL), cold 0.5 M HCl (2×100 mL), saturated $NaHCO_3$ (2×100 mL), and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to afford amide (*S*)-**39a**–**c**.

4.11. Protocol J: general procedure for the synthesis of the *N*-Cbz protected amides 27a,b

Triethylsilane (0.25 mL, 1.55 mmol) and trifluoroacetic acid (2.5 mL) were added dropwise to a stirred solution of (*R*)-**25a** and (*S*)-**25b**, respectively (0.50 mmol), in dry chloroform (2.5 mL) and the reaction mixture was stirred for one week at room temperature. The mixture was then evaporated to dryness and co-evaporated with toluene (3× 5 mL) to afford crude acid **26a** and **26b**, respectively, as an oily residue that was used in the following step without further purification. The later acid was dissolved in dry dichloromethane (5 mL) and the solution was cooled to 0 °C. Triethylamine (0.21 mL, 1.5 mmol) was added dropwise, followed by an addition of 3,5-dimethylaniline (0.075 mL, 0.6 mmol), 1-hydroxy-benzotriazole hydrate (HOBt; 117 mg, ca. 0.65 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 125 mg, 0.65 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (25 mL) and washed successively with water (10 mL), cold 0.5 M HCl (2× 10 mL), saturated $NaHCO_3$ (2×10 mL), brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel.

4.12. Protocol K: general procedure for the synthesis of 5-oxazolidinones 21a,b, 25a,b and 30

Camphorsulfonic acid (158 mg, 0.68 mmol) and paraformaldehyde (2.252 g, 75 mmol) were added to a solution of (*R*)-**18a**, (*S*)-**18b**, (*R*)-**24a**, (*S*)-**24b**, and (*S*)-**29**, respectively (8.80 mmol) in toluene (112 mL) and the mixture was heated under reflux for 1 h. The mixture was then cooled and filtered, the filtrate was diluted with ether (200 mL), and washed with 2.5% aqueous sodium bicarbonate solution (4×50 mL). The combined aqueous layers were extracted with ether (50 mL) and the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The oily residue was purified using column chromatography on silica gel to furnish pure oxazolidinone **21a**,**b**, **25a**,**b**, and **30**, respectively; the yield and chromatography conditions are shown below.

4.13. Protocol L: general procedure for the synthesis of *N*-BOC protected dipeptides (*S*,*S*)-41a–c

Trifluoroacetic acid (5 mL) was added dropwise to a cooled (0 °C) solution of (*S*)-**39a**–**c**, respectively (1.00 mmol), in dichloromethane (5 mL) and the reaction mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was co-evaporated with toluene (3×5 mL) to afford a TFA salt of the deprotected amide (*S*)-**40a**–**c** as a colorless solid, which was used in the following step without further purification. Triethylamine (0.42 mL, 3 mmol) was added dropwise to a suspension of (*S*)-**40a**–**c** TFA in dichloromethane (15 mL) at 0 °C. A solution of (*S*)-**14** (231 mg, 1 mmol) in dichloromethane (5 mL) was added dropwise to the resulting clear solution, followed by 1-hydroxy-benzotriazole hydrate (HOBt; 234 mg, ca. 1.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 249 mg, 1.3 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 20 h. The mixture was then diluted with ethyl acetate (50 mL) and washed successively with water (20 mL), cold 0.5 M HCl (2× 20 mL), saturated $NaHCO_3$ (2×20 mL), brine (20 mL), dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography on silica gel furnished the respective product (*S*,*S*)-**41a**–**c**.

4.13.1. *N*-methylformamide (*S*)-(−)-3a. Obtained from (*S*)-**15a** using protocol B (oil, 180 mg, 75%): $[\alpha]_D$ −187.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J= 6.6 Hz, 3H), 0.99 (d, J=6.7 Hz, 3H), 2.40 (m, 1H), 2.92 (s, 3H), 4.41 (d, J=10.3 Hz, 1H), 7.0 (t, J=7.4 Hz, 1H), 7.22 (t, J=7.8 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H), 8.09 (s, 1H), 8.50 (br s, 1H); ^{13}C NMR δ 17.59 (CH_3), 17.78 (CH_3), 18.49 (CH_3), 24.47 (CH), 30.60 (CH_3), 67.99 (CH), 118.95 (CH), 123.39 (CH), 127.92 (CH) 136.80 (C), (CHO), 166.31 (CO); IR (Golden Gate) ν 3274 (NH), 1650 (CO) cm^{-1}; MS *m*/*z* (%) 234 ($M^{\cdot+}$, 8), 142 (20), 114 (35), 85 (65), 47 (15); HRMS (EI) 234.1368 ($C_{13}H_{18}O_2N_2$ requires 234.1367).

4.13.2. *N*-methylformamide (*S*)-(−)-3b. Obtained from (*S*)-**15b** using protocol B (oil, 84 mg, 57%): $[\alpha]_D$ −201.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J= 6.6 Hz, 3H), 0.98 (d, J=6.5 Hz, 3H), 2.40 (m, 1H), 2.90 (s, 3H), 3.7 (s, 3H), 4.3 (d, J=11.2 Hz, 1H), 6.70 (d, J= 6.8 Hz, 2H), 7.30 (d, J=9.0 Hz, 2H), 7.90 (br s, 1H), 8.10 (s, 1H); ^{13}C NMR δ 18.94 (CH_3), 19.96 (CH_3), 25.65 (CH), 31.99 (CH_3), 55.88 (CH_3), 63.44 (CH), 114.51 (CH), 121.97 (CH), 131.16 (C), 156.87 (C), 164.34 (CHO), 167.3 (CO); IR (Golden Gate) ν 3274 (NH), 2834, 1648 (CO) cm^{-1}; MS *m*/*z* (%) 264 ($M^{\cdot+}$, 6), 249 (1), 192 (3), 162 (5), 142 (41), 114 (100), 83 (68), 47 (11); HRMS (EI) 264.1474, ($C_{14}H_{20}O_3N_2$ requires 264.1474).

4.13.3. *N*-methylformamide (*S*)-(−)-3c. Obtained from (*S*)-**15c** using protocol B (oil, 131 mg, 26%): $[\alpha]_D$ −137.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J= 6.7 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 2.49 (m, 1H), 3.02 (s, 3H), 3.79 (s, 6H), 4.38 (d, J=11.2 Hz, 1H), 6.25 (s, 1H), 6.78 (s, 2H), 8.04 (br s, 1H), 8.17 (s, 1H); ^{13}C NMR δ 18.89 (CH_3), 19.95 (CH_3), 25.57 (CH_3), 32.04 (CH), 55.79 (CH_3), 63.76 (CH), 97.5 (CH), 98.37 (CH), 139.73 (CH), 161.42 (C), 164.50 (CHO), 167.52 (CO); IR (NaCl) ν 3293 (NH),

1655 (CO) cm^{-1}; MS *m/z* (%) 294 ($M^{\cdot+}$, 4), 280 (41), 220 (3), 192 (11), 153 (100), 100 (40), 55 (19); HRMS (EI) 294.1580 ($C_{15}H_{22}O_4N_2$ requires 294.1582).

4.13.4. *N*-methylformamide (*S*)-(−)-3d. Obtained from (*S*)-**15d** using protocol B (142 mg, 82%): mp 83–86 °C; $[\alpha]_D$ −19.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J=6.6 Hz, 3H), 0.99 (d, J=6.5 Hz, 3H), 2.20 (s, 6H), 2.39 (m, 1H), 2.95 (s, 3H), 4.35 (d, J=11.2 Hz, 1H), 6.67 (s, 1H), 7.09 (d, J=8.3 Hz, 2H), 8.07 (s, 1H), 8.18 (br s, 1H); ^{13}C NMR δ 18.97 (CH_3), 19.92 (CH_3), 21.71 (CH_3), 25.74 (CH), 31.96 (CH), 63.47 (CH), 118.21 (CH), 126.56 (CH), 137.92 (C), 139.13 (C), 164.35 (CHO), 167.61 (CO); IR (Golden Gate) ν 3284 (NH), 1650 (CO) cm^{-1}; MS *m/z* (%) 262 ($M^{\cdot+}$, 29), 160 (7), 142 (43), 114 (100), 86 (21), 83 (19), 42 (7); HRMS (EI) 262.1681 ($C_{15}H_{22}O_2N_2$ requires 262.1680).

4.13.5. *N*-methylformamide (*S*)-(−)-3e. Obtained (via protocol B) from the free amine (*S*)-**17** so that no BOC deprotection was required prior to the formylation (189 mg, 95%): mp 152–154 °C; $[\alpha]_D$ −81.5 (*c* 1.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J=6.6 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H), 2.45 (m, 1H), 2.96 (s, 3H), 4.34 (d, J=11.3 Hz, 1H), 7.52 (s, 1H), 7.95 (s, 2H), 8.10 (s, 1H), 8.90 (br s, 1H); ^{13}C NMR δ 19.06 (CH_3), 19.85 (CH_3), 26.02 (CH_3), 32.29 (CH), 63.67 (CH), 69.41 (CH), 117.80 (CH), 119.94 (CH), 139.84 (C), 164.51 (CHO), 168.35 (CO); IR (NaCl) ν 3233 (NH), 1648 (CO) cm^{-1}; MS *m/z* (%) 370 ($M^{\cdot+}$, 24), 351 (65), 299 (16), 256 (15), 228 (26), 188 (8); HRMS 370.1118 ($C_{15}H_{16}O_2N_2F_6$ requires 370.1116).

4.13.6. *N*-methylformamide (*S*)-(−)-3f. Obtained from (*S*)-**15f** using protocol B (oil, 35 mg 41%): $[\alpha]_D$ −99.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H), 2.39 (m, 1H), 2.96 (s, 3H), 4.37 (d, J=11.2 Hz, 1H), 7.05 (s, 1H), 7.48 (s, 2H), 8.10 (s, 1H), 8.84 (br s, 1H); ^{13}C NMR δ 19.01 (CH_3), 19.85 (CH_3), 25.87 (CH), 32.25 (CH_3), 63.74 (CH), 118.55 (CH), 118.66 (CH), 124.64 (CH), 135.53 (C), 140.06 (C), 164.52 (CHO), 168.01 (CO); MS *m/z* (%) 303 ($M^{\cdot+}$, 100), 269 (9), 216 (5), 142 (39), 114 (25), 81 (52); HRMS (EI): 303.0067 ($C_{13}H_{17}O_2N_2Cl_2$ requires 303.0673).

4.13.7. *N*-methylformamide (*S*)-(−)-3g. Obtained from (*S*)-**15g** using protocol B; purification using column chromatography on silica gel with an ethyl acetate–methanol mixture (9/1) afforded the product as an oil (357 mg, 51%); $[\alpha]_D$ −8.10 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 9H), 1.32 (m, 2H), 1.49 (m, 2H), 2.41 (m, 1H), 3.00 (s, 3H), 3.21 (m, 2H), 4.24 (d, J=11.2 Hz, 1H), 6.14 (br s, 1H), 8.15 (s, 1H); ^{13}C NMR δ 14.00 (CH_3), 18.87 (CH_3), 19.86 (CH_3), 20.21 (CH_2), 25.68 (CH), 27.88 (CH_3) 31.68 (CH_2), 39.51 (CH_2), 62.58 (CH), 164.41 (CHO), 169.38 (CO); IR (NaCl) ν 3318 (NH), 1653 (CO), 1558 cm^{-1}; MS *m/z* (%) 215 ($M^{\cdot+}$, 100), 201 (5), 132 (8), 114 (6), 79 (4); HRMS (EI): 215.1760 ($C_{11}H_{23}O_2N_2$ requires 215.1760).

4.13.8. *N*-methylformamide (*S*)-(−)-4a. Obtained from (*S*)-**16a** using protocol B (oil, 20 mg, 37%): $[\alpha]_D$ −104.0 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (d, J=6.7 Hz, 3H), 0.86 (d, J=6.5 Hz, 3H), 2.37 (m, 1H), 2.76 (s, 3H), 3.20 (s, 3H), 4.54 (d, J=10.9 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 7.30 (t, J=7.8 Hz, 2H), 7.33 (d, J=7.7 Hz, 2H), 7.84 (s, 1H); ^{13}C NMR δ 18.50 (CH_3), 18.77 (CH_3), 27.29 (CH), 31.39 (CH_3), 38.01 (CH_3), 64.21 (CH), 128.11 (CH), 129.16 (CH), 130.65 (CH), 142.98 (C), 163.44 (CHO), 169.77 (CO); IR (Golden Gate) ν 1658 (CO) cm^{-1}; MS *m/z* (%) 248 ($M^{\cdot+}$, 3), 142 (21), 114 (53), 83 (100), 77 (5), 47 (16); HRMS 248.1526 ($C_{14}H_{20}O_2N_2$ requires 248.1525).

4.13.9. *N*-methylformamide (*S*)-(−)-4b. Obtained from (*S*)-**16b** using protocol B (oil, 75 mg, 83%): $[\alpha]_D$ −11.6 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J=6.7 Hz, 3H), 0.85 (d, J=6.8 Hz, 3H), 1.09 (m, 3H), 1.11 (m, 3H), 2.36 (m, 1H), 2.85 (s, 3H), 3.20 (m, 2H), 3.33 (m, 2H), 4.76 (d, J=10.7 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR δ 13.23 (CH_3), 15.51 (CH_3), 18.51 (CH_3), 19.87 (CH_3), 26.77 (CH), 31.26 (CH_3), 40.87 (CH_2), 42.06 (CH_2), 63.79 (CH), 163.23 (CHO), 168.43 (CO); MS *m/z* (%) 215 ($M^{\cdot+}$, 100), 187 (4), 142 (10), 114 (8), 81 (19); HRMS (EI): 215.1760 ($C_{11}H_{23}O_2N_2$ requires 215.1761).

4.13.10. Formamide (*S*)-(+)-5. Obtained from (*S*)-**37** using protocol B (191 mg, 60%): mp 151–153 °C; $[\alpha]_D$ +1.2 (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 2.12 (m, 1H), 3.69 (s, 6H), 6.50 (t, J=7.8 Hz, 1H), 6.16 (s, 1H), 6.48 (d, J=8.6 Hz, 1H), 6.70 (s, 2H), 8.21 (s, 1H), 8.37 (br s, 1H); ^{13}C NMR δ 18.76 (CH_3), 19.67 (CH_3), 31.83 (CH), 55.72 (CH_3), 58.44 (CH), 97.4 (CH), 98.58 (CH), 139.73 (CH), 161.36 (C), 161.74 (CHO), 169.79 (CO); IR (NaCl) ν 3272 (NH), 1645 (CO) cm^{-1}; MS (CI) *m/z* (%) 281 ($[MH]^{\cdot+}$, 100), 263 (2), 192 (3); HRMS (CI) 281.1501 ($C_{14}H_{21}O_4N_2$ requires 281.1501).

4.13.11. *N*-methylformamide (±)-6a. Obtained from (*R*)-**23a** as colorless solid (137 mg, 91%), using protocol F: mp 135–137 °C; $[\alpha]_D$ 0.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 5:1 ratio; the signals for the minor rotamer are marked by *) δ 0.8–1.06 (m, 2H), 1.13–1.38 (m, 3H), 1.55–1.87 (m, 5H), 2.11–2.21 (m, 1H), 2.28 (s, 6H), 2.96* (s, 0.5H) and 2.99 (s, 2.5H), 3.73* (d, J=10.8 Hz, 0.15H), 4.48 (d, J=11.2 Hz, 0.85H), 6.74 (s) and 6.77* (s, 1H), 7.16 (s) and 7.21* (s, 2H), 8.12 (br s, 0.85H), 8.13 (s, 0.85H), 8.21* (br s, 0.15H), 8.4* (s, 0.15H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 21.07 (CH_3), 25.62 (CH_2), 25.81 (CH_2), 28.44 (CH_2), 29.36 (CH_2), 40.56 (CH_3), 57.05 (CH), 117.71 (CH), 126.12 (CH), 137.18 (C), 138.43 (C), 161.72 (CHO), 169.45 (CO); IR (KBr) ν 3262, 2928, 2854, 1654, 1570, 1203, 1084, 892, 847, 822 cm^{-1}; MS (EI) *m/z* (%) 302 ($M^{\cdot+}$, 25), 182 (43), 154 (100), 121 (23), 95 (42), 83 (30), 72 (24); HRMS (EI) 302.1995 ($C_{18}H_{26}O_2N_2$ requires 302.1994).

4.13.12. *N*-methylformamide (*R*)-(+)-6a. Obtained from (*R*)-**27a** (226 mg, 92%) as a colorless foam using protocol D; purified by column chromatography on silica gel with a hexane–ethyl acetate mixture (6/4, R_f=0.58/0.33): $[\alpha]_D$ +153.9 (*c* 1.0, $CHCl_3$); all spectroscopic data were identical with those recorded for (±)-**6a**.

4.13.13. *N*-methylformamide (±)-6b. Obtained from (*S*)-**23b** (173 mg, 1 mmol), using protocol F; purification

by column chromatography on silica gel with a hexane–ethyl acetate mixture (65/35, R_f=0.49/0.24) afforded (±)-**6b** (201 mg, 73%) as a colorless solid: mp 98–100 °C; $[\alpha]_D$ 0.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 2:1 ratio; the signals for the minor rotamer are marked by *) δ 1.14* (s) and 1.15 (s, 9H), 2.28 (s, 6H), 3.07* (s, 1H) and 3.24 (s, 2H), 3.82* (s, 0.33H) and 4.79 (s, 0.66H), 6.76 (s, 1H), 7.16* (s) and 7.19 (s, 2H), 8.18 (s, 0.66H), 8.27* (s, 0.33H), 8.36 (br s) and 8.47* (br s, 1H); ^{13}C NMR δ 21.34 (CH_3), 27.43* (CH_3), 27.85 (CH_3), 30.38* (CH_3), 34.24 (CH_3), 35.47 (C), 35.65* (C), 62.66* (CH), 70.01 (CH), 117.76 (CH), 117.91* (CH), 126.18 (CH), 126.38* (CH), 137.37* (C), 137.53 (C), 138.64 (C), 138.68* (C), 164.54 (CHO), 165.31* (CHO), 166.44* (CO), 166.96 (CO); IR (KBr) ν 3280, 2958, 2915, 2870, 1660, 1559, 1180, 1068, 844, 829 cm^{-1}; MS (EI) *m/z* (%) 276 ($M^{\cdot+}$, 35), 156 (87), 128 (100), 121 (71), 100 (16), 60 (38); HRMS (EI) 276.1837 ($C_{16}H_{24}O_2N_2$ requires 276. 1837).

4.13.14. *N*-methylformamide (*S*)-(−)-6b. Obtained from mixture of (*S*)-**25a** and (*S*)-**27b** (206 mg) using protocol D; purification by column chromatography on silica gel with a hexane–ethyl acetate mixture (65/35, R_f=0.49/0.24) afforded (*S*)-(−)-**6b** (79 mg, 15% overall from **25b**) as a clear oil: $[\alpha]_D$ −108.7 (*c* 0.67, $CHCl_3$); all spectroscopic data were identical with those recorded for (±)-**6b**.

4.13.15. *N*-methylformamide (*R*)-(+)-6c. Obtained from (*R*)-**20c** using protocol B (solid, 292 mg, 34%): mp 149–150 °C; $[\alpha]_D$ +8.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 2.94 (s, 3H), 6.22 (s, 1H), 6.80 (s, 1H), 7.16 (s, 2H), 7.43–7.47 (m, 5H), 8.26 (s, 1H); ^{13}C NMR δ 21.04 (CH_3), 28.81 (CH_3), 58.34 (CH), 117.00–128.87 (CH), 134.65–138.45 (C), 167.52 (CO), 168.35 (CHO); IR (KBr) ν 3275 (NH), 1653 (CO) cm^{-1}; MS *m/z* (%) 296 ($M^{\cdot+}$, 24), 274 (5), 210 (1), 175 (33), 148 (100), 120 (50), 77 (14), 42 (24); HRMS (EI) 296.1525 ($C_{18}H_{20}O_2N_2$ requires 296.1524).

4.13.16. *N*-methylformamide (*S*)-(−)-6d. Obtained from (*S*)-**20d** using protocol B (solid, 1.50 g, 78%): mp 81–85 °C; $[\alpha]_D$ −87.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked by *) δ 2.29 (s, 6H), 2.94* (s, 0.6H), 2.98 (s, 2.4H), 3.01* (dd, *J*=14.4, 1.4 Hz, 0.2H), 3.12 (dd, *J*=14.4, 8.4 Hz, 0.8H), 3.43 (dd, *J*=14.4, 7.6 Hz, 0.8H), 3.56* (dd, *J*=14.8, 4.4 Hz, 0.2H), 5.25 (t, *J*=8.0 Hz, 1H), 6.76 (s, 0.8H), 6.85* (s, 0.2H), 7.13 (s, 1.6H), 7.18* (s, 0.4H), 7.28–7.36 (m, 5H), 8.06 (br s, 0.8H), 8.08 (s, 0.8H), 8.37* (s, 0.2H), 8.66* (s, 0.2H); ^{13}C NMR δ 20.94 (CH_3), 26.62 (CH_3), 34.78 (CH_2), 62.26 (CH), 115.15–126.52 (a set of signals, CH), 128.29–138.54 (a set of signals, C), 159.42–168.36 (a set of signals, CO); IR (KBr) ν 3308 (NH), 1703 (CO) cm^{-1}; MS *m/z* (%) 310 ($M^{\cdot+}$, 50), 251 (10), 190 (39), 162 (100), 134 (85), 91 (29), 42 (15); HRMS (EI) 310.1681 ($C_{19}H_{22}O_2N_2$ requires 310.1682).

4.13.17. *N*-methylformamide (*S*)-(−)-6e. Obtained from (*S*)-**20e** using protocol B (oil, 916 mg, 78%): $[\alpha]_D$ −222.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J*=7.2 Hz, 3H), 2.30 (s, 6H), 2.97 (s, 3H), 5.08 (q, *J*=7.2 Hz, 1H), 6.76 (s, 1H), 7.01 (s, 2H), 8.16 (s, 1H); ^{13}C NMR δ 12.64 (CH_3), 21.35 (CH_3), 30.98 (CH_3), 51.29 (CH), 117.83 (CH), 126.15 (CH), 137.50 (C), 138.01 (C), 163.87 (CHO), 168.04 (CO); IR (NaCl) ν 3289 (NH), 1644 (CO) cm^{-1}; MS *m/z* (%) 234 ($M^{\cdot+}$, 33), 199 (5), 147 (6), 113 (31), 82 (100), 58 (37), 49 (39); HRMS (EI) 234.1371 ($C_{13}H_{18}O_2N_2$ requires 234.1368).

4.13.18. *N*-methylformamide (*S*)-(−)-6f. Obtained from (*S*)-**20f** using protocol B (oil, 1.13 g, 84%): $[\alpha]_D$ −191.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J*=6.6 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H), 1.59 (hept, *J*=6.6 Hz, 1H), 1.72 (ddd, *J*=14.0, 8.0, 6.0 Hz, 1H), 1.87–1.94 (m, 1H), 2.30 (s, 6H), 2.90 (s, 3H), 4.99 (t, *J*=8.0 Hz, 1H), 6.76 (s, 1H), 7.16 (s, 2H), 8.03 (br s, 1H), 8.16 (s, 1H); ^{13}C NMR δ 21.37 (CH_3), 22.83 (CH_3), 24.77 (CH), 31.28 (CH_3), 35.61 (CH_2), 54.07 (CH), 117.90 (CH), 126.31 (CH), 137.24 (C), 138.71 (C), 164.12 (CHO), 167.88 (CO); IR (NaCl) ν 3299 (NH), 1681 (CO); MS *m/z* (%) 276 ($M^{\cdot+}$, 36), 220 (5), 176 (4), 156 (30), 128 (100), 86 (23), 58 (16); HRMS (EI) 276.1840 ($C_{16}H_{24}O_2N_2$ requires 276.1838).

4.13.19. *N*-methylformamide (*S*)-(+)-7. Obtained from (*S*)-**32** (62 mg, 0.3 mmol), using protocol F; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (7/3, R_f=0.2) afforded (*S*)-(+)-**7** (31 mg, 33%) as colorless solid: mp 125–126 °C; $[\alpha]_D$ +2.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 2:1 ratio; the signals for the minor rotamer are marked by *) δ 1.84* (s, 1H), 2.05 (s, 2H), 2.26* (s) and 2.29 (s, 6H), 2.94 (s, 2H), 3.11* (s, 1H), 6.72* (s, 0.33H), 6.8 (s, 0.66H), 7.09 (s) and 7.12* (s, 2H), 7.29–7.48 (m, 5.66H), 8.27 (s, 1H), 8.72 (br s, 0.33H); ^{13}C NMR δ 21.29 (CH_3), 25.24 (CH_3), 26.51* (CH_3), 28.87 (CH_3), 33.54* (CH_3), 68.65* (C), 69.63 (C), 117.62–130.26 (a set of signals, CH), 136.48– 140.39 (a set of signals, C), 163.68 (CHO), 164.35* (CHO), 169.01 (CO), 169.57* (CO); IR (KBr) ν 3433, 2917, 1695, 1671, 1616, 1561, 1371, 848 cm^{-1}; MS (EI) *m/z* (%) 310 ($M^{\cdot+}$, 14), 190 (57), 162 (100), 134 (79), 121 (45), 77 (10), 56 (41); HRMS (EI) 310.1680 ($C_{19}H_{22}O_2N_2$ requires 310.1681).

4.13.20. *N*-(3,5-dimethyl-phenyl)-2-formylamino-3-(τ-methyl-1*H*-imidazol-4-yl)-propionamide (*S*)-(8). A solution of [1-(3,5-dimethyl-phenylcarbamoyl)-2-(1-methyl-1*H*-imidazol-4-yl)-ethyl]-carbamic acid *tert*-butyl ester (*S*)-(**35**) and trifluoroacetic acid (5 mL) in dichloromethane (5 mL) was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the crude TFA salt of **36** was dissolved in formic acid (5 mL). Acetic anhydride (2.5 mL) was added and the solution was allowed to stir at room temperature for 72 h. The mixture was then evaporated to dryness and the crude product was purified by chromatography on a column of silica gel (60 g) with a CH_2Cl_2–MeOH mixture (5/1) to afford (*S*)-**8** (100 mg, 59%) as an orange solid: mp 92–94 °C (dec); $[\alpha]_D^{25}$ 0.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 6H), 2.94 (dd, *J*=15.2, 7.2 Hz, 1H), 3.11 (dd, *J*=15.2, 4.0 Hz, 1H), 3.59, (s, 3H), 4.77 (d, *J*=4.0 Hz, 1H), 6.66 (s, 1H), 6.73 (s, 1H), 7.10 (s, 2H), 7.39 (s, 1H), 7.64 (br s, 1H), 8.24 (s, 1H), 9.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 29.7, 33.7, 52.48, 117.6, 118.3, 126.0, 138.6, 161.4, 168.82; IR (NaCl) ν 3019, 2399, 1215 cm^{-1}; MS (CI/ISO) 318.29 [M+ NH_4] ($C_{16}H_{20}N_4O_2$ + NH_4 requires 300.14+18.04=318.18).

4.13.21. (*S*)-3-methyl-2-[methyl-(2,2,2-trifluoro-acetyl)-amino]-*N*-phenyl-butyramide (*S*)-(−)-(10). The BOC derivative (S)-**8** (92 mg, 0.3 mmol) was dissolved in trifluoroacetic acid (2 mL) at room temperature. After 1 h the reaction was evaporated in vacuo, dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0 °C. Trifluoroacetic anhydride (130 μL, 0.9 mmol) was added dropwise and the mixture was allowed to stir overnight at room temperature. The reaction was then diluted in DCM, washed with brine and dried over $MgSO_4$. The solvent was then removed by reduced pressure. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (3/1) afforded the product **10** as oil (57 mg, 63%): $[\alpha]_D$ −20.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J=6.7 Hz, 3H), 0.99 (d, J=6.5 Hz, 3H), 2.38 (m, 1H), 3.03 (s, 3H), 4.97 (d, J=11.2 Hz, 2H), 7.08 (t, J=7.5 Hz, 1H), 7.23 (t, J=7.8 Hz, 2H), 7.41 (d, J=7.6 Hz, 2H), 7.81 (br s, 1H); ^{13}C NMR 18.44 (CH_3), 19.77 (CH_3), 27.29 (CH), 31.57 (CH_3), 64.07 (CH), 120.51 (CH), 125.33 (CF_3), 129.45 (CH), 130.31 (CH), 138.51 (C), 172.10 (CO); IR (Golden Gate) ν 3338 (NH), 1666 (CO) cm^{-1}; MS *m*/*z* 302 ($M^{\cdot+}$, 3%), 182 (7), 118 (4), 83 (100), 47 (16); HRMS 302.1243 ($C_{14}H_{17}O_2N_2F_3$ requires 302.1242).

4.13.22. Urea derivative (*S*)-(−)-11. The BOC derivative (*S*)-**15d** (504 mg, 1.5 mmol) was dissolved in trifluoroacetic acid (2.0 mL) at room temperature. After 1 h the reaction mixture was evaporated in vacuo, the residue was dissolved in cold, dry Et_2O (50 mL) and the reaction stirred at room temperature, under argon, for 90 min. Phenylisocyanate (0.22 mL, 20.9 mmol) was then added dropwise to the solution and then allowed to stir over night at room temperature. The solvent was then removed in vacuo. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1) afforded (*S*)-**11** as a solid (292 mg, 55%): mp 131–133 °C; $[\alpha]_D$ −158.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J=6.4 Hz, 2H), 0.98 (d, J=6.4 Hz, 2H), 2.21 (s, 6H), 2.34 (m, 1H), 2.98 (s, 3H), 4.33 (d, J=11.6 Hz, 1H), 6.66 (s, 1H), 7.01 (t, J=7.4 Hz, 1H), 7.07 (s, 2H), 7.32 (t, J=5.6 Hz, 2H), 7.34 (d, J=7.6 Hz, 2H), 8.15 (br s, 1H); ^{13}C NMR δ 18.82 (CH_3), 19.87 (CH_3), 21.38 (CH_3), 26.33 (CH), 117.52 (CH), 120.32 (CH), 121.26 (CH), 123.75 (CH), 124.41 (CH), 125.99 (CH), 129.04 (CH), 129.39 (CH), 137.74 (C), 138.60 (C), 138.74 (C), 156.91 (CO), 168.87 (CO); IR (KBr) ν 3272 (NH), 1644 (CO); MS *m*/*z* (%) 353 ($M^{\cdot+}$, 10), 232 (33), 205 (19), 160 (5), 121 (48), 86 (100), 84 (18), 49 (17); HRMS (EI) 353.2106 ($C_{21}H_{27}O_2N_3$ requires 353.2103).

4.13.23. Dipeptide (*S*,*S*)-(−)-12a. Obtained from (*S*,*S*)-**41a** using protocol C (198 mg, 96%) as a colorless foam; purified by column chromatography on silica gel with hexane–ethyl acetate mixture (1/1, R_f=0.2): $[\alpha]_D$ −167.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 0.8–1.03 (m, 12H), 2.22* (s) and 2.25 (s, 6H), 2.09–2.46 (m, 2H), 2.91* (s, 0.9H), 3.04 (s, 2.1H), 3.5* (d, J=10.8 Hz, 0.3H), 4.3–4.42 (m, 0.7H), 6.73 (s) and 6.75* (s, 1H), 6.95* (d, J=8.8 Hz, 0.7H), 7.1* (s) and 7.12 (s, 2H), 7.21* (br s, 0.3H), 8.15 (s), 8.21 (s) and 8.23* (s, 2H); ^{13}C NMR δ 18.19–22.62 (a set of signals, CH_3), 25.54 (CH), 26.51* (CH), 27.19* (CH), 30.44 (CH), 31.10* (CH_3), 31.53 (CH_3), 59.43 (CH), 59.52* (CH), 61.86 (CH), 68.01* (CH), 117.57 (CH), 117.99* (CH), 125.98 (CH), 126.46* (CH), 137.03* (C), 137.47 (C), 138.49 (C), 138.58* (C), 163.38* (CHO), 163.64 (CHO), 169.27* (CO), 170.01 (CO), 170.25* (CO), 170.32 (CO); IR (KBr) ν 3301, 2965, 2932, 1651, 1619, 1558, 1073, 844 cm^{-1}; MS (EI) *m*/*z* (%) 361 ($M^{\cdot+}$, 10), 142 (59), 121 (100), 114 (75), 86 (20), 72 (15); HRMS (EI) 361.2363 ($C_{20}H_{31}O_3N_3$ requires 361.2365).

4.13.24. Dipeptide (*S*,*S*)-(−)-12b. Obtained from (*S*,*S*)-**41b** using protocol C (303 mg, 99%) as a colorless foam; purified by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1, R_f=0.33): $[\alpha]_D$ −58.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 0.82–0.9 (m), 0.99 (d, J=6.4 Hz) and 1.02 (d, J=6.4 Hz, 6H), 2.23* (s) and 2.24 (s, 6H), 2.3–2.39 (m, 1H), 2.75 (s, 0.65H), 2.81 (s, 1.35H), 2.91 (s, 0.3H), 2.94 (s, 0.7H), 3.59* (d, J=10.4 Hz, 0.3H), 4.45 (d, J=11.2 Hz, 0.7H), 5.57–5.65 (m, 1H), 6.72 (s) and 6.74*(s, 1H), 7.03*(s) and 7.05 (s, 2H), 7.3–7.44 (m, 5H), 7.71*(br s) and 7.76 (br s, 1H), 8.06*(s) and 8.16 (s, 1H); ^{13}C NMR (major rotamer) δ 18.53 (CH_3), 19.93 (CH_3), 21.23 (CH_3), 25.52 (CH), 31.39 (CH_3), 57.84 (CH), 61.65 (CH), 117.45 (CH), 126.10 (CH), 127.26 (CH), 128.70 (CH), 129.05 (CH), 136.82 (C), 137.35 (C), 138.47 (C), 163.60 (CHO), 167.48 (CO), 169.14 (CO); IR (KBr) ν 3301, 2965, 2921, 1651, 1619, 1560, 1072, 845, 733, 697 cm^{-1}; MS (EI) *m*/*z* (%) 395 ($M^{\cdot+}$, 7), 248 (28), 142 (100), 114 (90), 106 (44), 86 (26), 57 (11); HRMS (EI) 395.2210 ($C_{23}H_{29}O_3N_3$ requires 395.2209).

4.13.25. Dipeptide (*S*,*S*)-(−)-12c. Obtained from (*S*,*S*)-**41c** using protocol C (278 mg, 99%) as a colorless foam; purified by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1, R_f=0.33): $[\alpha]_D$ −137.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 3:1 ratio; the signals for the minor rotamer are marked by *) δ 0.77 (d, J=6.4 Hz), 0.81 (d, J=6.8 Hz), 0.86 (d, J=6.4 Hz) and 0.91 (d, J=6.4 Hz, 6H), 2.21* (s) and 2.24 (s, 6H), 2.1–2.37 (m, 1H), 2.6 (s, 2.25H), 2.69* (s, 0.75H), 2.97 (dd, J=14.1, 9.5 Hz, 0.75H), 3.06* (dd, J=13.8, 7.9 Hz, 0.25H), 3.18* (dd, J=13.8, 6.6 Hz, 0.25H), 3.27 (dd, J=14.1, 5.6 Hz, 0.75H), 3.44* (d, J=10.6 Hz, 0.25H), 4.37 (d, J=11.2 Hz, 0.75H), 4.83–4.93 (m, 1H), 6.73 (s, 1H), 7.0 (br s, 0.75H), 7.05 (s, 2H), 7.18–7.28 (m, 5H), 7.41* (br s, 0.25H), 7.85 (s, 0.75H), 8.12* (s, 0.25H), 8.24 (br s, 1H); ^{13}C NMR δ 18.31 (CH_3), 18.56* (CH_3), 19.48 (CH_3), 21.05* (CH_3), 21.25* (CH_3), 21.29 (CH_3), 25.11 (CH), 26.48* (CH), 27.04* (CH_3), 31.08 (CH_3), 37.43 (CH_2), 38.26* (CH_2), 55.03 (CH), 61.35 (CH), 68.08* (CH), 117.56 (CH), 118.01* (CH), 126.13 (CH), 126.60* (CH), 126.83 (CH), 127.21* (CH), 128.49 (CH), 128.80* (CH), 129.09* (CH), 129.23 (CH), 136.04* (C), 136.74 (C), 136.82 (C), 137.30 (C), 138.59 (C), 138.68* (C), 163.18* (CHO), 163.51 (CHO), 168.75 (CO), 169.20* (CO), 169.55* (CO), 169.69 (CO); IR (KBr) ν 3298, 2964, 2923, 1651, 1619, 1065, 842, 738, 699 cm^{-1}; MS (EI) *m*/*z* (%) 409 ($M^{\cdot+}$, 23), 142 (62), 121 (100), 114 (81), 86 (26), 55 (10); HRMS (EI) 409.2368 ($C_{24}H_{31}O_3N_3$ requires 409.2365).

4.13.26. (*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-3-methyl-butyric Acid (*S*)-14. Obtained from (*S*)-**13** as an oil (3.15 g, 13.6 mmol, 98%) using protocol G; this product

was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J=6.7 Hz, 3H), 1.05 (d, J=6.6 Hz, 3H), 1.49 (s, 9H), 2.39 (m, 1H), 2.90 (s, 3H), 4.01 (d, J=10.4 Hz, 1H), in agreement with literature.[16]

4.13.27. Amide (*S*)-15a. Obtained from (*S*)-**14**, using protocol H (oil, 803 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.4 Hz, 3H), 1.43 (s, 9H), 2.32 (m, 1H), 2.75 (s, 3H), 4.03 (d, J=10.2 Hz, 1H), 6.98 (t, J=7.4 Hz, 1H), 7.22 (t, J=7.8 Hz, 2H), 7.44 (d, J=7.8 Hz, 2H), 8.19 (br s, 1H); ^{13}C NMR δ 18.99 (CH_3), 20.30 (CH_3), 26.24 (CH_3), 28.76 (CH_3), 30.94 (CH_3), 66.70 (C), 81.10 (C), 120.06 (CH), 124.48 (CH), 129.37 (CH), 138.45 (C), 169.18 (CO); IR (Golden Gate) ν 3311 (NH), 1658 (CO) cm^{-1}; MS m/z (%) 306 (M^+, 6%) 214 (7), 186 (14), 130 (71), 83 (100), 57 (39), 47 (17); HRMS (EI): 306.1943 ($C_{17}H_{26}O_3N_2$ requires 306.1943).

4.13.28. Amide (*S*)-15b. Obtained from (*S*)-**14**, using protocol H (oil, 188 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H), 1.37 (s, 9H), 2.27 (m, 1H), 2.77 (s, 3H), 3.66 (s, 3H), 4.07 (d, J=10.9 Hz, 1H), 6.72 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.33 (br s, 1H); ^{13}C NMR δ 17.65 (CH_3), 18.79 (CH_3), 25.17 (CH), 27.33 (CH_3), 29.44 (CH_3), 64.76 (CH), 79.46 (CH), 113.02 (CH), 120.47 (CH), 130.27 (CH_3), 155.21 (C), 156.31 (C), 167.70 (C).

4.13.29. Amide (*S*)-15c. Obtained from (*S*)-**14**, using protocol H (oil, 451 mg, 29%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H), 1.39 (s, 9H), 2.95 (m, 1H), 2.75 (s, 3H), 3.70 (s, 6H), 4.00 (m, 1H), 6.15 (s, 1H), 6.68 (s, 2H), 8.18 (br s, 1H).

4.13.30. Amide (*S*)-15d. Obtained from (*S*)-**14**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (24/1) afforded pure product as an oil (240 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J=6.5 Hz, 3H), 0.88 (d, J=6.5 Hz, 3H), 1.38 (s, 9H), 2.17 (s, 6H), 2.25 (m, 1H), 2.76 (s, 3H), 4.08 (d, J=10.8 Hz, 1H), 6.62 (s, 1H), 7.07 (s, 2H), 8.24 (br s, 1H).

4.13.31. Amide (*S*)-15f. Obtained from (*S*)-**14**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (6/1) afforded a pure product as an oil (105 mg, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.4 Hz, 3H), 1.41 (s, 9H), 2.30 (m, 1H), 2.76 (s, 3H), 3.95 (d, J=10.8 Hz, 1H), 7.00 (s, 1H), 7.41 (s, 2H), 8.51 (br s, 1H).

4.13.32. Amide (*S*)-15g. Obtained from (*S*)-**14**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (3/1) afforded a pure product as an oil (928 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (m, 9H), 1.29 (m, 2H), 1.39 (s, 9H), 2.20 (m, 1H), 2.73 (s, 3H), 3.17 (m, 2H), 3.90 (d, J=10.9 Hz, 1H), 6.04 (br s, 1H).

4.13.33. Amide (*S*)-16a. Obtained from (*S*)-**14**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (3/1) afforded a pure product as an oil (72 mg, 22%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.7 Hz, 3H), 1.13 (s, 9H), 2.34 (m, 1H), 2.79 (s, 3H), 3.25 (s, 3H), 4.23 (d, J=10.8 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.33 (t, J=7.7 Hz, 2H), 7.41 (d, J=7.5 Hz, 2H).

4.13.34. Amide (*S*)-16b. *N*,*N*′-Dicyclohexylcarbodiimide (248 mg, 1.2 mmol) was added in small portions to a stirred solution of (*S*)-**14** (232 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (3 mL), followed by dropwise addition of a solution of diethylamine (145 μL, 1.4 mmol) in anhydrous CH_2Cl_2 (0.5 mL). The mixture was allowed to stir at room temperature overnight under an argon atmosphere. The solvent was then removed under reduced pressure. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (24/1) afforded (*S*)-**16b** as an oil (120 mg, 42%):^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J=6.6 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H), 1.04 (m, 3H), 1.08 (m, 3H), 1.42 (s, 9H), 2.3 (m, 1H), 2.68 (s, 3H), 3.18 (m, 2H), 3.34 (m, 2H), 4.52 (d, J=10.8 Hz, 1H); ^{13}C NMR δ 13.30 (CH_3), 15.01 (CH_3), 18.28 (CH_3), 20.16 (CH_3), 27.51 (CH), 28.70 (CH_3), 29.55 (CH_3), 40.72 (CH_2), 41.57 (CH_2), 61.37 (CH), 80.04 (C), 156.31 (CO), 169.71 (CO).

4.13.35. Amide (*S*)-17. Following a literature protocol,[17] a solution of pivalyl chloride (1.1 mL, 8.6 mmol) in anhydrous THF (8 mL) was added dropwise to a stirred solution of (*S*)-**14** (2.0 g, 8.6 mmol) and triethylamine (1.2 mL, 8.6 mmol) in anhydrous THF (16 mL) at −15 °C. The solution was then warmed to 0 °C and allowed to stir at this temperature for 5 min. The solution was then cooled again to −15 °C and a solution of 3,5-bis(trifluoromethyl)-aniline (1.34 mL) in anhydrous THF (8 mL) was added dropwise and the mixture was stirred at 0 °C for 1 h. The mixture was then warmed to room temperature and stirring was continued for 27 h under an argon atmosphere. The solvent was then removed under reduced pressure, the residue was diluted with water (20 mL) and then extracted with ethyl acetate (20 mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification using column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1) afforded (*S*)-**17** as an oil (185 mg, 7%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J=6.9 Hz, 3H), 0.99 (d, J=7.0 Hz, 3H), 2.15 (m, 1H), 2.42 (s, 3H), 2.87 (d, J=4.24 Hz, 1H), 7.50 (s, 1H), 8.05 (s, 2H), 9.69 (br s, 1H).

4.13.36. Compound (*R*)-19c. Obtained from (*R*)-**18c** as an oil (2.33 g, 78%) using protocol G; this product was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.62 (s, 3H), 7.21–7.45 (m, 5H).

4.13.37. Compound (*S*)-19d. Obtained from (*S*)-**18d** as an oil (2.38 g, 71%) using protocol G; this product was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$ a mixture of rotamers in ca. 1:1 ratio) δ 1.23 (s, 4.5H), 1.33 (s, 4.5H), 2.52 (s, 1.5H), 2.59 (s, 1.5H), 2.90 (m, 1H), 3.11 (m, 1H), 4.44 (dd, J=4.0, 10.4 Hz, 0.5H), 4.65 (dd, J=5.2, 10.8 Hz, 0.5H), 7.01–7.21 (m, 5H).

4.13.38. Compound (*S*)-19e. Obtained from (*S*)-**18e** as an oil (4.90 g, 98%) using protocol G; this product was used in

the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J=6.7 Hz, 3H), 1.40 (s, 9H), 2.89 (s, 3H), 4.19 (m, 1H).

4.13.39. Compound (*S*)-19f. Obtained from (*S*)-**18f** as an oil (2.60 g, 72%) using protocol G; this product was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 1.39 (s, 9H), 1.49 (m, 1H), 1.66 (m, 1H), 2.73 (s, 3H), 4.73 (m, 1H).

4.13.40. Amide (*R*)-20c. Obtained from (*R*)-**19c**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1) afforded a pure product as an oil (2.01 g, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.22 (s, 6H), 2.72 (s, 3H), 5.88 (br s, 1H), 6.69 (s, 1H), 7.09 (s, 2H), 7.23–7.46 (m, 5H).

4.13.41. Amide (*S*)-20d. Obtained from (*S*)-**19d**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (1/1) afforded a pure product as an oil (2.38 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.22 (s, 6H), 2.80 (s, 3H), 3.10 (dd, J=14, 8.2 Hz, 1H), 3.38 (dd, J=14, 6.8 Hz, 1H), 4.98–5.01 (m, 1H), 6.74 (s, 1H), 7.12 (s, 2H), 7.15–7.32 (m, 5H), 8.11 (br s, 1H).

4.13.42. Amide (*S*)-20e. Obtained from (*S*)-**19e**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (2/1) afforded a pure product as an oil (1.54 g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J=7.2 Hz, 3H), 1.43 (s, 9H), 2.26 (s, 6H), 2.74 (s, 3H), 4.75 (br s, 1H), 6.67 (s, 1H), 7.07 (s, 2H), 8.12 (br s, 1H).

4.13.43. Amide (*S*)-20f. Obtained from (*S*)-**19f**, using protocol H; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (2/1) afforded a pure product as an oil (1.70 g, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J=6.4 Hz, 3H), 0.91 (d, J=6.4 Hz, 3H), 1.43 (s, 9H), 1.46–1.54 (m, 1H), 1.56–1.64 (1H, m), 1.69–1.82 (m, 1H), 2.26 (s, 6H), 2.71 (s, 3H), 4.66 (br s, 1H), 6.67 (s, 1H), 7.06 (s, 2H), 8.05 (br s, 1H).

4.13.44. Oxazolidinone (*R*)-(−)-21a. Obtained from (*R*)-**18a** using protocol K; purification by chromatography on a column of silica gel with a hexane–ethyl acetate mixture (10/1, R_f=0.31) afforded the product (1.94 g, 87%) as a colorless oil, which solidified on standing: mp 63–64 °C, $[\alpha]_D$ −114.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.4 (m, 5H), 1.49 (s, 9H), 1.59–1.8 (m, 5H), 1.96 (br s, 1H), 4.15 (br s, 1H), 5.07 (br s, 1H), 5.57 (br d, 1H); ^{13}C NMR δ 25.77 (CH_2), 25.93 (CH_2), 27.87 (CH_2), 28.21 (CH_3), 41.06 (CH), 60.28 (CH), 78.76 (CH_2), 82.02 (C), 152.97 (CO), 172.57 (CO); IR (KBr) ν 2974, 2928, 2853, 1795, 1710, 1366, 1170, 1132, 1051 cm^{-1}; MS (CI) *m/z* (%) 270 ([MH]$^{\cdot+}$, 51), 226 (14), 214 (11), 198 (10), 170 (100); HRMS (CI) 270.1707 ($C_{14}H_{21}O_4N$ ([MH]$^{\cdot+}$) requires 270.1705).

4.13.45. Oxazolidinone (*S*)-(+)-21b. Obtained from (*S*)-**18b** using protocol K; purification using column chromatography on silica gel with a hexane–ethyl acetate mixture (10/1, R_f=0.35) afforded the product as a colorless solid (886 mg, 41%): mp 57–58 °C; $[\alpha]_D$ +98.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.49 (s, 9H), 4.04 (br s, 1H), 5.07 (d, J=4.4 Hz, 1H), 5.69 (br s, 1H); ^{13}C NMR δ 26.4 (CH_3), 28.15 (CH_3), 36.67 (C), 63.87 (CH), 78.9 (CH_2), 82.26 (C), 153.81 (CO), 171.71 (CO); IR (KBr) ν 2977, 2932, 2874, 1798, 1704, 1366, 1166, 1130, 1024 cm^{-1}; MS (CI) *m/z* (%) 244 ([MH]$^{\cdot+}$, 14), 144 (30), 89 (100), 81 (38), 71 (40); HRMS (CI) 244.1550 ($C_{12}H_{22}O_4N$ ([MH]$^{\cdot+}$) requires 244.1549).

4.13.46. *N*-methylformamide (*R*)-(+)-23a. Obtained from (*R*)-**21a** (166 mg, 83%) as a colorless solid using protocol E: mp 95–97 °C; $[\alpha]_D$ +1.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 2:1 ratio; the signals for the minor rotamer are marked by *) δ 0.85–1.35 (m, 5H), 1.58–2.05 (m, 6H), 2.92 (s, 2H) and 3.02* (s, 1H), 3.72 (d, J=10.4 Hz, 0.66H) and 4.69* (d, J=10.4 Hz, 0.33H), 8.12 (s) and 8.15* (s, 1H), 9.8 (br s, 1H); ^{13}C NMR δ 25.39, 25.46, 25.51, 25.96, 29.04 and 29.86 (CH_2 and C*H_2), 27.82 (CH), 32.39* (CH), 35.5* (CH_3), 36.05 (CH_3), 59.85* (CH), 66.53 (CH), 164.36 (CHO), 164.53* (CHO), 173.08 (CO), 173.49* (CO); IR (KBr) ν 3500–2200, 2939, 2858, 1748, 1666, 1235, 1069 cm^{-1}; MS (CI) *m/z* (%) 200 ([MH]$^{\cdot+}$, 100), 154 (10); HRMS (CI) 200.1286 ($C_{10}H_{18}O_3N$ ([MH]$^{\cdot+}$) requires 200.1287).

4.13.47. *N*-methylformamide (*S*)-(−)-23b. Obtained from (*S*)-**21b** (320 mg, 1.3 mmol) as a colorless solid (164 mg, 73%) using protocol E: mp 76–78 °C; $[\alpha]_D$ −1.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 2:1 ratio; the signals for the minor rotamer are marked by *) δ 1.11 (s) and 1.14* (s, 9H), 3.05 (s, 2H) and 3.16* (s, 1H), 3.86 (s, 0.66H) and 4.96* (s, 0.33H), 8.16* (s) and 8.17 (s, 1H), 7.85 (br s, 1H), in agreement with literature data;[21] ^{13}C NMR δ 27.72 (CH_3), 28.14* (CH_3), 31.11 (CH_3), 34.5* (C), 34.76 (C), 35.19* (CH_3), 61.81* (CH), 69.57 (CH), 165.01 (CHO), 165.04* (CHO), 172.58 (CO), 173.52* (CO).

4.13.48. Oxazolidinone (*R*)-(−)-25a. Obtained from (*R*)-**24a** (520 mg, 1.8 mmol) using protocol K; the reaction was carried out for 3 h and an additional amount of paraformaldehyde (1/4 of the initial quantity) was added in two equal portions after 1 and 2 h. Purification using column chromatography on silica gel with petroleum ether–ethyl acetate mixture (9/1, R_f=0.26) afforded the product as a colorless solid (345 mg, 64%): mp 77–79 °C; $[\alpha]_D$ −113.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08–1.45 (m, 5H), 1.6–1.79 (m, 5H), 2.0 (br s, 1H), 4.21 (br s, 1H), 5.12–5.24 (m, 3H), 5.61 (br d, 1H), 7.31–7.42 (m, 5H); ^{13}C NMR δ 25.73 (CH_2), 25.85 (CH_2), 25.91 (CH_2), 27.85 (CH_2), 28.63 (CH_2), 40.75 (CH), 59.88 (CH), 68.03 (CH_2), 78.56 (CH_2), 128.32 (CH), 128.59 (CH), 128.67 (CH), 135.35 (C), 153.6 (CO), 171.73 (CO); IR (KBr) ν 3068, 3033, 2933, 2852, 1791, 1691, 1503, 1049, 742, 698 cm^{-1}; MS (CI) *m/z* (%) 303 (M$^{\cdot+}$, 13), 220 (25), 168 (14), 91 (100), 86 (22); HRMS (EI) 303.1470 ($C_{17}H_{21}O_4N$ requires 303.1471).

4.13.49. Oxazolidinone (*S*)-(+)-25b. Obtained from (*S*)-**24b** (413 mg, 1.6 mmol) using protocol K; the reaction was

carried out for 7 h and an additional amount of paraformaldehyde (4×the initial quantity) was added in four equal portions after 2, 3, 5 and 6 h. Purification using column chromatography on silica gel with petroleum ether–ethyl acetate mixture (9/1, R_f=0.28) afforded the product as a colorless solid (350 mg, 81%): mp 35–36 °C; $[\alpha]_D$ +82.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 4.11 (br s, 1H), 5.11–5.23 (m, 3H), 5.7 (br s, 1H), 7.31–7.42 (m, 5H); ^{13}C NMR δ 26.35 (CH_3), 36.72 (C), 63.65 (CH), 68.35 (CH_2), 78.82 (CH_2), 128.45 (CH), 128.64 (CH), 128.67 (CH), 135.19 (C), 154.71 (CO), 171.11 (CO); IR (KBr) ν 3068, 3032, 2974, 2962, 2936, 1788, 1709, 1504, 1040, 1025, 760, 702 cm^{-1}; MS (CI) *m/z* (%) ([MH]$^{\cdot+}$, 100), 234 (71), 91 (16); HRMS (CI) 278.1391 ($C_{15}H_{20}O_4N$ ([MH]$^{\cdot+}$) requires 278.1392).

4.13.50. Cbz-protected amide (*R*)-(+)-27a. Obtained from (*R*)-**25a** via (*R*)-**26a**, using protocol J and purified by column chromatography on silica gel with petroleum ether–ethyl acetate mixture (9/1, R_f=0.28) to afford a pure product as clear oil (130 mg, 64%): $[\alpha]_D$ +58.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked by *) δ 0.87–1.03 (m, 2H), 1.12–1.38 (m, 3H), 1.66–1.87 (m, 5H), 2.05–2.14 (m, 1H), 2.28 (s, 6H), 2.94 (s, 3H), 4.11* (d, *J*=10.8 Hz, 0.2H), 4.25 (d, *J*=11.2 Hz, 0.8H), 5.05–5.22 (m, 2H), 6.74 (s, 1H), 6.85* (s, 0.4H), 7.05* (br s, 0.2H), 7.14 (s, 1.6H), 7.29–7.45 (m, 5H), 8.04 (br s, 0.8H); ^{13}C NMR (major rotamer) δ 21.31 (CH_3), 25.54 (CH_2), 25.56 (CH_2), 26.3 (CH_2), 28.84 (CH_2), 30.07 (CH_2), 30.32 (CH), 35.02 (CH_3), 65.39 (CH), 67.67 (CH_2), 117.43 (CH), 125.94 (CH), 127.61 (CH), 128.05 (CH), 128.5 (CH), 136.32 (C), 137.62 (C), 138.64 (C), 157.81 (CO), 168.21 (CO); IR (KBr) ν 3331, 2927, 2852, 1672, 1617, 1560, 1449, 1146, 1121, 843, 796, 696 cm^{-1}; MS (EI) *m/z* (%) 408 (M$^{\cdot+}$, 10), 288 (11), 260 (32), 216 (65), 91 (100); HRMS (EI) 408.2415 ($C_{25}H_{32}O_3N_2$ requires 408.2413).

4.13.51. Cbz-protected amide (*S*)-27b. Obtained from (*S*)-**25a** (460 mg, 1.66 mmol) via (*S*)-**26b**, using protocol J; purification by column chromatography on silica gel with petroleum ether–ethyl acetate mixture (9/1, R_f=0.33) afforded an inseparable mixture of (*S*)-**25a** and (*S*)-**27b** (206 mg) in ca. 1:3 ratio as a colorless oil, which was used for further transformations.

4.13.52. Oxazolidinone (*S*)-(+)-30. Obtained from (*S*)-**29** (485 mg, 1.6 mmol) using protocol K; the reaction was carried out for 2 h. Purification using column chromatography on silica gel with petroleum ether–ethyl acetate mixture (9/1, R_f=0.32) afforded the product as a colorless solid (220 mg, 50%): mp 74–75 °C; $[\alpha]_D$ +109.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.01 (s, 3H), 5.45 (br s, 1H), 5.49 (d, *J*=4.4 Hz, 1H), 7.29–7.4 (m, 5H); ^{13}C NMR δ 22.73 (CH_3), 28.05 (CH_3), 61.96 (C), 77.31 (CH_2), 81.86 (C), 125.43 (CH), 128.28 (CH), 128.72 (CH), 138.89 (C), 152.17 (CO), 173.96 (CO); IR (KBr) ν 3065, 3031, 2981, 2941, 1791, 1709, 1499, 1045, 759, 698 cm^{-1}; MS (EI) *m/z* (%) 277 (M$^{\cdot+}$, 1), 146 (8), 132 (25), 91 (15), 57 (100); HRMS (EI) 277.1313 ($C_{15}H_{19}O_4N$ requires 277.1314).

4.13.53. *N*-methylformamide (*S*)-(+)-32. Obtained from (*S*)-**30** (157 mg, 0.57 mmol) using protocol E and recrystallized from ethyl acetate–hexane to afford (*S*)-(+)-**32** (100 mg, 85%) as an off-white solid: mp 143–145 °C; $[\alpha]_D$ +42.9 (*c* 0.86, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD, a mixture of rotamers in ca. 5:1 ratio; the signals for the minor rotamer are marked by *) δ 1.85* (s) and 1.86 (s, 3H), 2.64* (s, 0.5H), 2.81 (s, 2.5H), 7.27–7.37 (m, 5H), 8.01 (s, 0.8H), 8.09* (s, 0.2H); ^{13}C NMR δ 19.99* (CH_3), 25.03 (CH_3), 29.02 (CH_3), 32.99* (CH_3), 65.22* (C), 68.5 (C), 126.67 (CH), 127.67 (CH), 128.29 (CH), 128.36 (CH), 128.81 (CH), 136.66* (C), 139.03 (C), 163.86* (CHO), 164.85 (CHO), 173.14* (CO), 173.57 (CO); IR (KBr) ν 3500–2200, 1721, 1612, 1493, 1379, 1269, 1096, 766, 800 cm^{-1}; MS (CI) *m/z* (%) 208 ([MH]$^{\cdot+}$, 100), 162 (13), 113 (8), 85 (12), 73 (18); HRMS (CI) 208.0975 ($C_{11}H_{14}O_3N$ ([MH]$^{\cdot+}$) requires 208.0974).

4.13.54. *N*-τ-Me-*N*-α-Boc-histidine (*S*)-(+)-(34). Sodium hydride (705 mg, 29.4 mmol) was placed in a two-neck flask, flushed with Ar, washed 3×with petroleum ether, and dried under vacuum. The dry NaH was then added slowly to a suspension of *N*-α-Boc-histidine (*S*)-**33** (2.5 g, 9.8 mmol) in CH_3CN at −15 °C and stirred for 30 min. Methyl iodide (1.53 g, 10.7 mmol) was added and the reaction mixture was then heated to −5 °C and allowed to stir overnight at this temperature. The reaction was quenched with excess MeOH and the solvent was removed on a rotary evaporator. The resulting solid was then extracted with $CHCl_3$ (3×50 mL), the solvent was evaporated and the resulting solid was purified by chromatography on a column of silica gel (50 g), with a CH_2Cl_2–MeOH mixture (5/1), to give *N*-τ-Me-*N*-α-Boc-histidine (*S*)-(+)-**34** as a pale yellow solid (1.64 g, 66%): mp 166–168 °C (dec); $[\alpha]_D^{25}$ +29.5 (*c* 1.0, $CHCl_3$) in accordance with the literature;[24] ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (s, 9H) 2.82 (d, *J*=4.8 Hz, 2H) 3.56 (s, 3H) 3.91 (br s, 1H) 6.17 (d, *J*=5.6 Hz, 1H), 6.77 (s, 1H) 7.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.5, 28.2, 32.9, 45.6, 54.9, 77.5, 117.8, 154.83.

4.13.55. [1-(3,5-Dimethyl-phenylcarbamoyl)-2-(1-methyl-1*H*-imidazol-4-yl)-ethyl]-carbamic acid *tert*-butyl ester (*S*)-(+)-(35). 3,5-Dimethylaniline, (472 mg, 3.9 mmol) was added to a solution of *N*-τ-Me-*N*-α-Boc-histidine (*S*)-**34**, (1.0 g, 3.9 mmol), in dry MeCN. The solution was cooled to 0 °C and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDCI; 910 mg, 4.7 mmol) was added and the reaction mixture was allowed to stir at room temperature for 48 h. The mixture was then poured into saturated $NaHCO_3$ solution and extracted 3×with AcOEt. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by chromatography on a column of silica gel (75 g) with a CH_2Cl_2–MeOH mixture (5/1) to afford (*S*)-(+)-**35** as a pale orange solid (896 mg, 60%):[25] $[\alpha]_D^{25}$ +53 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 9H) 2.20 (s, 6H) 2.91 (dd, *J*=15.6, 6.4 Hz, 1H) 3.05 (d, *J*=15.6 Hz, 2H), 3.64 (s, 3H), 4.46 (s, 1H), 6.23 (s, 1H), 6.65 (s, 1H), 6.67 (s, 1H), 7.19 (s, 2H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.3, 30.7, 33.4, 50.4, 117.6, 118.6, 125.9, 137.2, 138.5.

4.13.56. Amide (*S*)-37. Obtained from (*S*)-**13**, using protocol H; purification by column chromatography on

silica gel with a petroleum ether–ethyl acetate mixture (1/1) afforded a pure product as an oil (309 mg, 19%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H), 1.39 (s, 9H), 2.90 (m, 1H), 3.70 (s, 6H), 3.90 (t, J=6.4 Hz, 1H), 4.98 (br s, 1H), 6.16 (s, 1H), 6.69 (s, 2H), 7.78 (br s, 1H).

4.13.57. Amide (*S*)-(−)-39a. Obtained from (*S*)-**13** as an off-white solid (1.522 g, 95%) using protocol I; this product was used in the following step without further purification: mp 136–137 °C, $[\alpha]_D$ −39.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.4 Hz, 3H), 1.45 (s, 9H), 2.24 (s, 6H), 4.03–4.06 (m, 1H), 5.25 (d, J=8.8 Hz, 1H), 6.71 (s, 1H), 7.13 (s, 2H), 8.16 (br s, 1H), in agreement with literature data;[26] ^{13}C NMR δ 18.15 (CH_3), 19.36 (CH_3), 21.28 (CH_3), 28.29 (CH_3), 30.74 (CH), 60.88 (CH), 80.18 (C), 117.63 (CH), 126.01 (CH), 137.34 (C), 138.54 (C), 156.26 (CO), 170.17 (CO); IR (KBr) ν 3303, 2976, 2930, 1683, 1661, 1611, 1565, 1521, 1171, 845 cm^{-1}; MS (EI) *m*/*z* (%) 320 ($M^{\cdot+}$, 27), 247 (15), 172 (12), 148 (13), 121 (100), 116 (68), 72 (88), 57 (65); HRMS (EI) 320.2103 ($C_{18}H_{28}O_3N_2$ requires 320.2100).

4.13.58. Amide (*S*)-(+)-39b. Obtained from (*S*)-**18c** (401 mg, 1.6 mmol) using protocol I; recrystallization from hexane–ethyl acetate furnished a pure product (440 mg, 78%) as a colorless solid: mp 118–120 °C, $[\alpha]_D$ +33.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.25 (s, 6H), 5.30 (br s, 1H), 5.83 (br s, 1H), 6.73 (s, 1H), 7.06 (s, 2H), 7.31–7.44 (m, 5H); ^{13}C NMR δ 21.26 (CH_3), 28.29 (CH_3), 59.12 (CH), 80.38 (C), 117.66 (CH), 126.22 (CH), 127.24 (CH), 128.49 (CH), 129.07 (CH), 137.13 (C), 137.77 (C), 138.57 (C), 155.45 (CO), 168.34 (CO); IR (KBr) ν 3331, 1686, 1662, 1616, 1559, 1525, 1169, 847, 699 cm^{-1}; MS (EI) *m*/*z* (%) 354 ($M^{\cdot+}$, 9), 280 (21), 206 (27), 150 (100), 106 (82), 57 (56); HRMS (EI) 354.1945 ($C_{21}H_{26}O_3N_2$ requires 354.1943).

4.13.59. Amide (*S*)-(−)-39c. Obtained from (*S*)-**18d** (428 mg, 1.6 mmol) using protocol I; purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (9/1, R_f=0.17) afforded a pure product (574 mg, 97%) as a colorless solid: mp 122–123 °C, $[\alpha]_D$ −22.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.26 (s, 6H), 3.14 (d, J=7.2 Hz, 2H), 4.44 (br s, 1H), 5.13 (br s, 1H), 6.74 (s, 1H), 7.0 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR δ 21.27 (CH_3), 28.24 (CH_3), 38.49 (CH_2), 56.60 (CH), 80.45 (C), 117.76 (CH), 126.17 (CH), 126.96 (CH), 128.73 (CH), 129.30 (CH), 136.65 (C), 137.07 (C), 138.53 (C), 155.75 (CO), 169.52 (CO); IR (KBr) ν 3320, 2971, 2918, 1692, 1663, 1615, 1541, 1526, 1168, 836, 702 cm^{-1}; MS (EI) *m*/*z* (%) 368 ($M^{\cdot+}$, 37), 294 (19), 251 (15), 164 (47), 160 (35), 121 (100), 120 (99), 91 (57), 57 (88); HRMS (EI) 368.2102 ($C_{22}H_{28}O_3N_2$ requires 368.2100).

4.13.60. Dipeptide (*S*,*S*)-(−)-41a. Obtained from (*S*)-**39a** and (*S*)-**14** using protocol L. Purification by column chromatography on silica gel with a hexane–ethyl acetate mixture (8/2, R_f=0.34) afforded the product (259 mg, 60%) as a colorless solid: mp 90–91 °C; $[\alpha]_D$ −132.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers in ca. 4:1 ratio; the signals for the minor rotamer are marked by *) δ 0.86–0.98 (m, 12H), 1.47 (s, 9H), 2.11–2.38 (m, 2H), 2.28 (s, 6H), 2.81 (s, 3H), 3.97* (br s, 0.2H), 4.09 (d, J=11.2 Hz, 0.8H), 4.25–4.4 (m, 1H), 6.31* (br s, 0.2H), 6.74 (s, 1H), 6.77* (br s, 0.8H), 7.13 (s, 2H), 7.88* (br s, 0.2H), 8.01 (br s, 0.8H); ^{13}C NMR (major rotamer) δ 17.75 (CH_3), 18.56 (CH_3), 19.51 (CH_3), 19.86 (CH_3), 21.35 (CH_3), 22.67 (CH), 25.92 (CH), 28.41 (CH_3), 30.02 (CH_3), 59.24 (CH), 64.82 (CH), 80.57 (C), 117.69 (CH), 126.14 (CH), 137.41 (C), 138.69 (C), 157.01 (CO), 169.16 (CO), 171.48 (CO); IR (KBr) ν 3297, 2964, 2931, 1690, 1650, 1618, 1559, 1157, 845 cm^{-1}; MS (EI) *m*/*z* (%) 433 ($M^{\cdot+}$, 12), 186 (12), 158 (11), 130 (100), 121 (66), 86 (76), 57 (43); HRMS (EI) 433.2939 ($C_{24}H_{39}O_4N_3$ requires 433.2941).

4.13.61. Dipeptide (*S*,*S*)-(−)-41b. Obtained from (*S*)-**39b** and (*S*)-**14** using protocol L. Purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (8/2, R_f=0.33) afforded the product (420 mg, 90%) as a colorless solid: mp 76–78 °C; $[\alpha]_D$ −53.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 0.88 (d, J=6.8 Hz) and 0.98 (d, J=6.8 Hz, 6H), 1.45 (s) and 1.49* (s, 9H), 2.21* (s) and 2.23 (s, 6H), 2.2–2.39 (m, 1H), 2.67 (s, 2H), 2.81* (s, 1H), 4.03–4.27 (m, 1H), 5.77 (d, J=7.6 Hz, 1H), 6.68* (s) and 6.71 (s, 1H), 7.02* (s) and 7.08 (s, 2H), 7.27–7.46 (m, 5H), 7.58 (br s) and 7.69* (br s, 1H), 8.37 (br s) and 8.52* (br s, 1H); ^{13}C NMR (major rotamer) δ 18.47 (CH_3), 19.8 (CH_3), 21.23 (CH_3), 25.88 (CH), 28.34 (CH_3), 29.98 (CH_3), 57.55 (CH), 64.29 (CH), 80.4 (C), 117.53 (CH), 126.06 (CH), 128.35 (CH), 128.85 (CH), 128.93 (CH), 137.41 (C), 138.31 (C), 138.48 (C), 156.89 (CO), 167.63 (CO), 170.47 (CO); IR (KBr) ν 3311, 2968, 2930, 1690, 1650, 1562, 1154, 844, 695 cm^{-1}; MS (EI) *m*/*z* (%) 467 ($M^{\cdot+}$, 3), 264 (12), 214 (16), 158 (22), 130 (91), 116 (69), 86 (100), 57 (50); HRMS (EI) 467.2787 ($C_{27}H_{37}O_4N_3$ requires 467.2784).

4.13.62. Dipeptide (*S*,*S*)-(−)-41c. Obtained from (*S*)-**39c** and (*S*)-**14** using protocol L. Purification by column chromatography on silica gel with a petroleum ether–ethyl acetate mixture (8/2, R_f=0.32) afforded the product (420 mg, 92%) as a colorless solid: mp 65–67 °C; $[\alpha]_D$ −93.4 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 0.84 (d, J=6.8 Hz) and 0.89 (d, J=6.4 Hz, 6H), 1.46 (s, 9H), 2.27 (s, 6H), 2.2–2.3 (m, 1H), 2.64 (s, 3H), 3.0–3.26 (m, 2H), 3.95* (br s, 0.3H), 4.05 (d, J=10.8 Hz, 0.7H), 4.73 (dd, J=14.8, 7.2 Hz, 1H), 6.39* (br s, 0.3H), 6.74 (s, 1H), 6.8 (br s, 0.7H), 7.0* (s) and 7.02 (s, 2H), 7.22–7.32 (m, 5H), 7.52* (br s, 0.3H), 7.85 (br s, 0.7H); ^{13}C NMR (major rotamer) δ 18.44 (CH_3), 19.78 (CH_3), 21.29 (CH_3), 26.12 (CH), 28.35 (CH_3), 37.32 (CH_2), 55.04 (CH), 64.81 (CH), 80.46 (C), 117.69 (CH), 126.17 (CH), 126.92 (CH), 128.71 (CH), 129.12 (CH), 136.64 (C), 137.21 (C), 138.61 (C), 156.73 (CO), 168.64 (CO), 171.41 (CO); IR (KBr) ν 3304, 2969, 2930, 1695, 1650, 1561, 1155, 841, 699 cm^{-1}; MS (EI) *m*/*z* (%) 481 ($M^{\cdot+}$, 17), 186 (15), 130 (100), 121 (59), 86 (79), 57 (41); HRMS (EI) 481.2943 ($C_{28}H_{39}O_4N_3$ requires 481.2941).

Acknowledgements

We thank the EPSRC for grant No. GR/S87294/01, the University of Glasgow for a fellowship to K. N. McD, the

University of Rome 'La Sapienza' for a fellowship to A. M., and Degussa for the gift of cyclohexylglycine.

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33. A similar effect has been observed by us for amides derived from valine and picolinic acid, which served as ligands in the Cu-catalyzed conjugate addition of Et_2Zn. In this case, the *N*-Me was optimal, while derivatives with other *N*-R groups (R = H, Et, *i*-Pr, and Ph) were ineffective as catalysts.[9]
34. Preliminary experiments show striking conformational differences in the X-ray structures of several of these derivatives, which may lend further credence to this hypothesis. Details will be published in due course.
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Tetrahedron 62 (2006) 285–294

Influence of electronic and steric factors on 2,3-dihydroimidazo[1,2-*a*]pyridine-based enantioselective acylation catalysts

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Received 17 May 2005; revised 4 August 2005; accepted 31 August 2005

Available online 10 October 2005

Abstract—The catalytic activity and enantioselectivity of chiral 2,3-dihydroimidazo[1,2-*a*]pyridine (DHIP) derivatives was examined as a function of the steric environment of the nucleophilic nitrogen and the electronic properties of the pyridine ring. 2-Phenyl-6-trifluoromethyl-DHIP (CF_3-PIP) was confirmed to be the best catalyst in this series. In addition, three second-generation catalysts derived from the 1,2-dihydroimidazo[1,2-*a*]quinoline (DHIQ) core were tested and proved to be considerably more active than CF_3-PIP.

1. Introduction

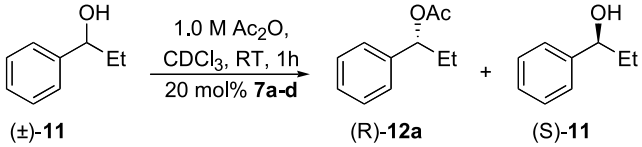
The challenge of developing easily accessible and effective non-enzymatic asymmetric acylation catalysts has attracted many research groups around the world over the last decade.[1,2] Two years ago, we envisioned a new class of enantioselective nucleophilic catalysts based on dihydroimidazo[1,2-*a*]pyridine (DHIP)[3] (**1**, R = X = H).[1n] Although no prior reports of the catalytic activity of this heterocyclic compound were to be found in the literature, we recognized its practical potential as a core structure for rational catalyst design. Chiral derivatives of DHIP (**1**, R ≠ H) could be obtained from chiral 2-amino alcohols (**4**) and substituted 2-halopyridines (**3**) in only two steps (Scheme 1). The commercial availability of a variety of these starting materials was expected to greatly facilitate the variation of the steric environment of the nucleophilic nitrogen and the tuning of the electronic properties of the system in search of the optimal catalytic activity and enantioselectivity.

After establishing the catalytic activity of the parent compound, we proceeded to investigate the efficacy of its chiral derivatives in kinetic resolution.[4] 2-Phenyl-DHIP **7a** (abbreviated H-PIP) and three of its analogs bearing electron-withdrawing groups at C6 (6-Br-PIP **7b**, 6-CF_3-PIP **7c** and 6-NO_2-PIP **7d**) were prepared from (*R*)-phenylglycinol (**5**), which happened to be the most abundant chiral 2-amino alcohol found in our laboratory (Scheme 2).

Testing these compounds as catalysts in acetylation of racemic phenyl ethyl carbinol provided the basis for their initial comparison. We determined that introduction of the trifluoromethyl at C6 produced not only a more reactive, but also a more enantioselective catalyst (**7c**) than either the stronger (NO_2) or the weaker (Br, H) electron-withdrawing groups (Table 1).

Optimization of the reaction conditions (use of *N*,*N*-diisopropylethylamine as auxiliary base and propionic anhydride as the stoichiometric acyl donor and lowering the reaction temperature to 0 °C) allowed us to obtain useful levels of selectivity (20–85) in kinetic resolution of a range of acyclic secondary benzylic alcohols with only 2 mol% catalyst loadings of CF_3-PIP. The most important selectivity/reactivity trends are illustrated with representative examples **14**–**18** (Fig. 1). The absolute sense of

Table 1. The first catalytic activity/selectivity test



(±)-**11**
1.0 M

(R)-**12a**

(S)-**11**

X	% ee_E[a]	% ee_A[a]	% Conversion[a]	Selectivity[a]
H	49	13	21	3.3
Br	74	25	25	8.6
CF_3	80	49	38	14
NO_2	82	13	11	11

[a] Averaged results of duplicate runs.

Keywords: Organocatalysis; Non-enzymatic asymmetric acylation catalysts; Enantioselective acyl transfer; Kinetic resolution.
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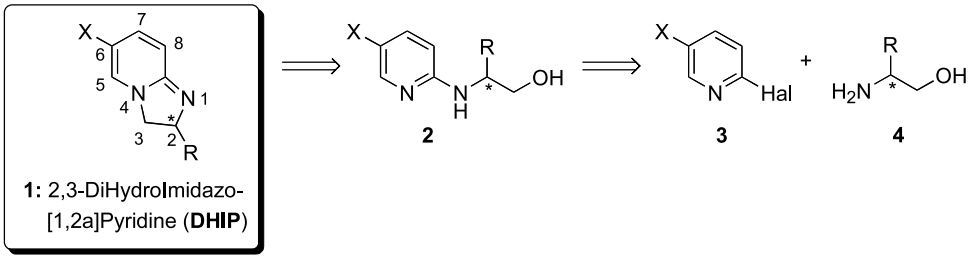
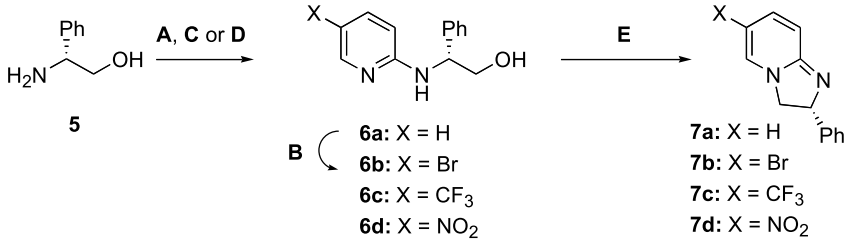
doi:10.1016/j.tet.2005.08.119



Scheme 1.



Conditions: **A.** 2-bromopyridine (**8**), *i*-Pr_2NEt, 165 °C (64%); **B.** 1 eq. NBS, MeCN, rt (93%) **C.** 2-chloro-5-trifluoromethyl-pyridine (**9**), *i*-Pr_2NEt, 110 °C (66%); **D.** 2-chloro-5-nitro-pyridine (**10**), NEt_3, EtOH reflux (92%); **E.** $SOCl_2$, $CHCl_3$, reflux; then aq. NaOH (**7a:** 62%,**7b:** 91%, **7c:** 85%, **7d:** 98%).

Scheme 2.

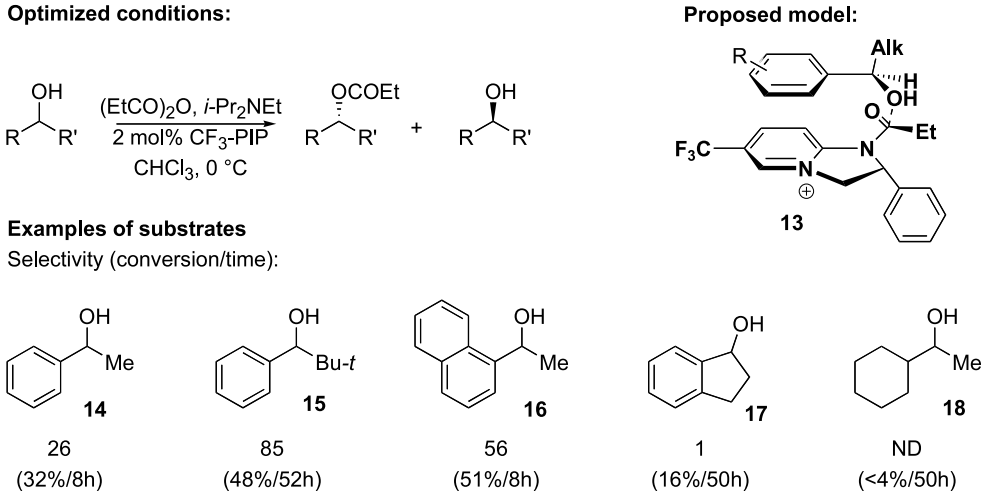


Figure 1. Kinetic resolution of secondary benzylic alcohols using CF_3-PIP.

enantioselectivity observed in the kinetic resolution of substrates **14**–**16** is consistent with our proposed transition state model **13**, which is based on π–π[5] and/or cation-π[6] interactions of the aromatic ring of the substrate with the pyridinium moiety of the acylated catalyst. This model also explains why the cyclic benzylic alcohol, 1-indanol **17**, which cannot adopt the required conformation, is acylated extremely slowly and with no detectable selectivity, while cyclohexyl methyl carbinol **18**, lacking an aromatic ring, simply fails to react to any appreciable extent.

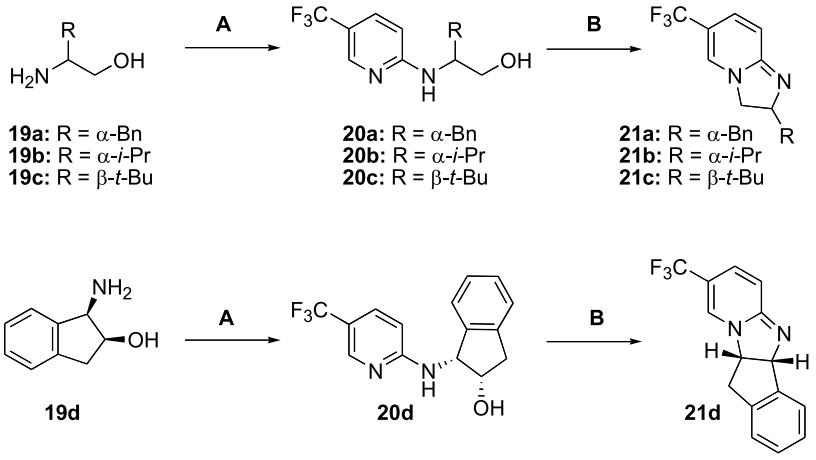
The success of this initial study prompted us to seek answers to the following two questions: (a) was our fortuitous choice of the phenyl group as the C2-substituent critical for the enantioselectivity? and (b) could we further improve the catalytic activity of our system by changing the substitution of the pyridine ring?

2. Results and discussion

2.1. The influence of substitution at C2 on the enantioselectivity

To answer the first of these questions, we prepared the 2-benzyl (**21a**), 2-isopropyl (**21b**) and 2-*t*-butyl (**21c**) analogs of CF_3-PIP as well as the conformationally restricted version of the latter, tetracycle **21d**, starting with the commercially available chiral 2-amino alcohols (*R*)-phenylalaninol **19a**, (*R*)-valinol **19b**, (*S*)-*tert*-leucinol **19c** and (1*R*,2*S*)-1-amino-2-indanol **19d**, respectively (Scheme 3).

Testing these catalysts under the conditions optimized for CF_3-PIP[1n] demonstrated how fortunate we were to have started our investigation with phenylglycinol (Table 2). **21a**



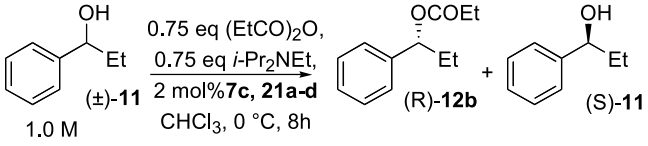
Conditions: **A.** 2-chloro-5-trifluoromethyl-pyridine (**9**), *i*-Pr_2NEt, 105-120 °C (**20a**: 84%; **20b**: 64%; **20c**: 51%; **20d**: 73%); **B.** $SOCl_2$, $CHCl_3$, reflux; then aq. NaOH (**21a:** 74%, **21b:** 52%, **21c:** 86%, **21d:** 31%).

Scheme 3.

and **21b** displayed catalytic activities comparable to CF_3-PIP, but drastically reduced enantioselectivities. The *t*-butyl derivative **21c** was even less selective and reacted extremely slowly, which ostensibly reflected the steric encumbrance of the nucleophilic nitrogen. Finally, the indane derivative **21d** reacted noticeably faster than CF_3-PIP and with barely detectable selectivity, suggesting that the two faces of the catalyst were no longer effectively discriminated. It is noteworthy that the low enantioselectivity seen in this case was opposite to that with the rest of the catalysts having (*R*)-configuration at C2 (**7c**, **21a**,**b**), which also suggests a change in the transition state. The same sense of chiral recognition was previously observed in the kinetic resolution of α-phenethylamine with an indane-based stoichiometric enantioselective acyl donor structurally similar to **21d**.[7]

The above results indicate that the selectivity critically depends not only on the nature of the C2 substituent, but also on its orientation. Clearly, the thermodynamically favored conformation of the benzene ring in CF_3-PIP (in which the plane of the ring is almost perpendicular to the C2–2 bond) is very different from that in the conformationally restricted analog **21d**. Currently, we surmise that the role of the phenyl group consists not only in blocking the approach of the nucleophile from one of the faces, but also in forcing the acyl group to adopt the conformation required for high selectivity. It will be of interest to examine modification of the phenyl ring, particularly by introducing *ortho*-substituents. However, substituted phenylglycinols are not commercially available and therefore, the preparation of such catalysts must await further study.

Table 2.



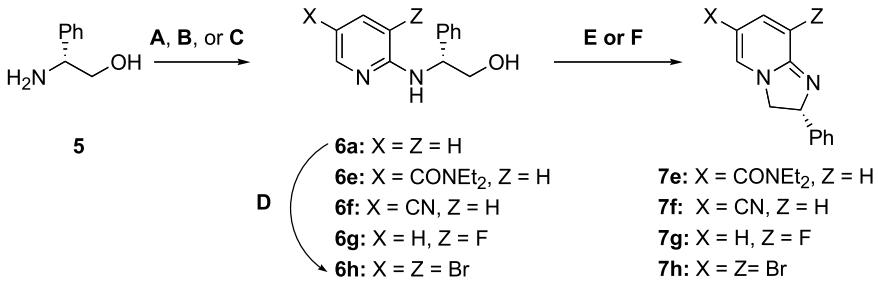
Catalyst	% ee_E[a]	% ee_A[a]	% Conversion[a]	Selectivity[a,b]
7c	91	59	39	36
21a	56	34	38	4.9
21b	51	23	31	3.9
21c	−31	—[c]	7[d]	−2.0
21d	−14	−19	58	−1.6

[a] Averaged results of duplicate runs.
[b] Catalysts **7c**, **21a** and **21b** produced the (*R*)-ester and the (*S*)-alcohol (the absolute configurations shown). Catalysts **21c** and **21d** gave the opposite selectivity.
[c] Too low for reliable HPLC measurements.
[d] Estimated from the ^1H NMR spectra of the crude reaction mixtures and used to calculate the selectivity factor.[4]

2.2. The influence of substitution of the pyridine ring

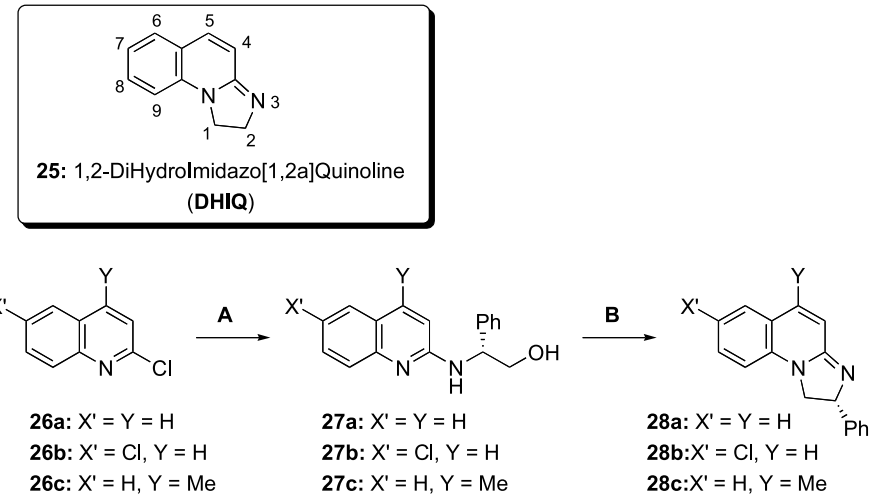
Since we had obtained the best results with a substituent of intermediate electron-withdrawing strength—trifluoromethyl—we decided to synthesize and test two additional catalysts, having substituents with a somewhat lower and a somewhat higher Hammett σ_{para} values.[8,9] For practical reasons, we chose to prepare the 6-diethylcarbamoyl and 6-cyano derivatives $CONEt_2$-PIP (**7e**) and CN-PIP (**7f**). We also wanted to verify our initial assumption that position *ortho*- to the nucleophilic nitrogen must remain unsubstituted. The commercially available 2-chloro-3-fluoropyridine afforded 8-F-PIP (**7g**) having the smallest possible non-hydrogen substituent at position 8. 6,8-Br_2-PIP (**7h**) was readily available by a simple modification of the procedure used to prepare Br-PIP (**7b**)[1n,10] (Scheme 4).

In addition, we had recently begun to explore the second generation of asymmetric acylation catalysts based on the structure of 1,2-dihydroimidazo[1,2-*a*]quinoline (DHIQ) **25**, which is simply the 5,6-benzannellated analog of the DHIP core. Chiral derivatives of DHIQ are just as easily accessible as those of DHIP, via the standard two-step procedure starting with 2-haloquinolines instead of 2-halopyridines.[11] Thus, the first three members of the series—H-PIQ **27a**, 7-Cl-PIQ **27b**, and 5-Me-PIQ **27c** were prepared from the commercially available 2-chloroquinoline **25a**, 2,6-dichloroquinoline **25b** and 2-chloro-4-methylquinoline **25c** (Scheme 5).



Conditions: **A.** 6-chloro-N, N-diethyl-nicotinamide (**22**), *i*-Pr_2NEt, 150 °C (77%); **B.** 2-chloro-5-cyano-pyridine (**23**), *i*-Pr_2NEt, isopropanol, reflux (63%); **C.** 2-chloro-3-fluoro-pyridine (**24**), *i*-Pr_2NEt, 165 °C (46%); **D.** 2 eq. NBS, MeCN, rt (98%) **E.** MsCl, NEt_3, CH_2Cl_2, 0 °C (**7e:** 68%); **F.** $SOCl_2$, $CHCl_3$, reflux; then aq. NaOH (**7f:** 75%,**7g:** 77%, **7h:** 88%).

Scheme 4.



Conditions: **A.** (R)-Phenylglycinol (**5**), *i*-Pr_2NEt, 130 °C (**26a:** 78%; **26b:** 87%; **26c:** 99%). **B.** $SOCl_2$, $CHCl_3$, reflux; then aq. NaOH (**27a:** 87%; **27b:** 91%; **27c:** 77%).

Scheme 5.

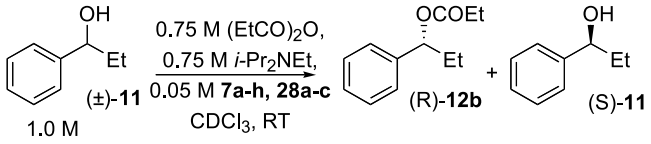
As mentioned above, the first catalyst performance test was carried out using acetic anhydride and without any auxiliary base. Since we already knew that addition of *i*-Pr_2NEt led to dramatic rate acceleration and propionic anhydride produced considerably higher selectivities than acetic anhydride, we modified the original set of conditions accordingly (Table 3). Furthermore, since the catalysts being studied this time were expected to differ by several orders of magnitude in their activity, we monitored each reaction by ^1H NMR spectroscopy and stopped it upon reaching approximately the same conversion (45–50%), rather than after a fixed period of time.

In addition, we sought to obtain 'fair' comparison of the catalytic activities. Since the conversions observed during kinetic resolution are dependent on the enantioselectivities and therefore, can serve only as an approximate measure of activity, we also determined the half-life of the fast-reacting (*R*)-enantiomer of phenyl ethyl carbinol with each catalyst under the conditions identical to those described above, except that 0.5 M concentration of (*R*)-**11** was used instead of 1.0 M (±)-**11**. In the case of the most reactive catalysts—CF_3-PIP and especially the three DHIQ derivatives—the half-lives with 0.05 M catalyst were too short to be measured reliably, and the measurements were repeated at 0.01 M catalyst concentrations. The results of these determinations are shown in the last column of Table 3.

The most practically important conclusion that may be drawn from these data is that the new generation of catalysts based on the DHIQ core is considerably more active than even the best catalyst in the DHIP series. The somewhat higher enantioselectivity of Cl-PIQ compared with CF_3-PIP observed in this trial is consistent with our recent study.[11]

The status of CF_3-PIP as the most active and selective DHIP catalyst has remained unchallenged, with the two new 6-substituted contenders, $CONEt_2$-PIP and CN-PIP, falling far behind. Br-PIP, on the other hand, displayed selectivity comparable to CF_3-PIP and also proved to be the second best in the DHIP series in terms of catalytic activity. It is noteworthy that $CONEt_2$-PIP is less active and selective than Br-PIP, although the σ_{para} value assigned to the amide group (0.36) is intermediate between that of Br (0.23) and CF_3 (0.54).[9] The order of the respective σ_{meta} values (0.35, 0.39, and 0.43)[9] is qualitatively consistent with the performances of these three catalysts in this trial. It remains to be seen whether the effect of other substituents on the

Table 3.



#	Catalyst	Time	% ee_E	% ee_A	% C_{HPLC}	S	$t_{½}(R)$
7a	H-PIP	11 h	73	65	47	12.5	2 h[a]
7b	6-Br-PIP	3 h	83	79	49	25	22 min[a]
7c	6-CF_3-PIP	40 min	85	77	47	28	4.5 min,[a] 45 min[b]
7d	6-NO_2-PIP	146 h	30	26	46	2.4	4 days[a]
7e	6-$CONEt_2$-PIP	4 h	77	74	49	17	34 min[a]
7f	6-CN-PIP	14 h	74	72	49	14	96 min[a]
7g	8-F-PIP	46 h	57	45	48	5.6	11.5 h[a]
7h	6,8-Br_2-PIP	120 h	56	46	45	5.5	4 days[a]
28a	H-PIQ	15 min	81	89	52	28	<2 min,[a] 10.5 min[b]
28b	7-Cl-PIQ	15 min	84	88	51	33	<2 min,[a] 12 min[b]
28c	5-Me-PIQ	27 min	84	82	50	29	≈2 min,[a] 17 min[b]

[a] Measured at 0.05 M catalyst concentration.
[b] Measured at 0.01 M catalyst concentration.

catalysts' performance can be reliably predicted from Hammett's parameters. At this point, however, it may be noted that both the trifluoromethyl and the bromine—the two most successful groups—exert purely inductive electron-withdrawing effect, in contrast to the rest of the C6-substituents tested.

As expected, the presence of a C8-substitutuent (cf. 8-F-PIP and 6,8-Br_2-PIP) proved to be highly detrimental to the catalytic activity and selectivity, presumably due to its interference with the acyl carbonyl in the acylated intermediate. In the case of the small fluoro substituent, it is not clear whether this effect is primarily due to the steric or the electronic repulsion with the carbonyl oxygen. Perhaps it is more surprising that 6,8-Br_2-PIP reacted at all, even producing modest enantioselectivity. Monitoring the reaction by NMR spectroscopy provided a possible explanation of this result. Virtually no reaction was observed during the first 10 h, but later the product gradually began to appear at an apparently increased rate. We speculate that in this case the catalytically incompetent 6,8-Br_2-PIP was slowly transformed into an active (and enantioselective) species, which catalyzed the acylation. The exact nature of this compound and the mechanism of its formation cannot be ascertained at this point, but we surmise that it may be a DHIP derivative lacking the bromine at C8.

Mention must also be made here of the low chemical stability of NO_2-PIP and, to a lesser extent, CN-PIP under the reaction conditions. In the acylations catalyzed by these compounds, decomposition was evident from the red colour and some precipitation developing in the course of the reaction. In the case of NO_2-PIP, the discoloration was observed even during the first trial conducted under relatively neutral conditions (see Table 1). Apparently, the presence of Hunig's base in the present experiment further facilitated the decomposition, which accounts for the very slow reaction and the low enantioselectivity. This last result is in sharp contrast to that obtained under the base-free conditions, wherein NO_2-PIP displayed selectivity comparable to CF_3-PIP.[1m]

3. Conclusions

We have examined the influence of several steric and electronic factors on the activity and enantioselectivity of a series of chiral catalysts derived from the DHIP core. The currently available data indicate the following:

(1) A conformationally unrestricted phenyl group at C2 provides by far the highest levels of enantioselectivity;
(2) Substitution at C8 is highly detrimental to both the catalytic activity and the enantioselectivity of DHIP catalysts;
(3) Trifluoromethyl is the optimal C6-substituent in the DHIP series, bromine being the second best;
(4) All three DHIQ-based catalysts examined are considerably more active than CF_3-PIP. Cl-PIQ is also more selective than the latter.

In conclusion, CF_3-PIP is likely to remain the best among the first-generation DHIP-based catalysts—at least those that can be conveniently prepared from commercially available starting materials. On the other hand, the second generation of enantioselective catalysts, based on the DHIQ core and represented so far by only three members, already offers significant improvement over the DHIP catalysts. There is little doubt that the structure-selectivity and structure-activity trends originally discovered and studied in the DHIP series will be applicable to DHIQ derivatives and thus will prove quite valuable for further optimization of our catalyst design.

4. Experimental

4.1. General methods

Preparation of catalysts **7a–d** and **28b**, methods of compound characterization, determination of ee by chiral HPLC and calculation of the selectivity factors and conversion in kinetic resolution have been described.[1n,11] (*R*)-enantiomer of phenyl ethyl carbinol was prepared by kinetic resolution of the racemic alcohol (on 5.0 g scale)

using 2 mol% of (*S*)-Cl-PIQ and was enantiomerically pure within the limits of HPLC detection (≥99.9% ee). Other reagents were obtained from commercial sources and used as received.

4.2. Preparation of the catalysts

4.2.1. (*R*)-*N*-(5-trifluoromethylpyridyl-2)-phenylalaninol (20a). Standard procedure A: a 25-mL pressure tube charged with 2-chloro-5-trifluoromethylpyridine **9** (493 mg, 2.72 mmol), (*R*)-(+)-phenylalaninol (345 mg, 2.28 mmol), *i*-Pr_2NEt (334 mg, 2.58 mmol) and a stir bar was flushed with nitrogen several times, stoppered and heated at 120±5 °C for 3 days. The tube was allowed to cool to room temperature, the contents was diluted with a small amount of CH_2Cl_2 and chromatographed (8% *i*-PrOH/hexanes) to afford 563 mg of white fluffy solid (84% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.54 (dd, J_1=8.8 Hz, J_2=2.2 Hz, 1H), 7.21–7.34 (m, 5H), 6.40 (d, J=8.8 Hz, 1H), 5.23 (s, 1H), 4.18–4.23 (m, 1H), 3.83 (dd, J_1=11.0 Hz, J_2=3.3 Hz, 1H), 3.69 (dd, J_1=11.0 Hz, J_2=6.0 Hz, 1H), 2.99 (dd, J_1=13.9 Hz, J_2=6.6 Hz, 1H), 2.91 (dd, J_1=13.9 Hz, J_2=7.7 Hz, 1H), 2.71 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 145.6 (q, J=4.5 Hz), 137.9, 134.6 (q, J=3.0 Hz), 129.3, 128.8, 126.8, 124.6 (q, J=270 Hz), 115.7 (q, J=33.2 Hz), 107.8, 64.4, 55.0, 37.5; IR (film, cm^{-1}): 3409 br, 1617, 1324; MS: HR-FAB calcd for $C_{15}H_{15}F_3N_2OLi$ ($M+Li^+$) *m/z*: 303.1297, found: 303.1302; mp 92.5–94.5 °C; $[\alpha]_D$ +37.4 (*c* 1.07, MeOH).

4.2.2. (*R*)-2-benzyl-6-trifluoromethyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (21a). Standard procedure B: a solution of **20a** (782 mg, 2.6 mmol) in 15 mL of $CHCl_3$ was treated with $SOCl_2$ (0.55 mL, 7.5 mmol) added dropwise at room temperature, then heated to reflux in an oil bath kept at 65 °C. After 1.5 h, the flask was taken out of the oil bath, allowed to cool somewhat and treated cautiously with 2–3 drops of MeOH (vigorous gas evolution!), then heated again for 5 min. The mixture was rotary evaporated and the evaporation residue was extracted with water. The aqueous extract was decanted from the gummy residue, brought to pH 7–8 with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (three times). More aqueous $NaHCO_3$/NaOH was added to the aqueous phase to pH 12 and extraction was continued until organic extracts were pale-yellow (four times). The organic phase was dried over Na_2SO_4 and then rotary evaporated. The crude mixture was chromatographed (20% *i*-PrOH, 2% NEt_3/hexanes) to give 545 mg of yellow solid (74% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.34 (m, 6H), 6.92 (dd, J_1=9.8 Hz, J_2=1.9 Hz, 1H), 6.45 (d, J=9.8 Hz, 1H), 4.47–4.58 (m, 1H), 3.94 (t, J=11.0 Hz, 1H), 3.73 (dd, J_1=11.0 Hz, J_2=8.0 Hz, 1H), 3.21 (dd, J_1=13.7 Hz, J_2=5.0 Hz, 1H), 2.71 (dd, J_1=13.7 Hz, J_2=9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 137.8, 133.8 (q, J=4.3 Hz), 132.0, 129.2, 128.5, 126.5, 123.8 (q, J=268 Hz), 115.3, 106.1 (q, J=34.6 Hz), 65.8, 53.7, 42.7; IR (film, cm^{-1}): 1666, 1335, 1283, 1150, 1105; MS: HR-FAB calcd for $C_{15}H_{13}F_3N_2$ ($M+H^+$) *m/z*: 279.1109, found: 279.1106; mp 122.5–123.5 °C; $[\alpha]_D$ +169 (*c* 1.10, MeOH).

4.2.3. (*R*)-*N*-(5-trifluoromethylpyridyl-2)-valinol (20b). Standard Procedure A was followed [237 mg (1.31 mmol) of **9**, 122 mg (1.18 mmol) of *R*-valinol, 0.185 g *i*-Pr_2NEt; 105±5 °C for 2 days; 10% *i*-PrOH/hexanes] to afford 188 mg of colorless oil. (64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (apparent s, 1H), 7.56 (dd, J_1=8.9 Hz, J_2=2.3 Hz, 1H), 6.51 (d, J=8.9 Hz, 1H), 5.10 (br d; J=5.8 Hz, 1H), 3.85–3.66 (m, 3H), 3.14 (s, 1H), 1.96 (octet; J=6.7 Hz, 1H), 1.00 (d, J=6.7 Hz, 3H), 0.99 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 145.4, 134.4, 124.4 (q, J=270.2 Hz), 115.3 (q, J=32.4 Hz), 107.3, 63.7, 59.3, 29.7, 19.2, 18.7; IR (film, cm^{-1}): 3434 (br), 1640; MS: HR-FAB calcd for $C_{11}H_{15}F_3N_2OLi$ ($M+Li^+$) *m/z*: 255.1297, found: 255.1298; $[\alpha]_D$ +48 (*c* 1.77, MeOH).

4.2.4. (*R*)-2-isopropyl-6-trifluoromethyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (21b). Standard procedure B was followed [93 mg (0.38 mmol) **20b**, 0.08 mL $SOCl_2$, 2 mL of $CHCl_3$; 20% *i*-PrOH, 2% NEt_3/hexanes] to afford 45 mg of product (52% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (apparent s; 1H), 6.87 (dd, J_1=9.7 Hz, J_2=2.0 Hz, 1H), 6.40 (d, J=9.7 Hz, 1H), 4.05–3.94 (m, 2H), 3.69 (dd, J_1=16.2 Hz, J_2=13.7 Hz, 1H), 1.79 (octet; J=6.6 Hz, 1H), 1.00 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 133.6 (q, J=3.7 Hz), 13.8, 123.7 (q, J=268.5 Hz), 115.2, 106.0 (q, J=34.6 Hz), 70.5, 52.0, 33.4, 18.5, 17.9; IR (film, cm^{-1}): 1664, 1334; MS: HR-FAB calcd for $C_{11}H_{14}F_3N_2$ ($M+H^+$) *m/z*: 231.1109, found: 231.1116; mp 75–76.5 °C; $[\alpha]_D$ +63 (*c* 2.0, MeOH).

4.2.5. (*R*)-*N*-(5-trifluoromethylpyridyl-2)-*tert*-leucinol (20c). Standard procedure A was followed [403 mg (2.22 mmol) of **9**, 243 mg (2.07 mmol) of (*S*)-*tert*-leucinol, 330 mg *i*-Pr_2NEt; 120±5 °C for 3 days; 7% *i*-PrOH/hexanes] to afford 277 mg of white fluffy solid (51% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.59 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 6.57 (d, J=8.8 Hz, 1H), 5.16 (d, J=7.4 Hz, 1H), 3.98 (dd, J_1=11.0 Hz, J_2=3.3 Hz, 1H), 3.84 (ddd, J_1=8.5 Hz, J_2=7.4 Hz, J_3=3.3 Hz, 1H), 3.60 (dd, J_1=11.0 Hz, J_2=8.5 Hz, 1H), 2.58 (s, br, 1H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 145.6 (q, J=4.3 Hz), 134.7 (q, J=3.2 Hz), 124.6 (q, J=270 Hz), 115.5 (q, J=33.2 Hz), 107.2, 63.4, 62.4, 34.5, 27.1; IR (film, cm^{-1}): 3329 (br), 1618, 1325; MS: HR-FAB calcd for $C_{12}H_{17}F_3N_2OLi$ ($M+Li^+$) *m/z*: 269.1453, found: 269.1445; mp 109.5–110.5 °C; $[\alpha]_D$ +15.0 (*c* 1.10, MeOH).

4.2.6. (*S*)-2-*tert*-butyl-6-trifluoromethyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (21c). Standard procedure B was followed [101 mg (0.385 mmol) of **20c**, 0.071 mL $SOCl_2$, 3 mL $CHCl_3$; 5% *i*-PrOH, 0.5% NEt_3/hexanes] to afford 82 mg of yellow crystalline product (86% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.84 (dd, J_1=9.9 Hz, J_2=2.2 Hz, 1H), 6.37 (d, J=9.9 Hz, 1H), 3.73–3.99 (m, 3H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 133.8 (q, J=3.7 Hz), 131.8, 124.0 (q, J=269 Hz), 115.4, 105.9 (q, J=34.6 Hz), 74.5, 50.5, 34.3, 25.8; IR (film, cm^{-1}): 1665, 1340, 1327, 1281, 1150, 1106; MS: HR-FAB calcd

for $C_{12}H_{16}F_3N_2$ ($M+H^+$) *m/z*: 245.1266, found: 245.1277; mp 55–56 °C; $[\alpha]_D$ −187 (*c* 1.01, MeOH).

4.2.7. (1*R*, 2*S*)-1-[(5-trifluoromethylpyridyl-2)-amino]-2-indanol (20d). Standard procedure A was followed [576 mg (3.17 mmol) of **9**, 448 mg (3.00 mmol) of (1*R*, 2*S*)-1-amino-2-indanol **19d**, 475 mg of *i*-Pr_2NEt; 105±5 °C for 2 days; 8% *i*-PrOH/hexanes] 640 mg of grayish solid 9 (73% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.65 (dd, J_1= 8.8 Hz, J_2=2.5 Hz, 1H), 7.22–7.31 (m, 4H), 6.63 (d, *J*= 8.8 Hz, 1H), 5.60 (d, *J*=7.4 Hz, 1H), 5.47 (dd, J_1=7.4 Hz, J_2=5.2 Hz, 1H), 4.77 (td, J_1=5.2 Hz, J_2=2.9 Hz, 1H), 3.24 (dd, J_1=16.4 Hz, J_2=5.2 Hz, 1H), 3.04 (dd, J_1= 16.4 Hz, J_2=2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 146.0 (q, *J*=4.0 Hz), 141.2, 140.3, 134.7 (q, *J*= 2.9 Hz), 128.5, 127.3, 125.6, 124.7 (q, *J*=271 Hz), 124.6, 116.2 (q, *J*=33.2 Hz), 107.5, 73.8, 60.0, 39.8; IR (film, cm^{-1}): 3331 (br), 1617, 1325; MS: HR-FAB calcd for $C_{15}H_{13}F_3N_2OLi$ ($M+Li^+$) *m/z*: 301.1140, found: 301.1137; mp 130.5–133 °C (partially decomposed before mp); $[\alpha]_D$ −10.1 (*c* 1.00, MeOH).

4.2.8. (4b*R*, 10a*S*)-8-trifluoromethyl-4b, 10a-dihydro-11*H*-indeno[1′, 2′, 4, 5]imidazo [1,2-*a*]pyridine (21c). General procedure B was followed, except that the $SOCl_2$ was added in two portions and the mixture was refluxed overnight [152 mg (0.517 mmol) of **20c**, 2×0.092 mL $SOCl_2$, 3 mL $CHCl_3$; 5% *i*-PrOH, 1% NEt_3/hexanes] to afford 43 mg of yellow solid (31% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J*=6.9 Hz, 1H), 7.37 (s, 1H), 7.21–7.31 (m, 3H), 6.83 (dd, J_1=9.9 Hz, J_2= 7.4 Hz, 1H), 6.36 (d, *J*=9.9 Hz, 1H), 5.67 (d, *J*=9.3 Hz, 1H), 4.92 (dd, J_1=9.3 Hz, J_2=7.4 Hz, 1H), 3.61 (dd, J_1= 17.0 Hz, J_2=7.4 Hz, 1H), 3.25 (d, *J*=17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 143.3, 138.7, 132.8 (q, *J*= 5.4 Hz), 131.9, 128.5, 128.2, 125.6, 125.1, 123.9 (q, *J*= 269 Hz), 116.4, 107.4 (q, *J*=34.6 Hz), 76.2, 64.1, 40.3; IR (film, cm^{-1}): 1661, 1332, 1161, 1145, 1108, 1054; MS: HR-FAB calcd for $C_{15}H_{12}F_3N_2$ ($M+H^+$) *m/z*: 277.0953, found: 277.0951; mp 121–123.5 °C (partially decomposed before mp); $[\alpha]_D$ +636 (*c* 0.99, MeOH).

4.2.9. (*R*)-*N*-(5-diethylcarbamoyl-pyridyl-2)-phenylglycinol (6e). (a) 6-Chloro-*N*,*N*-diethyl-nicotinamide **22**[12] was prepared from 6-chloronicotinoyl chloride (1.01 g, 5.7 mmol) and diethylamine (3.0 mL, 29 mmol) in 5 mL CH_2Cl_2. 1.06 g (88% yield) was obtained after chromatography (20% *i*-PrOH/hexanes).

(b) General procedure A was followed [719 mg (3.38 mmol) of 6-chloro-*N*,*N*-diethyl-nicotinamide **22**, 619 mg (4.52 mmol) of (*R*)-phenylglycinol **5**, 725 mg of *i*-Pr_2NEt; 150 °C for 3 days; 20% *i*-PrOH/hexanes to afford 817 mg of the product (77% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J*=1.7 Hz, 1H), 7.20–7.38 (m, 6H), 6.21 (d, *J*=8.5 Hz, 1H), 5.01 (s, br, 1H), 4.77 (m, 1H), 3.87 (dd, J_1=11.3 Hz, J_2=3.0 Hz, 1H), 3.75 (dd, J_1=11.3 Hz, J_2=7.4 Hz, 1H), 3.38 (q, *J*=6.2 Hz, 4H), 1.15 (t, *J*=6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 158.8, 146.3, 139.9, 136.4, 128.3, 127.1, 126.5, 121.0, 106.7, 66.4, 58.3, 25.0, 13.3; IR (film, cm^{-1}): 3330 (br), 1607; MS: HR-FAB calculated for $C_{18}H_{23}N_3O_2Li$ ($M+Li^+$) *m/z*: 320.1950, found: 320.1953; $[\alpha]_D$ −71.7 (*c* 0.99, MeOH).

4.2.10. (*R*)-5-diethylcarbamoyl-2-phenyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (7e). A solution of 63 mg (0.20 mmol) of **6e** in anhydrous CH_2Cl_2 (2 mL) was cooled to 0 °C under N_2 atmosphere and NEt_3 (0.085 mL, 0.61 mmol) was added followed by MsCl (0.024 mL, 0.31 mmol). The mixture was stirred at 0 °C for 1 h. The solvent was removed and residue was extracted with warm water. The aqueous extract was decanted from the residue, brought to pH 7–8 with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. More aqueous $NaHCO_3$/NaOH was added to the aqueous phase to pH 12 and extraction was continued until organic extracts were pale-yellow. The organic phase was dried over Na_2SO_4 and then rotary evaporated. The crude mixture was chromatographed (30% *i*-PrOH, 3% NEt_3/hexanes) to give 40 mg of yellow solid (68% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J*=1.9 Hz, 1H), 7.27–7.38 (m, 5H), 7.00 (dd, J_1=9.6 Hz, J_2=1.9 Hz, 1H), 6.51 (d, *J*=9.6 Hz, 1H), 5.31 (dd, J_1=11.3 Hz, J_2=8.5 Hz, 1H), 4.46 (dd, J_1=11.3 Hz, J_2=11.0 Hz, 1H), 3.93 (dd, J_1=11.0 Hz, J_2=8.5 Hz, 1H), 3.41 (q, *J*=7.1 Hz, 4H), 1.20 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 156.7, 143.7, 136.0, 135.9, 128.7, 127.4, 126.5, 113.2, 113.1, 67.0, 57.2, 41.6, 13.5; IR (film, cm^{-1}):1653, 1609; MS: HR-FAB calcd for $C_{18}H_{22}N_3O$ ($M+H^+$) *m/z*: 296.1763, found: 296.1757; $[\alpha]_D$ +256 (*c* 1.13, MeOH).

4.2.11. (*R*)-*N*-(5-cyanopyridyl-2)-phenylglycinol (6f). A solution of 277 mg (2.00 mmol) of 2-chloro-5-cyanopyridine **23**, 274 mg (2.00 mmol) of (*R*)-phenylglycinol **5** and 300 mg of *i*-Pr_2NEt in 1 mL of *i*-PrOH was heated to reflux in an oil bath kept at 100 °C. After 12 h, the flask was cooled and the solvent was removed under reduced pressure. 302 mg (63% yield) of colourless oil was produced after chromatography (EtOAc/hexanes=1:1→2.5:1).

^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J*=2.2 Hz, 1H), 7.46 (dd, J_1=8.8 Hz, J_1=2.2 Hz, 1H), 7.26–7.38 (m, 5H), 6.32 (s, 1H), 6.29 (d, *J*=8.8 Hz, 1H), 4.88 (m, 1H), 3.97 (dd, J_1=11.3 Hz, J_2=4.1 Hz, 1H), 3.87 (dd, J_1=11.3 Hz, J_2= 6.6 Hz, 1H), 3.23 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 152.8, 139.8, 138.9, 129.0, 128.0, 126.7, 118.4, 107.5, 97.1, 66.4, 58.1; IR (film, cm^{-1}): 3348 (br), 2218, 1605, 1509; MS: HR-FAB calcd for $C_{14}H_{13}N_3OLi$ ($M+Li^+$) *m/z*: 246.1219, found: 246.1222; mp 132–133 °C (partially decomposed before mp); $[\alpha]_D$ −131 (*c* 1.13, MeOH).

4.2.12. (*R*)-6-cyano-2-phenyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (7f). Standard procedure B was followed [181 mg (0.757 mmol) of **6f**, 0.14 mL of $SOCl_2$, 3.8 mL of $CHCl_3$; 20% *i*-PrOH, 2% NEt_3/hexanes] to afford 126 mg of yellow solid (75% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J*=1.7 Hz, 1H), 7.26–7.40 (m, 5H), 6.88 (dd, J_1=9.9 Hz, J_2=1.7 Hz, 1H), 6.48 (d, *J*=9.9 Hz, 1H), 5.34 (dd, J_1=11.3 Hz, J_2=8.7 Hz, 1H), 4.26 (t, *J*=11.3 Hz, 1H), 3.92 (dd, J_1=11.3 Hz, J_2=

8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 142.9, 141.9, 135.5, 128.9, 127.8, 126.5, 117.5, 115.4, 87.6, 67.7, 57.0; IR (film, cm^{-1}): 2215, 1653; MS: HR-FAB calcd for $C_{14}H_{12}N_3$, ($M+H^+$) *m/z*: 222.1031, found: 222.1026; $[\alpha]_D$ +370 (*c* 1.09, MeOH).

4.2.13. (*R*)-*N*-(3-fluoropyridyl-2)-phenylglycinol (6g). Standard procedure A was followed [530 mg (4.03 mmol) of 2-chloro-3-fluoropyridine **24**, 466 mg (3.40 mmol) of **5**, 0.89 mL of *i*-Pr_2NEt; 165±5 °C for 2.5 days, 40% EtOAc/hexanes] to afford 363 mg of colorless liquid product (46% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.25–7.40 (m, 5H), 7.15 (ddd, J_1=11.0 Hz, J_2=7.7 Hz, J_3=1.4 Hz, 1H), 6.51–6.57 (m, 1H), 5.22 (s, br, 1H), 5.11–5.14 (m, 1H), 4.64 (br s, 1H), 3.94 (d, J=6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6 (d, J=11.5 Hz), 147.5 (d, J=252 Hz), 142.4 (d, J=6.0 Hz), 140.4, 128.9, 127.8, 126.9, 120.7 (d, J=15.2 Hz), 112.8, 67.9, 58.3; IR (film, cm^{-1}): 3427 (br), 1622, 1504; MS: HR-FAB calcd for $C_{13}H_{13}FN_2OLi$ ($M+Li^+$) *m/z*: 239.1172, found: 239.1173; $[\alpha]_D$ −121 (*c* 1.06, MeOH).

4.2.14. (*R*)-8-fluoro-2-phenyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (7g). Standard procedure B was followed [62 mg (0.27 mmol) of **6g**, 0.049 mL of $SOCl_2$, 2 mL of $CHCl_3$; 20% *i*-PrOH, 2% NEt_3/hexanes] to afford 44 mg of yellow oil after chromatography (77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H), 6.89 (J=6.9 Hz, 1H), 6.66 (dd, J_1=9.9 Hz, J_2=6.9 Hz, 1H), 5.66 (m, 1H), 5.36 (dd, J_1=11.5 Hz, J_2=9.5 Hz, 1H), 4.50 (t, J=11.5 Hz, 1H), 3.98 (t, J=9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (d, J=26.0 Hz), 149.5 (d, J=253 Hz), 143.9, 129.5 (d, J=4.9 Hz), 128.5, 127.2, 126.5, 116.8 (d, J=14.9 Hz), 100.7 (d, J=4.9 Hz), 67.6, 57.7; IR (film, cm^{-1}): 1659, 1577, 1547; MS: HR-FAB calcd for $C_{13}H_{12}FN_2$ ($M+H^+$) *m/z*: 215.0985, found: 215.0983; $[\alpha]_D$ +385 (*c* 1.09, MeOH).

4.2.15. (*R*)-*N*-(3, 5-dibromopyridyl-2)-phenylglycinol (6h). A literature procedure[10] was used. A solution of 112 mg (0.523 mmol) *N*-pyridyl-phenylglycinol **6a**[1n] in 2.5 mL of CH_3CN was treated with 187 mg (1.05 mmol) of *N*-bromosuccinimide. The mixture was stirred at room temperature for 2 h, and then concentrated and chromatographed (15→20% EtOAc/hexanes) to afford 189 mg of white solid (98% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=2.2 Hz, 1H), 7.76 (d, J=2.2 Hz, 1H), 7.27–7.41 (m, 5H), 5.74 (d, J=6.6 Hz, 1H), 5.17–5.22 (m, 1H), 3.91–4.01 (m, 2H), 2.81 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 147.1, 141.6, 140.0, 128.9, 127.8, 126.8, 106.5, 106.0, 67.1, 57.9; IR (film, cm^{-1}): 3411 (br), 1579, 1490; MS: HR-FAB calcd for $C_{13}H_{12}Br_2ON_2Li$, ($M+Li^+$) *m/z*: 376.9476, found: 376.9480; $[\alpha]_D$ −5.0 (*c* 1.11, MeOH).

4.2.16. (*R*)-6, 8-dibromo-2-phenyl-2, 3-dihydroimidazo[1,2-*a*]pyridine (7h). Standard procedure B was followed [355 mg (0.954 mmol) of **6h**, 0.18 mL $SOCl_2$, 5 mL $CHCl_3$] to afford 295 mg of yellow solid (88% yield). The crude product is pure by ^{1}H NMR. If necessary it may be chromatographed (30% EtOAc, 1.5% NEt_3/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.37 (m, 6H), 7.10 (d, J=1.9 Hz, 1H), 5.33 (dd, J_1=11.5 Hz, J_2=8.8 Hz, 1H), 4.51 (dd, J_1=11.5 Hz, J_2=11.0 Hz, 1H), 3.99 (dd, J_1=11.0 Hz, J_2=8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 143.6, 141.4, 133.1, 128.8, 127.6, 126.8, 109.2, 92.9, 67.0, 59.7; IR (film, cm^{-1}): 1635, 1557; MS: HR-FAB calcd for $C_{13}H_{11}Br_2N_2$, ($M+H^+$) *m/z*: 352.9289, found: 352.9301; mp 147–149 °C (dec); $[\alpha]_D$ +183 (*c* 1.12, MeOH).

4.2.17. (*R*)-*N*-(quinolyl-2)-phenylglycinol (27a). Standard procedure A was followed (0.144 g, 0.880 mmol) of 2-chloroquinoline **26a**, 0.128 g (0.933 mmol) of (*R*)-phenylglycinol **5**, 0.156 g (1.20 mmol) of *i*-Pr_2NEt; 130± 5 °C for 43 h; 5→10% *i*-PrOH, 1% NEt_3/hexanes to afford 0.183 g of white solid (78% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J=9.1 Hz, 1H), 7.76–7.23 (m, 9H), 6.69 (d, J=9.1 Hz, 1H), 6.2 (br s, 1H), 5.5 (br s, 1H), 5.11 (br apparent d; J=3.0 Hz, 1H), 4.07 (dd, J_1=11.5 Hz, J_2=8.0 Hz, 1H), 3.99 (dd, J_1=11.5 Hz, J_2=3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 145.8, 140.1, 138.3, 130.2, 129.0, 128.0, 127.5, 126.8, 125.0, 123.2, 122.9, 112.0, 68.6, 60.2; IR (film, cm^{-1}): 3260 (br), 1608, 1620; MS: HR-FAB calcd for $C_{17}H_{16}N_2OLi$ ($M+Li^+$) *m/z*: 271.1423, found: 271.1425; mp 178.5–180 °C; $[\alpha]_D$ −173 (*c* 0.25, MeOH).

4.2.18. (*R*)-2-phenyl-1,2-dihydroimidazo[1,2-*a*]quinoline (28a). A slightly modified procedure B was followed. A solution of 105 mg (0.397 mmol) of **27a**, in 2 mL of $CHCl_3$ was treated with 0.23 mL (3.15 mmol) of $SOCl_2$ and heated to reflux. After 1.5 h, the solution was allowed to cool, treated with a few drops of MeOH, and then heated again for 10 min. The reaction mixture (without prior rotary evaporation) was treated with aqueous $NaHCO_3$ until the aqueous phase reached pH 8, then with 1 M NaOH to pH 14, and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4, concentrated, and chromatographed (10% IPA, 2% NEt_3/hexanes) to afford 847 mg of yellow oil (87%), which later crystallized.

^{1}H NMR (300 MHz, CD_3CN) δ 7.38–7.24 (m, 8H), 6.94 (td, J_1=7.4 Hz, J_2=1.1 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 6.53 (d, J=9.9 Hz, 1H), 5.28 (dd, J_1=11.4 Hz, J_2=8.8 Hz, 1H), 4.38 (dd, J_1=11.4 Hz, J_2=10.4 Hz, 1H), 3.74 (dd, J_1=10.4 Hz, J_2=8.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3CN) δ 157.2, 146.3, 140.5, 137.8, 131.5, 129.6, 129.2, 128.0, 127.8, 122.0, 120.9, 118.0, 112.8, 68.9, 54.8; IR(film, cm^{-1}): 1638, 1573, 1457; MS: HR-FAB calcd for $C_{17}H_{15}N_2$ ($M+H^+$) *m/z*: 247.1235, found: 247.1233; mp 130.5–132 °C; $[\alpha]_D$ +675 (*c* 0.26, MeOH).

4.2.19. (*R*)-*N*-(7-chloroquinolyl-2)-phenylglycinol (27b). Standard procedure A was followed, except for the workup [1.352 g (6.83 mmol) of 2,6-dichloroquinoline, 0.964 g, (7.03 mmol) of (*R*)-phenylglycinol **5**, 0.991 g (7.67 mmol) of *i*-Pr_2NEt; 130±5 °C for 2.5 days]. The tube was allowed to cool to room temperature and the content was diluted with CH_2Cl_2, which led to precipitation of a white solid. The

mixture was washed with saturated aqueous NH_4Cl to remove *i*-Pr_2NEt and then with saturated aqueous $NaHCO_3$. The solution was dried over Na_2SO_4 and evaporated to afford 1.770 g of the crystalline product (87%), which was sufficiently pure for the next step. If necessary, the product can be chromatographed (6% *i*-PrOH, 0.8% NEt_3/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=9 Hz, 1H), 7.62 (d, J=8.7 Hz, 1H), 7.62 (d, J=8.7 Hz, 1H), 7.55 (d, J=2.2 Hz, 1H), 7.48 (dd, J_1=9 Hz, J_2=2.2 Hz, 1H), 7.28–7.45 (m, 5H), 6.67 (d, J=9 Hz, 1H), 5.85 (s, 1H), 5.16 (dt, J_1=7.4 Hz, J_2=3.6 Hz, 1H), 4.05 (dd, J_1=11.3 Hz, J_2=7.4 Hz, 1H), 3.00 (dd, J_1=11.3 Hz, J_2=3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 144.8, 140.0, 137.0, 130.5, 129.0, 128.05, 127.98, 126.88, 126.81, 126.2, 123.9, 113.0, 68.3, 59.8; IR (film, cm^{-1}) 3316 (br) 1618.7, 1498.6, 1398.4; MS: HR-EI calcd for $C_{17}H_{15}ClN_2O$ (M^+) *m/z*: 298.0873, found: 298.0904; mp 172–174 °C; $[\alpha]_D$ −154 (*c* 0.26, MeOH).

4.2.20. (*R*)-7-chloro-2-phenyl-1,2-dihydroimidazo[1,2-*a*]quinoline (28b). Procedure described for **28a** was followed (365 mg, 1.22 mmol) of **27b**, 0.23 mL of $SOCl_2$, 6.4 mL of $CHCl_3$ to afford 311 mg of the product (91% yield) as yellow oil, which crystallized on standing.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 8H), 6.76 (d, J=9.3 Hz, 1H), 6.65 (d, J=8.8 Hz, 1H), 5.40 (dd, J_1=11.4 Hz, J_2=8.4 Hz, 1H), 4.40 (dd, J_1=11.4 Hz, J_2=10.3 Hz, 1H), 3.88 (dd, J_1=10.3 Hz, J_2=8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 143.9, 137.5, 135.8, 130.2, 128.7, 127.5, 127.4, 126.6, 125.4, 122.2, 118.4, 112.7, 67.7, 54.1; IR (film, cm^{-1}) 1640.3, 1568.9, 1433.9; MS: HR-EI calcd for $C_{17}H_{13}ClN_2$ (M^+) *m/z*: 280.0767, found: 280.0770; mp 134–136 °C; $[\alpha]_D$ +746 (*c* 0.27, MeOH).

4.2.21. (*R*)-*N*-(4-methylquinolyl-2)-phenylglycinol (27c). Standard procedure A was followed [212 mg (1.19 mmol) of 2-chloro-4-methylquinoline, 170 mg (1.24 mmol) of (*R*)-phenylglycinol **5**, 208 mg, of *i*-Pr_2NEt; 130±5 °C for 46 h; 5→10% *i*-PrOH, 1% NEt_3/hexanes to afford 328 mg of white solid (99% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, J_1=12.9 Hz, J_2=8.0 Hz, 2H), 7.53 (t, J=8.0 Hz, 1H), 7.42–7.23 (m, 6H), 6.45 (s, 1H), 5.10 (dd, J_1=7.4 Hz, J_2=3.3 Hz, 1H), 4.02 (dd, J_1=11.0 Hz, J_2=7.4 Hz, 1H), 3.97 (dd, J_1=11.0 Hz, J_2=3.3 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 146.4, 145.9, 140.4, 129.6, 129.0, 127.9, 126.8, 125.9, 123.7, 123.5, 122.5, 112.0, 68.8, 60.2, 18.7; IR (film, cm^{-1}): 3317 (br), 1617, 1494; MS: HR-FAB calcd for $C_{18}H_{18}N_2OLi$ ($M+Li^+$) *m/z*: 285.1579, found: 285.1572; mp 168–170 °C; $[\alpha]_D$ −145 (*c* 0.26, MeOH);

4.2.22. (*R*)-5-methyl-2-phenyl-1,2-dihydroimidazo[1,2-*a*]quinoline (28c). Procedure described for **28a** was followed (106 mg (0.381 mmol) of **27c**, 0.07 mL of $SOCl_2$, 2 mL of $CHCl_3$) to afford 0.0758 g of the product (77% yield).

^{1}H NMR (300 MHz, CD_3CN) δ 7.52 (dd, J_1=7.7 Hz, J_2=1.1 Hz, 1H), 7.40–7.23 (m, 6H), 6.98 (td, J_1=7.7 Hz; J_2=1.1 Hz, 1H), 6.79 (dd, J_1=8.0 Hz, J_2=0.7 Hz, 1H), 6.45 (d, J=1.1 Hz, 1H), 5.25 (dd, J_1=11.3 Hz, J_2=8.6 Hz, 1H), 4.39 (dd, J_1=11.3 Hz, J_2=10.4 Hz, 1H), 3.74 (dd, J_1=10.4 Hz, J_2=8.6 Hz, 1H), 2.34 (d, J=1.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 157.0, 146.4, 145.1, 140.1, 131.3, 129.5, 128.0, 127.8, 126.0, 122.5, 120.7, 116.6, 113.0, 68.6, 55.0, 19.5; IR (film, cm^{-1}): 1643, 1574, 1459, 1399; MS: HR-FAB calcd for $C_{18}H_{17}N_2$ ($M+H^+$) *m/z*: 261.1392, found: 261.1404; mp 118.5–120 °C; $[\alpha]_D$ +525 (*c* 0.33, MeOH).

4.3. Kinetic resolutions and measurements

4.3.1. Variation of the C2 substituent (Table 2). The previously published procedure[1n] was followed exactly. The data obtained from individual runs are given in (Table 4).

4.3.2. Variation of substitution on the pyridine ring. The stock solution of each catalyst was prepared by dissolving 0.05 mmol of the catalyst (**7a–h** and **28a–c**) and 98 mg (0.75 mmol) of *i*-Pr_2NEt in $CDCl_3$ in a 1.00 mL volumetric test tube and bringing the volume to the mark.

4.3.3. Enantioselectivity test (Table 3). A one dram vial was charged with 68 μL (0.50 mmol) of (±)-phenyl ethyl carbinol and 0.50 mL of the stock solution of the catalyst. 48 μL (0.375 mmol) of propionic anhydride was added (at which point the timing was started), the contents was mixed and transferred into a 5 mm NMR tube. The reaction was monitored by ^{1}H NMR at room temperature by comparing integration values of peaks at δ 4.5 and δ 5.6 ppm and stopped by pouring the contents into a vial with MeOH upon reaching conversion of 45–50%. Further workup procedure and determination of ee's of the product and the unreacted alcohol have been previously described.[1n]

Table 4

Catalyst	Expt (#)	% ee_E	% ee_A(%)	% C_{HPLC}(%)	*S*
6c	1	90.4	60.8	40.2	36.8
	2	90.6	57.2	38.7	36.0
21a	1	55.2	35.1	38.9	4.8
	2	57.1	33.2	36.8	5.0
21b	1	51.7	21.7	29.6	3.9
	2	51.2	24.7	32.5	3.9
21c	1	−32.5	—[a]	7[b]	−2.0
	2	−30.2	—[a]	7[b]	−1.9
21d	1	−14.1	−16.4	53.7	−1.5
	2	−14.1	−22.3	61.3	−1.6

[a] Too low for a reliable measurement by HPLC.
[b] Estimated from the ^{1}H NMR spectra of the crude reaction mixtures and used to calculate the selectivity factor.[4]

4.3.4. Half-life measurements (Table 3). The procedure described above was followed, except 34 μL (0.25 mmol) of (*R*)-phenyl ethyl carbinol was used instead of 68 μL of the racemate. The conversion was checked at appropriate intervals and plotted versus time. The $t_{1/2}$ value was determined from the resulting graph.

Acknowledgements

We gratefully acknowledge financial support of this study provided by NIGMS (NIH Grant R01 GM072682) and Washington University. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

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Tetrahedron 62 (2006) 295–301

Rapid, room-temperature acylative kinetic resolution of *sec*-alcohols using atropisomeric 4-aminopyridine/triphenylphosphine catalysis

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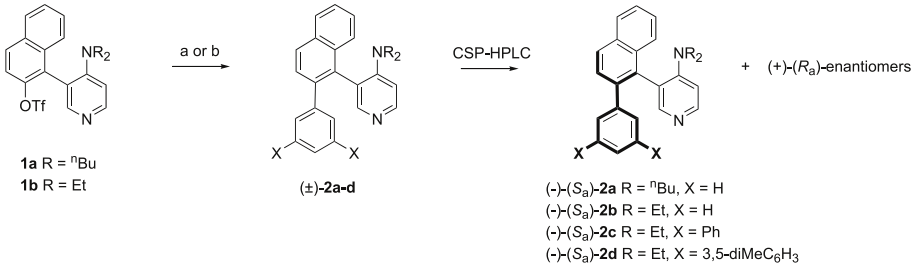
Received 16 May 2005; revised 29 July 2005; accepted 31 August 2005

Available online 7 November 2005

Abstract—Two new atropisomeric 4-aminopyridine-based nucleophilic catalysts containing terphenyl 'blocking groups' have been prepared and evaluated for kinetic resolution (KR) of aryl alkyl *sec*-alcohols. One of these biaryls is shown to be the most selective atropisomeric catalyst yet prepared for several *sec*-alcohols but its low reactivity makes it non-optimal for use at room temperature (rt). Optimisation of the conditions for conducting KRs at rt using a previously described catalyst (containing a phenyl blocking group) at the 1 mol% level indicates that PPh_3 (1 equiv) is beneficial for enantioselectivity and allows KR of (±)-1-(naphthyl)ethanol in less than 30 min with $s > 15$ (i.e., ~40% recovered alcohol with >95% ee). These conditions constitute a convenient and practical method for rapid KR of *sec*-alcohols and are anticipated to facilitate a detailed kinetic study of this catalytic manifold by calorimetry.

1. Introduction

The kinetic resolution (KR) of alcohols by enantioselective esterification using small-molecule nucleophilic chiral catalysts in combination with acid anhydrides or chlorides has been studied by an increasing number of groups over the past decade.[1–3] Indeed, this research area has been in the vanguard of the contemporary 'organocatalysis' renaissance,[4] and a number of attractive and practical KR protocols for a range of *sec*-alcohols have resulted.[5–9] Research from our laboratory has focused on the development of axially chiral, atropisomeric derivatives of 4-aminopyridine and, in particular, 4-dialkylaminopyridines **2a** and **2b** (Scheme 1) as catalysts for the KR of



Scheme 1. Synthesis of catalysts **2a–d** from triflates **1a** and **1b**. Reagents and conditions: For **2a** and **2b** see Refs. 11 and 12, respectively. For **2c** and **1b**: (a) i. 3,5-diPh(C_6H_3)Br, Mg, THF; ii. $PdCl_2$ (dppp) [23%]; (b) 3,5-diPh(C_6H_3)$B(OH)_2$, $Pd(OAc)_2$, P(biph)Cy_2, LiCl, K_3PO_4, toluene [50%]. For **2d** from **1b**: (a) 3,5-di-(3,5-diMeC_6H_3)$C_6H_3B(OH)_2$ (**3**), P(biph)Cy_2, LiCl, K_3PO_4, toluene [39%].

Keywords: Nucleophilic catalysis; Asymmetric catalysis; Organocatalysis; Atropisomerism; Esterification; Acylation; *sec*-Alcohols.
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doi:10.1016/j.tet.2005.08.124

sec-alcohols.[10,11] A drawback to using these catalysts to date has been the requirement to conduct the experiments for relatively long durations (typically ~10 h) at low temperature (−78 °C). We describe herein our endeavours to achieve rapid KR at ambient temperature. This stemmed from our desire to make the transformation more practical on a process scale and to define conditions under which we could conveniently study the detailed kinetics of such KR processes by calorimetry.

2. Results and discussion

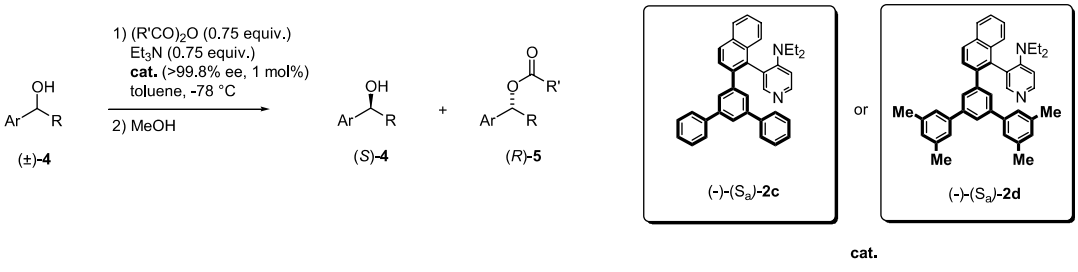
During the course of our studies towards the development of catalysts **2a** and **2b**, we prepared a related series of biaryls having an *N*-methyl-5-azaindoline catalytic core in place of the 4-dialkylaminopyridine.[12] Although this series of compounds give modest levels of enantioselectivity relative to **2b**, it was found that the presence of a terphenyl group at the 2-position of the naphthyl ring attached to the catalytic core gave improved enantioselectivity relative to its phenyl analogue. Reasoning that the improved stereoselectivity reflected more efficient facial discrimination between the front and back faces of the pyridine ring leading to increased $\Delta\Delta G^{\#}$ between the diastereomeric transition states for esterification, we were keen to investigate the performance of terphenyl-containing catalysts **2c** and **2d** relative to the parent compound **2b**. In particular, we were hopeful that these catalysts might allow for good levels of selectivity in KRs run at ambient temperature.

The synthesis of these two new catalysts **2c** and **2d** was achieved from triflate **1b** by either Kharasch or Suzuki-type coupling of the appropriate terphenyl Grignard reagent or boronic acid, respectively, followed by semi-preparative CSP-HPLC (Scheme 1). The absolute configurations of the atropisomeric axes were assigned using circular dichroism spectroscopy (see Section 4).[11]

Using the enantiomerically pure terphenyl catalysts **2c** and **2d**, a series of KR experiments were performed with an array of (±)-*sec*-alcohols **4a–f** as substrates (Table 1).

To allow direct comparison with results obtained with catalysts **2a** and **2b**, initial reactions were run at −78 °C in toluene under previously optimised conditions with the exception that acetic anhydride rather than isobutyric anhydride was employed as acyl donor.[10,12] Preliminary studies revealed that this led to higher levels of stereoselectivity across the board (e.g., $s=39$ vs $s=17$, respectively, for the use of catalyst **2c** with alcohol **4c**, entries 3 and 5; other data not shown). It can be seen that, despite their similar structures, terphenyl-containing catalyst **2c** is significantly more stereoselective than terphenyl-containing catalyst **2d** despite their similar structures. Catalyst **2c** is more stereoselective than phenyl-containing catalysts **2a** and **2b** for alcohols **4a**, **4c** and **4d** and similarly selective for the other alcohols. The rates of reactions catalysed by terphenyl-containing catalysts **2c** and **2d** are, however, lower by a factor of ~2 as compared to those catalysed by phenyl-containing catalysts **2a** and **2b**.

Table 1. KR of alcohols **4a–f** using enantiomerically pure biaryls **2c** and **2d**



Entry	Cat.	Alcohol, ester	**4**, **5**	Anhydride	Time (h)	(*S*)-**4**	(*R*)-**5**	C (%)[a]	s[b]	(s^{ref})[c]
			Ar, R	R′		ee_A (%)[d]	ee_E (%)[e]			
1[f]	**2c**	**4a**, **5a**	Ph, Me	Me	6.0	5.7	90.3	6	22	(13)
2	**2c**	**4b**, **5b**	Ph, Et	Me	9.0	17.1	83.2	17	13	(13)
3	**2c**	**4c**, **5c**	1-Nap, Me	Me	6.6	16.8	94.1	15	39	(29)
4	**2c**	**4c**, **5c**	1-Nap, Me	Me[g]	11.3	94.2	76.9	55	27	
5[f]	**2c**	**4c**, **5c**	1-Nap, Me	*i*-Pr	8.2	11.6	87.8	12	17	
6[f]	**2c**	**4d**, **4d**	2-MeC_6H_4, Me	Me	6.6	21.5	92.3	19	31	(25)
7	**2c**	**4e**, **5e**	2-$MeOC_6H_4$, Me	Me	6.6	5.8	90.8	6	22	(25)
8	**2c**	**4f**, **5f**	2,6-diMeC_6H_3, Me	Me	7.0	13.7	89.9	13	22	(25)
9[f]	**2d**	**4a**, **5a**	Ph, Me	Me	6.7	4.5	73.1	6	6.7	
10[f]	**2d**	**4c**, **5c**	1-Nap, Me	Me	6.8	10.6	85.1	11	14	
11	**2d**	**4d**, **4d**	2-MeC_6H_4, Me	Me	6.2	6.2	82.1	7	11	
12	**2d**	**4f**, **5f**	2,6-diMeC_6H_3, Me	Me	6.2	3.8	72.8	5	6.5	

[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ±2 in parallel runs.
[c] The s values in parentheses are those obtained for this substrate using catalyst **2b** with (^{i}PrCO)$_2$O (taken from Ref. 11).
[d] ee Of recovered alcohol, established by CSP-HPLC.
[e] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.
[f] The dextrorotatory enantiomer of catalyst was employed giving enantiomeric products to those shown.
[g] Ac_2O (2.5 equiv) used.

The modest increase in stereoselectivity and significant decrease in reactivity displayed by terphenyl-containing catalyst **2c** relative to phenyl-containing catalyst **2b** persuaded us to focus further studies on the more readily prepared and resolved catalyst **2b**. Our aim was to find optimal conditions for running rapid KR reactions with this catalyst at ambient temperature. Using (±)-1-(naphthyl)ethanol **4c** as a test substrate and isobutyric anhydride (0.5 equiv) as acyl donor we first surveyed the influence of the reaction solvent and auxiliary base on the KR process (Table 2).

Solvent screening (entries 1–7) in the absence of an auxiliary base revealed that the reactions conducted in *t*-amyl alcohol[14] (*t*-AmOH) and toluene (entries 1 and 2) reached completion (i.e., $C\sim50\%$, as limited by the amount of anhydride present) within 1 h and gave the highest levels of stereoselectivity. The reactions also reached completion in cyclohexane and THF but the stereoselectivities were reduced (entries 3 and 4). The reactions did not reach completion in DMF, CH_2Cl_2, or DMPU and, additionally, gave poor levels of enantioselectivity (entries 5–7).

Using both *t*-AmOH and toluene as solvents, Et_3N, pyridine, P4-*t*-Bu phosphazine [Schwessinger's base, *t*-BuN=P-(N=PNMe$_2$)$_3$],[15] 2,6-di-*t*-butylpyridine, 1,2,2,6,6-pentamethylpiperidine (PMP), K_2CO_3 and K_3PO_4 were surveyed as auxiliary bases (entries 8–21). With the exception of the reactions carried out using P4-*t*-Bu phosphazine base (entries 12 and 13), all the reactions reached completion and, although the levels of stereoselectivity did not vary dramatically, the use of 2,6-di-*t*-butyl pyridine gave the most stereoselective KRs in both solvent systems (entries 14 and 15).

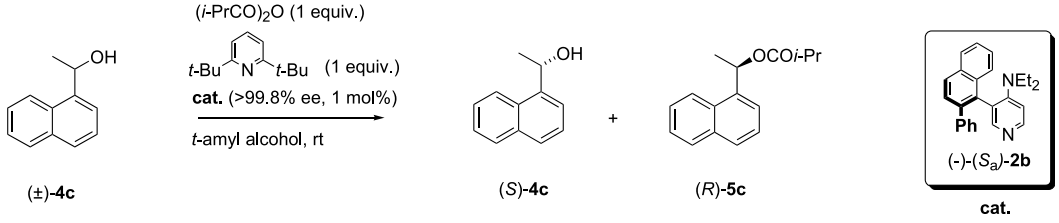
In order to determine the performance of these optimised conditions for KR at rt we conducted a larger scale KR of (±)-1-(naphthyl)ethanol **4c** using 1.0 rather than 0.5 equiv of isobutyric anhydride and removed aliquots for analysis by CSP-HPLC every 2 min (to 10 min), every 5 min (to 45 min) and at increasing intervals thereafter (to 20 h; Graphs 1 and 2) (Scheme 2).

The data show that the reaction reaches ~60% conversion in ~25 min under these conditions, and that at this point the ee of the recovered starting material is >95%.

Finally, we surveyed a number of achiral additives in order to optimise the selectivity further.[16] The reactions were performed using 0.5 equiv of isobutyric anhydride, 0.5 equiv of 2,6-di-*t*-butyl pyridine and 1 equiv of the additive in both *t*-amyl alcohol and toluene (Table 3).

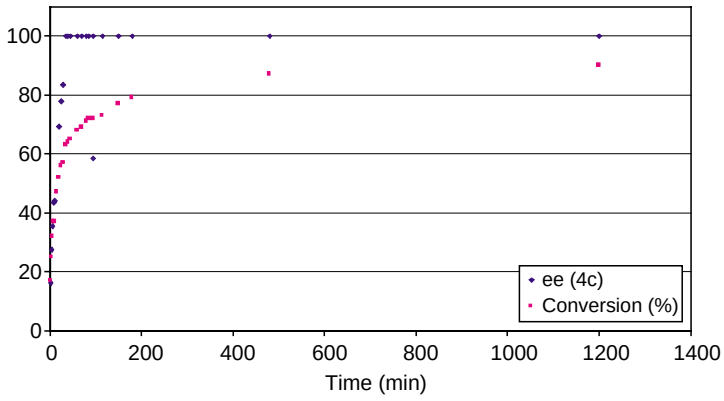
Surprisingly, given that Sc(OTf)$_3$ has been reported to act synergistically with 4-DMAP to accelerate esterification reactions,[17] this additive completely inhibited the reaction

Table 2. Effect of the solvent and auxiliary base on the KR of alcohol **4c** using catalyst **2b**

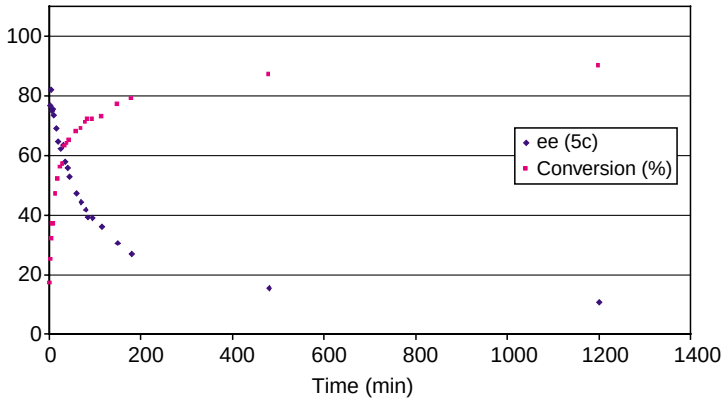


Entry	Base	Solvent	(*S*)-**4c**	(*R*)-**5c**	C (%)[a]	*s*[b]
			ee$_A$ (%)[c]	ee$_E$ (%)[d]		
1	None	*t*-AmOH	72.8	70.6	51	12.6
2		Toluene	68.4	68.6	50	10.8
3		Cyclohexane	46.0	45.4	50	4.1
4		THF	52.0	56.0	48	5.8
5		DMF	31.0	39.0	44	3.0
6		CH_2Cl_2	47.2	63.6	43	7.1
7		DMPU	16.0	34.0	32	2.4
8	NEt_3	*t*-AmOH	71.8	70.8	50	12.2
9		Toluene	69.7	63.7	52	9.1
10	Pyridine	*t*-AmOH	67.4	72.2	48	12.2
11		Toluene	64.0	66.6	49	9.5
12	P4-*t*-Bu-Phosphazene	*t*-AmOH	22.6	46.6	33	3.4
13		Toluene	10.4	17.2	38	1.6
14	2,6-di-(*t*-Bu)-Pyridine	*t*-AmOH	79.8	69.2	54	13.5
15		Toluene	71.0	68.4	51	11.1
16	1,2,2,6,6-PMP	*t*-AmOH	80.0	69.0	54	13.3
17		Toluene	69.0	65.2	51	9.5
18	K_2CO_3	*t*-AmOH	63.4	73.8	46	12.5
19		Toluene	62.6	66.4	49	9.4
20	K_3PO_4	*t*-AmOH	73.6	71.0	51	12.8
21		Toluene	68.0	65.6	51	9.6

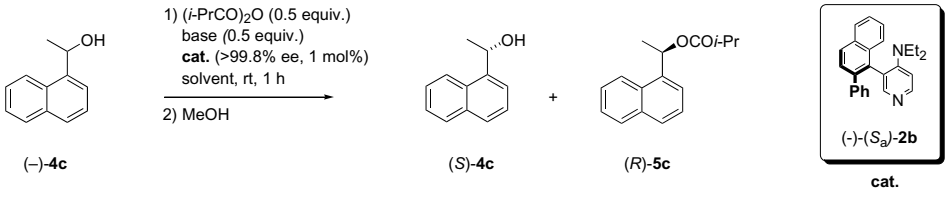
[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ±1 in parallel runs.
[c] ee Of recovered alcohol, established by CSP-HPLC.
[d] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.



Graph 1. ee Of **4c** and % conversion versus time.



Graph 2. ee Of **5c** and % conversion versus time.



Scheme 2.

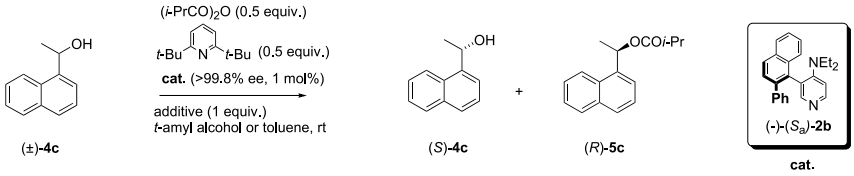
in both solvents (entries 1 and 2). The presence of 4 Å molecular sieves appeared to have no effect on the reaction (entries 3 and 4) and *n*-Bu_4NBr, 1-hydroxypyridine and HMPA were deleterious to the levels of selectivity in both solvents (entries 5–10). However, a small but reproducible increase in selectivity was observed in both solvents when using PPh_3 as an additive giving a selectivity of 15.5 in *t*-amyl alcohol and 13.5 in toluene (entries 11 and 12) compared to 13.5 and 11.1, respectively, when no additive was used (Table 2, entries 14 and 15). However, use of $P(O)Ph_3$, PEt_3, $P(4\text{-}FC_6H_4)_3$, $AsPh_3$ or $BiPh_3$ in place of the PPh_3 did not promote similar or further increases in stereoselectivity (entries 13–20).

Although the role of the PPh_3 is not clear at this time, its use in conjunction with 2,6-di-*t*-butyl pyridine/*t*-amyl alcohol allows for significantly more stereoselective KRs than under the conditions used as a starting point for this investigation (cf. Table 3, entry 11, $s=15.5$ and Table 2, entry 9, $s=9.1$).

3. Conclusions

Two approaches towards the development of efficient conditions for the rapid acylative KR of aryl alkyl *sec*-alcohols using atropisomeric 4-aminopyridine-based nucleophilic catalysts have been explored. Two new catalysts, **2c** and **2d**, containing terphenyl 'blocking groups' have been prepared and evaluated for this purpose. Catalyst **2c** was found to be more enantioselective than **2d**, and is the most selective atropisomeric catalyst yet described for KR of several *sec*-alcohols. The low reactivity of this catalyst, however, militates against its use for rapid KR at rt. Optimisation of the conditions for conducting KRs at rt using previously described catalyst **2b** at the 1 mol% level indicate that PPh_3 (1 equiv) is beneficial for selectivity and allows KR of (±)-1-(naphthyl)ethanol **4c** to occur in <30 min to give $\sim$40% recovered alcohol with $>95\%$ ee (i.e., $s\sim15$). This rapid KR process is expected to facilitate detailed kinetic studies by calorimetry; studies that we hope

Table 3. Effect of some additives on the KR of alcohol **4c** using catalyst **2b**



Entry	Additive	Solvent	(*S*)-**4c**	(*R*)-**5c**	C (%)[a]	*s*[b]
			ee_A (%)[c]	ee_E (%)[d]		
1	$Sc(OTf)_3$	*t*-AmOH	—	—	—	—
2		Toluene	—	—	—	—
3	MS (4 Å)	*t*-AmOH	73.8	72.4	50	13.3
4		Toluene	74.6	68.0	52	11.4
5	*n*-Bu_4NBr	*t*-AmOH	64.2	65.2	50	9.1
6		Toluene	61.4	60.6	50	7.4
7	2-Hydroxypyridine	*t*-AmOH	61.6	68.0	47	9.6
8		Toluene	50.2	56.4	47	5.8
9	HMPA	*t*-AmOH	76.2	69.0	52	11.1
10		Toluene	65.4	64.0	50	8.6
11	PPh_3	*t*-AmOH	81.4	72.4	53	15.5
12		Toluene	82.4	69.2	54	13.5
13	$P(O)Ph_3$	*t*-AmOH	71.0	70.1	50	12.3
14		Toluene	66.0	68.4	49	10.5
15	$AsPh_3$	*t*-AmOH	74.4	66.0	53	10.6
16		Toluene	62.2	63.4	50	7.9
17	$BiPh_3$	*t*-AmOH	69.2	66.3	51	10.0
18		Toluene	57.4	59.8	49	7.0
19	PEt_3	Toluene	64.2	71.0	47	11.1
20	$P(4\text{-}FC_6H_4)$	Toluene	74.0	62.0	54	9.0

[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ± 1 in parallel runs.
[c] ee Of recovered alcohol, established by CSP-HPLC.
[d] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.

will help unravel the complex interplay of factors responsible for catalysis and chirality transfer in these reactions,[18,19] and reveal the role of the PPh_3 additive.

4. Experimental

4.1. General procedures

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. Reagents were used as obtained from commercial sources or purified according to known procedures.[20] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230–400 mesh) silica gel. Only distilled solvents were used as eluents. Thin-layer chromatography (TLC) was performed on Merck DC-Alufolien plates pre-coated with silica gel 60 F_{254}, which were visualised either by quenching of ultraviolet fluorescence ($\lambda_{max}=254$ nm) or by charring with 10% $KMnO_4$ in 0.1 M NaOH. All reaction solvents were distilled immediately before use. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2, toluene by refluxing over Na, and THF by refluxing over Na/benzophenone ketyl. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. High-resolution mass spectrometry (HRMS) measurements are valid to ± 5 ppm. CSP-HPLC was performed on a Hewlett Packard Series 1100 instrument. CD spectra were recorded between 280 and 380 nm in CH_3CN ($\sim$1 mg/5 mL) with a Jasco J600 spectropolarimeter using 10 mm quartz cuvettes at 20 °C.

4.1.1. ($\pm$)-Diethyl[3-(2-[1,1′;3′,1″]terphenyl-5′-yl-naphthalen-1-yl)pyridin-4-yl]amine (2c). *Method 1*. To a suspension of 3-bromo-1,5-diphenylbenzene[21] (420 mg, 1.36 mmol) and Mg (49 mg, 2.0 mmol) in THF (6 mL) was added a crystal of I_2 and the mixture sonicated at 20–30 °C for 1 h. The resulting arylmagnesium bromide was transferred via syringe to a solution of 1-(4-diethylaminopyridin-3-yl)naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (192 mg, 0.45 mmol) and $PdCl_2$(dppp) (13 mg, 23 μmol) in THF (2 mL). The resulting brown solution was stirred at rt for 30 min and refluxed for 21 h. After cooling to rt, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography ($CH_2Cl_2\rightarrow$EtOAc) to give the recovered triflate **1b**[12] (83 mg, 43%) and the title compound **2c** (52 mg, 23%) as a pale yellow oil. $R_f=0.60$ (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2976, 1586, 1498, 1265; δ_H ($CDCl_3$, 250 MHz) 0.49 (t, $J=7.0$ Hz, 6H), 2.57–2.91 (4H), 6.57 (d, $J=6.0$ Hz, 1H), 7.30–7.69 (16H), 7.89–8.00 (3H), 8.31 (d, $J=6.0$ Hz, 1H), and 8.32 (s, 1H); δ_C ($CDCl_3$, 63 MHz) 12.1 ($2\times CH_3$), 44.8 ($2\times CH_2$), 112.1 (CH), 122.9 (C_q), 124.2 (CH), 126.1 (CH), 126.6 (CH), 126.8 (CH), 127.2 ($4\times$CH), 127.4 ($2\times$CH), 127.5 (CH), 127.5 (CH), 128.2 (CH), 128.4 (CH), 128.8 ($4\times$CH), 132.4 (C_q), 133.3 (C_q), 134.2 (C_q), 138.4 (C_q),

141.0 (2×C_q), 141.1 (2×C_q), 142.5 (2×C_q), 148.8 (CH), 154.4 (CH), 155.0 (C_q); *m/z* (EI^+) (rel intensity) 504 (50%, MH^+), 503 (95%, M^+), 488 (100), 231 (25), 57 (50); HRMS calculated for $C_{37}H_{32}N_2$ (MH^+) 504.2565, found 504.2555 (Δ=−2.0 ppm).

Method 2. To a solution of 1-(4-diethylaminopyridin-3-yl)naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (0.65 g, 1.5 mmol) in toluene (12 mL) was added K_3PO_4 (0.66 g, 3.0 mmol), LiCl (0.133 g, 3.0 mmol), $Pd(OAc)_2$ (0.035 g, 0.15 mmol), biphenyl-2-yl-dicyclohexylphosphane (0.22 g, 0.6 mmol) and 3,5-diphenylbenzeneboronic acid[22] (0.64 g, 2.3 mmol). The resulting orange solution was stirred vigorously at 80 °C for 20 h and then at reflux for 4 h. After cooling to rt, the reaction mixture was diluted with satd Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3×35 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (CH_2Cl_2→EtOAc) to give terphenylnaphthylpyridine **2c** (0.39 g, 50%) as a pale yellow oil. Analytical data as above.

4.2. General procedure for the optical resolution of (±)-2

The atropisomers were separated using semipreparative CSP-HPLC by repeated injection of ~2 mg of the racemate in 15 μL of CH_2Cl_2. In all cases the levorotatory enantiomer (−)-**2** eluted first. The enantiomers were further purified by flash chromatography (EtOAc). Analytical CSP-HPLC revealed >99.8% ee for both the levorotatory and the dextrorotatory enantiomers. Assignment of the absolute configuration of the atropisomeric axes follows from correlation of the sign of the Cotton-effect peaks in their CD spectra at ~320 nm with that of biaryl (−)-**2b** for which the absolute configuration has been unambiguously established by X-ray crystallography [as its salt with *N*-Boc-*O*-benzyl-(*S*)-tyrosine].[10,12]

4.2.1. (−)-(S_a) and (+)-(R_a)-Diethyl[3-(2-[1,1′;3′,1″]-terphenyl-5′-yl-naphthalen-1-yl)pyridin-4-yl]amine (2c).

CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 85:14.4:0.6; 3 mL min^{-1}; 35 °C; UV detection at 250 nm, reference at 525 nm. (−)-(S_a)-**2c**, white solid. Mp 80.5–82.0 °C, spectroscopic data as above; retention time 20.3 min; $[\alpha]_D^{25}$ −113 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (−ive). (+)-(R_a)-**2c**, white solid. Mp 81.0–82.0 °C, spectroscopic data as above; retention time 26.9 min; $[\alpha]_D^{25}$ +112 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (+ive).

4.2.2. 3,5-Bis(3,5-dimethylphenyl)benzeneboronic acid (3).

To a solution of 1,5-bis(3,5-dimethylphenyl)-3-bromobenzene[12] (1.0 g, 2.7 mmol) in Et_2O (25 mL) was added *n*-BuLi (1.20 mL, 2.5 M, 3.0 mmol) in hexanes at −78 °C. The reaction was stirred for 0.5 h at −78 °C, warmed to 0 °C over 15 min and then stirred at this temperature for a further 1.5 h. After re-cooling to −78 °C, the reaction mixture was treated with $B(OMe)_3$ (0.9 mL, 3.3 mmol) and allowed to warm to rt over 1.5 h. The reaction mixture was then treated with 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (hexane→EtOAc/hexane, 1:1) to give boronic acid **3** (0.73 g, 81%) as a white powder. Mp 106.5–107.0 °C; R_f=0.50 (EtOAc/hexane, 1:5); ν_{max}/cm^{-1} ($CHCl_3$) 2911, 1603, 1403, 1354, 1263, 844; δ_H ($CDCl_3$, 250 MHz) 2.38 (12H, s), 6.12 (2H, br s), 7.02 (2H, s), 7.30 (4H, s), 7.94 (1H, t, *J*=2.0 Hz), 8.05 (d, *J*=2.0 Hz); δ_C ($CDCl_3$, 63 MHz) 21.4 (4×CH_3), 125.3 (4×CH), 129.1 (3×CH), 132.4 (2×CH), 138.2 (4×C_q), 141.2 (2×C_q), 141.6 (2×C_q) [C_q-B not seen]; *m/z* (CI^+) (rel intensity) 331 (0.5%, MH^+), 304 (50%), 286 [100%, $MH^+ - B(OH)_2$]; HRMS calculated for $C_{22}H_{22}$ {$MH^+ - [B(OH)_2]$} 286.1722, found 286.1711 (Δ=−3.7 ppm).

4.2.3. Diethyl{3-[2-(3,5,3″,5″-tetramethyl[1,1′;3′,1″]-terphenyl-5′-yl)naphthalen-1-yl]pyridin-4-yl}-amine (2d).

To a solution of 1-(4-diethylaminopyridin-3-yl)-naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (0.215 g, 0.5 mmol) in toluene (4 mL) was added K_3PO_4 (0.215 g, 1.0 mmol), LiCl (0.043 g, 1.0 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), biscyclohexylbiphenylphosphine (0.071 g, 0.2 mmol) and boronic acid **3** (0.25 g, 0.75 mmol). The resulting orange solution was stirred vigorously at 80 °C for 20 h and then at reflux for 4 h. After cooling to rt, the reaction mixture was diluted with satd Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3×35 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (CH_2Cl_2→EtOAc) to give the title compound **2d** (0.110 g, 39%) as a pale yellow oil. R_f=0.65 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3008, 2931, 1589, 1502, 1379, 909, 850, 824; δ_H ($CDCl_3$, 250 MHz) 0.41 (6H, t, *J*=7.0 Hz), 2.31 (12H, s), 2.56 (2H, dq, *J*=7.0, 7.0 Hz), 2.73 (2H, dq, *J*=7.0, 7.0 Hz), 6.55 (1H, d, *J*=6.0 Hz), 6.91 (2H, s), 6.98 (4H, s), 7.25 (2H, d, *J*=1.0 Hz), 7.39–7.51 (3H), 7.63 (1H, d, *J*=8.0 Hz), 7.80–7.92 (3H), 8.25 (1H, s), 8.30 (1H, d, *J*=6.0 Hz); δ_C ($CDCl_3$, 63 MHz) 12.0 (2×CH_3), 21.4 (4×CH_3), 44.7 (2×CH_2), 112.1 (CH), 122.9 (C_q), 124.3 (CH), 125.1 (4×CH), 126.0 (CH), 126.6 (CH), 126.6 (CH), 127.3 (2×CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (2×CH), 132.4 (C_q), 133.2 (C_q), 134.0 (C_q), 138.2 (4×C_q), 141.1 (2×C_q), 141.2 (2×C_q), 142.1 (C_q), 148.6 (CH), 154.3 (CH), 154.9 (C_q); *m/z* (EI^+) (rel intensity) 561 (MH^+, 50%), 560 (100%, M^+), 545 (60), 531 (23); HRMS calculated for $C_{41}H_{40}N_2$ (M^+) 560.3191, found 560.3204 (Δ=+2.3 ppm).

4.2.4. (−)-(S_a) and (+)-(R_a)-Diethyl{3-[2-(3,5,3″,5″-tetramethyl[1,1′;3′,1″]terphenyl-5′-yl)naphthalen-1-yl]-pyridin-4-yl}amine (2d).

CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 89:10.6:0.4; 3 mL min^{-1}; 30 °C; UV detection at 254 nm, reference at 360 nm. (−)-(S_a)-**2d**, colourless oil, spectroscopic data as above; retention time 13.1 min; $[\alpha]_D^{25}$ −90 (*c* 1.6 in $CHCl_3$); CD λ_{max}/nm 320 (−ive). (+)-(R_a)-**2d**, colourless oil, spectroscopic data as above; retention time 21.4 min; $[\alpha]_D^{25}$ +89 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (+ive).

4.3. General procedure for catalytic acylative KR (Table 1; except entry 5)

A solution of (±)-alcohol **4** (1.00 mmol), Et_3N (104 μL, 0.75 mmol) and catalyst (−)-(S_a)-**2** (0.01 mmol, >99.8% ee) in toluene (2 mL) was cooled to −78 °C. Ac_2O (83 μL, 0.75 mmol) was then added dropwise with vigorous stirring.

After 6.0–11.3 h (see table) at −78 °C the reaction was quenched by the dropwise addition of MeOH (3 mL), the reaction mixture was allowed to warm to rt over 15 min, and the solvents were evaporated in vacuo. The alcohol and its ester were separated by flash chromatography (petrol/CH_2Cl_2, 2:1→CH_2Cl_2). The ester was hydrolysed by heating at reflux in a solution of 5% NaOH/MeOH (2 mL) for 5 min. After removal of the solvent the residue was passed through a small plug of flash silica eluting with EtOAc. The enantiomeric excesses for the unreacted alcohol and alcohol obtained from hydrolysis of the ester were established by CSP-HPLC.

4.4. Optimal procedure for catalytic acylative KR of (±)-1-(1-naphthyl)ethanol 4c at rt using catalyst 2b (Table 3, entry 11)

To a solution of (±)-alcohol **4c** (600 mg, 3.48 mmol), 2,6-di-*t*-butylpyridine (391 μL, 1.74 mmol), triphenylphosphine (915 mg, 3.48 mmol) and catalyst (−)-(S_a)-**2b** (12.3 mg, 3.5 μmol, >99.8% ee) in *t*-amyl alcohol (7 mL) was added (i-PrCO)$_2$O (263 μL, 1.74 mmol) dropwise with vigorous stirring. After 1 h the solvent was evaporated in vacuo and the residue purified by flash chromatography (petrol/CH_2Cl_2, 2:1→CH_2Cl_2) to give alcohol **4c** as a colourless oil (280 mg, 47, 81.4% ee by CSP-HPLC) and its ester **5c** as a colourless oil (438 mg, 52, 72.4% ee as determined following hydrolysis then CSP-HPLC, as above).

4.5. CSP-HPLC analysis of chiral alcohols (Tables 1–3).

4.5.1. 1-Phenylethanol 4a. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 99:1; 1 mL min^{-1}; 0 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 31 min (*R*), 49 min (*S*). Assigned by comparison with authentic samples supplied by Aldrich.[23]

4.5.2. 1-Phenylpropanol 4b. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 97:3; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 15 min (*S*), 17 min (*R*).[24]

4.5.3. 1-(1-Naphthyl)ethanol 4c. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 90:10; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 vnm. Retention times: 12 min (*S*), 24 min (*R*).[23]

4.5.4. 1-(2-Tolyl)ethanol 4d. Chiralcel OD (1 cm×25 cm); hexanes/*i*-PrOH, 99:1; 3 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 360 nm. Retention times: 6.1 min (*S*), 26.4 min (*R*).[25]

4.5.5. 1-(2-Methoxyphenyl)ethanol 4e. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 90:10; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 12 min (*S*), 19 min (*R*).[23]

4.5.6. 1-(2,6-Dimethylphenyl)ethanol 4f. Chiralcel OD (1 cm×25 cm); hexanes/*i*-PrOH, 93:7; 3 mL min^{-1}; 30 °C; UV detection at 210 nm, reference at 360 nm. Retention times: 8.6 min (*R*), 10.3 min (*S*).[23]

Acknowledgements

Grateful acknowledgement is made to the BBSRC, the EPSRC and the Leverhulme Trust for financial support of this work. Merck Sharp & Dohme Ltd and Pfizer Ltd are also thanked for unrestricted research funds.

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Chiral *N*-heterocyclic carbenes as asymmetric acylation catalysts

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Received 1 June 2004; revised 31 August 2005; accepted 16 September 2005

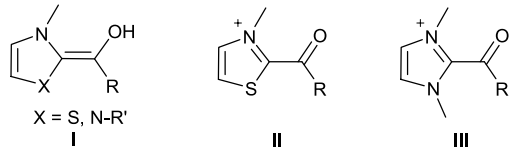
Available online 10 October 2005

Abstract—Chiral *N*-heterocyclic carbenes are generated from C_2-symmetric 1,3-bis(1-arylethyl)imidazolium salts and potassium *tert*-butoxide. These C_2-symmetric imidazolidenyl carbenes catalyze enantioselective acylation of racemic secondary alcohols. The asymmetric acylation of 1-(1-naphthyl)ethanol was achieved in up to 68% ee of the acylated product, using (*R*,*R*)-1,3-bis[(1-naphthyl)ethyl]imidazolium tetrafluoroborate as a precursor of the chiral *N*-heterocyclic carbene and vinyl propionate as the acyl donor.

1. Introduction

The catalytic ability of azolium salts such as thiazolium and imidazolium for benzoin/acyloin condensation was first reported by Ukai et al. in 1943.[1] Subsequently, Breslow proposed a mechanism of azolium-catalyzed benzoin condensation,[2] which is generally accepted at present. An *N*-heterocyclic carbene (NHC), derived from an azolium salt, nucleophilically adds to an aldehyde to form an acyl anion equivalent **I**. This nucleophilic intermediate adds to an aldehyde to produce the benzoin/acyloin. Another important example using this type of umpolung is the Stetter reaction.[3] In this case, the acyl anion equivalent nucleophilically adds to a Michael acceptor to produce 1,4-dicarbonyl compounds. Both reactions are synthetically useful and have been applied to asymmetric synthesis using chiral thiazolium and triazolium salts.[4–7]

The other types of catalytic actions of azolium salts/NHCs are acylation and transesterification reactions. Inoue et al. and Castells et al. reported a thiazolium-catalyzed ester synthesis from aldehydes and alcohols.[8] In this reaction, the acyl anion equivalent derived from thiazolidenyl carbene and aldehyde is oxidized to 2-acylthiazolium salt **II**, and the nucleophilic attack of alcohol on this intermediate at the carbonyl group yields esters. Recently, Nolan et al. and Hedrick et al. reported the NHC-catalyzed transesterification reaction in which acylazolium salts such as **III** are implicated as the key intermediate.[9] In contrast to the development of the asymmetric catalysis of chiral NHCs in benzoin condensation and Stetter reaction, there have been no reports on an asymmetric catalysis using chiral NHCs in this type of acylation reactions.[10,11]



As a part of our efforts focused on the development of NHC-catalysis,[12] we envisioned that the use of chiral NHC in acylation of racemic secondary alcohols could lead to a kinetic resolution. The kinetic resolution of racemic alcohols catalyzed by chiral nucleophilic acylation catalysts is one of the most intensively studied subjects of asymmetric organocatalysis. The organic acylation catalysts that are currently known are tertiary amines, *N*-hetero-aromatic compounds, phosphines, and small-molecule peptides.[4,13] In this paper, we report asymmetric acylation reactions catalyzed by chiral NHCs.

2. Results and discussion

N-heterocyclic carbenes derived from imidazolium and imidazolinium salts were reported to catalyze transesterification.[9] However, the latter has less catalytic ability in the transesterification than the former.[9] Thus, we examined the use of azolium salts **1**–**6** in an acylation of 1-(1-naphthyl)ethanol (**7**).

N-heterocyclic carbenes were generated from imidazolium salts and used in the reactions in situ. A mixture of catalytic amounts of imidazolium salts (3 mol%) and potassium

Keywords: Asymmetric acylation; Chiral *N*-heterocyclic carbene; Imidazolium; Kinetic resolution.
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doi:10.1016/j.tet.2005.09.071

tert-butoxide (*t*-BuOK, 2.5 mol%) in ether/THF was stirred for 30 min and was followed by the addition of vinyl acetate and **7**. The results are summarized in Table 1. Benzimidazolium **2**, triazolium **4**, and imidazolium **6** proved to be effective as a catalyst for acylation of **7**, while thiazolium **1** and pyrido[1,2-*c*]imidazolium **3** had less catalytic ability under these conditions. The low yield of acylated product **8** using **5** is due to the insolubility of **5** in ether.

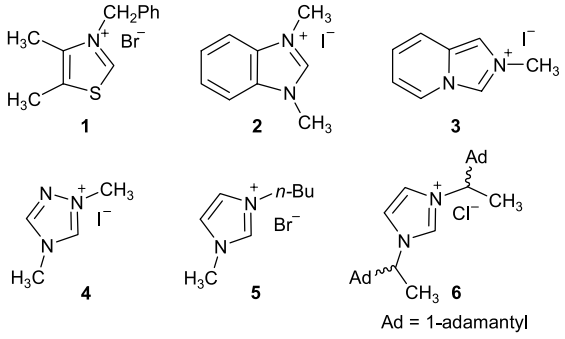
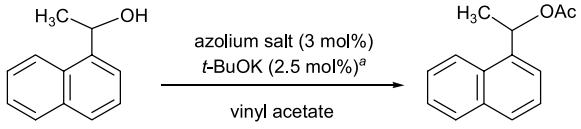


Table 1. The examination of the catalytic ability of various azolium salts[a]



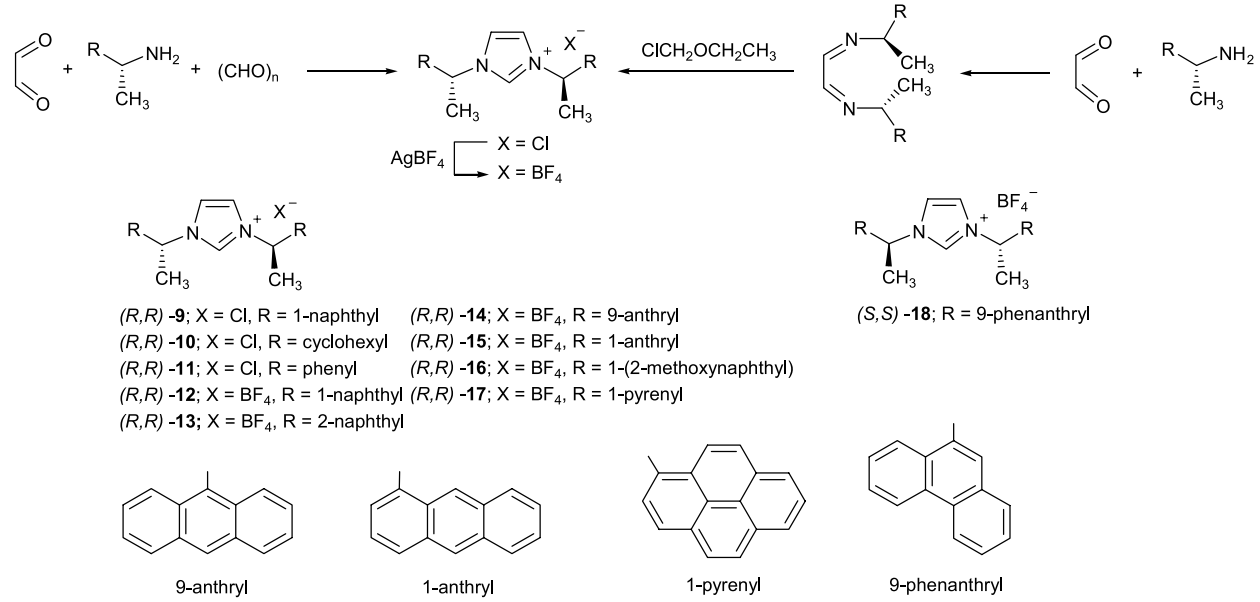
Entry	Azolium salt	Conditions	Yield (%)
1	**1**	THF, room temperature, 16 h	19
2	**2**	Ether, room temperature, 1 h	39
3	**3**	Ether, room temperature, 2 h	13
4	**4**	Ether, room temperature, 2.5 h	35
5	**5**	Ether, room temperature, 1 h	17
6	**6**	THF, room temperature, 1 h	61

[a] THF (1.0 M) solution was used.

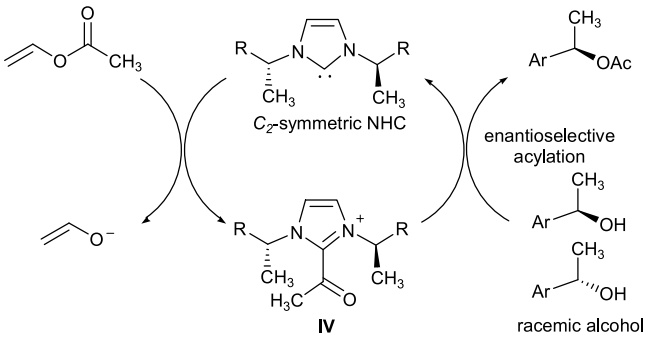
After obtaining these results, we selected C_2-symmetric imidazolidenyl carbenes as catalysts for asymmetric acylation. C_2-symmetric imidazolium salts can be readily prepared from inexpensive materials in one step or in two steps (Scheme 1).[14,15] We hypothesized that C_2-symmetric intermediate **IV**, which is formed from NHC and vinyl acetate, has sufficient enantio selectivity to react with the preferred enantiomer of racemic secondary alcohols (Scheme 2). The first choice was imidazolium salts (*R*,*R*)-**9**–**13**, which can be synthesized from commercially available chiral amines. Imidazolium tetrafluoroborates were prepared from the corresponding chlorides by a reaction with silver tetrafluoroborate.

The results of the kinetic resolution of the secondary alcohols catalyzed by (*R*,*R*)-**9**–**13** are summarized in Table 2. The acylation of **7** using (*R*,*R*)-**9**[14] at room temperature provided acetate **8** in 21% yield with 42% ee (entry 1). The unreacted **7** was recovered in 69% yield with 21% ee. At 0 °C with (*R*,*R*)-**9**, the selectivity was improved (entry 2). Under the same conditions at room temperature, the acylation of 1-phenylethanol (**19**) produced acetate **22** in 29% with 31% ee, and **19** was recovered in 36% yield with 20% ee (entry 13). The reaction rate increased when tetrafluoroborate (*R*,*R*)-**12** was used in the acylation of **7** (entry 5), instead of chloride (*R*,*R*)-**9**. The catalysts (*R*,*R*)-**10**,[14]**11**, **13** had lower selectivities than (*R*,*R*)-**9**, (*R*,*R*)-**12** (entries 3, 4, and 7). When an *N*-substituent of carbene is an (*R*)-1-arylethyl group, the acylation of 1-arylethanols proceeded with *R*-selectivities, and in the case of an (*R*)-1-cyclohexylethyl group, the reaction proceeded with *S*-selectivities.

These results led us to assume that an aromatic substituent on the *N*-ethyl group of the NHC is required to be bulkier than the 1-naphthyl group in order to achieve a better selectivity. Hence, imidazolium salts (*R*,*R*)-**14**, (*R*,*R*)-**15**, (*R*,*R*)-**16**, (*R*,*R*)-**17**, and (*S*,*S*)-**18** that have aromatic substituents 9-anthryl, 1-anthryl, 1-(2-methoxynaphthyl),



Scheme 1. C_2-symmetric imidazolium salts.



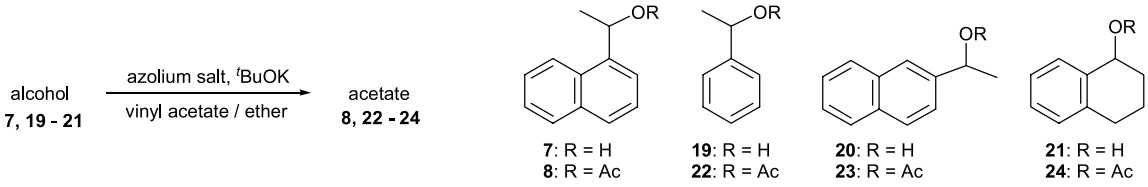
Scheme 2. Proposed mechanism for asymmetric acylation.

1-pyrenyl, and 9-phenanthryl, were synthesized and used in acylation reaction of **7**. Contrary to our prediction, (*R*,*R*)-**14**, (*R*,*R*)-**16** had lower selectivities, and the reaction rates were slow (entries 8, 10). 9-Anthryl and 1-(2-methoxynaphthyl) groups seem to hinder the attack of alcohol on the carbonyl carbon of the intermediate **IV** (Scheme 2). (*R*,*R*)-**15**, (*R*,*R*)-**17**, and (*S*,*S*)-**18** showed enantio selectivities comparable to (*R*,*R*)-**9**, (*R*,*R*)-**12** (entries 9, 11, and 12).

Next, we examined the effects of various vinyl esters as acyl donors. Vinyl propionate, vinyl butyrate, and vinyl benzoate were employed in the reaction. The results are shown in Table 3. In the acylation of **7** using (*R*,*R*)-**12** as catalysts, vinyl propionate functioned well as an acyl donor to increase the enantiomeric excess of produced ester up to 68% ee with *s* factor 6.1.

Very recently, Maruoka et al. have reported kinetic resolution of secondary alcohols by chiral NHC catalysis.[16] Using 5 mol% of (*R*,*R*)-**12** and bulkier vinyl esters (e.g.,

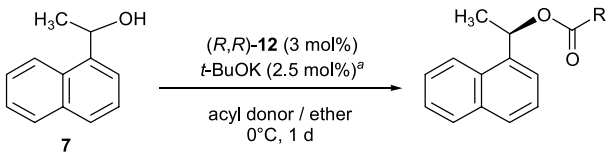
Table 2. Kinetic resolution of secondary alcohols



Entry	Racemic alcohol	Azolium salt		Condition		Acetate		Alcohol		*s*
		X				Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]	
1	**7**	(*R*,*R*)-**9**	Cl	Room temperature, 2 days	**8**	21	42 (*R*)	69	21 (*S*)	3.0
2	**7**	(*R*,*R*)-**9**	Cl	0 °C, 2 days	**8**	21	51 (*R*)	79	11 (*S*)	3.4
3	**7**	(*R*,*R*)-**10**	Cl	Room temperature, 18 h	**8**	15	19 (*S*)	83	1 (*R*)	1.5
4[c]	**7**	(*R*,*R*)-**11**	Cl	Room temperature, 16 h	**8**	52	18 (*R*)	47	17 (*S*)	1.7
5	**7**	(*R*,*R*)-**12**	BF_4	0 °C, 1 day	**8**	33	45 (*R*)	56	22 (*S*)	3.3
6	**7**	(*R*,*R*)-**12**	BF_4	−15 °C, 3 days	**8**	14	58 (*R*)	85	8 (*S*)	4.1
7	**7**	(*R*,*R*)-**13**	BF_4	0 °C, 18 h	**8**	43	14 (*R*)	47	14 (*S*)	1.5
8	**7**	(*R*,*R*)-**14**	BF_4	0 °C, 2 days	**8**	6	23 (*R*)	80	5 (*S*)	1.7
9[c]	**7**	(*R*,*R*)-**15**	BF_4	Room temperature, 4 days	**8**	17	50 (*R*)	83	—	—
10[c]	**7**	(*R*,*R*)-**16**	BF_4	0 °C, 2.5 days and then room temperature, 2 h	**8**	4	13 (*R*)	84	<1	—
11	**7**	(*R*,*R*)-**17**	BF_4	0 °C, 12 h	**8**	27	49 (*R*)	73	20 (*S*)	3.5
12	**7**	(*S*,*S*)-**18**	BF_4	0 °C, 18 h	**8**	37	39 (*S*)	60	23 (*R*)	2.8
13	**19**	(*R*,*R*)-**9**	Cl	Room temperature, 3 days	**22**	29	31 (*R*)	36	20 (*S*)	2.3
14	**20**	(*R*,*R*)-**12**	BF_4	0 °C, 18 h	**23**	44	44 (*R*)	49	37 (*S*)	3.6
15	**21**	(*R*,*R*)-**12**	BF_4	0 °C, 2 days	**24**	14	9	84	2	1.2

[a] Isolated yield.
[b] Enantioselectivities were measured by HPLC using a Chiralcel OD column or a Chiralpac AS column.
[c] THF (1.0 M) solution of ^{t}BuOK was used.

Table 3. Acylation with various acyl donors[a]



Entry	Acyl donor	R	Ester (ee %)[b]	Alcohol (ee %)[b]	Conversion (%)	*s*
1	Vinyl acetate	Me	48	16	25	3.3
2	Vinyl propionate	Et	68	16	19	6.1
3	Vinyl butyrate	*n*-Pr	66	11	14	5.4
4	Vinyl benzoate	Ph	33	17	34	2.3

[a] THF (1.0 M) solution was used.
[b] Enantioselectivities were measured by HPLC using a Chiralcel OD column, a Chiralcel OD-H column or a Chiralpac AD-H column.

vinyl diphenylacetylate) at −78 to −20 °C in THF, enantioselectivities improved up to 96% ee in asymmetric acylation of **7**, **19**, **20**, and related secondary alcohols.

3. Conclusion

We have demonstrated that chiral *N*-heterocyclic carbenes catalyze the enantioselective acylation of racemic secondary alcohols. We used simple C_2-symmetric carbenes, which were readily synthesized from chiral amines, glyoxal, and formaldehyde or chloromethyl ethyl ether. Further investigations to broaden the scope of this asymmetric acylation are ongoing in our laboratory.

4. Experimental

4.1. General

Melting points are determined using a Yazawa Micro Melting Point Apparatus without correction. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded on a JEOL ECA-500 NMR spectrometer. IR spectra were recorded on a JASCO FT/IR-8000 spectrometer and a SHIMADZU IR Prestige-21. HRMS (FAB) spectra were recorded on a JEOL MStation JMS-700 mass spectrometer using *m*-nitrobenzyl alcohol as a matrix. Column chromatography was performed with Merck Silica Gel 60 and Silica Gel 60 N (spherical, neutral, Kanto Chemical Co., Inc.). Optical rotations were measured using a JASCO DIP-360 or a JASCO P-1030 polarimeter.

4.2. Preparation of imidazolium chlorides: general procedure

4.2.1. Glyoxal-bis-[1-(1-adamantyl)ethyl]imine. A mixture of 40% aqueous solution of glyoxal (145 mg, 1 mmol), 1-propanol (0.16 mL), and water (0.4 mL) was added to a solution of racemic 1-(1-adamantyl)ethylamine (360 mg, 2 mmol) in 1-propanol (1.4 mL) at room temperature. The mixture was stirred at 70 °C for 2 h. Water was added to the mixture, and the resulting colorless precipitates were filtered, washed with water, and dried. The precipitates were identified as imine (335 mg, 88%) by ^{1}H NMR spectroscopy, and used in the subsequent reaction without further purification.

4.2.2. 1,3-Bis-[1-(1-adamantyl)ethyl]imidazolium chloride 6. A solution of glyoxal-bis-[1-(1-adamantyl)ethyl]imine (337 mg, 0.89 mmol) and one drop of water in THF (1.9 mL) was added to a solution of chloromethyl ethyl ether (96%, 88 mg, 0.89 mmol) and THF (0.2 mL) in a 10 mL single-necked flask. The flask was sealed under nitrogen with a septum and the mixture was stirred at room temperature for 24 h, and then at 40 °C for 15 h. Water and dichloromethane were added to the reaction mixture. The organic layer was taken, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography using dichloromethane/methanol as an eluent to afford **6** as a solid (145 mg, 39%). This product is assumed to comprise a mixture of meso and racemic forms.

4.3. General procedure for *N*-heterocyclic carbene-catalyzed acetylation of 1-(1-naphthyl)ethanol

Potassium *tert*-butoxide (0.25 mmol) was added to a suspension of azolium salt (0.3 mmol) in ether or THF (2 mL). The mixture was stirred at room temperature for 30 min. To the mixture were added vinyl acetate (1.2 mmol) and **7** (1 mmol). The resulting mixture was stirred at room temperature for 1–16 h (Table 2). The solvent was evaporated and the residue was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as an eluent.

4.3.1. 1,3-Bis-[(*R*)-1-cyclohexylethyl]imidazolium chloride (*R*,*R*)-10. Paraformaldehyde (120 mg, 4 mmol) with ice cooling was added to a solution of (*R*)-(−)-cyclohexylethylamine (595 μL, 4 mmol) in toluene (4 mL). After stirring for 30 min, another equivalent of the amine was added; subsequently, 3.3 N HCl (1.2 mL) was added dropwise at 0 °C. 40% aqueous gyloxal solution (580 μL, 4 mmol) was added dropwise at room temperature. The mixture was stirred for 20 h at 35 °C. Dichloromethane and water were added to the reaction mixture. The organic layer was taken, dried over $MgSO_4$, and evaporated to yield crude (*R*,*R*)-**10** as a solid. Recrystallization from acetonitrile/ether afforded (*R*,*R*)-**10** as colorless prisms (364 mg, 29%); mp 188–190.5 °C; $[\alpha]_D^{24}$ +11.2 (*c* 1.0, $CHCl_3$, 21.8 °C); ^{1}H NMR ($CDCl_3$) δ: 1.14 (8H, m), 1.57–1.83 (14H, m), 4.59 (2H, quintet, J=7.4 Hz), 7.13 (2H, d, J=1.7 Hz, imidazole C4-H, C5-H), 11.32 (1H, s, imidazole C2-H); ^{13}C NMR ($CDCl_3$) δ: 18.5, 25.6, 25.7, 25.8, 29.2, 29.2, 29.3, 43.7, 62.1, 119.6, 137.9; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{33}N_2$ (M^+): 289.2644, found: 289.2661.

4.3.2. 1,3-Bis-[(*R*)-1-(1-naphthyl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-12. $AgBF_4$ (90%) in hexane (476 mg, 2.2 mmol) was added to a solution of 1,3-bis-[(*R*)-1-(1-naphthyl)ethyl]imidazolium chloride (413 mg, 1 mmol) in dichloromethane (5 mL). The mixture was stirred for 2 h at room temperature. The resulting precipitates were filtered. The filtrate was purified by silica gel column chromatography using dichloromethane/methanol as an eluent to yield (*R*,*R*)-**12** (279 mg, 60%) as a coloreless solid; $[\alpha]_D^{24}$ −88.7 (*c* 1.0, $CHCl_3$, 21.7 °C); ^{1}H NMR ($CDCl_3$) δ: 2.13 (6H, d, J=6.5 Hz, CH_3CH), 6.85 (2H, q, J=6.5 Hz, CH_3C*H*), 6.90 (2H, s), 7.41–7.54 (8H, m), 7.83–7.84 (4H, m), 8.15 (2H, d, J=8.5 Hz), 11.59 (1H, s, imidazole C2-H); ^{13}C NMR ($CDCl_3$) δ: 21.6, 56.2, 120.6, 122.4, 124.5, 125.3, 126.5, 127.8, 129.2, 130.4, 130.5, 133.0, 134.0, 137.3.

4.4. Preparation of 1,3-bis-[(*R*)-1-(2-naphthyl)ethyl]-imidazolium tetrafluoroborate (*R*,*R*)-13

4.4.1. Glyoxal-bis-[(*R*)-1-(2-naphthyl)ethyl]imine. Following the general procedure given for the glyoxal-bis-imine, (*R*)-(+)-1-(2-naphthyl)ethylamine (342 mg, 2 mmol) was reacted with glyoxal for 4 h at 60 °C. The crude imine (362 mg, 99%) was extracted with ether. The product was used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) δ: 1.72 (6H, d, J=6.9 Hz, CH_3CH), 4.73 (2H, q, J=6.9 Hz, CH_3C*H*), 7.45–7.50 (4H,

m), 7.53 (2H, dd, J=8.6, 1.7 Hz), 7.82–7.86 (8H, m), 8.2 (2H, s).

4.4.2. 1,3-Bis-[(*R*)-1-(2-naphthyl)ethyl]imidazolium chloride. Following the general procedure given for **6**, glyoxal-bis-[(*R*)-1-(2-naphthyl)ethyl]imine (362 mg, 0.995 mmol) was reacted with chloromethyl ethyl ether at 40 °C for 18 h to afford imidazolium chloride (122 mg, 30%) as a yellow amorphous solid; $[\alpha]_D^{24}$+49.9 (*c* 1.0, $CHCl_3$, 22.8 °C); ^{1}H NMR ($CDCl_3$) δ: 2.03 (6H, d, J= 6.9 Hz, C*H*$_3$CH), 6.16 (2H, q, J=6.9 Hz, CH$_3$C*H*), 7.22 (2H, d, J=1.2 Hz), 7.40–7.45 (4H, m), 7.48 (2H, dd, J= 8.5, 1.9 Hz), 7.71–7.78 (6H, m), 7.90 (2H, s), 11.32 (1H, s, imidazole C2-H); ^{13}C NMR ($CDCl_3$) δ: 21.2, 60.0, 120.7, 124.2, 126.6, 126.9, 127.1, 127.8, 128.3, 129.6, 133.1, 133.4, 135.3, 136.6; $C_{27}H_{25}N_2$ (M^+): 377.2018, found: 477.2056.

4.4.3. 1,3-Bis-[(*R*)-1-(2-naphthyl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-13. Following the procedure given for (*R*,*R*)-**12**, 1,3-bis-[(*R*)-1-(2-naphthyl)ethyl]imidazolium chloride was treated with $AgBF_4$ to yield (*R*,*R*)-**13** (70%) as a yellow amorphous solid. This compound was used in the acylation reaction without further purification.

4.5. Preparation of 1,3-bis-[(*R*)-1-(9-anthryl)ethyl]-imidazolium tetrafluoroborate (*R*,*R*)-14

4.5.1. Glyoxal-bis-[(*R*)-1-(9-anthryl)ethyl]imine. Following the general procedure given for glyoxal-bis-imine, (*R*)-(+)-1-(9-anthryl)ethylamine[17] (221 mg, 1 mmol), was reacted with glyoxal for 2 h at 60 °C. The crude imine (202 mg, 87%) was extracted with dichloromethane. The product was used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) δ: 1.97 (6H, d, J=7.4 Hz, C*H*$_3$CH), 6.08 (2H, d, J=7.4 Hz, CH$_3$C*H*), 7.38–7.40 (8H, m), 7.94–7.96 (4H, m), 8.08 (2H, s), 8.34 (2H, s), 8.42 (4H, br).

4.5.2. 1,3-Bis-[(*R*)-1-(9-anthryl)ethyl]imidazolium chloride. Following the general procedure given for **6**, glyoxal-bis-[(*R*)-1-(9-anthryl)ethyl]imine (223 mg, 0.48 mmol) was reacted with chloromethyl ethyl ether at 40 °C for 64 h. The addition of water to the reaction mixture afforded precipitates of imidazolium chloride (224 mg, 91%). Slight brown granules (dichloromethane/ether); mp 161–162.5 °C; $[\alpha]_D^{24}$−88.7 (*c* 1.0, $CHCl_3$, 21.7 °C); ^{1}H NMR ($CDCl_3$) δ: 2.51 (6H, d, J=6.9 Hz, C*H*$_3$CH), 6.75 (2H, d, J=1.7 Hz), 7.29 (2H, q, J=6.9 Hz, CH$_3$C*H*), 7.46–7.52 (8H, m), 8.03–8.11 (8H, m), 8.53 (2H, s), 10.10 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.3, 56.4, 120.8, 122.5, 123.1, 123.6, 126.2, 127.2, 127.3, 127.8, 128.1, 128.9, 129.3, 130.5, 130.7, 130.9, 131.2, 136.6; HRMS (FAB) *m*/*z* calcd for $C_{35}H_{29}N_2$ (M^+): 477.2331, found: 477.2310.

4.5.3. 1,3-Bis-[(*R*)-1-(9-anthryl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-14. Following the procedure given for (*R*,*R*)-**12**, 1,3-bis-[(*R*)-1-(9-anthryl)ethyl]imidazolium chloride was treated with $AgBF_4$ to yield (*R*,*R*)-**14** (61%) as a slight brown solid. This compound was used in the acylation reaction without further purification.

4.6. Preparation of 1,3-bis-[(*R*)-1-(1-anthryl)ethyl]-imidazolium tetrafluoroborate (*R*,*R*)-9

4.6.1. (*R*)-(+)-1-(1-anthryl)ethylamine. A solution of 1-(1-anthranyl)ethylamine[18] (312 mg, 1.41 mmol) and (*R*)-16-hydroxy-14-oxabicyclo[11.2.2]heptadecane-1(16), 13(17)-diene-2,15-dione[19,20] (392 mg, 1.41 mmol) in benzene (14 mL) was refluxed for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on neutral silica gel by using hexane/ethyl acetate 4:1 as an eluent to first yield (*R*,*R*)-2-[1-(1-anthranyl)ethylamino]-14-oxabicyclo[11.2.2]heptadecane-1(2),13(17)-diene-15,16-dione (428 mg, 33%), and then (*R*,*S*)-2-[1-(1-anthranyl)-ethylamino]-14-oxabicyclo[11.2.2]heptadecane-1(2), 13(17)-diene-15,16-dione (147 mg, 20%).

(R,R)-2-[1-(1-anthranyl)ethylamino]-14-oxabicyclo[11.2.2] heptadecane-1(2),13(17)-diene-15,16-dione. Colorless needles (dichloromethane/ether); mp 199–202 °C; $[\alpha]_D^{24}$− 327.9 (*c* 1.0, $CHCl_3$, 21.6 °C); ^{1}H NMR ($CDCl_3$) δ: 1.11–1.34 (10H, m), 1.44–1.52 (2H, m), 1.61–1.72 (3H, m), 1.78–1.90 (4H, m), 2.18–2.24 (2H, m), 2.60 (1H, dt, J= 14.3, 4.5 Hz), 4.05 (1H, br), 5.82–5.86 (2H, m), 7.42–7.45 (2H, m), 7.50–7.54 (2H, m), 7.96–7.98 (1H, m), 8.02–8.08 (2H, m), 8.49 (1H, s), 8.51 (1H, s), 14.37 (1H, br, NH); HRMS (FAB) *m*/*z* calcd for $C_{32}H_{36}NO_3$ (M+1): 437.2229, found: 437.2230.

(R,S)-2-[1-(1-anthranyl)ethylamino]-14-oxabicyclo[11.2.2] heptadecane-1(2),13(17)-diene-15,16-dione. Colorless prisms (ether); mp 146–149 °C; $[\alpha]_D^{24}$+677.6 (*c* 1.0, $CHCl_3$, 22.1 °C); ^{1}H NMR ($CDCl_3$) δ: 0.62–1.03 (7H, m), 1.08–1.23 (5H, m), 1.26–1.34 (1H, m), 1.42–1.49 (1H, m), 1.58–1.67 (1H, m), 1.72–1.82 (1H, m), 1.85 (3H, d, J= 6.5 Hz), 2.16–2.22 (1H, m), 2.59 (1H, dt, J=13.6, 4.5 Hz), 2.72 (1H, br), 4.35 (1H, br), 5.83 (1H, s), 5.95–6.01 (1H, m), 7.44 (1H, dd, J=7.8, 7.1 Hz), 7.49–7.56 (3H, m), 7.94 (1H, d, J=8.4 Hz), 8.00 (1H, d, J=7.8 Hz), 8.08 (1H, d, J= 7.8 Hz), 8.47 (1H, s), 8.52 (1H, s), 14.50 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ: 23.9, 26.1, 26.6, 26.8, 28.5, 28.6, 33.9, 51.4, 98.7, 108.8, 120.6, 122.4, 125.0, 126.1, 126.2, 128.0, 128.1, 128.5, 128.9, 131.6, 132.0, 137.6, 164.6, 166.1, 178.0, 183.7; HRMS (FAB) *m*/*z* calcd for $C_{32}H_{36}NO_3$ (M+ 1): 437.2229, found: 437.2230.

A solution of (*R*,*R*)-2-[1-(anthranyl)amino]-14-oxabicyclo[11.2.2]heptadecane-1(2),13(17)-diene-15,16-dione (384 mg, 0.8 mmol) and KOH (179 mg, 3.2 mmol) in THF (10 mL)/H_2O (10 mL) was stirred for 20 h at room temperature. The mixture was alkalized with 10% aqueous KOH solution and extracted with dichloromethane. The organic layer was washed with brine, dried over K_2CO_3, and concentrated to give (*R*)-amine (176 mg, 99%). Colorless needles (ether); mp 62–64 °C; $[\alpha]_D^{24}$+4.8 (*c* 0.6, $CHCl_3$, 21.2 °C).

4.6.2. Glyoxal-bis-[(*R*)-1-(1-anthryl)ethyl]imine. Following the general procedure given for glyoxal-bis-imine, (*R*)-(+)-1-(1-anthryl)ethylamine (177 mg, 0.8 mmol) was reacted with glyoxal for 2 h at 70 °C. The crude imine (202 mg, 87%) was extracted with ethyl acetate. This product was used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) δ: 1.79 (6H,

d, J=6.3 Hz, CH_3CH), 5.56 (2H, q, J=6.3 Hz, CH$_3$CH), 7.41–7.48 (6H, m), 7.62 (2H, d, J=6.9 Hz), 7.91 (2H, d, J=8.6 Hz), 7.97–8.03 (4H, m), 8.22 (2H, s), 8.43 (2H, s), 8.65 (2H, s).

4.6.3. 1,3-Bis-[(*R*)-1-(1-anthryl)ethyl]imidazolium chloride. Following the general procedure given for 1,3-bis-[1-(1-adamantyl)ethyl]imidazolium chloride, glyoxal-bis-[(*R*)-1-(1-anthryl)ethyl]imine (171 mg, 0.37 mmol) was reacted with chloromethyl ethyl ether at 40 °C for 15 h. After addition of THF (2 mL), the mixture was refluxed for 8 h to afford imidazolium chloride (112 mg, 60%) as a yellow solid; mp 162–166 °C (dichloromethane/ether); $[\alpha]_D^{24}$ −298.6 (*c* 0.26, $CHCl_3$, 21.7 °C); ^{1}H NMR (DMSO-d_6) 2.09 (6H, d, J=6.9 Hz, CH_3CH), 6.73 (2H, q, J=6.9 Hz, CH$_3$CH), 7.37 (2H, d, J=8.0 Hz), 7.41–7.45 (4H, m), 7.51 (2H, t, J=7.5 Hz), 7.83–7.84 (2H, m), 8.05 (2H, d, J=8.6 Hz), 8.09 (2H, d, J=8.0 Hz), 8.61 (2H, s), 8.65 (2H, s), 9.89 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.4, 56.3, 120.0, 121.5, 124.0, 124.0, 126.2, 126.3, 127.4, 127.5, 128.2, 129.0, 130.6, 131.5, 131.6, 132.4, 132.7, 137.8; HRMS (FAB) *m*/*z* calcd for $C_{35}H_{29}N_2$ (M^+): 477.2331, found: 477.2310.

4.6.4. 1,3-Bis-[(*R*)-1-(1-anthryl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-15. Following the procedure given for 1,3-bis-[(*R*)-1-(1-naphthyl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-**12**, 1,3-bis-[(*R*)-1-(1-anthryl)ethyl]imidazolium chloride was treated with $AgBF_4$ to give (*R*,*R*)-**15** (80%) as a slight brown solid. This compound was used in the acylation reaction without further purification.

4.7. Preparation of 1,3-bis-{(*R*)-1-[1-(2-methoxynaphthyl)]ethyl}imidazolium tetrafluoroborate (*R*,*R*)-10

4.7.1. 1-[1-(2-Methoxynaphthyl)]ethylamine. Diethyl azodicarboxylate (40% in toluene, 2 mL) at room temperature was added to a solution of 1-[1-(2-methoxynaphthyl)] ethanol[21] (727 mg, 3.6 mmol), phthalimide (573 mg, 4 mmol), and triphenylphosphine (1.05 g, 4 mmol) in dry THF (20 mL). The mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by silica gel column chromatography using hexane/ethyl acetate 2:1 as an eluent to yield *N*-1-[1-(2-methoxynaphthyl)]ethylphthalimide (989 mg, 83%). Colorless needles (ethyl acetate/hexane); mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ: 2.12 (3H, d, J=7.4 Hz, CH_3CH), 3.95 (3H, s, CH$_3$O), 6.31 (1H, q, J=7.4 Hz, CH$_3$CH), 7.27 (1H, d, J=8.6 Hz), 7.31–7.34 (1H, m), 7.51 (1H, t, J=7.4 Hz), 7.63–7.64 (2H, m), 7.75–7.79 (4H, m), 8.25 (1H, d, J=9.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 18.5, 46.9, 56.8, 114.4, 121.5, 122.6, 123.0, 123.5, 27.1, 129.0, 129.4, 130.0, 132.1, 132.2, 133.8, 155.9, 168.9; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{17}NO_3$ (M^+): 331.1208, found: 331.1203.

A solution of *N*-1-[1-(2-methoxynaphthyl)]ethylphthalimide (993 mg, 3 mmol) and hydrazine monohydrate (0.3 mL) in THF (30 mL) was refluxed for 3.5 h. Ether was added to the reaction mixture and the resulting precipitates were filtered. The filtrate was alkalized with KOH aqueous solution to pH 11. The organic layer was taken and extracted with 10% aqueous solution. The aqueous layer was taken, alkalized with NaOH aqueous solution, and extracted with ether. The organic layer was washed with brine, dried over K_2CO_3, and evaporated to yield the amine (424 mg, 70%). Colorless prisms (ether); mp 49–51 °C; ^{1}H NMR ($CDCl_3$) δ: 1.59 (3H, d, J=6.9 Hz, CH_3CH), 2.11 (2H, br, NH_2), 3.95 (3H, s, CH$_3$O), 4.97 (1H, q, J=6.9 Hz, CH$_3$CH), 7.26 (1H, d, J=9.2 Hz), 7.33 (1H, t, J=7.4 Hz), 7.47 (1H, dd, J=8.6, 7.4 Hz), 7.73 (1H, d, J=9.2 Hz), 7.78 (1H, d, J=8.0 Hz), 8.16 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 23.2, 45.5, 56.2, 114.0, 122.9, 123.4, 126.5, 128.0, 128.5, 128.8, 129.5, 131.7, 155.1; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{16}NO$ (M+1): 202.1232, found: 202.1228.

4.7.2. (*R*)-(+)-1-[1-(2-methoxynaphthyl)]ethylamine. Following the procedure given for (*R*)-(+)-1-(1-anthryl) ethylamine, racemic 1-(2-methoxynaphthyl)ethylamine was resoluted. The (*R*,*R*)- and (*R*,*S*)-diastereomers were purified by column chromatography on neutral silica gel by using dichloromethane/hexane/ether 10:5:1 as an eluent.

(R,R)-2-{1-[1-(2-methoxynaphthyl)]ethylamino}-14-oxabicyclo[11.2.2]heptadecane-1(2),13(17)-diene-15,16-dione. Yield 32%; colorless needles (dichloromethane/ether); mp 149–150 °C; $[\alpha]_D^{24}$ −271.4 (*c* 1.0, $CHCl_3$, 21.7 °C); ^{1}H NMR ($CDCl_3$) δ: 0.97–1.42 (12H, m), 1.48–1.55 (3H, m), 1.62–1.86 (4H, m), 2.05 (1H, t, J=12.0 Hz), 2.30–2.46 (2H, m), 3.93 (3H, d, J=2.9 Hz), 4.00 (1H, br), 5.65 (1H, s), 5.79 (1H, br), 7.20 (1H, dd, J=9.2, 2.9 Hz), 7.28 (1H, t, J=6.9 Hz), 7.45 (1H, t, J=6.9 Hz), 7.72–7.75 (2H, m), 7.84 (1H, d, J=8.0 Hz), 14.1 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ: 20.6, 24.0, 25.48, 26.5, 27.1, 27.2, 27.5, 28.2, 28.6, 28.8, 33.9, 47.9, 56.4, 98.0, 109.0, 113.6, 121.3, 123.7, 127.8, 129.4, 130.5, 131.0, 164.9, 165.1, 165.4, 183.3; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{36}NO_4$ (M+1): 462.2644, found: 462.2655.

(R,S)-2-{1-[1-(2-methoxynaphthyl)]ethylamino}-14-oxabicyclo[11.2.2]heptadecane-1(2),13(17)-diene-15,16-dione. Yield 24%; colorless powder (ether); mp 127–128 °C; $[\alpha]_D^{24}$ +206.9 (*c* 1.0, $CHCl_3$, 21.2 °C); ^{1}H NMR ($CDCl_3$) δ: 0.74–1.17 (12H, m), 1.34–1.44 (1H, br), 1.50–1.63 (2H, m), 1.68–1.80 (4H, m), 2.08–2.14 (1H, m), 2.55 (1H, dt, J=13.6, 4.5 Hz), 2.72 (1H, br), 4.08 (3H, s, CH$_3$O), 4.20 (1H, br), 5.69 (1H, s), 5.92–5.94 (1H, m), 7.31 (1H, d, J=9.1 Hz), 7.36 (1H, t, J=7.1 Hz), 7.53–7.57 (1H, m), 7.81–7.84 (2H, m), 7.97 (1H, d, J=9.1 Hz), 14.2 (1H, br, NH); HRMS (FAB) *m*/*z* calcd for $C_{29}H_{36}NO_4$ (M+1): 462.2644, found: 462.2655.

(R)-(+)-1-[1-(2-methoxynaphthyl)]ethylamine. $[\alpha]_D^{24}$ +30.7 (*c* 1.0, $CHCl_3$, 24.4 °C).

4.7.3. Glyoxal-bis-{(*R*)-1-[1-(2-methoxynaphthyl)]ethyl}-imine. Following the general procedure given for glyoxal-bis-imine, (*R*)-(+)-1-[1-(2-methoxynaphthyl)]ethylamine was reacted with glyoxal for 2 h at 60 °C. The crude imine (brown oil, 98%) was extracted with dichloromethane. This product was used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) δ: 1.80 (6H, d, J=6.9 Hz, CH_3CH), 3.86 (6H, s, CH$_3$O), 5.73 (2H, q, J=6.9 Hz, CH$_3$CH), 7.21 (2H, dd, J=9.2, 1.7 Hz), 7.29 (2H, t, J=6.9 Hz), 7.37 (2H, dd, J=8.6, 6.9 Hz), 7.72–7.75 (4H, m), 8.03 (2H, s), 8.21 (2H, d, J=8.6 Hz).

4.7.4. 1,3-Bis-{(*R*)-1-[1-(2-methoxynaphthyl)]ethyl}-imidazolium chloride. Following the general procedure given for **6**, glyoxal-bis-{(*R*)-1-[1-(2-methoxynaphthyl)]-ethyl}imine (212 mg, 0.5 mmol) was reacted with chloromethy ethyl ether at 40 °C for 20 h. After addition of THF (2 mL), the mixture was refluxed for 24 h to afford imidazolium chloride (104 mg, 44%) as a brown amorphous solid; $[\alpha]_D^{24}$ −96.6 (*c* 0.54, $CHCl_3$, 20.8 °C); ^{1}H NMR ($CDCl_3$) *δ*: 2.19 (6H, d, *J*=6.3 Hz, C*H*$_3$CH), 3.69 (6H, s, CH_3O), 6.74 (2H, q, *J*=6.3 Hz, CH_3C*H*), 7.09 (2H, s), 7.18 (2H, d, *J*=9.2 Hz), 7.31 (2H, dd, *J*=8.0, 6.9 Hz), 7.50 (2H, t, *J*=6.9 Hz), 7.75 (2H, d, *J*=8.0 Hz), 7.82 (2H, d, *J*=8.6 Hz), 8.16 (2H, br), 10.47 (1H, s, imidazole C2-H); ^{13}C NMR ($CDCl_3$) *δ*: 19.4, 53.6, 56.2, 113.3, 118.2, 120.9, 122.0, 124.2, 128.3, 129.1, 129.3, 131.69, 131.8, 136.7, 155.8; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{29}N_2O_2$ (M^+): 437.2229, found: 437.2230.

4.7.5. 1,3-Bis-{(*R*)-1-[1-(2-methoxynaphthyl)]ethyl}-imidazolium tetrafluoroborate (*R*,*R*)-16. Following the procedure given for (*R*,*R*)-**12**, 1,3-bis-{(*R*)-1-[1-(2-methoxynaphthyl)]ethyl}imidazolium chloride was treated with $AgBF_4$ to give (*R*,*R*)-**16** (77%) as a solid. This compound was used in the acylation reaction without further purification.

4.8. Preparation of 1,3-bis-(*R*)-1-1-pyrenylimidazolium tetrafluoroborate (*R*,*R*)-11

4.8.1. Glyoxal-bis-[(*R*)-1-(1-pyrenyl)ethyl]imine. Following the general procedure given for glyoxal-bis-imine, (*R*)-(+)-1-(1-pyrenyl)ethylamine[22] (245 mg, 2 mmol) was reacted with glyoxal at 60 °C for 3 h. The extraction with dichloromethane yielded the crude imine quantitively as a slight brown solid. The product was used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) *δ*: 1.85 (6H, d, *J*=6.9 Hz, C*H*$_3$CH), 5.71 (2H, q, *J*=6.9 Hz, CH_3C*H*), 7.97 (2H, t, *J*=7.4 Hz), 8.00 (4H, s), 8.08 (2H, d, *J*=9.2 Hz), 8.13–8.15 (6H, m), 8.21 (2H, d, *J*=8.0 Hz), 8.27 (2H, s), 8.33 (2H, d, *J*=9.2 Hz).

4.8.2. 1,3-Bis-[(*R*)-1-(1-pyrenyl)ethyl]imidazolium chloride. Following the general procedure given for **6**, glyoxal-bis-[(*R*)-1-(1-pyrenyl)ethyl]imine (492 mg, 0.96 mmol) was reacted with chloromethyl ethyl ether at room temperature for 1 h, and then for 16 h at 40 °C. The resulting precipitates were collected by filtration and dissolved in dichloromethane/methanol. The solution was treated by an activated carbon and evaporated to afford the chloride (351 mg, 65%). Slight yellow granules (methanol/ether); mp 240–245 °C (decomp); $[\alpha]_D^{24}$ −32.5 (*c* 0.16, EtOH, 23.3 °C); ^{1}H NMR ($CDCl_3$) *δ*: 2.29 (6H, d, *J*=6.7 Hz, C*H*$_3$CH), 7.10 (2H, q, *J*=6.7 Hz, CH_3C*H*), 6.65 (2H, s), 7.93 (2H, d, *J*=8.0 Hz), 7.96 (2H, d, *J*=9.2 Hz), 8.00 (2H, t, *J*=7.4 Hz), 8.05 (2H, d, *J*=8.6 Hz), 8.07 (2H, d, *J*=8.0 Hz), 8.13–8.19 (6H, m), 8.41 (2H, d, *J*=9.2 Hz), 11.76 (1H, s); ^{13}C NMR ($CDCl_3$) *δ*: 20.2, 47.5, 121.0, 122.1, 124.3, 124.7, 125.1, 125.4, 125.7, 126.3, 126.9, 127.9, 128.0, 128.6, 130.6, 131.3, 131.4, 131.6; HRMS (FAB) *m*/*z* calcd for $C_{39}H_{29}N_2$ (M^+): 525.2331, found: 525.2340.

4.8.3. 1,3-Bis-[(*R*)-1-(1-pyrenyl)ethyl]imidazolium tetrafluoroborate (*R*,*R*)-17. Following the procedure given for (*R*,*R*)-**12**, 1,3-bis-[(*R*)-1-(1-pyrenyl)ethyl]imidazolium chloride was treated with $AgBF_4$ to give (*R*,*R*)-**17** (60%) as a slight brown solid. This compound was used in the acylation reaction without further purification.

4.9. Preparation of 1,3-bis-[(*S*)-1-(9-phenanthryl)ethyl] imidazolium tetrafluoroborate (*S*,*S*)-18

4.9.1. Glyoxal-bis-[(*S*)-1-(9-phenanthryl)ethyl]imine. Following the general procedure given for glyoxal-bis-imine, (*S*)-(−)-1-(9-phenanthryl)ethylamine[23] (69 mg, 0.8 mmol) was reacted with glyoxal for 30 min at room temperature, and then for 2 h at 60 °C. The imine was quantitively obtained by extraction with dichloromethane and used in the subsequent reaction without further purification; ^{1}H NMR ($CDCl_3$) *δ*: 1.80 (6H, d, *J*=6.9 Hz, C*H*$_3$CH), 5.45 (2H, q, *J*=6.9 Hz, CH_3C*H*), 7.56–7.69 (8H, m), 7.88 (2H, d, *J*=8.0 Hz), 7.95 (2H, s), 8.17 (2H, d, *J*=9.2 Hz), 8.27 (2H,s), 8.64 (2H, d, *J*=8.0 Hz), 8.74 (2H, d, *J*=9.2 Hz).

4.9.2. 1,3-Bis-[(*S*)-1-(9-phenanthryl)ethyl]imidazolium chloride. Following the general procedure given for **6**, glyoxal-bis-[(*S*)-1-(9-phenanthryl)ethyl]imine (186 mg, 0.4 mmol) was reacted with chloromethyl ethyl ether at 40 °C for 20 h to afford the imidazolium chloride (104 mg, 60%) as a solid. Slight yellow powder (dichloromethane/ether); mp 177–180 °C; $[\alpha]_D^{24}$ −69.6 (*c* 1.0, $CHCl_3$, 23.0 °C); ^{1}H NMR ($CDCl_3$) *δ*: 2.09 (6H, d, *J*=6.8 Hz, C*H*$_3$CH), 6.72 (2H, q, *J*=6.8 Hz, CH_3C*H*), 6.87 (2H, s), 7.51–7.61 (8H, m), 7.63 (2H, s), 7.75 (2H, d, *J*=8.0 Hz), 8.01 (2H, d, *J*=7.9 Hz), 8.50 (2H, d, *J*=8.6 Hz), 8.58 (2H, d, *J*=8.0 Hz), 10.83 (1H, s); ^{13}C NMR ($CDCl_3$) *δ*: 21.5, 56.3, 120.7, 122.5, 123.3, 123.6, 126.1, 127.2, 127.2, 127.8, 128.0, 128.9, 129.3, 130.5, 130.7, 130.9, 131.4, 137.3.

4.9.3. 1,3-Bis-[(*S*)-1-(9-phenanthryl)ethyl]imidazolium tetrafluoroborate (*S*,*S*)-18. Following the procedure given for (*R*,*R*)-**12**, 1,3-bis-[(*S*)-1-(9-phenanthryl)ethyl]-imidazolium chloride was treated with $AgBF_4$ to give (*R*,*R*)-**18** (61%) as a slight brown solid. This compound was used in the acylation reaction without further purification.

4.10. General procedure for *N*-heterocyclic carbene-catalyzed asymmetric aclation of secondary alcohols

Potassium *tert*-butoxide (0.25 mmol) was added to a suspension of azolium salt (0.3 mmol) in ether (2 mL). The mixture was stirred at room temperature for 30 min. Vinyl acetate (1.2 mmol) and alcohol (1 mmol) were added at the indicated temperature to the mixture. The resulting mixture was stirred for the indicated time. The solvent was evaporated and the residue was purified by silica gel column chromatography by using ethyl acetate/hexane.

The results summarized in Table 3 were obtained by taking 5 μL of the sample from the reaction mixture, filtering it through a short silica gel column, and then subjecting to chiral HPLC analysis.

4.10.1. 1-(1-Naphthyl)ethanol 7. Analytical chiral HPLC: Chiralcel OD column, 0.46×25 cm, hexane/2-propanol 9:1, 0.5 mL min^{-1}; *S*, 19.8 min, *R*, 29.4 min. Chiralcel OD-H

column, 0.46×15 cm, hexane/2-propanol 9:1, 1 mL min^{-1}; *S*, 6.2 min, *R*, 9.7 min.

4.10.2. 1-(1-Naphthyl)ethyl acetate 8. Analytical chiral HPLC: Chiralcel OD column, 0.46×25 cm, hexane/2-propanol 9:1, 1 mL min^{-1}; *R*, 5.3 min, *S*, 6.4 min.

4.10.3. 1-(1-Phenyl)ethanol 19. Analytical chiral HPLC: Chiralcel OD column, 0.46×25 cm, hexane/2-propanol 95:5, 0.5 mL min^{-1}; *S*, 16.5 min, *R*, 19.7 min.

4.10.4. 1-(1-Phenyl)ethyl acetate 22. Analytical chiral HPLC: Chiralpac AS column, 0.46×25 cm, hexane/2-propanol 100:0.1, 0.5 mL min^{-1}; *R*, 15.8 min, *S*, 19.8 min.

4.10.5. 1-(2-Naphthyl)ethanol 20. Analytical chiral HPLC: Chiralpac AS column, 0.46×25 cm, hexane/2-propanol 97.5:2.5, 0.5 mL min^{-1}; *S*, 30.1 min, *R*, 35.1 min.

4.10.6. 1-(2-Naphthyl)ethyl acetate 23. Analytical chiral HPLC: Chiralpac AS column, 0.46×25 cm, hexane/2-propanol 99:1, 0.5 mL min^{-1}; *R*, 13.5 min, *S*, 16.3 min.

4.10.7. 1,2,3,4-Tetrahydro-1-naphtol 21. Analytical chiral HPLC: Chiralpac AS column, 0.46×25 cm, hexane/2-propanol 97.5:2.5, 0.5 mL min^{-1}; 20.6 min, 26.6 min.

4.10.8. 1,2,3,4-Tetrahydro-1-naphthyl acetate 24. Analytical chiral HPLC: Chiralpac AS column, 0.46×25 cm, hexane/2-propanol 97.5:2.5, 0.5 mL min^{-1}; 12.2 min, 15.7 min.

4.10.9. 1-(1-Naphthyl)ethyl propionate. Analytical chiral HPLC: Chiralcel OD column, 0.46×25 cm, hexane/2-propanol 9:1, 0.5 mL min^{-1}; *R*, 9.7 min, *S*, 11.3 min.

4.10.10. 1-(1-Naphthyl)ethyl butyrate. Analytical chiral HPLC: Chiralcel OD–H column, 0.46×15 cm, hexane/2-propanol 98:2, 1 mL min^{-1}; *R*, 3.4 min, *S*, 4.2 min.

4.10.11. 1-(1-Naphthyl)ethyl benzoate. Analytical chiral HPLC: Chiralpac AD-H column, 0.46×15 cm, hexane/2-propanol 98:2, 1 mL min^{-1}; *R*, 5.6 min, *S*, 7.0 min.

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Synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide based on L-proline-catalyzed asymmetric aldol reactions

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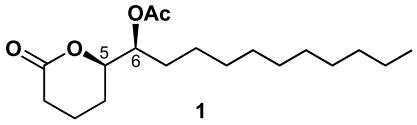
Received 1 June 2005; revised 8 August 2005; accepted 31 August 2005

Available online 3 October 2005

Abstract—A convenient method for proline-catalyzed asymmetric aldol reactions using synthons of straight-chain aliphatic aldehydes, and aldehydes bearing a 1,3-dithiane moiety at the β-position, has been developed. This method was successfully applied to the synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide, an oviposition attractant pheromone of the female *Culex* mosquito.

1. Introduction

Recent advances in the field of organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds in an environmentally benign manner.[1] Most attention has been focused on the use of proline due to its ready availability in either L- or D-form and the highly versatile nature of its reactivity.[1,2] In particular, proline-catalyzed asymmetric aldol reactions have been extensively studied from the viewpoint of their synthetic value as well as mechanistic considerations.[1–3] However, there is still a significant limitation on the use of unsubstituted aliphatic aldehydes as an aldol component.[4] Initially, we thought that this problem could be solved by applying a high-pressure technique,[5] but all attempts failed due to the formation of a rather complex mixture. Very recently, Sun et al. reported the use of undecanal itself for asymmetric aldol reactions of this type and applied it in their synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**1**).[6] This result prompted us to report our independent investigation on the development of new synthons of straight-chain aliphatic aldehydes and their application to the enantioselective synthesis of **1**.[7]



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(−)-(5*R*,6*S*)-6-Acetoxyhexadecanolide (**1**), an oviposition attractant pheromone of the female *Culex* mosquito, has attracted considerable attention from synthetic chemists[8] because of its ability to transmit the West Nile virus.[9] In this lab we reported the short synthesis of this compound based on a chiral triflate technology starting from D-tartrate as the chiral source.[10] In recent years, with the increasing demand for catalytic asymmetric transformations, major studies on the synthesis of **1** have focused on demonstrating of the power of newly discovered techniques.[11] Unfortunately, however, there are no reports on the use of organocatalytic systems to construct this fascinating molecule, except for the recent work of Sun et al.[6] We describe here our own approach using proline-catalyzed asymmetric aldol reactions as a key step along with straight-chain aliphatic aldehyde synthons.

2. Results and discussion

2.1. Model studies for L-proline-catalyzed asymmetric aldol reactions

To survey the possible candidates for straight-chain aliphatic aldehyde synthons, we designed three different types of substrates, that is, thiophenecarboxaldehydes **A** and aldehydes bearing a 1,3-dithiane moiety at the α- or β-position (**B** and **C**), because of the ease at which they are converted to the naked unbranched side chain structures after desulfurization (Fig. 1).[12] Thus, compounds **A** and **B** were chosen as representative aldehydes having no enolizable α-hydrogens, while with **C** it can be expected that the 1,3-dithiane function can act effectively as steric bulk to impede the undesired side reactions.[13]

To confirm the feasibility of our synthetic strategy, we then

Keywords: Proline; Aldol; Aldehydes; Oviposition attractant pheromone.
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doi:10.1016/j.tet.2005.08.111

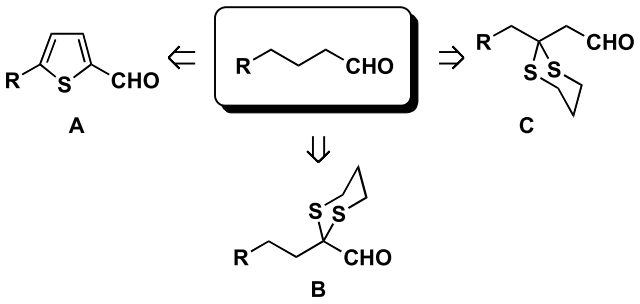


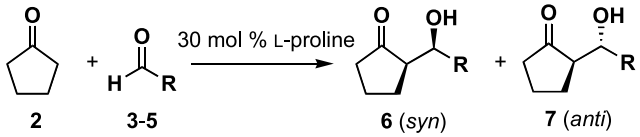
Figure 1. Straight-chain aliphatic aldehyde synthons.

aldehyde carbonyl center (runs 4–6). Fortunately, we found that the use of aldehyde **5** led to the preferential formation of *syn*-adduct **6** with high enantioselectivity (runs 7–9). Apparently, in **5** the β-dithiane functionality exerts a remarkable effect in determining the reaction course with favorable diastereo- and enantioselective control. With these results in hand, we proceeded with the asymmetric synthesis of **1**.

2.2. Total synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide (1)

The required aldehyde **11** was readily prepared from ethyl

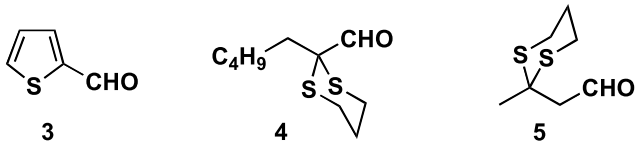
Table 1. L-Proline-catalyzed asymmetric aldol reactions of cyclopentanone (**2**) with aldehydes **3–5**



Run	Aldehyde	Conditions[a]	Yield (%)	dr **6**/**7**[b]	ee (%)[c]	
					6	**7**
1	**3**	DMSO, rt, 30 h[d]	82	48:52	31	34
2	**3**	Solvent-free, rt, 84 h	79	47:53	43	48
3	**3**	Solvent-free, 0.2 GPa, rt, 60 h	77	41:59	15	22
4	**4**	DMSO, rt, 72 h[d]	No reaction			
5	**4**	Solvent-free, rt, 72 h	No reaction			
6	**4**	Solvent-free, 0.2 GPa, rt, 24 h	No reaction			
7	**5**	DMSO, rt, 9 h[d]	75	80:20	93	86
8	**5**	Solvent-free, rt, 6 h	81	80:20	93	85
9	**5**	Solvent-free, 0.2 GPa, rt, 12 h	86	73:27	90	88

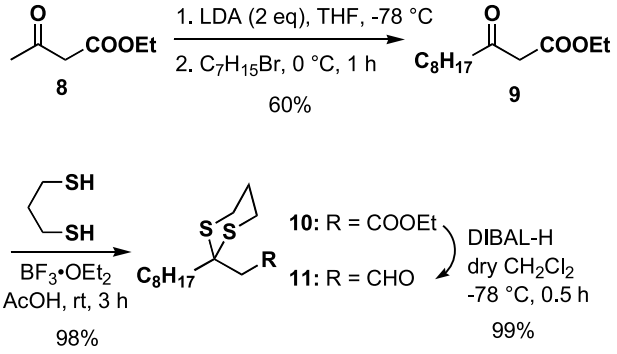
[a] Compound **2**:aldehyde 34:1, except in DMSO (6.5 equiv of **2**).
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC (Chiralpak AD).
[d] Compound **2**:DMSO 1:4 (vol%).

examined the asymmetric aldol reactions of cyclopentanone (**2**) with thiophenecarboxaldehyde **3** (**A**, R=H), aldehydes **4** (**B**, R=C_2H_5) and **5** (**C**, R=H) under the catalysis of L-proline. The starting aldehydes **4** and **5** were prepared from 2-pentyl-1,3-dithiane[14] via well-known lithiation/formylation or by the sequential treatment of ethyl acetoacetate according to the literature procedure.[15]



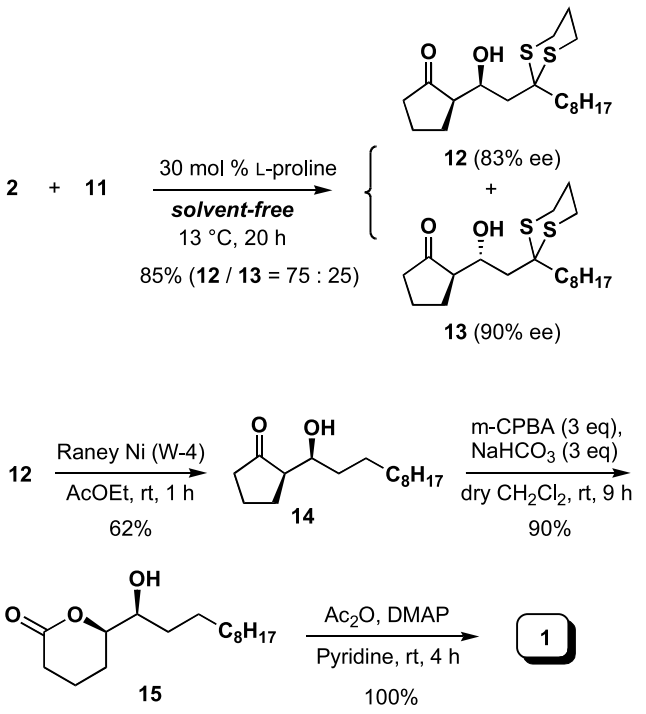
All reactions were examined under three different conditions: (1) in DMSO as a solvent at room temperature; (2) solvent-free at room temperature; and (3) solvent-free at 0.2 GPa pressure and room temperature. As can be seen from the results summarized in Table 1,[16] there is a significant difference in reactivity and stereoselectivity between **3–5**.

Thus, thiophenecarboxaldehyde (**3**) gave the desired adducts **6** and **7** in good yields, but diastereo- and enantioselectivity were only moderate under either condition (runs 1–3). Aldehyde **4** was inert under these conditions, indicating severe steric hindrance around the acetoacetate (**8**) after chain elongation[17] as illustrated in Scheme 1. We then proceeded to complete the total synthesis of **1** according to our original idea (Scheme 2).



Scheme 1.

The aldol reaction of **11** with cyclopentanone (**2**, ca. 30 equiv) in the presence of 30 mol% of L-proline under solvent-free conditions at 13 °C for 20 h proceeded quite smoothly to give *syn*- and *anti*-adducts, **12** and **13**, as a 75:25 mixture in a combined yield of 85%.[18,19] The enantiomeric purities of **12** and **13** were determined to be 83 and 90%, respectively, by chiral HPLC analysis (Chiralpak AD, elution with hexane/2-propanol 90:10). After chromatographic separation, careful treatment of the



Scheme 2.

syn-adduct **12** with Raney-Ni (W-4) in ethyl acetate[20] as a solvent gave the desired β-hydroxy ketone **14** in 62% yield as a somewhat unstable product. Therefore, this was immediately subjected to Baeyer–Villiger oxidation by exposure to 3 equiv of *m*-CPBA and 3 equiv of $NaHCO_3$, and the hydroxy-lactone **15** was obtained in 90% yield as a highly crystalline substance. Recrystallization from ether/hexane gave optically pure **15**; mp 67–68 °C, $[\alpha]_D^{20}-12.7$ (*c* 1.0, $CHCl_3$) (lit.[6] mp 66.5–68 °C, $[\alpha]_D-11.0$ (*c* 1.5, $CHCl_3$)), which was finally converted into **1** by acetylation under normal conditions in quantitative yield. This compound, $[\alpha]_D^{21}-36.8$ (*c* 1.55, $CHCl_3$) (lit.[10] $[\alpha]_D^{24}-36.8$ (*c* 1.0, $CHCl_3$)), was identical in all respects to the authentic sample.[10]

3. Conclusions

In conclusion, we have developed a convenient method for the asymmetric aldol reactions of ketones with aldehydes bearing a 1,3-dithiane moiety at the β-position as convenient synthons of straight-chain aliphatic aldehydes. The reaction was successfully applied to the synthesis of **1**. This approach might be useful for preparing a variety of enantiomerically enriched β-hydroxy ketone derivatives, and further studies to extend the scope of this method are now in progress.

4. Experimental

4.1. General

All reactions were performed in an oven-dried glassware under a positive pressure of nitrogen or argon. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. All high-pressure reactions were performed in a piston-cylinder type apparatus (Hikari Koatsu HR-15-B3).

All melting points were measured on Yanagimoto MP-S3 micro-melting point apparatus and were uncorrected. The NMR spectra were recorded on a JEOL LA 400 (400 MHz for ^1H NMR analysis and 100 MHz for ^{13}C NMR analysis). All NMR spectra were taken in $CDCl_3$ solution and were reported in part per millions (δ) downfield from TMS as an internal standard. The infrared spectra were measured with a JASCO FTIR-460plus Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analysis was carried out using a Hitachi L-6200 HPLC system.

Thin-layer chromatography (TLC) was conducted by using Merck Kieselgel 60F-254 plates (0.25 mm). For column chromatography, Fuji silicia BW-300 and, for flash chromatography, Merck Kieselgel (230–400 mesh) was employed.

4.1.1. 2-Pentyl-1,3-dithiane-2-carbaldehyde (3). To a stirred solution of 2-pentyl-1,3-dithiane (1.82 g, 9.6 mmol)[14] in dry THF (43 mL) at −78 °C was added *n*-BuLi (7.1 mL, 11.2 mmol; 1.58 M in hexanes) and the mixture was stirred for 2 h. To this light yellow solution was then added dry DMF (0.77 mL, 10 mmol) and the mixture was stirred at −78 °C for 1 h. The mixture was quenched with H_2O and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 9:1) to give **3** (1.3 g, 62%) as a colorless oil. R_f 0.47 (hexane/Et_2O 4:1); FTIR (neat) 1715, 1465, 1424; ^1H NMR: 0.88 (3H, t, J= 7.1 Hz), 1.22–1.36 (4H, m), 1.42–1.50 (2H, m), 1.74–1.86 (3H, m), 2.10 (1H, dtt, J=14.2, 4.1, 2.4 Hz), 2.60 (2H, ddd, J=14.6, 4.1, 3.2 Hz), 3.02 (2H, ddd, J=14.6, 12.9, 2.4 Hz); ^{13}C NMR: 13.8, 22.2, 23.4, 24.5, 26.7 (×2), 31.9, 35.9, 58.1, 189.6. Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.00; H, 8.31. Found: C, 55.08; H, 8.50.

4.2. General procedure for the L-proline-catalyzed asymmetric aldol reactions

Method A (in DMSO at 1 atm and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**, 0.3 mL, 3.4 mmol) and L-proline (17 mg, 0.15 mmol) in dry DMSO (1.2 mL) was stirred at room temperature under Ar. After completion of the reaction, the mixture was quenched with water and the aqueous phase was extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography to give the pure *syn*- and *anti*-aldol adducts.

Method B (solvent-free at 1 atm and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**, 1.5 mL, 17.0 mmol) and L-proline (17 mg, 0.15 mmol) was stirred at room temperature under Ar, and then treated as above.

Method C (solvent-free at 0.2 GPa and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**,

1.5 mL, 17.0 mmol) and L-proline (17 mg, 0.15 mmol) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.2 GPa and room temperature. After completion of the reaction, the mixture was treated as above.

4.2.1. *syn*-Adduct 6 from 3. Colorless needles; mp 64–67 °C (from Et_2O/hexane); R_f 0.32 (cyclohexane/Et_2O 1:1); $[\alpha]_D^{26}+62.2$ (*c* 1.75, $CHCl_3$; 30% ee); FTIR (KBr): 3366, 1719, 1450, 1401, 1161, 1029; ^{1}H NMR: 1.70–1.83 (1H, m), 1.98–2.10 (3H, m), 2.10–2.22 (1H, m), 2.33–2.41 (1H, m), 2.56 (1H, m), 2.71 (1H, d, $J=5.6$ Hz), 5.50 (1H, dd, $J=5.1$, 3.2 Hz), 6.95–6.99 (2H, m), 7.24 (1H, dd, $J=4.6$, 1.7 Hz); ^{13}C NMR: 20.5, 23.4, 39.1, 55.7, 68.8, 123.9, 124.6, 126.7, 146.3, 220.1. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.36; H, 6.26.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 90:10, 0.5 mL/min): t_R 17.2 and 19.1 min.

4.2.2. *anti*-Adduct 7 from 3. Colorless oil; R_f 0.25 (cyclohexane/Et_2O 1:1); $[\alpha]_D^{16}-88.2$ (*c* 1.05, $CHCl_3$; 48% ee); FTIR (neat): 3450, 1719, 1449, 1402, 1358, 1222, 1157; ^{1}H NMR: 1.51–1.62 (1H, m), 1.70–1.85 (1H, m), 1.87–2.04 (2H, m), 2.25 (1H, ddd, $J=19.3$, 11.0, 8.8 Hz), 2.40–2.55 (2H, m), 4.65 (1H, s), 5.02 (1H, d, $J=9.3$ Hz), 6.94–6.97 (2H, m), 7.28 (1H, dd, $J=4.9$, 1.4 Hz); ^{13}C NMR: 20.3, 27.0, 38.7, 55.8, 71.3, 124.4, 125.1, 126.4, 145.2, 222.4. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 60.88; H, 6.12.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 90:10, 0.5 mL/min): t_R 22.3 and 23.7 min.

4.2.3. *syn*-Adduct 6 from 5. Colorless oil; R_f 0.20 (cyclohexane/AcOEt 2:1); $[\alpha]_D^{18}+61.4$ (*c* 1.40, $CHCl_3$; 82% ee); FTIR (neat): 3449, 1732, 1449, 1421, 1403; ^{1}H NMR: 1.68 (3H, s), 1.69–1.83 (1H, m), 1.83–1.96 (1H, m), 1.97 (1H, dd, $J=15.0$, 1.6 Hz), 2.00–2.20 (6H, m), 2.28–2.36 (1H, m), 2.39 (1H, dd, $J=15.0$, 9.8 Hz), 2.78 (1H, dt, $J=14.4$, 3.2 Hz), 2.80 (1H, dt, $J=14.4$, 3.2 Hz), 2.97 (1H, ddd, $J=14.4$, 5.8, 2.9 Hz), 3.00 (1H, ddd, $J=14.4$, 5.8, 2.9 Hz), 3.21 (1H, d, $J=2.9$ Hz), 4.43 (1H, dd, $J=9.8$, 1.6 Hz); ^{13}C NMR: 20.7, 23.4, 24.6, 26.6, 26.8, 28.5, 39.0, 45.4, 47.6, 54.9, 67.2, 219.8. Anal. Calcd for $C_{12}H_{20}O_2S_2\cdot 1/8H_2O$: C, 54.87; H, 7.77. Found: C, 54.85; H, 7.66.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 80:20, 0.7 mL/min): t_R 12.8 and 13.8 min.

4.2.4. *anti*-Adduct 7 from 5. Colorless oil; R_f 0.24 (cyclohexane/AcOEt 2:1); $[\alpha]_D^{19}-85.8$ (*c* 1.79, $CHCl_3$; 93% ee); FTIR (neat): 3481, 1723, 1448, 1421; ^{1}H NMR: 1.70 (3H, s), 1.68–1.84 (2H, m), 1.85–1.96 (1H, m), 1.98 (1H, d, $J=15.1$ Hz), 1.99–2.12 (2H, m), 2.13–2.27 (3H, m), 2.32–2.39 (1H, m), 2.40 (1H, dd, $J=14.9$, 9.3 Hz), 2.79 (1H, ddd, $J=14.4$, 7.4, 3.4 Hz), 2.81 (1H, ddd, $J=14.4$, 7.4, 3.4 Hz), 2.91 (1H, ddd, $J=14.4$, 9.8, 2.9 Hz), 2.96 (1H, ddd, $J=14.4$, 9.8, 2.9 Hz), 4.06 (1H, br s), 4.13 (1H, m); ^{13}C NMR: 20.5, 24.8, 26.5, 26.7, 26.8, 28.3, 39.0, 45.5, 47.9, 53.9, 69.5, 221.7. Anal. Calcd for $C_{12}H_{20}O_2S_2$: C, 55.35; H, 7.74. Found: C, 55.28; H, 7.98.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 85:15, 0.7 mL/min): t_R 13.4 and 16.4 min.

4.2.5. Ethyl 3-oxoundecanoate (9). To a solution of LDA, prepared from *i*-Pr_2NH (9.12 mL, 65.1 mmol) and *n*-BuLi (44 mL, 65.08 mmol; 1.48 M in hexanes), in dry THF (60 mL) at −78 °C was added dropwise ethyl acetoacetate (3.32 mL, 26.0 mmol) and the mixture was stirred at −78 °C for 1 h. After warming to 0 °C, to this light yellow solution was added dropwise 1-bromoheptane (4.5 mL, 28.64 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was quenched with ice-cold 2 M HCl and extracted with Et_2O. The combined extracts were washed with satd NaCl, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (hexane/Et_2O 2:1) to give **9** (3.58 g, 60%) as a colorless oil; R_f 0.47 (hexane/Et_2O 2:1); FTIR (neat): 1747, 1718, 1466, 1234, 1031; ^{1}H NMR: 0.88 (3H, t, $J=7.2$ Hz), 1.27 (9H, m), 1.28 (3H, t, $J=7.3$ Hz), 1.60 (3H, m), 2.53 (2H, t, $J=7.4$ Hz), 3.43 (2H, s), 4.20 (2H, q, $J=7.3$ Hz); ^{13}C NMR: 14.0(5), 14.0(7), 22.6, 23.4, 29.0, 29.1, 29.3, 31.8, 43.0, 49.3, 61.3, 167.3, 203.0. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.47; H, 10.56.

4.2.6. Ethyl (2-octyl-1,3-dithian-2-yl)acetate (10). To a solution of **9** (3.5 g, 15 mmol) in AcOH at room temperature were added $BF_3\cdot Et_2O$ (1 g, 7.05 mmol) and 1,3-propanedithiol (1.8 g, 16.6 mmol) and the mixture was stirred for 3 h. After cooling to 0 °C, the mixture was quenched with H_2O, neutralized with aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **10** (4.7 g, 98%) as a colorless oil; R_f 0.58 (hexane/AcOEt 2:1); FTIR (neat): 1735, 1185; ^{1}H NMR: 0.88 (3H, t, $J=7.3$ Hz), 1.27 (3H, t, $J=7.1$ Hz), 1.30 (9H, m), 1.55 (3H, m), 1.87 (1H, ddt, $J=14.0$, 11.2, 3.2 Hz), 2.02–2.12 (3H, m), 2.73 (2H, ddd, $J=14.2$, 5.4, 3.4 Hz), 3.04 (2H, ddd, $J=14.2$, 11.2, 2.8 Hz), 3.05 (2H, s), 4.15 (2H, q, $J=7.1$ Hz); ^{13}C NMR: 14.1, 14.2, 22.6, 23.7, 25.0, 26.4 (×2), 29.2, 29.4, 29.7, 31.8, 39.5, 42.7, 50.3, 60.5, 168.9. HRMS calcd for $C_{16}H_{30}O_2S_2$ 318.1687, found 318.1678.

4.2.7. (2-Octyl-1,3-dithian-2-yl)acetaldehyde (11). To a solution of **10** (2.75 g, 8.6 mmol) in dry CH_2Cl_2 (70 mL) at −78 °C was added a solution of DIBAL-H in toluene (1.0 M; 10.8 mL, 10.8 mmol) over 0.5 h and the mixture was placed in a freezer at −78 °C for 0.5 h. The excess of DIBAL-H was quenched with AcOH (0.45 mL) and warmed to room temperature. The mixture was then stirred with satd Rochelle's salt until the suspension disappeared and a clear two-phase solution was obtained. The aqueous phase was extracted with CH_2Cl_2 and the extracts were washed with satd $NaHCO_3$ and satd NaCl, dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt 2:1) gave **11** (2.33 g, 99%) as a colorless oil; R_f 0.56 (hexane/AcOEt 2:1); FTIR (neat): 1718, 1465, 1423; ^{1}H NMR: 0.88 (3H, t, $J=7.1$ Hz), 1.27 (10H, m), 1.50 (2H, m), 1.90–2.09 (4H, m),

2.83 (2H, ddd, J=14.6, 6.8, 3.7 Hz), 2.91 (2H, d, J=2.7 Hz), 2.91 (2H, ddd, J=14.6, 9.5, 3.4 Hz), 9.78 (1H, t, J=2.7 Hz); ^{13}C NMR: 13.9, 22.4, 23.8, 24.5, 26.0 (×2), 29.0, 29.1, 29.5, 31.6, 40.2, 49.1, 49.9, 199.53. HRMS calcd for $C_{14}H_{26}OS_2$ 274.1425, found 274.1407.

4.2.8. L-Proline-catalyzed asymmetric aldol reaction of cyclopentanone (2) with aldehyde (11). The mixture of **11** (6.82 g, 24.8 mmol), cyclopentanone (**2**, 74.73 mL, 845 mmol) and L-proline (858 mg, 7.45 mmol) was stirred at 13 °C for 20 h under Ar. The mixture was quenched with H_2O and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **12** (5.64 g, 63% yield; 83% ee) and **13** (1.91 g, 22% yield; 90% ee) as a colorless oil, respectively. The ee of these adducts were determined by chiral HPLC (254 nm, flow rate: 0.7 mL/min) carried out with Chiralpak AD (hexane/2-propanol 90:10; product **12** t_R 9.5 and 11.5 min, product **13** t_R 11.7 and 13.3 min).

4.2.9. (2*R*)-2-[(1*S*)-1-Hydroxy-2-(2-octyl-1,3-dithian-2-yl)ethyl]cyclopentanone (12). R_f 0.36 (hexane/AcOEt 2:1); $[\alpha]_D^{22}$ +45.6 (*c* 1.6, $CHCl_3$); FTIR (neat): 3446, 1736, 1457, 1421; ^{1}H NMR: 0.88 (3H, t, J=7.3 Hz), 1.29 (10H, m), 1.41 (1H, m), 1.53 (1H, m), 1.70–1.80 (1H, m), 1.85–2.18 (10H, m), 2.31 (1H, m), 2.37 (1H, dd, J=15.1, 9.8 Hz), 2.73–2.81 (2H, m), 2.93 (1H, ddd, J=13.4, 10.2, 2.9 Hz), 2.99 (1H, ddd, J=13.4, 10.2, 2.9 Hz), 3.34 (1H, d, J=2.7 Hz), 4.42 (1H, d, J=9.5 Hz); ^{13}C NMR: 14.1, 20.7, 22.6, 23.3, 23.9, 24.9, 26.0, 26.4, 29.2, 29.4, 29.8, 31.8, 39.0, 39.7, 42.4, 52.1, 54.9, 66.9, 219.7. Anal. Calcd for $C_{19}H_{34}O_2S_2 \cdot 1/5\ H_2O$: C, 63.00; H, 9.57. Found: C, 62.93; H, 9.38.

4.2.10. (2*R*)-2-[(1*R*)-1-Hydroxy-2-(2-octyl-1,3-dithian-2-yl)ethyl]cyclopentanone (13). R_f 0.38 (hexane/AcOEt 2:1); $[\alpha]_D^{20}$ −70.3 (*c* 0.83, $CHCl_3$); FTIR (neat): 3483, 1722, 1456, 1418; ^{1}H NMR: 0.88 (3H, t, J=7.1 Hz), 1.30 (10H, m), 1.43 (1H, m), 1.55 (1H, m), 1.75–2.10 (8H, m), 2.14–2.26 (3H, m), 2.35 (1H, m), 2.47 (1H, dd, J=15.2, 9.3 Hz), 2.75–2.80 (2H, m), 2.89 (1H, ddd, J=14.0, 9.5, 3.2 Hz), 2.95 (1H, ddd, J=14.0, 9.5, 3.0 Hz), 4.07 (1H, s), 4.14 (1H, dd, J=9.3, 5.6 Hz); ^{13}C NMR: 14.1, 20.6, 22.7, 24.0, 25.1, 26.1, 26.4, 26.7, 29.3, 29.4, 29.8, 31.8, 39.1, 39.3, 42.3, 52.4, 54.0, 69.2, 221.4. Anal. Calcd for $C_{19}H_{34}O_2S_2$: C, 63.64; H, 9.56. Found: C, 63.56; H, 9.31.

4.2.11. (2*R*)-2-[(1*S*)-1-Hydroxyundecyl]cyclopentanone (14). To a solution of **12** (882 mg, 2.46 mmol) in AcOEt (100 mL) was added Raney-Ni (40 g; Aldrich Raney-Ni 2800 was washed successively with H_2O (×3), MeOH (×3), and AcOEt (×3)),[20] and the mixture was stirred at room temperature for 1 h. The insoluble material was removed by filtration and washed thoroughly with AcOEt and MeOH. After evaporation of the solvent, the crude product was purified quickly by silica gel column chromatography ($CHCl_3$/Et_2O 4:1) to give **14** (388 mg, 62%) as a colorless oil; R_f 0.39 ($CHCl_3$/Et_2O 4:1); FTIR (neat): 3419, 1730, 1468, 1454; ^{1}H NMR: 0.88 (3H, t, J=6.8 Hz), 1.26 (16H, s), 1.4–1.6 (2H, m), 1.6–2.0 (3H, m), 2.03–2.15 (3H, m), 2.15–2.24 (1H, m), 2.28–2.36 (1H, m), 4.10 (1H, br); ^{13}C NMR: 14.1, 20.6, 22.7, 22.9, 26.0, 29.3, 29.5, 29.6 (×3), 31.9, 34.8, 39.1, 54.4, 69.7, 221.5.

This sample was used immediately for the next reaction.

4.2.12. (5*R*,6*S*)-6-Hydroxy-5-hexadecanolide (15). To a solution of **14** (517 mg, 2.03 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C were added *m*-CPBA (98% activity; 700 mg, 4 mmol) and $NaHCO_3$ (340 mg, 4 mmol), and the mixture was stirred at room temperature for 4 h. To this mixture was added another portion of *m*-CPBA (98% activity; 350 mg, 2 mmol) and $NaHCO_3$ (170 mg, 2 mmol) and the mixture was stirred for 5 h. After completion of the reaction, the excess of *m*-CPBA was quenched with aq $Na_2S_2O_3$. The insoluble material was removed by filtration and washed with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with satd $NaHCO_3$ and satd NaCl, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 1:1) to give **15** (493 mg, 90%) as a colorless solid. Analytically pure **15** was obtained by recrystallization from Et_2O/hexane. Colorless needles; mp 67–68 °C (lit.[6] mp 66.5–68 °C); R_f 0.25 (hexane/AcOEt 1:1); $[\alpha]_D^{20}$ −12.7 (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]_D$ −11.0 (*c* 1.5, $CHCl_3$)); FTIR (KBr) 3421, 1714, 1267, 1054; ^{1}H NMR: 0.88 (3H, t, J=7.1 Hz), 1.26 (15H, s), 1.40–1.65 (4H, m), 1.71–2.02 (3H, m), 2.04 (1H, br), 2.45 (1H, ddd, J=17.6, 9.0, 7.1 Hz), 2.61 (1H, ddd, J=17.6, 7.1, 5.6 Hz), 3.83 (1H, m), 4.25 (1H, dt, J=10.7, 3.4 Hz); ^{13}C NMR: 14.1, 18.3, 21.2, 22.7, 25.9, 29.3, 29.5 (×2), 29.6 (×2), 29.8, 31.7, 31.9, 72.4, 83.4, 171.7. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.37; H, 11.26.

4.2.13. (5*R*,6*S*)-(−)-6-Acetoxy-5-hexadecanolide (1). The mixture of **15** (310 mg, 1.15 mmol), Ac_2O (0.33 mL, 3.5 mmol) and 4-(dimethylamino)pyridine (42 mg, 0.34 mmol) in dry pyridine (16 mL) was stirred at room temperature. After 4 h, the mixture was quenched with 10 M aq K_2CO_3 and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **1** (352 mg, 100%) as a colorless oil; R_f 0.23 (hexane/AcOEt 2:1); $[\alpha]_D^{21}$ −36.8 (*c* 1.55, $CHCl_3$) (lit.[10] $[\alpha]_D^{24}$ −36.8 (*c* 1.0, $CHCl_3$)); FTIR (neat): 1744, 1466, 1371, 1230; ^{1}H NMR: 0.88 (3H, t, J=6.9 Hz), 1.25 (16H, s), 1.55–1.70 (4H, m), 1.77–2.01 (2H, m), 2.08 (3H, s), 2.46 (1H, ddd, J=17.8, 9.2, 6.8 Hz), 2.60 (1H, dt, J=17.8, 6.4 Hz), 4.35 (1H, ddd, J=11.0, 4.9, 3.4 Hz), 4.98 (1H, dt, J=7.8, 5.1 Hz); ^{13}C NMR: 14.1, 18.3, 21.0, 22.7, 23.5, 25.3, 29.3(0), 29.3(9), 29.4(4), 29.4(8), 29.5(3), 29.5(5), 29.6(1), 31.9, 74.3, 80.5, 170.5, 170.9. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.41; H, 10.51.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture, and Sports, Japan, as well as a Special Research Grant for Green Science from Kochi University. We also thank Prof. Y. Fukuyama of Tokushima Bunri University for MS/HRMS measurements.

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19. The absolute configuration of **12** was confirmed after completion of the total synthesis.
20. After numerous trials with alternative procedures, we found Raney-Ni (Aldrich Raney 2800) in AcOEt to be most satisfactory. The use of MeOH or EtOH as a solvent gave poorer results.

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Tetrahedron 62 (2006) 317–328

Effect of additives on the proline-catalyzed ketone–aldehyde aldol reactions

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Received 3 June 2005; revised 15 August 2005; accepted 9 September 2005

Available online 21 October 2005

Abstract—The effect of bases, acids, and water as additives in proline-catalyzed ketone–aldehyde aldol reactions has been studied. While the reaction appears to be relatively tolerant to small amounts of tertiary amine bases or weak acids, it stops completely with strong acids. The use of water as an additive had a highly beneficial effect on reactions that were conducted with a stoichiometric ratio of ketone to aldehyde, especially with cyclic ketones. This allows the efficient use of more precious ketones such as 4-thianone as donors in the direct enantioselective aldol and facilitates purification.

1. Introduction

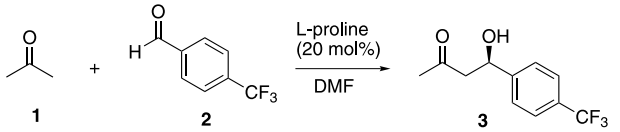
In the past 5 years, more than 10 different enantioselective proline-catalyzed reactions have been discovered.[1] Of the multitude of enantioselective reactions catalyzed by proline, the aldol reaction occupies a special position. The direct union of two carbonyl components by a proline-catalyzed aldol reaction often affords highly valuable products in high chemo-, diastereo- and enantioselectivity under very mild conditions. The intramolecular variant, known as the Hajos–Parrish–Eder–Sauer–Wiechert process,[2] was discovered in the 1970s and was soon adopted as the method of choice for the synthesis of steroidal ring systems. The intermolecular ketone–aldehyde variant was discovered by List, Barbas and Lerner in 2000,[3] and highly useful adaptations and applications of this procedure soon followed: enantioselective aldehyde–aldehyde coupling reactions,[4] very rapid carbohydrate[5] and polypropionate[6] syntheses, and very short total syntheses of natural products.[7]

Although L-proline is an inexpensive and readily available amino acid, it suffers from a number of problems that reduce its attractiveness as a catalyst: (1) poor solubility in most solvents except water (where it does function as a catalyst, but without any enantioselectivity),[8] and (2) potential side reactions such as oxazolidinone formation,[9] decarboxylation and subsequent [3+2] cycloaddition reactions.[10]

The mechanism of the proline-catalyzed aldol reactions has been thoroughly studied by both computational methods[11] and kinetic measurements.[12] These studies strongly suggest that only one proline molecule is involved in the enantioselectivity-determining step,[13] and the amine functionality most likely activates the carbonyl donor by the formation of the enamine.[11d,13] This allows the carboxylic acid moiety to form a hydrogen bond to the aldehyde (or ketone) acceptor.

Recent computational studies by Houk and co-workers suggest that although the enantioselectivity is determined at the aldol addition step, the rate-determining step could equally

Table 1. Effect of added base on the aldol reaction between acetone and *p*-trifluoromethylbenzaldehyde



1 (*excess, 20 vol%*) 2 3

Entry	Base (20 mol%)	pK_{aH}	Conversion after 2 h[a]	ee[a]
1	None		80	80
2	*N*,*N*-dimethylaniline	5.2	82	78
3	*N*-methylmorpholine	7.4	82	76
4	Triethylamine	10.6	87	79
5	Triethylamine (50 mol%)	10.6	84[b]	73[c]
6	Dimethylamine	10.7	74	54
7	DBU	11.6	80	2

[a] Determined by chiral GC.
[b] Average of three runs. The conversion varied between 74 and 93%.
[c] Average of three runs. The ee varied between 67 and 79%.

Keywords: Aldehydes; Aldol reactions; Bases; Ketones; Organocatalysis; Proline; Water.
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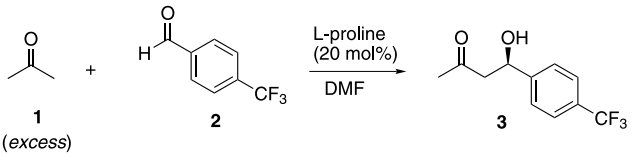
doi:10.1016/j.tet.2005.09.070

Table 2. Effect of temperature on the proline-catalyzed aldol reaction with and without triethylamine additive



1 (*excess*) 2 3

Entry	Base (50 mol%)	Temperature (°C)	Conversion after 5 min[a]	ee after 5 min[a]	Conversion after 2 h	ee
1	None	0	1	—	16	76
2	None	23	12	57	80	80
3	Triethylamine	0	15	3	35	38
4	Triethylamine	23	12	29	84	73

[a] The conversions and enantioselectivities were determined by chiral GC.

well be the formation of the enamine.[12,13] This immediately raises the possibility that certain acid or base additives might improve the overall rate of the reaction by promoting the enamine formation. Indeed, it has been reported that the direct aldol reaction catalyzed by L-valine was significantly accelerated by the addition of 10–30 mol% of an amine base.[14] On the other hand, Agami has proposed that proline could be acting as a Brønsted base in the intramolecular aldol process, promoting the formation of the racemic aldol product.[15] This suggests that perhaps the addition of a small amount of acid or a buffer might benefit the reaction.

Previously, we[16] and others[17] have reported that water, too, could act as a beneficial additive in aldol reactions with proline or its close derivatives. Herein, we report the full details of our study that led us to suggest the use of water as an additive in stoichiometric ketone–aldehyde aldol reactions catalyzed by proline.

2. Results and discussion

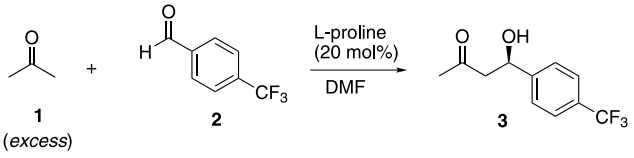
We initially studied the effect of base on the proline-catalyzed aldol reaction between 4-trifluorobenzaldehyde and acetone. This test system was selected because the products could readily be analyzed by chiral gas chromatography and the rate of reaction was reasonable (at rt, the reaction progressed to >85% conversion in 3 h). DMF was selected as the reaction solvent because it gave somewhat cleaner reactions and significantly less aldol condensation products than DMSO.[18]

The results of the effects of bases are collected in Tables 1 and 2. Disappointingly, none of the bases, with the exception of DBU, exerted a beneficial effect on the reaction rate. With DBU, the reaction was completed within 15 min, but with essentially no enantioselectivity. Apparently DBU is strong enough to act as a Brønsted base catalyst for the aldol reaction, overriding the slower proline-catalyzed process. Dimethylamine (entry 6) lowered the enantioselectivity, possibly as a result of competitive enamine catalysis.

Surprisingly, the addition of triethylamine caused a notable variability in the final ee of the reaction (ranging from 66 to 75% ee after 1 h reaction time with 50 mol% triethylamine). Furthermore, the enantioselectivity always rose during the reaction, from 29% ee (after 5 min) to 73% ee after 2 h (Table 2). This effect was even more pronounced when the reaction was conducted at 0 °C.[19] Other tertiary amine bases did not display this trend; with them, the enantioselectivity remained at 79±2% ee throughout the course of the reaction. In a control experiment without proline, no reaction was observed when the reactants were stirred together with 50 mol% triethylamine under the same conditions. Upon addition of proline to the reaction mixture, a rapid reaction ensued, resulting in 87% conversion in 30 min (65% ee).[†]

We then studied the effect of acids as additives (Table 3). Acetic acid had a slight retarding effect on the reaction,

Table 3. Effect of acids and amine salts on proline-catalyzed aldol reaction

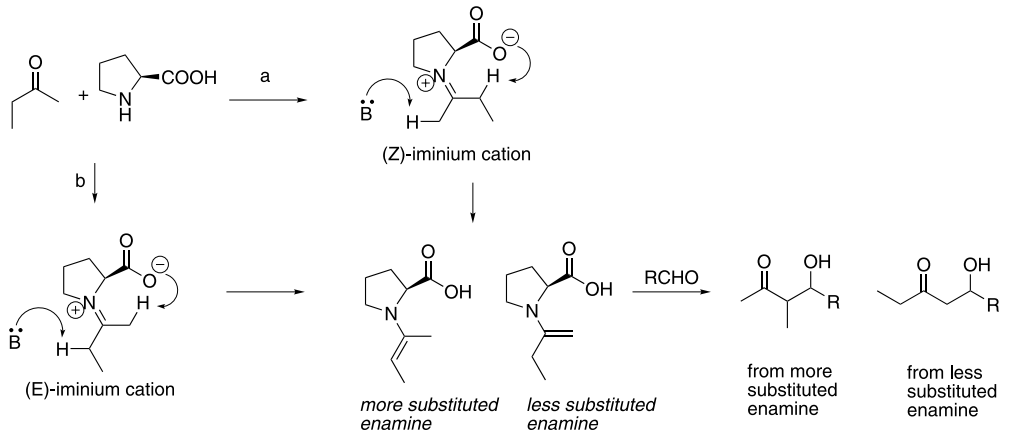


1 (*excess*) 2 3

Entry	Additive (50 mol%)	pK_a of the acid (pK_{aH} of the added base)	Conversion after 70 min[a]	ee[a]
1	None		65	77
2	CH_3COOH	4.8	45	77
3	CF_3COOH	−0.2	0	—
4	$Et_3N\cdot CH_3COOH$	4.8 (10.6)	67	64
5	$Et_3N\cdot HNO_3$	−1.3 (10.6)	52[b]	65[b]
6	$Et_3N\cdot HCl$	−8.0 (10.6)	57	79
7	Et_3N	(10.6)	50	73

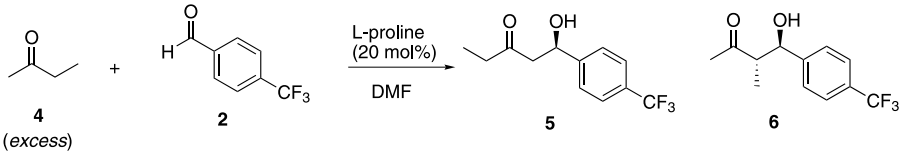
[a] Determined by chiral GC.
[b] After 50 min.

[†] Further control experiments revealed that initial racemization of the product in the reaction conditions could not explain the observed rise in ee. When the aldol product 3 (79% ee) was subjected to the reaction conditions without the aldehyde acceptor, only a very slow drop in enantioselectivity was observed (after 72 h, the product ee was 75%). In another control experiment, a second portion of the aldehyde was added to the reaction mixture after 1 h reaction time. After this addition, the reaction progressed along its usual course and no further change of ee was observed. We can only speculate that perhaps triethylamine serves to activate the proline catalyst in the initial stages of the reaction, perhaps by solubilizing the catalyst as a triethylammonium salt. Upon accumulation of the product, the product itself might be acting as a carrier of proline into the reaction mixture in its neutral or zwitterionic form, and the initial catalytic effect of the basic triethylammonium prolinate salt disappears when more and more proline is brought into solution where it may act as a buffer.



Scheme 1. Possible effect of external base on the enamine forming step of the proline-catalyzed aldol reaction.

Table 4. Effect of additives on the proline-catalyzed aldol reaction between 2-butanone and 4-trifluoromethylbenzaldehyde



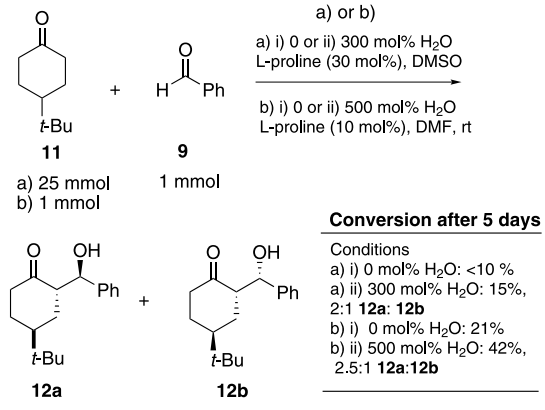
Entry	Additive (50 mol%)	pK_a	Conversion after 4 h	Product ratio **5**:**6**[a]	ee of the major product[a]
1	None		42	81:19	68
2	Et_3N	10.6	34	83:17	68
3	DBU	11.6	61	79:21	0

[a] Determined by chiral GC.

whereas trifluoroacetic acid, a stronger acid, brought the reaction to a complete halt. The enantioselectivity of the reaction was not affected by acetic acid. However, an equimolar mixture of acetic acid and triethylamine resulted in a slightly improved rate but lower ee. In this case, the enantioselectivity remained constant throughout the course of the reaction.[‡] Similar effects were observed with the triethylamine–nitric acid combination (entry 6). Interestingly, triethylammonium chloride had very little effect on the rate or the enantioselectivity of the reaction.

At this point, we reasoned that even if the external base or acid does not appear to boost the overall rate of the reaction, perhaps it could still affect the outcome of the enamine forming step (Scheme 1). In the case of unsymmetrical ketones such as 2-butanone, two different regiochemical outcomes can result, ultimately deriving from the two possible enamine regioisomers. Houk and co-workers have estimated that in the intramolecular proline-catalyzed aldol reaction, the transition state leading to the enamine is approximately equal in energy to the aldol addition step.[11d] Although the relative energies might well be different in intermolecular reactions, it seemed to us that the external base might nevertheless be able to affect the relative rates of enamine formation and thus, directly affect the product ratio in the case of 2-butanone. We were also encouraged by the fact that depending on the solvent used, widely differing product distributions have been reported for the proline-catalyzed reaction between 2-butanone and aromatic aldehydes such as **2**. The published product ratios range from essentially complete selectivity for the less substituted product[20] (e.g., **5**) to over 2:1 ratio[21] of **6** to **5** (see Table 4).

Unfortunately, as shown in Table 4, none of the additives had any appreciable effect on the regiochemical outcome. The products **5** and **6** were invariably formed as a ca. 4:1 mixture. Interestingly, DBU, a base that was clearly capable of acting alone as the catalyst, also afforded the product as a racemate in the same 4:1 ratio (entry 3).



Scheme 2. Effect of water and reaction stoichiometry on reactions of 4-*tert*-butylcyclohexanone with benzaldehyde. The conversions were determined by ^{1}H NMR analysis of the reaction mixture.

[‡] A control experiment with triethylamine–acetic acid combination but without proline gave no detectable conversion after 2 h.

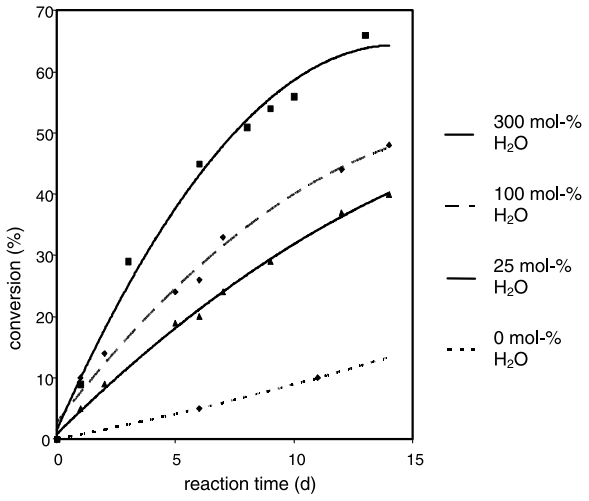


Figure 1. Effect of water on the rate of the reaction of 4-thianone and isobutyraldehyde (1 mmol 4-thianone, 2 mmol isobutyraldehyde, 10 mol% L-proline, 1 mL DMF, rt).

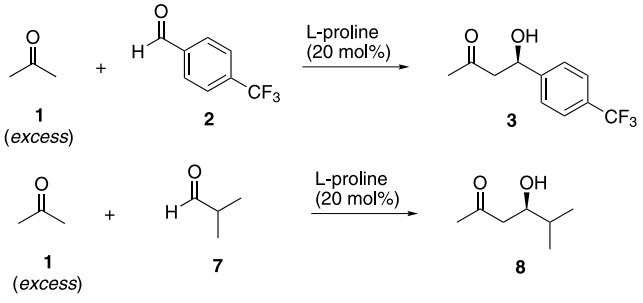
At this point, we concluded that none of the Brønsted acid or Brønsted base additives tried so far appeared to have beneficial effects. Perhaps quite surprisingly, the proline-catalyzed aldol reaction appears to be remarkably robust in that it can readily withstand the presence of either a weak acid (acetic acid) or weak base (triethylamine, *N*-methylmorpholine) without appreciable loss of activity or enantioselectivity. In all cases, the additives appeared to slow the reaction down slightly. We surmised, however, that a neutral additive such as water might help the turnover and possibly assist in the solubilization of proline into the reaction mixture. We were encouraged by the reports of Ohsawa and co-workers who reported that the enantioselectivities of proline-catalyzed Mannich reactions were significantly improved by the addition of water.[22]

Our initial experiments with acetone and water as the additive were not very encouraging. Both electron-poor aldehydes such as **2** as well as aliphatic, electron-rich aldehydes such as **7** gave lower conversions in the presence of water. The addition of small amounts of water did not appear to have any deleterious effect on the enantioselectivity of the reaction, however. These results are in perfect agreement with the results obtained by Barbas and co-workers, who demonstrated that these aldol reactions are tolerant of the addition of small amounts of water (up to 4 vol%, corresponding to ca. 2000 mol% in a 0.1 M reaction).

Water can play at least two different roles in the proline-catalyzed aldol process: it might help to increase the solubility into the reaction mixture, and it might also assist in the hydrolysis of the intermediate oxazolidinones that might be forming from the aldehyde, ketone, or the product. Since at least one of these components, the ketone, was present in a large excess we reasoned we should also test the effect of water in stoichiometric conditions, with 100 mol% of both ketone and aldehyde. Perhaps not entirely surprisingly, water had a completely different effect under these conditions (Tables 6 and 7). In all cases, the addition of water (100–500 mol%) both speeded up the reaction and increased the enantioselectivity.[23] With these reactions, DMSO gave somewhat higher reaction rates but significantly more enone formation was observed.[24]

With volatile and inexpensive ketones such as acetone and 2-butanone, the stoichiometric conditions offer only a limited advantage because the excess of ketone can readily

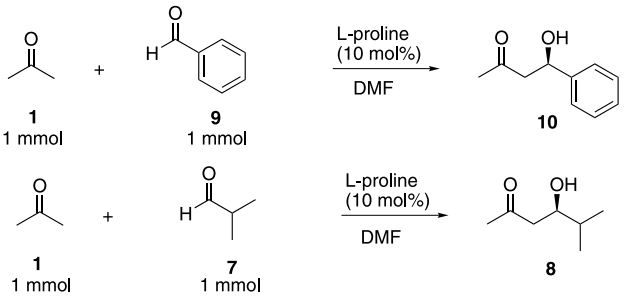
Table 5. Effect of water on the proline-catalyzed aldol reaction with excess acetone



Entry	Aldehyde acceptor	Solvent	Water (mol%)	Time (h)	Conversion[a]	ee[b]
1	**2**	DMF	0	1	61	77
2	**2**	DMF	0	2.5	87	77
3	**2**	DMF	0	4	92	77
4	**2**	DMF	100	4	85	nd
5	**2**	DMF	300	1	25	79
6	**2**	DMF	300	2.5	54	79
7	**2**	DMF	300	4	79	nd
8	**7**	DMF	0	24	15	nd
9	**7**	DMF	0	168	95	92
10	**7**	DMF	100	168	63	nd
11	**7**	DMF	300	168	68	nd
12	**7**	DMSO[c]	0	50	59	95
13	**7**	DMSO[c]	300	50	68	95

[a] Determined by GC (entries 1–7) or by ^{1}H NMR analysis of the crude reaction mixture (entries 8–13).
[b] Determined by chiral GC (entries 1–3, 5, 6) or by chiral HPLC (Chiralpak AD, entries 9, 12, 13).
[c] With 30 mol% L-proline.

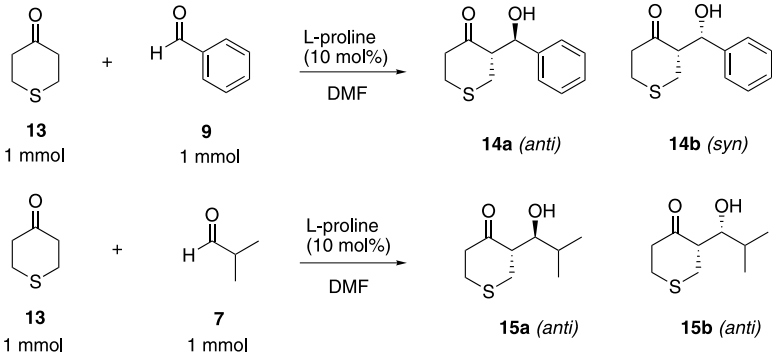
Table 6. Effect of water on the proline-catalyzed aldol reaction with a stoichiometric amount of acetone



Entry	Aldehyde acceptor	Water (mol%)[a]	Time (days)	Conversion[b]	ee[c]
1	**10**	0	3	30	71
2	**10**	50	3	37	69
3	**10**	**100**	**3**	**45**	**65**
4	**10**	200	3	35	66
5	**10**	300	3	28	67
6	**10**	500	3	21	73
7	**10**	50 vol%	7	2	nd
8	**7**	0	9	31	90
9	**7**	50	9	39	91
10	**7**	**100**	**9**	**42**	**92**
11	**7**	200	9	36	91
12	**7**	300	9	29	89
13	**7**	500	9	29	90

[a] Amount of added H_2O. All reactions were conducted in flame-dried glassware under argon using dry solvents.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC analysis (Chiralpak AD).

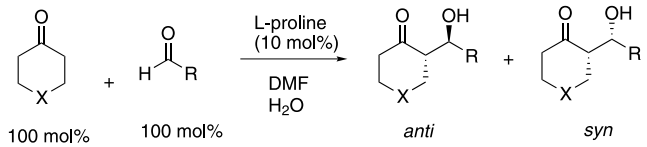
Table 7. Effect of water on the proline-catalyzed aldol reaction with 4-thianone



Entry	Aldehyde acceptor	Water (mol%)[a]	Time (days)	Conversion[b]	*Anti*:*syn*[b]	ee[c]
1	**10**	0	5	3	>20:1	65
3	**10**	100	5	22	>20:1	86
4	**10**	200	5	37	>20:1	93
5	**10**	**500**	**5**	**60**[d]	**>20:1**	**98**
6	**10**	1000	5	41	>20:1	92
7	**10**	1500	5	32	>20:1	95
8	**7**	0	9	11	2:1	96
9	**7**	100	9	36	10:1	96
10	**7**	100	13	49	12:1	87
11	**7**	**300**	**9**	**50**[d]	**15:1**	**95**
12	**7**[e]	300	9	65	9:1	83
13	**7**	500	9	42	10:1	96

[a] Amount of added H_2O. All reactions were conducted in flame-dried glassware under argon using dry solvents.
[b] Conversion to both syn and *anti* products, as determined by ^1H NMR analysis of the crude reaction mixture. The dehydrated enone side products were not formed in detectable amounts.
[c] ee of the major *anti* isomer.
[d] Isolated yield.
[e] Compound **7** (200 mol%).

Table 8. Stoichiometric, water-accelerated aldol reactions with non-volatile ketones



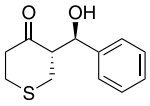
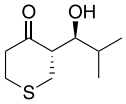
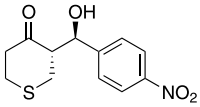
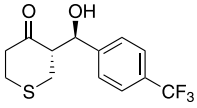
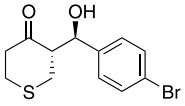
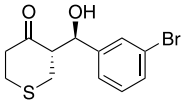
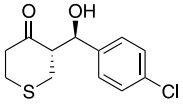
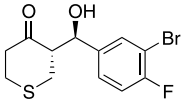
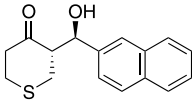
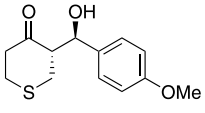
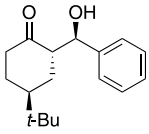
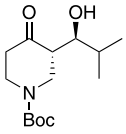
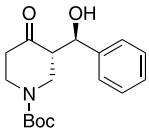
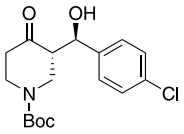
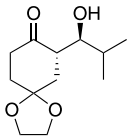
Entry	Product	Time (days)	Isolated yield[a]	*Anti*:*syn*[b]	ee[c]
1	 **14a**	5	60	>20:1	98
2	 **15a**	9	50	15:1	95
3	 **16**	5	45	20:1	99
4	 **17**	3	76	13:1	93
5	 **18**	4	53	10:1	98
6	 **19**	4	69	>20:1	98
7	 **20**	3	54	>20:1	98
8	 **21**	7	54	8:1	90
9	 **22**	7	58	20:1	98
10	 **23**	30	37	1.2:1	37

Table 8 (*continued*)

Entry	Product	Time (days)	Isolated yield[a]	*Anti*:*syn*[b]	ee[c]
11	 **12a**	8	45	2.5:1	74
12	 **24**	9	52	10:1	95
13	 **25**	5	45	6:1	73
14	 **26**	5	40	4:1	74
15	 **27**	9	31	2.4:1	89

[a] ee of the major *anti* isomer.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Combined yield of the *anti* and *syn* products.

be removed by distillation from the reaction mixture. However, with more expensive and less volatile ketones, the use of a large excess of ketone to push the reaction forward is neither economical nor practical. Purification of the product becomes extremely difficult if the starting material is present in any significant excess.

It has been established that cyclic ketones react much more slowly than acetone in proline-catalyzed aldol reactions.[3] Still, we were quite surprised to find out that 4-*tert*-butylcyclohexanone, a non-volatile cyclic ketone, showed only very little progress after 5 days in a reaction with benzaldehyde (Scheme 2) under the original List–Barbas conditions. Addition of water (300 mol%) did increase the reaction rate to some extent, but it was only the combination of stoichiometric conditions with added H_2O that finally afforded a synthetically viable reaction rate and yield. After 8 days, the aldol products **12a** and **12b** were obtained in 45% yield and 74% ee (see also Table 8, entry 11).[25]

We next turned to 4-thianone, a non-volatile heterocyclic ketone that has been used as a 3-pentanone surrogate in a wide variety of aldol-type processes.[26] The effect of water was very pronounced in aldol reactions with this donor. Indeed, only trace amounts of the aldol products were formed under scrupulously dry conditions (Table 7, entries 1 and 7). With benzaldehyde as the acceptor, 500 mol% of water was found to be optimal, whereas with isobutyraldehyde 300 mol% of water was sufficient for optimal conversion and diastereoselectivity.

The reaction was accelerated even further by the use of an excess of aldehyde. Unfortunately, the enantioselectivity suffered. With 200 mol% of isobutyraldehyde, the accelerating effect of water was very dramatic (Fig. 1). In these reactions, the formation of the aldehyde-derived oxazolidinone could be readily observed by ^{1}H NMR spectroscopy. We also found that the amount of oxazolidinone decreased upon addition of water.[27]

From a preparative standpoint, the ability to conduct the reactions in stoichiometric conditions represents a significant advantage. It should be noted, however, that the equilibrium constants for many ketone–aldehyde aldol reactions are just barely on the side of the products. As a result, the expected yields are not necessarily as high as those obtained with a large excess of the donor ketone. We were therefore pleased to find that a variety of ketone–aldehyde combinations we tested afforded reasonable yields of the products. The results of these preparative experiments

are collected in Table 8. Particularly pleasing results were obtained with 4-thianone, which gave very high enantio- and diastereoselectivities with both aliphatic and aromatic aldehydes (entries 1–10). The only exception was anisaldehyde (entry 9), with which the reaction was particularly sluggish. With other cyclic ketones, the enantio- and diastereoselectivities ranged from good to excellent (entries 11–15). Although somewhat slow in some cases, the reactions were nevertheless remarkably clean, with very little dehydration products or other side products observed. In addition, most of the products were highly crystalline solids.

In conclusion, we have shown that the proline-catalyzed aldol reaction is surprisingly insensitive to both basic and acidic additives, and in most cases the additives will simply slow down the reaction rate. With water as the additive, we have discovered a practical method for carrying out enantioselective proline-catalyzed aldol reactions with stoichiometric amounts of ketone and aldehyde. Significantly, this method allows the use of precious ketones such as 4-thianone in the aldol process and simplifies purification. The excellent enantio- and diastereoselectivities obtained in the 4-thianone aldol reactions also allow the rapid construction or polypropionate building blocks after removal of the sulfur bridge.[28]

Our observation that the enantioselectivity rises during the reaction with triethylamine additive raises interesting questions regarding the nature of the catalyst in the initial stages of the reaction. Studies are in progress to address these questions in more detail.

3. Experimental

3.1. General.[29] All reactions were conducted in sealed vessels under argon atmosphere using dry glassware. DMF and DMSO were dried by distillation over 4 Å molecular sieves. Acetone was distilled over anhydrous $CaSO_4$. 4-Trifluoromethylbenzaldehyde, benzaldehyde, anisaldehyde, and isobutyraldehyde were purified by fractional distillation under argon. All other commercial reagents were used as received. Optical rotations were determined in HPLC grade methanol or p.a. grade $CHCl_3$ (containing 0.7 vol% ethanol as a stabilizer) or in $CDCl_3$.

3.2. General procedure for the additive tests. To a stirred solution of ketone (1 mL) in DMF (4 mL) was added L-proline (11.5 mg, 0.10 mmol, 20 mol%), the additive (typically 20 or 50 mol%, see Tables 1–5) and aldehyde (0.50 mmol, 100 mol%), and the reaction mixture was stirred at the indicated temperature for 4–50 h. For reaction monitoring purposes, 0.2 mL aliquots of the reaction mixture were withdrawn at regular intervals. These aliquots were quenched with water (1 mL) and extracted with Et_2O (1 mL). For the aldol products **3** and **5/6**, the conversions and enantioselectivities were determined by GC analysis (Supelco β-DEX 120 column, 30 m×0.25 mm). In all other cases, the conversions and the diastereoselectivities were determined by ^1H NMR analysis of the crude reaction mixture and the enantioselectivity was determined by HPLC analysis using either Chiralcel OD, AD or AS columns and the corresponding guard columns.

3.3. General procedure for the stoichiometric aldol reactions with water (Tables 6–8). To a stirred mixture of solvent (DMF or DMSO, 1 mL), ketone donor (1 mmol) and L-proline (typically 10 mol%, see Tables 6–8) was added aldehyde (1 mmol) and H_2O (0–1500 mol%). The flask was capped and the reaction mixture was stirred at rt under argon for the indicated time (3–13 days). The reaction was then quenched with H_2O (10 mL) (Tables 7 and 8) or with saturated NH_4Cl solution (Table 6) and then extracted with Et_2O (3× 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The pure aldol products were obtained by flash column chromatography (silica gel) using the eluent system indicated for the TLC R_f value for each compound.

The racemic comparison samples were prepared by either using racemic proline as the catalyst or by the procedure of Hayashi[26b] (compounds **14a** and **15a**).

The aldol products **3**, **5**, **6**, **8** and **10** displayed spectral characteristics identical to those reported previously.[30] GC data (Supelco β-DEX 120 column, He carrier gas): For **3**: flow rate 5.8 mL/min, gradient from 130 to 180 °C at 0.2 °C min; τ_{minor} 21.05 min, τ_{major} 19.77 min. For **5**: flow rate 2.4 mL/min, gradient from 100 to 130 °C at 0.5 °C min; τ_{major} 77.36 min, τ_{minor} 77.84 min; for the minor regioisomer **6**: τ_{major} 76.67 min, τ_{minor} 76.06 min.

3.4. Characterization data for the aldol products (Table 8).

3.4.1. Compound 14a: (3*S*,1′*S*)-3-[(1′-hydroxy-2′-methyl)propyl]-tetrahydrothiopyran-4-one (Table 8, entry 1). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 98:2, flow rate 0.7 mL/min; τ_{minor}=26.1 min; τ_{major}=20.7 min, λ=254 nm). R_f (1:1 hexanes/MTBE)=0.27. $[\alpha]_D^{23}$ −72 (*c* 1.0, MeOH, 95% ee). ^1H NMR δ 3.50 (t, J=5.1 Hz, 1H), 2.93–2.77 (m, 5H), 2.70–2.65 (m, 2H), 1.83–1.70 (m, 1H), 0.91 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), ^{13}C NMR δ 212.4, 76.1, 55.7, 44.9, 33.5, 30.9, 29.9, 19.9, 16.0; IR (film) ν 3488, 2960, 2874, 1704, 1426, 1274, 990 cm^{-1}. HRMS (ESI) calcd for $C_9H_{16}O_2NaS$ (M+Na): 211.0769, found: 211.0762.

3.4.2. Compound 15a: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-phenyl)methyl]-tetrahydrothiopyran-4-one (Table 8, entry 2). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.5 mL/min; τ_{minor}= 40.8 min; τ_{major}=31.0 min, λ=254 nm). R_f (1:1 hexanes/MTBE)=0.19. Mp 126–127 °C. $[\alpha]_D^{23}$ −73 (*c* 1.1, MeOH, 98% ee). ^1H NMR δ 7.32–7.22 (m, 5H), 4.90 (dd, J=8.9, 3.0 Hz, 1H), 3.34 (s, 1H), 2.96–2.86 (m, 3H), 2.78 (dt, J= 13.5, 4.4 Hz, 1H), 2.71 (ddd, J=13.5, 10.2, 5.9 Hz, 1H), 2.49 (dd, J=13.8, 9.9 Hz, 1H), 2.44 (ddd, J=13.8, 5.2, 1.8 Hz, 1H), ^{13}C NMR δ 211.8, 140.2, 128.7, 128.3, 126.9, 73.8, 59.7, 44.5, 32.9, 30.9; IR (KBr disk) ν 3421, 2914, 1690, 1426, 1275, 1051, 706 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{14}O_2NaS$ (M+Na): 245.0612, found: 245.0605. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.8%; H, 6.4%. Found: C, 64.4%; H, 6.3%.

3.4.3. Compound 16: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-nitrophenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 3). The ee was determined by HPLC (Chiralpak AD column, hexanes/*i*-PrOH, 90:10, flow rate 1.0 mL/min;

τ_{minor}=43.7 min; τ_{major}=79.9 min, λ=254 nm). R_f (1:1 hexanes/MTBE)=0.08. Mp 140–141 °C. $[\alpha]_D^{23}$ +4.2 (*c* 0.7, $CHCl_3$, 99% ee). ^1H NMR δ 8.22 (d, *J*=8.8 Hz, 2H), 7.54 (d, *J*=8.8 Hz, 2H), 5.05 (d, *J*=8.0 Hz, 1H), 3.47 (br s, 1H), 3.03–2.94 (m, 3H), 2.83 (dt, *J*=13.5, 4.2 Hz, 1H), 2.77 (ddd, *J*=13.5, 10.2, 5.7 Hz, 1H), 2.65 (dd, *J*=13.7, 10.9 Hz, 1H), 2.52 (ddd, *J*=13.7, 4.8, 2.0 Hz, 1H), ^{13}C NMR δ 211.1, 147.8, 147.7, 127.8, 123.8, 73.2, 59.4, 44.7, 32.8, 30.8; IR (KBr disk) ν 3392, 2917, 1686, 1520, 1344, 1103 cm^{-1}. HRMS (ESI−) calcd for $C_{12}H_{12}NO_4S$ (M−H): 266.0487, found: 266.0489.

3.4.4. Compound 17: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-(trifluoromethyl)phenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 4). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=34.4 min; τ_{major}=21.8 min, λ=254 nm). R_f (40:60 EtOAc/hexanes)=0.26. Mp 117–118 °C. $[\alpha]_D^{23}$ +10.9 (*c* 1.1, $CHCl_3$, 93% ee). ^1H NMR δ 7.63 (d, *J*=8.3 Hz, 2H), 7.48 (d, *J*=8.3 Hz, 2H), 5.04 (dd, *J*=8.4, 3.7 Hz, 1H), 3.54 (d, *J*=3.7 Hz, 1H), 3.04–2.93 (m, 3H), 2.84 (dt, *J*=13.5, 4.2 Hz, 1H), 2.77 (ddd, *J*=13.5, 10.2, 5.8 Hz, 1H), 2.63 (dd, *J*=13.7, 10.6 Hz, 1H), 2.51 (ddd, *J*=13.7, 4.9, 2.2 Hz, 1H), ^{13}C NMR δ 211.4, 144.3, 130.4 (q, $^2J_{C-}$=32 Hz), 127.3, 125.6 (q, $^3J_{C-}$=4 Hz), 123.9 (q, $^1J_{C-}$=271 Hz), 73.3, 59.5, 44.6, 32.8, 30.8; IR (KBr disk) ν 3401, 2912, 1704, 1423, 1325, 1266, 1125, 1067 cm^{-1}. Anal. Calcd for $C_{13}H_{13}F4O_2S$: C, 53.8; H, 4.5. Found: C, 54.0; H, 4.3.

3.4.5. Compound 18: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-bromophenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 5). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=37.7 min; τ_{major}=25.9 min, λ=254 nm). R_f (40:60 EtOAc/hexanes)=0.25. Mp 159–160 °C. $[\alpha]_D^{23}$ +16.1 (*c* 1.0, $CHCl_3$, 98% ee). ^1H NMR δ 7.49 (d, *J*=8.4 Hz, 2H), 7.22 (d, *J*=8.4 Hz, 2H), 4.92 (dd, *J*=8.6, 3.5 Hz, 1H), 3.46 (d, *J*=3.5 Hz, 1H), 3.00–2.91 (m, 3H), 2.83 (dt, *J*=13.4, 4.4 Hz, 1H), 2.75 (dddd, *J*=13.4, 9.9, 5.8, 0.6 Hz, 1H), 2.56 (dd, *J*=13.7, 9.9 Hz, 1H), 2.50 (ddd, *J*=13.7, 5.3, 1.8 Hz, 1H), ^{13}C NMR δ 211.5, 139.4, 131.8, 128.6, 122.2, 73.3, 59.6, 44.5, 32.8, 30.8; IR (KBr disk) ν 3401, 2913, 1687, 1426, 1314, 1123, 1056 cm^{-1}. Anal. Calcd for $C_{12}H_{13}BrO_2S$: C, 47.9; H, 4.4. Found: C, 47.6; H, 4.2.

3.4.6. Compound 19: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(3″-bromophenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 6). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=28.7 min; τ_{major}=23.1 min, λ=254 nm). R_f (40:60 EtOAc/hexanes)=0.25. Mp 146–147 °C. $[\alpha]_D^{23}$ +8.1 (*c* 1.0, $CHCl_3$, 98% ee). ^1H NMR δ 7.52 (m, 1H), 7.46 (dt, *J*=7.5, 1.8 Hz, 1H), 7.27–7.21 (m, 2H), 4.92 (dd, *J*=8.6, 3.5 Hz, 1H), 3.54 (d, *J*=3.5 Hz, 1H), 3.00–2.93 (m, 3H), 2.84 (dt, *J*=13.5, 4.4 Hz, 1H), 2.76 (ddd, *J*=13.5, 10.2, 5.8 Hz, 1H), 2.59 (dd, *J*=13.7, 10.0 Hz, 1H), 2.53 (ddd, *J*=13.7, 5.3, 1.6 Hz, 1H), ^{13}C NMR δ 211.4, 142.7, 131.4, 130.1, 130.0, 125.6, 122.8, 73.2, 59.5, 44.5, 32.8, 30.8; IR (KBr disk) ν 3523, 2914, 1694, 1423, 1276, 1171, 1112 cm^{-1}. Anal. Calcd for $C_{12}H_{13}BrO_2S$: C, 47.9; H 4.4. Found: C, 47.7; H, 4.2.

3.4.7. Compound 20: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-chlorophenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 7). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=35.8 min; τ_{major}=24.2 min, λ=254 nm). R_f (40:60 EtOAc/hexanes)=0.30. Mp 148–149 °C. $[\alpha]_D^{23}$ +15.1 (*c* 0.6, $CHCl_3$, 98% ee). ^1H NMR δ 7.35 (d, *J*=8.6 Hz, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 4.94 (d, *J*=8.4 Hz, 1H), 3.43 (br s, 1H), 2.99–2.93 (m, 3H), 2.83 (dt, *J*=13.5, 4.4 Hz, 1H), 2.76 (ddd, *J*=13.5, 10.2, 5.9 Hz, 1H), 2.58 (dd, *J*=13.7, 10.4 Hz, 1H), 2.50 (ddd, *J*=13.7, 5.1, 1.8 Hz, 1H), ^{13}C NMR δ 211.5, 138.9, 134.0, 128.8, 128.3, 73.1, 59.6, 44.5, 32.8, 30.8; IR (KBr disk) ν 3401, 2915, 1688, 1426, 1266, 1088, 1056 cm^{-1}. HRMS (ESI+) calcd for $C_{12}H_{13}ClO_2SNa$ (M+Na): 279.0222, found: 279.0209.

3.4.8. Compound 21: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(3″-bromo-4″-fluorophenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 8). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.5 mL/min; τ_{minor}=46.4 min; τ_{major}=32.1 min, λ=254 nm). R_f (1:1 EtOAc/hexanes)=0.40. Mp 165–166 °C. $[\alpha]_D^{23}$ +13.6 (*c* 0.9, $CHCl_3$, 90% ee). ^1H NMR δ 7.58 (dd, *J*=6.6, 2.2 Hz, 1H), 7.27 (ddd, *J*=8.2, 4.0, 2.2 Hz, 1H), 7.12 (t, *J*=8.4 Hz, 1H), 4.92 (dd, *J*=8.4, 3.5 Hz, 1H), 3.54 (d, *J*=3.5 Hz, 1H), 3.02–2.92 (m, 3H), 2.85 (dt, *J*=13.5, 4.4 Hz, 1H), 2.77 (dddd, *J*=13.5, 9.9, 6.0, 0.5 Hz, 1H), 2.60 (dd, *J*=13.5, 10.2 Hz, 1H), 2.52 (ddd, *J*=13.5, 5.1, 1.8 Hz, 1H), ^{13}C NMR δ 211.4, 158.8 (d, $^1J_{CF}$=247 Hz), 137.9 (d, $^3J_{CF}$=4 Hz), 132.0, 127.5 (d, $^1J_{CF}$=7 Hz), 116.5 (d, $^2J_{CF}$=22 Hz), 109.4 (d, $^2J_{CF}$=21 Hz), 72.8, 59.6, 44.6, 32.7, 30.8; IR (KBr disk) ν 3479, 2920, 1699, 1497, 1265, 1047, 737 cm^{-1}. Anal. Calcd for $C_{12}H_{12}BrFO_2S$: C, 45.2; H, 3.8. Found: C, 44.9; H, 3.6.

3.4.9. Compound 22: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(2″-naphtyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 9). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=44.3 min; τ_{major}=36.8 min, λ=254 nm). R_f (1:1 MTBE/hexanes)=0.18. Mp 143–145 °C. $[\alpha]_D^{23}$ +11 (*c* 0.7, $CHCl_3$, 98% ee). ^1H NMR δ 7.89–7.80 (m, 4H), 7.53–7.49 (m, 3H), 5.17 (d, *J*=8.8 Hz, 1H), 3.48 (br s, 1H), 3.12 (dt, *J*=9.5, 4.9 Hz, 1H), 3.04–2.91 (m, 2H), 2.89 (dt, *J*=13.4, 4.2 Hz, 1H), 2.80 (ddd, *J*=13.4, 10.1, 5.3 Hz, 1H), 2.60 (dd, *J*=13.7, 10.1 Hz, 1H), 2.53 (ddd, *J*=13.7, 4.9, 2.0 Hz, 1H), ^{13}C NMR δ 211.8, 137.6, 133.3, 133.1, 128.7, 128.0, 127.7, 126.4, 126.2, 124.3, 120.8, 74.1, 59.7, 44.5, 33.0, 30.9; IR (KBr disk) ν 3401, 2917, 1688, 1272, 1118 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{16}O_2SNa$ (M+Na): 295.0769, found: 279.0778.

3.4.10. Compound 23: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-methoxyphenyl))methyl]-tetrahydrothiopyran-4-one (Table 8, entry 10). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 90:10, flow rate 0.7 mL/min; τ_{minor}=38.9 min; τ_{major}=28.7 min, λ=254 nm). R_f (1:1 MTBE/hexanes)=0.15. Mp 124–126 °C. $[\alpha]_D^{23}$ +2.9 (*c* 1.7, $CHCl_3$, 37% ee). ^1H NMR (major anti isomer): δ 7.28 (d, *J*=9.5 Hz, 2H), 6.92 (d, *J*=9.5 Hz, 2H), 4.96 (d, *J*=8.9 Hz, 1H), 3.82 (s, 3H), 3.30 (br s, 1H), 3.01–2.94 (m, 3H), 2.86 (dt, *J*=13.5, 4.6 Hz, 1H), 2.77 (ddd, *J*=13.5, 10.4, 5.8 Hz, 1H), 2.53 (d, *J*=7.7 Hz, 2H), ^{13}C NMR δ

211.9, 159.6, 132.4, 128.1, 114.1, 73.4, 59.8, 55.3, 44.4, 32.9, 30.9; IR (KBr disk) ν 3468, 2915, 1704, 1514, 1249, 1032, 835 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{16}O_3SNa$ (M+Na): 275.0718, found: 275.0723.

3.4.11. Compound 12a: (2*S*,4*S*,1′*S*)-4-*tert*-butyl-[(1′-hydroxy-1′-phenyl)-methyl]cyclohexanone (Table 8, entry 11). The ee was determined by HPLC (Chiralcel OD column, hexanes/*i*-PrOH, 95:5, flow rate 0.7 mL/min; τ_{minor}=34.5 min; τ_{major}=29.9 min, λ=254 nm). Data for the major *anti* isomer: R_f (acetone/hexanes 20:80)=0.21. Mp 135–137 °C (from CH_2Cl_2/hexanes). $[\alpha]_D^{23}$ −50 (*c* 2.8, CH_2Cl_2, 74% ee). ^{1}H NMR δ 7.39–7.29 (m, 5H), 4.90 (dd, 1H, *J*=9.6, 3.1 Hz), 3.04 (d, 1H, *J*=3.1 Hz), 2.67 (dt, 1H, *J*=9.6, 6.2 Hz), 2.52–2.48 (m, 1H), 2.03–1.97 (m, 1H), 1.58–1.52 (m, 3H), 1.51–1.43 (m, 1H), 1.38 (ddd, 1H, *J*=14.1, 10.2, 6.6 Hz), 0.78 (s, 9H), ^{13}C NMR δ 215.6, 141.5, 128.5, 128.2, 126.8, 74.7, 55.8, 42.0, 39.1, 32.6, 28.0, 27.1 (3C), 25.8; IR (in CH_2Cl_2) ν 3591, 3033, 2963, 2871, 1710, 1368, 1022 cm^{-1}. HRMS (ESI+): calcd for $C_{17}H_{24}O_2Na$ (M+Na): 283.1674, found: 283.1643.

3.4.12. Compound 24: (3*S*,1′*R*)-3-[(1′-hydroxy-2′-methyl)propyl]-4-oxo-piperidine-1-carboxylic acid, *tert*-butyl ester (Table 8, entry 12). The ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 98:2, flow rate 0.9 mL/min, τ_{major}=19.6 min; τ_{minor}=42.8 min, λ=220 nm). R_f (Et_2O/CH_2Cl_2 15:85)=0.28. Mp 88–89 °C (from CH_2Cl_2/hexanes). $[\alpha]_D^{23}$ −8.0 (*c* 1.9, CH_2Cl_2, 95% ee). ^{1}H NMR δ 4.04–4.02 (m, 2H), 3.53 (m, 1H), 3.34–3.27 (m, 1H), 3.09 (dd, 1H, *J*=13.4, 10.4 Hz), 2.95 (d, 1H, *J*=5.7 Hz), 2.52 (m, 1H), 2.43–2.38 (m, 2H), 1.77 (m, 1H), 1.45 (br s, 9H), 0.95 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H). For the minor *syn* diastereomer present in the product mixture, the following signals were also observed: δ 3.67 (t, 1H, *J*=6.2 Hz), 1.67–1.56 (m, 1H), 0.87 (d, *J*=6.8 Hz, 3H), ^{13}C NMR: δ 211.8, 154.6, 80.8, 73.5, 53.4, 46.1, 43.8, 41.8, 30.0, 28.4 (3C), 20.0, 15.3; IR (in $CDCl_3$): 3422, 2975, 2935, 2876, 1690, 1425, 1198, 908 cm^{-1}. HRMS (ESI+): calcd for $C_{14}H_{25}NO_4Na$ (M+Na): 294.1681, found: 294.1702. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3; N, 5.2. Found: C, 62.0; H, 9.6; N, 5.2.

3.4.13. Compound 25: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-phenyl)methyl]-4-oxo-piperidine-1-carboxylic acid, *tert*-butyl ester (Table 8, entry 13). The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 92:8, flow rate 0.7 mL/min; τ_{minor}=22.0 min; τ_{major}=25.2 min, λ=220 nm). Data for the major *anti* isomer: R_f (Et_2O/CH_2Cl_2 10:90)=0.15. Mp 136–138 °C (from CH_2Cl_2/hexanes). $[\alpha]_D^{23}$ +20 (*c* 2.8, $CDCl_3$, 73% ee). ^{1}H NMR δ 7.39–7.29 (m, 5H), 4.83 (dd, 1H, *J*=8.6, 3.2 Hz), 4.13–4.12 (m, 1H), 3.67 (m, 1H), 3.58 (d, 1H, *J*=3.2 Hz), 3.30–3.26 (m, 1H), 2.89 (dd, 1H, *J*=12.8, 10.6 Hz), 2.78–2.76 (m, 1H), 2.53–2.49 (m, 2H), 1.38 (br s, 9H), ^{13}C NMR: δ 211.2, 154.3, 140.1, 138.7, 138.4, 126.8, 80.6, 72.7, 58.7, 56.7, 43.6, 41.4, 28.2 (3C); IR (in $CDCl_3$): 3468, 2977, 2898, 1691, 908 cm^{-1}. HRMS (ESI+): calcd for $C_{17}H_{23}NO_4Na$ (M+Na): 328.1525, found: 328.1519.

3.4.14. Compound 26: (3*S*,1′*S*)-3-[(1′-hydroxy-1′-(4″-chlorophenyl))methyl]-4-oxo-piperidine-1-carboxylic acid, *tert*-butyl ester (Table 8, entry 14). The ee was determined by HPLC (Chiralpak pre-AD+OD column, hexane/*i*-PrOH 92:8, flow rate 0.7 mL/min; τ_{minor}=21.8 min; τ_{major}=23.8 min, λ=220 nm). R_f (Et_2O/CH_2Cl_2 10:90)=0.14. Mp 131–132 °C (from CH_2Cl_2/hexanes). $[\alpha]_D^{23}$ +39 (*c* 3.4, $CDCl_3$, 74% ee). ^{1}H NMR δ 7.35–7.25 (m, 4H), 4.81 (dd, *J*=8.4, 3.1 Hz, 1H), 4.10 (m, 1H), 3.70 (obs m, 1H), 3.68 (d, 1H, *J*=3.1 Hz), 3.28 (m, 1H), 2.89 (dd, *J*=13.0, 10.6 Hz, 1H), 2.73–2.70 (m, 1H), 2.58–2.43 (m, 2H), 1.42 (br s, 9H). For the minor *syn* diastereomer present in the product mixture, the following signals were also observed: δ 5.32 (m, 1H), 5.29 (d, 1H, *J*=0.6 Hz), 3.87 (ddd, 2H, *J*=13.5, 5.8, 2.0 Hz), 3.03 (m, 1H), ^{13}C NMR: δ 210.7, 154.2, 138.7, 134.1, 128.7, 128.1, 80.7, 71.9, 56.6, 45.8, 43.6, 41.4, 28.2 (3C). For the minor *syn* diastereomer, the following signals were also observed: δ 139.2, 133.2, 128.5, 126.9; IR (in $CDCl_3$): 3525, 3055, 2985, 1693, 1422, 1266, 744 cm^{-1}. HRMS (ESI+): calcd for $C_{17}H_{22}ClNO_4Na$ (M+Na): 362.1135, found: 362.1099.

3.4.15. Compound 27: (7*S*,1′*S*)-7-[(1-hydroxy-2-methyl)propyl]-1,4-dioxaspiro[4.5]decan-8-one (Table 8, entry 15). The ee was determined by HPLC (Chiralcel OD column, hexane- *i*-PrOH 99.5:0.5, flow rate 1.0 mL/min; τ_{major}=22.5 min; τ_{minor}=25.7 min, λ=215 nm). Data for the major anti isomer: R_f (MTBE/CH_2Cl_2 15:85)=0.38. $[\alpha]_D^{23}$ −15 (*c* 1.9, CH_2Cl_2, 89% ee). ^{1}H NMR δ 4.06–3.98 (m, 4H), 3.48 (dt, *J*=7.0, 4.6 Hz, 1H), 3.27 (d, *J*=4.6 Hz, 1H), 2.81 (app dqn, *J*=6.6 Hz, 0.7 Hz, 1H), 2.66 (tdd, *J*=13.7, 6.6, 1.0 Hz, 1H), 2.36 (ddd, *J*=14.2, 5.0, 3.4 Hz, 1H), 2.07–1.91 (m, 3H), 1.82 (t, *J*=13.2 Hz, 1H), 1.75 (dsept, 1H, *J*=6.8, 4.6 Hz), 0.96 (d, *J*=7.0 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H), ^{13}C NMR δ 214.7, 107.5, 75.9, 65.1, 64.9, 49.7, 39.2, 38.0, 34.7, 29.7, 20.2, 15.6; IR (in $CDCl_3$): 3421, 2963, 2935, 2890, 1703, 1254, 1199, 910 cm^{-1}. HRMS (ESI+): calcd for $C_{12}H_{20}O_4Na$ (M+Na) 251.1259, found 251.1266.

Acknowledgements

We thank Helsinki University of Technology (Outstanding Junior Research Group Award), TEKES, the Academy of Finland, and COST D28 for financial support. K. M. L. is the recipient of an undergraduate student stipend from the Taru, Ilmari, and Pentti Manninen Fund of the Finnish Cultural Foundation. We thank Mr. Kato Shum (exchange student from the University of Hong Kong) for experimental assistance and Dr. Jari Koivisto (TKK) for NMR assistance.

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24. In the reaction between acetone and isobutyraldehyde (**7**) in DMSO with 30 mol% L-proline, up to 28% of the enone was formed after 5 days (overall conversion 88%). Addition of water had only a marginal effect on the enone formation.
25. The assignment of the stereochemistry of **12a** and **12b** is based on the ^1H NMR coupling constants of the COCHC*H*(OH)Ph proton of the product (400 MHz, $CDCl_3$, characteristic shifts: **12a**: δ 4.90 (dd, 1H, $J=9.6$, 3.1 Hz, COC*H*CH(OH)Ph), 2.67 (dt, 1H, $J=9.6$, 6.2 Hz, 1H, COC*H*CH(OH)Ph), **12b**: δ 5.19 (d, $J=4.9$ Hz, 1H, COCHC*H*(OH)Ph), 2.68 (br q, $J=5$ Hz,

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Tetrahedron 62 (2006) 329–337

Direct asymmetric organocatalytic de novo synthesis of carbohydrates

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Received 10 May 2005; revised 10 August 2005; accepted 9 September 2005

Available online 3 October 2005

Abstract—A biomimetic organocatalytic asymmetric synthesis of carbohydrates can be accomplished by a proline catalyzed aldol reaction with the dihydroxyacetone equivalent 2,2-dimethyl-1,3-dioxan-5-one and various aldehydes. The biomimetic C_3+C_n strategy directly generates selectively protected carbohydrates in one step, which can be easily deprotected. Additionally, the stereoselective reduction of the keto functions allows a direct entry to different aldopentoses.

1. Introduction

Triggered by the exciting reports of List et al.[1] and MacMillan et al.[2] in the year 2000, asymmetric organocatalysis emerged as a rapidly growing and important field in organic chemistry.[3] In particular, reactions catalyzed by the amino acid proline, easily available as both enantiomers, showed a broad applicability.[4] The proline-catalyzed aldol reaction attracted great attention, because of the importance of this carbon–carbon bond formation in organic chemistry.[5] This new powerful organocatalytic methodology allows the direct cross-coupling between ketones and aldehydes[1b,6] as well as between different aldehydes[7] with remarkable diastereo- and enantioselectivities in most cases. Not surprisingly, the development of the basic methodology, as well as the first applications in organic synthesis, for example, natural product synthesis[8], dynamic kinetic resolution[9] or desymmetrization[10] have been reported recently. In addition, the proline-catalyzed aldol reaction has very recently paved the way for the direct assembly of carbohydrates.[11]

Carbohydrates are of enormous importance in the chemical, biological and medicinal sciences.[12] For example, they play key roles in many biological processes as part of glycoproteins, nucleic acids, glycolipids, peptide- and proteoglycans or liposaccharides.[13] Thus, they are important targets for the development of new drugs. Besides their biological and medicinal importance, carbohydrates are of great value in synthetic organic chemistry, for instance as chiral auxiliaries[14] or enantiopure building blocks.[15] In the view of this background the de novo synthesis of carbohydrates is of great importance. So far, a broad spectrum of different approaches has been described, but several steps and protecting group manipulations are necessary.[16] This has led to new ideas for more simple and direct entries. One alternative new route was introduced by MacMillan et al. who disclosed a 'two-step' synthesis of aldohexoses. This strategy consists of an initial proline-catalyzed aldol reaction between α-oxygenated aldehydes, followed by a Mukaiyama—aldol reaction to generate the carbohydrate.[17] Later on, Cordova et al. were able to carry out MacMillans concept employing solely proline catalysis.[18] Another approach can be borrowed from mother nature. Nature employs dihydroxyacetone phosphate (DHAP) in carbohydrate biosynthesis. The carbohydrate skeleton is assembled by an enzyme-catalyzed aldol reaction between DHAP and glyceraldehyde.[19]

Hence, the application of DHAP in carbohydrate synthesis has been investigated quite intensively employing biological methods in particular.[20] Furthermore, dihydroxyacetone and its derivatives could be employed as C_3 building blocks in asymmetric synthesis using chemical methods.[21] The application of organocatalytic methods were first reported by Barbas et al. They described a direct aldol reaction of dihydroxyacetone with various aldehydes, catalyzed by proline or derivatives of the latter, but generally with moderate diastereoselectivities and low enantioselectivities.[22]

Based on our previous studies using 2,2-dimethyl-1,3-dioxan-5-one (**1**, 'dioxanone') as a cyclic dihydroxy-

Keywords: Aldol reaction; Carbohydrates; Organocatalysis; Asymmetric synthesis; Stereoselective reduction.
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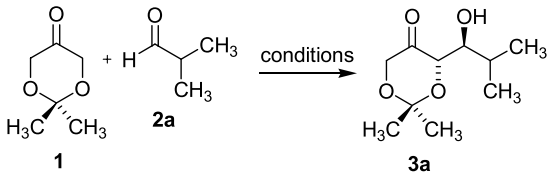
doi:10.1016/j.tet.2005.09.060



Scheme 1. (*S*)-Proline catalyzed aldol reaction of **1** with **2a**.

Besides (*S*)-proline, we also applied catalysts **5–12** to our model system. As it is shown in Table 1, especially catalyst **9** is also appropriate in terms of yield, diastereo- and enantioselectivity under these conditions (Table 1 and Fig. 1).

Our aim, however, was to elaborate a catalytic protocol, based on (*S*)-proline as the catalyst, because of its

Table 1. Optimization of the aldol reaction between **1** and **2a**

Entry	Cat (mol%)	Temperature	Solvent	Time (h)	Yield (%)[a]	*anti*/*syn* (%)[b]	ee (%)[c]
1	**4** [30]	rt	DMSO	65	91	>98:2	92
2	**4** [20]	2 °C	DMSO	115	60	>98:2	93
3	**4** [10]	rt	DMSO/DMF[d]	96	65	>98:2	93
4	**4** [20]	2 °C	DMSO/DMF[d]	115	60	>98:2	91
5	**4** [30]	rt	DMSO/DMF[d]	65	85	>98:2	88
6	**4** [20]	rt	DMF	48	47	>98:2	90
7	**4** [30]	2 °C	DMF	120	97	>98:2	94
8	**4** [30]	rt	$CHCl_3$	48	44	>98:2	90
9	**5** [20]	rt	DMSO/DMF[d]	92	35	>98:2	73
10	**6** [30]	rt	DMSO	48	—	—	—
11	**7** [30]	rt	DMSO	48	—	—	—
12	**8** [30]	rt	DMSO/DMF[d]	336	Traces	nd	nd
13	**9** [20]	2 °C	DMF	72	87	>98:2	97
14	**10** [20]	2 °C	DMF	72	58	>98:2	89
15	**11** [20]	2 °C	DMF	72	Traces	nd	nd
16	**12** [20]	2 °C	DMF	72	44	nd	72

[a] Yield of isolated **2a** after column chromatography (SiO_2, diethyl ether, pentane).
[b] Determined by ^1H and ^{13}C NMR spectroscopy.
[c] Determined by HPLC using a chiral stationary phase (Chiralpak AD, *n*-heptane/*iso*-propanol 95:5, major isomer 14.9 min, minor isomer 12.2 min).
[d] DMSO and DMF were used in a 1:1 ratio (v:v).

acetone equivalent in asymmetric synthesis, we planned to develop a direct asymmetric organocatalytic synthesis of carbohydrates and derivatives by a proline-catalyzed aldol reaction between **1** and various aldehydes. In our preceeding communication[23] we first described this biomimetic C_3+C_n-strategy, which allows the direct assembly of selectively protected carbohydrates in one-step. Herein, we present in detail the development of this methodology.

2. Results and discussion

The aim of our project was to develop a practical catalytic protocol for a proline catalyzed aldol reaction of dioxanone **1** with a broad variety of aldehydes **2** to obtain the corresponding aldol products **3** with good to excellent stereoselectivities and yields. Our initial investigations were concerned with the proline-catalyzed aldol reaction of **1** with 2-methylpropanal (**2a**) as a model system. We chose this system in order to optimize the reaction conditions in terms of the yield, the diastereo- and enantioselectivity (Scheme 1).

For the optimization process we investigated four reaction parameters: solvent, temperature, catalyst loading and catalyst system. As it is shown in Table 1 we found out that when using (*S*)-proline (30 mol%) as the catalyst and DMF as solvent at 2 °C are the best conditions. The desired *anti*-aldol product **3a** was obtained in excellent yield (97%), *anti*/*syn* ratio of >98:2 and a high enantiomeric excess of 94%.

commercial availability as both enantiomers. Therefore, we applied **4** in our further studies and investigated the application of various aldehydes. In general, a broad scope of aldehydes can be employed in the (*S*)-proline-catalyzed aldol reaction with **1**. We could show that the α-branched aldehydes **2a**, **2b**, **2i**, **2k–o** are particularly appropiate, in terms of yield, *anti*/*syn*-ratio and enantioselectivity. Only in the case of aldehyde **2i** a moderate ee of 68% was obtained using (*S*)-proline. But by employing the TBS-protected hydroxyproline catalyst **9**, the ee could be increased to 84%. The application of linear aldehydes like **2j** led to a drastic decrease of the yield (40%), but still excellent stereoselectivities (*anti*/*syn*>98:2, ee=97%) were maintained.

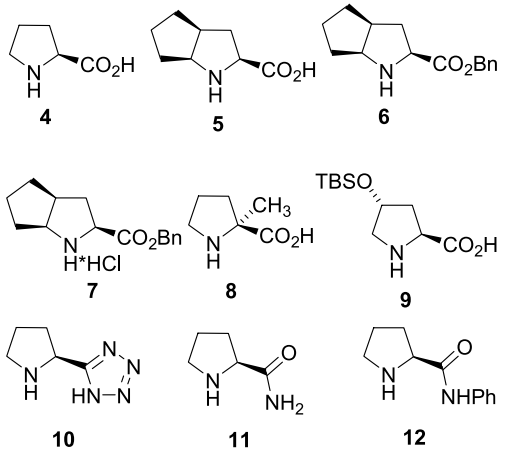
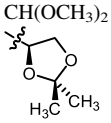
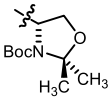
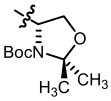
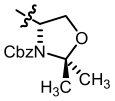


Figure 1. Different catalysts used in the aldol reaction of **1** with **2a** to the corresponding aldol product **3**.

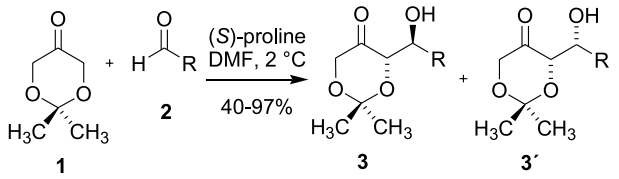
Table 2. (*S*)-Proline catalyzed aldol reaction of **1** with different aldehydes **2** to afford the aldol products **3**[a]

3	R	Yield (%)[b]	*anti/syn* (%)[c]	ee (%)[d]
a	$CH(CH_3)_2$	97	>98:2	94
b	*c*-C_6H_{11}	86	>98:2	90
c	$C(CH_3)_3$	—	—	—
d	$CH{=}CHCH_3$	—	—	—
e	H	—	—	—
f	C_6H_5	57	1.5:1	76 (49)
g	*o*Cl–C_6H_4	73	4:1	86 (75)
h		61	4:1	25 (5)
i		88 (93)[e]	>98:2 (>98:2)[e]	68 (84)[e]
j	CH_2OBn	40	>98:2	97
k	$CH(OCH_3)_2$	69	94:6	90
l[f]		76	>98:2	≥98[g]
m		80	>98:2	≥96[h]
n[f]		31	>98:2	≥96[h]
o		80	>98:2	≥96[i]

[a] General reaction conditions: 2.3 mmol dioxanone, 2.3 mmol aldehyde, 30 mol% (*S*)-proline, 1.2 mL DMF, 2 °C, 3–6 days.
[b] Yields of isolated **3** after flash-chromatography on silica gel.
[c] Determined by ^1H and ^{13}C NMR spectroscopy.
[d] Determined by HPLC on chiral stationary phases (Chiralpak AD, Chiralpak IA 5μ, Daicel IA, Daicel OJ, Whelk 01).
[e] Catalyst **9** was used.
[f] (*R*)-proline was used as the catalyst.
[g] Based on the ee value of **2l**.
[h] Based on the ee value of **2m**.
[i] Based on the ee value of **2n**.

The moderate yield can be explained by a competing self-aldolization of aldehyde **2j**. Less good results were obtained with the aromatic aldehydes **2f–h**, because in all cases the *anti*/*syn*-ratio decreased and in certain cases the ee value also deteriorated drastically. The attempt to use sterically demanding aldehydes like **2c** or allylic aldehydes like crotonaldehyde (**2d**) failed as well as the use of an aqueous formaldehyde solution (**2e**).

Subsequently, we investigated the application of enantiomerically pure, α-substituted aldehydes in the proline-catalyzed aldol reaction with **1**. We could demonstrate that in the case of (*S*)-configured α-substituted aldehydes (*S*)-proline is the appropriate catalyst for the aldol reaction, whereas in the case of using (*R*)-proline a mismatched case exists. (see Table 2, entry **m**, **n** and **o**). Indeed, the yield decreases in the (*R*)-proline catalyzed aldol reaction of **1** with **2m** to 31%, however, the selectivities remained at the same level. This could be confirmed by using 2,3-*O*-(isopropylidene)-D-glyceraldehyde (**2l**) in the aldol reaction



Scheme 2. (*S*)-Proline catalyzed aldol reaction of **1** with various aldehydes **2**.

with **1** in the presence of (*R*)-proline (Table 2, entry **l**) (Scheme 2).

As we already emphasized in our preceding communication, the resulting aldol products **3i–o** illustrate selectively and in some cases doubly protected sugars and aminosugars, for example, 5-deoxy-L-ribulose (**3i**), L-ribulose (**3j**), D-erythro-pentos-4-ulose (**3k**), D-psicose (**3l**), 5-amino-5-deoxy-L-psicose (**3m**, **3o**), 5-amino-5-deoxy-L-tagatose (**3n**) (Fig. 2).

For example the deprotection of **3l** could be easily carried out under acidic condition using an ion exchange resin (Dowex W50X2-200) to quantitatively afford D-psicose **13** as a mixture of the four isomers α,β-D-psicofuranose and α,β-D-psicopyranose (Scheme 3).[24]

The clearly preferred formation of the *anti*-aldol products and the stated absolute configurations are consistent with the Houk-List model for the proline-catalyzed aldol reaction. The absolute configuration could be corroborated through polarimetric comparison with independently synthezised aldol products (Fig. 3).[25]

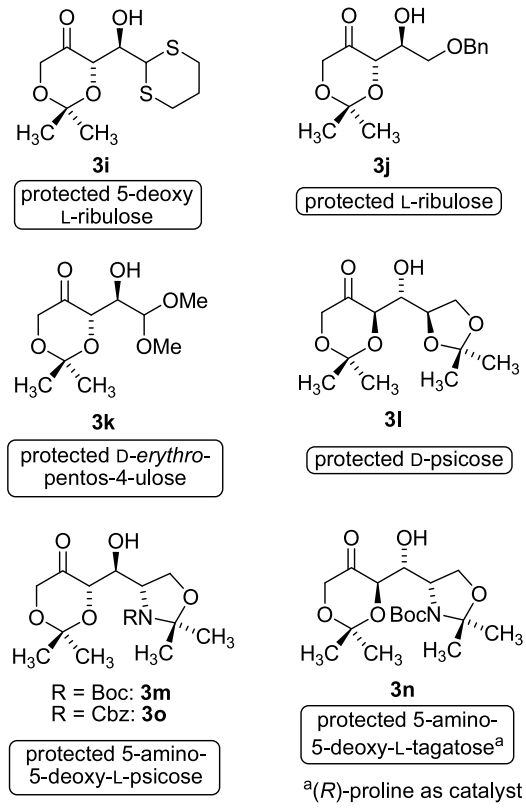
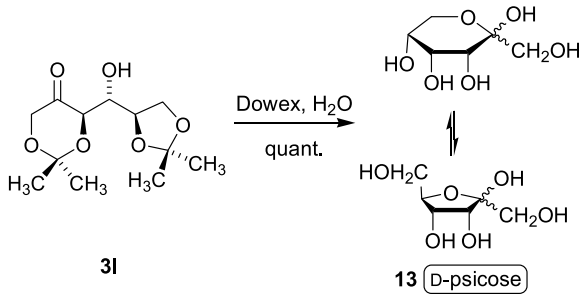


Figure 2. Selectively protected sugars and aminosugars.



Scheme 3. Deprotection of **3l** to D-psicose (**13**).

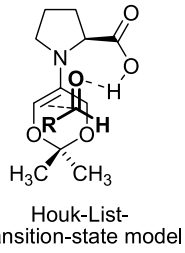
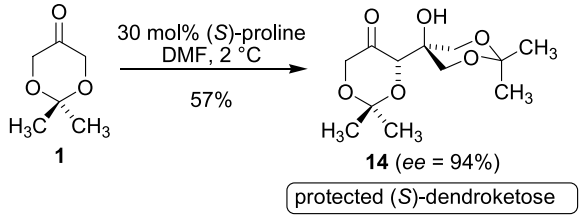


Figure 3. Postulated transition state model.

We could also demonstrate that under proline catalysis a self-aldolization of **1** is possible. The corresponding aldol product **14** (57%, 94% ee) was obtained with high enantioselectivity and represents a protected form of (*S*)-dendroketose (Scheme 4).



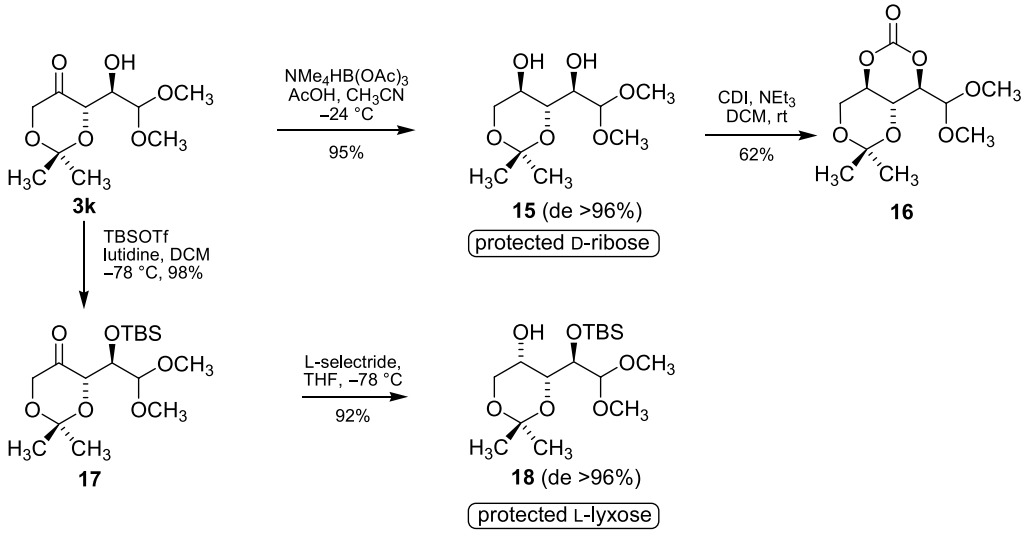
Scheme 4. (*S*)-Proline-catalyzed asymmetric self-aldolization of dioxanone **1** to the protected (*S*)-dendroketose **14**.

As already reported in our previous publication, the reduction of the ketone function of **3k** leads to a direct entry to selectively protected aldopentoses. This strategy was first described by Whitesides et al. and is known as the inversion strategy.[26] It was our aim to show the reduction of **3k** and to control the relative configuration of the newly generated stereogenic center. For the stereoselective reduction of β-hydroxy ketones many powerful methods are already described, many of them for acyclic derivatives.[27]

In the beginning of our investigations we were concerned with the direct reduction of **3k** to afford the diol **15**. In order to achieve a selective *anti*-reduction we chose the Evans protocol using tetramethylammonium triacetoxyborohydride, which is in general successful for acyclic cases.[28] We were able to apply this method to our system. To our surprise, however, we observed a *syn*-selective reduction with high diastereocontrol (>98:2). This could be corroborated by formation of the cyclic carbonate **16** with carbonyl diimidazole in the presence of triethylamine and subsequent NOE-measurements (Scheme 5). The *syn*-selectivity may be explained by an intramolecular hydride transfer where the dioxanone unit exists predominantly in a twisted boat conformation and the side-chain is located in a *pseudo*-equatorial position. The hydride attacks the carbonyl function selectively from the *Si*-face to generate the *syn*-1,3-diol (Fig. 4).

The *anti* 1,3-diol of **3k** could be obtained, however, after the conversion of the alcohol function into the corresponding TBS-ether **17**. The formation of the TBS-ether was accomplished with TBSOTf and lutidine in dichloromethane at −78 °C to afford **17** in 98% yield.[30] Compound **17** was reduced with L-selectride to afford selectively the *anti* 1,3-diol **18** (>98:2). The relative configurations of **18** are proven by NOE-measurements. The reduced aldol products **15** and **18** represents the protected aldopentoses D-ribose (**15**) and L-lyxose (**18**).

Besides reduction, further transformations of the keto function of **3k**, for example, reductive amination,



Scheme 5. Stereoselective *syn*- and *anti*-reduction of **3k** to **15** and **18**.

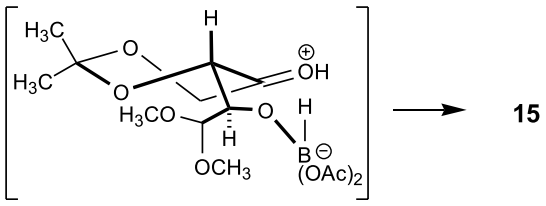
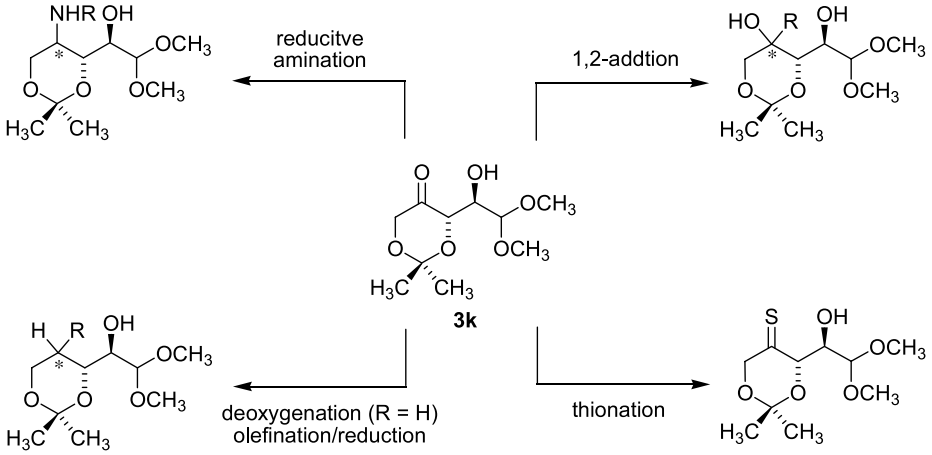


Figure 4. Proposed transition-state for the *syn*-selective reduction of **3k** to **15** using tetramethylammonium triacetoxyborohydride.



Scheme 6. Manipulation of the keto function of **3k**.

nucleophilic 1,2-addtion, deoxygenation or olefination/reduction and thionation will greatly expand the scope of this method to prepare variety of diverse carbohydrates (Scheme 6).

In summary, our asymmetric, organocatalytic aldol reaction of the dihydroxyacetone equivalent **1** with various aldehydes represents a direct approach to simple and selectively protected carbohydrates in practically one-step. Furthermore, this biomimetic C_3+C_n strategy generates the same absolute and relative configuration as the enzyme tagatose-aldolase (tagA).[29] Whereas the tagA-catalyzed aldol reaction proceeds non-selective, our methodology offers an impressively simple alternative. In addition, we were able to show the stereoselective reduction of the aldol product **3k** to afford highly selectively both the *syn*- and the *anti*-1,3-diols, which opens a direct entry to differently protected D- and L-aldopentoses.

3. Experimental

3.1. General

Starting materials and reagents were purchased from commercial suppliers and used without further purification. THF was freshly distilled from sodium-lead alloy under Ar. Dichloromethane and acetonitril were freshly distilled from CaH_2 under Ar. Acetic acid was destilled from CrO_3 under Ar. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates from Merck, Darmstadt. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or stained using acidic ammonium molybdate. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (EI 70 eV) spectrometer. High-resolution mass spectra were recorded on a Finnigan MAT95 spectrometer. IR spectra were taken on a Perkin-Elmer FT-IR 1760. ^1H and ^{13}C spectra were recorded on Varian Mercury 300, Inova 400 or Unity 500 spectrometers with tetramethylsilane as internal standard and at ambient temperature unless otherwise stated. Analytical HPLC was performed on Hewlett-Packard 1100 Series chromatographs. All racemic samples were obtained according to GP 1 using equal amounts of (*S*)- and (*R*)-proline.

Compounds **2i**[31], **2l**[32], **2o**[33], **9**[34], **10**[35], **11**[36], **12**[37] were synthesized by standard procedures.

3.2. General procedure for the (*S*)-proline catalyzed aldol reaction (GP 1)

To a suspension of (*S*)-proline (0.1–0.3 equiv) in DMF (0.5 mL/mmol) was added dioxanone **1** (1.0 equiv) and stirred for 30 min at ambient temperature. After cooling down to 2 °C the aldehyde **2** (1.0 equiv) was added and the suspension was stored at 2 °C. After 48–120 h, the resulting mixture was quenched with satd ammonium chloride solution and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, pentane/diethyl ether).

Compounds **3a**, **3b**, **3f** and **3j** were obtained according to GP 1 and they are already fully characterised.[25] **3l** and **13** are already described in our preceding communication.[23a]

3.2.1. Compound 3f′. According to GP 1 benzaldehyde **2f** (245 mg, 2.31 mmol)) was reacted with dioxanone **1** (300 mg, 2.31 mmol) in the presence of (*S*)-proline (80 mg, 0.69 mmol) to give a diastereomeric mixture of **3f** and **3f′**, which can be easily separated on silica gel, to afford

3f (180 mg, 34%) and **3f′** (125 mg, 23%) as colourless oils. The ee of the product was measured by HPLC using a chiral stationary phase (Chiralcel OD, *n*-heptane/*iso*-propanol 95:5) relative to the racemic sample: major isomer 24.7 min, minor isomer 26.3 min. IR ($CHCl_3$) 3411, 3080, 3031, 2989, 2899, 2257, 1748, 1600, 1490, 1460, 1375, 1220, 1110, 923 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, C*H*$_3$, 3H), 1.48 (s, C*H*$_3$, 3H), 4.03 (d, $J=17.0$ Hz, C*H*$_2$, 1H), 4.28 (dd, $J=17.0$, 1.4 Hz, C*H*$_2$, 1H), 4.45 (dd, $J=2.7$, 1.4 Hz, C*H*, 1H) 5.23 (d, $J=2.7$ Hz, C*H*, 1H), 7.27–7.47 (m, Ar, 4H), 8.08–8.12 (m, Ar, 1H)), no OH signal observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.2, 67.1, 71.2, 80.0, 100.9, 126.3, 127.6, 127.8, 140.0, 207.3. MS (EI, 70 eV): *m*/*z* (%) 165 (29) [$M^+-C_4H_9O$], 130 (10), 107 (100), 91 (6), 79 (30), 77 (39) [$C_6H_5^+$], 72 (37), 59 (87). Anal. Calcd for $C_{13}H_{16}O_4$ (236.27): C, 66.08; H, 6.83. Found: C, 65.85; H, 6.91.

3.2.2. Compound 3g. According to GP 1 *ortho*-chlorobenzaldehyde **2g** (325 mg, 2.31 mmol) was reacted with dioxanone **1** (300 mg, 2.31 mmol) in the presence of (*S*)-proline (53 mg, 0.46 mmol) to give a diastereomeric mixture of **3g** and **3g′**(73%, 4:1), which can be easily separated on silica gel, to afford **3g** (355 mg, 57%) and **3g′** (89 mg, 14%) as colourless oils. The ee of the product was measured by HPLC using a chiral stationary phase (Whelk O1, *n*-heptane/*iso*-propanol 9:1) relative to the racemic sample: major isomer 14.2 min, minor isomer 10.6 min. $[\alpha]_D^{25}-98.5$ (*c* 1.04, $CHCl_3$). IR ($CHCl_3$) 3499, 2990, 2939, 2896, 1744, 1441, 1380, 1224, 1164, 1094, 1036, 955, 886, 864, 758, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, C*H*$_3$, 3H), 1.39 (s, C*H*$_3$, 3H), 3.60 (s, O*H*, 1H), 4.01 (d, $J=$ 16.3 Hz, C*H*$_2$, 1H), 4.27 (dd, $J=16.3$, 1.4 Hz, C*H*$_2$, 1H), 4.47 (dd, $J=6.0$, 1.4 Hz, C*H*, 1H), 5.35 (d, $J=6$ Hz, C*H*, 1H), 7.18–7.33 (m, Ar, 3H), 7.58 (dd, $J=7.7$, 1.6 Hz, Ar, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.1, 67.2, 69.8, 76.2, 101.1, 126.8, 128.4, 129.0, 129.2, 132.9, 136.8, 209.4. MS (EI, 70 eV): *m*/*z* (%) 199 (39), 141 (100), 130 (12), 77 (15), 72 (29), 59 (62). HRMS: *m*/*z* calcd for $C_{13}H_{15}O_4Cl$–OH (M^+-OH) 253.0631, found 253.0633.

3.2.3. Compound 3g′. The ee of the product was measured by HPLC using a chiral stationary phase (Daicel AD, *n*-heptane/*iso*-propanol 8:1) relative to the racemic sample: major isomer 12.2 min, minor isomer 9.9 min. IR ($CHCl_3$) 3499, 2990, 2939, 2896, 1744, 1441, 1380, 1224, 1164, 1094, 1036, 955, 886, 864, 758, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, C*H*$_3$, 3H), 1.47 (s, C*H*$_3$, 3H), 2.83 (s, O*H*, 1H), 4.11 (d, $J=17.3$ Hz, C*H*$_2$, 1H), 4.35 (dd, $J=17.3$, 1.4 Hz, C*H*$_2$, 1H), 4.56 (*app*-s, C*H*, 1H), 5.75 (br, C*H*, 1H), 7.23–7.37 (m, Ar, 3H), 7.57 (dd, $J=7.7$, 1.6 Hz, Ar, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.4, 67.4, 68.1, 76.6, 101.0, 126.7, 128.5, 128.9, 129.3, 131.3, 137.3, 207.1. MS (EI, 70 eV): *m*/*z* (%) 199 (39), 141 (100), 130 (12), 77 (15), 72 (29), 59 (62).

3.2.4. Compound 3h. According to GP 1 pyridin-2-carbaldehyde **2h** (247 mg, 2.31 mmol) was reacted with dioxanone **1** (300 mg, 2.31 mmol) in the presence of (*S*)-proline (80 mg, 0.69 mmol) to give a diastereomeric mixture of **3h** and **3h′**, which can be easily separated on silica gel, to afford **3h** (267 mg, 49%) as a pale yellow oil and **3h′** (67 mg, 12%) as a yellow solid. The ee of the product was measured by HPLC using a chiral stationary phase (Daicel AD, *n*-heptane/*iso*-propanol 92:8) relative to the racemic sample: major isomer 18.8 min, minor isomer 21.1 min. IR ($CHCl_3$) 3201, 2992, 2934, 2890, 1745, 1597, 1480, 1440, 1377, 1331, 1224, 1154, 1077, 1036, 1003, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, C*H*$_3$, 3H), 1.41 (s, C*H*$_3$, 3H), 4.02 (d, $J=17.0$ Hz, C*H*$_2$, 1H), 4.30 (dd, $J=17.0$, 1.3 Hz, C*H*$_2$, 1H), 4.74 (dd, $J=4.7$, 1.3 Hz, C*H*, 1H), 5.17 (d, $J=4.7$ Hz, C*H*, 1H), 7.23 (dd, $J=7.4$, 5.0 Hz, C*H*, 1H), 7.38 (d, $J=7.7$ Hz, C*H*, 1H), 7.72 (dt, $J=7.7$, 1.6 Hz, C*H*, 1H), 8.55 (m, C*H*, 1H), no OH signal observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.2, 67.0, 72.5, 77.3, 100.9, 121.8, 122.9, 136.8, 148.0, 157.5, 209.5. MS (EI, 70 eV): *m*/*z* (%) 238 (18) [M^++H], 222 (3) [M^+-CH_3] 179 (25) [$M^+-C_3H_6O$], 149 (33), 138 (22), 108 (100), 72 (19), 59 (13). Anal. Calcd for $C_{12}H_{15}NO_4$ (237.10): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.40; H, 6.14; N, 5.60.

3.2.5. Compound 3h′. The ee of the product was measured by HPLC using a chiral stationary phase (Daicel AD, *n*-heptane/*iso*-propanol 9:1) relative to the racemic sample: major isomer 15.9 min, minor isomer 12.1 min. Mp 104–106 °C. IR (KBr) 3195, 2991, 1743, 1597, 1480, 1439, 1377, 1330, 1225, 1153, 1079, 1033, 1003, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, C*H*$_3$, 3H), 1.40 (s, C*H*$_3$, 3H), 4.06 (d, $J=16.6$ Hz, C*H*$_2$, 1H), 4.31 (dd, $J=16.6$, 1.4 Hz, C*H*$_2$, 1H), 4.83 (dd, $J=2.5$, 1.4 Hz, C*H*, 1H), 4.33 (d, $J=$ 2.5 Hz, C*H*, 1H), 7.26 (m, C*H*, 2H), 7.75 (t, $J=7.4$ Hz, C*H*, 1H), 8.56 (m, C*H*, 1H), no OH signal observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.2, 60.3, 67.1, 71.3, 100.7, 120.6, 122.4, 136.5, 148.1, 158.5, 209.7. MS (EI, 70 eV): *m*/*z* (%) 238 (18) [M^++H], 222 (3) [M^+-CH_3], 179 (25) [$M^+-C_3H_6O$], 149 (33), 138 (22), 108 (100), 72 (19), 59 (13).

3.2.6. Compound 3i. According to GP 1 [1,3]-dithian-2-aldehyde **2i** (342 mg, 2.31 mmol) was reacted with dioxanone **1** (300 mg, 2.31 mmol) in the presence of (*S*)-proline (80 mg, 0.69 mmol) to give **3i** (514 mg, 88%) as a colourless solid. The ee of the product was measured by HPLC using a chiral stationary phase (Daicel OD, *n*-heptane/*iso*-propanol 95:5) relative to the racemic sample: major isomer 8.0 min, minor isomer 9.9 min. Mp 74–76 °C. $[\alpha]_D^{23}-77.6$ (*c* 1.05, $CHCl_3$). IR (KBr) 3505, 2984, 2932, 2894, 2833, 1733, 1428, 1381, 1290, 1225, 1164, 1109, 1041, 1003, 969, 881, 803, 737, 669, 647, 610, 543, 491 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, C*H*$_3$, 3H), 1.50 (s, C*H*$_3$, 3H), 1.96–2.12 (m, 2H), 2.44–2.61 (m, 2H), 2.86 (ddd, $J=14.0$, 10.2, 3.7 Hz, C*H*$_2$, 1H), 3.15 (ddd, $J=14.0$, 10.2, 3.7 Hz, C*H*$_2$, 1H), 3.20 (s, O*H*, 1H), 3.89 (d, $J=7.4$ Hz, C*H*, 1H), 4.01 (d, $J=16.6$ Hz, C*H*$_2$, 1H), 4.46 (dd, $J=16.6$, 1.5 Hz, C*H*$_2$, 1H), 4.53–4.59 (m, C*H*, 1H), 4.63 (dd, $J=4.2$, 1.5 Hz, C*H*, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 24.2, 25.0, 25.3, 26.2, 43.3, 66.7, 72.3, 75.3, 100.9, 207.6. MS (EI, 70 eV): *m*/*z* (%) 278 (14) [M^+], 148 (14) [$M^+-C_4H_7OS_2$], 119 (100). Anal. Calcd for $C_{11}H_{18}O_4S_2$ (278.39): C, 47.46; H, 6.52. Found: C, 47.47; H, 6.59.

3.2.7. Compound 3k. According to GP 1 a 60% aqueous solution of 2,2-dimethoxyacetaldehyde **2k** (2.7 g, 15.4 mmol) was reacted with dioxanone **1** (2.0 g, 15.4 mmol) in the presence of (*S*)-proline (355 mg, 3.09 mmol) to give **3k** (2.27 g, 69%) as a pale yellow oil.

The ee of the product was measured by HPLC using a chiral stationary phase (Daicel AD, *n*-heptane/*iso*-propanol 8:2) relative to the racemic sample: major isomer 14.4 min, minor isomer 12.8 min. $[\alpha]_D^{23}$ −121.7 (*c* 1.05, $CHCl_3$). IR ($CHCl_3$): 3467, 2991, 2940, 2835, 1749, 1457, 1380, 1225, 1199, 1126, 1087, 982, 873, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 2×CH_3, 6H), 2.75 (s, O*H*, 1H), 3.40 (s, OCH_3, 3H), 3.46 (s, OCH_3, 3H), 4.05 (d, J=16.6 Hz, CH_2, 1H), 4.13 (dd, J=7.0, 2.7 Hz, C*H*, 1H), 4.28 (dd, J=16.6, 1.6 Hz, CH_2, 1H), 4.47 (dd, J=2.7, 1.6 Hz, C*H*, 1H), 4.67 (d, J=7.0 Hz, C*H*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 25.0, 54.1, 55.4, 67.0, 71.1, 76.4, 100.4, 103.3, 206.1. MS (EI, 70 eV): *m*/*z* (%) 234 (22) [M^+], 190 (10), 91.1 (100). Anal. Calcd for $C_{10}H_{18}O_6$ (234.11): C, 55.27; H, 7.75. Found: C, 55.01; H, 7.78.

3.2.8. Compound 3m. According to GP 1 the protected Garner aldehyde **2m** (553 mg, 1.54 mmol) was reacted with **1** (200 mg, 1.54 mmol) in the presence of (*S*)-proline (53 mg, 0.46 mmol) to give **3m** (442 mg, 80%) as a colourless oil. $[\alpha]_D^{25}$ −86.2 (*c* 1.03, $CHCl_3$). IR ($CHCl_3$) 3488, 2983, 2938, 2885, 1747, 1694, 1477, 1458, 1386, 1252, 1224, 1170, 1091, 948, 853, 760, 668 cm^{-1}. ^1H NMR (300 MHz, C_6D_6, 70 °C) δ 1.19 (s, CH_3, 3H), 1.20 (s, CH_3, 3H), 1.44 (s, C(CH_3)$_3$, 9H), 1.56 (s, CH_3, 3H), 1.72 (s, CH_3, 3H), 2.88 (s, O*H*, 1H), 3.73 (d, J=17.0 Hz, CH_2, 1H), 3.76, (dd, J=9.1, 7.0 Hz, C*H*, 1H), 3.95 (dd, J=17.0, 1.2 Hz, CH_2, 1H), 4.21–4.29 (m, 3H), 4.40–4.48 (m, C*H*, 1H). ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 23.6, 24.0, 24.7, 26.8, 28.6, 59.0, 63.9, 67.2, 71.0, 75.7, 80.0, 94.5, 101.0, 152.6, 208.1. MS (EI, 70 eV): *m*/*z* (%) 344 [M^+-CH_3] (13), 301 [$M^+-C_3H_6O$] (8), 255 [$M^+-C_5H_7O_3$] (19), 200 (24), 186 (23), 144 (23), 100 (65), 57 (100). Anal. Calcd for $C_{17}H_{29}NO_7$ (359.41): C, 56.81; H, 8.13; N, 3.90. Found: C, 56.90; H, 8.03; N, 3.88.

3.2.9. Compound 3n. According to GP 1 the protected Garner aldehyde **2m** (553 mg, 1.54 mmol) was reacted with **1** (200 mg, 1.54 mmol) in the presence of (*R*)-proline (53 mg, 0.46 mmol) to give **3n** (171 mg, 31%) as a colourless oil. $[\alpha]_D^{25}$ −65.7 (*c* 0.86, $CHCl_3$). IR ($CHCl_3$) 3548, 2983, 2937, 2885, 1746, 1698, 1387, 1252, 1225, 1171, 1099, 859 cm^{-1}. ^1H NMR (300 MHz, C_6D_6, 70 °C) δ 1.28 (s, CH_3, 3H), 1.31 (s, CH_3, 3H), 1.43 (s, C(CH_3)$_3$, 9H), 1.48 (s, CH_3, 3H), 1.64 (s, CH_3, 3H), 3.53–4.42 (m, 7H), no OH signal observed. ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 23.1, 24.0 (2C), 26.7, 27.8, 60.6, 64.7, 66.8, 70.4, 75.3, 80.2, 93.9, 100.3, 153.9, 207.5. MS (EI, 70 eV): *m*/*z* (%) 344 [M^+-CH_3] (13), 301 [$M^+-C_3H_6O$] (8), 255 [$M^+-C_5H_7O_3$] (19), 200 (24), 186 (23), 144 (23), 100 (65), 57 (100). Anal. Calcd for $C_{17}H_{29}NO_7$ (359.41): C, 56.81; H, 8.13; N, 3.90. Found: C, 56.90; H, 8.03; N, 3.88.

3.2.10. Compound 3o. According to GP 1 the protected Garner aldehyde **2o** (635 mg, 2.31 mmol) was reacted with **1** (300 mg, 2.31 mmol) in the presence of (*S*)-proline (80 mg, 0.69 mmol) to give **3o** (726 mg, 80%) as a colourless oil. $[\alpha]_D^{23}$ −99.0 (*c* 1.05, $CHCl_3$). IR ($CHCl_3$) 3490, 2987, 2939, 2887, 1747, 1701, 1456, 1411, 1379, 1353, 1256, 1224, 1156, 1094, 862, 765, 736, 699 cm^{-1}. ^1H NMR (300 MHz, C_6D_6, 70 °C) δ 1.12 (s, 2×CH_3, 6H), 1.55 (s, CH_3, 3H), 1.73 (s, CH_3, 3H), 3.63 (d, J=17.3 Hz, CH_2, 1H), 3.72 (d, J=15.3 Hz, CH_2, 1H), 3.75 (d, J=15.3 Hz, CH_2, 1H), 3.85 (d, J=17.3 Hz, CH_2, 1H)), 4.09 (d, J=5.7 Hz, C*H*, 1H), 4.22 (dd, J=8.9, 3.0 Hz, C*H*, 1H), 4.47 (m, 1H), 5.09 (d, J=2.8 Hz, CH_2, 2H), 7.0–7.37 (m, Ar, 5H), no OH signal observed. ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 23.6, 24.0, 24.7, 26.5, 59.0, 64.0, 66.9, 67.1, 70.5, 75.6, 94.9, 100.9, 127.8, 128.1, 128.3, 137.4, 153.1, 209.8. MS (EI, 70 eV): *m*/*z* (%) 378 [M^+-CH_3] (10), 335 [$M^+-C_3H_6O$] (12), 264 [$M^+-C_5H_9O$] (6), 234 (13), 190 (13), 91 (100). Anal. Calcd for $C_{20}H_{27}NO_7$ (393.43): C, 61.06; H, 6.92; N 3.56. Found: C, 60.90; H, 7.01; N, 3.18.

3.2.11. Compound 14. According to GP 1 dioxanone **1** (300 mg, 2.31 mmol) was reacted with (*S*)-proline (80 mg, 0.69 mmol) to give **14** (171 mg, 57%) as a colourless oil. The ee of the product was measured HPLC using a chiral stationary phase (Chiralpak AD, *n*-heptane/*iso*-propanol (8:2) relative to the racemic sample: major isomer 10.8 min, minor isomer 9.0 min. $[\alpha]_D^{26}$ −163.7 (0.97, $CHCl_3$). IR ($CHCl_3$) 3474, 2992, 2941, 2881, 1747, 1454, 1379, 1225, 1160, 1076, 1040, 879, 833, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, CH_3, 3H), 1.45 (s, CH_3, 3H), 1.48, (s, CH_3, 3H), 1.49 (s, CH_3, 3H), 2.99 (s, O*H*, 1H), 3.65 (dd, J=11.8, 1.0 Hz, CH_2, 1H), 3.84 (dd, J=11.8, 1.0 Hz, CH_2, 1H), 4.01 (d, J=17.0 Hz, CH_2, 1H), 4.02 (dd, J=11.8, 1.2 Hz, CH_2, 1H), 4.13 (dd, J=11.8, 1.2 Hz, CH_2, 1H), 4.27 (dd, J=17.0, 1.5 Hz, CH_2, 1H), 4.48 (d, J=1.5 Hz, C*H*, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 23.4, 23.6, 24.0, 64.6, 65.3, 67.4, 68.8, 74.0, 98.5, 101.3, 208.5. MS (EI, 70 eV): *m*/*z* (%) 245 [M^+-CH_3] (12), 187 (19), 172 (20), 131, (42), 130 (34), 115 (15), 72 (58), 59 (100). HRMS: *m*/*z* calcd for $C_{12}H_{20}O_6$–CH_3 (M^+-CH_3) 245.1025, found 245.1026.

3.2.12. Compound 15. Tetramethylammonium triacetoxyborohydride (842 mg, 3.20 mmol) was dissolved in acetonitrile (1.0 mL) and acetic acid (0.37 mL, 6.4 mmol) and cooled to −30 °C. Then ketone **3k** (150 mg, 0.64 mmol, dissolved in 0.5 mL acetonitrile) was added and stored overnight at −24 °C in a freezer. The reaction was quenched with 0.5 N sodium tatrate-solution (2 mL) and extracted with dichloromethane (4×5 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by flash chromatography (SiO_2, pentane/diethyl ether 1:2) to afford product **15** (143 mg, 95%) as a colourless oil. $[\alpha]_D^{24}$ −101.3 (1.00, $CHCl_3$). IR ($CHCl_3$) 3435, 2991, 2937, 2840, 1458, 1377, 1269, 1201, 1165, 1125, 1074, 978, 864, 738, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, CH_3, 3H), 1.48 (s, CH_3, 3H), 2.82 (s, O*H*, 1H), 3.49 (s, OCH_3, 3H), 3.52 (s, OCH_3, 3H), 3.64 (dd, J=11.0, 8.9 Hz, CH_2, 1H), 3.74 (dd, J=9.0, 6.4 Hz, C*H*, 1H), 3.82 (dd, J=6.4, 3.0 Hz, C*H*, 1H), 3.84 (td, J=8.9, 5.5 Hz, C*H*, 1H), 3.93 (dd, J=11.0, 5.5 Hz, CH_2, 1H), 4.48 (d, J=3.0 Hz, C*H*, 1H), 1 OH signal is not observed. ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 28.4, 55.9, 56.4, 63.9, 65.3, 72.3, 74.9, 98.6, 103.4. MS (EI, 70 eV): *m*/*z* (%) 221 (7) [M^+-CH_3], 129 (3), 75 (100), 59 (26). HRMS: *m*/*z* calcd for $C_{10}H_{20}O_6$–CH_3 (M–CH_3) 221.1025, found 221.1025.

3.2.13. Compound 16. To a solution of **15** (30 mg, 0.13 mmol) in dichloromethane (1.0 mL) were added carbonyl diimidazole (62 mg, 0.4 mmol) and triethylamine (0.1 mL, 0.75 mmol) at rt. After 3 h satd ammonium chloride-solution (2 mL) was added, extracted with dichloromethane (3×5 mL) and the combined organic

layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, pentane/diethyl ether 1:2) to afford the carbonate **16** (21 mg, 62%) as a colourless solid. Mp 67–69 °C. $[\alpha]_D^{25}+10.7$ (0.90, $CHCl_3$). IR (KBr) 2997, 2942, 1786, 1463, 1384, 1337, 1277, 1211, 1110, 1050, 984, 918, 846, 753, 689, 536 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 1.14 (s, CH_3, 3H), 1.27 (s, CH_3, 3H), 3.03 (s, OCH_3, 3H), 3.21 (s, OCH_3, 3H), 3.37 (t, $J=10.2$ Hz, CH_2, 1H), 3.48 (m, CH, 1H), 3.57 (dd, $J=10.2$, 5.0 Hz, CH_2, 1H), 3.99 (dd, $J=9.6$, 8.0 Hz, CH, 1H), 4.08 (dd, $J=8.0$, 2.7 Hz, CH, 1H), 4.11 (d, $J=2.7$ Hz, CH, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 18.7, 28.9, 55.4, 56.7 61.2, 64.4, 69.1, 81.0, 100.3, 103.5, 154.7. MS (EI, 70 eV): *m/z* (%) 247 (14) [M^+-CH_3], 75.2 (100) [$C_3H_7O_2^+$]. HRMS: *m/z* calcd for $C_{11}H_{18}O_7$–CH_3 (M–CH_3) 247.0818, found 247.0818.

3.2.14. Compound 17. To a solution of **3k** (200 mg, 0.85 mmol) in dichloromethane (1.5 mL) were added dropwise TBSOTf (0.6 mL, 2.55 mmol) and lutidine (0.4 mL, 3.42 mmol) at −78 °C. After 1.5 h satd sodium hydrocarbonate-solution (2 mL) was added, extracted with dichloromethane (3×5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, pentane/diethyl ether 2:1) to afford the TBS-protected aldol product **17** (292 mg, 98%) as a colourless oil. $[\alpha]_D^{24}-101.3$ (1.00, $CHCl_3$). IR ($CHCl_3$) 2987, 2934, 2857, 1751, 1468, 1379, 1252, 1225, 1196, 1128, 1001, 867, 839, 812, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, $SiCH_3$, 3H), 0.11 (s, $SiCH_3$, 3H), 0.88 (s, $SiC(CH_3)_3$, 9H), 1.44 (s, CH_3, 3H), 1.47 (s, CH_3, 3H), 3.39 (s, OCH_3, 3H), 3.47 (s, OCH_3, 3H), 3.89 (d, $J=15.8$ Hz, CH_2, 1H), 4.46 (dd, $J=7.4$, 1.8 Hz, CH, 1H), 4.23 (dd, $J=15.8$, 1.3 Hz, CH_2, 1H), 4.35 (m, CH, 1H), 4.61 (d, $J=7.4$ Hz, CH, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.6, 18.1, 22.9, 24.9, 25.7, 55.6, 56.0, 67.1, 73.5, 77.8, 100.2, 105.4, 206.0. MS (EI, 70 eV): *m/z* (%) 333 (2) [M^+-CH_3], 317 (6) [$M^+-C_2H_6$], 259 (21), 233 (8), 201 (28), 173 (16), 129 (71), 75 (100), 59 (15). Anal. Calcd for $C_{16}H_{32}O_6Si$ (348.2): C, 55.14; H, 9.25. Found: C, 55.16; H, 9.19.

3.2.15. Compound 18. To a solution of **18** (64 mg, 0.18 mmol) in THF (0.8 mL) were added dropwise a 1 M solution of L-selectride in THF (0.24 mL, 0.24 mmol) at −78 °C. After 2 h the reaction mixture was warmed to rt, then diethyl ether (4 mL) and satd ammonium chloride-solution (2 mL) were added, stirred for 10 min and was extracted with ethyl acetate (3×5 mL). The combined organic phases were washed with brine (5 mL) dried over $MgSO_4$ and were concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, pentane/diethyl ether 2:1) to afford the product **18** (58 mg, 92%) as a colourless oil. $[\alpha]_D^{23}+6.1$ (0.39, $CHCl_3$). IR ($CHCl_3$) 3013, 2932, 2859, 1464, 1380, 1253, 1216, 1071, 838, 758, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, $SiCH_3$, 3H), 0.16 ($SiCH_3$, 3H), 0.92 (s, $SiC(CH_3)_3$, 9H), 1.44 (s, CH_3, 3H), 1.45 (s, CH_3, 3H), 3.42 (s, OCH_3, 3H), 3.48 (s, OCH_3, 3H), 3.72 (s, OH, 1H), 3.83 (dd, $J=12.4$, 2.2 Hz, CH_2, 1H), 3.90 (t, $J=4.9$ Hz, CH, 1H), 3.92–3.96 (m, 2×CH, OH, 3H), 3.98 (dd, $J=12.4$, 1.7 Hz, CH_2, 1H), 4.37 (d, $J=4.9$ Hz, CH, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.7, 18.3, 18.7, 25.9, 29.4, 55.3, 56.4, 64.3, 65.7, 69.7, 74.3, 98.7, 104.8. MS (EI, 70 eV): *m/z* (%) 335 (9) [M^+-CH_3], 261 (44), 203 (35), 131 (48), 75 (100), 59 (27). HRMS: *m/z* calcd for $C_{16}H_{34}O_6Si$–CH_3 (M–CH_3) 335.1890, found 335.1889.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SPP Organokatalyse) and the Fonds der Chemischen Industrie (C. G. thanks for a Kekulé fellowship). We thank Degussa AG, BASF AG, Lanxess and Wacker-Chemie for the donation of chemicals. The NOE-measurements by Dr. J. Runsink are gratefully acknowledged.

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Tetrahedron 62 (2006) 338–345
Tetrahedron

L-Proline catalysed asymmetric aldol reactions in PEG-400 as recyclable medium and transfer aldol reactions

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Received 31 May 2005; revised 8 September 2005; accepted 16 September 2005

Available online 25 October 2005

Abstract—L-Proline-catalysed direct asymmetric aldol reaction of acetone with various aldehydes in PEG-400 is described. Recycling of the catalyst and solvent (PEG) was possible up to ten runs without loss of catalyst activity. L-Proline was also found to be an efficient catalyst for the asymmetric transfer aldol reaction between various aldehydes and diacetone alcohol for the first time. Good yields and enantioselectivities were observed with both methods.

1. Introduction

In general, most of the methodologies, which are available for the asymmetric aldol[1,2] reactions fall into one of the following categories: (a) the chiral auxiliary assisted aldol reactions based on the use of stoichiometric quantities of chiral appendage;[3] (b) chiral Lewis acid-catalysed Mukaiyama type and chiral Lewis-base catalysed aldol reactions;[4] (c) heterobimetallic bifunctional Lewis acid/Bronsted base-catalysed direct aldol reactions[5]; and (d) aldol reactions catalysed by aldolase enzymes and antibodies.[6] A significant characteristic of the later two methodologies is the employment of unmodified carbonyl compounds as aldol donor substrates, whereas the first two methodologies require some degree of preactivation of the substrates involved.

Asymmetric versions of the aldol reaction rely upon the use of chiral auxiliaries, however, it must be noted that there has been some success of using asymmetric catalysts, although they normally rely on a Mukaiyama type process.

The development of catalytic and enantioselective C– bond forming reactions is currently among the prime objectives in organic synthesis. Direct catalytic and enantioselective aldol reactions of unmodified ketones or aldehydes were reported by the research groups of Shibasaki,[7] Trost,[8] Jorgensen,[9] MacMillan,[10] List,[11] Barbas III[12] and Cordova[13] using organometallic or purely organic catalysts. Recent work has been attempted by using a recyclable ionic liquid as the solvent,[14] buffered aqueous media,[15] Zn-proline complexes in aqueous media or aqueous micelles.[16]

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain a metal atom. The application of enantiomerically pure 'small' organic molecules represents a promising alternative catalytic concept in addition to other frequently used syntheses based on metal containing catalysts.[17] Some new direct asymmetric intermolecular reactions such as Mannich,[18] Michael[19] and other analogous reactions have been reported by Barbas III,[20] and others using proline as catalyst.[21]

2. Results and discussion

It is always economical if the catalytic reaction is performed in an ecofriendly solvent, which allows both solvent and catalyst to recycle. Poly(ethylene glycol) (PEG) is non-toxic and used as a rapid and recyclable reaction medium for the Heck reaction,[22] asymmetric dihydroxylation[23] and Baylis–Hillman reactions.[24] In continuation of this work, an efficient synthesis of chiral β-hydroxy ketones from various aldehydes and acetone in poly (ethylene glycol)-400 catalysed by L-proline has been developed (Scheme 1).[25]

Several groups studied the mechanism of L-proline catalysed direct asymmetric aldol reaction and proposed

Keywords: L-Proline; PEG-400; Aldol reaction; Transfer aldol reaction.
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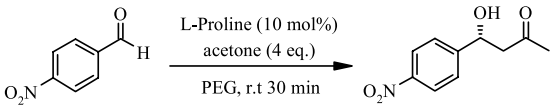
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.122



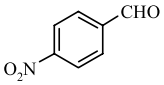
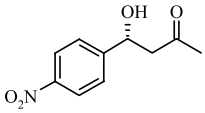
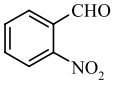
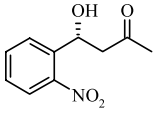
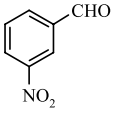
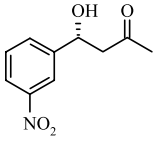
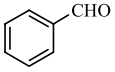
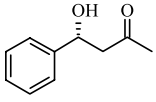
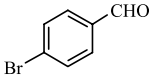
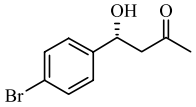
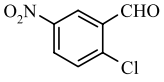
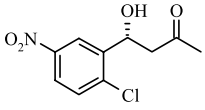
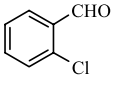
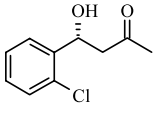
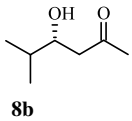
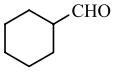
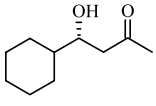
Scheme 1.

an enamine mechanism based on the Hajos–Parrish–Eder–Sauer–Wiechert reaction mechanism.[26]

We were particularly interested in developing an eco-friendly approach for the direct aldol reaction using PEG as a solvent for the following reasons.

(a) PEG is biologically compatible.[27]

Table 1. L-Proline catalysed asymmetric aldol reactions in PEG-400

Entry	Substrate	Time (min)	Product	Yield (%)[a]	ee (%)
1	 **1a**	30	 **1b**	94	67[b]
2	 **2a**	30	 **2b**	90	64[b]
3	 **3a**	30	 **3b**	88	70[b]
4	 **4a**	30	 **4b**	58	58[b]
5	 **5a**	30	 **5b**	85	65[b]
6	 **6a**	30	 **6b**	90	61[b]
7	 **7a**	30	 **7b**	88	60[c]
8	 **8a**	120	 **8b**	90	84[c]
9	 **9a**	180	 **9b**	65	71[c]

[a] Isolated yields after column chromatography; the products were characterised by spectral data.
[b] ee% by chiral HPLC.
[c] ee% by optical rotation.

(b) The polymer is available at a very low affordable price [ionic liquid cost 1200 – 2400 USD/kg, as against PEG-400, which cost 43 USD/kg].
(c) Requires only a low concentration of catalyst.
(d) Highly practical and a simple work-up procedure.

First we initiated our study by using 4-nitrobezaldehyde (entry 1, Table 1), acetone and L-proline (10 mol %) in PEG-400. The reaction was completed in 30 min and yielded 94% of product **1b** with 67% ee. Enantiomeric excess was determined using chiralcel OB-H column. After workup (extraction with ether) mother liquor (PEG+ proline) was kept aside for further runs. The transformation in conventional solvent (DMSO) took 4 h for completion of the reaction.

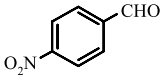
2-Nitrobenzaldehyde and 3-nitrobenzaldehydes (entries 2 and 3, Table 1) were reacted with acetone to give the aldol products **2b** and **3b** in good yields and enantioselectivities. Aldol reaction between simple benzaldehyde (entry 4, Table 1) and acetone afforded the product **4b** in 58% yield and 58% ee. The 4-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde and 2-chlorobenzaldehyde (entries 5, 6 and 7, Table 1) underwent the aldol reaction smoothly giving the products **5b**, **6b** and **7b** in 85, 90 and 88% yields with 65, 61 and 60% ee's, respectively.

The aliphatic aldehydes, isobutyraldehyde and cyclohexane carboxaldehyde (entries 8 and 9, Table 1) have also proved to be efficient by producing the products **8b** and **9b** in 90 and 65% yields, respectively. The optical purity of the products was determined by their optical rotation (compared with the literature value). High enantioselectivity of 84% ee was obtained for the reaction of isobutyraldehyde with acetone in PEG.

We found L-proline to be an efficient catalyst for the direct asymmetric aldol reaction of acetone with aromatic and aliphatic aldehydes in PEG. Enantioselectivities depend on the aldehyde component and are typically in the seventies with aromatic aldehydes and in the eighties with aliphatic α-branched aldehydes.

We have studied the reusability of the catalyst as well as the solvent. A second run was performed without any modification. The simple addition of 4-nitrobenzaldehyde (entry 1, Table 2) and acetone to the mother liquor with stirring for 30 min resulted in the formation of the aldol product **1b** in 93% yield with similar enantioselectivity. Except for the third run, which showed a slight increase in enantioselectivity (71%), all the runs were similar in product yields and enantioselectivities. The efficient recycling was then proved by additional experiments until the tenth run (Table 2).

Table 2. L-Proline catalysed asymmetric aldol reactions in PEG

Entry	Substrate	Time (min)	Yield (%)[a]	ee (%)[b]
1		30	94	67
2	2nd run	30	93	68
3	3rd run	30	90	71
4	4th run	30	89	67
5	5th run	30	90	66
6	6th run	30	88	64
7	7th run	30	87	67
8	8th run	30	88	65
9	9th run	30	86	67
10	10th run	30	84	66

[a] Isolated yields after chromatography.
[b] ee% by chiral HPLC.

2.1. L-Proline catalysed asymmetric transfer aldol reaction

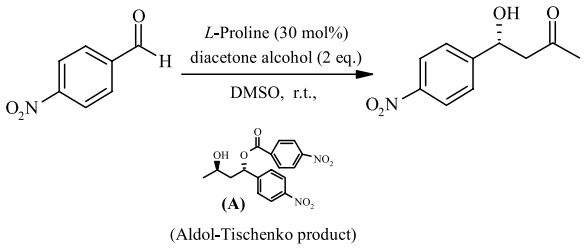
To further expand the scope of the L-proline catalysed C–bond forming reaction, we sought to apply this amine catalysed enamine generation to asymmetric transfer aldol reaction. The addition of nucleophiles to carbonyl compounds has been under investigation for decades. Examples include the addition of enolates to aldehydes and the Meerwein–Ponndorf–Verley reduction of ketones (hydride as a nucleophile). Recent achievements in this area are: alkynyl transfer reactions,[28] allyl transfer reaction[29] (as proposed to occur by a stepwise ionic mechanism) and cyanide transfer reactions.[30]

This concept of transfer aldol reaction has originated from above mentioned reactions. Aldol and retro aldol reactions are catalysed by either acid or base. The reversibility of the aldol reaction, that is, equilibrium between aldol and carbonyl compounds is one of the most important characteristics of the aldol reaction.[31] The retro aldol reaction has been recently found to have several new applications, for instance antibodies and enzymes have been found to catalyse retro aldol reactions allowing efficient kinetic resolution of racemic aldols. The retro aldol reaction has been utilised for the synthesis of bicyclo-[2.2.1]-heptane and cyclopentane derivatives, which in turn have been employed in the synthesis of a variety of diterpenoids, sesquiterpenes, biaryl compounds and bicyclo-[4.3.0]-nonane derivatives.[32]

Transfer aldol reaction involving diacetone alcohol as a source of ketone (acetone) is studied with several alkoxides, in these reactions Aldol–Tischenko reaction is competitive to get mono protected 1,3-diols and in few cases normal aldol products were observed.[33]

We initiated this study to explore L-proline as a mild organocatalyst for asymmetric transfer aldol reaction[34] between diacetone alcohol and various aldehydes. Interestingly the present procedure not only allowed to achieve condensation with good selectivity but also was mild enough to avoid Tischenko–Aldol product A (Scheme 2) in Lewis acid catalysed transfer aldol reactions.

First we examined the transfer aldol reaction between 4-nitrobenzaldehyde (entry 1, Table 3) and diacetone alcohol in the presence of L-proline (30 mol%) in DMSO to afford the corresponding β-hydroxy ketone **1b** in 86% yield and 71% ee. Even after increasing the catalyst concentration (100 mol%), there was no difference in yields and ee's (entry 2, Table 3). This reaction was also attempted in PEG-400 as solvent, however,



Scheme 2.

product yield and ee were lower compared to the standard solvent.

There is no direct evidence for the mechanism by which the reaction proceeds. However, we believe a cyclic transition state (re-facial attack of aldehyde to proline derivative) where a retro aldol and aldol reactions are initiated by the same catalyst (Scheme 3).

Similarly various other aldehydes such as 3-nitrobenzaldehyde, 4-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde and 2-chlorobenzaldehyde (entries 3, 5, 6 and 7, Table 3) were subjected to this transformation and observed the yields of aldol products up to 88% and ee's up to 71%.

Transfer aldol reaction between simple benzaldehyde (entry 4, Table 3) and diacetone alcohol gave the product **4b** in 50% yield and 57% ee. In the case of anisaldehyde (entry 10, Table 3)(electron rich benzaldehyde) the aldol product **10b** was observed only after 5 days stirring at room temperature with 48% ee and 40% yield along with the dehydrated aldol condensation product.

Aliphatic aldehydes (entries 8 and 9, Table 3) were also good substrates for this reaction, wherein isobutyraldehyde provided aldol product **8b** in 80% yield and 84% ee and cyclohexane carboxaldehyde furnished **9b** in 91% yield with 86% ee.

Since, in principle aldol reactions are reversible, another question to be addressed in this context is whether the optical purity varies as a function of time. This is an important feature to be determined and we found that the ee of the aldol product in our model reaction (entry 1) does not vary significantly (ee = 71%) when monitored at different intervals (4, 8, 12 and 24 h), however, the formation of dehydrated aldol condensation product was observed after 8 h. In the case of aliphatic aldehydes having α-hydrogens (phenyl propanol), we have observed that the self-aldolisation of aldehyde was competitive.

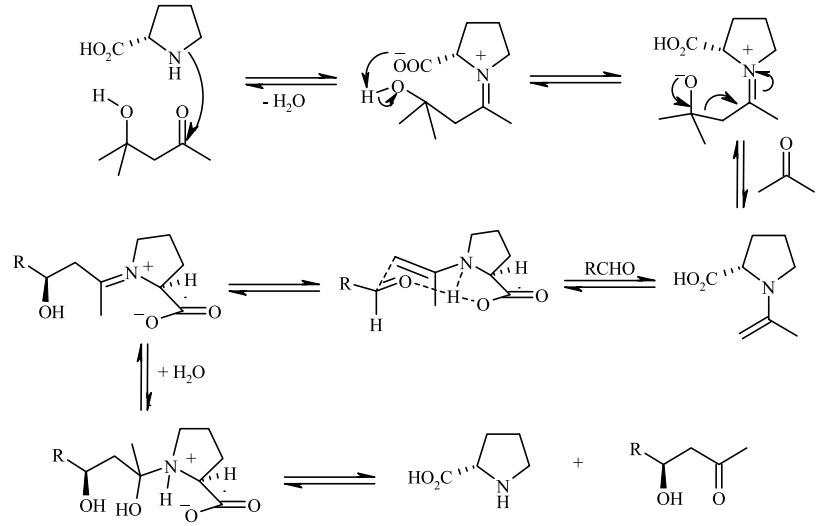
3. Conclusion

In summary, poly(ethylene glycol) (PEG) has been shown to be a rapid and reusable reaction medium for L-proline- catalysed asymmetric aldol reaction. The reusability of this solvent was studied over ten runs without loss of activity of either the catalyst or the solvent and we have also developed the first asymmetric transfer aldol reaction catalysed by L-proline. In this reaction no Aldol–Tischenko product was observed in contrast to other reported methods.

4. Experimental

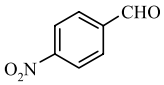
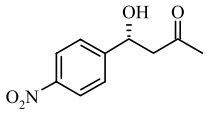
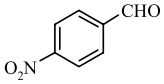
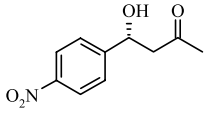
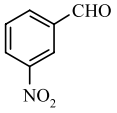
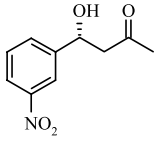
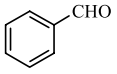
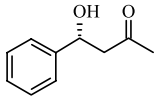
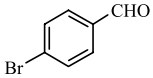
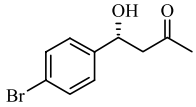
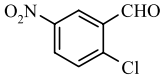
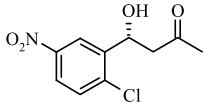
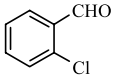
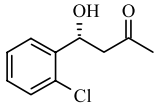
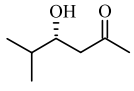
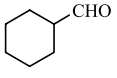
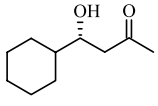
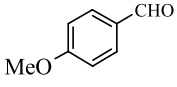
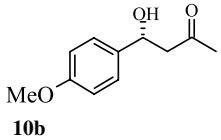
4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 meshes. IR spectra were recorded on Perkin-Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts were reported in ppm with respect to internal TMS.



Scheme 3.

Table 3. L-Proline catalysed asymmetric transfer aldol reaction

Entry	Substrate	Time (min)	Product	Yield[a] (%)	ee (%)
1	 **1a**	4	 **1b**	86	71[b]
2	 **1a**	4	 **1b**	85	72[b,c]
3	 **3a**	6	 **3b**	88	70[b]
4	 **4a**	12	 **4b**	50	57[b]
5	 **5a**	12	 **5b**	65	71[d]
6	 **6a**	6	 **6b**	82	60[b]
7	 **7a**	8	 **7b**	70	60[d]
8	 **8a**	12	 **8b**	80	84[d]
9	 **9a**	12	 **9b**	91	86[d]
10	 **10a**	120	 **10b**	40	48[b]

[a] Isolated yields after column chromatography; the products were characterised by spectral data.
[b] ee% by chiral HPLC.
[c] L-Proline used 100 mol%.
[d] ee% by optical rotation.

Coupling constants (J) are quoted in Hz. Mass spectra were obtained on Finnegan MAT 1020B or micro mass VG 70-70H spectrometer operating at 70 eV using direct inlet system. HPLC was recorded on SHIMADZU HPLC using chiralcel OB-H column, hexane and isopropyl alcohol as eluents.

4.2. General procedure for the aldol reaction: procedure A

To a stirred solution of L-proline (10 mol%) in PEG (2 mL) was added acetone (4 mmol) at room temperature under inert atmosphere. After being stirred this mixture for 5 min, aldehyde (1 mmol) was added and allowed to stir for 30 min. The reaction medium was diluted with anhydrous ether (5 mL), stirred for 5 min, allowed to separate out and the ether layer was decanted. This process was repeated twice to obtain the product in ether where as the mother liquor (PEG + proline) was kept aside for further runs. This process was repeated up to ten runs without loss of the activity of the catalyst. Solvent was removed under vacuo and purified by silica gel column chromatography to give the pure product.

4.3. General procedure for transfer aldol reaction: procedure B

To a stirred solution of L-proline (30 mol%) in DMSO was added diacetone alcohol (4 mmol) at room temperature under inert atmosphere. After being stirred for 5 min aldehyde (2 mmol) was added, and allowed to stir for 4 h. After completion of the reaction (monitored by TLC), water was added and extracted with ethyl acetate twice (2× 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate. Solvent was removed under vacuo and purified by silica gel column chromatography to afford the pure product.

4.3.1. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (1b).[21] Pale brown viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J=7.0 Hz, 2H, Ar-*H*), 7.52 (d, J=7.0 Hz, 2H, Ar-*H*), 5.30–5.20 (m, 1H, –C*H*OH), 3.56 (br s, 1H, –O*H*), 2.85–2.80 (m, 2H, –CH_2CO), 2.21 (s, 3H, -COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3419, 2930, 1716, 1514, 1480, 1370 cm^{-1}; $[\alpha]_D^{25}$ +44.3 (c 1, $CHCl_3$) for 67% ee. Enantiomeric excess: 67% by procedure A and 71% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 28.49 min and minor isomer, t_R 34.20 min.

4.3.2. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (2b).[14] Pale brown viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.91 (dd, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.71 (dt, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.44 (dt, J=1.2, 8.1 Hz, 1H, Ar-*H*), 5.70 (d, J=9.3 Hz, 1H, –C*H*OH), 3.76–3.70 (m, 1H, –O*H*), 3.15 (dd, J=2.1, 17.7 Hz, 1H, CH_2CO), 2.70 (dd, J=9.6, 18 Hz, 1H, –CH_2CO), 2.24 (s, 3H, –COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3416, 2934, 1719, 1512, 1376 cm^{-1}; $[\alpha]_D^{25}$ −109.2 (c 1, $CHCl_3$) for 64% ee. Enantiomeric excess: 64% by procedure A, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 12.72 min and minor isomer, t_R 11.82 min.

4.3.3. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (3b).[21] Yellow viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H. Ar-*H*), 8.13 (d, J=8.6 Hz, 1H, Ar-*H*), 7.71 (d, J=7.5 Hz, 1H, Ar-*H*), 7.53 (t, J=7.5 Hz, 1H, Ar-*H*), 5.27–5.15 (m, 1H, –C*H*OH), 3.50 (br s, 1H, –O*H*), 2.82 (d, J=12.0 Hz, 2H, –CH_2CO), 2.23 (s, 3H, –COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3414, 2931, 1715, 1519, 1370 cm^{-1}; $[\alpha]_D^{25}$ +49.9 (c 1.2, $CHCl_3$) for 70% ee. Enantiomeric excess: 70% by procedure A and B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 31.55 min and minor isomer, t_R 36.58 min.

4.3.4. (4*R*)-Hydroxy-4-phenyl-butan-2-one (4b).[35,21] Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.17 (m, 5H, Ar-*H*), 5.15–5.04 (m, 1H, –C*H*OH), 3.17 (br s, 1H, –O*H*), 2.80–2.75 (m, 2H, –CH_2CO), 2.17 (s, 3H, –COCH_3); Mass (EI): m/z 164 (M^+), 43; IR (neat): 3413, 2932, 1718, 1450, 890 cm^{-1}; $[\alpha]_D^{25}$ +60.0 (c 1, $CHCl_3$) for 83% ee [lit. value]. Enantiomeric excess: 58% by procedure A and 57% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.5. (4*R*)-Hydroxy-4-(4′-bromophenyl)-butan-2-one (5b).[21] Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=8.4 Hz, 2H, Ar-*H*), 7.22 (d, J=8.4 Hz, 2H, Ar-*H*), 5.08 (dd, J=5.6, 7.8 Hz, 1H, –C*H*OH), 3.38 (br s, 1H, –O*H*), 2.80–2.70 (m, 2H, –CH_2CO), 2.20 (s, 3H, –COCH_3); Mass (EI): m/z 243 (M^+), 43; IR (neat): 3418, 2934, 1713, 1489, 1369, 1077, 538 cm^{-1}; $[\alpha]_D^{25}$ +53.3 (c 1, $CHCl_3$) for 90% ee [lit. value]. Enantiomeric excess: 65% by procedure A and 71% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.6. (4*R*)-Hydroxy-4-(2′-chloro-5′-nitrophenyl)-butan-2-one (6b). Colourless viscous oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.66 (s, 1H, Ar-*H*), 8.10 (dd, J=1.7, 8.8 Hz, 1H, Ar-*H*), 7.44 (d, J=9.6 Hz, 1H, Ar-*H*), 5.43 (d, J=12.0 Hz, 1H, –C*H*OH), 3.65 (s, 1H, –O*H*), 3.02 (dd, J=4.1, 12.5 Hz, 1H, –CH_2CO), 2.61 (dd, J=8.3, 16.6 Hz, 1H, –CH_2CO), 2.24 (s, 3H, –COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 208.3, 147.1, 142.3, 137.6, 130.2, 123.2, 122.7, 66.1, 49.3, 30.4; Mass (EI): m/z 243 (M^+), 183, 43; HRMS calcd for $C_{10}H_{10}ClNO_4$ (M^+) 243.0928, found 243.0898; IR (KBr): 3414, 2932, 1718, 1517, 1373, 1167, 1069 cm^{-1}; $[\alpha]_D^{25}$ + 84.45 (c 0.5, $CHCl_3$) for 64% ee. Enantiomeric excess: 64% by procedure A and 60% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 12.72 min and minor isomer, t_R 11.82 min.

4.3.7. (4*R*)-Hydroxy-4-(2′-chlorophenyl)-butan-2-one (7b).[21] Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=8.6 Hz, 1H, Ar-*H*), 7.34–7.14 (m, 3H, Ar-*H*), 5.46 (d, J=10.4 Hz, 1H, –C*H*OH), 3.58 (s, 1H, –O*H*), 3.05–2.90 (m, 1H, –CH_2CO), 2.73–2.53 (m, 1H, –CH_2CO), 2.22 (s, 3H, –COCH_3); Mass (EI): m/z 198 (M^+), 43; IR (neat): 3410, 2930, 1712, 1440, 840 cm^{-1}; $[\alpha]_D^{25}$ +97.0 (c 1,

$CHCl_3$) for 85% ee [lit. value]. Enantiomeric excess: 60% by procedure A and procedure B, which was determined by optical rotation (compared with the literature value).

4.3.8. (4*R*)-Hydroxy-5-methyl-hexan-2-one (8b).[21] Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85–3.75 (m, 1H, –C*H*OH); 2.90 (br s, 1H, –O*H*), 2.58–2.50 (m, 2H, –CH_2CO), 2.20 (s, 3H, –CO CH_3), 1.76–1.58 (m, 1H, $(CH_3)_2$C*H*), 1.00–0.85 (m, 6H, –CH(CH_3)$_2$); IR (neat): 3410, 2929, 1710, 1350, 702 cm^{-1}; $[\alpha]_D^{25}+75.5$ (*c* 1.2, $CHCl_3$) for 99% ee [lit. value]. Enantiomeric excess: 84% by procedure A and 84% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.9. (4*R*)-4-(Cyclohexyl)-4-hydroxy-2-butanone (9b).[21] Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83–3.76 (m, 1H, –C*H*OH), 2.60–2.50 (m, 2H, –CH_2CO), 2.40–2.25 (m, 1H, –O*H*), 2.18 (s, 3H, –COCH_3), 1.77–1.62 (m, 5H, –$CH_2CH_2CHCH_2CH_2$), 1.25–0.97 (m, 6H, –(CH_2)$_3$); Mass (EI): *m*/*z* 169 (M^+-1), 87, 43; IR (neat): 3419, 2930, 1715, 1450, 1364, 1165 cm^{-1}; $[\alpha]_D^{25}+45.9$ (*c* 1.2, $CHCl_3$) for 97% ee [lit. value]. Enantiomeric excess: 71% by procedure A and 86% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.10. (4*R*)-Hydroxy-4-(4′-methoxyphenyl)-butan-2-one (10b).[35] Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, $J=8.8$ Hz, 2H, Ar-*H*), 6.88 (d, $J=8.8$ Hz, 2H, Ar-*H*), 5.10 (dd, $J=9.0$, 3.3 Hz, 1H, –C*H*OH), 3.80 (s, 3H, –OCH_3), 3.22 (br s, 1H, –O*H*), 2.86–2.78 (m, 2H, –CH_2CO), 2.19 (s, 3H, –COCH_3); Mass (EI): *m*/*z* 194 (M^+), 43; IR (neat): 3424, 2917, 1730, 1450, 1100, 1070 cm^{-1}; $[\alpha]_D^{25}+38.5$ (*c* 0.7, $CHCl_3$) for 48% ee. Enantiomeric excess: 48% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85).

Acknowledgements

Three of us (N.R.R., S.S.S. and C.N.) thank CSIR New Delhi for financial support. IICT Communication no. 050704

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Tetrahedron 62 (2006) 346–351
Tetrahedron

L-Proline amide-catalyzed direct asymmetric aldol reaction of aldehydes with chloroacetone

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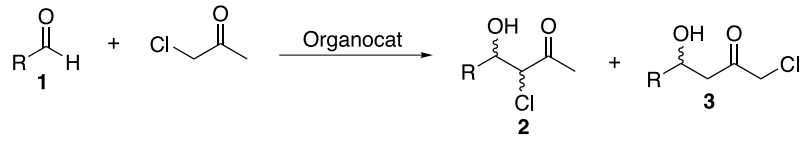
Received 5 July 2005; revised 24 August 2005; accepted 9 September 2005

Available online 10 October 2005

Abstract—L-Proline amides were evaluated for catalyzing the direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone. The presence of 30 mol% (*S*)-pyrrolidine-2-carboxylic acid (2,4,6-trimethyl-phenyl)-amide catalyzed the direct aldol reactions of a range of aldehydes with chloroacetone to give *anti*-α-chloro-β-hydroxyketones with high regio-, diastereo- and enantioselectivity.

1. Introduction

The aldol reaction has emerged as one of the most powerful carbon–carbon bond-forming reactions.[1] The asymmetric direct aldol reaction, because of its atom-economy,[2] has recently received great attention, and thus many chiral catalyst including biocatalysts,[3] transition metal complexes,[4–6] and organocatalysts[7–12] have been discovered for this transformation. The direct aldol reaction of an unsymmetric ketone with an aldehyde principally generates the β-hydroxyketone as a mixture of its regio-, diastereo-, and enantiomers. It is quite difficult to control the reaction to produce a single isomer. β-Hydroxyketones have been used as donors in the direct aldol reactions promoted by biocatalysts,[3] chiral transition metal complexes,[4b,5b] and organocatalysts.[7i–k,11] Both 1,2- and 1,4-diols with high enantioselectivities can be regioselectively approached under suitable reaction conditions. Very recently, Zhong and Barbas reported a L-prolinol catalyzed direct aldol reaction of fluoroacetone with aldehydes to regio- and diastereoselectively afford *anti*-α-fluoro-β-hydroxyaketones with good enantioselectivities (up to 87% ee).[13] However, the aldol reaction with chloroacetone as a donor has not yet been documented. Optically active α-chlorocarbonyl compounds are very useful in organic synthesis, the development of efficient method to access these molecules is therefore, of great importance. An important advance has been made on the asymmetric catalytic electronic α-chloronation of carbonyl compounds, which is considered a direct method to obtain optically active α-chloroketone or -esters.[14] The direct aldol reaction of chloroacetone with aldehydes provides an alternative to α-chloronation for preparing α-chloroketones (Scheme 1). Encouraged by our recent success in the L-proline amide catalyzed direct aldol reactions,[10] we herein extend the application of these organocatalysts (Fig. 1) to the direct aldol reaction of chloroacetone. As a result, high enanantioselectivities of up to 98% ee were provided for



Scheme 1. Aldol reactions of aldehydes with chloroacetone.

Keywords: Organocatalyst; L-proline amides; Direct aldol reaction; Asymmetric catalysis; Chloroacetone.
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doi:10.1016/j.tet.2005.09.061

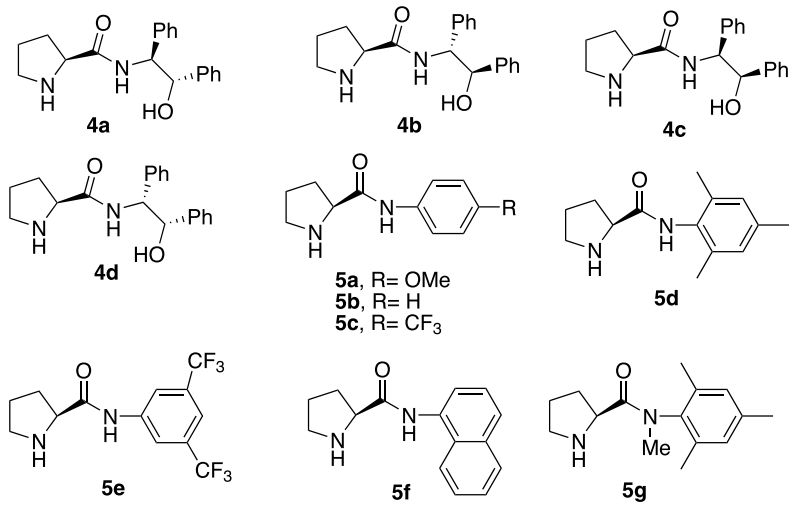


Figure 1. L-proline amides evaluated in this study.

anti-α-chloro-β-hydroxyketones by an optimal L-proline amide.

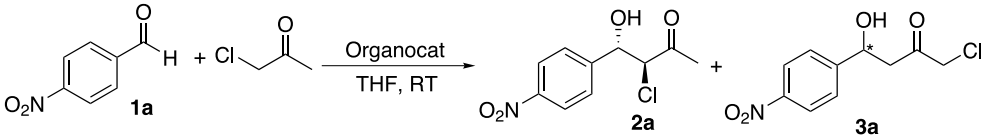
2. Results and discussion

2.1. The direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone catalyzed by L-proline amides 4 and 5: catalyst screening

The catalytic efficiency of L-proline amides **4** and **5** was evaluated by the direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone at room temperature in THF. The results are summarized in Table 1.

All the L-proline amides catalyzed the reaction to give *anti*-3-chloro-4-hydroxy -4-(4′-nitro-phenyl)-butan-2-one (**2a**) as a favored product, however, low to moderate yields for **2a** were obtained probably due to low reactivity of chloroacetone relative to hydroxyacetone[7i–k,11] and fluoroacetone.[13] The L-proline amides **4a** and **4c**, which exhibited higher enantioselectivity than their diastereomers **4b** and **4d** at catalyzing the direct aldol reaction of aldehydes with acetone, however, catalyzed the reaction of 4-nitrobenzaldehyde with chloroacetone in lower yields and enantioselectivities (entries 1–4). We previously reported that simple L-proline amides such as **5a**–**g** catalyzed the direct aldol reaction of 4-nitrobenzaldehyde with acetone with very low enantioselectivity (up to 45% ee). Surprisingly, most of them showed higher enantioselectivities than **4a**–**d**, of which **5a**–**d** mediated the reaction with higher than 90% ees (entries 5–8). Results from organocatalysts **5a**–**c** demonstrated that the electron-nature of the substituent on the phenyl group of L-proline amide does not affect the enantiochemical outcome dramatically (entries 5–7). The sterical bulkiness of the aryl group in the organocatalyst trends to be an important factor to influence the reaction selectivity, for example, **5d** enabled the best result in the

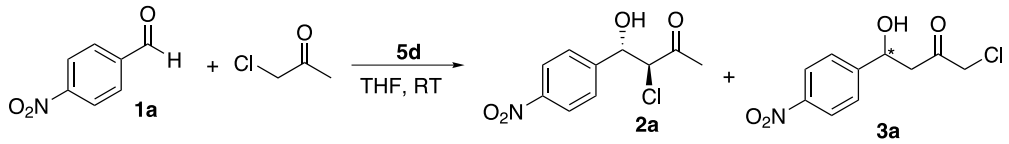
Table 1. Screening organocatalysts **4** and **5**[a]



Entry	Catalyst	Yield (%)[b]	Regioselectivity (**2a**/**3a**)[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	**4a**	23	4:1	3:1	82
2	**4b**	37	5:1	9:2	89
3	**4c**	19	8:1	3:1	78
4	**4d**	36	4:1	9:2	88
5	**5a**	25	4:1	6:1	92
6	**5b**	24	4:1	9:1	90
7	**5c**	29	3:1	9:1	92
8	**5d**	42	7:1	12:1	94
9	**5e**	33	5:1	9:2	87
10	**5f**	28	>20:1	12:1	86
11	**5g**	Trace	—	—	—
12	L-proline	8	—	—	74

[a] Unless indicated otherwise, the reaction of aldehyde (0.5 mmol) with chloroacetone (l.0 mL) in THF (1.0 mL) in the presence of 20 mol% organocatalyst.
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

Table 2. Effect of catalyst loading on the reaction[a]



Entry	Amount of **5d** (mol%)	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	20	42	7:1	12:1	94
2	30	57	7:1	7:1	91
3	40	56	7:1	5:1	89
4	45	55	7:1	5:1	88
5	50	53	6:1	4:1	86

[a] The reaction of aldehyde (0.5 mmol) with chloroacetone (l mL) was performed in THF (1.0 mL).
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

model reaction (entry 8). The proton on the amide function of the organocatalyst determines the catalytic efficacy. Thus, small organic molecule **5g**, which was derived from **5d** by a methylation, failed to catalyze the reaction (entry 11). However, the reaction proceeded incompletely in the presence of 20 mol% L-proline to give **2a** in only 8% yield with 74% ee (entry 12).

2.2. Optimization of reaction conditions

L-proline amide **5d** was found to be the best for the reaction in terms of enantioselectivity among all the organocatalysts tested (Table 1), but it gave only moderate yield. In principle, variation of the catalyst loading will change the reaction conversion. We therefore, investigated the relationship between the amount of organocatalyst **5d** and reaction conversion, and hoped that the yield of the desired product **2a** would be improved by using increased amounts of **5d**.

The reaction of 4-nitrobenzaldehyde with chloroacetone was performed in THF at room temperature with various amounts of **5d**. The results are recorded in Table 2. The yield was increased to 57% by using 30 mol% **5d** (entry 2), however, the yield could not be further improved as the catalyst loading was increased (entries 3–5). In addition to that, both diastereo- and enantioselectivity dropped to some degree with the increase of the catalyst loading (entries 1–5). In terms of the yield and enantioselectivity, 30 mol% of **5d** can be considered an optimal catalyst loading.

Another possibility to enhance the conversion is variation of the amount of chloroacetone. In the presence of 30 mol% catalyst **5d**, the direct aldol reaction of 4-nitrobenzaldehyde with different amounts of chloroacetone was carried out. As shown in Table 3, the yield, diastereo- and enantioselectivity are independent on the amount of chloroacetone. However, regioselectivity gradually decreases as the amount of chloroacetone increases (entries 1–5). Study on the temperature effect revealed that the yield could be improved by performing the reaction at low temperature (entries 6–8). However, both diastereo- and enantioselectivity dropped as the decrease in the reaction temperature. For example, when the reaction was carried on at −10 °C, significantly high yield of 76% was isolated, but the dr of *anti*/*syn* was only 2:1 and enantioselectivity was decreased to 87% ee (entry 8).

In organocatalyzed direct aldol reactions, the solvent affects the reaction performance dramatically. Some common organic solvents were therefore, examined for the reaction of chloroacetone with 4-nitrobenzaldehyde. The related results are presented in Table 4. It was found that the use of THF, diethyl ether or 1-dioxane as a solvent gave better results in terms of both yield and enantioselectivity than the use of other organic solvents (entries 1–7). Performing the reaction in a polar solvent, for example, in either CH_3CN or DMSO, provided an excellent enantioselectivity, but a poor yield (entries 4 and 5). Neither chloroform nor toluene is a good solvent for the reaction. Although fair yields were

Table 3. Effects of the amount of chloroacetone and the reaction temperature[a]

Entry	Amount of chloroacetone (mL)	Temperature (°C)	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	0.4	25	56	17:1	6:1	89
2	0.6	25	56	10:1	7:1	89
3	0.8	25	56	7:1	7:1	89
4	1	25	57	7:1	7:1	91
5	2	25	50	8:1	6:1	89
6	1	10	58	5:1	5:1	89
7	1	0	68	5:1	3:1	88
8	1	−10	76	6:1	2:1	87

[a] The reaction was performed on a 0.5 mmol scale in THF (1.0 mL) in the presence of 30 mol% **5d**.
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

Table 4. Solvent effect[a]

Entry	Solvent	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	THF	57	7:1	7:1	91
2	Et_2O	45	8:1	5:1	90
3	Dioxane	34	5:1	5:1	90
4	CH_3CN	23	4:1	4:1	90
5	DMSO	22	9:1	6:1	92
6	$CHCl_3$	33	5:1	3:1	74
7	Toluene	49	7:1	2:1	79

[a] The reaction of 4-nitrobenzaldehyde (0.5 mmol) with chloroacetone (1 mL) was performed in a solvent (1.0 mL) in the presence of 30 mol% **5d** at room temperature.
[b] Isolated yield of **2a**.
[c] The ratio of **2a/3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^1H NMR.
[e] Determined by HPLC.

observed when the reaction were carried out in chloroform and toluene, diastereo- and enantioselectivity were much lower than those with THF as the solvent (entries 6 and 7).

2.3. Scope and limitations

Under the optimal conditions, a range of aldehydes including aromatic and aliphatic ones were examined to react with chloroacetone. As demonstrated in Table 5, the organocatalyst **5d** exhibited generally excellent enantioselectivities ranging from 91–98% ee for most of aldehydes tested, with exception of the case involving 2-chlorobenzaldehyde, in which 86% ee was provided (entry 5). The *ortho*-substituted benzaldehydes reacted much more diastereoselectively than *para*- and *meta*-substituted benzaldehydes with chloroacetone (entries 1–8). Diastereomeric ratios of *anti*/*syn* from 10:1 to 30:1 were obtained for benzaldehyde derivatives bearing an *ortho*-substituent (entries 2, 5, 7, and 8). On the contrary, much lower drs of *anti*/*syn* from 5:1 to 7:1 were given for *para*- and *meta*-substituted benzaldehydes (entries 1, 3, 4, and 6). The aliphatic aldehyde is less reactive than aromatic aldehydes toward chloroacetone. Low yield of 18% was therefore, observed for cyclohexylformaldehyde, but a very high enantioselectivity of 98% ee was induced (entry 9).

3. Conclusion

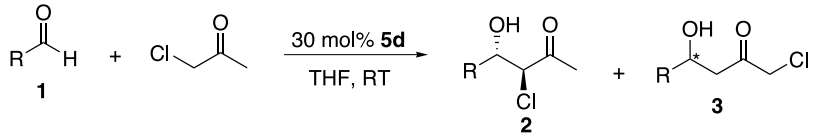
A series of L-prolinamides, derived from L-proline and optically pure 1,2-diphenyl-2-aminoethanols, simple aliphatic, and aromatic amines, were evaluated for catalyzing the direct aldol reaction of chloroacetone and 4-nitrobenzaldehyde. The proton of the amide function in the organocatalyst determined its catalytic efficacy. An L-proline amide **5d**, which was prepared from L-proline and 2,4,6-trimethyl-phenylamine, was found to be the best catalyst. Under the optimal conditions, the direct adol reactions of chloroacetone with aldehydes catalyzed by 30 mol% **5d** gave rise to *anti*-α-chloro-β-hydroxyketones with high diastereo- and enantioselectivity.

4. Experimental

4.1. General

Chemicals were purchased from Acros and organic solvents were distilled before use. NMR spectra were recorded on a Bruker-300 MHz spectrometer. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectromter. HPLC analysis was performed

Table 5. Study on the scope and limitation of aldehydes[a]



Entry	Product	R	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	**2a**	4-$NO_2C_6H_4$	57	7:1	7:1	91
2	**2b**	2-$NO_2C_6H_4$	35	4:1	30:1	93
3	**2c**	3-$NO_2C_6H_4$	37	>20:1	5:1	94
4	**2d**	4-CNC_6H_4	31	>20:1	7:1	91
5	**2e**	2-ClC_6H_4	52	>20:1	19:1	86
6	**2f**	4-$MeO_2CC_6H_4$	40	>20:1	6:1	91[f]
7	**2g**	2-FC_6H_4	28	5:1	10:1	97[f]
8	**2h**	2-BrC_6H_4	43	5:1	29:1	91[f]
9	**2i**	*c*-C_6H_{11}	18	>20:1	31:1	98[f]

[a] Unless indicated otherwise, the reaction of aldehyde (0.5 mmol) with chloroacetone (l mL) was performed in THF (1.0 mL).
[b] Overall yield of *anti*-**2** and *syn*-**2**.
[c] The ratios of **2/3** were calculated on the basis of the isolated yields of **2** and **3**, and the enantioselectivities of **3** were not determined.
[d] Determined by ^1H NMR.
[e] Determined by HPLC.
[f] The reaction was performed at 0 °C.

on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, AD columns were purchased from Daicel Chemical Industries, LTD. Chiral GC analysis was performed on VARIAN CP-3380 with a CP CHIPASIL-DEX column.

4.2. General procedure for the direct aldol reaction of chloracetone with aldehydes

To a solution of an aldehyde (0.5 mmol) and chloroacetone (1.0 mL) in anhydrous THF (1.0 mL) was added L-prolinamide **5d** (34.8 mg, 0.15 mmol). After being stirred at room temperature for 96 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (3×10 mL) and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified through a flash column chromatography on silica gel to give desired aldol products **2**.

4.2.1. 3-Chloro-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one (2a). Yield: 57%, as a 7:1 inseparable mixture of *anti*-**2a** and *syn*-**2a**. *Anti*-**2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.86 (d, J=4.2 Hz, 1H), 4.26 (d, J=8.1 Hz, 1H), 5.12 (dd, J=8.1, 4.2 Hz, 1H), 7.57 (d, J=8.7 Hz, 2H), 8.19 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 63.5, 73.8, 123.5, 127.3, 128.1, 145.9, 202.9; IR (neat): γ 3488, 2947, 1718, 1606, 1519, 1348, 1085, 857, 699 cm^{-1}. Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=18.498 min; t_{Rmajor}=23.248 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0294; found: 243.0314.

4.2.2. 3-Chloro-4-hydroxy-4-(2′-nitrophenyl)-butan-2-one (2b). Yield: 35%, as a 30:1 inseparable mixture of *anti*-**2b** and *syn*-**2b**. *Anti*-**2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.82 (br s, 1H), 4.55 (d, J=7.0 Hz, 1H), 5.73 (d, J=7.0 Hz, 1H), 7.49–7.55 (m, 1H), 7.65–7.74 (m, 2H), 7.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.1, 63.3, 70.9, 124.8, 129.2, 129.4, 133.4, 133.8, 148.5, 202.9; IR (neat): γ 3485, 2925, 1718, 1525, 1344, 1097, 857, 789, 744, 703 cm^{-1}. Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=13.707 min; t_{Rmajor}=15.46 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0293; found: 243.0288.

4.2.3. 3-Chloro-4-hydroxy-4-(3′-nitrophenyl)-butan-2-one (2c). Yield: 37%, as a 5:1 inseparable mixture of *anti*-**2c** and *syn*-**2c**. *Anti*-**2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (d, J=2.5 Hz, 3H), 3.46 (d, J=3.2 Hz, 1H), 4.27 (d, J=8.3 Hz, 1H), 5.12 (dd, J=8.3, 3.2 Hz, 1H), 7.53 (m, 1H), 7.72 (d, J=7.7 Hz, 1H), 8.18–8.21 (m, 1H), 8.27–8.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 63.5, 73.7, 122.1, 123.5, 129.4, 133.4, 141.0, 148.1, 203.0; IR (neat): γ 3482, 2928, 1719, 1531, 1352, 1096, 737, 692 cm^{-1}. Enantiomeric excess: 94%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=15.024 min; t_{Rmajor}=16.960 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0293; found: 243.0305.

4.2.4. 3-Chloro-4-hydroxy-4-(4′-cyanophenyl)-butan-2-one (2d). Yield: 31%, as a 7:1 inseparable mixture of *anti*-**2d** and *syn*-**2d**. *Anti*-**2d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (d, J=3.6 Hz, 3H), 3.28 (d, J=4.2 Hz, 1H), 4.24 (d, J=8.1 Hz, 1H), 5.07 (dd, J=8.1, 4.2 Hz, 1H), 7.51 (d, J=8.3 Hz, 2H), 7.67 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 28.0, 63.6, 74.0, 112.4, 118.5, 127.9, 132.2, 143.9, 202.9; IR (KBr): γ 3438, 2921, 2230, 1718, 1360, 1052, 837, 795 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=21.30 min; t_{Rmajor}=25.27 min; HR-MS for $C_{11}H_{10}ClNO_2$: calcd 223.0395; found: 223.0399.

4.2.5. 3-Chloro-4-hydroxy-4-(2′-chlorophenyl)-butan-2-one (2e). Yield: 52%, as a 19:1 inseparable mixture of *anti*-**2e** and *syn*-**2e**. *Anti*-**2e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H), 3.36 (d, J=5.2 Hz, 1H), 4.54 (d, J=6.5 Hz, 1H), 5.48 (dd, J=6.5, 5.2 Hz, 1H), 7.25–7.35 (m, 2H), 7.37–7.40 (m, 1H), 7.48–7.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.1, 46.6, 63.2, 127.2, 128.1, 129.7, 129.7, 132.9, 136.2, 202.8; IR (neat): γ 3453, 2926, 1721, 1439, 1358, 1032, 756, 699 cm^{-1}. Enantiomeric excess: 86%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=6.726 min; t_{Rmajor}=8.411 min; HR-MS for $C_{10}H_{10}Cl_2O_2$: calcd 232.0052; found: 232.0062.

4.2.6. 4-(2-Chloro-1-hydroxy-3-oxo-butyl)-benzoic acid methyl ester (2f). Yield: 40%, as a 6:1 inseparable mixture of *anti*-**2f** and *syn*-**2f**. *Anti*-**2f**: ^{1}H NMR (300 MHz $CDCl_3$): δ 2.36 (s, 3H), 3.17 (d, J=4.2 Hz, 1H), 3.92 (s, 3H), 4.30 (d, J=7.9 Hz, 1H), 5.07 (dd, J=7.9, 4.2 Hz, 1H), 7.47 (d, J=8.2 Hz, 2H), 8.03 (d, J=8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 52.2, 63.9, 74.5, 127.1, 128.7, 129.7, 143.6, 166.7, 203.0; IR (neat): γ 3510, 2956, 1726, 1709, 1700, 1435, 1291, 1118, 1107, 1047, 767, 705 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=8.687 min; t_{Rmajor}=11.108 min; HR-MS for $C_{12}H_{13}ClO_4$: calcd 256.0497; found: 256.0488.

4.2.7. 3-Chloro-4-hydroxy-4-(2′-fluorophenyl)-butan-2-one (2g). Yield: 28%, as a 10:1 inseparable mixture of *anti*-**2g** and *syn*-**2g**. *Anti*-**2g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.27 (br s, 1H), 4.46 (d, J=7.7 Hz, 1H), 5.31 (d, J=7.7 Hz, 1H), 7.04–7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.8, 63.1, 69.7, 115.4 (d, J=21.7 Hz), 124.4 (d, J=2.9 Hz), 125.9 (d, J=12.8 Hz), 128.4 (d, J=3.5 Hz), 130.2 (d, J=8.3 Hz), 158.6 (d, J=245.4 Hz), 202.9; IR (neat): γ 3431, 2924, 1718, 1490, 1358, 1228, 1030, 757 cm^{-1}. Enantiomeric excess: 97%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=8.601 min; t_{Rmajor}=9.142 min; HR-MS for $C_{10}H_{10}ClFO_2$: calcd 216.0348; found:216.0341.

4.2.8. 3-Chloro-4-hydroxy-4-(2′-bromophenyl)-butan-2-one (2h). Yield: 43%, as a 29:1 inseparable mixture of *anti*-**2h** and *syn*-**2h**. *Anti*-**2h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.35 (br s, 1H), 4.56 (d, J=6.4 Hz, 1H), 5.46 (dd, J=6.4, 4.9 Hz, 1H), 7.18–7.26 (m, 1H), 7.34–7.39 (m, 1H), 7.46 (dd, J=7.8, 1.7 Hz, 1H), 7.56 (dd, J=8.0,

1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.2, 63.2, 74.1, 123.0, 127.8, 128.3, 130.0, 132.9, 137.8, 202.8; IR (neat): γ 3439, 2944, 1716, 1357, 1031, 762 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=7.056 min; t_{Rmajor}=8.289 min; HR-MS for $C_{10}H_{10}ClBrO_2$: calcd 275.9547; found: 275.9554.

4.2.9. 4-Cyclohexyl-3-chloro-4-hydroxy-butan-2-one (2i). Yield: 18%, as a 31:1 inseparable mixture of *anti*-**2i** and *syn*-**2i**. *Anti*-**2i**: ^1H NMR (300 MHz $CDCl_3$): δ (ppm) 1.09–1.32 (m, 6H), 1.58–1.76 (m, 5H), 2.36 (s, 3H), 2.37–2.42 (m, 1H), 3.76 (m, 1H), 4.19 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.7, 25.9, 26.2, 27.6, 29.8, 38.9, 61.8, 76.1, 203.9; IR (neat): γ 3461, 2958, 2929, 1718, 1357, 1083, 789 cm^{-1}. Enantiomeric excess: 98%, determined by chiral GC analysis (CP CHIRASIL-DEX), inject temperature 240 °C, column temperature 145 °C, FID Oven temperature 260 °C, inlet pressure 10 psi, t_{Rminor}= 6.465 min, t_{Rmajor}=6.732 min; HR-MS for $C_{10}H_{17}ClO_2$, calcd 204.0911; found: 204.0908.

Acknowledgements

We are grateful for financial support from National Natural Science Foundation of China (projects 20472082, 203900505 and 20325211).

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Tetrahedron 62 (2006) 352–356
Tetrahedron

Kinetic isotope and thermodynamic analysis of the nornicotine-catalyzed aqueous aldol reaction

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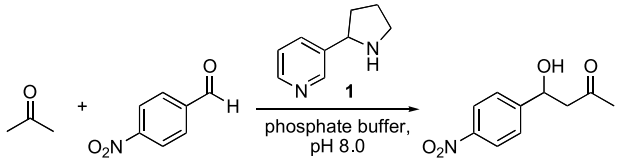
Received 5 July 2005; revised 17 August 2005; accepted 9 September 2005

Available online 11 October 2005

Abstract—A series of kinetic isotope effects and thermodynamic studies were performed to test key predictions of a computationally derived model for a nornicotine-catalyzed aqueous aldol reaction. The relative energies of the two computationally-derived transition states were challenged using the proton inventory, which demonstrated that a single water molecule from the solvent is involved in, or before, the rate-limiting step. These results suggest the importance of proton transfer in the aqueous aldol reaction and may assist the development of other aqueous organocatalytic processes.

1. Introduction

Recently, organocatalysis has become an increasingly useful tool in the construction of complex molecular skeletons.[1] The intense interest in the field has led to the development of a wide variety of catalysts capable of accelerating a diverse set of reactions including aldol additions,[2] Mannich reactions,[3] [4+2][4] and [3+2][5] cycloadditions, α-aminations,[6] epoxidations,[7] and cyclopropanations.[8] Despite this flurry of activity, there are few examples of truly aqueous organocatalysts.[9] The development of synthetically viable aqueous organocatalysts would be a boon to the field of green chemistry, assisting the development of environmentally benign chemical processes. In our laboratory, we have shown that nornicotine **1**, a metabolite of nicotine and constituent of tobacco, can catalyze aqueous aldol reactions under physiologically relevant conditions (Scheme 1).[10] Aside from the pharmacological implications,[11] this reaction is noteworthy because it was the first, and still one of the few, examples of non-enzymatic aqueous enamine-based chemistry.[9] While the reaction proceeds in good yield with sufficiently activated substrates, the rate and substrate compatibility of the reaction must be improved before it can be considered synthetically useful. With these thoughts in mind, we recently initiated a research program aimed at explicating the mechanism of this reaction to better understand the molecular basis for rate enhancement, and thus develop improved aqueous organocatalysts.



Scheme 1. An aqueous aldol reaction catalyzed by 30 mol % nornicotine **1** in 200 mM phosphate buffer at 37 °C.

To elucidate the structural requirements for effective catalysis, a series of nornicotine analogs were used to determine the linear free energy relationship between small changes in the structure of the catalyst and the rate of the reaction.[12] By replacing nornicotine with *meta* and *para* substituted 2-arylpyrrolidines, the rate of the reaction increased with a corresponding increase in the electron-withdrawing nature of the substituents on the aryl ring of the catalyst. The positive value of the slope of the Hammett plot, ρ, may be due to the lower pK_a of the pyrrolidine nitrogen of analogs containing electron-withdrawing groups on the aryl ring. Thus, the perturbed pK_a of these analogs effectively increases the amount of available catalyst under the reaction conditions. While these results explained why proline (predominantly zwitterionic at pH 8.0) and pyrrolidine (pK_a=11.4) are poor aqueous organocatalysts, it did not give insight into why the nornicotine-catalyzed aldol reaction similarly fails in organic solvent.[9,10]

Keywords: Nornicotine; Organocatalysis; Kinetic isotope effects.
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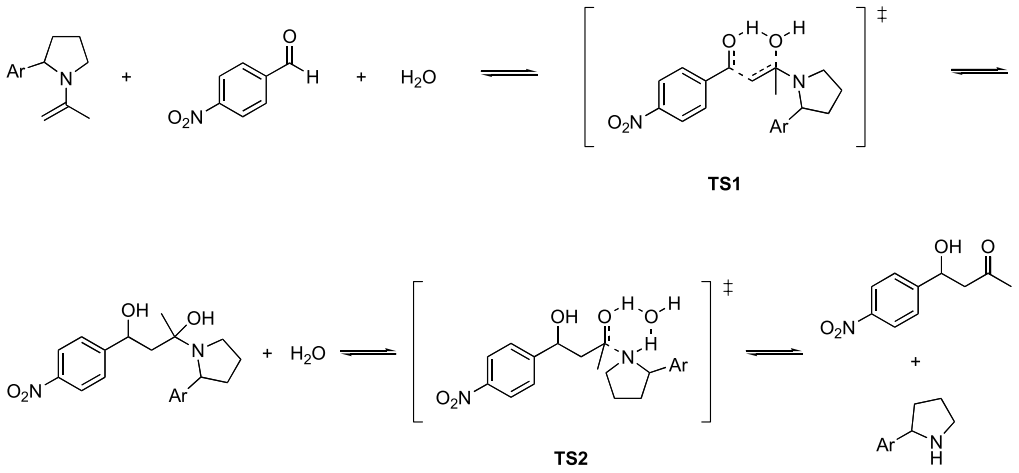
doi:10.1016/j.tet.2005.09.094



Scheme 2. A computationally derived mechanism for a nornicotine-catalyzed aldol reaction in water.

A rational explanation of this phenomenon is that an explicit proton must transfer at the transition state for the reaction to occur. This explanation was supported by the results of a computational study into the mechanism of the nornicotine-catalyzed aqueous aldol reaction.[13] In this study, the calculations were simplified by assuming that the enamine was preformed, and the energy of the enamine was the zero-point for the reaction. Based on this assumption, the predicted mechanism revealed that, unlike an aldol reaction in organic solvent, the reaction proceeds through a two-step mechanism, with each step requiring an explicit water molecule from the solvent (Scheme 2). Carbon–carbon bond formation proceeds through a trimolecular six-membered transition state **TS1** and forms a stable, albeit short-lived, hemiaminal intermediate. The rate-limiting step is hydrolysis of the hemiaminal via **TS2** to give the product with concomitant regeneration of the catalyst.

Although the trimolecular **TS1** is unusual and would seem to be entropically unfavorable, there is empirical evidence that the concerted transfer of a proton in the transition state is important. For example, the calculations for the uncatalyzed reaction required proton transfer in the transition state for both organic and aqueous media. Considering that a hydrogen-bound water could activate the aldehyde for nucleophilic attack, and the large excess of water in the reaction ($\sim$55 M), the assumption of an explicitly involved water molecule is reasonable. Furthermore, there is evidence for a trimolecular transition state involving water in the aqueous Diels–Alder reaction of methyl vinyl ketone and cyclopentadiene.[14] Analogous to the proposed mechanism for the nornicotine-catalyzed aqueous aldol reaction, water accelerates the reaction by acting as a Lewis acid by providing a hydrogen bond to methyl vinyl ketone. We report herein upon a series of kinetic isotope and thermodynamic experiments designed to help determine the validity of the computationally derived mechanism for the nornicotine-catalyzed aqueous aldol reaction.

2. Results and discussion

A key prediction of the computational mechanism is that two explicit water molecules from the solvent are involved in, or before, the rate-limiting step. Therefore, the rate of the reaction in deuterium oxide should be significantly reduced relative to the rate of the reaction in water, as two O–(D) bonds should be broken based on this prediction. The isotope effect was determined in buffered water and buffered deuterium oxide.[15] Rate constants were measured under pseudo-first-order conditions by using acetone as the donor and 4-nitrobenzaldehyde as the acceptor. Experiments were performed at 37 °C, under conditions in which the reaction rate was maximized relative to the uncatalyzed reaction (pH 8.0). While a large isotope effect was predicted based upon the proposed computational mechanism, the measured value ($k_H/k_D \approx 3$) was surprisingly small. To provide an explanation for the magnitude of the kinetic isotope effect, the number of water molecules involved in the reaction, the proton inventory, was determined by observing the effect of increasing the atom fraction of deuterium (n) on the corresponding observed rate constant (k_n). In addition to the number of protons from the solvent involved in the transition state, the transition state fractionation factors can be calculated for the reaction.[16] The fractionation factor (ϕ) is a measure of the preference of the solute (SH) for combination with deuterium, relative to water (ROH),[17] that is,

$$\phi = \frac{[\mathrm{SD}]/[\mathrm{SH}]}{[\mathrm{ROD}]/[\mathrm{ROH}]}$$

The proton inventory requires application of the Gross–Butler Eq. (1),

$$k_n = k_H \frac{\prod_{i}^{\text{Transition state}} (1 - n + n\phi_i)}{\prod_{j}^{\text{Reaction state}} (1 - n + n\phi_j)} \quad (1)$$

where ϕ_i and ϕ_j are the fractionation factors for all exchangeable hydrogens in the transition state and reactant state, respectively. According to the proposed mechanism, the two protons from water in **TS1** and **TS2** show a change between reagent and transition state, thus Eq. (1) simplifies to give,

$$k_n = k_H(1 - n + n\phi^{\ddagger}_{TS1})(1 - n + n\phi^{\ddagger}_{TS2}) \quad (2)$$

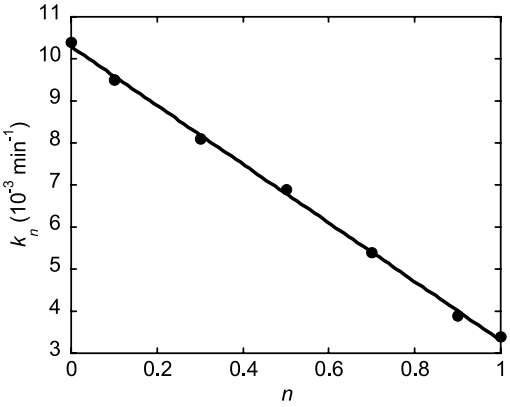


Figure 1. Proton inventory for the nornicotine-catalyzed aqueous aldol reaction. The magnitude of the error bars are obscured by the corresponding point.

where $\phi^{\ddagger}$ is the transition-state fractionation factor. Therefore, the theoretical mechanism predicts a non-linear dependence between k_n and n.

In contrast to the predicted dependence, a plot of the observed rate constant versus increasing atom fraction of deuterium was linear ($R^2=0.999$, Fig. 1), indicating only one water molecule from the solvent is involved in the transition state. Therefore, a key prediction of the computational mechanism appears to be incorrect. When applied to the data, the Gross–Butler equation simplifies to give,

$$k_n = k_H(1-n+n\phi^{\ddagger}) \tag{3}$$

consistent with the involvement of a single water molecule, with $\phi^{\ddagger}=0.32$. In this case, the value of the transition state fractionation factor is also the inverse of the isotope effect.

Having established that a single water molecule participates in the reaction at or prior to the rate-limiting step, we considered the implications of the magnitude of the primary kinetic isotope effect, as the value is significantly lower than the theoretical maximum. An explanation for this reduction is that isotope effects are lower for proton transfer between two oxygen atoms than for a transfer from oxygen to carbon.[16] However, the magnitude of the isotope effect also depends on the geometry of the transition state. Isotope effects are maximized when the geometry of the proton-in-flight during the transition state approaches linearity. Interestingly, the reduced isotope effect is consistent with the predicted geometry of both six-membered transition states **TS1** and **TS2**, as the bond angles required ($\sim$109°) would lower the magnitude of the isotope effect.[18]

While the results of proton inventory experiment are contradictory with the predicted involvement of two molecules of water involved in or before the rate-limiting step, these results provide evidence that one molecule of water is involved in the reaction, and are consistent with the proposed six-membered transition state. Furthermore, these results are in accord with the computational mechanism, provided the relative energies are inaccurate as a result of the lack of entropic corrections in the computational

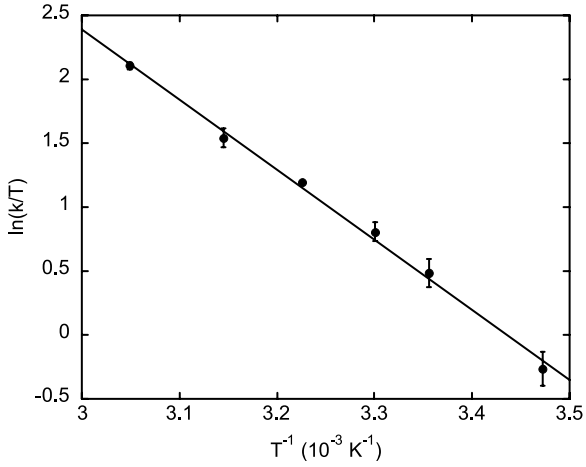


Figure 2. Eyring analysis for the nornicotine-catalyzed aqueous aldol reaction evaluated over a range of temperatures between 15–55 °C.

experiments. Provided that $\Delta G_{TS1} > \Delta G_{TS2}$ upon inclusion of the entropic penalties in the calculation, the results of the proton inventory are entirely consistent with the proposed mechanism. Since **TS1** requires ordering three molecules, the entropic penalty is expected to be larger than the penalty for **TS2**, thus it is possible that their inclusion could make the first step rate limiting.

To further characterize the mechanism, the activation parameters $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ were calculated. Measuring the rate of the reaction at different temperatures allowed for the application of the Erying equation,

$$\ln(k) = \frac{\Delta S^{\ddagger}}{R} + \ln\left(\frac{k_B}{h}\right) - \frac{\Delta H^{\ddagger}}{RT} \tag{4}$$

where k_B and h are the Boltzman and Planck's constants, respectively. The plot of $\ln(k/T)$ versus $1/T$ was found to be linear over the range of temperatures examined ($R^2=0.996$, Fig. 2). The calculated value of $\Delta S^{\ddagger}$ was -9.8 ± 1.2 cal K^{-1} mol^{-1} and $\Delta H^{\ddagger}$ was 10.9 ± 0.4 kcal mol^{-1}. While the value of $\Delta S^{\ddagger}$ is negative, as predicted, it is not possible to make any mechanistic determinations based on the sign or the magnitude of the value without a reference reaction of the same standard state.[19]

Further investigation into the mechanistic assumptions was provided by isotopic substitution of the hydrogens at reactive centers of the aldehyde and acetone. For example, an inverse α-secondary kinetic isotope effect was expected upon isotopic substitution of the aldehydic proton due to the $sp^2 \rightarrow sp^3$ transition at the reactive carbon. The effect of this substitution was measured with 4-nitro-(α-d_1)benzaldehyde, synthesized according to a known procedure.[20] Indeed, the deuterated aldehyde perturbed the rate of the reaction by a magnitude consistent with an inverse secondary isotope effect (Table 1).

Upon substitution of acetone with d_6-acetone, a primary isotope effect was observed due to C–(D) bond cleavage when forming the enamine. Additionally, the hybridization change at the enamine methylene after carbon–carbon bond formation should result in an inverse secondary kinetic isotope effect. However, the magnitude of the effect was

Table 1. Summary of kinetic and thermodynamic parameters for the nornicotine-catalyzed aqueous aldol reaction

Entry	Parameter	Value[a]
1	k_H/k_D (Water)	3.05 ± 0.10
2	k_H/k_D (aldehyde)	0.89 ± 0.08
3	k_H/k_D (acetone)	4.76 ± 0.11
4	$\phi^{\ddagger}$	0.32 ± 0.01
5	$\Delta S^{\ddagger}$	-9.8 ± 1.2[b]
6	$\Delta H^{\ddagger}$	10.9 ± 0.4[c]

[a] Error for all parameters determined by propagation of error analysis.
[b] Value given in cal K^{-1} mol^{-1}.
[c] Value given in kcal mol^{-1}.

obscured by the primary isotope effect. Considering multiple isotope effects are assumed to be additive, we attempted to deconvolute the secondary kinetic isotope effect by directly measuring the observed K_{eq} of enamine formation via 2D ^1H–^1H ROESY and NOESY NMR spectroscopy. Unfortunately, the error associated with the measurement was too large to calculate a reasonable equilibrium constant as the diagonal peak of the enamine methyl overlapped substantially with adjacent nornicotine peaks of much greater intensity (data not shown). Nonetheless, the results of the acetone and aldehyde kinetic isotope effects indicate that carbon–carbon bond and enamine formation occur in or before the rate-limiting step, consistent with the proposed mechanism.

3. Conclusion

Based on the data obtained in this study, we are able to reject the relative energies of the computationally derived mechanism for the nornicotine-catalyzed aqueous aldol reaction. Provided **TS1** is the rate-limiting step, the data is entirely in accord with the computational mechanism. However, this does not preclude other mechanistic possibilities that are also consistent with the data. While we were not able to provide evidence to directly support the proposed trimolecular transition state, these results underscore the importance of proton transfer in aldol organocatalysis, as the nornicotine-catalyzed reaction fails in organic solvent most likely because there are few available protons to participate in the transition state. Combined with our previous results,[12] we are able to provide a clearer picture into the mechanistic demands of the aqueous aldol reaction, which should assist in the development of future green organocatalysts.

4. Experimental

4.1. General methods

All chemicals were obtained from commercial suppliers. Nornicotine was distilled prior to use. HPLC solvents were filtered and degassed prior to use. All isotopic solvents and reagents were above 99.9% enrichment, if available, otherwise the highest commercially available enrichment was used. All HPLC experiments were preformed using a C_{18} reverse-phase column and an isocratic mobile phase of 25% acetonitrile in water with 0.1% TFA, with a flow rate of 1.0 mL min^{-1}, monitoring at 254 nm. Product formation was followed by monitoring the height and area of the peak corresponding to 4-hydroxy-4-(4-nitrophenyl)butan-2-one ($t_R = 6.2$ min) and extrapolating concentrations from a standard curve obtained using a synthetic standard.[21]

4.2. General procedure for kinetic experiments

Nornicotine was added as a 300 mM solution in DMSO to a solution of 200 mM phosphate buffer (pH 8.0) and acetone. The solution was briefly vortexed, and then incubated at 37 °C. The reaction was initiated by the addition of 4-nitrobenzaldehyde as a 100 mM solution in DMSO. The final concentrations of reactants were 2.4 mM nornicotine, 240 mM acetone, and 1–8 mM 4-nitrobenzaldehyde in 10% DMSO. The progress of the reaction was monitored by removing 10 μL aliquots of the solution at various times during the reaction and diluting them to a total volume of 500 μL. Then, 20 μL of these samples were injected onto an analytical RP-C18 HPLC column for analysis. Pseudo-first-order rate constants were determined by linear regression analysis.

4.3. General procedure for kinetic isotope experiments

Kinetic isotope effects were measured by substituting the appropriate amount of deuterated substrate into the reaction. The observed rate constant (k_D) was then compared to the rate of the reaction with only protiated substrates (k_H). The proton inventory was determined by measuring the observed rate constant at increasing percent of phosphate buffered D_2O (200 mM potassium phosphate, pD 8.0)[16] in phosphate buffered H_2O (200 mM potassium phosphate, pH 8.0).

Acknowledgements

We thank the reviewer for valuable suggestions and gratefully acknowledge financial support from The Skaggs Institute for Chemical Biology.

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Tetrahedron 62 (2006) 357–364

Direct organocatalytic enantioselective α-aminomethylation of ketones

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Received 30 May 2005; revised 8 August 2005; accepted 31 August 2005

Available online 3 October 2005

Abstract—The scope and limitations of the direct organocatalytic asymmetric α-aminomethylation of ketones are disclosed. The proline-catalyzed classical Mannich reactions between unmodified ketones, aqueous formaldehyde and aromatic amines furnished the desired Mannich bases in high yield with up to >99% ee. Moreover, methyl alkyl ketones were regioselectively α-aminomethylated at the methylene carbon affording the corresponding Mannich products with up to >99% ee. In addition, the proline-catalyzed one-pot three-component reaction between *p*-anisidine, aqueous formaldehyde and 4,4-dimethyl-2-cycloxehen-1-one furnished the corresponding bicyclic aza-Diels–Alder adduct with >99% ee.

1. Introduction

The classical Mannich reaction,[1] in which an aminomethyl group is introduced in the α-position to a carbonyl compound, is an important transformation in organic chemistry.[2] The resulting Mannich bases are of particular interest due to their use as synthetic building blocks and precursors of pharmaceutically valuable γ-amino alcohols for different therapeutic areas.[2] However, there are only a few enantioselective α-aminomethylation reactions that have been developed and most of them are diastereoselective employing chiral auxiliaries or enantiomerically pure substrates.[3] For example, Enders and co-workers have developed excellent diastereoselective α-aminomethylation reactions.[4]

The initial stoichiometric and indirect stereoselective Mannich-type reactions utilize preformed chiral enol equivalents or imines.[5] Thus, the first successful example of catalytic asymmetric additions of preformed enolates to imines by Kobayashi and co-workers was an important advancement.[6] These results inspired the research and development of several catalytic indirect stereoselective Mannich reactions catalyzed by organometallic complexes.[7–9] Shibasaki and co-workers reported the first example of direct catalytic enantioselective Mannich-type reactions that were catalyzed by heterobimetallic complexes.[10] Recently, Shibasaki and Matsunaga,[11] and Trost and co-workers[12] developed di-nuclear zinc organometallic complexes as catalyst for the direct catalytic enantioselective Mannich-type reactions between hydroxyarylketones and preformed imines. In addition, Jørgensen and co-workers have developed elegant direct asymmetric Mannich reactions involving activated ketones as donors and chiral copper(II) bisoxazoline (BOX) complexes as catalysts.[13] The rapidly growing research in organocatalysis has also led to development of several amino acid catalyzed stereoselective reactions.[14] List reported the first one-pot three-component Mannich reaction between in situ generated imines and unmodified ketones as donors.[15] This initial report led to the development of several novel Mannich-type reactions by several groups that are catalyzed by amino acid derivatives.[16] More recently, we developed the first direct organocatalytic one-pot three-component Mannich reaction involving aldehydes as nucleophiles.[17] Moreover, Jacobsen,[18] Terada,[19] Akiyama[20] and Jørgensen[21] have reported excellent catalytic asymmetric Mannich-type reactions that are catalyzed by organocatalysts.

The first attempt to catalyze the one-pot three-component direct catalytic α-aminomethylation reaction of a ketone was reported by Shibasaki and co-workers.[10] In this reaction, the desired Mannich base was isolated in 16% yield and 64% ee. Inspired by this initial attempt and our interest in amino acid catalysis,[22] we most recently disclosed the first organocatalytic α-aminomethylation of ketones.[23] Herein, we present the scope and limitations of this one-pot three-component reaction, which also led to

Keywords: Asymmetric catalysis; Proline derivatives; Ketones; α-Aminomethylation; Classical Mannich reaction.
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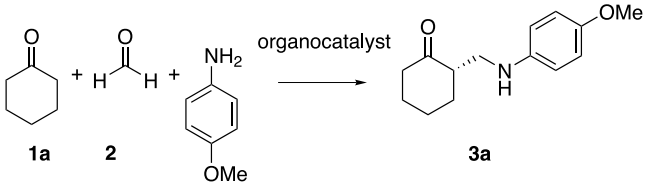
doi:10.1016/j.tet.2005.08.113

the discovery of the first one-pot three-component aza-Diels–Alder reaction.[24]

2. Results and discussion

The focus of our project was to develop a direct amino acid-catalyzed classical one-pot three-component Mannich reaction between aqueous formaldehyde, aromatic amines and ketones to furnish chiral Mannich bases in high yields and enantioselectivities. We initially investigated the proline-catalyzed reaction between cyclohexanone **1a**, aqueous formaldehyde **2** and *para*-anisidine that yields Mannich product **3a** as a model system (Eq. 1).



(1)

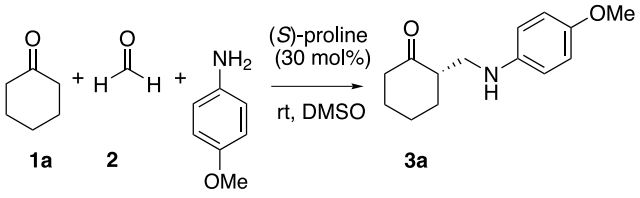
We conducted the reaction in different organic solvents and found that the highest enantioselectivity as well as efficiency was obtained in DMSO (Table 1).

In this solvent, *p*-methoxyphenyl (PMP) protected Mannich base **3a** is isolated in high yield with >99% ee. Increasing the equivalents of ketone **1a** from two to ten significantly increased the enantioselectivity as well as the rate of the reaction in DMF (Entry 5). Importantly, we found that the Mannich bases should be purified by neutral aluminium oxide column chromatography since they racemize upon silica-gel column chromatography.

In addition to proline, we also investigated other organo-catalysts ability to mediate the model reaction (Table 2).

All the investigated catalysts catalyzed the reaction and furnished the desired Mannich base **3a** in high yield. However, (*S*)-proline-catalyzed the reaction with the highest stereoselectivity under the set reaction conditions.

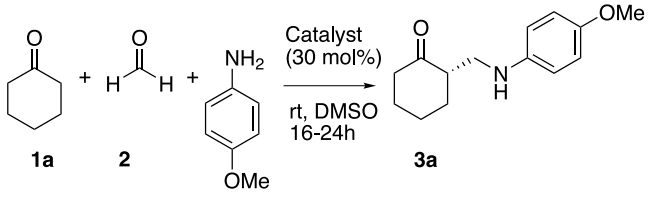
Table 1. Selected examples from the solvent screen[a]

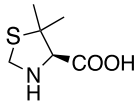
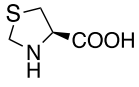
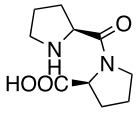
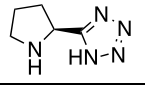


Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	DMSO	16	94	>99
3	NMP	33	87	77
4	DMF	33	80	87
5	DMF	14[d]	61[d]	98[d]
6	Acetonitrile	33	87	25

[a] Experimental conditions: a mixture of **1a** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.
[d] Ten equivalents ketone **1a** was used.

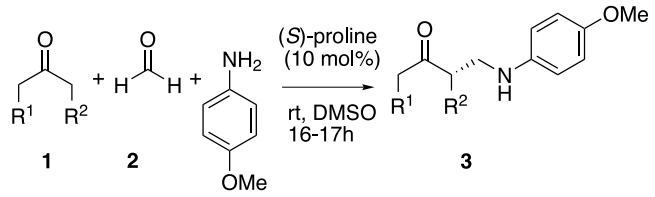
Table 2. Catalyst screened for the direct asymmetric α -hydroxymethylation of ketone **1a**[a]

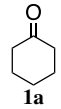
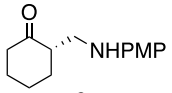
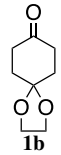
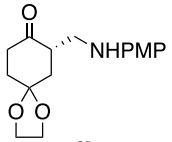
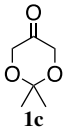
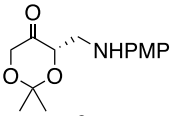
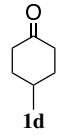
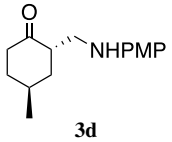
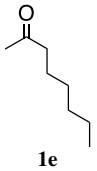
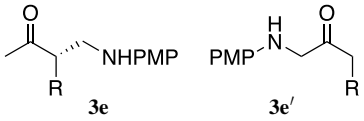
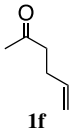
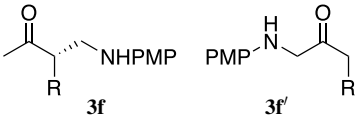
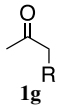
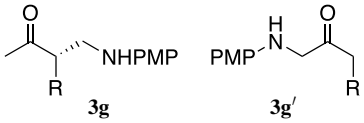
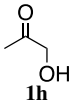
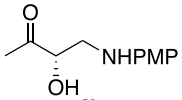


Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	(*S*)-proline	16	94	>99
3		33	71	<5
4		33	92	<5
5		33	62	<5
6		17	96	51

[a] Experimental conditions: a mixture of **1a** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and chiral organocatalyst was stirred at room temperature for 16–33 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.

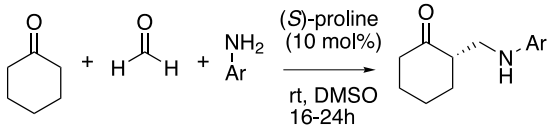
Table 3. Proline-catalyzed one-pot three-component direct α-aminomethylation fo different ketones[a]



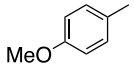
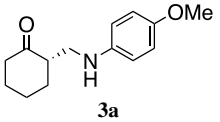
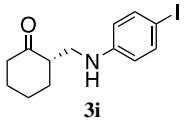
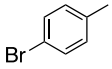
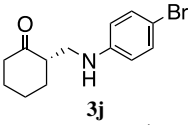
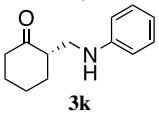
Entry	Ketone	Product	Yield (%)[b]	3/3′	ee (%) of 3[c]
1	 **1a**	 **3a**	90		>99
2	 **1b**	 **3b**	85		>99
3	 **1c**	 **3c**	84[d]		>99[d]
4	 **1d**	 **3d**	85[e]		>99[f]
5	 **1e**	 **3e** **3e′** R=*n*-pent	80	2:1	>99
6	 **1f**	 **3f** **3f′** R=$CH_2CH=CH_2$	94	4:1	84
7	 **1g**	 **3g** **3g′** R=*n*-hept	72	6:1	>99
8	 **1h**	 **3h**	60[d,g]		70[d,g]

[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), *p*-anisidine (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16–17 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of the pure products after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.
[d] Proline (30 mol%) was used.
[e] Trans/cis 3:1.
[f] ee of the trans-isomer.
[g] Purified by silica-gel column chromatography.

Table 4. Direct catalytic one-pot three-component α-aminomethylation reactions with different aromatic amines[a]



1a 2 3

Entry	Ar	Product	Yield (%)[b]	ee (%)[c]
1		 **3a**	90	>99
2		 **3i**	45	>99
3		 **3j**	71	>99
4		 **3k**	92	>99

[a] Experimental conditions: a mixture of **1** (2 mmol, 2 equiv), aniline (1.1 mmol), **2** (1 mmol) and (*S*)-proline was stirred at room temperature for 16–24 h. The crude product obtained after aqueous work-up was purified by column chromatography.
[b] Isolated combined yield after neutral aluminum oxide chromatography.
[c] Determined by chiral-phase HPLC analyses.

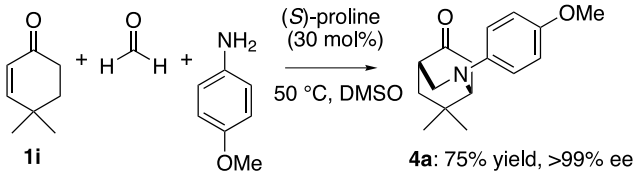
Based on these results and the practical aspects of employing proline catalysis we decided to investigate the proline-catalyzed one-pot three-component direct catalytic asymmetric Mannich reactions for a set of different aliphatic ketones (Table 3).

The reactions proceeded smoothly, and the corresponding Mannich bases **3a**–**3h** were isolated in high yield with up to >99% ee. For example, the proline-catalyzed α-aminomethylation of dihydroxyacetone phosphate mimic **1c** furnished aminosugar **3c** in 84% yield with >99% ee.[25] The reactions exhibited excellent chemoselectivity and no aldol adducts could be detected. Moreover, reactions with linear ketones were regioselective and the α-aminomethylation occurred predominantly at the methylene carbon atoms of the ketones. The amino acid-catalyzed one-pot three-component reaction was also extended to other aromatic amines than *p*-anisidine (Table 4).

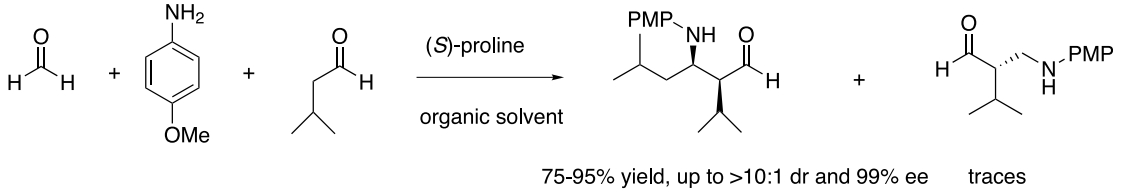
The proline-catalyzed reactions between substituted anilines, aqueous formaldehyde and cyclohexanone **1a** yielded the corresponding Mannich bases **3i**–**3k** in 45–92% yield with >99% ee, respectively. Thus, α-aminoarylated ketones can be synthesized in moderate to high yield with almost absolute stereocontrol.

We also investigated the proline-catalyzed direct asymmetric one-pot three-component α-aminomethylation of aldehydes (Scheme 1). However, under all the reaction conditions tested the self-Mannich adducts were formed with excellent stereoselectivity and only trace amounts of the desired product was detected. Thus, in this case, proline exhibited a high chemoselectivity for the formation of the self-Mannich adduct.

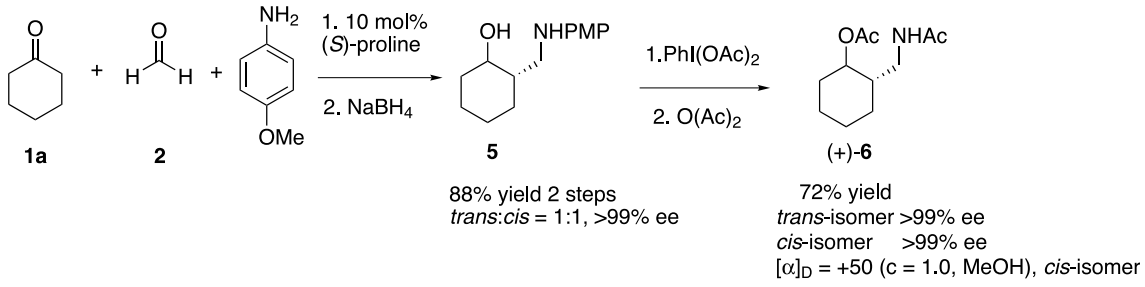
The high efficiency and stereoselectivity of the amino acid catalyzed direct catalytic asymmetric α-aminomethylation



Scheme 2. Proline-catalyzed one-pot three-component asymmetric aza-Diels–Alder reaction.



Scheme 1. Chemoselectivity in the proline-catalyzed asymmetric α-aminomethylation of aldehydes.

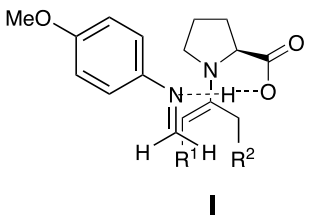


Scheme 3. Asymmetric synthesis of diacetylated *cis*-**6** and *trans*-**6**.

reactions of ketones inspired us to investigate the reactions between aqueous formaldehyde, *p*-anisidine and α,β-unsaturated cyclic ketones. The transformations constitute the first examples of direct catalytic asymmetric aza-Diels–Alder reactions.[24] For example, the proline-catalyzed aza-Diels–Alder reaction between *p*-anisidine, aqueous formaldehyde and 2-cyclohexenone **1h** furnished the aza-Diels–Alder product **4a** in 75% yield and >99% ee (Scheme 2).

The absolute configuration of the amino acid derived Mannich bases was determined by converting Mannich product **3a** into the known diacetylated amino alcohol **6** (Scheme 3). Thus, α-aminomethylated ketone **3a** was reduced with $NaBH_4$ in situ to the corresponding mono-protected amino alcohol **5**, which was isolated in 88% yield, over the two steps, with dr 1:1 (trans/cis) and >99%ee. Removal of the *p*-methoxyphenyl (PMP) group under oxidative conditions followed by acetylation afforded the *cis*- and *trans*-diacetylated amino alcohols **6** in 72% combined yield. The optical rotation of the cis-isomer and comparison with the literature revealed that the absolute configuration of the product was *cis*-(1*S*,2*S*)-**6** ($[\alpha]_d^{25}+50.2$ (*c* 1.0, MeOH), $[\alpha]_d^{25}+55.9$ (*c* 0.8, MeOH)[26]).

On the basis of the absolute configuration, we propose transition-state model **I** to account for the regio- and enantio-selectivity of the α-aminomethylation reaction of unmodified substituted ketones (Fig. 1). Hence, (*S*)-proline derivative forms an enamine with the ketone that is attacked by the imine from its *Si*-face providing (2*S*)-α-aminomethylated ketones. This is in accordance with the transition states of previously reported proline-catalyzed Mannich reactions, in which a *Si*-facial attack occurs.[15–17]



I

Figure 1. Transition state models evoked to account for the enantioselectivity of the (*S*)-proline-catalyzed reaction.

In summary, our catalytic enantioselective one-pot three-component α-aminomethylation of various ketones represents a direct approach for the construction of nearly enantiomerically pure Mannich bases in high yield. The reactions were simply performed without tedious elaboration in wet solvents and in the presence of air. In addition, other proline-derivatives including dipeptides catalyzed the reaction. The proline-catalyzed one-pot three-component α-aminomethylation of ketones opens up a new entry for the construction of pharmaceutically active Mannich bases.

3. Experimental

3.1. General

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2\cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concd H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard (δ 0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ 77.0 ppm) for ^{13}C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (λ=589 nm, 1 dm cell). High resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

3.2. Typical experimental procedure for the direct asymmetric α-aminomethylation of ketones

To a vial containing **2** (1 mmol, 36% aqueous solution), aniline (1.1 mmol) and a catalytic amount of (*S*)-proline (10 or 30 mol%) in DMSO (4 mL) was added the ketone **1** (2 mmol). After 20 h of vigorously stirring the reaction was quenched by addition of aqueous NH_4Cl and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by neutral aluminum oxide

column chromatography (EtOAc/pentane 1:10) to afford α-aminomethylated ketone **3**. The ee of the ketones was determined by chiral-phase HPLC analysis (Daicel Chiralpak AD column, $\lambda=244$ nm, *v* 0.5 mL/min, hex/*i*-PrOH).

3.2.1. (2*S*)-(4-Methoxyphenylamino-methyl)-cyclohexanone 3a. Yellow solid (219 mg), 94% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, CH [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, CH [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, CHC=O), 3.05 (dd, $J=13.3$, 4.7 Hz, 1H, C*H*HN), 3.37 (dd, $J=13.3$, 7.8 Hz, 1H, CH*H*N), 3.74 (s, 3H, OCH_3), 6.59 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.3, 42.5, 45.6, 50.0, 56.1, 114.9, 115.2, 142.2, 152.6, 213.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 96:4, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=44.31$ min; minor isomer: $t_R=58.79$ min; $[\alpha]_D^{25}+4.6$ (*c* 2, $CHCl_3$); MALDI-TOF MS: 256.1008; $C_{14}H_{19}NO_2$ ($M+Na^+$: calcd 256.1313).

3.2.2. Compound (2*S*)-3b. 248 mg, 85% ^{1}H NMR (400 MHz, $CDCl_3$) white solid δ (ppm): 1.99 (m, 2H, CH_2 [Cy]), 2.08 (m, 2H, CH_2 [Cy]), 2.38 (m, 1H, CH [Cy]), 2.65 (m, 1H, CH [Cy]), 2.95 (m, CH, [Cy]), 3.10 (dd, $J=13.2$, 4.7 Hz, 1H, C*H*HN), 3.33 (dd, $J=13.2$, 7.3 Hz, 1H, CH*H*N), 3.73 (s, 3H, OCH_3), 4.00 (m, 4H, $2\times OCH_2$), 6.56 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 34.4, 38.4, 38.7, 44.8, 45.9, 55.7, 64.6, 107.2, 142.1, 152.2, 211.8; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=148.04$ min; minor isomer: $t_R=160.40$ min; $[\alpha]_D^{25}-2.0$ (*c* 1.0, $CHCl_3$).

3.2.3. Compound (2*S*)-3c. 223 mg, 84% ^{1}H NMR (400 MHz, $CDCl_3$) yellowish oil δ (ppm): 1.44 (s, 3H, Me), 1.96 (s, 3H, Me), 3.29 (m, 1H), 3.37 (m, 1H), 3.73 (s, 3H, OMe), 4.0 (d, $J=17.8$ Hz, 1H), 4.27 (d, $J=17.8$ Hz, 1H), 4.43 (m, 1H), 6.65 (d, $J=8.9$ Hz, 2H, ArH), 6.78 (d, $J=8.9$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.8, 24.2, 44.5, 55.8, 66.8, 73.4, 101.1, 115.0, 115.4, 141.7, 152.9, 208.9; (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=44.63$ min; minor isomer: $t_R=54.14$ min; $[\alpha]_D^{25}-129.3$ (*c* 2.5, $CHCl_3$).

3.2.4. Compound *trans*-(2*S*)-3d. (**3d**+**3d′**, 210.2 mg, 85%) yellow solid, major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.0 (d, $J=6.3$ Hz, 3H, $CHCH_3$), 1.29 (m, 1H, CH [Cy]), 1.71 (m, 2H, CH_2 [Cy]), 2.01 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.7 (m, 1H, CH [Cy]), 3.05 (m, H, C*H*HN), 3.35 (m, 1H, CH*H*N), 3.73 (s, 3H, OCH_3), 6.56 (m, 2H, ArH), 6.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.2, 31.7, 35.6, 40.2, 41.6, 45.0, 48.6, 55.7, 114.4, 114.9, 142.2, 152.1, 213.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 96:4, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=48.8$ min; minor isomer: $t_R=52.9$ min.

3.2.5. Compound 3e. Yellow oil 211 mg, 80% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.80 (m, 3H), 1.30 (m, 8H), 2.15 (s, 3H), 2.82 (m, 1H), 3.17 (dd, $J=12.8$, 4.7 Hz, 1H), 3.32 (dd, $J=12.8$, 8.6 Hz, 1H), 3.73 (s, 3H), 6.56 (d, $J=9.1$ Hz, 2H), 7.26 (d, $J=9.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.3, 42.5, 45.6, 50.0, 56.1, 114.9, 115.2, 142.2, 152.6, 213.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=25.40$ min; minor isomer: $t_R=26.98$ min; $[\alpha]_D^{25}+6.1$ (*c* 1.1, $CHCl_3$).

3.2.6. Compound 3f. Yellow oil, 219 mg, 94% ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.16 (s, 3H, CH_3C=O), 2.27 (m, 1H, C*H*CH=CH_2), 2.47 (m, 1H, C*H*CH=CH_2), 3.93 (m, 1H, C*H*CH_2), 3.20 (dd, $J=12.8$, 4.8 Hz, 1H, C*H*HN), 3.35 (dd, $J=12.9$, 8.3 Hz, 1H, CH*H*N), 3.74 (s, 3H, OCH_3), 5.10 (m, 2H, CH_2=CH), 5.75 (m, 1H, CH_2=C*H*), 6.57 (d, $J=8.9$ Hz, 2H, ArH), 6.77 (d, $J=8.9$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 30.1, 34.1, 45.8, 51.8, 56.0, 114.7, 115.2, 117.8, 135.0, 142.0, 152.7, 211.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=43.40$ min; minor isomer: $t_R=47.20$ min; $[\alpha]_D^{25}+3.6$ (*c* 2.5, $CHCl_3$).

3.2.7. Compound 3g. Yellow oil (220 mg, 72%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J=6.7$ Hz, 3H), 1.28 (m, 12H), 2.15 (s, 3H), 2.82 (m, 1H), 3.17 (dd, $J=12.8$, 4.6 Hz, 1H), 3.32 (dd, $J=12.9$, 8.6 Hz, 1H), 3.73 (s, 3H), 6.56 (d, $J=8.9$ Hz, 2H), 6.77 (d, $J=9.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 22.8, 27.5, 29.2, 29.8, 29.9, 32.0, 46.2, 52.6, 114.5, 115.1, 120.0, 142.2, 152.5, 212.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=41.50$ min; minor isomer: $t_R=43.10$ min; $[\alpha]_D^{25}+2.0$ (*c* 1.4, $CHCl_3$).

3.2.8. Compound 3h. Yellow oil (126 mg, 60%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (s, 3H, CH_3), 3.76 (s, 3H, OMe), 4.56 (dd, $J=5.5$, 7.8 Hz, 1H, C*H*OH), 4.86 (d, $J=2.5$ Hz, 1H, CH_2NHAr), 5.04 (d, $J=2.5$ Hz, 1H, CH_2-NHAr), 6.60 (d, $J=9.0$ Hz, 2H), 6.85 (d, $J=9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.5, 50.6, 55.9, 83.7, 114.9, 115.8, 140.4, 153.6, 209.5; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 90:10, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=18.97$ min; minor isomer: $t_R=23.53$ min; $[\alpha]_D^{25}-9.4$ (*c* 1, $CHCl_3$).

3.2.9. Compound 3i. Yellow solid (148 mg, 45%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, C*H* [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.07 (dd, $J=13.3$, 4.5 Hz, 1H, CH_2NHAr), 3.37 (dd, $J=13.6$, 7.8 Hz, 1H, CH_2NHAr), 6.36 (d, $J=8.8$ Hz, 2H, Ar*H*), 7.39 (d, $J=8.8$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 28.0, 32.2, 42.5, 44.0, 49.9, 115.4, 117.4, 138.0, 147.8, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=53.80$ min; minor isomer: $t_R=78.80$ min; $[\alpha]_D^{25}+2.2$ (*c* 1.1, $CHCl_3$).

3.2.10. Compound 3j. Yellow solid (200 mg, 71%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, CH [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.07 (dd, $J=13.3$, 4.5 Hz, 1H, CH_2NHAr), 3.37 (dd, $J=13.4$, 7.7 Hz, 1H, CH_2NHAr), 6.45 (d, $J=8.9$ Hz, 2H, Ar*H*), 7.21 (d, $J=8.9$ Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.1, 27.9, 32.2, 42.4, 44.1,

45.0, 109.0, 114.7, 132.1, 147.3, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=45.22$ min; minor isomer: $t_R=63.04$ min; $[\alpha]_D^{25}-5.6$ (*c* 1.0, $CHCl_3$).

3.2.11. Compound 3k. Yellow solid (187 mg, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (m, 1H, C*H* [Cy]), 1.67 (m, 2H, CH_2 [Cy]), 1.90 (m, 1H, C*H* [Cy]), 2.10 (m, 2H, CH_2 [Cy]), 2.35 (m, 2H, CH_2 [Cy]), 2.65 (m, 1H, C*H*C=O), 3.12 (dd, $J=13.5$, 4.7 Hz, 1H, CH_2NHAr), 3.44 (dd, $J=13.5$, 7.7 Hz, 1H, CH_2NHAr), 6.6 (d, $J=8.4$ Hz, 2H, Ar*H*), 6.70 (m, 1H, Ar*H*), 7.18 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.0, 27.9, 32.2, 42.4, 43.9, 49.9, 113.0, 117.4, 129.4, 148.2, 213.3; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 98:2, flow rate 0.5 mL/min, $\lambda=254$ nm): major isomer: $t_R=35.86$ min; minor isomer: $t_R=30.95$ min; $[\alpha]_D^{25}+7.5$ (*c* 2.4, $CHCl_3$).

3.3. Typical experimental procedure for the direct catalytic aza-Diels–Alder reactions

To a vial containing aqueous formaldehyde (1 mmol, 36% aqueous solution), aniline (1.1 mmol) and a catalytic amount of (*S*)-proline (30 mol%) in DMSO (4 mL) was added the 4,4-dimethyl-2-cyclohexen-1-one **1h** (2 mmol). After 24–37 h of vigorously stirring at 50 °C the reaction was quenched by directly purifying the reaction mixture by silica-gel column chromatography (EtOAc/pentane-mixtures) to afford the desired aza-Diels–Alder products **4** (194.5 mg, 75%). Alternatively the reactions can also be quenched by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by neutral aluminum oxide column chromatography (EtOAc/pentane-mixtures) to furnish pure **4** as a yellow solid. The ee of the aza-Diels–alder products **4** were determined by chiral-phase HPLC analysis (Daicel AD column, $\lambda=244$ nm, $v=0.5$ mL/min, Hex/IPA) or chiral-phase GC analyses.

3.3.1. Compound 4a. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 3H), 1.77 (d, $J=2.98$ Hz, 2H), 2.47 (dd, $J=18.7$, 3.4 Hz 1H), 2.62 (m, 1H), 2.68 (dd, $J=18.9$, 2.3 Hz 1H), 3.48 (d, $J=2.5$ Hz, 2H), 3.75 (m, 1H), 3.76 (s, 3H), 6.61 (d, $J=9.2$ Hz, 2H), 6.84 (d, $J=9.2$ Hz, 2H); ^{13}C NMR δ 28.8 (CH_3), 30.2 (CH_3), 36.1 (C), 38.9 (CH_2), 41.3 (CH), 46.0 (CH_2), 47.9 (CH_2), 56.1 (CH_3), 58.5 (CH), 112.1 (CH), 115.5 (CH_3), 141.1, 151.4, 214.0; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 1.2 mL/min, $\lambda=254$ nm): major isomer: $t_R=24.94$ min; minor isomer: $t_R=27.31$ min; $[\alpha]_D-71.8$ (*c* 1.7, $CHCl_3$); MALDI-TOF MS: 256.1689; $C_{16}H_{22}NO_2$ ($M+H^+$: calcd 261.1683). Mp 71–73 °C.

3.4. Experimental procedure for protective group removal and the preparation of *cis*-6

To the reaction mixture (Table 3, entry 1), 5 mL of MeOH was added, and then 10 equiv of $NaBH_4$ at 0 °C. After 15 min, 15 mL of brine was added, and the mixture extracted with EtOAc (2×25 mL). The organic phases were dried ($MgSO_4$), evaporated and, after purification by column chromatography, the corresponding reduced alcohols **5** (trans/cis 1:1) were obtained (82%, 193 mg). Subsequent acetylation for 2 h in CH_2Cl_2 (10 mL) using Ac_2O (10 equiv, 1 mL) and catalytic 4,4′-dimethylaminopyridine (DMAP), extraction with water, drying with $MgSO_4$ and evaporation of the organic phase, and purification by column chromatography afforded the cis-monoacetylated compound. This compound was dissolved in MeOH (2 mL) and added to and an oxidant solution of iodobenzene acetate (1.5 g, 4.5 mmol in 15 mL of MeOH) over 30 min, the reaction allowed to stir for an additional 30 min and then acidified with 1 N HCl (30 mL) and allowed to stir for 1.5 h. The reaction mixture was washed with CH_2Cl_2 (2×30 mL) and the combined organics were back extracted with 0.1 N HCl (20 mL). CH_2Cl_2 was added to the combined acidic aqueous layers with vigorous stirring to yield a biphasic system. The reaction was brought to pH ~ 10–11 with solid Na_2CO_3. After 1.5 h the two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL). The combined organics were dried with $MgSO_4$ and concentrated. The oil obtained was dissolved in CH_2Cl_2 (5 mL), and Ac_2O (1 mL) and catalytic DMAP were added. After 2 h, the reaction was extracted with water, the organic phase dried and evaporated, and then purified by column chromatography, obtaining the pure *cis*-2-aminocyclohexanol diacetylated with 40% yield (86 mg).

N,*O*-diacetylated-*cis*-(1*S*, 2*S*)-2-aminomethyl-1-cyclohexanol **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.24 (m, 9H, 4×CH_2 and C*H*CH_2N), 1.97 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.95 (m, 1H, C*H*HNH), 3.53 (m, 1H, CH*H*NH), 4.58 (m, 1H, C*H*OOCH_3), 6.13 (br s, 1H, NH); $[\alpha]_D^{25}+50.2$ (*c* 1.0, MeOH).

Acknowledgements

A. C. thanks the Swedish Research Council, Lars Hierta Foundation, Carl-Trygger Foundation and Wenner-Gren Foundation for financial support.

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Enantioselective tandem Michael reaction to nitroalkene catalyzed by bifunctional thiourea: total synthesis of (−)-epibatidine

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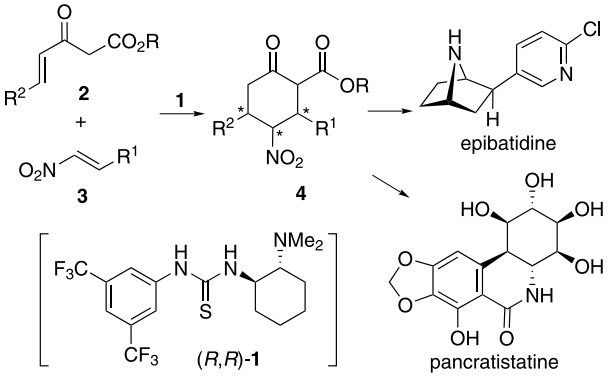
Received 1 March 2005; revised 18 July 2005; accepted 31 August 2005

Available online 21 September 2005

Abstract—Successive treatment of γ,δ-unsaturated β-ketoesters and nitroalkenes with a bifunctional thiourea and TMG promoted the tandem Michael addition, giving rise to highly functionalized cyclohexanones in good yields. The three contiguous stereogenic centers of the obtained products were constructed with high diastereo- and enantioselectivity (up to >99% de and 92% ee). The reaction was successfully applied to the asymmetric synthesis of (−)-epibatidine, which was synthesized from the cyclohexanone derivative in seven steps in 30% overall yield.

1. Introduction

In the past decade, urea and thiourea derivatives[1] have been intensively investigated as organocatalysts in asymmetric reactions because of their strong hydrogen bonding activity.[2] These catalysts can be used as an acidic promoter in a variety of reactions such as Diels–Alder cycloaddition, Strecker reaction, Mannich reaction, Michael addition, and so on.[1a–f] We reported that novel bifunctional thioureas, which had both a thiourea moiety and an amino group on a chiral scaffold, significantly promoted the Michael reaction of 1,3-dicarbonyl compounds to nitroalkenes to give the Michael adducts with high enantioselectivity.[1c] On the other hand, the enantioselective construction of multiple stereogenic centers in a single operation has been the subject of recent research.[3] In particular, such methods have been developed to synthesize highly functionalized chiral cyclohexanes[4–7] due to their versatility as synthetic intermediates for natural products such as epibatidine and pancratistatin. Although substantial progress has been achieved in the development of asymmetric Michael additions,[8] few of these reactions succeeded in the enantioselective construction of contiguous stereogenic centers.[9] Recently, we have already reported the bifunctional thiourea **1** could be applied to tandem Michael addition of γ,δ-unsaturated β-ketoesters **2** to nitroalkens **3**, providing the chiral 4-nitrocyclohexanone derivatives bearing three contiguous stereogenic centers with high diastereo- and enantioselectivity[10] (Scheme 1). In this article, we describe the details of the thiourea-catalyzed tandem Michael reaction and the asymmetric synthesis of (−)-epibatidine.



Scheme 1. Tandem Michael reaction of **2** and **3** with thiourea **1**.

2. Results and discussion

2.1. Thiourea-catalyzed tandem Michael reaction

We first investigated the tandem Michael addition of γ,δ-unsaturated-β-ketoesters **2a–c**[11] to nitrostyrene **3a** in the presence of bifunctional thiourea **1** (Scheme 2). According to the previous report,[1c] **2a** and **3a** were combined in toluene

Keywords: Thiourea; Organocatalyst; Michael addition; Asymmetric synthesis; Tandem reaction; Nitroalkenes; (−)-Epibatidine.
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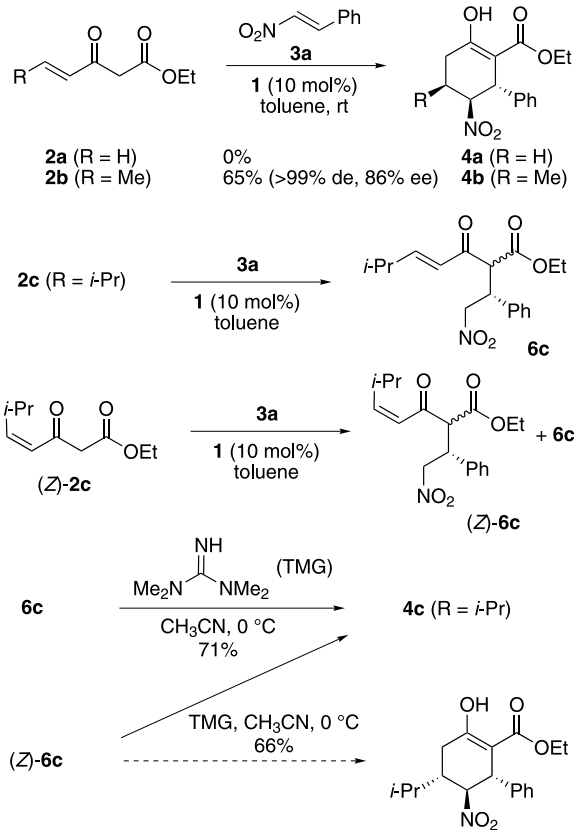
doi:10.1016/j.tet.2005.08.109

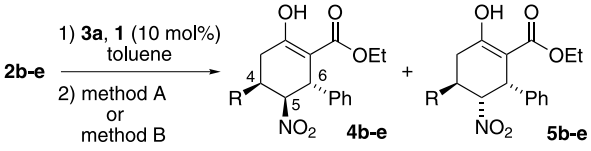


Scheme 2. Tandem Michael addition of ketoesters **2a–c** and nitroalkene **3a** in the presence of **1**.

together with 10 mol% of the catalyst **1** at room temperature. However, the reaction gave a complex mixture due to instability of **2a** and we could obtain neither Michael adducts nor the desired cyclized product **4a**. In contrast to **2a**, the same reaction with **2b** bearing a methyl group at the δ-position proceeded cleanly to provide the tandem Michael adduct **4b** as a single product in 65% yield with 86% ee. The result demonstrates that, according to expectation, the bifunctional thiourea **1** catalyzed both the inter- and intramolecular Michael additions of **2** and **3a**. Unfortunately, the same treatment of **2c** bearing a more bulky *iso*-propyl group as that of **2b** provided only Michael adduct **6c** but not **4c**. After several experiments, we found that the subsequent treatment (method A) of the obtained adduct **6c** with 0.1 equiv of 1,1,3,3-tetramethylguanidine (TMG) did give rise to the desired product **4c** stereoselectively (71% yield, >99% de, 88% ee). Based on these results, it was revealed that the high diastereoselectivity of the intramolecular Michael addition would be attributed to the reaction substrates, but not to the catalysts employed.

Therefore, we next investigated the two-step cyclization of **2b–e**[11] using catalytic amounts of thiourea **1** and TMG (Table 1, method A). Reexamination of the reaction of **2b** and **3a** using method A revealed that **4b** could be prepared as a single product with higher enantioselectivity than that obtained by the one-pot method (entry 1). We next employed (*Z*)-**2c** as a Michael acceptor with the aim of synthesizing another diastereomer as a major product. Although the first thiourea-catalyzed conjugate addition of (*Z*)-**2c** with **3a** proceeded smoothly, an unexpected product **6c** was produced along with the desired product (*Z*)-**6c** due to the isomerization of (*Z*)-**6c** into **6c** (Scheme 2). Furthermore, subsequent treatment of diastereomerically pure (*Z*)-**6c** by method A led to the exclusive formation of **4c**, which was derived from (*E*)-**6c**, with no desired 4,5-*anti*-5,6-*anti* adduct (entries 2 and 3). These results suggest that the intramolecular cyclization of (*Z*)-**6c** into an all-*anti* adduct would be an energetically unfavorable process. In contrast to **2b** and **2c**, the tandem Michael reaction of phenyl substituted derivative **2d** gave a mixture of diastereoisomers **4d** and **5d** in a ratio of 95/5. Similarly, the methoxy substituted derivative **2e** afforded an 82/18 mixture of **4e** and **5e**. In both cases, the same 3,4-*anti*-4,5-*syn* adducts **4d** and **4e** were obtained as major products with high enantioselectivity (entries 4 and 5). Since the diastereomers **5d** and **5e** seemed to be generated by a base-catalyzed epimerization of the major products **4d** and **4e**, we screened a variety of bases other than TMG for the intramolecular Michael reaction. Consequently, replacement of TMG with KOH in ethanol was revealed to suppress the epimerization of **4** into **5**, affording **4d** and **4e** in good yield as a single isomer, respectively, (entries 6 and 7). It is worthy to note that this is the first report of successful asymmetric synthesis

Table 1. Tandem Michael reaction of **2b–e** and **3a** catalyzed by thiourea **1** and TMG/KOH

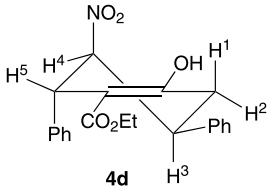


Entry	**2** (R)	Temperature (°C)	Method[a]	Yield (%)[b]	de (%)[c]	ee (%)[d]
1	**2b** (Me)	−20	A	87	>99	92
2	**2c** (*i*-Pr)	Room temperature	A	71	>99	88
3	(*Z*)-**2c** (*i*-Pr)	Room temperature	A[e]	66	>99	86
4	**2d** (Ph)	−40	A	79	90	89
5	**2e** (OMe)	Room temperature	A	63	64	85
6	**2d** (Ph)	−40	B	62	>99	92
7	**2e** (OMe)	Room temperature	B	79	>99	84

[a] Method A: TMG (0.1 equiv), CH_3CN, 0 °C, method B: KOH (0.1 equiv), EtOH, 0 °C.
[b] Isolated yield.
[c] The ratio of **4/5** was determined by isolated yields.
[d] Determined by HPLC analysis.
[e] The reaction was conducted at room temperature.

of three contiguous stereogenic centers by the tandem Michael reaction with nitroalkenes.

The relative configuration of **4b–e** was determined by ^{1}H NMR analysis. For an example, coupling constants (H^1–H^5) and NOE experiment of **4d** unambiguously demonstrated that **4d** possessed the conformation as shown in Figure 1. Furthermore, the absolute configuration of C-6 of **4b–e** was assumed to be *S* from the previous results.[1c] Based on these results, we determined the absolute configuration of **4d** to be (4*R*,5*S*,6*S*). Therefore, the stereoselective formation of **4b–e** would be rationally explained by considering the transition state A shown in Figure 2. The transition state A, giving the major adducts **4**, would be energetically more stable than the other transition state B, giving the minor adducts **5**, due to the steric hindrance between the phenyl ring and the nitronate anion.



coupling constant (Hz)	NOE (%)
H^1: 18.3, 11.7	H^3 - H^4: 7.8
H^2: 18.3, 6.5	H^4 - H^5: 7.8
H^3: 11.7, 6.5, 3.5	H^3 - H^5: 0.0
H^4: br s ($W_{1/2}$ = 6.6)	
H^5: br s ($W_{1/2}$ = 5.2)	

Figure 1. Determination of relative configuraion of **4d**.

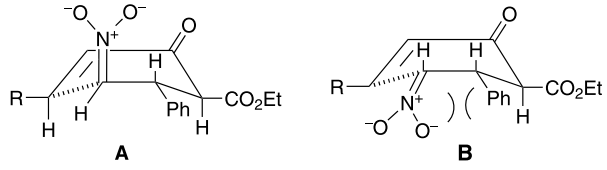
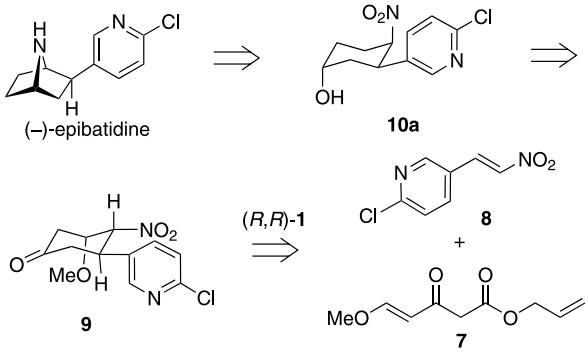


Figure 2. Diastereoselective formation of **4b–e**.

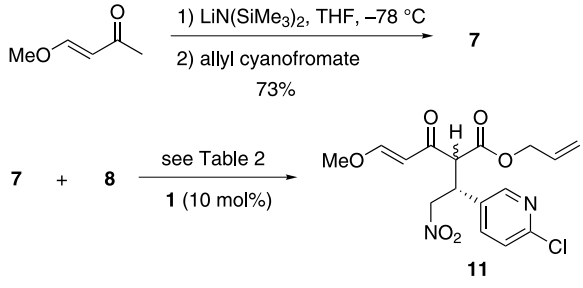
2.2. Asymmetric synthesis of (−)-epibatidine

Having established the two-step procedure to synthesize chiral 4-nitrocyclohexanones, we next applied this manipulation to the total synthesis of (−)-epibatidine, an alkaloid isolated from the skin of the Ecuadorian frog *Epibatidores tricolor* in 1992 by Daly et al.[12] From biological investigations, it has been found that epibatidine possesses extremely interesting pharmacological properties such as a nonopiate analgesic approximately 200 times more potent than morphine.[13] Epibatidine is a potent nicotinic acetylcholine receptor agonist, and these receptors are involved in the mediation of several human disorders such as Alzheimer's and Parkinson's diseases. In addition, a unique feature of this alkaloid is the presence of a strained nitrogen-bridged six-membered carbon ring system with an *exo*-oriented aryl group. Because of the unprecedented biological activity and the unique structural feature, widespread efforts have culminated in numerous total and formal syntheses. Although a variety of synthetic studies on the natural product have been reported,[14] enantioselective total syntheses are few.[15] In particular, the catalytic version was only achieved by Trost et al.[15f] Our synthetic approach to (−)-epibatidine relies on the thiourea-catalyzed tandem Michael addition of γ,δ-unsaturated-β-ketoester **7** to nitroalkene **8**. By taking advantage of the axial methoxy group, the corresponding cyclic adduct **9** would be stereoselectively transformed into *trans*-nitroalcohol **10a**, which is a key intermediate for the synthesis of (−)-epibatidine (Scheme 3).



Scheme 3. Retrosynthetic analysis of (−)-epibatidine.

The asymmetric synthesis of (−)-epibatidine commenced from the base-catalyzed condensation of *trans*-4-methoxy-3-buten-2-one with allyl cyanoformate to obtain **7**[11] (Scheme 4). Treatment of **7** and a known compound **8**[16] under the standard conditions (10 mol% of **1**, toluene, 0 °C) afforded the Michael adduct **11** in 90% yield, but the ee of **11** was revealed to be only 75% ee. (Table 2, entry 1). To improve the ee of **11**, the Michael reaction was examined under several reaction conditions, but all attempts proved fruitless (entries 2–4). It is not clear why the conjugate reaction of **7** with **8** proceeded with lower enantioselectivity compared to the previous results of **4b–e**. We therefore decided to improve the enantiomeric excess by recrystallization of **14** at a late stage of the synthetic route (Scheme 5). The second cyclization of **11** (75% ee) successfully occurred by the reaction with KOH in ethanol at 0 °C to provide cyclic ketoester **12** in 85% yield as a single isomer. Subsequent decarboxylation of **12** using the Tsuji conditions [$Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, room temperature][17] gave rise to the desired ketone **9** in quantitative yield.



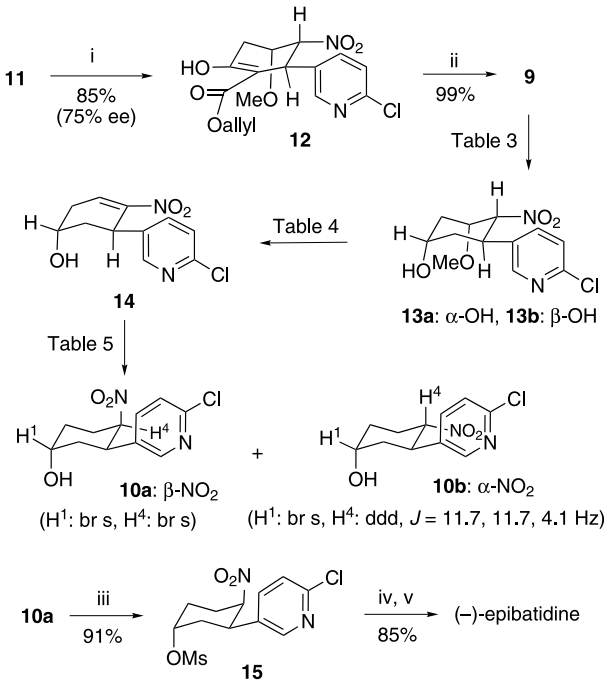
Scheme 4. Enantioselective Michael addition of **7** and **8** with **1**.

The remaining key task for the total synthesis of (−)-epibatidine was the conversion of 3,4-*trans*-adduct **9** to 3,4-*cis* adduct **10a**. For this purpose, we planned to employ the axial methoxy group of **9** for the stereoselective reduction of the ketone **9** and formation of the requisite nitroalkene **14**. We initially investigated the former reaction (Table 3). Treatment of **9** with smaller hydride reagents such as $NaBH_4$ and DIBAL-H gave a mixture of diastereoisomers **13a** and **13b** in good yield (entries 1 and 2). The axial

Table 2. Thiourea-catalyzed Michael reaction of **7** and **8**[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	Toluene	0	5	90	75
2	Toluene	−40 to −20	56	82	75
3	CH_2Cl_2	−20	16	90	71
4	THF	−20	78	88	57

[a] The reaction was carried out with 10 mol% of **1**.
[b] Isolated yield.
[c] Determined by HPLC analysis, after **11** was converted into **9**.



Scheme 5. Enantioselective total sysnthesis of (−)-epibatidine. (i) KOH, EtOH, 0 °C; (ii) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, rt; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (iv) Zn, AcOH, THF, rt; (v) $CHCl_3$, 60 °C.

alcohol **13a** was predominantly produced in both cases. However, the reduction of **9** with L-Selectride afforded the desired alcohol **13a** in 71% yield as a single isomer (entry 3).[6d] Subsequently, the elimination of methanol from **13a** was examined under several conditions as shown in Table 4. The initial attempt for the reaction of **13a** with methanesulfonic acid resulted in recovery of the starting material (entry 1). Similarly, no desired product was obtained by the reaction of **13a** with a catalytic amount of TMG in acetonitrile (entry 2). On the other hand, switching the base from TMG to KOH promoted the elimination of methanol to yield the aimed compound **14** in moderate yield, regardless of the solvent employed (entries 3 and 4). We finally found that the reaction of **13a** with 1.5 equiv of NaOMe in *tert*-BuOH gave the best result to yield **14** in 71% yield (81% yield based on the recovered starting material) as colorless crystals (entries 5 and 6). At this stage, the ee of **14** could be improved to 99% ee by recrystallization from $CHCl_3$.

We finally undertook the 1,4-hydride reduction of nitrocycloalkene **14** to obtain 1,4-*cis*-nitroalcohol **10a** (Table 5). The initial attempt to reduce **14** utilizing a sterically demanding hydride reagent, 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester, HEH),[18a] led to recovery of the starting material (entry 1). However, reduction of **14** with relatively smaller reducing agents such as $NaBH_4$ and $NaBH_3CN$[18b] afforded the axial nitroalkane **10a** as a major product (entries 2–4).[7c–d,19] The best result (87% yield, **10a/10b**=9:1) was obtained by reduction with

Table 3. Hydride reduction of ketone **9**

Entry	Reagent	Solvent	Temperature (°C)	Yield (%)[a]	
				13a	**13b**
1	$NaBH_4$	MeOH	−78	65	25
2	*i*-Bu_2AlH	Toluene	−78	63	18
3	L-selectride[b]	THF	−78	71	0

[a] Isolated yield.
[b] Lithium tri-*sec*-butylborohydride.

Table 4. Transformation of **13a** into nitroalkene **14** with several reagents[a]

Entry	Reagent (equiv)	Solvent	Yield (%)[b]
1	$MeSO_3H$ (1.0)	CH_2Cl_2	0
2	TMG (0.1)	MeCN	0
3	KOH (0.1)	EtOH	29[c]
4	KOH (0.1)	*t*-BuOH	22
5	NaOMe (1.5)	*t*-BuOH	71
6	NaOMe (3.0)	*t*-BuOH	41

[a] The reaction was carried out at room temperature.
[b] Isolated yield.
[c] Michael adduct of ethanol to **14** was produced.

$NaBH_3CN$ in AcOH and MeOH at −20 °C. The structural assignment of **10a** and **10b** was confirmed from the coupling constants of their ^1H NMR spectra (Scheme 5). To complete the total synthesis of (−)-epibatidine, alcohols **10a/10b** were converted into the corresponding mesylates (MsCl, Et_3N, DMAP), from which diastereomerically pure product **15** was isolated in 91% yield by column chromatography. Successive treatment of **15** with zinc dust in a mixture of AcOH and THF and refluxing in $CHCl_3$ gave the final compound (−)-epibatidine ($[\alpha]_D^{25}$ −6.0 (*c* 0.58, $CHCl_3$)) in 85% yield. The structure of the synthetic sample was

Table 5. Diastereoselective 1,4-reduction of nitroalkene **14**

Entry	Reagent	Temperature (°C)	Time (h)	Yield (%)[a]	Ratio (**10a/10b**)[b]
1	HEH	80	12	0	
2	$NaBH_4$	−78	0.25	45	2.5/1
3	$NaBH_3CN$	0	1.0	78	9/1
4	$NaBH_3CN$	−20	6.5	87	9/1

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

confirmed by comparison with reported literature data (^1H, ^{13}C NMR, IR, Mass).[15c]

3. Conclusion

We have developed thiourea/TMG-catalyzed tandem Michael reaction of γ,δ-unsaturated-β-ketoesters and nitroalkenes to synthesize chiral 4-nitrocyclohexanone derivatives bearing three contiguous stereogenic centers. In some cases, the diastereoselectivity of the tandem Michael adducts could be improved by using a thiourea/KOH combination (method B). Furthermore, we have revealed that the tandem reaction of (*Z*)-γ,δ-unsaturated β-ketoesters **2c** with **3a** provided the same product **4c** regardless of the (*E*)/(*Z*) stereochemistry of the starting material **2c** due to the isomerization of the intermediates **6**. The synthetic utility of these products has been demonstrated by the asymmetric synthesis of (−)-epibatidine.

4. Experimental

4.1. General information

Nominal (LR-MS) and exact mass (HR-MS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. ^1H and ^{13}C NMR spectra were registered on JEOL JNM-LA500 using TMS as an internal standard. (s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublets, t=triplet, q=quartet, m=multiplet, br=broad). Optical rotations were measured in $CHCl_3$ unless otherwise noted with a JASCO DIP-360 digital polarimeter. For column chromatography, Kanto Silica gel 60 (spherical, 63–210 μm) was employed and preparative thin-layer chromatography (PTLC) was carried out using Silica gel 60 (Merck). Enantiomer ratios were determined by chiral HPLC using a Shimadzu SPD-10A with Daicel Chemical Industries, LTD. Chiralpak AD-H (0.46 cm×25 cm) or Chiralpak OD-H (0.46 cm×25 cm) or Chiralpak AS-H (0.46 cm×25 cm). Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used without purification. The ketoesters **2a–e** and nitroolefin **8** were synthesized according to the literature procedures.[20]

4.2. Tandem Michael reaction

4.2.1. Tandem Michael addition catalyzed by thiourea 1. To a stirred solution of **2b** (23.4 mg, 0.150 mmol) and thiourea-catalyst **1** (0.010 mmol, 4.1 mg) in dry toluene (0.20 mL) was added *trans*-β-nitrostyrene **3a** (14.9 mg, 0.10 mmol) at room temperature. After being stirred for 44 h, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC (hexane/AcOEt=10:1 as eluent) to afford desired product **4b** (19.8 mg, 65% yield) as a single diastereomer.

4.2.2. Typical procedure for tandem Michael addition catalyzed by thiourea 1 and TMG (Method A). To a stirred solution of **2b** (23.4 mg, 0.15 mmol) and thiourea **1** (4.1 mg, 0.010 mmol) in dry toluene (0.20 mL) was added *trans*-β-nitrostyrene **3a** (14.9 mg, 0.10 mmol) at −20 °C. After being stirred for 17 h, thiourea **1** was removed by silica gel column chromatography, and the obtained residue was treated with 1,1,3,3-tetramethylguanidine (0.1 equiv, 1.2 mg) in acetonitrile (1 mL) at 0 °C for 0.5 h. The reaction mixture was diluted with AcOEt and quenched with 1 N HCl. The separated aqueous phase was extracted with AcOEt twice, and then the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/AcOEt=10:1 as eluent) to afford desired product **4b** (26.5 mg, 87% yield) as a single diastereomer.

4.2.3. Typical procedure for tandem Michael addition catalyzed by thiourea 1 and KOH (Method B). To a stirred solution of **2d** (48.0 mg, 0.22 mmol) and thiourea **1** (8.2 mg, 0.020 mmol) in dry toluene (0.40 mL) was added *trans*-β-nitrostyrene **3a** (29.8 mg, 0.20 mmol) at −40 °C. After being stirred for 17 h, thiourea **1** was removed by silica gel column chromatography, and the obtained residue was treated with KOH (1.1 mg, 0.020 mmol) in EtOH (2 mL) at 0 °C for 1.5 h. The reaction mixture was diluted with AcOEt and quenched with a saturated NH_4Cl solution. The separated aqueous phase was extracted with AcOEt twice, and then the combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/AcOEt=10:1 as eluent) to afford desired product **4d** (45.6 mg, 62% yield) as a single diastereomer.

4.2.4. (4*S*,5*S*,6*S*)-2-Hydroxy-4-methyl-5-nitro-6-phenylcyclohex-1-enecarboxylic acid ethyl ester 4b. Yellow oil; $[\alpha]_D^{27}$ +83.6 (*c* 0.57, $CHCl_3$, 87% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 12.6 (s, 1H), 7.38–7.17 (m, 5H), 4.65 (s, 1H), 4.46 (s, 1H), 4.07–3.93 (m, 2H), 2.56 (dd, *J*=18.6, 6.7 Hz, 1H), 2.48 (dd, *J*=18.6, 10.3 Hz, 1H), 2.39–2.24 (m, 1H), 1.06 (d, *J*=6.7 Hz, 3H), 0.9 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.5, 141.6, 128.8, 127.8, 127.4, 96.1, 91.2, 60.5, 43.6, 32.6, 26.2, 16.9, 13.6 ppm; IR ($CHCl_3$) ν 3029, 1656, 1622, 1549 cm^{-1}; MS (FAB^+) 306 (MH^+, 88), 213 (100); HRMS (FAB^+) Calcd for $[C_{16}H_{20}NO_5]^+$: 306.1341. Found: 306.1339; HPLC [Chiralcel AS-H, hexane/2-propanol=95:5, 0.5 mL/min,

λ=210 nm, retention times: (major) 12.5 min, (minor) 14.9 min].

4.2.5. (4*R*,5*S*,6*S*)-2-Hydroxy-4-*iso*-propyl-5-nitro-6-diphenylcyclohex-1-enecarboxylic acid ethyl ester 4c. Colorless solid; mp 195–196 °C (Hexane/AcOEt); $[\alpha]_D^{24}$ +63.6 (*c* 1.00); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.6 (s, 1H), 7.21–7.36 (m, 5H), 4.91 (s, 1H), 4.49 (s, 1H), 4.00–4.04 (m, 2H), 2.64 (dd, *J*=18.9, 6.4 Hz, 1H), 2.52 (dd, *J*=18.9, 10.4 Hz, 1H), 1.58–1.63 (m, 2H), 0.96 (t, *J*=6.2 Hz, 3H), 0.93 (d, *J*=6.1 Hz, 3H), 0.82 (d, *J*=6.1 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 171.5, 141.3, 128.8, 127.7, 127.4, 95.6, 87.6, 60.5, 44.4, 37.6, 29.9, 29.5, 20.5, 20.2, 13.7 ppm; IR ($CHCl_3$) ν 2971, 1658, 1626, 1548 cm^{-1}; MS (FAB$^+$) 334 (MH^+, 100). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.56; H, 6.87; N, 3.90. Determination of ee was accomplished by reduction with zinc followed by di-benzoylation. *Benzoic acid (3S,4S,5R)-4-benzoylamino-2-ethoxycarbonyl-5-iso-propyl-3-phenylcyclohex-1-enyl ester*. Colorless amorphous; $[\alpha]_D^{25}$ +83.6 (*c* 0.82); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J*=7.9 Hz, 2H), 7.98 (d, *J*=7.6 Hz, 2H), 7.64–7.67 (m, 1H), 7.50–7.55 (m, 5H), 7.36–7.43 (m, 4H), 7.25–7.28 (m, 1H), 6.81 (d, *J*=9.5 Hz, 1H), 4.89 (d, *J*=9.5 Hz, 1H), 4.37 (s, 1H), 3.88–3.97 (m, 2H), 2.72 (dd, *J*=6.7, 6.7 Hz, 1H), 2.27 (dd, *J*=11.0, 11.3 Hz, 1H), 1.57–1.63 (m, 1H), 1.45–1.52 (m, 1H), 0.82–0.85 (m, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.3, 164.6, 157.2, 140.6, 134.3, 133.9, 131.6, 130.3, 129.1, 128.6, 127.3, 126.9, 118.4, 60.7, 50.7, 48.6, 38.1, 31.1, 29.6, 20.6, 20.2, 13.6 ppm; IR ($CHCl_3$) ν 1724, 1661, 1602, 1517 cm^{-1}; MS (FAB$^+$) 512 (MH^+, 18), 105 (100); HRMS (FAB$^+$) Calcd for $[C_{32}H_{34}NO_5]^+$: 512.2437. Found: 512.2435; HPLC [Chiralcel OD-H, hexane/2-propanol=90:10, 0.5 mL/min, λ=254 nm, retention times: (major) 12.5 min, (minor) 10.8 min].

4.2.6. (4*R*,5*S*,6*S*)-2-Hydroxy-5-nitro-4,6-diphenyl-cyclohex-1-enecarboxylic acid ethyl ester 4d. Colorless solid; mp 106–108 °C (hexane); $[\alpha]_D^{26}$ +32.8 (*c* 1.00, $CHCl_3$, 89% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.7 (s, 1H), 7.39 (t, *J*=7.5 Hz, 2H), 7.35–7.19 (m, 6H), 7.05 (d, *J*=7.0 Hz, 2H), 4.91–4.96 (m, 1H), 4.55 (s, 1H), 4.11–3.97 (m, 2H), 3.43 (ddd, *J*=11.7, 6.5, 3.5 Hz, 1H), 3.32 (dd, *J*=18.3, 11.7 Hz, 1H), 2.78 (dd, *J*=18.3, 6.4 Hz, 1H), 0.97 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 171.6, 141.4, 137.7, 129.1, 129.0, 128.0, 127.8, 127.7, 127.3, 96.0, 91.5, 60.8, 44.4, 36.3, 29.8, 13.8 ppm; IR ($CHCl_3$) ν 3029, 1675, 1624, 1550 cm^{-1}; MS (FAB$^+$) 368 (MH^+, 78), 154 (100). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.50; H, 3.79; N, 5.08; HPLC [Chiralcel OD-H, hexane/2-propanol=70:30, 0.5 mL/min, λ=210 nm, retention times: (major) 14.0 min, (minor) 10.4 min].

4.2.7. (4*R*,5*R*,6*S*)-2-Hydroxy-5-nitro-4,6-diphenyl-cyclohex-1-enecarboxylic acid ethyl ester 5d. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 1H), 7.36–7.07 (m, 10H), 5.30 (dd, *J*=12.5, 5.8 Hz, 1H), 4.64 (d, *J*=5.8 Hz, 1H), 4.12–3.99 (m, 2H), 3.68–3.58 (m, 1H), 2.98 (dd, *J*=19.4, 6.9 Hz, 1H), 2.64 (dd, *J*=19.2, 11.3 Hz, 1H), 1.01 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.1, 139.6, 137.6, 129.0, 128.5, 128.4, 128.1, 127.7, 127.2, 98.3, 89.1, 60.9, 43.4, 37.0, 36.9, 13.7 ppm; IR ($CHCl_3$) ν 3031, 1658, 1623, 1554 cm^{-1}; MS (FAB$^+$) 368 (MH^+, 91), 275 (100); HRMS (FAB$^+$) Calcd for $[C_{21}H_{22}NO_5]^+$: 368.1498. Found: 368.1507.

4.2.8. (4*S*,5*R*,6*S*)-2-Hydroxy-4-methoxy-5-nitro-6-phenylcyclohex-1-enecarboxylic acid ethyl ester 4e (mixture of keto and enol form). Yellow oil; $[\alpha]_D^{24}$ +52.4 (*c* 1.12); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 0.68H), 7.20–7.30 (m, 5H), 5.20 (dd, *J*=11.9, 2.8 Hz, 0.32H), 4.91 (t, *J*=4.0 Hz, 0.68H), 4.50–4.56 (m, 1.32H), 3.91–4.09 (m, 2.68H), 3.62 (d, *J*=12.5 Hz, 0.32H), 3.39 (s, 0.96H), 3.33 (s, 2.04H), 3.07 (dd, *J*=15.0, 3.7 Hz, 1H), 2.76–2.89 (m, 1.68H), 1.08 (t, *J*=7.0 Hz, 0.96H), 0.90 (t, *J*=7.3 Hz, 2.04H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 171.2, 169.1, 166.6, 141.5, 137.0, 128.9, 128.8, 128.2, 128.1, 127.7, 127.4, 97.2, 88.6, 88.4, 78.7, 72.2, 61.5, 61.4, 60.6, 57.6, 57.0, 42.8, 42.7, 42.0, 31.6, 13.8, 13.5 ppm; IR ($CHCl_3$) ν 1747, 1626, 1658, 1625, 1556 cm^{-1}; MS (FAB$^+$) 322 (MH^+, 85), 197 (100); HRMS (FAB$^+$) Calcd for $[C_{16}H_{20}NO_6]^+$: 322.1291. Found: 322.1299; HPLC [Chiralcel OJ-H, hexane/2-propanol=90:10, 0.5 mL/min, λ=210 nm, retention times: (major) 20.3 min, (minor) 25.1 min].

4.2.9. (4*S*,5*S*,6*S*)-2-Hydroxy-4-methoxy-5-nitro-6-phenylcyclohex-1-enecarboxylic acid ethyl ester 5e. $[\alpha]_D^{24}$ +217 (*c* 1.06); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.4 (s, 1H), 7.26–7.29 (m, 3H), 6.99–7.01 (m, 2H), 4.81 (dd, *J*=11.0, 6.4 Hz, 1H), 4.51 (d, *J*=6.4 Hz, 1H), 3.99–4.10 (m, 3H), 3.35 (s, 3H), 3.23 (dd, *J*=18.6, 7.3 Hz, 1H), 2.51 (dd, *J*=18.6, 8.6 Hz, 1H), 1.00 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 168.6, 137.5, 128.5, 128.1, 128.0, 98.3, 88.8, 70.6, 60.9, 57.8, 42.7, 34.2, 13.6 ppm; IR ($CHCl_3$) ν 1658, 1624, 1558 cm^{-1}; MS (FAB$^+$) 322 (MH^+, 100). Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 60.04; H, 5.94; N 4.28.

4.3. Total synthesis of (−)-epibatidine

4.3.1. 5-Methoxy-3-oxo-4-pentenoic acid allyl ester 7. To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (4.84 g, 30.0 mmol) in THF (75 mL) at −78 °C was added *n*-BuLi (19.0 mL of a 1.58 M solution, 30.0 mmol). The reaction mixture was stirred for 15 min and then a solution of *trans*-3-methoxy-2-butenone (90% purity, 1.67 g, 15.0 mmol) in THF (75 mL) was added dropwise over 20 min via canula. After 30 min, a solution of hexamethylphosphoramide (4.52 g, 25.2 mmol) and allyl cyanoformate[20] in THF (15 mL) were added. Quenching with a saturated NH_4Cl solution, extraction with AcOEt, washing with brine, drying over $MgSO_4$, evaporation of the solvent and flash chromatography (hexane/AcOEt=2:1) afforded **7** (2.02 g, 73%). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=12.8 Hz, 1H), 6.00–5.83 (m, 1H), 5.68 (d, *J*=12.5 Hz, 1H), 5.35 (dd, *J*=17.1, 1.5 Hz, 1H), 5.25 (dd, *J*=10.7, 1.2 Hz, 1H), 4.64 (d, *J*=5.8 Hz, 2H), 3.75 (s, 3H), 3.51 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7, 167.3, 164.3, 131.7, 118.7, 104.8, 65.9, 57.8, 48.0 ppm; IR ($CHCl_3$) ν 3027, 1739, 1685, 1656, 1621, 1594 cm^{-1}; MS (EI$^+$) 184 (M^+), 85 (100). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.69; H, 6.48.

4.3.2. Allyl (4*E*)-2-[(1*R*)-1-(6-chloropyridin-3-yl)-2-nitroethyl]-5-methoxy-3-oxo-4-pentenoate 11 (Table 2,

entry 1). To a solution of **7** (235 mg, 1.28 mmol) and thiourea (35.1 mg, 0.0850 mmol) in toluene (1.7 mL) was added **8** (157 mg, 0.850 mmol) at 0 °C. After 5 h, flash chromatography (hexane/AcOEt=3:2) of the obtained residue afforded **11** (282 mg, 90%). (Table 2, entry 2). To a solution of **7** (55.2 mg, 0.300 mmol) and thiourea (8.2 mg, 0.020 mmol) in toluene (0.4 mL) was added **8** (36.9 mg, 0.200 mmol) at −40 °C, and the mixture was stirred for 46 h. The reaction mixture was warmed up to −20 °C and stirred for additional 10 h. Flash chromatography of the crude residue (hexane/AcOEt=3:2) afforded **11** (60.4 mg, 82%). (Table 2, entry 3). To a solution of **7** (55.2 mg, 0.300 mmol) and thiourea (8.2 mg, 0.020 mmol) in toluene (0.4 mL) was added **8** (36.9 mg, 0.200 mmol) at −20 °C. After being stirred for 16 h, flash chromatography of the obtained residue (hexane/AcOEt=3:2) afforded **11** (66.4 mg, 90%). (Table 2, entry 4). To a solution of **7** (27.6 mg, 0.150 mmol) and thiourea (4.1 mg, 0.010 mmol) in toluene (0.2 mL) was added **8** (18.5 mg, 0.100 mmol) at −20 °C. After 78 h, flash chromatography of the obtained residue (hexane/AcOEt=3:2) afforded **11** (32.5 mg, 88%). The diastereomers could not be separated. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J=2.4 Hz, 0.59H), 8.30 (d, J=2.8 Hz, 0.41H), 7.79 (d, J=12.5 Hz, 0.59H), 7.62–7.55 (m, 1.41H), 7.32–7.26 (m, 1H), 5.93–5.84 (m, 0.41H), 5.77 (d, J=12.2 Hz, 0.59H), 5.70–5.61 (m, 0.59H), 5.60 (d, J=12.2 Hz, 0.41H), 5.38–5.27 (m, 0.82H), 5.23–5.14 (m, 1.18H), 4.91–4.62 (m, 2.82H), 4.43 (d, J=6.1 Hz, 1.18H), 4.37–4.28 (m, 1H), 4.10 (d, J=10.4 Hz, 0.59H), 4.05 (d, J=9.5 Hz, 0.41H), 3.78 (s, 1.77H), 3.72 (s, 1.23H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.9, 189.4, 167.3, 166.6, 166.0, 165.8, 151.4, 151.3, 149.7, 149.4, 138.6, 138.5, 131.8, 131.6, 130.8, 130.6, 124.5, 124.4, 119.8, 103.6, 103.5, 77.1, 66.7, 66.6, 59.8, 59.7, 58.4, 39.6, 39.4 ppm; IR ($CHCl_3$) ν 3030, 3003, 1738, 1684, 1590, 1559 cm^{-1}; MS (EI^+) 368 (MH^+), 85 (100). Anal. Calcd for $C_{16}H_{17}ClN_2O_6$: C, 52.11; H, 4.65; N, 7.60. Found: C, 52.29; H, 4.62; N, 7.34.

4.3.3. (4*S*,5*R*,6*S*)-6-(6-Chloropyridin-3-yl)-2-hydroxy-4-methoxy-5-nitrocyclohex-1-enecarboxylic acid allyl ester 12. To a solution of **7** (235 mg, 1.28 mmol) and thiourea (35.1 mg, 0.085 mmol) in toluene (1.7 mL) was added **8** (157 mg, 0.85 mmol) at 0 °C. After 5 h, purification of the obtained crude product by flash chromatography (hexane/AcOEt=3:2) afforded **11** (282 mg, 90%). A solution of KOH (0.422 mmol, 23.6 mg) in 42 mL EtOH was poured onto **11** (1.56 g, 4.22 mmol) at 0 °C. After 10 h, the reaction mixture was diluted with AcOEt, quenched with a saturated NH_4Cl solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (hexane/AcOEt=3:2) afforded **12** (1.33 g, 85%). Colorless solid; mp 114–116 °C (Et_2O); $[\alpha]_D^{28}$ +61.8 (*c* 1.00, $CHCl_3$, 75% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.5 (s, 1H), 8.31 (d, J=2.8 Hz, 1H), 7.52 (dd, J=8.4, 2.6 Hz, 1H), 7.28 (d, J=8.2 Hz, 1H), 5.61–5.49 (m, 1H), 5.12 (d, J=10.4 Hz, 1H), 5.01 (d, J=17.1 Hz, 1H), 4.70 (dd, J=6.7, 3.1 Hz, 1H), 4.66 (d, J=6.7 Hz, 1H), 4.46 (d, J=13.1, 5.8 Hz, 1H), 4.41 (dd, J=13.0, 6.0 Hz, 1H), 4.11–4.07 (m, 1H), 3.37 (s, 3H), 2.85 (d, J=5.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.6, 150.5, 149.7, 138.3, 136.5, 130.8, 124.2, 119.2, 96.7, 88.6, 73.3, 65.6, 57.4, 38.1, 32.0 ppm; IR ($CHCl_3$) ν 3029, 3000, 2935, 1731, 1662, 1621, 1559, 1460 cm^{-1}; MS (FAB^+) 369 (MH^+, 100). Anal. Calcd for $C_{16}H_{17}ClN_2O_6$: C, 52.11; H, 4.65; N, 7.60. Found: C, 51.98; H, 4.67; N, 7.50.

4.3.4. (3*R*,4*R*,5*S*)-3-(6-Chloropyridin-3-yl)-5-methoxy-4-nitrocyclohexanone 9. To a stirred solution of palladium acetate (0.0461 mmol, 10.3 mg) and PPh_3 (0.0922 mmol, 24.2 mg) in THF (3 mL) was added in one portion a mixture of formic acid (0.922 mmol, 42.4 mg) and Et_3N (1.15 mmol, 160 μL) in THF (2 mL) at room temperature under an argon atmosphere. The mixture was vigorously stirred and a solution of **12** (0.461 mmol, 170 mg) in THF (1 mL) was added, and then the resulting mixture was stirred for additional 1 h. The reaction mixture was passed through a short SiO_2 column, followed by AcOEt washing. Evaporation of the organic solvent afforded **9** (130 mg, 99%). Yellow amorphous; $[\alpha]_D^{29}$ +43.1 (*c* 1.00, $CHCl_3$, 75% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J=2.4 Hz, 1H), 7.59 (dd, J=8.1, 2.6 Hz, 1H), 7.33 (d, J=8.2 Hz, 1H), 5.10 (dd, J=11.8, 2.6 Hz, 1H), 4.52 (ddd, J=2.6, 2.5, 2.5 Hz, 1H), 4.19 (ddd, J=12.5, 11.8, 5.2 Hz, 1H), 3.38 (s, 3H), 3.00 (dt, J=15.4, 2.7 Hz, 1H), 2.75–2.66 (m, 1H), 2.55–2.47 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 151.1, 148.8, 137.6, 134.1, 124.7, 88.2, 78.8, 57.7, 45.8, 42.7, 37.4 ppm; IR ($CHCl_3$) ν 3030, 3002, 1730, 1561 cm^{-1}; MS (FAB^+) 285 (MH^+, 100); HRMS (FAB^+) Calcd for $[C_{12}H_{14}ClN_2O_4]^+$: 285.0642. Found: 285.0639; HPLC [Chiralcel AD-H, hexane/2-propanol=70:30, 0.5 mL/min, λ=210 nm, retention times: (major) 23.8 min, (minor) 20.2].

4.3.5. (1*S*,3*R*,4*R*,5*S*)-3-(6-Chloropyridin-3-yl)-5-methoxy-4-nitrocyclohexanol 13a and (1*R*,3*R*,4*R*,5*S*)-3-(6-chloropyridin-3-yl)-5-methoxy-4-nitrocyclohexanol 13b (Table 3, entry 1). To a stirred solution of **9** (14.5 mg, 0.0508 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (2.3 mg, 0.0609 mmol) at −78 °C. After 20 min, the reaction mixture was diluted with AcOEt, quenched with a saturated NH_4Cl solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and preparative TLC ($CHCl_3$/MeOH=20:1) afforded **13a** (9.4 mg, 65%) and **13b** (3.6 mg, 25%). (Table 3, entry 2) To a stirred solution of **9** (18.4 mg, 0.0647 mmol) in toluene (0.7 mL) was added a solution of *i*-Bu_2AlH in toluene (1 M, 97.1 μL, 0.0971 mmol) dropwise at −78 °C. After 40 min, the reaction mixture was quenched with 1 N HCl, and extracted with AcOEt twice. The combined organic phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and preparative TLC ($CHCl_3$/MeOH=20:1) afforded **13a** (11.6 mg, 63%) and **13b** (3.3 mg, 18%). (Table 3, entry 3) To a stirred solution of **9** (0.223 mmol, 63.5 mg) in dry THF (2.5 mL) was added a solution of L-Selectride in THF (1 M, 223 μL, 0.223 mmol) dropwise at −78 °C. The reaction mixture was allowed to warm up to 0 °C after addition of 0.2 mL of 30% hydrogen peroxide, and 5% HCl was added until the solution was slightly acidic. Extraction with AcOEt three times, washing with brine, drying over Na_2SO_4, evaporation of the solvent and flash chromatography (Et_2O/MeOH=20:1) afforded **13a**

(45.7 mg, 71%). *Compound* **13a**. Colorless solid; mp 123–126 °C (Hexane/AcOEt); $[\alpha]_D^{27}$ −13.7 (*c* 0.97, $CHCl_3$, 75% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J=2.4 Hz, 1H), 7.56 (dd, J=8.2, 2.8 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H), 4.72 (dd, J=12.1, 3.2 Hz, 1H), 4.39 (q, J=2.4 Hz, 1H), 4.12 (dt, J=9.8, 2.7 Hz, 1H), 4.01 (td, J=12.7, 4.1 Hz, 1H), 3.72 (d, J=10.1 Hz, 1H), 3.45 (s, 3H), 2.58–2.50 (m, 1H), 2.27–2.20 (m, 1H), 1.76 (dt, J=15.4, 2.8 Hz, 1H), 1.68 (td, J=13.7, 2.8 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 148.9, 137.7, 135.6, 124.4, 89.0, 79.3, 65.4, 59.0, 40.1, 32.4, 32.3 ppm; IR ($CHCl_3$) ν 3519, 3006, 2942, 1556 cm^{-1}; MS (EI^+) 286 (M^+), 221 (100). Anal. Calcd for $C_{12}H_{15}ClN_2O_4$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.13; H, 5.24; N, 9.67. *Compound* **13b**. Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.55 (dd, J=8.2, 2.1 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 4.67 (dd, J=11.8, 2.9 Hz, 1H), 4.28 (s, 1H), 4.19–4.10 (m, 1H), 3.77 (td, J=12.5, 3.7 Hz, 1H), 3.37 (s, 3H), 2.56 (d, J=14.0 Hz, 1H), 2.20 (d, J=11.3 Hz, 1H), 1.60–1.46 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 149.1, 137.5, 135.4, 124.4, 89.4, 78.3, 64.3, 57.8, 41.4, 36.5, 36.2 ppm; IR ($CHCl_3$) ν 3611, 2932, 1556 cm^{-1}; MS (FAB^+) 287 (MH^+, 100); HRMS (FAB^+) Calcd for $[C_{12}H_{16}ClN_2O_4]^+$: 287.0798. Found: 287.0804.

4.3.6. (1*S*,5*R*)-5-(6-Chloropyridin-3-yl)-4-nitrocyclohex-3-enol 14 (Table 4, entry 3). To a stirred solution of **13a** (0.024 mmol, 7.0 mg) in EtOH (0.24 mL) was added KOH (0.0024 mmol, 0.14 mg). After 1 h, the reaction mixture was diluted with AcOEt, quenched with a saturated NH_4Cl solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and flash chromatography ($CHCl_3$/MeOH=20:1) afforded **14** (1.8 mg, 29%). (Table 4, entry 4) To a stirred solution of **13a** (0.027 mmol, 7.7 mg) in *t*-BuOH (0.27 mL) was added KOH (0.0027 mmol, 0.15 mg). The same treatment of the mixture as described above afforded **14** (1.5 mg, 22%). (Table 4, entry 5). To a stirred solution of **13a** (1.28 mmol, 366 mg) in *t*-BuOH (64 mL) was added NaOMe (1.92 mmol, 104 mg). The same treatment of the mixture as described above afforded **14** (231 mg, 71%). (Table 4, entry 6). To a stirred solution of **13a** (0.017 mmol, 5.0 mg) in *t*-BuOH (0.87 mL) was added NaOMe (0.052 mmol, 2.8 mg). The same treatment of the mixture as described above afforded **14** (1.8 mg, 41%). Colorless solid; mp 165–158 °C ($CHCl_3$); $[\alpha]_D^{28}$ −152.1 (*c* 0.48, $CHCl_3$, >99% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J=2.4 Hz, 1H), 7.49 (t, J=4.1 Hz, 1H), 7.42 (dd, J=8.2, 2.8 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 4.42 (t, J=5.2 Hz, 1H), 4.12–4.04 (m, 1H), 2.85 (dt, J=19.6, 4.7 Hz, 1H), 2.51–2.41 (m, 1H) 2.23 (ddd, J=13.3, 9.3, 6.1 Hz, 1H), 2.00–1.92 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 149.2, 148.5, 137.3, 136.2, 134.6, 124.4, 62.0, 39.4, 36.6, 33.5 ppm; IR ($CHCl_3$) ν 3610, 2930, 1564, 1524 cm^{-1}; MS (FAB^+) 255 (MH^+, 90), 154 (100). Anal. Calcd for $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; N, 11.00. Found: C, 51.61; H, 4.12; N, 11.00; HPLC [Chiralcel AD-H, hexane/2-propanol=70:30, 0.5 mL/min, λ=254 nm, retention times: (major) 14.6 min, (minor) 12.8 min].

4.3.7. (1*R*,3*R*,4*R*)-3-(6-Chloropyridin-3-yl)-4-nitro-cyclohexanol 10a and (1*R*,3*R*,4*S*)-3-(6-chloropyridin-3-yl)-4-nitrocyclohexanol 10b (Table 5, entry 2). To a stirred solution of **14** (2.0 mg, 0.0079 mmol) in MeOH (0.1 mL) was added $NaBH_4$ (0.60 mg, 0.016 mmol) at −78 °C. After 20 min, the reaction mixture was diluted with AcOEt, quenched with a saturated NH_4Cl solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and short chromatography (Et_2O) afforded **10a** and **10b** (0.9 mg, 45%, dr=2.5/1). (Table 5, entry 3) To a solution of **14** (0.038 mmol, 9.6 mg) in MeOH (0.4 mL) were added acetic acid (20 μL) and $NaBH_3CN$ (0.045 mmol, 2.8 mg) at 0 °C. After 1 h, the reaction mixture was diluted with AcOEt, washed with a saturated Na_2CO_3 solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over Na_2SO_4. Evaporation of the solvent and short chromatography (Et_2O) afforded **10a** and **10b** (7.5 mg, 87%, dr=9/1). (Table 5, entry 4) To a solution of **14** (0.161 mmol, 41.1 mg) in MeOH (1.6 mL) were added acetic acid (70 μL) and $NaBH_3CN$ (0.242 mmol, 15.2 mg) at −20 °C. After 6.5 h, the reaction mixture was diluted with AcOEt, washed with a saturated Na_2CO_3 solution, and separated. The aqueous phase was extracted with AcOEt twice, and the combined organic phases were washed with brine, dried over Na_2SO_4. Evaporation of the solvent and short chromatography (Et_2O) afforded **10a** and **10b** (36.0 mg, 87%, dr=9/1). Colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J=2.1 Hz, 1H), 7.51 (dd, J=8.2, 2.4 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 4.89 (m, 0.9H), 4.66 (dt, J=11.7, 4.1 Hz, 0.1H), 4.44 (br s, 0.9H), 4.27 (s, 0.1H), 3.65 (td, J=12.1, 3.7 Hz, 0.1H), 3.65 (td, J=13.1, 4.0 Hz, 0.9H), 2.69 (t, J=13.6 Hz, 1H), 2.53–2.43 (m, 1H), 2.27–2.18 (m, 1H), 2.15–2.04 (m, 1H), 1.92 (d, J=14.0 Hz, 1H), 1.80 (d, J=14.3 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) for major diastereomer δ 150.5, 149.2, 137.9, 137.4, 124.3, 86.3, 64.6, 35.4, 31.3, 26.5, 24.1 ppm; IR ($CHCl_3$) ν 3614, 2932, 2863, 1549 cm^{-1}; MS (EI^+) 256 (M^+), 192 (100); HRMS (EI^+) Calcd for $[C_{11}H_{13}Cl_3N_2O_3]^+$: 256.0615. Found: 256.0615.

4.3.8. Methanesulfonic acid (1*R*,3*R*,4*R*)-3-(6-chloropyridin-3-yl)-4-nitrocyclohexyl ester 15. To a stirred solution of **10a**. (0.172 mmol, 44.1 mg), **10b** (0.019 mmol, 4.9 mg), and 4-(*N*,*N*-dimethylamino)pyridine (0.019 mmol, 2.3 mg) in CH_2Cl_2 (2 mL) were added MsCl (0.382 mmol, 29.6 μL) and Et_3N (0.573 mmol, 79.7 μL) at 0 °C. After 10 min, quenching with a saturated NH_4Cl solution, extraction with AcOEt three times, washing with brine, drying over Na_2SO_4, evaporation of the solvent and flash chromatography (hexane/AcOEt=1:2) afforded **15** (52.4 mg, 91%) in pure form. Colorless solid; mp 113–116 °C (hexane/AcOEt); $[\alpha]_D^{30}$ −102.3 (*c* 0.89, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J=1.5 Hz, 1H), 7.49 (dd, J=8.7, 1.7 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H), 5.31 (s, 1H), 4.95 (s, 1H), 3.54 (dt, J=14.0, 4.0 Hz, 1H), 3.08 (s, 3H), 2.84 (t, J=13.1 Hz, 1H), 2.46–2.31 (m, 2H), 2.29–2.11 (m, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 149.1, 137.4, 133.2, 124.4, 85.3, 76.7, 38.5, 35.6, 29.5, 24.8, 24.1 ppm; IR ($CHCl_3$) ν 2940, 1550, 1462 cm^{-1}; MS (EI^+) 335 (MH^+, 100). Anal. Calcd for $C_{12}H_{15}ClN_2O_5S$: C, 43.05; H, 4.52; N, 8.37. Found: C, 42.95; H, 4.51; N, 8.15.

4.3.9. (−)-Epibatidine. To a stirred solution of **15**

(0.0651 mmol, 21.8 mg) in THF (0.4 mL) were added AcOH (0.4 mL) and Zn (2.41 mmol, 158 mg) at room temperature. After 2 h, the mixture was filtrated through a pad of Celite (AcOEt as eluent). Washing with a saturated Na_2CO_3 solution and brine, drying over K_2CO_3, evaporation of the solvent afforded amine product. A solution of the amine product in $CHCl_3$ (3 mL) was heated at 60 °C. After 3 days, the reaction mixture was diluted with additional $CHCl_3$, then 10% aqueous K_2CO_3 was added. The mixture was extracted with $CHCl_3$. The combined extracts were dried over K_2CO_3, filtrated and evaporated. The residue was purified by preparative TLC ($CHCl_3$/MeOH/30% aqueous NH_3=20:1:0.1 as eluent) to afford (−)-epibatidine (11.5 mg, 85%). Colorless solid; mp 62–63 °C (hexane); $[\alpha]_D^{29}$ −6.00 (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J=2.4 Hz, 1H), 7.72 (dd, J=8.2, 2.4 Hz, 1H), 7.23 (d, J=8.2 Hz, 1H), 3.80 (t, J=4.0 Hz, 1H), 3.56 (d, J=2.4 Hz, 1H), 2.77 (dd, J=9.0, 4.7 Hz, 1H), 1.91 (dd, J=12.2, 8.9 Hz, 1H), 1.67–1.46 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.8, 141.1, 137.7, 123.9, 62.7, 56.4, 44.5, 40.3, 31.3, 30.1 ppm; IR ($CHCl_3$) ν 2969, 2876, 1584, 1565, 1459 cm^{-1}; MS (EI$^+$) 208 (M^+, 33), 69 (100); HRMS (EI$^+$) Calcd for $[C_{11}H_{13}ClN_2]^+$: 208.0768. Found: 208.0777.

Acknowledgements

This work was supported by grants from 21st Century COE Program 'Knowledge Information Infrastructure for Genome Science' and Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (KAKENHI/16390006).

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Enantioselective aza-Henry reaction using cinchona organocatalysts

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Received 5 July 2005; revised 9 September 2005; accepted 16 September 2005

Available online 19 October 2005

Abstract—The aza-Henry reaction of imines with nitromethane was promoted by cinchona alkaloids and modified cinchona bases to give optically active β-nitroamines. Various *N*-protected imines were examined as substrates. *N*-Boc, *N*-Cbz, and *N*-Fmoc protected imines gave the best results in terms of chemical yields and enantioselectivities. After a careful screening of a series of chiral bases, very good enantioselectivities up to 94% ee were obtained using a cinchona-based thiourea organocatalyst under the optimized reaction conditions.

1. Introduction

The aza-Henry reaction is a carbon–carbon bond-forming process, which allows a straightforward entry to a variety of nitrogen-containing chiral building blocks. Among them 1,2-diamines, a structural motif present in biologically active natural products, in medicinal chemistry, and as a core unit in chiral ligands for asymmetric catalysis, can be obtained by reduction of the nitro group in the β-nitroamine derivatives,[1] whereas α-amino carbonyl compounds can be generated by means of the Nef reaction.[2] As a result of the importance of this reaction, a considerable effort has been directed over the last years toward the development of the catalytic asymmetric version of the aza-Henry reaction.[3] Shibasaki et al. have described the enantioselective addition of nitroalkanes to *N*-phosphinoyl imines using chiral ytterbium,[4] and aluminum catalysts,[5] while Jørgensen et al. have reported the asymmetric copper-catalyzed addition to α-iminoesters.[6–8] Several drawbacks of the reactions catalyzed or promoted by metal salts may lie in the cost and the toxicity of the metal species. To face these problems, beyond these metal-catalyzed variants, the first reports of enantioselective organocatalytic aza-Henry reaction have recently appeared. Takemoto et al. have reported that the aza-Henry reaction of *N*-phosphinoyl imines with nitroalkanes can be promoted by chiral thiourea bearing an *N*,*N*-dimethylamino group leading with moderate enantioselectivities to β-nitroamine derivatives,[9] while Johnston et al. have developed a chiral bisamidine triflate salt that effects the enantio- and diastereoselective addition of nitroethane to a range of electron deficient *N*-Boc imines.[10] More recently Jacobsen using a new thiourea based bifunctional catalyst was able to promote the highly stereoselective addition of a range of nitroalkanes to aromatic *N*-Boc imines.[11]

In a recent paper, we described a new metal- and solvent-free procedure for the aza-Henry reaction organocatalyzed by a nitrogen-contaning superbase such as 1,1,3,3-tetramethyl guanidine (TMG).[12] Herein, we present an extensive investigation on the effectiveness of chiral nitrogen-containing bases as organocatalysts in promoting reactivity and asymmetric induction in the aza-Henry reaction of differently *N*-protected imines.

2. Results and discussion

The groups bound at nitrogen of imines are not fully innocent groups since besides protecting the C=N moiety they can greatly affect its stability and electrophilicity. Therefore, despite the considerable advances made in the field of the aza-Henry reaction there remain limitations to its general applicability. To tackle the goal of envisaging the optimized reaction conditions under which differently protected imines can undergo the aza-Henry reaction in the presence of chiral bases and to prepare the ground for the asymmetric version of this reaction, a range of possible benzaldehyde imine candidates **1a–f** were synthesized and screened (Scheme 1).

Keywords: Organocatalysis; Imines; Nitromethane; β-Nitroamines; Aza-Henry reaction; Cinchona alkaloids; Enantioselectivity.
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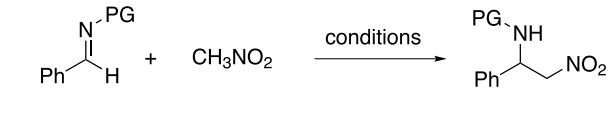
doi:10.1016/j.tet.2005.09.076



1a PG = Cbz **1b** PG = Boc
1c PG = Fmoc **1d** PG = DPP (Diphenylphosphinoyl)
1e PG = Ts **1f** PG = PMP (*p*-Methoxyphenyl)
1g PG = *t*-BuCO

Scheme 1.

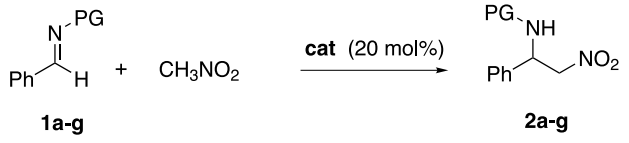
Inspired by previous work,[13] we focused at first on the use of chiral bases directly accessible from the chiral pool such as cinchona alkaloids, as organocatalysts for this reaction.[14]

The β-nitroamines **2a–g** were obtained (Table 1) in fairly good yields with moderate enantioselectivities from Cbz-, Boc-, and Fmoc- *N*-protected benzaldehyde imines **1a–c** in the presence of quinine (**QN**) (entries 1–4) and of quinidine (**QD**) (entries 10 and 11). In the case of the (diphenylphosphinoyl) DPP-, Ts-, and *t*-BuCO- benzaldehyde imines **1d**,**e**,**g** a drop of the ee was noticed (entries 5, 6, and 9) accompanied in the case of the former by a sizeable decrease in the chemical yield. Even more disappointing were the results with (*p*-methoxyphenyl) PMP imine **1f**, which gave even under forcing conditions (entry 7) poor conversion and no ee at all. However, by running the reaction in the presence of 20% TFA a significant improvement was observed in terms both of conversion and ee (entry 8). We speculated that the reaction on an electron rich imine can proceed efficiently only if the imine is activated by protonation with a Brønsted acid such as TFA.[15]

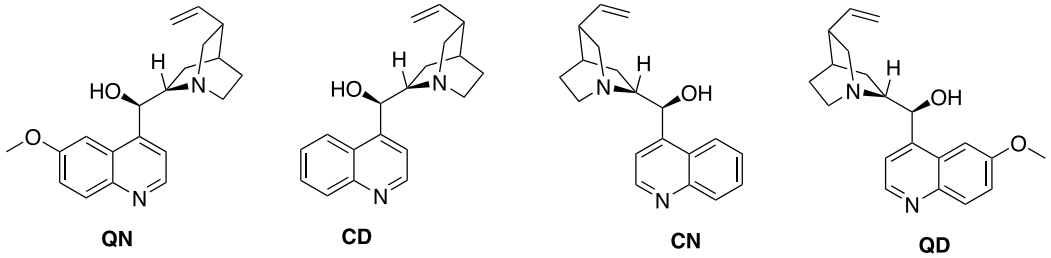
On changing the nature of the organocatalysts, cinchona alkaloids **CD** and **CN** not bearing any oxygen-based substituent at position 6′ in the quinoline ring were found to afford (entries 12 and 13) the desired adduct **2a** in poor yields and with enantioselectivities significantly lower than those bearing a 6′-methoxyquinoline moiety. Next, the influence of modifications on the natural cinchona bases reported in Figure 1 was studied using Cbz-, Boc-, and Fmoc- imines **1a–c**, which had shown the most promising results in the previous screening.

As shown in Table 2, unlike the catalytic efficiency shown by **QN** catalyst (entry 1), derivatives **II** and **V**, in which the OH of the quinine moiety has been protected via acetylation or carbamate formation, and derivative **III** with the alcoholic function replaced by a benzamido moiety, did not give rise to the formation of the desired adducts in significant yields (entries 2, 3, and 9). Neither the presence of a newly formed NH bond in **III** and **V** seemed to convey to these modified cinchona alkaloids any catalytic activity. Modest catalytic efficiency, accompanied by moderate enantioselectivity, was observed (entry 4) on the other hand in the case of the conformationally more rigid catalyst

Table 1. Results from the screening of various imines **1a–g** using unmodified cinchona alkaloids as catalysts[a]



1a-g **2a-g**



QN **CD** **CN** **QD**

Entry	Imine	PG	Adduct	Catalyst	Conversion (%)[b]	ee (%)[c]
1	**1a**	Cbz	**2a**	**QN**	>95	53
2	**1a**	Cbz	**2a**	**QN**	90	61[d]
3	**1b**	Boc	**2b**	**QN**	>95	51
4	**1c**	Fmoc	**2c**	**QN**	>95	48
5	**1d**	DPP	**2d**	**QN**	50	12
6	**1e**	Ts	**2e**	**QN**	>95	30
7	**1f**	PMP	**2f**	**QN**	10[e]	*rac*
8	**1f**	PMP	**2f**	**QN**	>95[e,f]	40
9	**1g**	*t*-BuCO	**2g**	**QN**	>95	27
10	**1c**	Fmoc	**2c**	**QD**	>95	52
11	**1a**	Cbz	**2a**	**QD**	80	55
12	**1a**	Cbz	**2a**	**CN**	15	25
13	**1a**	Cbz	**2a**	**CD**	15	40

[a] Unless noted, reactions were run at 20 °C, for 18 h in toluene (0.1 M).
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] Reaction performed in mesitylene as the solvent.
[e] Reaction performed in CH_3NO_2 (0.25 M).
[f] Reaction performed in the presence of TFA (20 mol%).

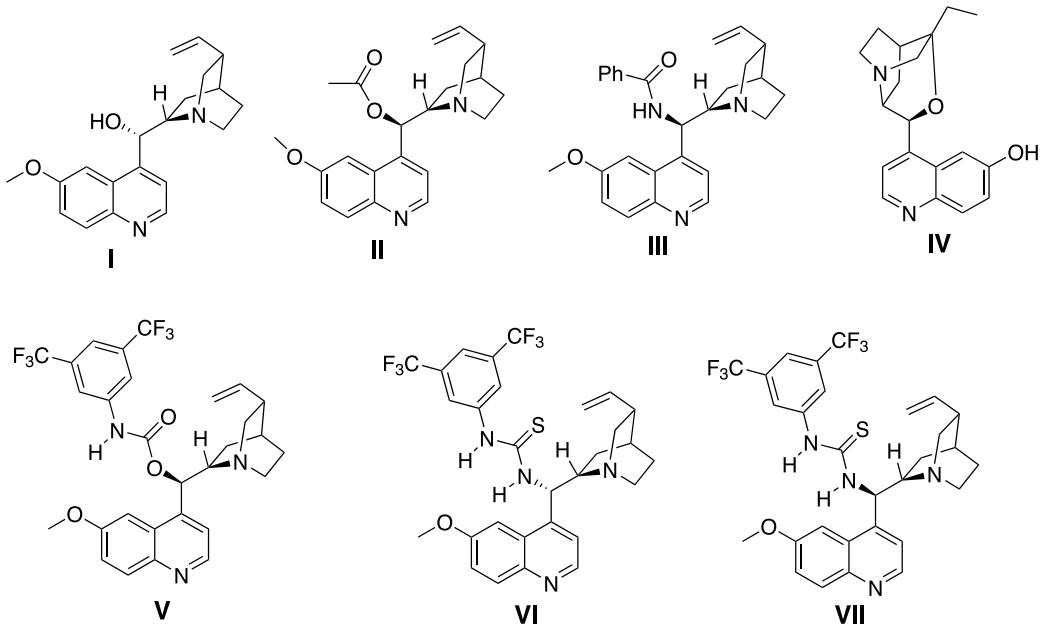


Figure 1. Modified cinchona bases screened for the aza-Henry reaction using imines **1a–c**.

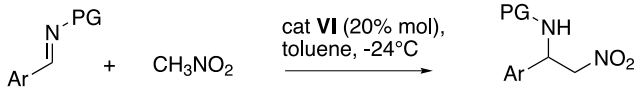
IV bearing a phenolic moiety, which could eventually provide a site for hydrogen bonding.[16] To explore the influence, in terms of catalytic efficiency and enantioselectivity, of the quinine-epiquinine change,[17] epiquinine **I** catalysed addition of nitromethane to the *N*-Boc protected imine **1b** was examined. Even though the conversion in the reaction was lower, the comparable enantioselectivities (compare entries 7 and 8) suggested that the proper conformation of the cinchona derivatives as such may not be crucial in the case for successful catalysis. Within the range of enantioselectivities observed, the best results were obtained with catalysts bearing methoxy and hydroxy functionalities. These findings prompted us to apply to the aza-Henry reaction under study the recently reported bifunctional cinchona-based catalysts **VI** and **VII** bearing a stronger Lewis acid thiourea moiety.[18] By running the reaction with quinine-derived catalyst **VI** under the standard conditions adducts **2a** and **2b** were obtained (entries 5 and 11) in satisfactory isolated yields and with ee's up to 76%, whereas also in line with the findings regarding the asymmetric addition of nitromethane to *trans*-chalcone,[18] organocatalyst **VII** with the natural configuration, derived from epiquinine turned out to be much less efficient (entry 10). Next, the influence of two experimental parameters (temperature and concentration) was evaluated using the most efficient catalyst **VI**. Very good levels of enantioselectivity were observed on lowering the temperature (entries 6, 11–13) and at −24 °C with an increase of the imine concentration to 0.2 M, adducts **2b** and **2c** were obtained (entries 15 and 16) with up to 90% ee. Adduct **2b** in Table 2 was determined to have the (*S*) configuration by comparison with the literature data.[10,11]

Table 2. Effect of modified cinchona alkaloid catalysts **I–VII** and optimisation of reaction conditions[a]

Entry	Imine	PG	Adduct	Catalyst	*T* (°C)	*t* (h)	Conversion (%)[b]	ee (%)[c]
1	**1a**	Cbz	**2a**	**QN**	20	18	>95	53
2	**1a**	Cbz	**2a**	**II**	20	120	<10	—
3	**1a**	Cbz	**2a**	**V**	20	120	<10	—
4	**1a**	Cbz	**2a**	**IV**	20	120	20	37
5	**1a**	Cbz	**2a**	**VI**	20	22	46[d]	61
6	**1a**	Cbz	**2a**	**VI**	−24	22	64[d]	84
7	**1b**	Boc	**2b**	**QN**	20	18	>95	51
8	**1b**	Boc	**2b**	**I**	20	18	45	56
9	**1b**	Boc	**2b**	**III**	20	120	<10	—
10	**1b**	Boc	**2b**	**VII**	20	18	30	19
11	**1b**	Boc	**2b**	**VI**	20	18	60[d]	76
12	**1b**	Boc	**2b**	**VI**	0	20	58[d]	81
13	**1b**	Boc	**2b**	**VI**	−24	20	52[d]	86
14	**1b**	Boc	**2b**	**VI**	−24	23	63[d,e]	85
15	**1b**	Boc	**2b**	**VI**	−24	18	72[d,f]	88
16	**1c**	Fmoc	**2c**	**VI**	−24	43	60[d,f]	90

[a] Unless noted, reactions were run 0.1 M in toluene.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] Yield of product isolated after silica gel chromatography.
[e] Reaction (0.05 M).
[f] Reaction (0.2 M).

Table 3. Scope of the aza-Henry reaction using imines **1h–o** and catalyst **VI**



1h-o **2h-o**

Entry	Ar	PG	Imine	Adduct	*t* (h)	Yield (%)[a]	ee (%)[b]
1	1-Napht	Boc	**1h**	**2h**	20	87	88
2	2-Napht	Boc	**1i**	**2i**	23	95	85
3	2-Napht	Boc	**1i**	**2i**	38	82	94[c]
4	4-ClC_6H_4	Boc	**1j**	**2j**	68	77	94
5	4-ClC_6H_4	Cbz	**1k**	**2k**	45	58	90
6	2-BrC_6H_4	Boc	**1l**	**2l**	24	66	80
7	2-BrC_6H_4	Boc	**1l**	**2l**	72	82	88[c]
8	4-$MeOC_6H_4$	Boc	**1m**	**2m**	45	65	82
9	2-Thienyl	Boc	**1n**	**2n**	40	50	82
10	2-Furyl	Boc	**1o**	**2o**	40	70	44
11	2-Furyl	Boc	**1o**	**2o**	48	58	63[c]

[a] Yield of product isolated after silica gel chromatography.
[b] Determined by chiral stationary phase HPLC.
[c] Reaction performed at −40 °C.

To establish the generality of this reaction in substrate scope we finally examined the aza-Henry reaction with representative *N*-Boc imines under catalysis by **VI** and the results are reported in Table 3. The reaction appears tolerant with respect to the nature of the imine and the benefits of catalyst **VI** extend over a wide range of substrates. The desired adducts were isolated in satisfactory to good yields and synthetically useful levels of enantioselectivity, with 1- and 2-naphthaldehyde-derived imines **1h–i** (entries 1–3) and with benzaldimine derivatives **1j–m** bearing both electron donating and electron withdrawing substituents (entries 4–8). The good results obtained using the Cbz-protected imine **1k** further confirm the tolerance of this catalytic reaction to different *N*-acyl protecting groups (entry 5). Among the aromatic heterocyclic aldimines, the 2-thiophenecarboxyaldehyde derived imine **1n** (entry 9) gave better results with respect to the oxygenated analogue **1o** (entry 10 and 11).

Any insight about the exact nature of the stereochemical-determining catalyst-substrate complex would be premature at this time and different mechanistic scenarios can be considered for this catalytic transformation. However, it is clear from these experiments that cinchona-bases herein studied and particularly thiourea derivatives, which are known to bind to and modulate the reactivity of nitronate anions,[9,18] are likely to act as bifunctional organocatalysts, but the role in activating the nitroalkane or in the dual activation of both reaction partners still remains obscure.

3. Conclusion

In summary, we have developed a highly enantioselective organocatalyzed aza-Henry reaction using nitromethane and a range of aromatic and heteroaromatic differently protected imines. This new system will nicely complement the very few examples of organocatalyzed aza-Henry reactions reported to date. Further investigations into the mechanism and use of new organocatalysts for this reaction are underway and will be reported in due course.

4. Experimental

4.1. General methods

All reactions were carried out in test tubes. ^1H and ^{13}C NMR spectra were measured on a Varian AS 400 spectrometer running at 400 and 100 MHz, respectively, in $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^1H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Flash column chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 22 °C. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H). Melting points are uncorrected. Imines **1a**,**c**,**k**,[19] **1b**,**h–j**,**l–o**,[20] as well as catalyst **VI**[18] were prepared following literature procedures.

4.2. Optimized general procedure for the catalytic enantioselective aza-Henry reaction

In a test tube, to a cooled (−24 °C) solution of the imine **1** (0.1 mmol) and catalyst **VI** (11.9 mg, 0.02 mmol) in toluene (500 μL), nitromethane (27 μL, 0.5 mmol) was added in one portion. The test tube was placed in a freezer at −24 °C for the time reported in Tables 2 and 3, then the products **2** were obtained by FC on silica gel (CH_2Cl_2).

4.2.1. 2-Nitro-1-phenylethyl carbamic acid benzyl ester (2a). Following the general procedure, compound **2a** was obtained as a yellow solid in 64% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=80:20, flow rate 0.75 mL/min, τ_{major}=17.1 min; τ_{minor}=24.9 min). R_f 0.41 (*n*-hexane/EtOAc, 7:3); mp 67–70 °C; ^1H NMR δ 4.65 (dd, J=4.6, 12.6 Hz, 1H), 4.72–4.88 (br s, 1H), 5.04 (s, 2H), 5.33–5.42 (br s, 1H), 5.46–5.57 (br s, 1H), 7.17–7.35 (m, 10H); ^{13}C NMR δ 53.2, 67.4, 78.6, 126.3, 128.2, 128.4,

128.6, 128.9, 129.2, 135.8, 136.4, 155.4; ESIMS *m/z* 323 [M+Na$^+$]; $[\alpha]_D^{22}$ +5 (*c* 0.348, $CHCl_3$), 84% ee.

4.2.2. (*S*)-2-Nitro-1-phenylethyl carbamic acid *t*-butyl ester (2b). Following the general procedure, compound **2b** was obtained as a white solid in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=95:5, flow rate 0.75 mL/min, τ_{major}=36.0 min; τ_{minor}=38.2 min). $[\alpha]_D^{22}$ +14 (*c* 0.578, $CHCl_3$), 88% ee. The ^{1}H and ^{13}C NMR spectra and mp are consistent with values previously reported in the literature.[10]

4.2.3. (9-*H*-Fluoren-9-yl)methyl 2-nitro-1-phenylethyl-carbamate (2c). Following the general procedure, compound **2c** was obtained as a white solid in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=80:20, flow rate 0.75 mL/min, τ_{major}=23.7 min; τ_{minor}=42.3 min). R_f 0.51 (*n*-hexane/EtOAc, 7:3); mp 148–150 °C; ^{1}H NMR δ 4.20 (t, *J*=6.6 Hz, 1H), 4.38–4.62 (br s, 2H), 4.62–4.94 (br s, 2H), 5.36–5.60 (br s, 2H), 7.22–7.64 (m, 11H), 7.66 (d, *J*=7.6 Hz, 2H); ^{13}C NMR δ 47.1, 53.1, 67.1, 78.4, 120.0, 124.9, 126.3, 127.1, 127.8, 128.8, 129.3, 136.4, 141.3, 143.6, 155.4; ESIMS *m/z* 411 [M+Na$^+$]; $[\alpha]_D^{22}$ +11 (*c* 0.675, $CHCl_3$), 90% ee.

4.2.4. 1-(1-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (2h). Following the general procedure, compound **2h** was obtained as a white solid in 87% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=17.0 min; τ_{minor}=25.7 min). R_f 0.64 (*n*-hexane/EtOAc, 7:3); mp 174–177 °C; ^{1}H NMR δ 1.43 (s, 9H), 4.80–4.98 (br s, 2H), 5.24–5,38 (br s, 1H), 6.22–6.34 (br s, 1H), 7.44–7.48 (m, 2H), 7.52–7.58 (m, 1H), 7.60–7.64 (m, 1H), 7.84–7.86 (m, 1H), 7.88–7.92 (m, 1H), 8.11–8.13 (m, 1H); ^{13}C NMR δ 28.2, 49.2, 78.2, 80.8, 122.2, 123,2, 125.2, 126.3, 127.3, 129.2, 129.5, 130.3, 132.6, 134.1, 154.7; ESIMS *m/z* 339 [M+Na$^+$]; $[\alpha]_D^{22}$ +7 (*c* 0.498, $CHCl_3$), 88% ee.

4.2.5. 1-(2-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (2i). Following the general procedure, performing the reaction at −40 °C, compound **2i** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=17.8 min; τ_{minor}=21.5 min). R_f 0.79 (*n*-hexane/EtOAc, 7:3); mp 144–146 °C; ^{1}H NMR δ 1.45 (s, 9H), 4.80 (dd, *J*=5.5, 12.6 Hz, 1H), 4.88–5.00 (br s, 1H), 5.34–5.46 (br s, 1H), 5.50–5.60 (br s, 1H), 7.40 (dd, *J*=1.8, 8.5 Hz, 1H), 7.48–7.54 (m, 2H), 7.76 (m, 1H), 7.82–7.88 (m, 3H); ^{13}C NMR δ 28.3, 53.0, 78.8, 80.8, 123.7, 125.6, 126.7, 126.7, 127.7, 128.0, 129.2, 133.2, 133.2, 134.2, 154.8; ESIMS *m/z* 339 [M+ Na$^+$]; $[\alpha]_D^{22}$ +38 (*c* 0.505, $CHCl_3$), 94% ee.

4.2.6. 1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2j). Following the general procedure, compound **2j** was obtained as a white solid in 77% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=12.8 min; τ_{minor}=16.1 min). R_f 0.68 (*n*-hexane/EtOAc, 7:3); mp 128–131 °C; ^{1}H NMR δ 1.44 (s, 9H), 4.68 (dd, *J*=5.0, 12.6 Hz, 1H), 4.76–4.9 (br s, 1H), 5.28–5.40 (br s, 2H), 7.23–7.27 (m, 2H), 7.34–7.37 (m, 2H); ^{13}C NMR δ 28.2, 52.2, 78.6, 80.9, 127.7, 129.4, 134.6, 135.4, 154.6; ESIMS *m/z* 323 [M+Na$^+$]; $[\alpha]_D^{22}$ +20 (*c* 0.790, $CHCl_3$), 94% ee.

4.2.7. 1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid benzyl ester (2k). Following the general procedure, compound **2k** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 0.75 mL/min, τ_{major}=36.7 min; τ_{minor}=59.0 min). R_f 0.45 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 4.68 (dd, *J*=5.1, 12.7 Hz, 1H), 4.76–4.89 (br s, 1H), 5.10 (s, 2H), 5.36–5.45 (br s, 1H), 5.63–5.71 (br s, 1H), 7.20–7.41 (m, 9H); ^{13}C NMR δ 52.6, 67.5, 78.3, 127.7, 128.4, 128.6, 128.9, 129.4, 129.9, 134.8, 135.7, 155.3; ESIMS *m/z* 357 [M+Na$^+$]; $[\alpha]_D^{22}$ +8 (*c* 0.160, $CHCl_3$), 90% ee.

4.2.8. 1-(*o*-Bromophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2l). Following the general procedure, performing the reaction at −40 °C, compound **2l** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=18.4 min; τ_{minor}=12.9 min). R_f 0.60 (*n*-hexane/EtOAc, 7:3); mp 130–133 °C; ^{1}H NMR δ 1.43 (s, 9H), 4.72–4.92 (br s, 2H), 5.64–5.76 (br s, 2H), 7.20 (dt, J_d=8.0 Hz, J_t=4.5 1H), 7.34 (d, *J*=4.2 Hz, 2H), 7.59 (dt, J_d=7.9 Hz, J_t=0.9 Hz, 1H); ^{13}C NMR δ 28.2, 52.4, 77.5, 80.8, 122.7, 127.9, 128.1, 130.1, 133.6, 135.9, 154.5; ESIMS *m/z* 367 [M+Na$^+$]; $[\alpha]_D^{22}$ −8 (*c* 0.402, $CHCl_3$), 88% ee.

4.2.9. 1-(*p*-Methoxyphenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2m). Following the general procedure, compound **2m** was obtained as a white solid in 65% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=98:2, flow rate 1 mL/min, τ_{major}=91.6 min; τ_{minor}=97.5 min). R_f 0.53 (*n*-hexane/EtOAc, 7:3); mp 141–144 °C; ^{1}H NMR δ 1.44 (s, 9H), 3.80 (s, 3H), 4.66 (dd, *J*=5.9, 12.4 Hz, 1H), 4.75–4.9 (br s, 1H), 5.14–5.24 (br s, 1H), 5.25–5.35 (br s, 1H), 6.89 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ 28.2, 52.4, 55.3, 78.9, 80.6, 114.5, 127.6, 128.8, 154.7, 159.8; ESIMS *m/z* 319 [M+Na$^+$]; $[\alpha]_D^{22}$ +28 (*c* 0.693, $CHCl_3$), 82% ee.

4.2.10. 2-Nitro-1-(thiophen-2-yl)ethyl carbamic acid *t*-butyl ester (2n). Following the general procedure, compound **2n** was obtained as a yellow oil in 50% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=98:2, flow rate 1 mL/min, τ_{major}=54.0 min; τ_{minor}=57.4 min). R_f 0.52 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.75 (dd, *J*=5.6, 12.9 Hz, 1H), 4.84–4.98 (br s, 1H), 5.22–5.36 (br s, 1H), 5.56–5.70 (br s, 1H), 6.97–7.02 (m, 2H), 7.27–7.29 (m, 1H); ^{13}C NMR δ 28.2, 48.9, 77.3, 78.6, 81.0, 125.7, 127.3, 140.0, 154.4; ESIMS *m/z* 295 [M+Na$^+$]; $[\alpha]_D^{22}$ +12 (*c* 0.445, $CHCl_3$), 82% ee.

4.2.11. 1-(Furan-2-yl)-2-nitro-ethyl carbamic acid *t*-butyl ester (2o). Following the general procedure,

performing the reaction at −40 °C, compound **2o** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=97:3, flow rate 0.75 mL/min, τ_{major}=33.8 min; τ_{minor}=31.2 min). R_f 0.67 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.72 (dd, J=6.0, 12.9 Hz, 1H), 4.84 (dd, J=6.0, 12.9 Hz, 1H), 5.08–5.26 (br s, 1H), 5.38–5.50 (br s, 1H), 6.28–6.36 (m, 2H), 7.34–7.40 (m, 1H); ^{13}C NMR δ 28.2, 47.2, 80.9, 88.1, 107.8, 110.7, 142.9, 149.4, 154.6; ESIMS *m/z* 279 [M+Na$^+$]; $[\alpha]_D^{22}$ +11 (*c* 0.305, $CHCl_3$), 63% ee.

Acknowledgements

We gratefully acknowledge financial support by the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni, 2003', by the RTN project 'Design, Analysis and Computation for Catalytic Organic Reactions', contract HPRN-CT-2001-00172, and by the ex-60% MURST-funds 2004. R.P.H. thanks the European Union for a post-doctoral fellowship.

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β-Isocupreidine–hexafluoroisopropyl acrylate method for asymmetric Baylis–Hillman reactions

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Received 30 August 2005; revised 16 September 2005; accepted 16 September 2005

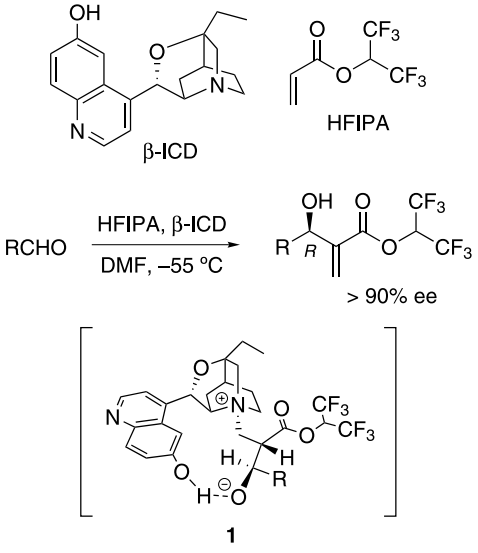
Available online 10 October 2005

Abstract—Key features of the β-isocupreidine (β-ICD)-catalyzed asymmetric Baylis–Hillman reaction of aldehydes with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) are presented. In addition, an improved method using azeotropically dried β-ICD is described.

1. Introduction

The Morita–Baylis–Hillman reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a Lewis base and the promising utility of the multifunctional products. However, the major problems associated with this reaction are its slow reaction rate and difficulty in realization of a high level of asymmetric induction. This situation has brought about significant progress in rate acceleration as well as asymmetric induction based on various imaginative ideas.[1] Recently, we have developed a highly enantioselective asymmetric Baylis–Hillman reaction of aldehydes[2] as well as imines[3] by use of β-isocupreidine (β-ICD)[4,5] as a chiral Lewis base catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene. In addition, we have successfully demonstrated the synthetic utility of this reaction via syntheses of biologically intriguing natural products.[6] This β-ICD–HFIPA method has remarkable advantages in terms of the high enantioselectivity, the broad applicability, and the availability of both β-ICD and HFIPA. We speculate that hydrogen bonding between the oxy anion and the phenolic OH should play the crucial role during the enantio-controlling event as depicted in **1**.[2]

For the purpose of attaining more mechanistic information about the β-ICD–HFIPA method and seeking a better reaction system, we have investigated asymmetric Baylis–Hillman reactions using various congeners of β-ICD[7] as well as a panel of fluorine-containing acrylates (Scheme 1).



Scheme 1. β-ICD–HFIPA method.

2. Results and discussion

2.1. Preparation of the β-ICD-congeners

In order to investigate the structure-catalytic ability relationship of β-ICD, its seven congeners **2**–**8**[7] were prepared from quinidine (Scheme 2). Hoffmann et al. reported[7b] that treatment of quinidine with 3 equiv of KBr in 85% H_3PO_4 at 100 °C for 3 days produced a mixture of tricyclic ethers **2**, **3**, and **6**. We found that when this reaction

Keywords: β-Isocupreidine; 1,1,1,3,3,3-Hexafluoroisopropyl acrylate; Organic catalysis.
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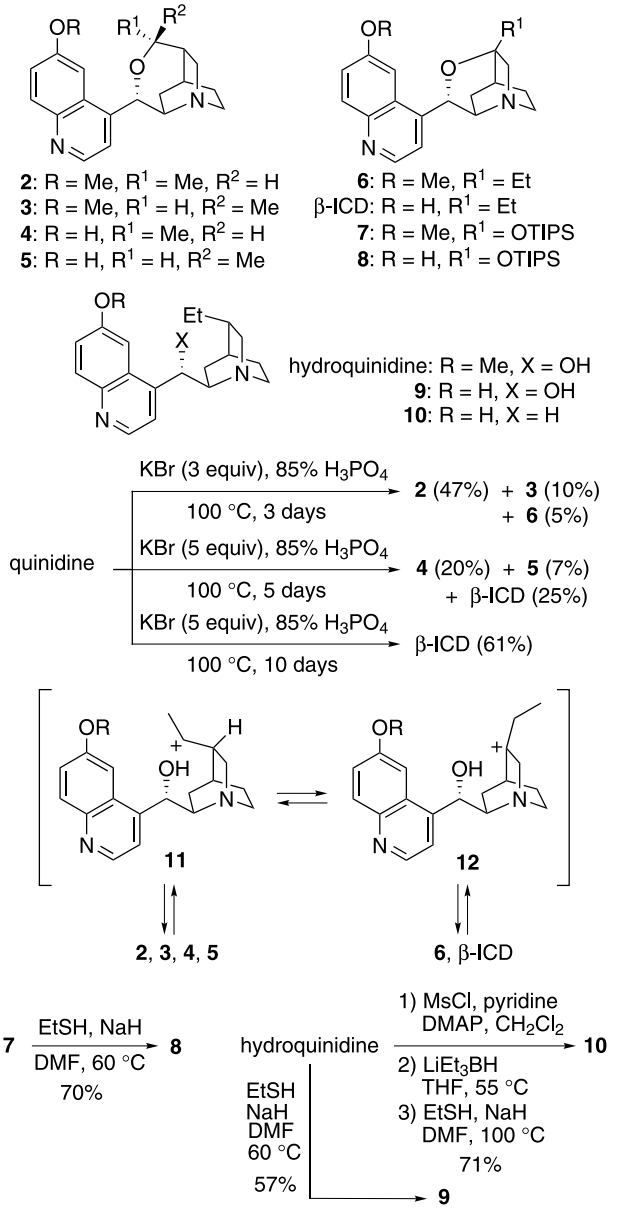
doi:10.1016/j.tet.2005.09.072

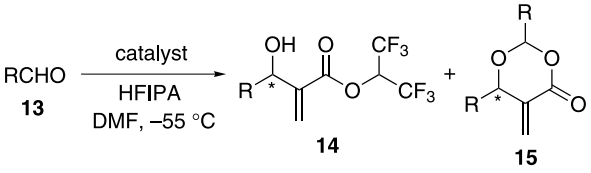


Scheme 2. Preparation of β-ICD-congeners.

was conducted using the increased amount of KBr (5 equiv) for longer reaction time (10 days), demethylation of the methoxy group also occurred together with cycloisomerization of quinidine to give **4**, **5**, and β-ICD in 20, 7, and 25% yields, respectively. In addition, it was gratifyingly found that, under the harsher conditions (KBr (10 equiv), 10 days), β-ICD was directly obtained from quinidine in 61% yield through the equilibration involving **11** and **12**. TIPS ether **8** was prepared by demethylation[8] of the known compound **7**[7b] available from quinidine. Compounds **9** and **10**[9] were also prepared from hydroquinidine.

2.2. Catalytic ability of the β-ICD-congeners

To evaluate the catalytic ability of the β-ICD-congeners, we examined the reaction of *p*-nitrobenzaldehyde with HFIPA using 0.1 equiv of compounds **2**–**10** in DMF at −55 °C (Scheme 3, Table 1). Interestingly, compounds **4**,**5**, and **8** exhibited similar catalytic ability to that of β-ICD (entries 1–4), while compounds **2**, **3**, **6**, **7**, **9**, and **10** were found to be very poor catalysts (entries 9–14). Importantly, the results listed in entries 4–8 indicate that compound **8** is also a useful catalyst for asymmetric Baylis–Hillman reactions of aromatic aldehydes.



Scheme 3. Chiral amine-catalyzed Baylis–Hillman reaction.

Table 1. Chiral amine-catalyzed reaction of aldehydes with HFIPA[a]

Entry	Aldehyde	Catalyst	Time (h)	Yield (%),[b] Config (% ee)[c,d]	
				14	**15**[e]
1	**13a**	β-ICD	1	58, *R* (91)	11, *R* (4)
2	**13a**	**4**	1	59, *R* (89)	19, *R* (38)
3	**13a**	**5**	1	51, *R* (89)	18, *R* (26)
4	**13a**	**8**	7	41, *R* (93)	20, *R* (51)
5	**13b**	**8**	24	68, *R* (98)	0
6	**13c**	**8**	28	71, *R* (95)[f]	0
7	**13g**	**8**	61	25, *R* (100)	20, *R* (17)
8	**13h**	**8**	42	15, *R* (92)	21, *S* (61)
9[g]	**13a**	**2**	6	18, nd[h]	29, *R* (45)
10[g]	**13a**	**3**	6	24, *R* (36)	32, *R* (32)
11[g]	**13a**	**6**	1	74, *R* (10)	7, nd[h]
12	**13a**	**7**	6	2, *R* (3)	9, *R* (11)
13	**13a**	**9**	3	0	26, *R* (4)
14	**13a**	**10**	3	0	27, *R* (2)

[a] Reactions were carried out at −55 °C in DMF (1 M) using **13** (1 equiv), HFIPA (1.3 equiv), and catalyst (0.1 equiv), unless otherwise stated.
[b] Isolated yield.
[c] Determined by comparison of the specific rotation of the corresponding methyl ester with that of the authentic sample obtained by kinetic resolution under Sharpless asymmetric epoxidation conditions.
[d] Determined by HPLC analysis using a chiral column.
[e] *Cis*:*trans*; **15a**: 99:1, **15g**: 70:30, **15h**: 90:10.
[f] Determined by ^{1}H NMR analysis of the *R*- and *S*- MTPA derivatives of the corresponding methyl ester, unless otherwise stated.
[g] HFIPA (3 equiv) was used.
[h] Not determined.

These results suggest that both the rigid tricylic structure and the phenolic OH are indispensable for obtaining a high degree of asymmetric induction as well as the remarkable rate acceleration. As seen in β-ICD,[2] such a cage-like structure is responsible for rate enhancement because it

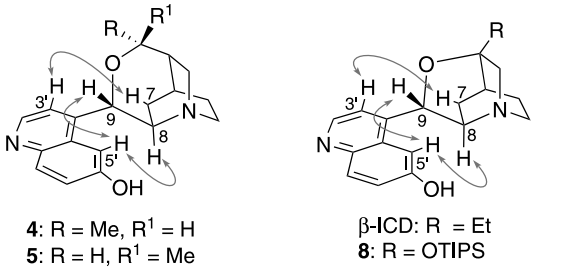


Figure 1. Significant NOE observed in NOESY spectra in DMF-d_7.

renders the quinuclidine moiety more nucleophilic by relieving steric congestion arising from C8–C9 bond rotation. In addition, the tricyclic structure makes the nucleophilic nitrogen face to the phenolic OH as indicated by the NOESY spectra (Fig. 1), so that the oxy anion intermediate stabilized by hydrogen bonding becomes operative resulting in high enantioselectivity as depicted in **1**.[2]

2.3. Improved β-ICD–HFIPA method

During ^{1}H NMR tracing experiments of a 1:1 mixture of β-ICD and HFIPA in DMF-d_7 at −40 °C, we incidentally found that HFIPA was partially hydrolyzed to produce 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and acrylic acid. The employed β-ICD was prepared from quinidine (Scheme 2) and purified by silica gel chromatography using 10% methanol–chloroform as the eluent followed by recrystallization from MeOH–H_2O. The combustion elemental analysis and X-ray analysis[10] of β-ICD thus obtained suggested the molecular formula to be $C_{19}H_{22}N_2O_2\cdot MeOH\cdot H_2O$. We therefore, concluded that the water bound to β-ICD caused the unexpected partial hydrolysis of HFIPA. This finding allowed us to come up with azeotropic removal of the water of β-ICD by repeating evaporation of its THF solution prior to use.

To our surprise, the azeotropically dried β-ICD showed remarkable catalytic activity, in particular, for aromatic aldehydes apart from the very reactive *p*-nitrobenzaldehyde (Scheme 3, Table 2). Thus, benzaldehyde was converted into **14b** in 97% ee in 75% yield, which was previously obtained as 95% ee in 57% yield using the catalyst without azeotropic operation[2] (entries 3, 4). The drying effect was also demonstrated by the reactions of cinnamaldehyde and 2-naphthylaldehyde, which gave the corresponding products in 64% (94% ee) and 82% (97% ee) yields, respectively (entries 5, 6, 9). In addition, even less reactive *p*-methoxybenzaldehyde and 1-naphthylaldehyde were converted to the corresponding adducts with excellent enantioselectivity although the yields were still unsatisfactory (entries 7, 8). These reactions failed under the original conditions using the undried β-ICD. In the case of aliphatic aldehydes, the use of the dried β-ICD exerted little effect on yield and enantioselectivity although the reaction rate increased (entries 10–13). It is important to note that this improved procedure using the dried β-ICD did not work at all for pivalaldehyde (entry 14), thus defining the steric limitation of this method.

Table 2. Improved β-ICD–HFIPA method[a]

Entry	Aldehyde	Catalyst[b]	Time (h)	Yield (%),[c] Config (% ee)[d]	
				14	**15**[e]
1	**13a**	A	1	58, *R* (91)	11, *R* (4)
2	**13a**	B	1.5	57, *R* (95)	17, *R* (49)
3	**13b**	A	48	57, *R* (95)	0
4	**13b**	B	48	75, *R* (97)	0
5[f]	**13c**	A	72	24, *R* (92)	0
6[f]	**13c**	B	4	64, *R* (94)	0
7	**13d**	B	72	27, *R* (95)	0
8	**13e**	B	120	23, *R* (97)	0
9	**13f**	B	58	82, *R* (97)	0
10	**13g**	A	65	21, *R* (100)	29, *R* (53)
11	**13g**	B	17	38, *R* (98)	21, *Racemate*
12	**13h**	A	72	31, *R* (97)	23, *S* (76)
13	**13h**	B	19	36, *R* (99)	22, *S* (65)
14	**13i**	B	72	0	0

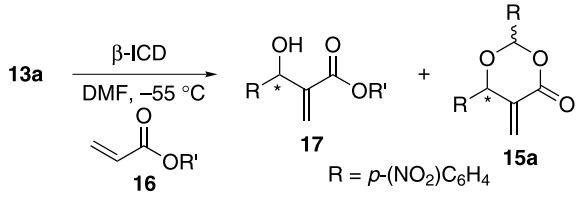
[a] All reactions were carried out at −55 °C in DMF (1 M) using **13** (1 equiv), HFIPA (1.3 equiv), and catalyst (0.1 equiv).
[b] A: undried β-ICD, B: dried β-ICD.
[c] Isolated yield.
[d] Determined in the same manner as noted in Table 1.
[e] *Cis*:*trans*; **15a**: 99:1, **15g**: 70:30, **15h**: 90:10.
[f] Catalyst (0.2 equiv) was used.

The enhanced catalytic activity of the dried β-ICD is ascribed to the prevention of the partial hydrolysis of HFIPA giving two acidic products, acrylic acid (pK_a 4.3[11]) and HFIP (pK_a 9.3[12]). In fact, addition of 10 mol% of acrylic acid completely inhibited the β-ICD-catalyzed reaction of 3-methylbutanal with HFIPA, while HFIP did not affect the reaction significantly. In view of the pK_a value of the phenolic OH of 6-hydroxy quinoline (pK_a 9.3[13]), it is reasonable that HFIP is less influential against β-ICD. It is assumed that, in the case of the less reactive aromatic aldehydes apart from *p*-nitrobenzaldehyde, the reaction rate is comparable with that of hydrolysis of HFIPA and therefore, the reaction is retarded by the generated acrylic acid, which attenuates the catalytic activity of β-ICD by protonation of the nucleophilic nitrogen. On the other hand, *p*-nitrobenzaldehyde reacts with HFIPA so rapidly that the reaction cannot be influenced by moisture contents of β-ICD. It was observed that the procedure using the dried β-ICD is markedly more effective than the previous one for aliphatic aldehydes having moderate reactivity in terms of rate acceleration.

2.4. HFIPA and its related fluorine-containing acrylates as an activated alkene

Table 3 summarizes β-ICD-catalyzed reaction of *p*-nitrobenzaldehyde with a panel of commercially available

Table 3. β-ICD-catalyzed reaction of *p*-nitrobenzaldehyde with fluorine-containing acrylates[a]



a: R' = CH_3, **b**, R' = CH_2CF_3, **c**: R' = $CH_2CF_2CF_3$
d: R' = $CH_2CF_2CF_2CF_3$

Entry	Acrylate	Time (h)	Yield (%),[b] Config (% ee)[c]	
			Ester	**15a**[d]
1[e]	**16a**	36	**17a**: 69, *S* (8)	0
2	**16b**	72	**17b**: 43, *S* (3)	6, *S* (6)
3	**16c**	72	**17c**: 50, *S* (2)	8, *S* (4)
4	**16d**	72	**17d**: 53, (0)	4, *R* (4)
5	HFIPA	1	**14a**: 58, *R* (91)	11, *R* (4)

[a] Reactions were carried out at −55 °C in DMF (0.5 M) using **13a** (1 equiv), acrylate (1.3 equiv), and β-ICD (0.1 equiv).
[b] Isolated yield.
[c] Determined in the same manner as noted in Table 1.
[d] *Cis*:*trans*; **15a**: 99: 1.
[e] The reaction was conducted at 20 °C.

fluorine-containing acrylates **16b–d** and HFIPA as well as methyl acrylate. It was observed that, compared with methyl acrylate, all fluorine-containing acrylates brought about remarkable rate acceleration due to the high electron-withdrawing nature of fluorine atom. It should be stressed that HFIPA having a branched alkoxy group exerts the striking effect both on rate acceleration and enantioselectivity. Other fluorine-containing acrylates **16b–d** having a linear alkoxy group did not induce any appreciable level of enantioselectivity.

3. Summary

In the present work, we proved that both the cage-like tricyclic structure and the phenolic OH of β-ICD as well as the branched structure of HFIPA are necessary for obtaining a high level of asymmetric induction as well as rate acceleration. This fact implies that intermediate **1** stabilized by hydrogen bonding would be responsible for the highly enantioselective production of *R* enriched adducts. In addition, we demonstrated that compound **8** is also able to serve as a chiral catalyst for asymmetric Baylis–Hillman reactions, suggesting that the C3 substituent on the quinuclidine ring exerts little effect on the catalytic ability. It should be highlighted that the azeotropically dried β-ICD was found to display remarkable catalytic ability. By this improved β-ICD–HFIPA method, the aromatic aldehydes except very reactive *p*-nitrobenzaldehyde can be converted into the corresponding Baylis–Hillman adducts in >94%ee without concomitant formation of undesired dioxanones.

4. Experimental

4.1. General

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. All extracts were dried over K_2CO_3 and concentrated by rotary evaporation below 30 °C at ca. 25 Torr unless otherwise noted. Thin-layer chromatography was performed using Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230–400 mesh ASTM, Merk). Commercial reagents and solvents were used as supplied with the following exceptions. Anhydrous tetrahydrofuran (THF) (stabilizer free) was purchased from Kanto Chemical Co., Inc. Dichloromethane (CH_2Cl_2), triethylamine, and *N*,*N*-dimethyformamide (DMF) were distilled from CaH_2. All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. Infrared spectra were measured on a JASCO FT/IR-230 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300, JEOL JNM-AL 400, or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in hertz. TMS was defined as 0 ppm for ^{1}H NMR spectra and the center of the triplet of $CDCl_3$ was also defined as 77.10 ppm for ^{13}C NMR spectra. HRMS (EI) spectra were measured on a JEOL JMS-DX303 or a JEOL JMS-700N.

4.2. Reaction of quinidine with KBr–H_3PO_4

Method A. Quinidine (2.0 g, 6.16 mmol) was added portionwise to a solution of KBr (2.20 g, 18.5 mmol) in 85% H_3PO_4 (30 mL) at room temperature, and the mixture was stirred at 100 °C for 3 days. After being cooled to room temperature, the mixture was added dropwise to an ice-cooled 25% KOH (200 mL). The pH was adjusted to ca. 8 with 25% NH_4OH and extracted with $CHCl_3$. The organic layer was washed with brine, dried over K_2CO_3, and chromatographed (SiO_2, $CHCl_3$/MeOH=9:1–4:1) to give **2** (938 mg, 47%), **3** (199 mg, 10%), and **6** (100 mg, 5%).

Method B. A mixture of quinidine (660 mg, 2.00 mmol), KBr (1.20 g, 10.0 mmol) in 85% H_3PO_4 (10 mL) was heated at 100 °C for 5 days and worked up in the same manner as described in Method A. Purification of the crude material by column chromatography (SiO_2, $CHCl_3$/MeOH=9:1–4:1) gave **4** (124 mg, 20%), **5** (43 mg, 7%), and β-ICD (155 mg, 25%).

Method C. A mixture of quinidine (10.0 g, 30.8 mmol), KBr (36.7 g, 308 mmol) in 85% H_3PO_4 (150 mL) was heated at 100 °C for 10 days and worked up in the same manner as described in Method A. Purification of the crude material by column chromatography (SiO_2, $CHCl_3$/MeOH=9:1–4:1) gave β-ICD (5.85 g, 61%) as a pale yellow amorphous solid, which was spectroscopically pure. β-ICD thus obtained was dissolved in NH_3–MeOH and filtered to remove insoluble precipitates. Concentration of the filtrate gave β-ICD as a crystalline solid, which was recrystallized from MeOH–H_2O to afford colorless needles.

4.2.1. (8*R*,9*S*,10*R*)-10,11-dihydro-9,10-epoxy-6′-methoxycinchonane (2). A pale yellow amorphous solid; $[\alpha]_D^{18}$ +79.2 (*c* 1.06, MeOH); FT-IR (neat) 3369, 2937, 2562, 2206, 1621, 1510, 1232, 1103, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J*=4.5 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.62 (dd, *J*=4.5, 1.0 Hz, 1H), 7.36 (dd, *J*=9.0, 2.5 Hz, 1H), 7.32 (d, *J*=3.0 Hz, 1H), 5.95 (s, 1H), 4.26 (dq, *J*=1.5, 6.5 Hz, 1H), 4.03 (s, 3H), 3.77 (d, *J*=14.0 Hz, 1H), 3.49 (d, *J*=9.0 Hz, 1H), 3.23–3.19 (m, 2H), 2.86–2.82 (m, 1H), 2.45 (ddd, *J*=13.0, 6.0, 2.0 Hz, 1H), 2.38 (ddd, *J*=5.0, 5.0, 5.0 Hz, 1H), 1.85 (dd, *J*=8.0, 5.5 Hz, 1H), 1.74–1.65 (m, 2H), 1.48 (d, *J*=6.5 Hz, 3H), 1.27 (dd, *J*=12.5, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.5, 145.3, 144.2, 131.7, 126.0, 121.6, 117.8, 101.7, 79.1, 72.4, 62.5, 56.6, 51.7, 47.3, 38.8, 25.2, 23.0, 22.3, 20.9; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1837, found 324.1840. The spectral data were identical with those reported.[7b]

4.2.2. (8*R*,9*S*,10*S*)-10,11-dihydro-9,10-epoxy-6′-methoxycinchonane (3). A pale yellow amorphous solid; $[\alpha]_D^{17}$ +60.4 (*c* 1.02, MeOH); FT-IR (neat) 3350, 2931, 2459, 2210, 1622, 1508, 1471, 1232, 1136, 1076, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J*=5.0 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.58 (dd, *J*=4.5, 1.0 Hz, 1H), 7.35, (dd, *J*=9.0, 2.5 Hz, 1H), 7.24 (d, *J*=2.5 Hz, 1H), 6.03 (s, 1H), 4.70 (dq, *J*=1.0, 6.5 Hz, 1H), 3.96 (s, 3H), 3.79, (d, *J*=14.0 Hz, 1H), 3.42 (d, *J*=9.5 Hz, 1H), 3.08 (dd, *J*=13.0, 8.5 Hz, 1H), 2.87 (dd, *J*=12.5, 8.5 Hz, 1H), 2.83–2.76 (m, 1H), 2.24 (ddd, *J*=13.0, 5.5, 2.5 Hz, 1H), 2.11 (ddd, *J*=5.5, 5.5, 5.5 Hz, 1H), 1.83–1.80 (m, 1H), 1.74–1.70 (m, 1H),

1.60–1.53 (m, 1H), 1.32 (d, J=6.5 Hz, 3H), 1.23 (ddd, J=13.5, 9.5, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.5, 146.7, 144.1, 131.6, 126.1, 121.4, 118.2, 101.4, 75.7, 74.1, 60.1, 56.1, 47.3, 44.9, 39.6, 26.5, 24.9, 22.9, 22.1; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1837, found 324.1838. The spectral data were identical with those reported.[7b]

4.2.3. (8*R*,9*S*,10*R*)-10,11-dihydro-9,10-epoxy-6′-hydroxycinchonane (4). A pale yellow amorphous solid; $[\alpha]_D^{17}$ +114.0 (*c* 1.00, MeOH); FT-IR (neat) 3200–2600, 2939, 2567, 1620, 1508, 1468, 1232, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J=4.5 Hz, 1H), 7.94 (d, J=9 Hz, 1H), 7.86 (d, J=2.5 Hz, 1H), 7.55 (dd, J=4.5, 1.0 Hz, 1H), 7.24 (dd, J=9.0, 2.5 Hz, 1H), 5.92 (s, 1H), 4.23 (q, J=6.5 Hz, 1H), 3.73 (d, J=13.5 Hz, 1H), 3.47 (d, J=8.0 Hz, 1H), 3.25–3.18 (m, 2H), 2.92–2.87 (m, 1H), 2.51 (ddd, J=13.0, 6.0, 1.5 Hz, 1H), 2.42 (m, 1H), 1.88 (dd, J=9.0, 5.5 Hz, 1H), 1.79–1.70 (m, 2H), 1.48 (d, J=6.5 Hz, 3H), 1.28 (dd, J=13.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 146.9, 144.7, 143.3, 131.5, 125.9, 121.9, 117.3, 105.7, 79.0, 72.1, 62.6, 51.0, 47.0, 39.0, 25.2, 22.8, 22.2, 20.9; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1683. The spectral data were identical with those reported.[7b]

4.2.4. (8*R*,9*S*,10*S*)-10,11-dihydro-9,10-epoxy-6′-hydroxycinchonane (5). A pale yellow amorphous solid; $[\alpha]_D^{18}$ +47.8 (*c* 1.06, MeOH); FT-IR (neat) 3100–2500, 2929, 1842, 1618, 1510, 1469, 1236, 1138, 1092, 910, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J=4.5 Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.93 (dd, J=3.0, 1.0 Hz, 1H), 7.54, (d, J=4.5 Hz, 1H), 7.24 (dd, J=9.0, 3.0 Hz, 1H), 6.02 (s, 1H), 4.69 (dq, J=7.0, 1.5 Hz, 1H), 3.81, (d, J=14.0 Hz, 1H), 3.36 (d, J=8.5 Hz, 1H), 3.14 (dd, J=12.5, 9.5 Hz, 1H), 2.93 (dd, J=14.0, 9.0 Hz, 1H), 2.83–2.77 (m, 1H), 2.34 (ddd, J=13.0, 6.0, 2.0 Hz, 1H), 2.18 (ddd, J=6.0, 6.0, 6.0 Hz, 1H), 1.87 (dd, J=9.0, 6.0 Hz, 3H), 1.79–1.73 (m, 1H), 1.66–1.61 (m, 1H), 1.30 (d, J=7.0 Hz, 3H), 1.26 (dd, J=13.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.8, 146.2, 143.3, 131.3, 126.6, 122.3, 117.9, 106.3, 75.5, 73.0, 60.4, 47.0, 44.5, 39.6, 26.5, 25.1, 22.5, 22.6; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1691. The spectral data were identical with those reported.[7b]

4.2.5. (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-methoxycinchonane (6). A pale yellow amorphous solid; $[\alpha]_D^{19}$ −8.2 (*c* 1.02, MeOH); FT-IR (neat) 3350, 2966, 2517, 1622, 1508, 1232, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J=4.5 Hz, 1H), 8.03 (d, J=9.0 Hz, 1H), 7.73 (dd, J=4.5, 1.0 Hz, 1H), 7.35 (dd, J=9.0, 2.5 Hz, 1H), 7.16 (d, J=3.0 Hz, 1H), 5.94 (s, 1H), 3.96 (s, 3H), 3.55 (d, J=13.5 Hz, 1H), 3.48 (d, J=6.0 Hz, 1H), 3.02–3.00 (m, 2H), 2.68 (d, J=14.0 Hz, 1H), 2.14 (dd, J=5.5, 5.0 Hz, 1H), 1.77 (ddd, J=13.0, 6.5, 2.5 Hz, 1H), 1.70–1.64 (m, 1H), 1.66 (q, J=7.5 Hz, 2H), 1.54–1.49 (m, 1H), 1.27 (dd, J=13.5, 6.5 Hz, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.6, 144.0, 142.3, 131.7, 126.4, 121.6, 119.3, 100.5, 77.1, 73.0, 56.2, 55.9, 54.7, 46.7, 32.9, 27.4, 24.2, 23.5, 7.3; HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$ (M^+): 324.1838, found 324.1827. The spectral data were identical with those reported.[7b]

4.2.6. (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-hydroxycinchonane (β-ICD). Colorless needles; mp 258–259 °C; $[\alpha]_D^{22}$ +8.6 (*c* 1.00, MeOH); FT-IR (neat) 3400–3200, 2962, 2713, 1620, 1508, 1469, 1280, 1240, 1012, 858 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J=4.5 Hz, 1H), 7.99 (br s, 1H), 7.97 (d, J=9.0 Hz, 1H), 7.57 (dd, J=4.5, 1.0 Hz, 1H), 7.24 (dd, J=9.0, 2.5 Hz, 1H), 6.00 (s, 1H), 3.68 (d, J=13.5 Hz, 1H), 3.46 (d, J=6.0 Hz, 1H), 3.19 (dd, J=13.0, 8.5 Hz, 1H), 3.09–3.03 (m, 1H), 2.77 (d, J=14.0 Hz, 1H), 2.21–2.19 (m, 1H), 1.87 (ddd, J=13.0, 6.5, 2.0 Hz, 1H), 1.79–1.73 (m, 1H), 1.69 (dq, J=3.5, 7.5 Hz, 2H), 1.63–1.58 (m, 1H), 1.24 (dd, J=13.6, 1.0 Hz, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.7, 143.0, 142.2, 131.3, 127.0, 122.3, 119.1, 105.2, 77.0, 72.7, 56.0 54.0, 46.4, 32.7, 27.4, 23.5, 23.3, 7.3; HRMS (EI) calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1681, found 310.1691. Anal. Calcd for $C_{19}H_{22}N_2O_2\cdot CH_3OH\cdot H_2O$: C 66.64, H 7.83, N 7.77; found C 66.51, H 7.50, N 7.58.

4.2.7. (3*R*,8*R*,9*S*)-3-triisopropylsilyloxy-3,9-epoxy-6′-hydroxy-10,11-dinorcinconane (8). NaH (60% in mineral oil; 2.00 g, 50.1 mmol) was washed with hexane, dried, and suspended in DMF (40 mL). Ethanethiol (8.17 μL, 110.3 mmol) was added dropwise to the suspension over 20 min with cooling in an ice bath, and the mixture was stirred at room temperature for 10 min. A solution of **7**[7b] (2.35 g, 5.01 mmol) in DMF (35 mL) was added at room temperature and the mixture was heated at 60 °C for 12 h. The reaction mixture was allowed to cool to room temperature, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography (SiO_2 75 g, $CHCl_3$/MeOH=10:1), followed by lyophilization gave **8** (1.59 g, 70%) as a pale yellow amorphous solid; $[\alpha]_D^{23}$ −18.6 (*c* 1.35, $CHCl_3$); FT-IR (neat) 3600–2300, 1622, 1468, 1348, 1238, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J=8.0 Hz, 1H), 8.11 (br s, 1H), 7.97 (d, J=12.0 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.23 (dd, J=4.0, 12.0 Hz, 1H), 6.13 (s, 1H), 3.82 (d, J=12.0 Hz, 1H), 3.41 (d, J=8.0 Hz, 1H), 3.31–3.21 (m, 1H), 3.10–2.98 (m, 1H), 2.94 (d, J=8.0 Hz, 1 H), 2.36 (m, 1H), 2.14–1.97 (m, 2H), 1.69 (m, 1H), 1.32–0.98 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.4, 142.7, 140.8, 130.8, 126.7, 121.6, 118.5, 106.1, 99.2, 73.7, 55.9, 55.9, 46.1, 37.4, 24.4, 22.8, 17.9, 17.8, 12.8; HRMS (EI) calcd for $C_{26}H_{38}N_2O_3Si$ (M^+): 454.2651, found 454.2644.

4.2.8. (3*R*,8*R*,9*S*)-10,11-dihydro-3,6′-dihydroxycinchonane (9). NaH (60% in mineral oil; 122 mg, 3.06 mmol) was washed with hexane, dried, and suspended in DMF (2 mL). Ethanethiol (500 μL, 6.75 mmol) was added dropwise to the suspension, and the mixture was stirred at room temperature for 10 min. To this mixture was added a solution of hydroquinidine (100 mg, 0.31 mmol) in DMF (3 mL), and stirring was continued at room temperature for 1 h and at 100 °C for 20 h. The reaction mixture was allowed to cool to room temperature, acidified with 1 M HCl, and extracted with CH_2Cl_2. The aqueous layers were adjusted to pH 8 with 25% aqueous ammonia and extracted with CH_2Cl_2. Combined extracts were washed with brine, dried over K_2CO_3, and concentrated. Purification of the residue by column chromatography (SiO_2 deactivated by

exposure to MeOH and Et_3N, 10 g, $CHCl_3$/MeOH=10:1), followed by lyophilization gave **9** (55 mg, 57%) as a colorless amorphous solid; $[\alpha]_D^{20}$ +250.1 (*c* 1.03, MeOH); FT-IR (neat) 3130–2636, 2944, 1616, 1466, 1234 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.57 (d, *J*=4.5 Hz, 1H), 7.88 (d, *J*=9.3 Hz, 1H), 7.61, (d, *J*=4.5 Hz, 1H), 7.31 (dd, *J*=9.0, 2.7 Hz, 1H), 7.22 (d, *J*=2.7 Hz, 1H), 5.56 (d, *J*=2.7 Hz, 1H), 3.41–3.35 (m, 1H), 3.10–3.01 (m, 1H), 2.99–2.85 (m, 2H), 2.85–2.75 (m, 1H), 2.18–2.11 (m, 1H), 1.72 (br s, 1H), 1.60–1.47 (m, 5H), 1.08–0.99 (m, 1H), 0.93 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.7, 149.4, 147.1, 143.7, 131.3, 128.4, 123.7, 119.6, 105.1, 72.0, 60.7, 51.8, 50.9, 38.3, 27.5, 27.4, 26.0, 20.7, 12.3; HRMS (EI) calcd for $C_{19}H_{24}N_2O_2$ (M^+): 312.1838, found 312.1853.

4.2.9. (3*R*,8*R*)-10,11-dihydro-3,6′-methoxycinchonane (10). To an ice-cooled solution of hydroquinidine (1.20 g, 3.68 mmol) in CH_2Cl_2 (5 mL) were added 4-DMAP (45 mg, 0.34 mmol), pyridine (0.89 mL, 11.0 mmol) and methanesulfonyl chloride (0.57 mL, 7.35 mmol), and the mixture was stirred at room temperature for 3 days. The mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 30 g, $CHCl_3$/MeOH=20:1) gave the corresponding mesylate (1.20 g, 81%). To a solution of the mesylate in THF (10 mL) was added dropwise lithium triethylborohydride (1 M in THF, 5.9 mL, 5.92 mmol) at −70 °C. The mixture was allowed to slowly warm to −55 °C, and stirred at that temperature for 3 days. The reaction mixture was acidified with 1 M HCl, and extracted with $CHCl_3$. The aqueous layers were adjusted to pH 8 with 25% NH_4OH and extracted with $CHCl_3$. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated. Purification of the residue by column chromatography (SiO_2 25 g, $CHCl_3$/MeOH=20:1) gave **10** (673 mg, 73%) as a pale yellow amorphous solid; $[\alpha]_D^{18}$ +117.8 (*c* 1.02, MeOH); FT-IR (neat) 3371, 2937, 2868, 1622, 1510, 1466, 1234, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J*=4.5 Hz, 1H), 8.01 (d, *J*=9.5 Hz, 1H), 7.37 (dd, *J*=9.0, 2.5 Hz, 1H), 7.33, (d, *J*=2.5 Hz, 1H), 7.23 (d, *J*=4.5 Hz, 1H), 3.97 (s, 3H), 3.49–3.47 (m, 1H), 3.18 (dt, *J*=14, 8.5 Hz, 1H), 3.07 (dd, *J*=13.5, 9.5 Hz, 1H), 3.01 (dd, *J*=14, 9.5 Hz, 1H), 2.99–2.89 (m, 1H), 2.70 (ddd, *J*=13.5, 7.5, 2.5 Hz, 1H), 1.69 (br s, 1H), 1.60–1.44 (m, 4H), 1.47 (q, *J*=7.5 Hz, 2H), 1.42–1.36 (m, 1H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 147.3, 144.3, 143.6, 132.5, 128.5, 121.7, 121.3, 101.5, 55.5, 55.5, 49.2, 49.2, 37.4, 37.2, 27.9, 26.9, 25.9, 25.6, 11.9; HRMS (EI) calcd for $C_{20}H_{26}N_2O$ (M^+): 310.2045, found 310.2048.

4.3. General procedure for asymmetric Baylis–Hillman reactions

To a solution of aldehyde **13** (1.0 mmol) and the chiral amine catalyst (0.1 mmol) in DMF (1 mL) at −55 °C was added HFIPA or **16** (1.3 mmol). After stirring at −55 °C for the indicated time in Tables 1–3, the reaction was quenched by the addition of 0.1 M HCl (3 mL). The reaction mixture was extracted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane).

Dried β-ICD. β-ICD (0.1 mmol) was dissolved into THF (2 mL) and the solution was evaporated by rotary evaporation at room temperature. After repeating this operation three times, the resulting amorphous solid was dried under vacuum at room temperature for 10 min.

4.4. Conversion of 14 and 15 into the corresponding methyl ester for the determination of their optical purity

A mixture of **14** or **15** (1.0 mmol) and triethylamine (0.7 mL) in MeOH (7 mL) was stirred at room temperature for 30 min and the reaction was quenched by the addition of Dowex 50 (H^+ form). The reaction mixture was filtered, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane). The optical purity of the methyl ester was determined by HPLC analysis using a chiral column.

4.4.1. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (14a). A colorless oil (95% ee); $[\alpha]_D^{24}$ −40.9 (*c* 0.87, $CHCl_3$); FT-IR (neat) 3533, 1751, 1525, 1352, 1286, 1232, 1120, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J*=8.7 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 6.66 (s, 1H), 6.27 (s, 1H), 5.80–5.74 (m, 2H), 2.47 (d, *J*=4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 147.9, 147.5, 139.2, 130.9, 127.6, 123.9, 120.3 (q, $^1J_{C,F}$=281 Hz), 71.8, 66.9 (hept, $^2J_{C,F}$=34.2 Hz); HRMS (EI) calcd for $C_{13}H_9NO_5F_6$ (M^+): 373.0385, found 373.0389.

4.4.2. (2*R*,6*R*)-2,6-di(4-nitrophenyl)-5-methylene-1,3-dioxan-4-one (15a). A colorless oil (49% ee); $[\alpha]_D^{25}$ +3.2 (*c* 0.57, $CHCl_3$); FT-IR (neat) 3082, 2862, 1741, 1523, 1348, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J*=8.7 Hz, 2H), 8.31 (d, *J*=8.7 Hz, 2H), 7.79 (d, *J*=8.7 Hz, 2H), 7.64 (d, *J*=8.7 Hz, 2H), 6.74 (d, *J*=2.7 Hz, 1H), 6.62 (s, 1H), 5.92 (br s, 1H), 5.42 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 149.0, 148.6, 144.2, 141.1, 135.2, 130.6, 128.8, 127.5, 124.3, 123.9, 99.5, 80.4; HRMS (EI) calcd for $C_{17}H_{12}N_2O_7$ (M^+): 356.0644, found 356.0663.

4.4.3. Methyl (*R*)-3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (methyl ester obtained from 14a). A colorless oil (95% ee); $[\alpha]_D^{23}$ −85.6 (*c* 0.54, MeOH); FT-IR (neat) 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J*=6.9, 1.8 Hz, 2H), 7.58 (d, *J*=6.9 Hz, 2H), 6.40 (s, 1H), 5.87 (s, 1H), 5.64 (d, *J*=6.3 Hz, 1H), 3.75 (s, 3H), 3.30 (d, *J*=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 147.8, 146.0, 127.9, 123.5, 71.5, 58.4, 53.0, 50.0; HRMS (EI) calcd for $C_{11}H_{11}NO_6$ (M^+): 253.0586, found 253.0578. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:10 (0.5 mL/min), t_R=29.0 min (*R*) and 32.4 min (*S*).

4.4.4. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-phenylpropanoate (14b). A colorless oil (97% ee); $[\alpha]_D^{19}$ −51.1 (*c* 1.04, $CHCl_3$); FT-IR (neat) 3375, 2970, 1755, 1387, 1298, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 6.60 (s, 1H), 6.24 (s, 1H), 5.75 (hept, *J*=6.0 Hz, 1H), 5.63 (br s, 1H), 2.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 140.5, 140.0, 129.6, 128.8, 128.5, 126.8, 120.4 (q, $^1J_{C,F}$=305.6 Hz), 72.6, 66.8 (hept,

$^{2}J_{C,F}$=35.3 Hz); HRMS (EI) calcd for $C_{13}H_{10}NO_5F_6$ (M^+): 328.0534, found 328.0538.

4.4.5. Methyl (*R*)-3-hydroxy-2-methylene-3-phenylpropanoate (methyl ester obtained from 14b). A colorless oil (95% ee); $[\alpha]_D^{20}$ −124.6 (*c* 1.30, MeOH); {lit.[14] $[\alpha]_D^{18}$ −111.1 (*c* 1.11, MeOH)}; FT-IR (neat) 3363, 3032, 2952, 1704, 1496, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 6.34 (s, 1H), 5.84 (s, 1H), 5.57 (d, *J*= 5.4 Hz, 1H), 3.73 (s, 3H), 3.02 (d, *J*=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 142.1, 141.3, 128.5, 127.9, 126.6, 126.1, 73.3, 52.0; HRMS (EI) calcd for $C_{11}H_{12}O_5$ (M^+): 192.0786, found 192.0788. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (0.5 mL/min), t_R= 26.4 min (*R*) and 32.4 min (*S*).

4.4.6. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*E*,*R*)-3-hydroxy-2-methylene-5-phenyl-4-pentenoate (14c). A colorless oil (94% ee); $[\alpha]_D^{26}$ −39.1 (*c* 0.95, $CHCl_3$); FT-IR (neat) 3390, 3032, 2970, 1754, 1664, 1633, 1387, 1290, 1126, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 6.69 (d, *J*=15.9 Hz, 1H), 6.55 (s, 1H), 6.26 (s, 1H), 6.24 (dd, *J*=15.9, 6.6 Hz, 1H), 5.85 (hept, *J*= 6.0 Hz, 1H), 5.22 (d, *J*=6.6 Hz, 1H), 2.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 139.3, 136.1, 132.8, 129.7, 128.7, 128.3, 128.2, 126.8, 120.5 (q, $^{1}J_{C,F}$=281 Hz), 71.3, 66.8 (hept, $^{2}J_{C,F}$=34 Hz); HRMS (EI) calcd for $C_{15}H_{12}NO_5F_6$ (M^+): 354.0691, found 354.0675.

4.4.7. Methyl (*E*,*R*)-3-hydroxy-2-methylene-5-phenyl-4-pentenoate (methyl ester obtained from 14c). A colorless oil (94% ee); $[\alpha]_D^{22}$ +12.5 (*c* 0.56, $CHCl_3$); FT-IR (neat) 3442, 3028, 2952, 1718, 1631, 1440, 1277, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 6.67 (d, *J*= 16.0 Hz, 1H), 6.36 (dd, *J*=16.0, 6.3 Hz, 1H), 6.30 (s, 1H), 5.92 (s, 1H), 5.13 (dd, *J*=6.3, 6.3 Hz, 1H), 3.79 (s, 3H), 3.02 (d, *J*=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 141.3, 136.5, 131.6, 129.3, 128.6, 127.9, 126.7, 126.0, 72.2, 52.1; HRMS (EI) calcd for $C_{13}H_{14}O_5$ (M^+): 218.0943, found 218.0951. HPLC conditions: Daicel Chiralcel OD, 2-propanol/hexane 1:10 (0.5 mL/min), t_R= 26.4 min (*R*) and 29.3 min (*S*).

4.4.8. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate (14d). A pale yellow oil (95% ee); $[\alpha]_D^{20}$ −60.6 (*c* 1.44, $CHCl_3$); FT-IR (neat) 3475, 2966, 1763, 1616, 1514, 1304, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J*= 8.4 Hz, 2H), 6.88 (d, *J*=8.1 Hz, 2H), 6.58 (t, *J*=0.8 Hz, 1H), 6.26 (dd, *J*=1.5, 0.6 Hz, 1H), 5.75 (hept, *J*=6.1 Hz, 1H), 5.58 (d, *J*=4.2 Hz, 1H), 3.80 (s, 3H), 2.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 159.7, 140.1, 132.7, 129.1, 128.2, 120.4, (q, $^{1}J_{C,F}$=280.1 Hz), 114.1, 72.1, 66.6 (hept, $^{2}J_{C,F}$=34.7 Hz), 55.3; HRMS (EI) calcd for $C_{14}H_{12}F_6O_4$ (M^+): 358.0632, found 358.0639.

4.4.9. Methyl (*R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate (methyl ester obtained from 14d). A pale yellow oil (95% ee); $[\alpha]_D^{22}$ −112.2 (*c* 0.54, $CHCl_3$); FT-IR (neat) 3512, 2951, 2841, 1712, 1506, 1444, 1242, 1144, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J*=9.0 Hz, 2H), 6.87 (d, *J*=9.0 Hz, 2H), 6.32 (s, 1H), 5.86 (s, 1H), 5.52 (d, *J*=5.1 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 1H), 2.82 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.3, 142.2, 133.5, 128.0, 125.7, 113.9, 72.8, 55.3, 52.0; HRMS (EI) calcd for $C_{12}H_{14}O_4$ (M^+): 222.0892, found 222.0892. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (0.5 mL/min), t_R= 53.3 min (*R*) and 70.3 min (*S*).

4.4.10. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-1-yl)propanoate (14e). A colorless oil (97% ee); $[\alpha]_D^{23}$ −42.4 (*c* 1.65, $CHCl_3$); FT-IR (neat) 3433, 2969, 1718, 1441, 1286, 1151, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*= 9.0 Hz, 1H), 7.89–7.81 (m, 2H), 7.55–7.42 (m, 4H), 6.61 (s, 1H), 6.39 (br d, *J*=3.9 Hz, 1H), 6.03 (s, 1H), 5.79 (hept, *J*= 6.0 Hz, 1H), 2.68 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 140.0, 136.1, 134.3, 131.1, 130.9, 129.6, 129.2, 126.9, 126.3, 120.7 (q, $^{1}J_{C,F}$=280 Hz), 69.2, 67.2 (hept, $^{2}J_{C,F}$=35.3 Hz); HRMS (EI) calcd for $C_{17}H_{12}F_6O_3$ (M^+): 378.0690, found 378.0698.

4.4.11. Methyl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-1-yl)propanoate (methyl ester obtained from 14e). A pale yellow oil (97% ee); $[\alpha]_D^{23}$ −46.3 (*c* 0.83, $CHCl_3$); FT-IR (neat) 3433, 1718, 1441, 1286, 1151, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (m, 1H), 7.87–7.79 (m, 2H), 7.62 (d, *J*=6.9 Hz, 1H), 7.51–7.44 (m, 3H), 6.36 (br s, 1H), 6.34 (s, 1H), 5.57 (s, 1H), 3.76 (s, 3H), 3.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 141.8, 136.4, 133.7, 130.7, 128.7, 128.5, 127.1, 126.1, 125.5, 125.3, 124.4, 123.7, 69.2, 52.1; HRMS (EI) calcd for $C_{15}H_{14}O_3$ (M^+): 242.0943, found 242.0936. HPLC conditions: Daicel Chiralcel OJ–H, 2-propanol/hexane 1:2 (0.5 mL/min), t_R=27.6 min (*R*) and 57.8 min (*S*).

4.4.12. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-2-yl)propanoate (14f). A colorless oil (97% ee); $[\alpha]_D^{26}$ −72.8 (*c* 1.04, $CHCl_3$); FT-IR (neat) 3388, 1755, 1385, 1238, 1120, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.54–7.44 (m, 3H), 6.64 (s, 1H), 6.27 (s, H), 5.80 (d, *J*=4.8 Hz, 1H), 5.75 (hept, *J*=6.0 Hz, 1H), 2.58 (d, *J*=4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 139.8, 137.7, 133.3, 130.0, 128.7, 128.2, 127.8, 126.5, 126.1, 124.3, 120.4 (q, $^{1}J_{C,F}$= 279.7 Hz), 72.7, 66.7 (hept, $^{2}J_{C,F}$=35.3 Hz); HRMS calcd for $C_{17}H_{12}F_6O_3$ (M^+): 378.0690, found 378.0696.

4.4.13. Methyl (*R*)-3-hydroxy-2-methylene-3-(naphthalen-2-yl)propanoate (methyl ester obtained from 14f). A colorless solid (97% ee); $[\alpha]_D^{21}$ −31.1 (*c* 0.68, $CHCl_3$); FT-IR (neat) 3448, 2950, 1716, 1441, 1277, 1151, 1043, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86–7.81 (m, 4H), 7.49–7.45 (m, 3H), 6.38 (t, *J*=0.9 Hz, 1H), 5.88 (t, *J*=0.9 Hz, 1H), 5.74 (d, *J*=5.1 Hz, 1H), 3.72 (s, 3H), 3.14 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 141.9, 138.6, 133.3, 133.1, 128.3, 128.2, 127.7, 126.4, 126.2, 126.1, 125.6, 124.6, 73.4, 73.3, 52.1; HRMS (EI) calcd for $C_{15}H_{14}O_3$ (M^+): 242.0943, found 242.0947. HPLC conditions: Daicel Chiralcel OJ, 2-propanol/hexane 1:5 (1.0 mL/min), t_R=52.8 min (*R*) and 62.9 min (*S*).

4.4.14. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-hydroxy-2-methylene-5-phenylpentanoate (14g). A colorless oil

(98% ee); $[\alpha]_D^{22}$ +11.5 (*c* 1.41, $CHCl_3$); FT-IR (neat) 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 7.22–7.17 (m, 3H), 6.49 (s, 1H), 6.15 (s, 1H), 5.85 (hept, J=6.0 Hz, 1H), 4.52 (dd, J=3.6, 4.2 Hz, 1H), 2.85–2.66 (m, 2H), 2.24 (br s, 1H), 2.08–1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 142.2, 140.6, 129.2, 128.6, 128.5, 126.2, 120.5 (q, $^1J_{C,F}$=282.3 Hz), 70.1, 66.7 (hept, $^2J_{C,F}$=34.7 Hz), 37.8, 32.0; HRMS (EI) calcd for $C_{15}H_{14}F_6O_3$ (M^+): 356.0847, found 356.0863.

4.4.15. (6*R*)-2,6-Diphenethyl-5-methylene-1,3-dioxan-4-one (15g) (70:30 *cis*/*trans*-mixture). A colorless oil; FT-IR (neat) 3028, 2931, 1730, 1446, 1379, 1234, 1161, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 7.23–7.17 (m, 10H), 6.49–6.47 (m, 1H), 5.58 (d, J=2.1 Hz, 0.7H), 5.54 (d, J=2.1 Hz, 0.3H), 5.45 (t, J=5.1 Hz, 0.3H), 5.27 (d, J=5.1 Hz, 0.7H), 4.71–4.67 (m, 0.3H), 4.51–4.46 (m, 0.7H), 2.93–2.65 (m, 4H), 2.22–1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 140.9, 140.6, 140.5, 136.8, 136.0, 128.7, 128.6, 128.5, 128.4, 126.8, 126.4, 126.2, 125.7, 101.1, 96.4, 77.5, 77.1, 76.7, 76.5, 74.2, 36.6, 35.8, 35.6, 35.3, 31.4, 30.8, 29.4, 29.3; HRMS (EI) calcd for $C_{21}H_{22}O_3$ (M^+): 322.1569, found 322.1567.

4.4.16. Methyl (*R*)-3-hydroxy-2-methylene-5-phenylpentanoate (methyl ester obtained from 14g). A colorless oil (98% ee); $[\alpha]_D^{22}$ +28.1 (*c* 0.83, $CHCl_3$); FT-IR (neat) 3487, 3024, 2947, 1720, 1631, 1444, 1149, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.15 (m, 5H), 6.24–6.23 (m, 1H), 5.81 (t, J=0.9 Hz, 1H), 4.45–4.39 (m, 1H), 3.76 (s, 3H), 2.87–2.64 (m, 3H), 2.01–1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 142.2, 141.7, 128.5, 128.5, 126.0, 125.4, 71.2, 52.0, 37.7, 32.1; HRMS (EI) calcd for $C_{15}H_{16}O_3$ (M^+): 220.1099, found 220.1123. HPLC conditions: Daicel Chiralcel OD–H, 2-propanol/hexane 1:5 (0.5 mL/min), t_R=13.0 min (*R*), t_R=15.8 min (*S*).

4.4.17. 1,1,1,3,3,3-Hexafluoropropan-2-yl (*R*)-3-cyclohexyl-3-hydroxy-2-methylenepropanoate (14h). A colorless oil (99% ee); $[\alpha]_D^{24}$ −2.6 (*c* 1.00, $CHCl_3$); FT-IR (neat) 3419, 2935, 2857, 1749, 1647, 1387, 1365, 1294, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.07 (s, 1H), 5.84 (hept, J=6.0 Hz, 1H), 4.26 (dd, J=6.3, 6.3 Hz, 1H), 2.04 (d, J=6.9 Hz, 1H), 1.92–1.50 (m, 6H), 1.32–0.94 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 139.6, 129.9, 120.5 (q, $^1J_{C,F}$=281.2 Hz), 75.8, 66.7 (hept, $^2J_{C,F}$=35.3 Hz), 42.7, 29.8, 27.8, 26.4, 26.2, 26.0; HRMS (EI) calcd for $C_{13}H_{16}O_5F_6$ (M^+): 334.1003, found 334.0993.

4.4.18. (2*S*,6*S*)-dicyclohexyl-5-methylene-1,3-dioxan-4-one (15h) (90:10 *cis*/*trans*-mixture). A colorless oil; FT-IR (neat) 2929, 2854, 1739, 1631, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, J=2.4 Hz, 1H), 5.53 (d, J=1.8 Hz, 1H), 4.98 (d, J=5.1 Hz, 1H), 4.43 (m, 1H), 1.88–1.62 (m, 12H), 1.38–1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 136.7, 125.0, 103.6, 81.5, 43.6, 41.7, 29.0, 26.6, 26.4, 26.4, 26.3, 26.3, 26.2, 26.0, 25.6, 26.5; HRMS (EI) calcd for $C_{17}H_{26}O_3$ (M^+): 278.1882, found 278.1880.

4.4.19. Methyl (*R*)-3-cyclohexyl-3-hydroxy-2-methylenepropanoate (methyl ester obtained from 14h). A colorless oil (99% ee); $[\alpha]_D^{24}$ −8.1 (*c* 0.93, $CHCl_3$); FT-IR (neat) 3448, 2929, 2852, 1718, 1628, 1440, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J=1.2 Hz, 1H), 5.73 (d, J=1.2 Hz, 1H), 4.06 (dd, J=7.8, 7.8 Hz, 1H), 3.78 (s, 3H), 2.56 (d, J=8.4 Hz, 1H), 1.97 (m, 1H), 1.79–1.50 (m, 5H), 1.29–0.91 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 141.1, 126.2, 77.1, 51.9, 42.4, 30.0, 28.3, 26.4, 26.1, 26.0; HRMS (EI) calcd for $C_{11}H_{18}O_5$ (M^+): 198.1256, found 198.1264. HPLC conditions: Daicel Chiralcel OD, 2-propanol/hexane 1:50 (0.5 mL/min), t_R=21 min (*R*) and 26 min (*S*).

4.4.20. 1,1,1-Trifluoroethyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17b). A pale yellow oil; FT-IR (neat) 3523, 1734, 1522, 1348, 1282, 1173, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.55 (d, J=0.6 Hz, 1H), 6.10 (s, 1H), 5.96 (d, J=5.1 Hz, 1H), 4.50 (dq, J=1.5, 8.1 Hz, 2H), 2.94 (dd, J=4.5, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.2, 147.5, 140.1, 129.0, 127.6, 123.7, 122.7 (q, $^1J_{C,F}$=275.5 Hz), 71.9, 60.7 (q, $^2J_{C,F}$=36.5 Hz); HRMS calcd for $C_{12}H_{10}NO_5F_3$ (M^+): 305.0511, found 305.0529.

4.4.21. 1,1,1,2,2-Pentafluoropropyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17c). A pale yellow oil; FT-IR (neat) 3523, 1734, 1603, 1523, 1348, 1271, 1207, 1149, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.53 (s, 1H), 6.10 (s, 1H), 5.69 (d, J=5.4 Hz, 1H), 4.58 (dt, J=0.9, 12.6 Hz, 2H), 2.94 (dd, J=5.4, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.2, 147.6, 140.0, 129.0, 127.6, 123.7, 118.4 (dt, 2 $J_{C,F}$=34.0 Hz, $^1J_{C,F}$=283 Hz), 111.9 (dt, $^1J_{C,F}$=254.0 Hz, $^2J_{C,F}$=38.0 Hz), 71.9, 59.6 (t, $^2J_{C,F}$=28.5 Hz); HRMS calcd for $C_{13}H_{10}NO_5F_5$ (M^+): 355.0479, found 355.0490.

4.4.22. 1,1,1,2,2,3,3-Heptafluorobutyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanoate (17d). A pale yellow oil; FT-IR (neat) 3529, 1736, 1604, 1525, 1404, 1350, 1236, 1136, 1059, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.0 Hz, 2H), 7.58 (d, J=9.0 Hz, 2H), 6.53 (s, 1H), 6.10 (d, J=0.9 Hz, 1H), 5.69 (d, J=5.4 Hz, 1H), 4.62 (td, J=13.2, 1.5 Hz, 2H), 2.94 (d, J=6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 148.1, 147.7, 140.1, 129.1, 127.6, 123.8, 117.5 (dt, $^2J_{C,F}$=33.0 Hz, $^1J_{C,F}$=285.7 Hz), 113.8 (dd, $^1J_{C,F}$=254.9 Hz, $^2J_{C,F}$=30.7 Hz), 108.6 (m), 72.1, 59.8 (t, $^2J_{C,F}$=27.3 Hz); HRMS calcd for $C_{14}H_{10}NO_5F_7$ (M^+): 405.0447, found 405.0454.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Reseach from Ministry of Education, Culture, Sports, Science and Technology, Japan.

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Chiral base-catalyzed aldol reaction of trimethoxysilyl enol ethers: effect of water as an additive on stereoselectivities

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Received 5 July 2005; revised 30 August 2005; accepted 16 September 2005

Available online 10 October 2005

Abstract—An aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate is described. The aldol reaction of trimethoxysilyl enol ether derived from cyclohexanone under anhydrous conditions predominantly afforded the *anti*-aldol adduct with moderate enantioselectivity, whereas the reaction under aqueous conditions predominantly resulted in the *syn*-adduct and the enantioselectivity of the *syn*-adduct was considerably improved. The best enantioselectivity was obtained in the reaction of trimethoxysilyl enol ether derived from 1-indanone with cyclohexanecarboxaldehyde (97% ee (*syn*)). This is the first example of an aldol reaction of trimethoxysilyl enol ether catalyzed by a chiral base.

1. Introduction

The asymmetric aldol reaction is well-recognized as one of the most important methods for constructing optically active β-hydroxy carbonyl compounds.[1] Recent significant developments in asymmetric aldol reactions are mostly based on the principles of conventional Mukaiyama-type catalysis, in which aldol acceptors are activated by chiral Lewis acid catalysts.[2,3] In 1996, Denmark and co-workers reported the first Lewis base-catalyzed enantioselective aldol reactions of trichlorosilyl enol ethers employing chiral phosphoramides[4] as organocatalysts, wherein the aldol donors were activated to form hypervalent silicate intermediates.[5] We have also reported asymmetric aldol reaction of trichlorosilyl enol ethers catalyzed by chiral *N*-oxides.[6] These base-catalyzed reactions afforded the corresponding adducts with high diastereo- and enantioselectivities, however, aldol reactions of trichlorosilyl enol ethers are not widely utilized in organic synthesis since the enol ethers are extremely water sensitive.

Trialkoxysilyl compounds,[7] which are more stable than its trichlorosilyl derivatives, are expected to form reactive hypervalent silicates with bases. In 2001, Yamamoto and co-workers reported an asymmetric aldol reaction of trimethoxysilyl enol ethers with high enantioselectivity wherein BINAP–silver(I) complex was employed as a Lewis acid catalyst.[7b] However, base-catalyzed aldol reactions of trimethoxysilyl enol ethers have yet to be developed, although hypervalent silicates derived from trimethoxysilyl compounds are well-investigated.[5,7c] In our pursuit to develop base-catalyzed reactions involving hypervalent silicate intermediate,[6,8] herein we describe the details of an enantioselective aldol reaction of trimethoxysilyl enol ethers catalyzed by chiral base, wherein water as an additive played a pivotal role in stereoselectivities.[9,10]

2. Results and discussion

2.1. Synthesis of trialkoxysilyl enol ethers

Trialkoxysilyl enol ethers that were sufficiently stable to survive an aqueous work-up or silica gel column chromatography were easily prepared from the corresponding enones or ketones. Starting from the corresponding conjugated enones, trimethoxysilyl enol ethers **1a** and **1b** were prepared by hydrosilylation with trimethoxysilane catalyzed by $Rh(PPh_3)_3Cl$ using a literature procedure (Eq. 1).[7b] Trimethoxysilyl enol ethers **1c**–**1g** and triethoxysilyl enol ether **1h**[17] were prepared by silylation of lithium enolates from the corresponding ketones with chlorotrimethoxysilane[11] (or chlorotriethoxysilane) in THF or silylation of ketones with iodotrimethoxysilane prepared in situ in acetonitrile in the presence of triethylamine (Eq. 2). An aqueous work-up followed by distillation in vacuo gave pure silyl enol ethers in moderate to good yields.

Keywords: Chiral catalyst; Enantioselectivity; Aldol reaction; Silyl enol ether; Binaphthol.
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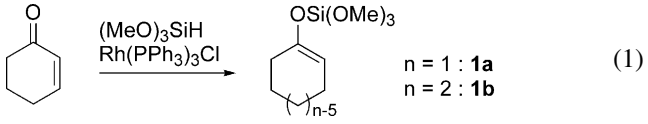
doi:10.1016/j.tet.2005.09.074



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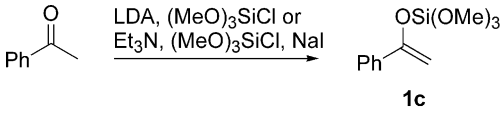

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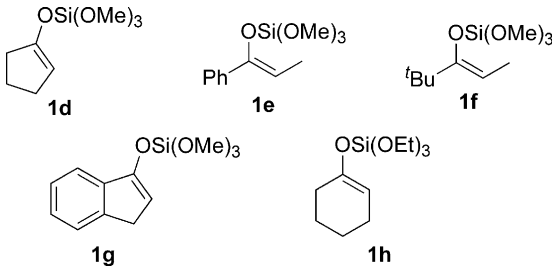
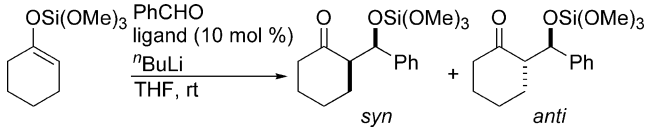


2.2. Aldol reaction of trimethoxysilyl enol ether under anhydrous condition

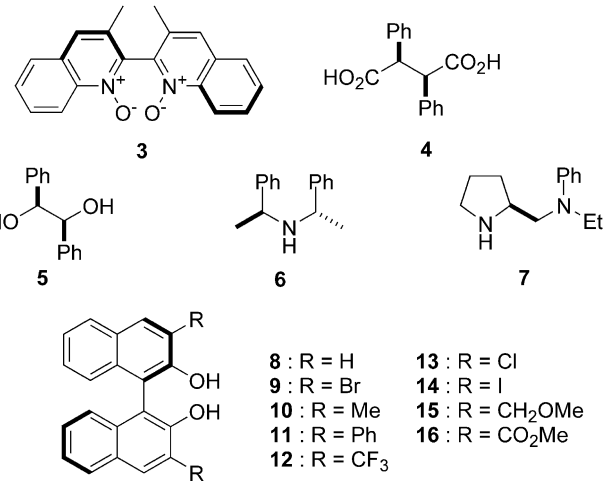
Our initial studies examined the addition of trimethoxysilyl enol ether **1a** derived from cyclohexanone with benzaldehyde using various bases (10 mol%) in THF (Table 1). Although aromatic *N*-oxides efficiently catalyzed the aldol reaction of trichlorosilyl enol ethers, *N*-oxide **3** did not afford the aldol adduct for trimethoxysilyl enol ether (entry 1). On the other hands, lithium salts of chiral alcohol **5**, amines **6**, **7**, and binaphthol **8** gave silyl ether of corresponding adduct in moderate to high yield (entries 3–6). Further catalyst screening based on binaphthol revealed that the dilithium salt of 3,3′-dibromobinaphthol **9** gave the most promising result (entry 7, 16% ee (*syn*), 12% ee (*anti*)). Decreasing the reaction temperature to −23 °C with **9** significantly improved the stereoselectivities (entry 8, *syn*/*anti* 1:3.7, 51% ee (*anti*)) without eroding the reaction rate.[12]

Table 1. Screening the catalyst



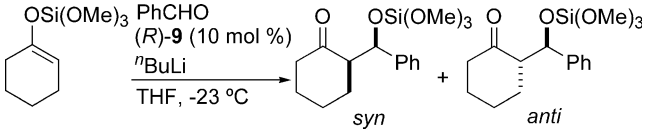
Entry	Ligand	^{n}BuLi (mol%)	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%) (*syn*/*anti*)[b]
1	**3**	0	24	0		—
2	**4**	20	24	0		—
3	**5**	20	24	46	1:1.1	~0/9
4	**6**	10	5	59	1:1.5	~0/~0
5	**7**	10	0.5	59	1:1.4	~0/~0
6	**8**	20	0.5	98	1:1.3	~0/~0
7	**9**	20	0.5	83	1:1.9	16/12
8[c]	**9**	20	0.5	97	1:3.7	8/51

[a] Isolated as alcohol.
[b] Determined by HPLC analysis.
[c] At −23 °C.



Since dilithium salt and monolithium salt of **9** may form different reactive species,[7c] we then examined the stoichiometry of lithium to **9** (Table 2). Surprisingly, a slight difference in the equivalents of BuLi extensively influenced the reaction rate and stereoselectivities. Catalysts prepared with 10–14 mol% of BuLi predominantly afforded the *syn*-adduct in a moderate chemical yield with a decreased reaction rate (entries 1–3), while *anti*-adduct was predominantly formed using 16–20 mol% of BuLi (entries 4–6). Although the origin of the dramatic change in stereoselectivity is unclear, the catalyst in following studies was a dilithium salt. Screening of binaphthols revealed that dibromide **9** and dichloride **13** were superior in terms of diastereo- and enantioselectivity (Table 3).

Table 2. Effect of molar equivalent of ^{n}BuLi



Entry	^{n}BuLi (mol%)	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%) (*syn*/*anti*)[b]
1	10	100	42[c]	1.8:1	27/14
2	12	30	59[c]	2.4:1	51/31
3	14	30	66[c]	2.2:1	55/38
4	16	0.5	98	1:2.7	12/50
5	18	0.5	98	1:2.8	7/47
6	20	0.5	97	1:3.7	8/51
7	22	0.5	98	1:3.5	18/49

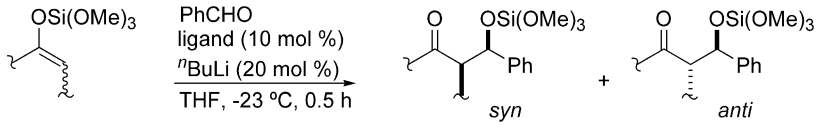
[a] Isolated as alcohol.
[b] Determined by HPLC analysis.
[c] Not completed.

Table 3. Screening binaphthol derivatives

Entry	Substituent on 3,3-positon	Yield (%)[a]	*syn*:*anti*[b]	ee (%) (*syn*/*anti*)[b]
1	Me (**10**)	91	1:1.4	14/29
2	Ph (**11**)	98	1:2.3	5/33
3	CF_3 (**12**)	98	1:2.1	24/13
4	Cl (**13**)	87	1:3.8	20/56
5	Br (**9**)	97	1:3.7	8/51
6	I (**14**)	89	1:3.7	4/31

[a] Isolated as alcohol.
[b] Determined by HPLC analysis.

Table 4. Aldol reaction of various silyl enol ethers with benzaldehyde



Entry	Ligand	Enol ether	Product	Yield (%)[a]	*syn*: *anti*[b]	ee (%) (*syn*/*anti*)[b]
1	**13**	**1a**	**2a**	87	1:3.8	20/56
2	**13**	**1b**	**2b**	91	1.4:1	39/42
3	**13**	**1c**	**2c**	98	—	50
4	**9**	**1d**	**2d**	93	3.4:1	46/30
5	**13**	**1e**	**2e**	98	1:1.7	~0/~0
6	**13**	**1f**	**2f**	87[c]	1.8:1	~0/~0

[a] Isolated as alcohol.
[b] Determined by HPLC analysis.
[c] At room temperature (45 h).

Table 5. Aldol reaction of **1a** with aldehydes catalyzed by dilithium salt of **13**

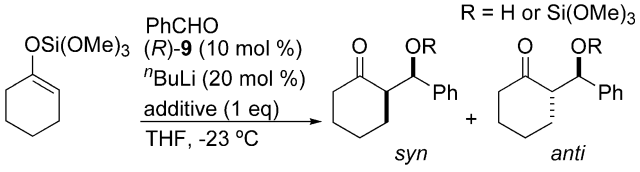
Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%) (*syn*/*anti*)[b]
1	PhCHO	**2a**	0.5	87	1:3.8	20/56
2	PhCH=CHCHO	**2h**	0.5	98	1:1.5	44/6
3	$PhCH_2CH_2CHO$	**2i**	3[c]	14	2.9:1	40/16

[a] Isolated as alcohol.
[b] Determined by HPLC analysis.
[c] Not completed.

Table 4 shows the results of the aldol reaction of trimethoxysilyl enol ethers derived from various ketones with benzaldehyde using the optimized catalyst at −23 °C. (*E*)-Enolates and enolate without substituents at the α-position afforded the corresponding aldol adducts in good to high yields, although the diastereo- and enantioselectivities were moderate (entries 1–4). On the other hand, (*Z*)-enolates gave low selectivities (entries 5 and 6), and the enolate with bulky substituent slowed the reaction rate (entry 6), probably due to steric hindrance.

The aldol reactions of other aldehydes with **1a** were investigated (Table 5). The reaction of conjugate aldehyde proceeded smoothly, but the stereoselectivity decreased (entry 2). The unconjugate aldehyde was much less reactive (entry 3), as is often observed in the base-catalyzed aldol reactions involving hypervalent silicate intermediate.

Table 6. Screening the additives



Entry	Additive	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%) (*syn*/*anti*)[b]
1	None	0.5	97	1:3.7	8/51
2	EtCN	1	97	1:1.7	12/47
3	HMPA	1	91	1.1:1	9/3
4	IQNO[c]	1	80	1.1:1	30/56
5	TMEDA	5	63	1.8:1	41/32
6	$^{i}Pr_2NEt$	5	71	2.0:1	48/19
7	$^{n}PrNH_2$	2	59	1.4:1	25/16
8	NH_3	1	70	1.7:1	52/39
9	MeOH	0.5	98	1.2:1	39/40
10	H_2O	0.5	93	3.0:1	78/47

[a] Isolated as alcohol.
[b] Determined by HPLC analysis.
[c] Isoquinoline *N*-oxide.

2.3. Aldol reaction of trimethoxysilyl enol ether under aqueous condition

To enhance the stereoselectivity, we then examined the effect of the additives. As shown in Table 6, the additive structure strongly affected both diastereo- and enantioselectivities. Among various additives surveyed, water gave the best result and predominantly afforded the *syn*-adduct as the alcohol in good enantioselectivity. (entry 10).

Table 7 summarizes more detailed studies on the equivalent of water. Interestingly, the ratio of *syn* to *anti* and the enantioselectivity of *syn*-adduct increased as a function of the increasing amount of water. Equimolar amounts of water to silyl enol ether (1.5 equiv to aldehyde, i.e., 1.0 equiv to silyl enol ether) were sufficient to optimize the diastereo- and enantioselectivity (entry 5, *syn*/*anti* 3.2:1, 80% ee (*syn*), 51% ee (*anti*)), which suggests that water (or the hydroxy ion) may strongly coordinate to the silicon atom of silyl enol ether. [13,14]

Table 7. Effect of equivalent of H_2O

Entry	H_2O (equiv)	Yield (%)	*syn*:*anti*[a]	ee (%) (*syn*/*anti*)[a]
1	0	97	1:3.7	8/51
2	0.1	93	1:1.1	15/46
3	0.5	97	1.7:1	60/44
4	1.0	93	3.0:1	78/47
5	1.5	94	3.1:1	80/50

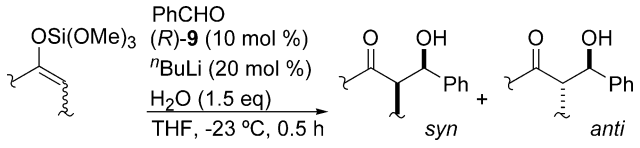
[a] Determined by HPLC analysis.

Table 8. Screening binaphthol derivatives

Entry	Substituent on 3,3′-position	Yield (%)	*syn*:*anti*[a]	ee (%) (*syn*/*anti*)[a]
1	H (**8**)	76	1.2:1	24/5
2	Me (**10**)	98	2.3:1	55/15
3	Ph (**11**)	98	2.0:1	34/5
4	CF_3 (**12**)	95	2.6:1	69/38
5	Cl (**13**)	98	3.0:1	78/48
6	Br (**9**)	94	3.1:1	80/50
7	I (**14**)	98	2.9:1	73/35
8	CH_2OMe (**15**)	98	1.6:1	14/1
9	CO_2Me (**16**)	76	1:1.1	17/46

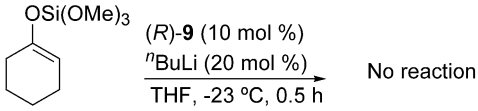
[a] Determined by HPLC analysis.

Table 9. Aldol reaction of various silyl enol ethers with benzaldehyde under hydrous condition



Entry	Silyl enol ether	Product	Yield (%)	*syn*:*anti*[a]	ee (%) (*syn*/*anti*)[a]
1	**1a**	**2a**	94	3.1:1	80/50
2	**1c**	**2c**	88	—	75
3	**1d**	**2d**	98	2.9:1	72/6
4	**1e**	**2f**	91	1.9:1	19/38
5	**1g**	**2g**	78	2.9:1	83/48
6	**1h**	**2a**	83[b]	2.9:1	77/45

[a] Determined by HPLC analysis.
[b] Eighteen hours.



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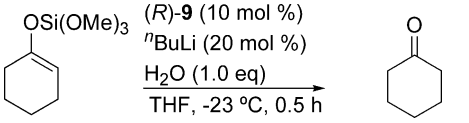

(4)

Control experiments showed that the trimethoxysilyl enol ether, which was stable under anhydrous conditions even in the presence of lithium binaphtholate, quickly decomposed into the corresponding ketone in aqueous conditions in the presence of lithium binaphtholate (Eqs. 3 and 4).[15] This suggests that the coordination of water (or hydroxy ion) to silicon atom may increase the nucleophilicity of the silicate complex to predominantly afford the *syn*-adduct via an acyclic transition state, while under anhydrous conditions the reaction may proceed via a cyclic chairlike transition state[4,5] to predominantly yield the *anti* adduct, but the details of reaction mechanism are unclear.

An evaluation of the binaphthol derivatives is shown in Table 8. Although both steric and electronic factor influenced the selectivity, binaphthols with halogen substituents at 3,3′-position gave relatively superior results. Consequently, dibromide **9** gave the best result in terms of diastereo- and enantioselectivity.

Table 9 shows the results of the aldol reactions of trimethoxysilyl enol ethers derived from various ketones and benzaldehyde under optimal conditions. In all cases, the corresponding *syn*-adducts were predominantly obtained in good to excellent yields. Enantioselectivities of (*E*)-enolates (entries 2, 3 and 5) were comparable to that of **1a** (entry 1), while (*Z*)-enolate demonstrated relatively low selectivity, similar to anhydrous conditions (entry 4). Among various silyl enol ethers, indanone derivative **1g** gave the best enantioselectivity (entry 5). Triethoxysilyl enol ether **1h**

Table 10. Aldol reaction of **1g** with various aldehydes under hydrous condition

Entry	Aldehyde	Product	Yield (%)	*syn*:*anti*[a]	ee (%) (*syn*/*anti*)[a]
1	PhCHO	**2g**	78	2.9:1	83/48
2	*p*-$MeOC_6H_4CHO$	**2j**	89	2.4:1	70/25
3	*p*-$CF_3C_6H_4CHO$	**2k**	88	2.1:1	48/39
4	PhCH=CHCHO	**2l**	98	3.4:1	73/10
5	$PhCH_2CH_2CHO$	**2m**	90	2.6:1	92/47
6	[c]HexCHO	**2n**	94	1.4:1	97/84

[a] Determined by HPLC analysis.

Table 11. Aldol reaction of **1a** with various aldehyde under hydrous condition

Entry	Aldehyde	Product	Yield (%)	*syn*:*anti*[a]	ee (%) (*syn*/*anti*)[a]
1	PhCHO	**2a**	94	3.1:1	80/50
2	1-NaphCHO	**2o**	90	1.4:1	81/65
3	2-NaphCHO	**2p**	94	1.6:1	72/45
4	PhCH=CHCHO	**2h**	96	1.4:1	75/5
5	$PhCH_2CH_2CHO$	**2i**	75	1.2:1	91/40

[a] Determined by HPLC analysis.

showed a significantly decreased reactivity, although the yield and stereoselectivities were about the same (entry 6).

Table 10 summarizes the aldol reactions of indanone derivative **1g** with various aldehydes. Introducing both electron donating/withdrawing groups decreased the enantioselectivity (entries 2 and 3). Interestingly, rather high enantioselectivities were observed in the reaction of unconjugate aldehydes (entries 5–7), which showed quite low reactivities under anhydrous conditions (Table 5, entry 3). The best enantioselectivity (97% ee) was obtained in the reaction of cyclohexenecarboxaldehyde, though the diastereoselectivity decreased (entry 6).

Table 11 shows the reaction of cyclohexanone derivative **1a** with various aldehydes. Though diastereoselectivities are not satisfactory, modest to high enantioselectivities were generally obtained. The best enantioselectivity was observed in the reaction of unconjugate aldehyde **2i** (entry 7, 91% ee). It is noteworthy that the aldol reaction of unconjugate aldehydes, which often gives inferior results under Lewis base-catalyzed condition, afforded adducts in high yield and with high enantioselectivity.

3. Conclusion

An aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate was developed, wherein water served as an additive and played a pivotal role in stereoselectivities. This is the first example of an aldol reaction of trimethoxysilyl enol ether catalyzed by a chiral base. Mechanistic studies as well as designing a new chiral catalyst to enhance the stereoselectivities are currently underway.

4. Experimental

4.1. General

Melting points were measured using a Büchi 535 melting point apparatus and were not corrected. Optical rotations were obtained on a JASCO P-1030 digital polarimeter. Infrared spectra were recorded on a JASCO FT/IR-5300. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL EX-270 (^{1}H, 270 MHz; ^{13}C, 68 MHz) spectrometer in deuteriochloroform. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Coupling constants (J) are reported in Hertz (Hz). NMR data are presented as follows: chemical shift, multiplicity, integration, coupling constant. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on JEOL JMS-DX303 or JEOL FABmate. HPLC was performed on a JASCO PU-1580 with a JASCO UV-1575 (λ=254 nm) and chiral separations were performed using Daicel chiralpak or chiralcel columns (φ 0.46×25 cm). Hexane and 2-propanol for HPLC were HPLC grade and filtered and degassed before use. HPLC peaks of *syn*/*anti* isomers were assigned by the comparing to authentic samples prepared with racemic binaphthol as a catalyst. The relative configurations of new compounds were assigned based on the splitting pattern of the hydroxyl bearing methine.[4b]

Column chromatography was conducted on Silica Gel 60 N (spherical, neutral, 60–210 μm, Kanto Chemical Co.). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet and stains. TLC stains were prepared as follows; *p*-anisaldehyde stain: EtOH (460 mL), *p*-anisaldehyde (13 mL), AcOH (5 mL), concd H_2SO_4 (17 mL).; PMA stain: EtOH solution of phosphomolybdic acid (5% wt); PMA/H_2SO_4 stain: H_2O (400 mL), phosphoric acid (6 mL), concd H_2SO_4 (20 mL), phosphomolybdic acid (9.6 g).

Reagents and solvents were purchased and purified by standard means or used as received unless otherwise noted. Dehydrated stabilizer free THF and dichloromethane were purchased from Kanto Chemical Co., Inc. and used as received. Concentration of *n*-butyllithium was estimated by titrating with diphenylacetic acid in THF.[16]

4.2. Representative procedures for the synthesis of trimethoxysilyl enol ethers by hydrosilylation

Trimethoxysilyl enol ethers **1a** and **1b** were prepared by modifying a literature procedure.

4.2.1. 1-Trimethoxysilyloxycyclohexene (1a).[7b] To an orange solution of $Rh(PPh_3)_3Cl$ (20.5 mg, 23 μmol, 0.025 mol%) in 2-cyclohexen-1-one (8.6 g, 90 mmol) was added trimethoxysilane (14.3 g, 117 mmol, 1.3 equiv) under an argon atmosphere at room temperature. After heating at 90 °C for 30 min, the reaction mixture was cooled to room temperature. Ice-cooled satd $NaHCO_3$ (15 mL) was added and the mixture was vigorously stirred. After removing the cloudy material by Celite filtration and washing with hexane, the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the crude product as a pale yellow oil. Distillation in vacuo (118–119 °C, 20 mmHg) gave the silyl enol ether as a colorless oil (15.1 g, 77%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.46–1.54 (m, 2H), 1.59–1.70 (m, 2H), 1.97–2.10 (m, 2H), 3.58 (s, 9H), 5.05–5.07 (m, 1H).

4.2.2. 1-Trimethoxysilyloxycycloheptene (1b).[7b] Following the representative procedure, silyl enol ether **1b** was obtained from 2-cyclohepten-1-one (0.28 g, 2.5 mmol) as a colorless oil (0.32 g, 56%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.47–1.81 (m, 6H), 1.91–2.02 (m, 2H), 2.28–2.32 (m, 2H), 3.58 (s, 9H), 5.21 (t, 1H, J=6.5 Hz).

4.3. Representative procedure for the synthesis of trimethoxysilyl enol ethers via enolate

4.3.1. 1-Trimethoxysilyloxy-1-phenylethylene (1c). *Method A*. To a solution of diisopropylamine (2.9 g, 28.8 mmol, 1.15 equiv) in THF (50 mL) was added *n*-butyllithium in hexane (1.6 M, 17.2 mL, 27.5 mmol, 1.1 equiv) at −78 °C. After stirring for 15 min, acetophenone (3.0 g, 25 mmol) was added dropwise to the pale yellow mixture via a cannula over a 30 min period. After stirring an additional 15 min, chlorotrimethoxysilane[11] (4.31 g, 27.5 mmol, 1.1 equiv) was added dropwise and

the entire mixture was stirred for 30 min. The mixture was evaporated and the resulting white precipitate was removed by Celite filtration and washed with hexane. Ice-cooled satd $NaHCO_3$ (30 mL) was added to the filtrate and the mixture was stirred vigorously. After removing the cloudy material by Celite filtration, the organic layer was dried over Na_2SO_4 and evaporated to give the crude product as a brown oil. Distillation in vacuo (122–124 °C, 14 mmHg) gave the silyl enol ether as a colorless oil (2.7 g, 45% yield).

Method B. To a solution of anhydrous sodium iodide (8.25 g, 55 mmol, 1.1 equiv; dried over 5 mmHg, 150 °C, 6 h) in acetonitrile (60 mL) was added chlorotrimethoxysilane[11] (8.61 g, 55 mmol, 1.1 equiv) at room temperature under an argon atmosphere. After stirring for 5 min, acetophenone (6.0 g, 50 mmol) was added and the mixture was stirred for additional 5 min. Triethylamine (12.6 g, 125 mmol, 2.5 equiv) was added dropwise to the pale yellow mixture. After refluxing for 3 h, the mixture was extracted with hexane (5×80 mL). The organic layer was evaporated and the precipitates were removed by Celite filtration. Ice-cooled satd $NaHCO_3$ was added to the filtrate and the mixture was vigorously stirred. After removing the cloudy material by Celite filtration, the organic layer was dried over Na_2SO_4 and evaporated to give the crude product as a brown oil. Distillation in vacuo (108–110 °C, 9 mmHg) gave the silyl enol ether as a colorless oil (5.0 g, 42% yield).

Compound **1c**. ^{1}H NMR δ 3.62 (s, 9H, SiOC*H*$_3$), 4.72 (d, 1H, J=2.2 Hz), 5.00 (d, 1H, J=2.2 Hz), 7.34–7.28 (m, 3H), 7.65–7.60 (m, 2H); ^{13}C NMR δ 51.6, 92.0, 125.1, 128.2, 128.4, 136.3, 153.8; IR (neat) 2945, 2840, 1692, 1621, 1573, 1492, 1317, 1201, 1096, 1037, 828, 775, 743, 715 cm^{-1}; LR-EIMS 241 ((M+H)$^+$), 120, 105, 77; HR-EIMS calcd for $C_{11}H_{16}O_4Si$ 241.0896, found 241.0892.

4.3.2. (*Z*)-*tert*-butylpropenyloxytrimethoxysilane (1f).[7b] Following the representative procedure A, silyl enol ether **1f** was obtained from 2,2-dimethyl-3-pentanone (0.57 g, 5 mmol) as a colorless oil (0.87 g, 74%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.09 (s, 9H), 1.57 (d, 3H, J=6.5 Hz), 3.68 (s, 9H), 4.64 (q, 1H, J=6.6 Hz).

4.3.3. 1-Trimethoxysilyloxycyclopentene (1d).[7b] Following the representative procedure A, silyl enol ether **1d** was obtained from cyclopentanone (2.1 g, 25 mmol) as a colorless oil (2.7 g, 53%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.86–1.95 (m, 2H), 2.26–2.38 (m, 4H), 3.62 (s, 9H), 4.84–4.86 (m, 1H).

4.3.4. (*Z*)-trimethoxy-(1-phenylpropenyloxy)silane (1e). Following the representative procedure A, silyl enol ether **1e** was obtained from propiophenone (3.4 g, 25 mmol) as a colorless oil (1.7 g, 27%, *E*/*Z* 1:34). Bp 116 °C, 11 mmHg; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.80 (d, 3H, J=6.5 Hz), 3.49 (s, 9H), 5.37 (q, 1H, J=6.5 Hz), 7.32–7.18 (m, 3H), 7.51 (d, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 148.0, 137.9, 128.2, 127.4, 125.0, 105.8, 51.4, 11.0; IR (neat) 3057, 2947, 2847, 2361, 1948, 1690, 1659, 1599, 1495, 1447, 1381, 1323, 1267, 1196, 1100, 1032 cm^{-1}; LR-EIMS 254 (M$^+$), 225 (bp), 121; HR-EIMS calcd for $C_{12}H_{17}O_4Si$ 254.0974, found 254.0966.

4.3.5. 1-Trimethoxysilyloxy-3*H*-indene (1g). Following the representative procedure A, silyl enol ether **1g** was obtained from 1-indanone (3.3 g, 25 mmol) as a colorless oil (1.7 g, 62%). Bp 125 °C, 4 mmHg; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.27 (d, 2H, J=2.5 Hz), 3.65 (s, 9H), 5.67 (t, 1H, J=2.5 Hz), 7.1–7.5 (m, 4H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 151.6, 142.6, 140.5, 126.0, 125.2, 123.8, 118.0, 107.3, 51.5, 33.8; IR (neat) 2948, 2847, 1605, 1578, 1366, 1181, 1082, 901, 837 cm^{-1}; LR-EIMS 252 (M$^+$), 236 (bp), 121, 91; HR-EIMS calcd for $C_{12}H_{16}O_4Si$ 252.0818, found 252.0806.

4.3.6. 1-Triethoxysilyloxycyclohexene (1h).[17] Following the representative procedure A, silyl enol ether **11** was obtained from cyclohexanone (0.98 g, 10 mmol) and chlorotriethoxysilane (2.2 g, 11 mmol) as a colorless oil (1.6 g, 62%). Bp 87–89 °C, 9 mmHg; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.22 (t, 9H, J=6.5 Hz), 1.47–1.56 (m, 2H), 1.63–1.67 (m, 2H), 1.97–2.10 (m, 4H), 3.85 (q, 6H, J=6.5 Hz), 5.07 (m, 1H).

4.4. Synthesis of 3,3′-disubstituted binaphthol derivatives

Binaphthol derivatives **10**–**16** were prepared by literature procedure.

4.4.1. (*R*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diol (10).[18] TLC R_f=0.5 (benzene, PMA/H_2SO_4); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.49 (s, 6H), 5.10 (s, 2H), 7.05 (d, 2H, J=8.6 Hz), 7.20 (d, 2H, J=7.3 Hz), 7.32 (t, 2H, J=6.5 Hz), 7.79–7.81 (m, 4H); mp 199–201 °C; $[\alpha]_D$ +33.7 (*c* 1.0, $CHCl_3$); $[\alpha]_{546}$ +43.9 (*c* 1.0, $CHCl_3$).

4.4.2. (*R*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol (11).[19] TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.34 (s, 2H), 7.20–7.51 (m, 12H), 7.70–7.74 (m, 4H), 7.91 (d, 2H, J=7.8 Hz), 8.01 (s, 2H); mp 197–199 °C; $[\alpha]_D$ +104.3 (*c* 1.0, $CHCl_3$).

4.4.3. (*R*)-3,3′-dichloro-1,1′-binaphthalene-2,2′-diol (13).[20] TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.55 (s, 2H), 7.09 (d, 2H, J=8.4 Hz), 7.28–7.40 (m, 8H), 7.80 (d, 2H, J=8.6 Hz), 8.06 (s, 2H); mp 167–170 °C; $[\alpha]_D$ +90.3 (*c* 1.0, $CHCl_3$).

4.4.4. (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol (14).[20] TLC R_f=0.5 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.41 (s, 2H), 7.05 (d, 2H, J=8.6 Hz), 7.26–7.38 (m, 8H), 7.77 (d, 2H, J=8.6 Hz), 8.50 (s, 2H); mp>300 °C; $[\alpha]_D$ +100.9 (*c* 1.0, THF).

4.4.5. (*R*)-3,3′-bis(methoxycarbonyl)-1,1′-binaphthalene-2,2′-diol (16).[21] TLC R_f=0.4 (hexane/AcOEt 4:1, PMA/H_2SO_4); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.04 (s, 6H), 7.11–7.15 (m, 2H), 7.29–7.35 (m, 4H), 7.88–7.92 (m, 2H), 8.67 (s, 2H); mp 244–246 °C; $[\alpha]_D$ +170.5 (*c* 1.1, THF).

4.4.6. (*R*)-3,3′-bis(trifluoromethyl)-1,1′-binaphthalene-2,2′-diol (12).[22] To a double-necked 20 mL round-bottomed flask equipped with a magnetic stirring bar, septum, and dry-ice condenser containing activated cadmium (675 mg,

6 mmol) was added DMF (2.5 mL) under argon atmosphere. Dibromodifluoromethane (0.28 mL, 3 mmol) was added to the mixture at 0 °C and the entire mixture was immediately warmed to room temperature. After stirring for 2 h, the suspension was filtered with glass filter under argon pressure and the precipitate was washed with DMF (0.5 mL). To the resulting brown solution, HMPA (3.0 mL) was added followed by cuprous bromide (215 mg, 1.5 mmol) in one portion at 0 °C. After stirring for a few minutes, 3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (62.6 mg, 0.1 mmol), which was prepared by the literature procedure[20] was added in one portion and then the reaction mixture was heated at 70 °C for 6 h. Benzene (10 mL) and H_2O (5 mL) were added to the reaction mixture and the mixture was vigorously stirred at room temperature for 12 h. After removing the precipitate by Celite filtration, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The brown residue was purified with silica gel column chromatography (hexane/benzene, 1:1). Dichloromethane (2 mL), methanol (2 mL), and concd HCl (0.3 mL) were added to the resulting yellow oil and the mixture was stirred overnight at room temperature. Then the organic layer was washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. Purification with silica gel column chromatography (hexane/AcOEt, 20:1) afforded 3,3′-bis(trifluoromethyl)-1,1′-binaphthalene-2,2′-diol (34.0 mg, 81% yield) as pale yellow prisms. TLC $R_f=0.4$ (hexane/AcOEt 8:1, UV); ^{1}H NMR δ 5.35 (br, 2H), 7.10 (d, 2H, $J=7.3$ Hz), 7.44 (m, 4H), 7.86 (d, 2H, $J=7.3$ Hz), 8.36 (s, 2H); IR (KBr) 3549, 3063, 1630, 1332, 1207, 1155 cm^{-1}; $[\alpha]_D^{23}$ +657 (*c* 1.01, THF); mp 235–237 °C; LR-FABMS 422 (M^+); 154, 136; HR-FABMS calcd 422.0742 found 422.0752; Anal. Calcd for $C_{22}H_{12}F_6O_2$: C, 62.57; H, 2.86 found C, 62.18; H, 2.96.

4.4.7. (*R*)-3,3′-bis(methoxymethyl)-1,1′-binaphthalene-2,2′-diol (16). To a 20 mL round-bottomed flask equipped with magnetic stirring bar containing sodium hydride (65%, 57 mg, 1.5 mmol, 2.4 equiv) and THF (5 mL) was added THF (5 mL) solution of (*R*)-3,3′-bis(hydroxymethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (277 mg, 0.64 mmol) prepared by the literature procedure[23] via a cannula. After stirring for 1 h, methyl iodide (0.25 mL, 4.0 mmol, 6.3 equiv) was added to the resulting yellow solution, which was then stirred additional 2 days. After the reaction was completed, water (10 mL) was added to the mixture and the entire mixture was extracted with AcOEt (3×50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give (*R*)-3,3′-bis(methoxymethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl as a yellow oil (288 mg, 98% (crude)). Dichloromethane (5 mL) was added to this crude product, followed by concd HCl aq (0.3 mL), and the solution was stirred for 2 h at room temperature. The reaction mixture was neutralized with satd $NaHCO_3$ and extracted with AcOEt (3×50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The resulting yellow oil was purified with silica gel column chromatography (12 g SiO_2, CH_2Cl_2/AcOEt 100:1→20:1). Recrystalization of resulting yellow solid (hexane/AcOEt 4:1) gave 3,3′-bis(methoxymethyl)-1,1′-binaphthalene-2,2′-diol as colorless prisms (1st crop, 90.2 mg, 38%) and pale yellow prisms (2nd crop, 55.4 mg, 23%). TLC $R_f=0.25$ (hexane/AcOEt 1:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.51 (s, 3H), 4.84 (dd, 2H, $J=12.7$, 16.4 Hz), 7.11 (d, 1H, $J=8.4$ Hz), 7.2–7.4 (m, 2H), 7.82 (s, 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 58.5, 72.5, 113.9, 123.8, 124.5, 125.5, 126.8, 128.1, 128.5, 128.8, 133.5, 151.3; IR (KBr) 3526, 3294, 1626, 1504, 1392, 1194, 1107, 922 cm^{-1}; mp 143–144 °C; $[\alpha]_D$ +20.2 (*c* 0.78, $CHCl_3$); LR-FABMS 374 (M^+); HR-FABMS calcd 374.1518 found 374.1505; Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92 found C, 77.20; H, 6.02.

4.5. General procedure for the aldol reaction of trimthoxysilyl enol ethers under anhydrous conditions

To a stirred solution of (*R*)-3,3′-dibromo-1,1′-binaphthalene-2,2′-diol **9** (21.0 mg, 0.047 mmol, 0.1 equiv) in THF (3 mL) was added *n*-butyllithium in hexane (0.16 M, 0.6 mL, 0.094 mmol, 0.2 equiv) at −23 °C, and the resulting yellow mixture was stirred for a few minutes. Then a solution aldehyde in THF (1.0 M, 0.47 mL, 0.47 mmol) and trimethoxysilyl enol ether (0.70 mmol, 1.5 equiv) were added. The mixture was stirred for 0.5 h at the same temperature and the reaction was quenched with KF/KH_2PO_4 aq (15% KF, 10% KH_2PO_4 solution, 2 mL). The entire mixture was stirred for an additional 2 h and the mixture was diluted with AcOEt (10 mL). The organic layer was washed three times with brine, dried over Na_2SO_4, and then evaporated. The crude product was purified by silica gel column chromatography (9.0 g SiO_2, CH_2Cl_2/hexane 8:1, then CH_2Cl_2/AcOEt 160:1→10:1) to give the corresponding aldol adduct as a *syn*/*anti* mixture. The enantiomeric excess of the adduct was determined by chiral HPLC.

4.5.1. 2-(Hydroxyphenylmethyl)cyclohexanone (2a).[7b] Following the general procedure, the aldol adduct **2a** was obtained from silyl enol ether **1a** and benzaldehyde as a colorless oil (93.4 mg, 97%, *syn*/*anti* 1:3.7, *syn* 8% ee, *anti* 51% ee). TLC $R_f=0.35$ (*syn*), 0.30 (*anti*) (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.4–1.9 (m, 8H), 2.0–2.1 (m, 4H), 2.3–2.7 (m, 4H), 2.99 (d, 1H, $J=2.7$ Hz), 3.93 (m, 1H), 4.79 (d, 1H, $J=8.9$ Hz), 5.40 (d, 1H, $J=2.7$ Hz), 7.2–7.4 (m, 10H); HPLC (Daicel chiralcel OD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 9.4 (*syn*-minor, 2*S*, 1′*S*), 10.6 (*syn*-major, 2*R*, 1′*R*), 12.5 (*anti*-major, 2*S*, 1′*R*), 18.5 min (*anti*-minor, 2*R*, 1′*S*).

4.5.2. 2-(Hydroxyphenylmethyl)cycloheptanone (2b).[7b] Following the general procedure, the aldol adduct **2b** was obtained from silyl enol ether **1b** and benzaldehyde as a colorless oil (93.0 mg, 91%, *syn*/*anti* 1.4:1, *syn* 39% ee, *anti* 42% ee). TLC $R_f=0.5$ (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.2–1.9 (m, 14H), 2.4–2.7 (m, 4H), 2.85 (m, 1H), 3.00 (m, 1H), 3.3–3.5 (m, 2H), 4.82 (d, 1H, $J=8.4$ Hz), 5.19 (d, 1H, $J=2.7$ Hz), 7.2–7.5 (m, 10H); HPLC (Daicel chiralpak AD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 11.8 (*syn*-major), 13.4 (*syn*-minor), 20.2 (*anti*-minor), 23.5 min (*anti*-major).

4.5.3. 2-(Hydroxyphenylmethyl)cyclopentanone (2d).[7b] Following the general procedure, the aldol adduct **2d** was obtained from silyl enol ether **1d** and benzaldehyde as a colorless oil (83.0 mg, 93%, *syn*/*anti* 3.4:1, *syn* 46% ee, *anti* 30% ee). TLC $R_f=0.4$ (hexane/AcOEt 4:1,

p-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.6–2.5 (m, 14H), 4.69 (d, 1H, J=9.5 Hz), 5.29 (t, 1H, J=4.0 Hz), 7.2–7.4 (m, 10H); HPLC (Daicel chiralcel OD-H, hexane/IPA 9:1, 1.0 mL/min): t_R 7.9 (*syn*-minor), 9.5 (*syn*-major), 11.5 (*anti*-minor, 2*S*, 1′*R*), 13.7 min (*anti*-major, 2*R*, 1′*S*).

4.5.4. 3-Hydroxy-1,3-diphenyl-1-propanone (2c).[24] Following the general procedure, the aldol adduct **2c** was obtained from silyl enol ether **1c** and benzaldehyde as a colorless oil (98.0 mg, 92%, 50% ee). TLC R_f=0.25 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.38 (d, 2H, J=6.1 Hz), 5.36 (t, 1H, J=6.1 Hz), 7.3–7.6 (m, 8H), 7.9–8.0 (m, 2H); HPLC (Daicel chiralcel OB-H, hexane/IPA 9:1, 1.0 mL/min) t_R 17.8 min (major, *R*), 25.8 min (minor, *S*).

4.5.5. 3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (2e).[4b] Following the general procedure, the aldol adduct **2e** was obtained from silyl enol ether **1e** and benzaldehyde as a colorless oil (111 mg, 98%, *syn*/*anti* 1:1.7, *syn* ~0% ee, *anti* ~0% ee). TLC R_f=0.20 (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.06 (d, 3H, J=7.3 Hz), 1.18 (d, 3H, J=7.3 Hz), 2.94 (d, 1H, J=4.6 Hz), 3.7–3.9 (m, 3H), 4.95 (m, 1H), 5.23 (s, 1H), 7.2–7.6 (m, 17H), 7.9–8.0 (m, 3H); HPLC (Daicel chiralcel OD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 10.5 (*syn*), 12.3 (*syn*), 15.2 (*anti*), 16.9 min (*anti*).

4.5.6. 1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one (2f).[7b] Following the general procedure, the aldol adduct **2f** was obtained from silyl enol ether **1f** and benzaldehyde as a colorless oil (91.0 mg, 87%, *syn*/*anti* 1.8:1, *syn* ~0% ee, *anti* ~0% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, KI/I_2 aq, H_2SO_4); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.9–1.1 (m, 24H), 3.1–3.4 (m, 3H), 3.5–3.6 (m, 1H), 4.75 (d, 1H, J=7.3 Hz), 5.23 (d, 1H, J=4.1 Hz), 7.1–7.4 (m, 10H); HPLC (Daicel chiralpak AD-H, hexane/IPA 40:1, 1.0 mL/min): t_R 11.1 (*syn*), 11.7 (*syn*), 12.8 (*anti*), 15.1 min (*anti*).

4.5.7. 2-(1-Hydroxy-3-phenyl-2-propenyl)cyclohexanone (2h).[4b] Following the general procedure, the aldol adduct **2h** was obtained from silyl enol ether **1a** and cinnamaldehyde as a colorless oil (106 mg, 98%, *syn*/*anti* 1:1.5, *syn* 44% ee, *anti* 6% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.3–1.8 (m, 8H), 1.8–1.9 (m, 2H), 2.0–2.2 (m, 2H), 2.3–2.6 (m, 6H), 4.43 (t, 1H, J=8.1 Hz), 4.77 (m, 1H), 6.1–6.3 (m, 2H), 6.5–6.7 (m, 2H), 7.1–7.4 (m, 10H); HPLC (Daicel chiralcel AD-H, hexane/IPA 19:1, 1mL/min) t_R 32.8 (*syn*-major), 40.0 (*syn*-minor), 44.3 (*anti*-minor), 53.1 min (*anti*-major).

4.5.8. 2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (2i).[4b] Following the general procedure, the aldol adduct **2i** was obtained from silyl enol ether **1a** and hydrocinnamaldehyde as a colorless oil (15 mg, 14%, *syn*/*anti* 2.9:1, *syn* 40% ee, *anti* 16% ee). TLC R_f=0.35 (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.5–1.9 (m, 12H), 2.0–2.2 (m, 4H), 2.3–2.5 (m, 4H), 2.5–2.7 (m, 3H), 2.8–3.0 (m, 2H), 3.51 (m, 1H), 3.73 (m, 1H), 4.10 (m, 1H), 7.1–7.3 (m, 10H, Ar-H); HPLC (Daicel chiralcel OJ-H, hexane/IPA 40:1, 1.0 mL/min): t_R 16.1 (*syn*-major), 20.5 (*syn*-minor), 23.2 (*anti*-major), 24.8 min (*anti*-minor).

4.6. The general procedure for the aldol reaction of trimethoxysilyl enol ethers under aqueous conditions. To a stirred solution of (*R*)-3,3′-dibromo-1,1′-binaphthalene-2,2′-diol **9** (21.0 mg, 0.047 mmol, 0.1 equiv) in THF (3 mL) was added H_2O in THF (2.8 M, 0.25 mL, 0.70 mmol, 1.5 equiv) and *n*-butyllithium in hexane (0.16 M, 0.6 mL, 0.094 mmol, 0.2 equiv) at −23 °C. The resulting yellow mixture was stirred for a few minutes and then a solution of aldehyde in THF (1.0 M, 0.5 mL, 0.47 mmol) and trimethoxysilyl enol ether (0.70 mmol, 1.5 equiv) were added. The mixture was stirred for 0.5 h at the same temperature and the reaction was quenched with KF/KH_2PO_4 aq (15% KF, 10% KH_2PO_4 solution, 2 mL). The mixture was diluted with AcOEt (10 mL) and washed three times with brine. The organic layer was dried over Na_2SO_4 and then evaporated. The crude product was purified by silica gel column chromatography (CH_2Cl_2/hexane 8:1, then CH_2Cl_2/AcOEt 160:1→10:1) to give the corresponding aldol adduct as a *syn*/*anti* mixture. The enantiomeric excess of the adduct was determined by chiral HPLC.

4.6.1. 2-(Hydroxyphenylmethyl)cyclohexanone (2a).[7b] Following the general procedure, the aldol adduct **2a** was obtained from silyl enol ether **1a** and benzaldehyde as a colorless oil (89.2 mg, 93%, *syn*/*anti* 3.1:1, *syn* 80% ee, *anti* 50% ee). TLC R_f=0.35 (*syn*), 0.30 (*anti*) (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.4–1.9 (m, 8H), 2.0–2.1 (m, 4H), 2.3–2.7 (m, 4H), 2.99 (d, 1H, J=2.7 Hz), 3.93 (m, 1H), 4.79 (d, 1H, J=8.9 Hz), 5.40 (d, 1H, J=2.7 Hz), 7.2–7.4 (m, 10H); HPLC (Daicel chiralcel OD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 9.4 (*syn*-minor, 2*S*, 1′*S*), 10.6 (*syn*-major, 2*R*, 1′*R*), 12.5 (*anti*-major, 2*S*, 1′*R*), 18.5 min (*anti*-minor, 2*R*, 1′*S*).

4.6.2. 2-(Hydroxyphenylmethyl)cyclopentanone (2d).[7b] Following the general procedure, the aldol adduct **2d** was obtained from silyl enol ether **1d** and benzaldehyde as a colorless oil (88 mg, 98%, *syn*/*anti* 2.9:1, *syn* 72% ee, *anti* 6% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.6–2.5 (m, 14H), 4.69 (d, 1H, J=9.5 Hz), 5.29 (t, 1H, J=4.0 Hz), 7.2–7.4 (m, 10H); HPLC (Daicel chiralcel OD-H, hexane/IPA 9:1, 1.0 mL/min): t_R 7.9 (*syn*-minor), 9.5 (*syn*-major), 11.5 (*anti*-minor, 2*S*, 1′*R*), 13.7 min (*anti*-major, 2*R*, 1′*S*).

4.6.3. 3-Hydroxy-1,3-diphenyl-1-propanone (2c).[24] Following the general procedure, the aldol adduct **2c** was obtained from silyl enol ether **1c** and benzaldehyde as a colorless oil (94 mg, 88%, 75% ee). TLC R_f=0.25 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.38 (d, 2H, J=6.1 Hz), 5.36 (t, 1H, J=6.1 Hz), 7.3–7.6 (m, 8H), 7.9–8.0 (m, 2H); HPLC (Daicel chiralcel OB-H, hexane/IPA 9:1, 1.0 mL/min) t_R 17.8 min (major, *R*), 25.8 min (minor, *S*).

4.6.4. 3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (2e).[4b] Following the general procedure, the aldol adduct **2e** was obtained from silyl enol ether **1e** and benzaldehyde as a colorless oil (103 mg, 91%, *syn*/*anti* 1.9:1, *syn* 19% ee, *anti* 38% ee). TLC R_f=0.20 (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.06 (d, 3H, J=7.3 Hz), 1.18 (d, 3H, J=7.3 Hz), 2.94 (d, 1H, J=4.6 Hz), 3.7–3.9 (m, 3H), 4.95 (m, 1H), 5.23 (s, 1H), 7.2–7.6

(m, 17H), 7.9–8.0 (m, 3H); HPLC (Daicel chiralcel OD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 10.5 (*syn*-major), 12.3 (*syn*-minor), 15.2 (*anti*-minor), 16.9 min (*anti*-major).

4.6.5. 2,3-Dihydro-2-(hydroxyphenylmethyl)-1*H*-inden-1-one (2g).[25] Following the general procedure, the aldol adduct **2g** was obtained from silyl enol ether **1g** and benzaldehyde as a colorless oil (88 mg, 78%, *syn*/*anti* 2.9:1, *syn* 83% ee, *anti* 48% ee). TLC R_f=0.35 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.24 (d, 1H, J= 4.9 Hz), 2.67 (m, 1H), 2.8–3.1 (m, 3H), 3.25 (dd, 1H, J= 4.0, 16.7 Hz), 4.78 (d, 1H, J=9.5 Hz), 5.59 (m, 1H), 7.2–7.4 (m, 14H), 7.5–7.6 (m, 2H), 7.6–7.8 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 26.6, 54.7, 71.9, 124.1, 126.5, 127.0, 128.5, 135.5, 137.0, 142.6, 154.8, 207.3 (*syn*); 29.8, 53.1, 75.6, 124.1, 126.5, 127.2, 128.4, 134.9, 136.4, 141.3, 154.0, 209.6 (*anti*); $[\alpha]_D^{25}$ +108 (*c* 1.0, $CHCl_3$); IR (KBr) 3553, 3449, 3055, 2910, 1703, 1605, 1462, 1449, 1329, 1294, 1280, 1095, 765 cm^{-1}; LR-EIMS 238 (M^+), 219, 132; HR-EIMS calcd for $C_{16}H_{14}O_2$ 238.0994 found 238.0990; HPLC (Daicel chiralpak AS-H, hexane/IPA 9:1, 1.0 mL/min): t_R 15.4 (*anti*-minor), 16.9 (*anti*-major), 22.1 (*syn*-minor), 34.2 min (*syn*-major).

4.6.6. 2,3-Dihydro-2-[hydroxy-(4-methoxyphenyl)-methyl]-1*H*-inden-1-one (2j). Following the general procedure, the aldol adduct **2j** was obtained from silyl enol ether **1g** and *p*-anisaldehyde as a colorless oil (113 mg, 89%, *syn*/*anti* 2.4:1, *syn* 70% ee, *anti* 25% ee). TLC R_f=0.3 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.6–2.7 (m, 1H), 2.8–3.0 (m, 4H), 3.2–3.3 (m, 1H), 3.77 (s, 6H), 4.78 (d, 1H, J=19.1 Hz), 5.51 (s, 1H), 6.8–6.9 (m, 4H), 7.3–7.8 (m, 12H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 26.7, 29.8, 53.1, 54.7, 55.1, 71.4, 75.0, 76.6, 113.6, 113.8, 123.7, 124.0, 126.4, 126.5, 126.6, 127.1, 127.5, 128.1, 133.4, 134.8, 135.3, 136.2, 136.9, 153.9, 154.8, 158.6, 159.3, 207.5, 209.6 (*syn*/*anti* mixture); $[\alpha]_D^{25}$ +143 (*c* 1.2, $CHCl_3$); IR (KBr) 3493, 1692, 1609, 1512, 1298, 1256, 1092, 1028, 853 cm^{-1}; LR-EIMS 268 (M^+), 132; HR-EIMS calcd for $C_{17}H_{16}O_3$ 268.1099 found 268.1102; HPLC (Daicel chiralpak AS-H, hexane/IPA 3:1, 1.0 mL/min): t_R 10.2 (*anti*-minor), 13.7 (*anti*-major), 17.6 (*syn*-major), 30.2 min (*syn*-minor).

4.6.7. 2,3-Dihydro-2-[hydroxy-(4-trifluoromethyl-phenyl)methyl]-1*H*-inden-1-one (2k). Following the general procedure, the aldol adduct **2k** was obtained from silyl enol ether **1g** and *p*-(trifluoromethyl)benzaldehyde as a colorless oil (128 mg, 88%, *syn*/*anti* 2.1:1, *syn* 48% ee, *anti* 39% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.4–2.7 (m, 1H), 2.7–3.3 (m, 7H), 4.89 (d, 1H, J=8.9 Hz), 5.67 (br s, 1H), 7.3–7.8 (m, 16H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 26.5, 29.6, 53.0, 54.7, 71.1, 75.1, 122.3, 123.9, 124.2, 125.3, 125.4, 125.5, 125.6, 125.7, 125.8, 126.5, 126.6, 127.3, 127.4, 127.9, 129.3, 129.7, 130.2, 130.6, 135.2, 135.7, 136.1, 136.8, 145.2, 146.8, 153.7, 154.7, 207.0, 209.1 (*syn*/*anti* mixture); $[\alpha]_D^{25}$ +40.1 (*c* 1.0, $CHCl_3$); IR (KBr) 3433, 1693, 1604, 1467, 1413, 1325, 1298, 1163, 1109, 1064, 1016 cm^{-1}; LR-EIMS 306 (M^+), 288, 173, 132 (bp); HR-EIMS calcd for $C_{17}H_{13}O_2F_3$ 306.0868 found 306.0858; HPLC (Daicel chiralpak AS-H, hexane/IPA 9:1, 1.0 mL/min): t_R 12.5 (*anti*-minor), 14.5 (*anti*-major), 15.6 (*syn*-major), 22.2 min (*syn*-minor).

4.6.8. 2,3-Dihydro-2-(1-hydroxy-3-phenyl-2-propen-yl)-1*H*-inden-1-one (2l). Following the general procedure, the aldol adduct **2l** was obtained from silyl enol ether **1g** and cinnamaldehyde as a colorless oil (122 mg, 98%, *syn*/*anti* 3.4:1, *syn* 73% ee, *anti* 10% ee). TLC R_f=0.2 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.8–3.0 (m, 2H), 3.1–3.3 (m, 4H), 4.52 (t, 1H, J=6.5 Hz), 5.02 (m, 1H), 6.2–6.3 (m, 2H), 6.7–6.8 (m, 2H), 7.2–7.8 (m, 18H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 27.3, 29.6, 52.0, 52.6, 71.6, 74.0, 123.8, 124.1, 126.4, 126.5, 126.6, 127.3, 127.6, 127.7, 127.8, 128.5, 128.7, 129.4, 131.0, 132.2, 135.0, 135.4, 136.3, 136.3, 136.4, 137.0, 154.0, 154.8, 207.8, 209.0 (*syn*/*anti* mixture); $[\alpha]_D^{25}$ +82.2 (*c* 0.96, $CHCl_3$); IR (KBr) 3478, 1698, 1605, 1464, 1329, 1296, 1205, 963, 765, 705 cm^{-1}; LR-EIMS 264 (M^+), 246, 132; HR-EIMS calcd for $C_{18}H_{16}O_2$ 264.1150 found 264.1158; HPLC (Daicel chiralpak AS-H, hexane/IPA 9:1, 1.0 mL/min): t_R 22.1 (*anti*-major), 26.8 (*anti*-minor), 31.8 (*syn*-minor), 37.2 min (*syn*-major).

4.6.9. 2,3-Dihydro-2-(1-hydroxy-3-phenylpropyl)-1*H*-inden-1-one (2m). Following the general procedure, the aldol adduct **2m** was obtained from silyl enol ether **1g** and hydrocinnamaldehyde as a colorless oil (113 mg, 90%, *syn*/*anti* 2.6:1, *syn* 92% ee, *anti* 47% ee). TLC R_f=0.3 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.7–2.0 (m, 4H), 2.4–2.9 (m, 8H), 3.1–3.3 (m, 2H), 3.84 (m, 1H), 4.38 (m, 1H), 7.1–7.7 (m, 18H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 27.2, 29.6, 29.7, 31.3, 32.4, 36.6, 37.3, 51.9, 53.1, 70.2, 71.7, 123.6, 123.9, 125.8, 125.9, 126.4, 126.5, 127.2, 127.6, 128.3, 128.4, 128.5, 128.7, 134.9, 135.3, 136.4, 137.0, 141.7, 142.0, 153.7, 154.7, 208.4, 209.9 (*syn*/*anti* mixture); $[\alpha]_D^{25}$ +39.6 (*c* 0.93, $CHCl_3$); IR (KBr) 3486, 1698, 1605, 1464, 1329, 1296, 1209, 1039, 770 cm^{-1}; LR-EIMS 266 (M^+), 248, 161, 132; HR-EIMS calcd for $C_{18}H_{18}O_2$ 266.1306 found 266.1299; HPLC (Daicel chiralpak AS-H, hexane/IPA 9:1, 1.0 mL/min) t_R 15.4 (*anti*-minor), 16.9 (*anti*-major), 22.1 (*syn*-minor), 34.2 min (*syn*-major).

4.6.10. 2,3-Dihydro-2-(hydroxycyclohexylmethyl)-1*H*-inden-1-one (2n). Following the general procedure, the aldol adduct **2n** was obtained from silyl enol ether **1g** and hydrocinnamaldehyde as a colorless oil (109 mg, 94%, *syn*/*anti* 1.4:1, *syn* 97% ee, *anti* 84% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.9–1.4 (m, 8H), 1.5–1.9 (m, 12H), 2.0–2.1 (m, 2H), 2.8–2.9 (m, 2H), 3.0–3.3 (m, 3H), 3.66 (d, 1H, J=9.2 Hz), 4.10 (d, 1H, J= 7.3 Hz), 4.2–4.3 (m, 1H), 7.3–7.8 (m, 8H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 25.6, 25.8, 26.1, 26.2, 26.4, 26.6, 26.7, 29.3, 29.5, 29.8, 30.1, 41.5, 41.9, 49.3, 50.8, 74.9, 76.4, 123.5, 123.8, 126.4, 126.5, 127.0, 127.5, 134.7, 135.2, 136.5, 137.2, 153.8, 154.9, 209.0, 211.0 (*syn*/*anti* mixture); $[\alpha]_D^{25}$ +46.8 (*c* 1.2, $CHCl_3$); IR (KBr) 3409, 2924, 2847, 1678, 1605, 1466, 1296, 1084, 1024, 960 cm^{-1}; LR-EIMS 244 (M^+), 161, 132; HR-EIMS calcd for $C_{16}H_{20}O_2$ 244.1463 found 244.1455; HPLC (Daicel chiralpak AD-H, hexane/IPA 19:1, 1.0 mL/min): t_R 15.4 (*anti*-minor), 19.4 (*anti*-major), 22.4 (*syn*-major), 28.4 min (*syn*-minor).

4.6.11. 2-(Hydroxy-1-naphthalenylmethyl)cyclohexanone (2o).[7b] Following the general procedure, the aldol adduct **2o** was obtained from silyl enol ether **1a** and 1-naphthaldehyde as a colorless oil (108 mg, 90%, *syn*/*anti*

1.4:1, *syn* 81% ee, *anti* 65% ee). TLC R_f=0.35 (*syn*), 0.30 (*anti*) (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.3–1.9 (m, 8H), 2.0–2.2 (m, 4H), 2.3–2.6 (m, 4H), 2.77 (m, 1H), 2.97 (m, 1H), 3.08 (d, 1H, J=3.3 Hz), 4.11 (d, 1H, J=3.3 Hz), 5.57 (m, 1H), 6.24 (br s, 1H), 7.4–7.6 (m, 7H), 7.7–7.9 (m, 6H), 8.25 (m, 1H); HPLC (Daicel chiralcel OD-H, hexane/IPA 40:1, 0.7 mL/min): t_R 19.0 (*syn*-minor), 26.3 (*syn*-major), 44.2 (*anti*-minor), 52.7 min (*anti*-major).

4.6.12. 2-(Hydroxy-2-naphthalenylmethyl)cyclohexanone (2p).[26] Following the general procedure, the aldol adduct **2p** was obtained from silyl enol ether **1a** and 2-naphthaldehyde as a colorless oil (113 mg, 94%, *syn*/*anti* 1.6:1, *syn* 72% ee, *anti* 45% ee). TLC R_f=0.30 (*syn*), 0.25 (*anti*) (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.3–1.8 (m, 8H), 2.0–2.2 (m, 4H), 2.3–2.6 (m, 4H), 2.7–2.8 (m, 2H), 3.13 (d, 1H, J=3.3 Hz), 4.03 (d, 1H, J=3.0 Hz), 4.95 (m, 1H), 5.56 (br s, 1H), 7.36 (d, 1H, J=8.7 Hz), 7.4–7.5 (m, 5H), 7.75 (m, 1H), 7.8–7.9 (m, 7H); HPLC (Daicel chiralcel OD-H, hexane/IPA 9:1, 1.0 mL/min): t_R 9.0 (*syn*-minor), 9.7 (*syn*-major), 11.0 (*anti*-minor), 13.5 min (*anti*-major).

4.6.13. 2-(1-Hydroxy-3-phenyl-2-propenyl)cyclohexanone (2h).[4b] Following the general procedure, the aldol adduct **2h** was obtained from silyl enol ether **1a** and cinnamaldehyde as a colorless oil (104 mg, 95%, *syn*/*anti* 1.4:1, *syn* 75% ee, *anti* 5% ee). TLC R_f=0.4 (hexane/AcOEt 4:1, UV); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.3–1.8 (m, 8H), 1.8–1.9 (m, 2H), 2.0–2.2 (m, 2H), 2.3–2.6 (m, 6H), 4.43 (t, 1H, J=8.1 Hz), 4.77 (m, 1H), 6.1–6.3 (m, 2H), 6.5–6.7 (m, 2H), 7.1–7.4 (m, 10H); HPLC (Daicel chiralpak AD-H, hexane/IPA 19:1, 1.0 mL/min) t_R 32.8 (*syn*-major), 40.0 (*syn*-minor), 44.3 (*anti*-minor), 53.1 min (*anti*-major).

4.6.14. 2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (2i).[4b] Following the general procedure, the aldol adduct **2i** was obtained from silyl enol ether **1a** and hydrocinnamaldehyde as a colorless oil (83 mg, 75%, *syn*/*anti* 1.2:1, *syn* 92% ee, *anti* 40% ee). TLC R_f=0.35 (hexane/AcOEt 4:1, *p*-anisaldehyde); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.5–1.9 (m, 12H), 2.0–2.2 (m, 4H), 2.3–2.5 (m, 4H), 2.5–2.7 (m, 3H), 2.8–3.0 (m, 2H), 3.51 (m, 1H), 3.73 (m, 1H), 4.10 (m, 1H), 7.1–7.3 (m, 10H); HPLC (Daicel chiralcel OJ-H, hexane/IPA 40:1, 1.0 mL/min): t_R 16.1 (*syn*-major), 20.5 (*syn*-minor), 23.2 (*anti*-major), 24.8 min (*anti*-minor).

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan, the Novartis Foundation for the Promotion of Science, and the SUNBOR GRANT.

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(*anti*); K: 12 h, 66% yield, *syn*/*anti* 1:1.5, <10% ee (*syn*), 28% ee (*anti*); Rb: no reaction).
13. Lowering the reaction temperature did not increase the selectivities (−45 °C: 77% yield, *syn*/*anti* 3.0:1, 76% ee (*syn*), 45% ee (*anti*)).
14. Catalyst prepared from 10 mol% of BuLi only resulted in trace amounts of product, while excess BuLi (40 mol%) did not influence the yields or selectivities (98% yield, *syn*/*anti* 3.0:1, 80% ee (*syn*), 50% ee (*anti*)).
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Novel metal-free Lewis acid catalysis by phosphonium salts through hypervalent interaction

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Received 5 July 2005; revised 30 August 2005; accepted 16 September 2005

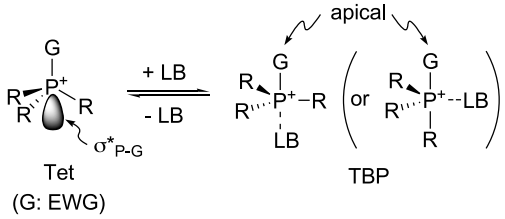
Available online 12 October 2005

Abstract—Phosphonium salts as a novel metal-free Lewis acid catalyst can be considered as organocatalysts. The introduction of a five-membered dioxaphosphacycle to the phosphonium salt is critical to its function as a Lewis acid catalyst for the Diels–Alder reaction. The key to the successful catalysis by the phosphonium salt is the utilization of hypervalent bonding as a strategic interaction for the generation of an active species.

1. Introduction

Over the past half-century, organophosphorus compounds have been extensively utilized in organic synthesis ranging from equimolar to catalytic usage.[1] In particular, their benefits have been widely appreciated in the field of organometallic chemistry and they have become indispensable for versatile organic transformations catalyzed by transition metal complexes. In recent years, the challenges associated with the use of organophosphorus compounds without metal salts as catalysts have received considerable interest[2] from the viewpoint of organocatalysis.[3] Among them, the Morita–Baylis–Hillman reaction has been extensively investigated.[2d,4,5] Catalytic processes have been successfully accomplished by taking advantage of the nucleophilic or Lewis basic nature of organophosphorus compounds.[6] However, little attention has been paid to catalysis on the basis of the electrophilic, and hence the Lewis acidic nature of pentavalent organophosphorus compounds. Herein, we report the use of phosphonium salts as novel Lewis acid catalysts, which offers a new entry to a rapidly growing area in organocatalysis.[3] The key to the success of the catalysis is the utilization of hypervalent bonding as a strategic interaction for the generation of an active species[7,8] by the phosphonium salt (Scheme 1).[9]

The formation of pentacoordinate organophosphorus compounds, namely, hypervalent compounds,[10] which have



Scheme 1. Hypervalent interaction between phosphonium salt and Lewis base.

electronic structures with formal valence shell electrons over octet, are well investigated in terms of their unique structure and reactivity.[11] A hypervalent bond is formed by adding an unshared electron pair of a Lewis base (LB) to a cationic organophosphorus compound, a phosphonium salt, where the lower lying σ^* orbital of the P^+–G bond accepts those electrons.[12] The hypervalent bond thus formed is stabilized when an electron-withdrawing substituent (G) occupies the apical position of a trigonal bipyramidal (TBP) arrangement.

2. Results and discussion

2.1. Preparation of phosphonium salts

As illustrated in Figure 1, several phosphonium salts (**1**–**3**) bearing mono- or bicyclic structures have been synthesized. In order to stabilize the hypervalent bonding,[13] we introduced an oxygenated functionality as the electron-withdrawing group. **1**–**3** were prepared from the corresponding hydroxy phosphine oxide (**4**) or phosphinate (**5**)

Keywords: Hypervalent compounds; Lewis acid; Phosphorus; Organocatalyst; Diels–Alder reaction.
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doi:10.1016/j.tet.2005.09.075

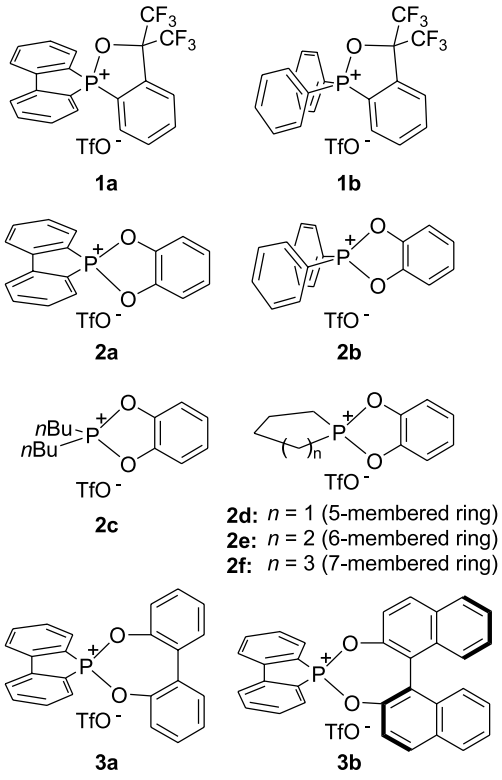
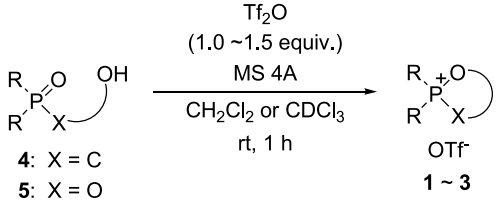


Figure 1. Chemical structures of phosphonium salts (**1**–**3**) prepared.

and trifluoromethanesulfonic anhydride at room temperature for 1 h in the presence of 4 Å molecular sieves (MS) as a desiccant and a base to trap the trifluoromethanesulfonic acid generated (Scheme 2).[14] The generation of phosphonium salts (**1**–**3**) was confirmed by ^{31}P NMR analysis, in which significant downfield shifts were observed.[15] During this transformation, the chemical shift pattern observed in the ^{1}H NMR spectra changed in a symmetric fashion. This can be ascribed to the formation of phosphonium salts with tetrahedral configuration.



Scheme 2. Preparation of phosphonium salts (**1**–**3**) from **4** or **5**.

2.2. Coordination studies

Initially, we attempted ^{31}P NMR analysis to estimate the interaction between phosphonium salts (**1**–**3**) and dimethylformamide (DMF) as a representative carbonyl Lewis base in $CDCl_3$. It is noteworthy that not only the ring size but also the substituent on the phosphorus atom is essential for the coordination of DMF to phosphonium salts (**1**–**3**). Phosphonium salts (**1a**,**b**) derived from the Martin ligand, which is known to stabilize a hypervalent species,[16] exhibited no chemical shift change in the ^{1}H and ^{31}P NMR spectra. In contrast, marked upfield shifts were observed in the spectra of catechol-derived phosphonium salts (**2a**,**b**).[17] Interestingly enough, the spectra of biphenol-derived phosphonium salts (**3a**,**b**) did not show any chemical shift change even though the salts (**3**) had a similar dioxaphosphacycle to **2**. These NMR studies indicate clearly that the five-membered 1,3,2-dioxaphosphacycle is the key structural factor for gaining coordination ability.[18] Detailed analysis of the ^{1}H NMR spectra of the **2**/DMF complex gave further information on the coordination mode of the phosphonium salts (**2**) with DMF (Fig. 2). When bicyclic phosphonium salt (**2a**) was exposed to 3.0 equiv of DMF, two sets of DMF signals were observed along with upfield shifts of the signals in the aromatic region (Fig. 2b). One set of DMF signals appeared significantly downfield compared with the original shift (Fig. 2e vs b). The other set was assigned to uncoordinated DMF because of little chemical shift change. Furthermore, the aromatic region of **2a** showed a more complex shift pattern (Fig. 2a vs b). 2D NMR experiments of the **2a**/DMF complex revealed that the catechol moiety was separated into four signals whereas the dibenzophosphole moiety retained symmetry.[19] These chemical shift changes strongly suggest that phosphonium

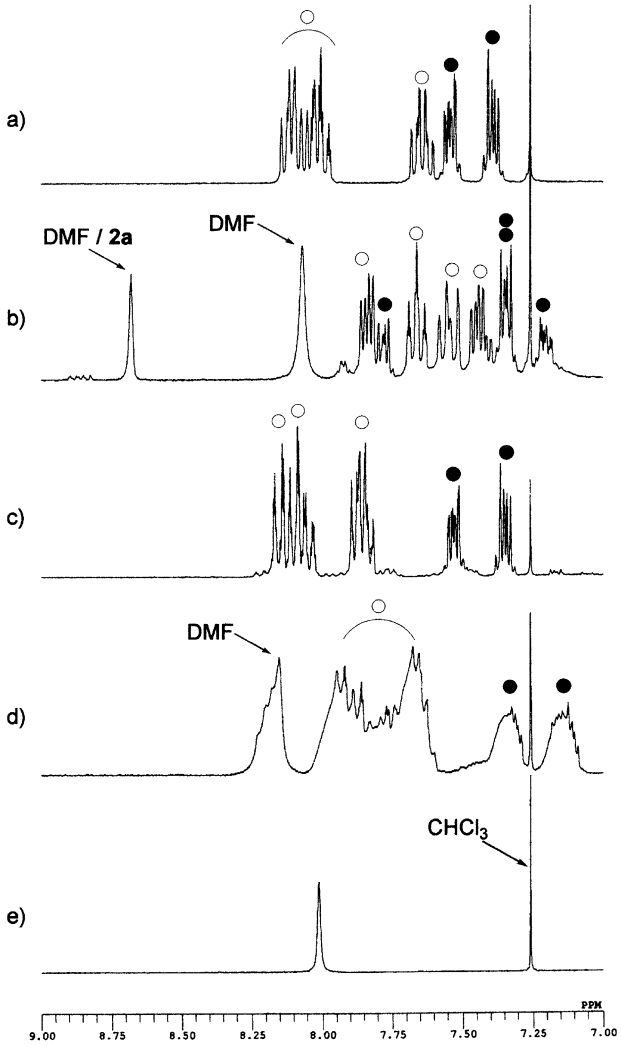


Figure 2. ^{1}H NMR analysis of phosphonium salts (**2**) with or without DMF in $CDCl_3$ (30 mM solution). Solid circles (●) indicate catechol moiety. Hollow circles (○) indicate aromatic substituents of phosphorus atom: (a) **2a**; (b) **2a** with DMF (3.0 equiv); (c) **2b**; (d) **2b** with DMF (3.0 equiv); (e) DMF.

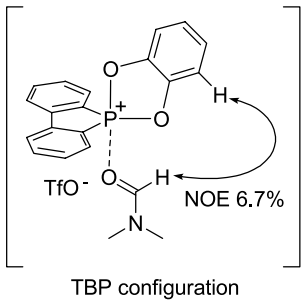


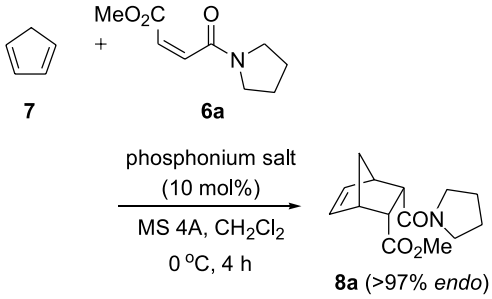
Figure 3. Coordination mode of DMF/phosphonium salt (**2a**) complex.

salt (**2a**) arranged into the TBP configuration upon coordination with DMF and one of the two oxygen atoms of the catechol moiety as well as the carbonyl oxygen of DMF occupied the apical position of the TBP arrangement (Fig. 3). In fact, marked NOE was observed at the C3-proton of the catechol moiety upon irradiation of the formyl proton of DMF, in contrast to little NOE detected at the dibenzophosphole moiety. On the other hand, only one set of DMF signals was observed (Fig. 2e), when monocyclic phosphonium salt (**2b**) was exposed to excess DMF (3.0 equiv). As seen in the spectra for **2a**, signals assigned to the aromatic region shifted upfield but showed significant broadening (Fig. 2c vs d). It is obvious that the complexation between **2b** and DMF is in equilibrium within the NMR timescale at room temperature.

2.3. Lewis acid catalysis by phosphonium salts

In the next phase of our investigation, we focused on Lewis acid catalysis by the phosphonium salts. In order to estimate the catalytic activity, we chose the Diels–Alder reaction as the probe reaction (Table 1). α,β-Unsaturated amides (**6**) were employed as the dienophile because NMR experiments have indicated that phosphonium salts, in particular, catechol derivatives (**2**), function as an activator of amide functionality. The Diels–Alder reaction of unsaturated amide (**6a**) with cyclopentadiene (**7**) catalyzed by 10 mol% phosphonium salts (**1**–**3**), which were prepared in situ from **4** or **5** (10 mol%) and Tf_2O (10 mol%) in the presence of MS 4 Å, was carried out at 0 °C for 4 h. As expected, the catechol-derived phosphonium salts (**2**) gave Diels–Alder product (**8a**) in moderate to good chemical yield (entries 3 and 4).[20] By contrast, under similar reaction conditions, phosphonium salts bearing the Martin ligand (**1**) and biphenol derivatives (**3**) gave **8a** in low chemical yield (entries 1 and 2) and in trace amounts (entries 5 and 6), respectively. These results are consistent with the tendency of the coordination ability observed in ^1H and ^{31}P NMR studies of DMF/phosphonium salt mixtures. Thus, higher catalytic activity is attained with stronger coordination ability of the phosphonium salt to the Lewis base. An increase in the amount of Tf_2O from 1.0 to 1.5 equiv with respect to the amount of the starting phosphinate (**5**) increased the chemical yield (entries 8 and 9). It was confirmed by control experiments that Tf_2O (10 mol%) did not catalyze the reaction at all in the absence of **5** (entry 7). The phosphonium salts (**2c** to **2f**) derived from dialkylphosphinate also worked well (entries 10–13) except for the five-membered phosphacarbocyclic derivative (**2d**) (entry 10). The absence of rate acceleration in the case of **2d** is due to its low solubility in a halogenated solvent. Again, the importance of the five-membered 1,3,2-dioxaphosphacyclic structure in achieving high catalytic efficiency should be emphasized.

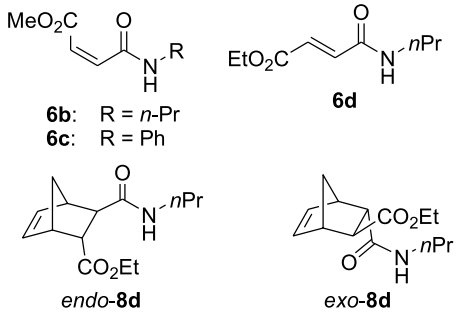
Table 1. Diels–Alder reaction catalyzed by various phosphonium salts[a]



Entry	Phosphonium salt	Yield (%)
1	**1a**	34
2	**1b**	7
3	**2a**	75
4	**2b**	41
5	**3a**	No reaction
6	**3b**	Trace
7[b]	—	Trace
8[c]	**2a**	91
9[c]	**2b**	88
10[c]	**2c**	89
11[c]	**2d**	Trace
12[c]	**2e**	91
13[c]	**2f**	85

[a] The reactions were carried out under the conditions shown in Section 4 unless otherwise noted. Phosphonium salts were prepared from **4** or **5** (10 mol%) and Tf_2O (10 mol%).
[b] The reaction was carried out in the presence of Tf_2O (10 mol%) without phosphonium salts.
[c] Phosphonium salts were prepared from phosphinate (**5**) (10 mol%) and Tf_2O (15 mol%).

Table 2. Diels–Alder reaction of amide dienophiles (**6**)[a]



Entry	2	6	Conditions	Yield (%)	*Endo*/*exo*
1	**2a**	**6b**	0 °C, 2 h	99	>99:<1
2	**2e**	**6b**	0 °C, 2 h	99	>99:<1
3	**2a**	**6c**	−20 °C, 1 h	99	>99:<1
4	**2e**	**6c**	−20 °C, 4 h	87	>99:<1
5	**2a**	**6d**	0 °C, 4 h	31	1:5.3
6	**2e**	**6d**	0 °C, 4 h	46	1:6.7
7[b]	—	**6d**	Room temperature, 17 h	82	1.9:1
8[c]	—	**6d**	0 °C, 4 h	74	1:3.6

[a] The reactions were carried out under the conditions shown in Section 4 unless otherwise noted. Phosphonium salts were prepared from phosphinate (**5**) (10 mol%) and Tf_2O (15 mol%).
[b] The reaction was carried out in the absence of a catalyst.
[c] TfOH (5 mol%) was employed as the catalyst without MS 4 Å.

As listed in Table 2, phosphonium salts **2a** and **2e** are applicable to the reaction of several dienophiles (**6**) with amide functionality.[21] When *Z*-dienophile (**6b**, **6c**) was employed, either **2a** or **2e** gave the product (**8b**, **8c**) in high chemical yield with extremely high *endo* selectivity (entries 1–4). On the other hand, in the reaction with *E*-dienophile (**6d**), *exo*-**8d** was obtained predominantly in moderate chemical yield (entries 5 and 6).[22] The *exo* selectivity thus achieved is in contrast to the reaction yielding *endo*-**8d** as the major product under thermal conditions (entry 7). The difference in *endo*/*exo* selectivity suggests that phosphonium salts activate the amide carbonyl functionality of dienophile (**6d**). In the transition state, the amide moiety coordinates with phosphonium salts oriented to the *endo* direction to increase secondary orbital interactions, which leads to the formation of *exo*-**8d** as the major stereoisomer. In order to rule out the possibility of the catalysis by adventitious acids, we employed TfOH as a catalyst and observed the *endo*/*exo* selectivity (entry 8). The TfOH catalyst exhibited lower *exo* selectivity than that of phosphonium salts (**2a** and **2e**). The differences in *endo*/*exo* selectivity thus observed clearly indicate that the Diels–Alder reaction of the dienophiles (**6**) bearing an amide functionality is accelerated by phosphonium salts.

3. Conclusion

In summary, we have demonstrated novel Lewis acid catalysis by phosphonium salts in which the five-membered dioxaphosphacycle is critical for the salt to function efficiently as a Lewis acid catalyst. The Diels–Alder reaction of α,β-unsaturated amides was markedly accelerated by a catalytic amount of catechol-derived phosphonium salt to afford the products in high chemical yield. We have also concluded that hypervalent interaction is essential for activating the amide functionality based on observations of the interaction between phosphonium salt and the Lewis base.

4. Experimental

4.1. General

Infrared spectra were recorded on a Shimazu FTIR-8200PC spectrometer. ^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz) or Brüker AM-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad, m=multiplet) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL GSX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard. ^{31}P NMR spectra were recorded on a Brüker Avance 400 (162 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from H_3PO_4 resonance as the external standard. Mass spectra analysis was performed at the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University. Analytical thin-layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was performed on silica gel 60 N (spherical, neutral, 100–210 μm; Kanto Chemical Co., Inc.). All reactions were carried out under a nitrogen (N_2) atmosphere in dried glassware. All substrates were purified by column chromatography or distillation prior to use. Dichloromethane and THF were supplied from Kanto Chemical Co., Inc. as 'Dehydrated solvent system'. Chloroform-*d*1 was dried over activated molecular sieves 4 Å and used under nitrogen atmosphere. Molecular sieves 4 Å activated powder was purchased from Aldrich (Catalogue no. 23,366-8) and activated at 300 °C for 3 h under reduced pressure prior to use. Other solvents and other simple chemicals were purchased and used as such. 5-Chloro-5*H*-benzo[*b*]-phosphindole 5-oxide was prepared by the literature method.[23] *Z*-dienophiles (**6a–c**)[24] and *E*-dienophiles (**6d**)[25] were prepared according to the literature procedure, respectively.

4.2. Preparation of hydroxy phosphine oxide (4) and phosphinate (5)

4.2.1. General procedure for the synthesis of hydroxy phosphine oxide (4). To a stirred solution of *n*-butyllithium (12.4 mL of an 1.6 M *n*-hexane solution, 22 mmol) was added TMEDA (0.66 mL, 4.4 mmol). The mixture was stirred at room temperature for 15 min until it become cloudy. The mixture was then cooled to 0 °C and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (1.68 mL, 10 mmol), dissolved in 1.5 mL of THF, was then added dropwise to the mixture. After being stirred for 30 min, the ice bath was removed and the mixture was stirred for 12 h at ambient temperature. Diarylphosphinic chloride (9 mmol), dissolved in 5 mL of THF, was added dropwise to the solution of lithium reagent at −78 °C. After being stirred for 30 min at −78 °C, the reaction mixture was gradually warmed up to room temperature and stirring was continued for additional 8 h at ambient temperature. The mixture was quenched by adding 30 mL of saturated NH_4Cl solution. Following extraction with ethyl acetate (3×30 mL), the combined organic layers were washed with 0.5 M HCl solution and brine. The resultant organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give crude product (**4**). Purification by silica-gel column chromatography and recrystallization gave pure product (**4**) as a colorless solid in 60–70% yield.

4.2.1.1. 2-(5-Oxido-5*H*-benzo[*b*]phosphindol-5-yl)-α,α-bis(trifluoromethyl)benzenemethanol (precursor of 1a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.17–7.30 (2H, m), 7.44 (2H, td, *J*=7.3, 3.8 Hz), 7.65–7.65 (3H, m), 7.83 (2H, dd, *J*=7.3, 3.2 Hz), 7.97–8.04 (3H, m), 10.22 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 79.40 (quin, J_{F-}=29.5 Hz, J_{P-}=2.4 Hz), 121.42 (d, J_{P-}=10.8 Hz), 123.04 (q, J_{F-}=287.8 Hz), 129.48 (d, J_{P-}=13.8 Hz), 129.74 (dd, J_{P-}=8.8 Hz, J_{F-}=3.9 Hz), 129.78 (d, J_{P-}=11.3 Hz), 130.34 (d, J_{P-}=94.3 Hz), 131.57 (d, J_{P-}=111.5 Hz), 131.42 (d, J_{P-}=8.9 Hz), 132.40 (d, J_{P-}=1.4 Hz), 132.89 (d, J_{P-}=14.7 Hz), 134.02 (d, J_{P-}=2.4 Hz), 137.99 (d, J_{P-}=5.4 Hz), 141.71 (d, J_{P-}=23.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.2; IR (KBr): 3082, 2925, 1442, 1271, 1245, 1205, 1193, 1164,

1151, 1130, 954, 931, 856, 759, 729, 715, 704, 551 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{14}F_6O_2P$ ($[M+H]^+$) 443.0636. Found 443.0630.

4.2.1.2. 2-(Diphenylphosphinyl)-α,α-bis(trifluoromethyl)benzenemethanol (precursor of 1b). ^1H NMR (270 MHz, $CDCl_3$): δ 7.24 (1H, dd, $J=16.2$, 7.6 Hz), 7.39 (1H, t, $J=7.6$ Hz), 7.44–7.66 (9H, m), 7.98 (1H, t, $J=5.7$ Hz), 10.57 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 79.51 (quind, $J_{F-}=29.0$ Hz, $J_{P-}=2.5$ Hz), 122.88 (q, $J_{F-}=289.3$ Hz), 128.69 (d, $J_{P-}=12.3$ Hz), 128.73 (d, $J_{P-}=13.3$ Hz), 130.30 (dd, $J_{P-}=8.3$ Hz, $J_{F-}=3.9$ Hz), 130.85 (d, $J_{P-}=95.8$ Hz), 131.96 (d, $J_{P-}=2.5$ Hz), 131.23 (d, $J_{P-}=109.0$ Hz), 132.11 (d, $J_{P-}=9.8$ Hz), 132.57 (d, $J_{P-}=2.5$ Hz), 136.03 (d, $J_{P-}=12.7$ Hz), 138.07 (d, $J_{P-}=3.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 46.3; IR (KBr): 3043, 2925, 1436, 1267, 1240, 1195, 1153, 1126, 954, 933, 866, 758, 727, 696, 542 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{16}F_6O_2P$ ($[M+H]^+$) 445.0792. Found 445.0787.

4.2.2. General procedure for the synthesis of hydroxy phosphinate (5). To a stirred solution of diol (1.8 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.56 mL, 4 mmol). The mixture was cooled to 0 °C and the corresponding phosphinic chloride (2 mmol), dissolved in 1.5 mL of CH_2Cl_2, was added dropwise to the mixture. After being stirred for 30 min, the ice bath was removed and the mixture was stirred for 3 h at ambient temperature. The mixture was quenched by adding 10 mL of water. Following extraction with CH_2Cl_2 (3×15 mL), the combined organic layers were washed with 0.5 M HCl solution and saturated $NaHCO_3$ solution. The resultant organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product (**5**). Purification by silica-gel column chromatography and recrystallization gave pure product (**5**) as a colorless solid in 45–83% yield.

4.2.2.1. *o*-[(5-Oxido-5*H*-benzo[*b*]phosphindol-5-yl)oxy]phenol (precursor of 2a). ^1H NMR (270 MHz, $CDCl_3$): δ 6.70–6.80 (2H, m), 7.08–7.16 (2H, m) 7.39 (2H, td, $J=7.6$, 4.1 Hz), 7.58–7.67 (4H, m), 7.82 (2H, dd, $J=7.8$, 4.1 Hz), 8.60 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 119.67 (d, $J_{P-}=1.5$ Hz), 120.66 (d, $J_{P-}=1.5$ Hz), 121.37 (d, $J_{P-}=12.7$ Hz), 122.27 (d, $J_{P-}=3.9$ Hz), 126.10 (d, $J_{P-}=139.5$ Hz), 126.85 (d, $J_{P-}=1.5$ Hz), 129.30 (d, $J_{P-}=11.9$ Hz), 129.45 (d, $J_{P-}=15.3$ Hz), 134.41 (d, $J_{P-}=2.5$ Hz), 139.46 (d, $J_{P-}=9.8$ Hz), 140.47 (d, $J_{P-}=30.0$ Hz), 148.08 (d, $J_{P-}=2.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 48.9; IR (KBr): 3177, 1590, 1515, 1460, 1291, 1238, 1224, 1179, 1132, 1106, 936, 928, 832, 759, 749, 727, 552 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{14}O_3P$ ($[M+H]^+$) 309.0681. Found 309.0685.

4.2.2.2. Diphenylphosphinic acid 2-hydroxyphenyl ester (precursor of 2b). ^1H NMR (270 MHz, $CDCl_3$): δ 6.66–6.72 (1H, m), 6.85 (1H, d, $J=8.1$ Hz), 6.96–7.05 (2H, m), 7.45–7.62 (6H, m), 7.89 (4H, dd, $J=12.7$, 7.0 Hz), 9.00 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 119.70 (d, $J_{P-}=1.5$ Hz), 120.41 (d, $J_{P-}=1.0$ Hz), 122.38 (d, $J_{P-}=4.4$ Hz), 126.38 (d, $J_{P-}=1.5$ Hz), 128.65 (d, $J_{P-}=137.1$ Hz), 128.74 (d, $J_{P-}=13.2$ Hz), 131.86 (d, $J_{P-}=10.8$ Hz), 133.11 (d, $J_{P-}=3.0$ Hz), 139.03 (d, $J_{P-}=9.8$ Hz), 148.04 (d, $J_{P-}=3.0$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 39.1; IR (KBr): 3123, 1518, 1460, 1439, 1292, 1240, 1215, 1176, 1134, 1103, 943, 932, 748, 729, 546 cm^{-1}; HRMS (ESI) Calcd for $C_{18}H_{16}O_3P$ ($[M+H]^+$) 311.0837. Found 311.0832.

4.2.2.3. Dibutylphosphinic acid 2-hydroxyphenyl ester (precursor of 2c). ^1H NMR (270 MHz, $CDCl_3$): δ 0.89 (6H, t, $J=7.3$ Hz), 1.40 (4H, sext, $J=7.3$ Hz), 1.50–1.78 (4H, m), 1.82–1.99 (4H, m), 6.76–6.85 (1H, m), 6.94 (1H, d, $J=7.8$ Hz), 6.99–7.07 (2H, m), 9.09 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 23.41 (d, $J_{P-}=1.0$ Hz), 23.56, 23.72 (d, $J_{P-}=15.3$ Hz), 26.71 (d, $J_{P-}=86.9$ Hz), 119.85 (d, $J_{P-}=1.5$ Hz), 120.37 (d, $J_{P-}=0.1$ Hz), 121.80 (d, $J_{P-}=4.4$ Hz), 126.29 (d, $J_{P-}=0.9$ Hz), 139.28 (d, $J_{P-}=9.8$ Hz), 147.94 (d, $J_{P-}=2.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 67.4; IR (neat): 3074, 2958, 2933, 1494, 1460, 1294, 1242, 1164, 1101, 931, 923, 752, 732 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{24}O_3P$ ($[M+H]^+$) 271.1463. Found 271.1458.

4.2.2.4. *o*-[(1-Oxido-1-phospholanyl)oxy]phenol (precursor of 2d). ^1H NMR (270 MHz, $CDCl_3$): δ 1.72–2.09 (8H, m), 6.80–6.87 (1H, m), 6.94 (1H, d, $J=8.1$ Hz), 7.04–7.12 (2H, m), 8.77 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 22.91 (d, $J_{P-}=12.8$ Hz), 23.36 (d, $J_{P-}=87.9$ Hz), 120.05 (d, $J_{P-}=1.5$ Hz), 120.61 (d, $J_{P-}=1.5$ Hz), 121.88 (d, $J_{P-}=4.4$ Hz), 126.67 (d, $J_{P-}=1.5$ Hz), 139.37 (d, $J_{P-}=10.3$ Hz), 148.17 (d, $J_{P-}=2.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 91.3; IR (KBr): 3109, 1508, 1458, 1290, 1274, 1234, 1168, 1099, 920 cm^{-1}; HRMS (ESI) Calcd for $C_{10}H_{14}O_3P$ ($[M+H]^+$) 213.0681. Found 213.0675.

4.2.2.5. *o*-[(1-Oxido-1-phosphorinanyl)oxy]phenol (precursor of 2e). ^1H NMR (270 MHz, $CDCl_3$): δ 1.36–1.41 (1H, m), 1.78–2.18 (9H, m), 6.79–6.88 (1H, m.), 6.99–7.11 (3H, m), 9.06 (1H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 23.76 (d, $J_{P-}=5.9$ Hz), 25.77 (d, $J_{P-}=8.9$ Hz), 26.17 (d, $J_{P-}=82.5$ Hz), 120.04, 120.40, 121.80 (d, $J_{P-}=4.4$ Hz), 126.51 (d, $J_{P-}=1.4$ Hz), 138.76 (d, $J_{P-}=9.8$ Hz), 148.15 (d, $J_{P-}=3.0$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 60.8; IR (KBr): 3070, 2953, 1516, 1460, 1294, 1242, 1184, 1163, 1103, 916, 825, 760 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{16}O_3P$ ($[M+H]^+$) 227.0837. Found 227.0832.

4.2.2.6. *o*-[(1-Oxido-1-phosphepanyl)oxy]phenol (precursor of 2f). ^1H NMR (270 MHz, $CDCl_3$): δ 1.73–2.22 (12H, m), 6.78–6.84 (1H, m), 6.95 (1H, d, $J=8.4$ Hz), 7.01–7.09 (2H, m), 9.09 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 20.68 (d, $J_{P-}=1.5$ Hz), 28.44 (d, $J_{P-}=83.1$ Hz), 29.54, 119.95 (d, $J_{P-}=0.1$ Hz), 120.41 (d, $J_{P-}=1.0$ Hz), 122.04 (d, $J_{P-}=3.9$ Hz), 126.41 (d, $J_{P-}=1.5$ Hz), 139.02 (d, $J_{P-}=9.8$ Hz), 148.20 (d, $J_{P-}=2.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 73.9; IR (KBr): 3074, 2931, 1508, 1458, 1380, 1290, 1240, 1197, 1178, 1153, 937, 918, 781 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{18}O_3P$ ($[M+H]^+$) 241.0994. Found 241.0988.

4.2.2.7. 2′-[(5-Oxido-5*H*-benzo[*b*]phosphindol-5-yl)oxy][1,1′-biphenyl]-2-ol (precursor of 3a). ^1H NMR (270 MHz, $CDCl_3$): δ 6.14 (1H, s), 6.84–6.97 (3H, m), 7.23–7.35 (7H, m), 7.52 (2H, t, $J=7.3$ Hz), 7.63 (2H, dd, $J=7.3$, 3.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 117.24, 120.84 (d, $J_{P-}=9.8$ Hz), 121.10, 121.68 (d, $J_{P-}=3.4$ Hz), 125.84, 126.08 (d, $J_{P-}=2.0$ Hz), 127.43 (d, $J_{P-}=139.5$ Hz), 128.81 (d, $J_{P-}=8.8$ Hz), 129.25, 129.41 (d, $J_{P-}=2.0$ Hz), 129.54 (d, $J_{P-}=1.4$ Hz), 131.08, 131.63 (d, $J_{P-}=3.9$ Hz), 132.42

(d, J_{P-}=1.5 Hz), 133.89 (d, J_{P-}=2.4 Hz), 140.09, 140.53, 153.53; ^{31}P NMR (162 MHz, $CDCl_3$): δ 42.9; IR (KBr): 3134, 1560, 1508, 1440, 1222, 1205, 1188, 1130, 1068, 920, 758, 748 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{18}O_3P$ ([M+H]$^+$) 385.0994. Found 385.0988.

4.2.2.8. 2′-[(5-Oxido-5*H*-benzo[*b*]phosphindol-5-yl)oxy][1,1′-binaphthalen]-2-ol (precursor of 3b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.43 (1H, dd, J=11.3, 7.6 Hz), 6.91 (1H, d, J=8.4 Hz), 6.99–7.14 (3H, m), 7.24–7.41 (6H, m), 7.45–7.57 (3H, m), 7.62–7.69 (3H, m), 7.86 (1H, d, J=8.1 Hz), 7.96 (1H, d, J=6.8 Hz), 7.99 (1H, d, J=8.4 Hz), 8.09 (1H, d, J=8.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 117.24, 120.03 (d, J_{P-}=2.0 Hz), 120.57, 120.71 (d, J_{P-}=13.3 Hz), 121.18 (d, J_{P-}=12.8 Hz), 123.54, 124.47, 124.90 (d, J_{P-}=4.4 Hz), 125.93, 126.44 (d, J_{P-}=93.4 Hz), 126.60, 127.66 (d, J_{P-}=22.6 Hz), 128.12 (d, J_{P-}=1.0 Hz), 128.65 (d, J_{P-}=8.2 Hz), 129.18 (d, J_{P-}=4.4 Hz), 129.39, 129.40 (d, J_{P-}=11.8 Hz), 130.12, 130.84 (d, J_{P-}=1.4 Hz), 131.84 (d, J_{P-}=1.5 Hz), 133.90 (d, J_{P-}=2.0 Hz), 133.96 (d, J_{P-}=2.4 Hz), 140.18 (d, J_{P-}=2.9 Hz), 140.62 (d, J_{P-}=2.4 Hz), 146.68 (d, J_{P-}=9.4 Hz), 152.59; ^{31}P NMR (162 MHz, $CDCl_3$): δ 44.1; IR (KBr): 3195, 1624, 1593, 1438, 1230, 1203, 1132, 1070, 985, 956, 840, 817, 756, 721 cm^{-1}; HRMS (ESI) Calcd for $C_{32}H_{22}O_3P$ ([M+H]$^+$) 485.1307. Found 485.1301.

4.3. ^{1}H and ^{31}P NMR analysis of phosphonium salt (1–3)

To a suspension of an activated MS 4 Å (100 mg: activated at 300 °C for 3 h under reduced pressure) and hydroxy phosphineoxide (**4**) or hydroxy phosphinate (**5**) (0.03 mmol) in anhydrous deuterated chloroform (0.9 mL) was added trifluoromethanesulfonic anhydride (0.03 mmol) under nitrogen atmosphere at room temperature. After stirring for 1 h at ambient temperature, the resultant suspension was centrifuged to separate MS 4 Å and the supernatant solution was replaced to an NMR tube under nitrogen atmosphere. The sample thus prepared was measured by ^{1}H and ^{31}P NMR at room temperature.

4.3.1. 1,3-Dihydro-3,3-bis(trifluoromethyl)spiro[5*H*-dibenzophospholium-2,1-benzoxaphospholium] salt with trifluoromethanesulfonic acid (1a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.52–7.63 (4H, m), 7.95–8.02 (2H, m), 8.06–8.26 (5H, m), 8.59 (1H, dd, J=12.4, 7.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 92.3.

4.3.2. 1,3-Dihydro-1,1-diphenyl-3,3-bis(trifluoromethyl)-2,1-benzoxaphospholium salt with trifluoromethanesulfonic acid (1b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.73–7.81 (4H, m), 7.88–7.97 (7H, m), 8.10–8.25 (2H, m), 9.11–9.17 (1H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 92.7.

4.3.3. Spiro[5*H*-dibenzophospholium-1,3,2-benzodioxaphospholium] salt with trifluoromethanesulfonic acid (2a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.36–7.42 (2H, m), 7.51–7.56 (2H, m), 7.64 (2H, tdd, J=7.6, 4.1, 1.1 Hz), 7.97–8.14 (6H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 100.5.

4.3.4. 2,2-Diphenyl-1,3,2-benzodioxaphospholium salt with trifluoromethanesulfonic acid (2b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33–7.39 (2H, m), 7.45–7.55 (2H, m), 7.82–7.90 (4H, m), 8.03–8.16 (6H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 97.2.

4.3.5. 2,2-Dibutyl-1,3,2-benzodioxaphospholium salt with trifluoromethanesulfonic acid (2c). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 (6H, t, J=7.3 Hz), 1.48 (4H, td, J=14.6, 7.3 Hz), 1.59–1.74 (4H, m), 3.13 (4H, dd, J=15.9, 9.2 Hz), 7.23–7.28 (2H m), 7.32–7.37 (2H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 142.6.

4.3.6. Spiro[1,3,2-benzodioxaphospholium-2,2′-phospholanium] salt with trifluoromethanesulfonic acid (2d). Not available due to low solubility of **2d** in $CDCl_3$.

4.3.7. Spiro[1,3,2-benzodioxaphospholium-2,2′-phosphorinanium] salt with trifluoromethanesulfonic acid (2e). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.93–2.02 (2H, m), 2.27–2.45 (4H, m), 3.07 (2H, t, J=6.7 Hz), 3.14 (2H, t, J=6.7 Hz), 7.23–7.30 (2H, m), 7.32–7.39 (2H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 137.7.

4.3.8. Spiro[1,3,2-benzodioxaphospholium-2,2′-phosphepanium] salt with trifluoromethanesulfonic acid (2f). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.88–1.90 (4H, m), 2.11–2.25 (4H, m), 3.13 (2H, t, J=6.5 Hz), 3.19 (2H, t, J=6.5 Hz), 7.20–7.27 (2H, m), 7.29–7.36 (2H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 146.8.

4.3.9. Spiro[dibenzo[*d*,*f*][1,3,2]dioxaphosphepinium-5*H*-dibenzophospholium] salt with trifluoromethanesulfonic acid (3a). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.38–7.43 (2H, m), 7.49–7.74 (8H, m), 7.77–7.82 (2H, m), 8.04 (2H, tt, J=7.8, 1.4 Hz), 8.26 (2H, dd, J=7.8, 5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 83.0.

4.3.10. Spiro[dinaphto[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepinium-5*H*-dibenzophospholium] salt with trifluoromethanesulfonic acid (3b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.30 (2H, m), 7.46–7.50 (4H, m), 7.53–7.61 (4H, m), 7.69 (2H, ddd, J=8.1, 5.7, 2.4 Hz), 8.04 (2H, t, J=7.8 Hz), 8.15 (2H, d, J=8.4 Hz), 8.27 (2H, dd, J=7.8, 5.4 Hz), 8.32 (1H, d, J=9.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 83.5.

4.4. Typical procedure for the Diels–Alder reaction

To a suspension of activated MS 4 Å (100 mg: activated at 300 °C for 3 h under reduced pressure) and hydroxy phosphinate (**5**) (0.06 mmol) in anhydrous dichloromethane (1.8 mL) was added trifluoromethanesulfonic anhydride (0.06 or 0.09 mmol) under nitrogen atmosphere at room temperature. The mixture was stirred for 1 h at ambient temperature and then cooled to the indicated temperature. A dienophile (**6**) (0.6 mmol) was added to the suspension at that temperature. After stirring for 30 min, a ca. 3.0 M solution of cyclopentadiene (**7**) (ca. 1.5 mmol) in dichloromethane was added to the suspension. Stirring was continued under the indicated conditions and the reaction mixture was quenched with sodium bicarbonate. Conventional workup followed by silica-gel column chromatography purification gave pure product (**8**).

4.4.1. 2-*endo*-Methoxycarbonyl-3-*endo*-(pyrrolidin-1-yl)carbonylbicyclo[2.2.1]hept-5-ene (8a). ^{1}H NMR

(270 MHz, $CDCl_3$): δ 1.14 (1H, d, J=8.1 Hz), 1.23 (1H, d, J=8.6 Hz), 1.69 (2H, td, J=13.5, 6.5 Hz), 1.70–1.79 (2H, m), 2.91 (1H, br s), 2.96 (1H, br s), 3.06 (2H, dd, J=10.0, 3.2 Hz), 3.14–3.21 (3H, m); 3.30 (1H, t, J=6.5 Hz), 3.37 (3H, s), 6.04 (1H, dd, J=8.1, 2.7 Hz), 6.10 (1H, dd, J=8.1, 2,7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 23.60, 25.54, 45.15, 45.55, 45.63, 45.69, 47.42, 47.88, 48.03, 60.69, 133.32, 134.85, 169.80, 172.22; IR (neat): 3462, 2972, 2949, 2871, 1739, 1643, 1434, 1352, 1340, 1251, 1195, 1149, 1076, 1041, 914, 723, 707 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{20}NO_3$ ($[M+H]^+$) 250.1443. Found 250.1438.

4.4.2. 2-*endo*-Methoxycarbonyl-3-*endo*-(*N*-propylcarbamoyl)bicyclo[2.2.1]hept-5-ene (8b). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85 (3H, t, J=7.6 Hz), 1.29 (1H, d, J=8.4 Hz), 1.39–1.47 (3H, m), 3.04–3.12 (4H, m), 3.19–3.20 (2H, m), 3.54 (3H, s), 5.68 (1H, br s), 6.10 (1H, dd, J=5.7, 3.0 Hz), 6.44 (1H, dd, J=5.7, 3.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 11.24, 22.68, 41.13, 45.64, 47.11, 48.92, 49.05, 50.21, 51.29, 133.36, 136.47, 171.43, 173.44; IR (KBr): 3321, 3003, 2952, 2877, 1720, 1647, 1556, 1440, 1336, 1263, 1226, 1197, 1151, 1035, 792, 690, 615 cm^{-1}; HRMS (ESI) Calcd for $C_{13}H_{20}NO_3$ ($[M+H]^+$) 238.1443. Found 238.1438.

4.4.3. 2-*endo*-Methoxycarbonyl-3-*endo*-(*N*-phenylcarbamoyl)bicyclo[2.2.1]hept-5-ene (8c). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (1H, d, J=8.6 Hz), 1.50 (1H, dt, J=8.6, 1.6 Hz), 3.18 (1H, br s), 3.19 (1H, br s), 3.23 (1H, dd, J=10.3, 1.6 Hz), 3.39 (1H, dd, J=10.3, 3.0 Hz), 3.54 (3H, s), 6.22 (1H, dd, J=5.7, 3.0 Hz); 6.55 (1H, dd, J=5.7, 3.0 Hz), 7.05 (1H, t, J=7.3 Hz), 7.26 (2H, t, J=7.3 Hz), 7.46 (2H, d, J=7.8 Hz), 7.63 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 45.76, 47.40, 49.12, 49.35, 51.03, 51.59, 119.67, 123.96, 128.81, 133.49, 136.76, 137.97, 170.09, 173.44; IR (KBr): 3342, 1716, 1685, 1600, 1542, 1490, 1442, 1307, 1255, 1213, 1176, 754, 696 cm^{-1}; HRMS (ESI) Calcd for $C_{16}H_{18}NO_3$ ($[M+H]^+$) 272.1287. Found 272.1281.

4.4.4. 2-*endo*-Ethoxycarbonyl-3-*exo*-(*N*-propylcarbamoyl)bicyclo[2.2.1]hept-5-ene (*endo*-8d). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (3H, t, J=7.3 Hz), 1.16–1.25 (3H, m), 1.41–1.56 (3H, m), 1.82 (1H, d, J=7.0 Hz), 2.32 (1H, d, J=4.9 Hz), 2.99 (1H, s), 3.15–3.23 (4H, m), 4.02–4.14 (2H, m); 5.99 (3H, br s), 6.06 (1H, dd, J=5.4, 2.4 Hz), 6.21 (1H, dd, J=5.4, 3.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 11.28, 14.17, 22.84, 41.22, 44.76, 46.76, 47.55, 48.42, 49.41, 60.63, 135.30, 137.87, 173.91, 174.11; IR (neat): 3311, 2970, 2939, 1733, 1645, 1544, 1458, 1315, 1269, 1209, 1190, 1116, 1033, 864, 729, 698 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{22}NO_3$ ($[M+H]^+$) 252.1600. Found 252.1594.

4.4.5. 2-*exo*-Ethoxycarbonyl-3-*endo*-(*N*-propylcarbamoyl)bicyclo[2.2.1]hept-5-ene (*exo*-8d). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85–0.92 (3H, m), 1.17–1.31 (3H, m), 1.43–1.55 (4H, m), 2.54 (1H, dd, J=4.9, 1.4 Hz), 3.08–3.20 (5H, m), 4.12–4.19 (2H, m), 5.95 (1H, br s), 6.17–6.21 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 11.29, 14.19, 22.87, 41.13, 45.45, 46.66, 47.60, 48.37, 49.67, 60.93, 135.69, 136.37, 172.53, 175.03; IR (KBr): 3317, 2970, 2937, 1726, 1641, 1552, 1458, 1382, 1325, 1276, 1242, 1213, 1172, 1033, 873, 698 cm^{-1}; HRMS (ESI) Calcd for $C_{14}H_{22}NO_3$ ($[M+H]^+$) 252.1600. Found 252.1594.

4.5. Stereochemical assignment of 8d

4.5.1. Transformation to hexahydro-6-iodo-2-oxo-*N*-propyl-3,5-methano-2*H*-cyclopenta[*b*]furan-7-carboxamide (9). To a stirred solution of **8d** (40.0 mg, 0.16 mmol: one diastereomer obtained from the major product of Table 2 entry 7) in methanol (1.0 mL) was added dropwise 2 M NaOH solution (0.5 mL) at 0 °C. After being stirred for 15 min, the ice bath was removed and the mixture was stirred for 1 h at room temperature. The resultant mixture was quenched by adding 1 M HCl solution (2 mL). Following extraction with CH_2Cl_2 (4×15 mL), the combined organic layers were concentrated under reduced pressure to give crude carboxylic acid. The crude material thus obtained was used for the next lactonization without further purification. To a stirred solution of crude carboxylic acid in CH_2Cl_2 (1.0 mL) at room temperature was added $NaHCO_3$ (67.2 mg, 0.8 mmol), water (2.0 mL), KI (265 mg, 1.60 mmol), and I_2 (142 mg, 0.56 mmol) in this order. After being stirred for 3 h at ambient temperature, the reaction mixture was quenched by adding saturated $Na_2S_2O_3$ solution. Following extraction with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude lactone (**9**). Purification by silica-gel column chromatography gave pure lactone (**9**) (52.1 mg, 92% form **8d**), ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 (3H, t, J=7.6 Hz), 1.51 (2H, sex, J=7.6 Hz), 2.28 (2H, m), 2.61 (1H, s), 2.84 (1H, s), 3.05 (1H, d, J=3.5 Hz), 3.14–3.21 (3H, m), 3.85 (1H, d, J=1.6 Hz), 5.12 (1H, d, J=4.9 Hz), 5.91 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 11.40, 22.72, 28.66, 35.11, 41.52, 41.77, 46.21, 51.55, 51.69, 88.89, 169.45, 178.49; IR (neat): 3327, 2964, 2933, 1781, 1651, 1539, 1458, 1346, 1305, 1247, 1172, 1116, 1006, 985, 912, 840, 736 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{16}INNaO_3$ ($[M+Na]^+$) 372.0067. Found 372.0067.

Acknowledgements

The authors are grateful to Central Glass Co., Ltd for the generous gifts of hexafluorocumyl alcohol and trifluoromethanesulfonic anhydride. This work was partially supported by Grants-in-Aid for Scientific Research (Nos. 14340227 and 15036210) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Asahi Glass Foundation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.075. This comprises a scanned image of the ^{1}H NMR spectra of phosphonium salts (**1**), table of ^{31}P NMR chemical shifts of **1**–**5**, and scanned image of 2D (COSY) and NOE spectra of **2a**/DMF complex.

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(from δ 46.2); **1b**: δ 92.7 (from δ 46.3); **2a**: δ 100.5 (from δ 48.9); **2b**: δ 97.2 (from δ 39.1); **2c**: δ 142.6 (from δ 67.4); **2d**: δ (low solubility in $CDCl_3$) (from δ 91.3); **2e**: δ 137.7 (from δ 60.8); **2f**: δ 146.8 (from δ 73.9); **3a**: δ 83.0 (from δ 42.9); **3b**: δ 83.5 (from δ 44.1).

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19. See Supplementary data.
20. When **2a** was exposed to 2 equiv of dienophile (**6a**), several peaks [42.4 (major), 41.5 (minor), −26.5 (minor)] with marked upfield shifts were observed in the ^{31}P NMR spectrum, and a significant broadening of the peak assigned to phosphonium salt (**2a**) was observed in the ^{1}H NMR spectrum.
21. In all cases, the thermal reaction gave no or a trace amount (less than 5%) of the Diels–Alder products under the same conditions except for the absence of phosphonium salt.
22. The stereochemistry of **8d** was confirmed via conventional operations. Ester hydrolysis of **8d** followed by iodolactonization gave five-membered lactone (**9**) that was assigned to be the *endo*-stereoisomer by IR measurement [C═O(lactone); 1781 cm^{-1}].
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The α-effect in iminium ion catalysis

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Received 19 May 2005; revised 4 July 2005; accepted 31 August 2005

Available online 23 September 2005

Abstract—The α-effect can be used as an effective means to promote iminium ion catalysed transformations, providing acyclic scaffolds to aid in catalyst design. A thorough investigation of the structure–activity relationship of the catalyst architecture reveals optimal substituents of a disubstituted carbamate and a secondary alkyl group around a hydrazine scaffold. Molecular modelling investigations provide a mechanistic rationale to the results observed.

1. Introduction

The use of secondary amines to accelerate traditional organic transformations through LUMO-lowering has recently caught the imagination of the synthetic community. Although simple in both design and mechanistic rationale, the catalysts reported to be effective in these reactions are having a major impact on contemporary organic synthesis and the way in which chemists think about preparing molecules, offering practically simple ways to prepare complex targets. The scope and number of transformations are continuing to expand[1] and now include Diels–Alder cycloaddition,[2] [3+2] cycloadditions,[3] conjugate addition reactions of pyrroles,[4] indoles,[5] anilines,[6] nitro alkanes[7] and hydride,[8] Mukaiyama–Michael reactions,[9] cyclopropanations[10] and [4+3] cycloaddition reactions.[11]

We have recently become interested in the design and synthesis of novel catalyst architectures that will allow for the lowering of catalyst loading within these reactions.[12] Based on the original proposal by MacMillan that the rate determining step of these processes is iminium ion formation,[2b] we believed that increasing the nucleophilicity of secondary amine catalysts may well allow us to meet our original goals. To this end, we recently reported that the α-effect can be used as an effective platform with which to accelerate the iminium ion catalysed Diels–Alder reaction between a variety of dienes and dienophiles, providing novel acyclic structures for future catalyst design.[12] Herein, we provide a full report on our synthetic and theoretical investigations to gain a greater understanding of iminium ion formation and the factors controlling this fascinating and vibrant area of organocatalysis.

The most effective catalysts in both iminium ion and enamine catalysis share a common structure of a secondary amine embedded within a five-membered ring (Fig. 1).[13] We rationalized that this enhances the nucleophilicity of the secondary amine, allowing effective formation of iminium ions, and postulate that such an increase in nucleophilicity could also be achieved by exploiting the α-effect.

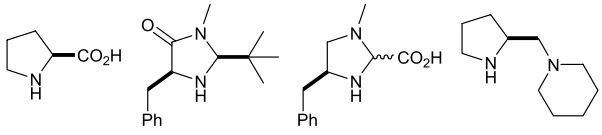

Figure 1. Effective secondary amine catalysts.

The α-effect is defined as a positive deviation of an α-nucleophile (a nucleophile bearing an unshared pair of electrons on an atom adjacent to the nucleophilic site) from a Brønsted-type plot of log K_{nuc} versus pK_a constructed for a series of normal related nucleophiles.[14] More generally, it is the influence of an atom bearing a lone pair of electrons on the reactivity at the adjacent site. The enhanced reactivity of α-nucleophiles was first reported in 1947, and the phenomenon was later given its name by Edwards and Pearson in 1962.[15] The origins of the observation are of some debate and several possible explanations have been offered. These include the ground state of the nucleophile

Keywords: α-Effect; Iminium ion catalysis; DFT calculations.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.08.110

being destabilized by repulsion between the adjacent pairs of electrons,[16] stabilization of the transition state by the extra pair of electrons,[17] and the adjacent pair of electrons reducing solvation of the nucleophile.[18] It is notable that this phenomenon is generally believed to have several origins, and that the nature of the individual effects and the exact conditions under which they are operative have not been unambiguously identified. Nonetheless, the effect is genuine and has been invoked to explain chemical reactivity.[19] Within this paper we report our results on the use of the α-effect in the acceleration of the Diels–Alder reaction with acyclic secondary amine containing scaffolds from both a theoretical and practical basis.

2. Results and discussion

In order to establish if the α-effect provided an effective platform for iminium ion catalysis we conducted a series of experiments in order to compare the aminocatalytic activity of a pyrrolidine-type system, an acyclic secondary amine and an acyclic secondary amine with an α-heteroatom. We examined four commercially available acyclic secondary amines **1**–**4**, and compared their reactivity to proline methyl ester **5**, which has previously been reported to be effective in catalyzing the Diels–Alder reaction and allows direct comparison to the level of activity attainable with cyclic amine systems (Fig. 2). The results obtained are outlined in Table 1. We initially adopted standard reaction conditions

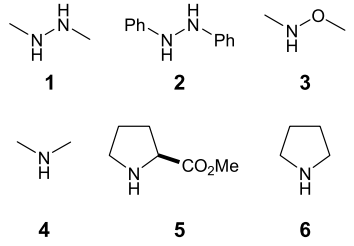
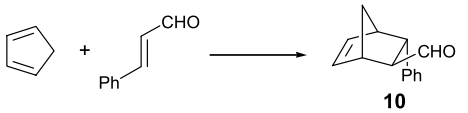


Figure 2. Commercially available amines.

Table 1. Catalysis of the Diels–Alder reaction with commercially available amines[a]



7 **8** **10** + *endo* isomer **9**

Entry	Catalyst	Time (h)	*endo*:*exo*[b]	Yield (%)
1	None	48	64:36	7
2[c]	NEt_3·HCl	48	63:37	7
3[c]	**4**·HCl	48	38:62	22
4[c]	**3**·HCl	48	34:66	65
5[c]	**3**·HCl	72	34:66	80
6[d]	**1**·HCl	72	68:32	48
7[d]	**2**·HCl	48	38:62	33
8[c]	**5**·HCl	48	29:71	85
9[c]	**6**·HCl	24	32:68	9

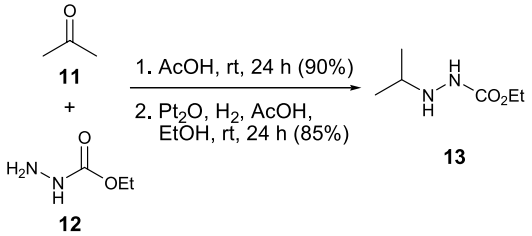
[a] Carried out in methanol/water 19:1 at room temperature with 10 mol% catalyst.
[b] Ratio determined by ^{1}H NMR of crude reaction mixture.
[c] Catalyst used as HCl salt.
[d] Catalyst used as bis-HCl salt.

of 10 mol% catalyst, in a methanol/water mixture 19:1 and examined the Diels–Alder reaction between *trans*-cinnamaldehyde **8** and cyclopentadiene **7**.

In the absence of any catalyst, or in the presence of only the protonic acid co-catalyst, the reaction proceeded to just 7% completion in 48 h with the *endo*-isomer predominating (Table 1, entries 1 and 2). Observations by MacMillan and others suggest that the *exo*-isomer of the product **10** predominates when iminium ion catalysis is occurring, as was observed with the proline methyl ester **5** (Table 1, entry 8). The use of *N*,*N*-dimethylamine hydrochloride as the catalyst afforded a 22% yield of adduct **8** with the *exo*-isomer predominating (Table 1, entry 3), suggesting that iminium ion catalysis was occurring, albeit sluggishly. Significantly, the use of *N*,*O*-dimethylhydroxylamine hydrochloride as the catalyst led to a significant increase in the yield observed for the reaction (Table 1, entry 4), which suggested that it would indeed be possible to accelerate these reactions by taking advantage of the α-effect. Extension of the reaction time further did allow for the increased formation of the Diels–Alder adduct to 80% (Table 1, entry 5). Changing to a nitrogen based α-heteroatom with the commercially available hydrazines—*N*,*N*′-dimethylhydrazine (Table 1, entry 6) and *N*,*N*′-diphenylhydrazine (Table 1, entry 7)—showed lower yield for the transformation but did show a marked increase from *N*,*N*-dimethylamine.

Having shown that the α-effect could be used to accelerate these iminium ion catalysed transformations, we then sought to further develop the catalyst structure to enhance the rate of the catalytic cycle to match or increase those displayed by cyclic secondary amines. In the search for further modification of the catalyst architecture we made the observation that pyrrolidine hydrochloride **6**·HCl was ineffective in catalysing the Diels–Alder reaction between cyclopentadiene and cinnamaldehyde (Table 1, entry 9) when compared to proline methyl ester hydrochloride **5**·HCl (Table 1, entry 8). This suggested that a carbonyl-group β- to the nucleophilic nitrogen was also involved within the iminium ion formation. We, therefore, targeted a series of catalysts that incorporated both the α-heteroatom and a carbonyl functionality in the β-position to discover if these had further effect on the reactivity of these secondary amines.

Our initial target was the ethyl carbazate derived system **13**, easily prepared in two-steps from commercially available starting materials via a condensation–reduction protocol in 77% overall yield (Scheme 1). Evaluation of the activity of **13**·HCl under standard conditions (10 mol% cat, MeOH/



Scheme 1. Synthesis of catalyst **13**.

H_2O 19:1, room temperature, 48 h) gave the Diels–Alder adducts in 93% isolated yield (*endo*:*exo* ratio 34:66). Thus, introduction of a carbonyl group β- to the reactive centre does indeed markedly increase catalytic activity, providing a new molecular scaffold for catalyst design and development.

Having established a positive effect on activity, we set about optimising our catalyst structure. We examined five variables within our system (Fig. 3) to provide further insight into the catalysts' structure–activity relationship (SAR), with the ultimate goal of designing a second generation catalyst capable of accelerating these reactions at lower catalyst loading and reaction times.

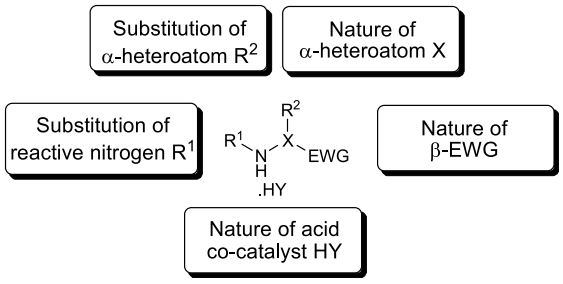


Figure 3. Variables altered for SAR of catalyst.

SAR studies on the catalyst architecture began by varying substitution of the reactive nitrogen centre R^1 with the amines **13**, **14** and **15** (Fig. 4) (see Section 5 for full details of catalyst synthesis). These compounds contained primary, secondary and tertiary substitution directly adjacent to the reactive nitrogen.

The results obtained for these catalysts are outlined in Table 2. The optimal substitution pattern proved to be a secondary centre directly attached to the nucleophilic

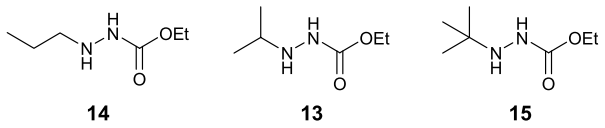


Figure 4. Substitution of reactive nitrogen R^1.

nitrogen (entry 2, **13**·HCl, 90%) with both primary (entry 1, **14**·HCl, 75%) and tertiary (entry 3, **15**·HCl, 32%) substitution providing significantly lower yields of product. Reducing the reaction time to just 6 h with **13**·HCl (entry 4) gave the product in 74% isolated yield, and performing the reaction in methanol led to a further dramatic increase in the amount of isolated product (entry 5, 90%).

In order to ascertain whether the enhanced catalyst activity observed was due to the α-heteroatom, the β-carbonyl, or both, we prepared the glycine ethyl ester derived catalyst **16**.[20] The catalysts **17**·HCl[21] and **18**·HCl,[22] containing an oxygen α-heteroatom and a β-carbonyl, were also synthesised allowing us to compare the effects of carbon, nitrogen and oxygen in the α-position. With oxygen as the α-heteroatom the reactions were sluggish (Table 2, entries 8–10) providing the adducts **9** and **10** in <28% isolated yield after 6 h. Examination of a range of solvents and reaction conditions with these catalysts showed significantly lower conversions, confirming that methanol appears to be the most appropriate solvent for this class of transformation. The glycine ethyl ester derived catalyst **16**·HCl (Table 2, entries 6 and 7) showed that the α-heteroatom is essential for effective reactivity of our systems with the products only being isolated in up to 5% yield. This set of results, therefore, suggested that a synergistic effect of both the α-heteroatom and the β-carbonyl was responsible for the reactivity within the acyclic catalysts used (Fig. 5).

Curiosity into what lay behind the need for an electron

Table 2. Iminium ion catalysed SAR studies[a]

Entry	Catalyst	Solvent	Time (h)	*endo*:*exo*[b]	Yield (%)
1	**14**·HCl	MeOH[c]	24	35:65	75
2	**13**·HCl	MeOH[c]	24	37:63	90
3	**15**·HCl	MeOH[c]	24	35:65	32
4	**13**·HCl	MeOH[c]	6	34:66	74
5	**13**·HCl	MeOH	6	33:67	90
6	**16**·HCl	MeOH	6	35:65	5
7	**16**·HCl	MeOH[c]	6	34:66	3
8	**17**·HCl	MeOH	6	35:65	28
9	**17**·HCl	MeOH[c]	6	34:66	13
10	**18**·HCl	MeOH	6	50:50	12
11	**19**·HCl	MeOH	6	33:67	82
12	**20**·HCl	MeOH	6	33:67	86
13	**21**·HCl	MeOH	24	42:58	69
14	**19**·TFA	MeOH	24	33:67	81
15	**19**·$MeSO_3H$	MeOH	48	36:64	74
16	**19**·$PhCO_2H$	MeOH	48	47:53	10
17	**19**·HBr	MeOH	24	35:65	97
18	**19**·HI	MeOH	24	32:68	98
19	**19**·HPF_6	MeOH	24	30:70	98
20	**22**·HCl	MeOH	6	35:65	98
21	**23**·HCl	MeOH	6	35:65	89
22	**24**·HCl	MeOH	6	34:66	34
23	**24**·HCl	MeOH	24	35:65	70

[a] Diels–Alder reaction between cyclopentadiene and cinnamaldehyde at room temperature with 10 mol% catalyst.
[b] Ratio determined by ^1H NMR of crude reaction mixture.
[c] Water (5%) added by volume.

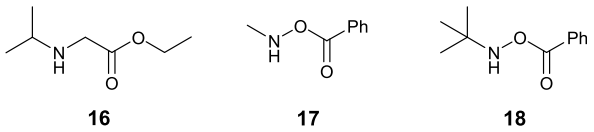


Figure 5. Alteration of α-heteroatom X.

withdrawing group on the α-heteroatom, led us to synthesize a further family of compounds varying the nature of this group (Fig. 6). The amides **19** and **20** and the sulfonamide **21** were prepared to measure their influence when compared to the carbamate derivative **13**.

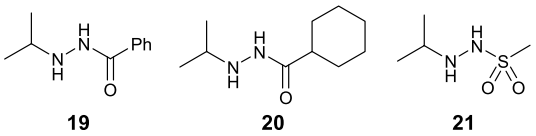


Figure 6. Modification of EWG.

Each of these hydrazine derivatives appeared to be effective catalysts, although they did not perform as well as the carbamate **13**·HCl. With the amides **19** and **20** the Diels–Alder adducts were isolated in 82 and 86% yields, respectively, (Table 2, entries 11 and 12) after just 6 h. Although the sulfonamide performed well when compared to the catalysts without an electron withdrawing group on the α-heteroatom, it still returned significantly less product when compared to the carbamates and amides, with an extended reaction time of 24 h needed in order to obtain a respectable yield (entry 13).

The next variable we addressed was the nature of acid co-catalyst HX. Our initial work revealed that as the pK_a of the acid co-catalyst decreased, the length of time necessary for the reaction to proceed increased (Table 2, entries 14–16). Interestingly, however, we found that with benzoic acid as the co-catalyst, the *endo*:*exo* ratio of the products was significantly different to the usual 2:1 ratio observed with most other reactions (entry 16). An interesting phenomenon of these iminium ion catalysed Diels–Alder reactions is that with α,β-unsaturated aldehydes the *exo*-isomer predominates, a complementary and potentially synthetically significant alternative to the Lewis acid catalysed process, which tends to give the *endo*-adduct preferentially. To check the effect of counter anion size on the geometry of the reaction products, we prepared the ·HBr and ·HI salts of **19**, and compared the diastereomeric ratio of the Diels–Alder adducts (Table 2, entries 17–19). However, in all cases the ratio of the *endo* and *exo* isomers was 2:1, even for the non-coordinating anion PF_6^-, that is, the ratio observed for most of the systems used within this investigation (Fig. 7).

Finally, the effect of the substituent on the α-heteroatom was examined by preparing the methyl substituted carbamate **22** and amide **23** as well as the more sterically encumbered *tert*-butyl carbamate **24**. As in the substitution of the reactive nitrogen, catalyst reactivity is sensitive to steric encumbrance around the α-heteroatom, the *tert*-butyl derivative requiring 24 h in order to reach 70% conversion for the reaction (Table 2, entries 22 and 23). However, we were delighted to discover that with a methyl substituent on the α-heteroatom, an increase in the amount of isolated product was observed. This was the case for both the carbamate (entry 20) and the amide (entry 21) derivatives leading to our most effective catalyst system observed to date.

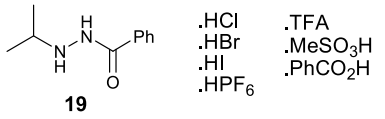


Figure 7. Nature of the acid co-catalyst HX.

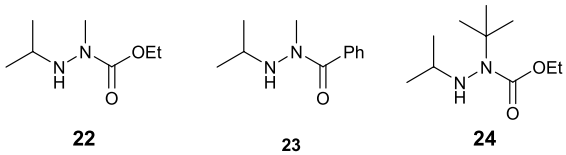


Figure 8. Substitution of α-heteroatom R^2.

3. Theoretical calculations

Along with experimental work, theoretical calculations were carried out on the formation of iminium ions in order to provide a basis for further catalyst design as well as aid in interpretation of our synthetic results. We aimed to establish a mechanism for the formation of the active species, and hence to understand the effect of functional groups surrounding the reactive nitrogen centre on reactivity, ultimately with the aim of developing a predictive scale for amine reactivity (Fig. 8).

Initially, we constructed a realistic model of the reaction conditions used in the practical work above, namely an ensemble including the hydrochloride salt of dimethylamine, acrolein as a model electrophile, and a single explicit water molecule, all enclosed within a spherical dielectric approximation of methanol solvation. Optimization of this

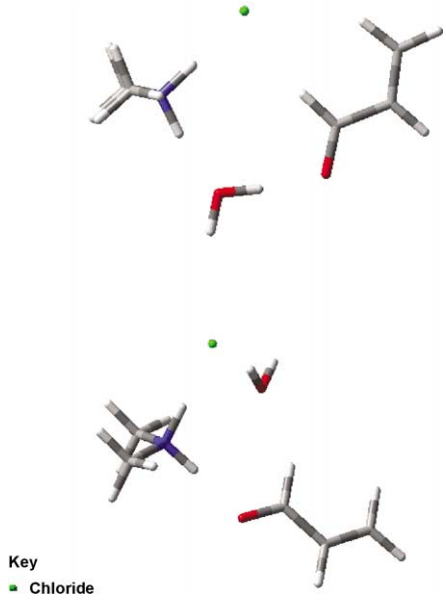


Figure 9. Two optimized reaction geometries.

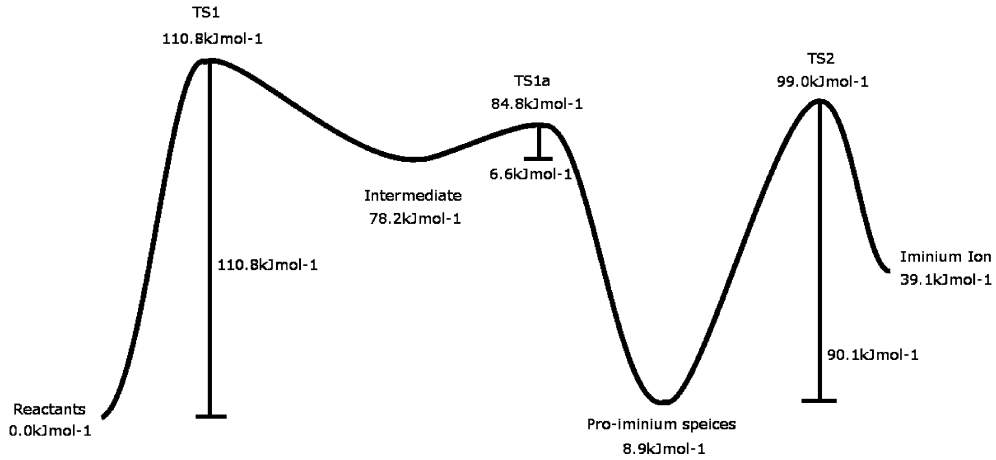
Figure 10. (a) Optimised geometry of 'pro-iminium' and (b) iminium ion products.

reaction mixture from varying starting points revealed a number of stable conformations of very similar energy, and with negligible barriers to inter-conversion of each. Figure 9 shows two such starting conformations, which differ in energy by just 2.9 kJ mol^{-1}. Addition of further explicit water molecules to this ensemble led to the chloride occupying a comparable position as shown in Figure 9, that is forming a close contact with the protonated amine (Cl$\cdots$H = 1.9–2.1 Å), with minor changes in other geometrical details.

A second stable structure is found, ca. 10 kJ mol^{-1} higher in energy than the reactant complex, in which the N–C bond has formed and a proton transferred from amine to carbonyl (see Fig. 10a). Here again, the chloride ion is closely associated with the protonated amine centre, with the water hydrogen bonded to both Cl^- and OH. The N–C bond length in this 'pro-iminium ion' species is 1.56 Å, that is, somewhat longer than a typical N–C single bond (cf. 1.46 Å in dimethylamine). A third low energy minimum, corresponding to the iminium ion product after elimination of water from the pro-iminium species, was located ca. 40 kJ mol^{-1} above the reactants. This product contains the expected N=C double bond, as evidenced by the planar disposition of groups about N, and the N=C length of 1.31 Å (Fig. 10b).

Transition states connecting these minima were located using the QST3 approach in G03, specifying reactant and product structures along with a guess of a transition state obtained from relaxed potential energy surface (PES) scans. A transition state linking the reactant and pro-iminium product (denoted TS1) was located in this manner, with a single imaginary frequency of 139.9*i* cm^{-1}. TS1 is 110 kJ mol^{-1} higher in energy than the reactant complex, a sizeable barrier due largely to transfer of a proton from the amine to chloride, accompanied by small re-orientation of acrolein and water. A second transition state, TS2, accompanies the elimination of water from this initial product, again essentially a proton transfer from amine to oxygen, mediated by the presence of chloride. TS2, with imaginary frequency 405.6*i* cm^{-1}, is ca. 90 kJ mol^{-1} above the pro-iminium species. Thus, the barrier associated with initial formation of the N–C bond is rather higher in energy than subsequent elimination of water to the final product.

In order to check whether these transition states do indeed link the expected reactants and products, we perturbed each TS both forwards and backwards along the imaginary eigenvalue, then carried out geometry optimisation. This process resulted in previously located minima from TS2, as shown in Scheme 2. Perturbing backwards from TS1 gave the reactant complex as expected, but forward from TS1 resulted in a new minimum structure, confirmed as such via harmonic frequency calculation, just 32.6 kJ mol^{-1} below TS1. This 'intermediate' structure differs from the TS only by relative rotation of the various moieties, with both acrolein and HCl rotated towards their orientation in the pro-iminium product.



Scheme 2. Reaction profile of dimethylamine hydrochloride and acrolein.

A third transition state, TS1a, separates this intermediate from the pro-iminium structure, with a barrier of just 7 kJ mol^{-1}, that is, essentially negligible when compared to the barriers associated with TS1 and TS2. The structure of this transition state is interesting, as it appears the water molecule mediates proton transfer from H–Cl to oxygen, acting as a 'proton shuttle'. Thus, it appears that only this step requires the presence of an explicit water molecule, and hence explains the frequent requirement for trace water in the reaction mixture.

In order to test this choice of theoretical method, we re-calculated this potential energy surface (PES) using both a larger basis set, 6-311++G (2d,p), and a density functional, mPW1PW91, reported to give improved barriers for model organic reactions.[26] In both cases, neither structures nor relative energies of stationary points differed significantly from those reported above. The larger basis set reduced barriers at TS1 and TS2 by 6.8 and 0.8 kJ mol^{-1}, respectively, while the alternative functional increased these by 4.8 and 2.0 kJ mol^{-1}, respectively.

Therefore, we have confidence in our B3LYP/6-31+G(d) calculations that indicate a three-step, rather than a two-step mechanism for formation of an iminium ion from dimethylamine hydrochloride and acrolein, albeit with one energetically unimportant step, as shown in Scheme 2. There is, therefore, considerable scope for electronic and/or steric effects, through modification of the amine, to alter the kinetics of iminium ion formation.

Applying the same methods to two α-nucleophiles, namely *N*,*N*′-dimethylhydrazine **1** and *N*,*O*-dimethylhydroxyl amine **3**, yields a broadly similar PES to that shown in Scheme 2 in each case (Fig. 11). Both reaction paths show a clear effect of the α-heteroatom, reducing the barriers at TS1 and TS2 by between 5 and 35 kJ mol^{-1}. Specific effects are apparent in these results: the *N*-heteroatom reduces the second barrier by substantially more than the first, while the opposite is true for the *O*-heteroatom. Thus, there appears to be a subtle interplay of effects at work here, consistent with the generally accepted view that the α-effect is a complex one. Subsequent theoretical studies will attempt to explain these results in terms of the electronic structure of the relevant minima and transition states.

These results are directly relevant to those in Table 1, and are, therefore, consistent with the rather small increase in catalytic activity seen for *N*,*N*′-dimethylhydrazine and the rather larger effect found with *N*,*O*-dimethyl-hydroxyl-amine. The reaction pathway proposed here is also consistent with the effect of counter anion noted in Table 2: a key step in iminium ion formation is transfer of a proton from *N* to *O*, mediated by the counter anion. Acids of increasing pK_a should be progressively worse at mediating such a step, and, therefore, lead to lower catalytic activity.

A further interesting observation linking both synthetic and theoretical investigations is the addition of water to some reaction mixtures, which is only required for catalysts lacking a β-carbonyl. This suggests the possiblity that the carbonyl group is intimately involved with iminium ion formation, acting as a proton shuttle in an analogous manner to the water molecule in the calculations presented. Introduction of the β-carbonyl may, therefore, provide an intramolecular route for this, and hence may explain why this functionality removes the need for water in the reaction medium.

4. Conclusion

In summary, through a combination of both synthetic and theoretical studies we have shown that the α-effect is an effective platform for iminium ion catalysis. The synthetic studies have shown an arrangement of a tertiary centre on the reactive nitrogen together with a methyl substituent and an ethyl carbamate on the α-heteroatom leads to a highly effective catalyst architecture. DFT calculations have revealed a realistic mechanistic pathway for iminium ion formation and have shown that transition state energies can be significantly perturbed through the incorporation of an α-heteroatom. Of particular note is the fact that both a counter-anion and a proton-shuttle (water) are necessary for this process to occur. A possible reason for the counter-intuitive need for an electron-withdrawing-group on the

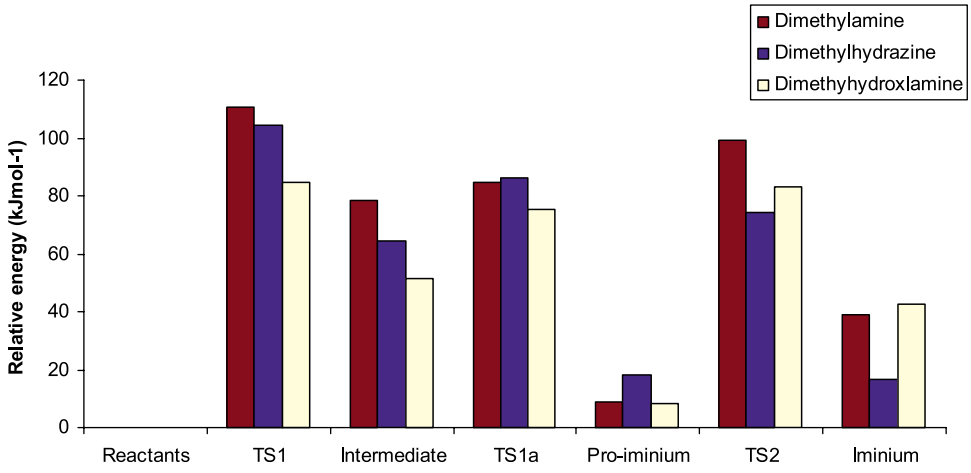


Figure 11. Comparison of reaction path of three amines.

α-heteroatom may lie in the mechanism of formation of the iminium ion. Further studies are now underway to explain the need for a β-carbonyl within our catalyst structure and to incorporate these fundamental findings within a chiral catalyst for use in iminium ion catalysed transformations.

5. Experimental

5.1. General

All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX-400, Bruker Avance 500 or Bruker DPX-250 spectrometer, with ^{13}C spectra being recorded at 100, 125 or 62.5 MHz. Mass spectra were obtained using a Fisons VG platform II spectrometer. High resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. Melting points were determined on a Khofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 1600 series spectrophotometer as thin films or as nujol mulls. Thin-layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

All DFT calculations were carried out using the Gaussian03 package.[23] Initial optimisations and transition state searches were carried out at the B3LYP/6-31+G(d,p) level,[24,25] within an Onsager solvent shell of methanol. Subsequent calculations to test these methods employed the larger 6-311++G(2d,p) basis set, as well as the mPW1PW91 functional,[26] and an alternative PCM model of methanol solvation.[27] All minima and transition states were characterised as such via harmonic frequency calculation and examination of any resulting imaginary eigenvalues.

5.1.1. *N′*-Isopropylidenehydrazinecarboxylic acid ethyl ester. Ethyl carbazate (2.20 g, 21.1 mmol) was stirred in an excess of acetone (10 mL), containing acetic acid (30 μL, 0.5 mmol), for 24 h at ambient temperature. Water (20 mL) was added and the reaction mixture extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and reduced in vacuo to afford the title compound (2.75 g, 90%) as a colourless solid; mp 72–73 °C [lit.[28] mp 75–76 °C]; ν_{max} (nujol)/cm^{-1} 3236, 1730, 1649, 1530, 1239; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s, N*H*) 4.06 (2H, q, J=6.4 Hz, OCH_2CH$_3$) 1.83 (3H, s, N=CCH_3) 1.71 (3H, s, N=CCH_3) 1.11 (3H, t, J=6.4 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (C) 151.0 (C) 61.6 (CH_2) 25.4 (CH_3) 16.3 (CH_3) 14.5 (CH_3); *m/z* (EI) $[M]^+$144 (19%), 98 (93), 44 (100), 41 (69); HRMS (EI) (found 144.0898 $[M]^+$; $C_6H_{12}N_2O_2$ requires 144.0899).

5.1.2. *N′*-Isopropylhydrazinecarboxylic acid ethyl ester 13. Platinum oxide (17 mg, 73 μmol) was placed in nitrogen flushed flask with ethanol (3.4 mL) and acetic acid (1.7 mL). *N′-iso*propylidene-hydrazinecarboxylic acid ethyl ester (0.50 g, 3.5 mmol) was added, the flask was charged with hydrogen stirred for 24 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (25 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5×10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **13** (0.43 g, 85%) as a colourless viscous liquid; ν_{max} (film)/cm^{-1} 3314, 1701, 1529, 1266; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (1H, s, N*H*) 4.13 (2H, q, J=6.9 Hz, OCH_2CH$_3$) 3.15 (1H, sept, J=6.6 Hz, NC*H*(CH$_3$)$_2$) 1.24 (3H, t, J=6.9 Hz, OCH$_2$CH_3) 1.01 (6H, d, J=6.6 Hz, NCH(CH_3)$_2$) δ_C (100 MHz, $CDCl_3$) 158.0 (C) 61.7 (CH_2) 51.2 (CH) 20.9 (CH_3) 15.0 (CH_3); *m/z* (EI) $[M]^+$147 (21%), 131 (100), 103 (64), 85 (91), 42 (74); HRMS (EI) (found 146.1053 $[M]^+$; $C_6H_{14}N_2O_2$ requires 146.1055).

Treatment with dry ethereal HCl gave the corresponding salt **13**·HCl as a colourless solid; mp 85–87 °C; ν_{max} (nujol)/cm^{-1} 3397, 2922, 2853, 1732, 1538, 1462, 1377, 1263, 1022; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (2H, br s, NH_2) 9.58 (1H, br s, N*H*) 4.22 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 3.82 (1H, sept, J=6.6 Hz, NC*H*(CH$_3$)$_2$) 1.39 (6H, d, J=6.6 Hz, NCH(CH_3)$_2$) 1.24 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C) 62.4 (CH_2) 55.1 (CH) 17.5 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$147 (100%); HRMS (ES) (found 147.1127 $[M+H–HCl]^+$; $C_6H_{14}N_2O_2$ requires 147.1128).

5.1.3. *N′*-*t*Butylhydrazinecarboxylic acid ethyl ester 15. *tert*-Butylhydrazine hydrochloride (5.00 g, 40.1 mmol, 1 equiv) was cooled to 0 °C in a suspension of dichloromethane (50 mL) and aqueous sodium bicarbonate solution (50 mL). Ethyl chloroformate (4.35 g, 3.84 mmol, 40.1 mmol, 1.0 equiv) was added drop wise to the suspension and stirring was continued at 0 °C for 30 min and at ambient temperature overnight. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×20 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed in vacuo to give a colourless oil. Purification by flash column chromatography eluting with ether/light petroleum 1:1 afforded the title compound **15** (662 mg, 10%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 3302, 2973, 1713, 1538, 1475, 1445, 1388, 1364, 1335, 1269, 1214, 1150, 1062, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (1H, br s, N*H*) 4.10 (2H, q, J=6.8 Hz, OCH_2CH$_3$) 1.20 (3H, t, J=6.8 Hz, OCH$_2$CH_3) 1.02 (9H, s, NC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C) 61.4 (CH_2) 54.9 (C) 27.0 (CH_3) 14.6 (CH_3); *m/z* (APcI) $[M+H]^+$161 (100%); HRMS (ES) (found 161.1285 $[M+H]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

Treatment with dry ethereal HCl gave the corresponding salt **15**·HCl as a colourless solid; mp 157–158 °C; ν_{max} (nujol)/cm^{-1} 3238, 2924, 2684, 2326, 1714, 1531, 1463, 1376, 1275, 1176; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (2H, br s, NH_2) 9.38 (1H, s, N*H*) 4.23 (2H, q, J=6.9 Hz, OCH_2CH$_3$) 1.41 (9H, s, NC(CH_3)$_3$) 1.26 (3H, t, J=6.9 Hz, OCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C) 63.9 (CH_2) 63.3 (C) 24.8 (CH_3) 14.3 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$161

(100%); HRMS (ES) (found 161.1284 $[M+H–HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

5.1.4. *N*-Isopropylglycine ethyl ester 16. A solution of isopropyl amine (13.6 g, 230 mmol, 19.6 mL, 2.3 equiv) in toluene (100 mL) was treated with ethyl bromoacetate (16.7 g, 100 mmol, 11.1 mL, 1.0 equiv) at ambient temperature. The solution was refluxed for 2 h and subsequently stirred at room temperature for 16 h during which time a crystalline precipitate was formed. The solution was made alkaline with sodium hydroxide (50% solution, 20 mL) dissolving the precipitate. The organic layer was separated and washed with water, brine, and dried ($MgSO_4$). The volatiles were removed in vacuo and the product purified by distillation (5 mbar, 73–75 °C) [lit.[29] bp 30 °C at 2.00 Torr] to give the title compound **16** (12.3 g, 85%) as a clear colourless liquid; ν_{max} (film)/cm^{-1} 3335, 2966, 1740, 1466, 1379, 1347, 1098, 1028; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (2H, q, $J=7.2$ Hz, OCH_2CH_3) 3.34 (2H, s, $NHCH_2CO$) 2.73 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$) 1.52 (1H, br s, NH) 1.21 (3H, t, $J=7.2$ Hz, OCH_2CH_3) 0.99 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C) 60.8 (CH_2) 48.7 (CH_2) 48.3 (CH_2) 22.7 (CH_3) 14.2 (CH_3); *m/z* (APcI) $[M+H]^+$146 (100%); HRMS (ES) (found 146.1177 $[M+H]^+$; $C_7H_{15}N_1O_2$ requires 146.1176).

Treatment with dry ethereal HCl gave the corresponding salt **16**·HCl as a colourless solid; mp 111–112 °C; ν_{max} (nujol)/cm^{-1} 3330, 2926, 2853, 2705, 2455, 1757, 1590, 1463, 1377; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (2H, br s, NH_2) 4.21 (2H, q, $J=7.1$ Hz, OCH_2CH_3) 3.76 (2H, s, NCH_2COO) 3.56 (1H, m, $NCH(CH_3)_2$) 1.44 (6H, d, $J=6.7$ Hz, $NCH(CH_3)_2$) 1.24 (3H, t, $J=7.1$ Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C) 62.5 (CH_2) 50.8 (CH) 44.2 (CH_2) 18.9 (CH_3) 14.0 (CH_3); *m/z* (APcI) $[M+H–HCl]^+$146 (100%); HRMS (ES) (found 146.1177 $[M+H–HCl]^+$; $C_7H_{15}N_1O_2$ requires 146.1176).

5.1.5. Benzoic acid isopropylidene hydrazide. Benzoic hydrazide (5.00 g, 36.7 mmol) was stirred in an excess of acetone (22 mL, 0.3 mmol), containing acetic acid (40 μL, 0.7 mmol), for 48 h at ambient temperature. Water (30 mL) was added and the reaction mixture was extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and reduced in vacuo to afford the title compound (5.57 g, 86%) as a colourless solid; mp 141–143 °C [lit.[30] mp 142–143 °C]; ν_{max} (nujol)/cm^{-1} 3221, 1655, 1578, 1578, 1531, 1490, 718, 668; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, s, NH) 7.79 (2H, d, $J=7.1$ Hz, ArH) 7.52 (1H, t, $J=7.1$ Hz, ArH) 7.44 (2H, dd, $J=7.1$, 7.1 Hz, ArH) 2.15 (3H, s, CH_3) 1.97 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C) 156.9 (C) 134.1 (C) 132.1 (CH) 129.0 (CH) 127.6 (CH) 26.0 (CH_3) 17.3 (CH_3); *m/z* (EI) $[M]^+$176 (8%), 161 (50), 105 (100), 77 (31); HRMS (EI) (found 176.0950 $[M]^+$; $C_{10}H_{12}N_2O$ requires 176.0950).

5.1.6. Benzoic acid *N*′-Isopropylhydrazide 19. Platinum oxide (68 mg, 0.3 mmol) was placed in a nitrogen flushed flask with ethanol (12 mL) and acetic acid (6 mL). Benzoic acid isopropylidene hydrazide (2.50 g, 14.2 mmol) was added, the flask was charged with hydrogen and stirred for 48 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The volatiles were removed under reduced pressure and the aqueous phase was extracted with diethyl ether (5×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **19** (2.18 g, 86%) as a colourless powder; mp 110–112 °C [lit.[31] mp 115–117 °C]; ν_{max} (nujol)/cm^{-1} 3289, 1640, 1537, 725, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, s, NH) 7.69 (2H, d, $J=7.7$ Hz, ArH) 7.46 (1H, t, $J=7.7$ Hz, ArH) 7.38 (2H, dd, $J=7.7$, 7.7 Hz, ArH) 4.81 (1H, s, NH) 3.18 (1H, sept, $J=6.2$ Hz, $NCH(CH_3)_2$) 1.05 (6H, d, $J=6.2$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C) 132.9 (C) 131.9 (CH) 128.7 (CH) 126.9 (CH) 51.4 (CH) 20.9 (CH_3); *m/z* (EI) $[M]^+$173 (3%), 163 (9), 122 (13), 105 (100), 77 (34); HRMS (EI) (found 178.1105 $[M]^+$; $C_{10}H_{14}N_2O$ requires 178.1106).

Treatment with dry ethereal HCl gave the corresponding salt **19**·HCl as a colourless solid; mp 215–218 °C; ν_{max} (nujol film)/cm^{-1} 3408, 2923, 2853, 2645, 1678, 1600, 1549, 1527, 1463, 1377; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, $J=7.5$ Hz, ArH) 7.45 (1H, t, $J=7.4$ Hz, ArH) 7.31 (2H, dd, $J=7.5$, 7.4 Hz, ArH) 3.94 (1H, sept, $J=6.6$ Hz, $NCH(CH_3)_2$) 1.41 (6H, d, $J=6.6$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C) 133.5 (C) 128.7 (CH) 128.6 (CH) 128.5 (CH) 56.0 (CH) 18.0 (CH_3); *m/z* (ApcI) $[M+H–HCl]^+$179 (100%).

5.1.7. Cyclohexanecarboxylic acid *N*′-Isopropylhydrazide 20. Platinum oxide (108 mg, 0.48 mmol) was placed in a nitrogen flushed flask with ethanol (50 mL) and acetic acid (25 mL). Benzoic acid isopropylidene hydrazide (4.20 g, 23.8 mmol) was added, the flask was charged with hydrogen and stirred for 96 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (450 mL), which caused the product to precipitate and the suspension was extracted with diethyl ether (5×100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **20** (2.31 g, 53%) as a colourless powder; mp 120–124 °C [lit.[32] mp 122–123 °C]; ν_{max} (nujol)/cm^{-1} 3397, 2926, 1708, 1549, 1525, 1462, 1377, 1336, 1173, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, br s, NH) 4.61 (1H, m, NH) 3.08 (1H, m, $NCH(CH_3)_2$) 2.06 (1H, m, Cy) 1.80 (4H, m, Cy) 1.68 (1H, m, Cy) 1.46 (2H, m, Cy) 1.25 (3H, m, Cy) 1.03 (6H, d, $J=6.4$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C) 51.5 (CH_2) 44.2 (CH_2) 38.2 (CH) 29.8 (CH) 26.0 (CH_3) 21.1 (CH_2); *m/z* (APcI) $[M+H]^+$185 (95%) 143 (100); HRMS (ES) (found 185.1645 $[M+H]^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

Treatment with dry ethereal HCl gave the corresponding salt **20**·HCl as a colourless solid; mp 193–194 °C; ν_{max} (nujol)/cm^{-1} 3330, 2923, 1707, 1548, 1525, 1461, 1377, 1336, 1259, 1192, 1174, 1111; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, s, NH) 3.81 (1H, sept, $J=6.6$ Hz, $NCH(CH_3)_2$) 2.60–2.50 (1H, m, O=CCH) 1.89–1.20 (10H, m, Cy) 1.43 (6H, d, $J=6.6$ Hz, $NCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C) 55.6 (CH_2) 42.3 (CH_2) 29.0 (CH) 25.5 (CH) 25.2 (CH_3) 17.8 (CH_2); *m/z* (APcI) $[M+H–HCl]^+$185 (100%);

HRMS (ES) (found 185.1653 $[M+H-HCl]^+$; $C_{10}H_{21}N_2O$ requires 185.1648).

5.1.8. Methanesulfonylhydrazide hydrochloride.[33] Methanesulfonyl chloride (5.75 g, 50 mmol) was added slowly to a stirred ice-cold solution of hydrazine hydrate (2.5 g, 50 mmol) in water (7.5 mL), followed by 2 M aq NaOH (25 mL), such that the temperature did not exceed 8 °C. On completion, hydrochloric acid (25 mL) was added, which led to the precipitation of a small amount of di-methanesulfonyl hydrazide, which was filtered off. The filtrate was concentred in vacuo and the resulting residue recrystallised twice from boiling ethanol to give the title compound (2.0 g, 36%) as a coluorless crystaline solid; mp 152–153 °C; ν_{max} (nujol mull)/cm^{-1} 3440, 2652, 1953, 1461, 1376, 1146, 978; ^{1}H NMR (400 MHz, D_2O) δ 3.1 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, D_2O) δ 38.4 (CH_3).

5.1.9. *N*-Isopropylidene-*N′*-methanesulfonylhydrazone hydrochloride. Methanesulfonylhydrazide hydrochloride (400 mg, 3.5 mmol) was stirred in an excess of acetone (20 mL) at room temperature for 24 h. The solvent was removed in vacuo and the solid residue was recrystallised twice from ethanol/ether to give the title compound as a colourless solid (824 mg, 64%); mp 120 °C dec; ν_{max} (nujol mull)/cm^{-1} 3410, 1977, 1672 (C=N), 1462, 1351 (SO_2), 1165 (SO_2), 784; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.5 (1H, s, SO_2N*H*), 3.05 (3H, s, C*H*$_3$), 2.0 (3H, s, C*H*$_3$), 1.8 (3H, s, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.74 (C) 38.59 (CH_3) 25.70 (CH_3) 17.56 (CH_3).

5.1.10. Methanesulfonic acid *N′*-isopropyl hydrazide 21·HCl. To a stirred solution of *N*-isopropylidene-*N′*-methanesulfonylhydrazone hydrochloride (0.4 g, 2.14 mmol) in methanol (3 mL) was added a solution $NaCNBH_3$ in THF (1 M, 2.14 mL, 2.14 mmol) at room temperature, followed by 2 M HCl at a rate sufficient to maintain a pH of 2–3. After 10–15 min the pH changed less rapidly and the mixture was allowed to stir for an additional 3 h. The pH was lowered to 1 and the volatiles were removed under reduced pressure. The resulting residue was taken up in water (10 mL) and the pH adjusted to 8 with 20% K_2CO_3 and extracted with ether (6×20 mL). The ethereal extracts were dried ($MgSO_4$) and concentrated to afford an oil, which was dissolved in ether (10 mL) and the solution was treated with 2 M HCl in ether to give a solid, which was recrystallised from ethanol/ether to afford the title compound **21**·HCl as a colourless solid (54 mg, 13%); mp 100–103 °C; ν_{max} (nujol mull)/cm^{-1} 1942, 1562, 1462, 1348 (SO_2), 1175 (SO_2), 795, 779; ^{1}H NMR (400 MHz, D_2O) δ 3.42 (1H, sept, J=6.5 Hz, C*H*(CH_3)$_2$), 3.1 (3H, s, C*H*$_3$), 1.14 (6H, d, J=6.5 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, D_2O) δ 54.5 (CH) 39.8 (CH_3) 16.9 (CH_3).

5.1.11. *N*-Isopropylidene-*N′*methylhydrazine. Methyl hydrazine (13.6 g, 295 mmol, 15.7 mL) was added drop wise to acetone (23.7 g, 409 mmol, 30 mL) maintaining the reaction temperature below 35 °C. The solution was stirred for 1 h after which the top layer was removed and allowed to stand over potassium hydroxide (5 g) for a further 1 h. The upper liquid was decanted from the lower aqueous layer and allowed to stand over two successive portions of potassium hydroxide (2×2.5 g) for 30 min each. Purification was by distillation (110 °C) [lit.[34] bp 116–118 °C] under nitrogen affording the title compound (17.85 g, 70%); ν_{max} (liquid film)/cm^{-1} 3394, 3262, 2911, 2794, 1711, 1631; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (1H, br s, N*H*) 2.76, (3H, s, NHC*H*$_3$) 1.88 (3H, s, N=CC*H*$_3$ *trans*) 1.68 (3H, s, N=C–C*H*$_3$ *cis*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (C) 37.9 (CH_3) 25.0 (CH_3) 15.5 (CH_3); *m/z* (APcI) $[M+H]^+$87 (100%); HRMS (EI) (found 86.0841 $[M]^+$; $C_4H_{10}N_2$ requires 86.0838).

5.1.12. *N′*-Isopropyl-*N*-methylhydrazinecarboxylic acid ethyl ester hydrochloride 22·HCl. Ethyl chloroformate (1.26 g, 1.11 mL, 11.6 mmol) was added drop wise to a stirred solution of *N*-isopropylidene-*N′*-methylhydrazine (1.00 g, 11.6 mmol) in dichloromethane (10 mL) and saturated sodium bicarbonate solution (10 mL) at 0 °C. After addition the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The organics were separated and the aqueous layer extracted with dichloromethane (2×20 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask, charged with platinum oxide (132 mg, 0.58 mmol) in ethanol (20 mL) and acetic acid (10 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (300 mL). The single phase solution was extracted with diethyl ether (3×50 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure to give a clear oil, which was purified by flash column chromatography eluting with ether/light petroleum 1:1. The solvent was removed under reduced pressure and ethereal hydrochloric acid (1 M, 58.0 mmol, 58 mL, 5 equiv) was added to the solution with swirling for 30 min at ambient temperature. The precipitate was filtered under nitrogen affording the title compound **22**·HCl as a colourless powder (808 mg, 35%); mp 85–86 °C; ν_{max} (nujol)/cm^{-1} 3399, 2921, 5852, 2612, 1729, 1562, 1503, 1462, 1378, 1332, 1312, 1202, 1122, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (2H, q, J=7.2 Hz, OC*H*$_2$CH$_3$) 5.48 (1H, sept, J=6.6 Hz, NC*H*(CH_3)$_2$) 3.46 (3H, s, NC*H*$_3$) 1.50 (6H, d, J=6.6 Hz, NCH(C*H*$_3$)$_2$) 1.36 (3H, t, J=7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2 (C) 64.1 (CH_2) 54.6 (CH) 35.9 (CH_3) 17.8 (CH_3) 14.3 (CH_3); *m/z* (ES) $[M+H-HCl]^+$161 (90%) 119 (60) 115 (100); HRMS (ES) (found 161.1286 $[M+H-HCl]^+$; $C_7H_{16}N_2O_2$ requires 161.1285).

5.1.13. Benzoic acid *N′*-isopropyl-*N*-methylhydrazine hydrochloride 23·HCl. Benzoyl chloride (817 mg, 5.8 mmol, 0.67 mL) was added drop wise to a stirred solution of *N*-isopropylidene-*N′*-methylhydrazine (500 mg, 5.8 mmol) in dichloromethane (5 mL) and saturated sodium bicarbonate solution (5 mL) at 0 °C. After addition the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The organics were separated and the aqueous layer extracted with dichloromethane (2×10 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The organics were added to a nitrogen flushed flask charged with platinum oxide (66 mg, 0.29 mmol, 5 mol%) in ethanol

(12 mL) and acetic acid (6 mL). The atmosphere was replaced with hydrogen and the reaction stirred for 16 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (180 mL). The single phase solution was extracted with diethyl ether (3×50 mL) and the combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure resulting in a clear oil, which was purified by flash column chromatography eluting with diethyl ether in light petroleum 1:1. The volume of elutent was reduced and ethereal hydrochloric acid (1 M, 13.0 mmol, 13 mL, 5 equiv) was added to the solution with swirling for 30 min at ambient temperature. The precipitate was filtered under nitrogen affording the title compound **23**·HCl as a colourless solid (150 mg, 11%); mp 145–146 °C; ν_{max} (nujol)/cm^{-1} 3408, 2923, 2091, 1638, 1460, 1377, 1333, 1122, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, J=8.0 Hz, *o*-Ar) 7.49, (1H, d, J=7.1 Hz, *p*-Ar) 7.42 (2H, dd, J=8.0, 7.1 Hz, *m*-Ar) 3.94 (1H, sept, J=6.6 Hz, NC*H*$(CH_3)_2$) 3.61 (3H, s, NCH_3) 1.51 (6H, d, J=6.6 Hz, NCH(C$H_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 C) 132.3 (Ar) 130.7 (Ar) 128.9 (Ar) 128.2 (Ar) 53.7 (CH_3) 38.6 (CH) 18.0 (CH_3); *m*/*z* (ES) $[M+H–HCl]^+$193 (72%) 151 (100%); HRMS (ES) (found 193.1336 $[M+H–HCl]^+$; $C_{11}H_{17}N_2O$ requires 193.1335).

5.1.14. *N*-^{t}Butyl-*N*′-isopropylidenehydrazine. *tert*-Butylhydrazine dihydrochloride (10 g, 80 mmol, 1 equiv) was added to acetone (4.66 g, 80 mmol, 5.89 mL, 1.0 equiv) maintaining the temperature under 35 °C. Potassium hydroxide (5 g) was added the mixture stirred for 1 h. The liquid portion was decanted from the solid residue and allowed to stand over two successive portions of potassium hydroxide (5 g) for 1 h each. The clear colourless liquid was purified by distillation (4 mbar, 40–41 °C) affording the title compound (6.60 g, 64%); ν_{max} (liquid film)/cm^{-1} 3418, 3265, 2972, 1705, 1441, 1385, 1361, 1279, 1237, 1116; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (1H, br s, N*H*) 1.70 (3H, s, N=C(C$H_3)_2$) 1.49 (3H, s, N=C(C$H_3)_2$) 0.95 (9H, s, NHC(C$H_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (C) 53.0 (C) 28.6 (CH_3) 25.5 (CH_3) 15.3 (CH_3); *m*/*z* (APcI) $[M+H]^+$129 (100%).

5.1.15. *N*-^{t}Butyl-*N*′-isoproylidenehydrazinecarboxylic acid ethyl ester. To a suspension of *N*-*tert*-butyl-*N*′-*iso*propylidene-hydrazine (1.00 g, 7.80 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C was added saturated sodium bicarbonate solution (10 mL). Ethyl chloroformate (1.02 g, 9.36 mmol, 0.89 mL, 1.2 equiv) was added drop wise to the suspension and stirring was continued at 0 °C for 30 min and at ambient temperature overnight. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×5 mL). The combined organics were dried (Na_2SO_4) and the volatiles removed in vacuo to give a yellow oil. Purification by flash chromatography eluting with diethyl ether in light petroleum 1:1 afforded the title compound (662 mg, 64%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 2975, 2923, 1698, 1652, 1482, 1456, 1393, 1367, 1304, 1257, 1224, 1170, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 1.91 (3H, s, NC(C$H_3)_2$) 1.71 (3H, s, NC(C$H_3)_2$) 1.21 (9H, s, NC(C$H_3)_3$) 1.04 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C) 153.6 (C) 60.8 (CH_2) 58.3 (CH_2) 28.2 (CH_3) 24.5 (CH_3) 19.5 (CH_3) 14.6 (CH_3); *m*/*z* (APcI) $[M+H]^+$201 (100%); HRMS (ES) (found 201.1597 $[M+H]^+$; $C_{10}H_{21}N_2O_2$ requires 201.1598).

5.1.16. *N*-^{t}Butyl-*N*′-isopropylhydrazinecarboxylic acid ethyl ester 24. Platinum oxide (28 mg, 0.12 mmol, 5 mol%) was placed in a nitrogen flushed flask with ethanol (6 mL) and acetic acid (3 mL). *N*-*tert*-butyl-*N*′-isoproylidene-hydrazinecarboxylic acid ethyl ester (500 mg, 2.50 mmol) was added, the flask was charged with hydrogen and stirring was continued for 24 h at ambient temperature. The reaction mixture was filtered over Celite® and the filtrate was neutralised with saturated sodium bicarbonate solution (25 mL), which caused the product to precipitate. The suspension was extracted with diethyl ether (5× 15 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and reduced in vacuo to give the title compound **24** (467 mg, 93%) as a colourless oil; ν_{max} (liquid film)/cm^{-1} 3314, 2971, 1702, 1467, 1396, 1367, 1308, 1250, 1223, 1168, 1081; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (2H, q, J=7.1 Hz, OCH_2CH$_3$) 3.80 (1H, br s, N*H*) 3.01 (1H, sept, J=6.4 Hz, NC*H*$(CH_3)_2$) 1.28 (9H, s, NC(C$H_3)_3$) 1.22 (3H, t, J=7.1 Hz, OCH$_2$CH_3) 0.92 (6H, d, J=6.4 Hz, NCH(C$H_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C) 61.2 (CH_2) 58.9 (CH_3) 50.6 (CH) 29.0 (CH_3) 21.3 (CH_3) 20.8 (CH_3) 14.5 (CH_3); *m*/*z* (APcI) $[M+H]^+$203 (100%); HRMS (ES) (found 203.1756 $[M+H]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

Treatment with dry ethereal HCl gave the corresponding salt **24**·HCl as a colourless solid; mp 115–117 °C; ν_{max} (nujol)/cm^{-1} 2924, 2853, 1732, 1541, 1464, 1376, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (2H, br s, NH_2) 4.26 (2H, q, J= 7.1 Hz, OCH_2CH$_3$) 3.69 (1H, sept, J=6.6 Hz, NC*H*$(CH_3)_2$) 1.61 (9H, s, NC(C$H_3)_3$) 1.46 (6H, br s, NCH(C$H_3)_2$) 1.32 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (C) 64.4 (CH_2) 62.3 (C) 57.6 (CH) 29.0 (CH_3) 18.5 (CH_3) 14.3 (CH_3); *m*/*z* (APcI) $[M+H]^+$203 (100%); HRMS (ES) (found 203.1753 $[M+H–HCl]^+$; $C_{10}H_{23}N_2O_2$ requires 203.1754).

5.1.17. Typical experimental procedure for catalytic runs. *trans*-Cinnamaldehyde **8** (252 mg, 1.9 mmol, 0.24 mL, 1.0 equiv) was added to a solution of catalyst (10 mol%, 0.19 mmol) in methanol (2.0 mL) at 25 °C and the resulting mixture was stirred for 5 min to initiate iminium ion formation. Freshly cracked cyclopentadiene **7** (323 mg, 4.9 mmol, 0.38 mL, 2.5 equiv) was added in a single aliquot and stirring was continued for 24 h. The volatiles were removed under reduced pressure and the resulting organics were hydrolysed in a chloroform (2 mL), water (1 mL) trifluoroacetic acid (1 mL) mixture over night. Saturated sodium hydrogen carbonate solution (18 mL) was added to neutralise the solution and the aqueous phase was extracted with dichloromethane (2×20 mL). The combined organics were washed with water (10 mL) and dried (Na_2SO_4) prior to the removal of the volitiles under reduced pressure. ^{1}H NMR of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: δ_H (400 MHz, $CDCl_3$) 9.8 (*exo*) 9.65 (cinnamaldehyde) 9.53 (*endo*). The products were then purified by flash column chromatography eluting with 10% ethyl acetate in light petrol

resulting in a mixture of the *exo*- and *endo*-isomers of 3-phenyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **9** and **10** as a pale yellow oil. ^{1}H NMR, ^{13}C NMR and IR data were consistent with previously reported literature values;[35] ν_{max} (liquid film)/cm^{-1} 1718, 1601, 1497; *exo*-**10**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, d, $J=2.02$ Hz, C*H*O) 7.4–7.0 (5H, m, Ar*H*) 6.27 (1H, dd, $J=5.63$, 3.61 Hz, C*H*=CH) 6.01 (1H, dd, $J=5.62$, 3.64 Hz, CH=C*H*) 3.66 (1H, dd, $J=5.03$, 3.42 Hz, C*H*Ph) 3.25–3.05 (2H, m, C*H*CH$_2$) 2.55–2.45 (1H, m, C*H*CHO) 1.65–1.45 (2H, m, CH$_2$); *endo*-**9**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, d, $J=2.16$ Hz, C*H*O) 7.4–7.0 (5H, m, Ar*H*) 6.36 (1H, dd, $J=5.63$, 3.61 Hz, C*H*=CH) 6.10 (1H, dd, $J=5.62$, 3.64 Hz, CH=C*H*) 3.26 (1H, m, C*H*Ph) 3.05 (1H, m, C*H*CH$_2$) 3.01 (1H, m, C*H*CH$_2$) 2.91 (1H, m, C*H*CHO) 1.49 (2H, m, CH$_2$); *m/z* (EI) [M]$^{+}$198 (10%) 132 (89) 131 (100) 103 (52) 77 (21) 66 (54).

Acknowledgements

The authors wish to express their gratitude to the EPSRC, the UK Computational Chemistry Facility for a generous grant of time on the Columbus central facility and The Mass Spectrometry Service, Swansea for high resolution spectra.This work was sponsored by EPSRC under grant ref. GR/S69337/01.

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Tetrahedron 62 (2006) 422–433

Bulky diarylammonium arenesulfonates as mild and extremely active dehydrative ester condensation catalysts

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Received 5 June 2005; revised 18 August 2005; accepted 9 September 2005

Available online 10 October 2005

Abstract—More environmentally benign alternatives to current chemical processes, especially large-scale, fundamental reactions like ester condensations, are highly desirable for many reactions. Bulky diarylammonium pentafluorobenzenesulfonates and tosylates serve as extremely active dehydration catalysts for the ester condensation reaction of carboxylic acids with equimolar amounts of sterically demanding alcohols and acid-sensitive alcohols. Typically, the esterification reaction is performed in heptane by heating at 80 °C in the presence of 1 mol% of the catalyst without removing water. Esterification with primary alcohols proceeds without solvents even at room temperature. Furthermore, 4-(*N*-mesitylamino)polystyrene resin-bound pentafluorobenzenesulfonate can be recycled more than 10 times without a loss of activity.

1. Introduction

A great deal of research has been focused on more environmentally benign alternatives to ester condensation processes, which are in great demand by the chemical industry.[1–3] In general, the ester condensation reaction of carboxylic acids with alcohols is catalyzed by Brønsted acids such as HCl, H_2SO_4, *p*-TsOH, etc. for acid-resistant substrates. For acid-sensitive substrates, weak Brønsted acids such as pyridinium *p*-toluenesulfonate (PPTS) are usually employed. However, their catalytic activity is also somewhat lower, and the reactants that can be used are rather limited. In 2000, Tanabe et al. reported that diphenylammonium triflate ($[Ph_2NH_2]^+[OTf]^-$, 1.0–10 mol%) efficiently catalyzed the ester condensation reaction of carboxylic acids with equimolar amounts of alcohols while heating at 80 °C without removing water.[4] According to the literature,[4] although $[Ph_2NH_2]^+[OTf]^-$ can be used without removing water, it is still strongly acidic because it is a salt of a superacid and a weak base. Therefore, it is difficult to apply the method reported by Tanabe and co-workers to sterically demanding and acid-sensitive alcohols. In addition, its turnover is much lower than those of Hf(IV) and Zr(IV) catalysts, which were reported by Ishihara and Yamamoto et al. in the same year.[5]

Recently, we reported bulky diarylammonium pentafluorobenzenesulfonates and tosylates, which are much milder acids than the corresponding ammonium triflates, as extremely active ester condensation catalysts.[6] The hydrophobic effect of the bulky ammonium sulfonates promoted the dehydrative ester condensation reactions and its steric hindrance effectively suppressed the dehydrative elimination of secondary alcohols to produce alkenes. In this report, we describe in detail bulky diarylammonium pentafluorobenzenesulfonates and tosylates that can be used in a variety of sterically demanding alcohols and acid-sensitive alcohols (Fig. 1).

2. Results and discussion

2.1. Synthesis of bulky diarylammonium arenesulfonates

The preparation of bulky diarylammonium arenesulfonates is shown in Figure 2. Bulky diarylamines (Ar^1Ar^2NH) were prepared by palladium-catalyzed cross-coupling of arylbromide (Ar^2Br) with the corresponding anilines (Ar^1NH_2) in 73–97% yield.[7] Diarylammonium arenesulfonates ($[Ar^1Ar^2NH_2]^+[O_3SAr^3]^-$) were prepared in quantitative yield by treating Ar^1Ar^2NH with an equal amount of the corresponding arenesulfonic acids (Ar^+SO_3H). The crystal structure of iminodibenzyl pentafluorobenzenesulfonate ($[(2\text{-}CH_2C_6H_4)_2NH_2]^+[O_3SC_6F_5]^-$) was supported by X-ray diffraction analysis (Fig. 3).[8]

Keywords: Ester condensation; Dehydration; Ammonium sulfonates; Hydrophobic effect; Steric effect.
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doi:10.1016/j.tet.2005.09.059

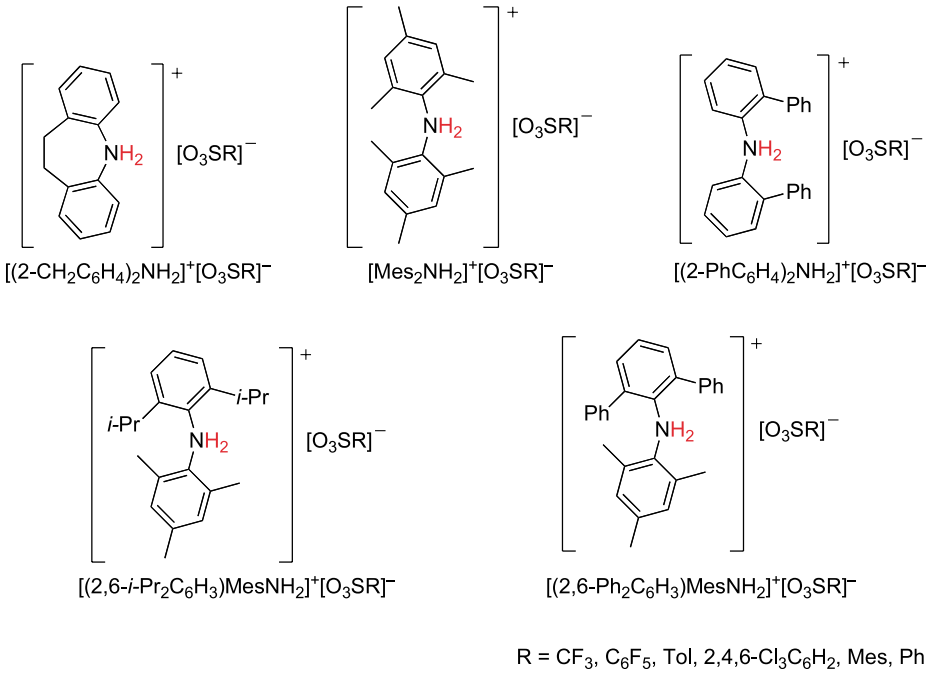


Figure 1. Bulky diarylammonium arenesulfonates as extremely active ester condensation catalysts.

2.2. Ester condensation reaction catalyzed by diarylammonium sulfonates

The ester condensation of 4-phenylbutyric acid with an equimolar amount of cyclododecanol was examined in the presence of 5 mol% of bulky arylammonium perfluoroalkanesulfonates in heptane under reflux conditions (bath temperature 115 °C) (Fig. 4). Cyclododecyl 4-phenylbutyrate and the undesired cyclododecene were produced in the presence of $[Ph_2NH_2]^+[OTf]^-$ (graph **A**). When a more acidic $[Ph_3NH]^+[OTf]^-$ was used, the yield of cyclododecene increased, but cyclododecanol and the ester were converted to cyclododecene (graph **B**). When bulky iminodibenzyl triflate ($[(2\text{-}CH_2C_6H_4)_2NH_2]^+[OTf]^-$) and dimesitylammonium triflate ($[Mes_2NH_2]^+[OTf]^-$) were used, the esterification rates increased, but the dehydration rates from cycldodecanol to cyclododecene decreased (graphs **C** and **D**). Next, when iminodibenzyl pentafluorobenzenesulfonate $\{[(2\text{-}CH_2C_6H_4)_2NH_2]^+[O_3SC_6F_5]^-\}$ and dimesitylammonium pentafluorobenzenesulfonate ($[Mes_2NH_2]^+[O_3SC_6F_5]^-$) were used instead of $[(2\text{-}CH_2C_6H_4)_2NH_2]^+[OTf]^-$ and $[Mes_2NH_2]^+[OTf]^-$, respectively, the yield of the ester increased to more than 90% and the yield of cyclododecene was suppressed to less than 10% (graphs **E** and **F**). Bulky diarylammonium arenesulfonates were effective for the selective esterification of secondary alcohols. They preferentially activated less-hindered carboxylic acids rather than secondary alcohols and dehydrative elimination of secondary alcohols to alkenes was suppressed because of steric hindrance.

Next, the ester condensation reaction of 4-phenylbutyric acid with 6-undecanol in hexane was compared between reflux conditions without removing water and azeotropic reflux conditions while removing water (Fig. 5). The reaction catalyzed by $[Ph_2NH_2]^+[OTf]^-$ was slightly decelerated under reflux conditions without removing the water produced (graph **G**). In contrast, the reaction catalyzed by more bulky catalyst $[(2,6\text{-}i\text{-}Pr_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ proceeded very well without the influence of water (graph **H**).

2.3. Ester condensation reaction catalyzed by alkanesulfonic acids

Trifluoromethanesulfonic acid (TfOH) is a superacid [pK_a (CD_3CO_2D) = −0.74, H_0 = −14.00] that is stronger than concd H_2SO_4 [pK_a (CD_3CO_2D) = 7.5, H_0 = −11.93].[9,10] In contrast, pentafluorobenzenesulfonic acid [$C_6F_5SO_3H$, pK_a

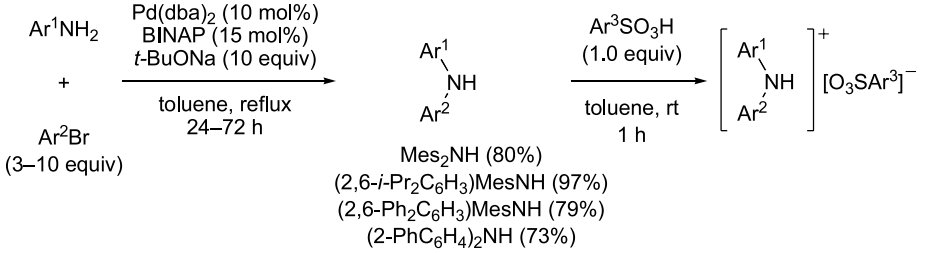


Figure 2. Preparation of bulky diarylammonium arenesulfonates.

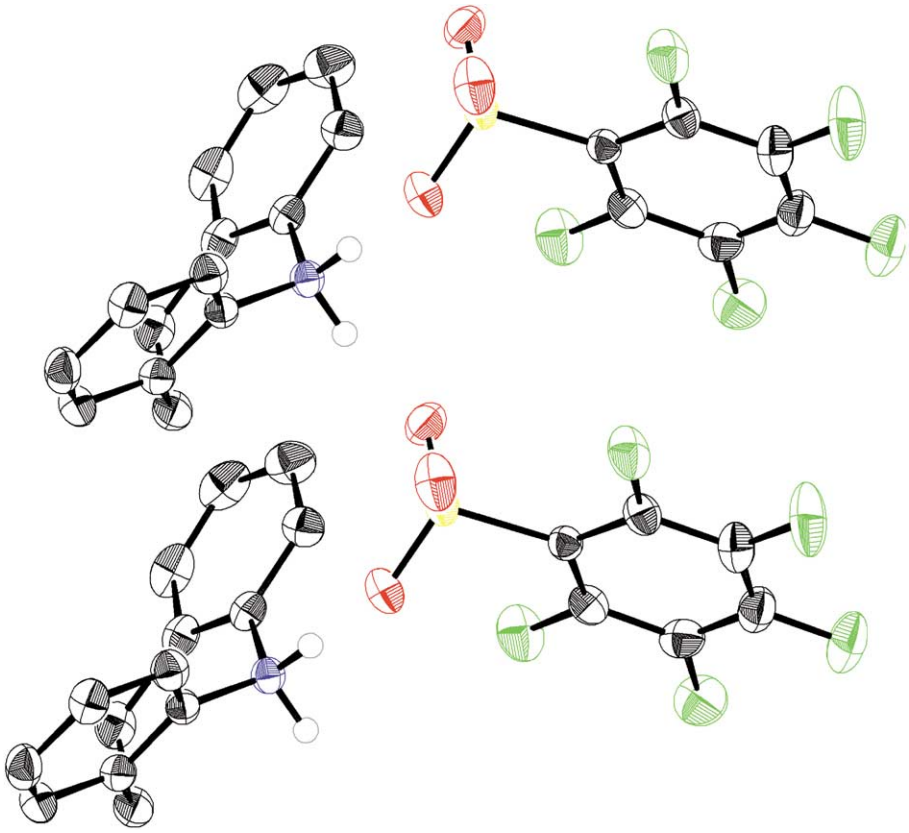


Figure 3. ORTEP plot of $[(2\text{-}CH_2C_6H_4)_2NH_2]^+[O_3SC_6F_5]^-$.

$(CD_3CO_2D)=11.1$, $H_0=-3.98$] is a weaker acid than *p*-toluenesulfonic acid [TsOH, pK_a $(CD_3CO_2D)=8.5$].[9,10] The relationship between the Brønsted acidity and catalytic activity of alkanesulfonic acids was examined (Fig. 6). In the presence of 1 mol% of alkanesulfonic acids, ester condensation of 4-phenylbutyric acid with an equimolar amount of cyclododecanol was conducted at 80 °C without removing water. TfOH (black line) showed catalytic activity similar to those of other arenesulfonic acids despite its stronger acidity. The experimental results in Figure 6 show that the catalytic activities of sulfonic acids are almost independent of their sulfonate anions (specific acid catalysis[11]).

2.4. Ester condensation reaction catalyzed by dimesitylammonium sulfonates

Next, the ester condensation reaction was conducted in the presence of various dimesitylammonium sulfonates ($[Mes_2NH_2]^+[O_3SR]^-$) under the same conditions to investigate the effects of sulfonate anions of $[Mes_2NH_2]^+[O_3SR]^-$ (Fig. 7). Interestingly, dimesitylammonium tosylate ($[Mes_2NH_2]^+[OTs]^-$) (blue line), pentafluorobenzenesulfonate ($[Mes_2NH_2]^+[O_3SC_6F_5]^-$) (red line) and mesitylenesulfonate ($[Mes_2NH_2]^+[O_3SMes]^-$) (orange line) showed slightly less catalytic activity than the corresponding sulfonic acids, while dimesitylammonium triflate ($[Mes_2NH_2]^+[OTf]^-$) (black line) and 2,4,6-trichlorobenzenesulfonate ($[Mes_2NH_2]^+[O_3S\text{–}2,4,6\text{-}Cl_3C_6H_2]^-$) (green line) showed catalytic activities about 20% lower than the corresponding acids. The catalytic activity of $[Mes_2NH_2]^+[O_3SR]^-$ depended slightly on the structure of $[O_3SR]^-$ (general acid catalysis[11]). Therefore, the hydrophobicities and steric effects of *S*-aryl groups of the catalysts as well as their acidities might influence the activation of the ester condensation reaction.

2.5. Ester condensation reaction catalyzed by bulky diarylammonium tosylates and pentafluorobenzenesulfonates

We then examined the catalytic activities of various bulky diarylammonium tosylates ($[Ar_2NH_2]^+[OTs]^-$) and pentafluorobenzenesulfonates ($[Ar_2NH_2]^+[O_3SC_6F_5]^-$) (Fig. 8). Bulky diarylammonium tosylates showed catalytic activities similar to TsOH (graph **I**). The catalytic activities of diarylammonium tosylates were almost independent of the structures of diarylamines, whereas the catalytic activities of diarylammonium pentafluorobenzenesulfonates depended on the structures of arylamines (graph **J**). Compared with $C_6F_5SO_3H$ (red line), less bulky diphenylammonium pentafluorobenzenesulfonate ($[Ph_2NH_2]^+[O_3SC_6F_5]^-$) had lower catalytic activity due to its weaker acidity (blue line). More bulky catalysts dimesitylammonium pentafluorobenzenesulfonate ($[Mes_2NH_2]^+[O_3SC_6F_5]^-$) (orange line), (2,6-diisopropylphenyl)mesitylammonium pentafluorobenzenesulfonate $\{[(2,6\text{-}i\text{-}Pr_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-\}$ (black line), bis(2-biphenyl)ammonium pentafluorobenzenesulfonate $\{[(2\text{-}PhC_6H_4)_2NH_2]^+[O_3SC_6F_5]^-\}$ (purple line) and (2,6-diphenylphenyl)mesitylammonium pentafluorobenzenesulfonate $\{[(2,6\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-\}$ (green line) showed higher catalytic activities than

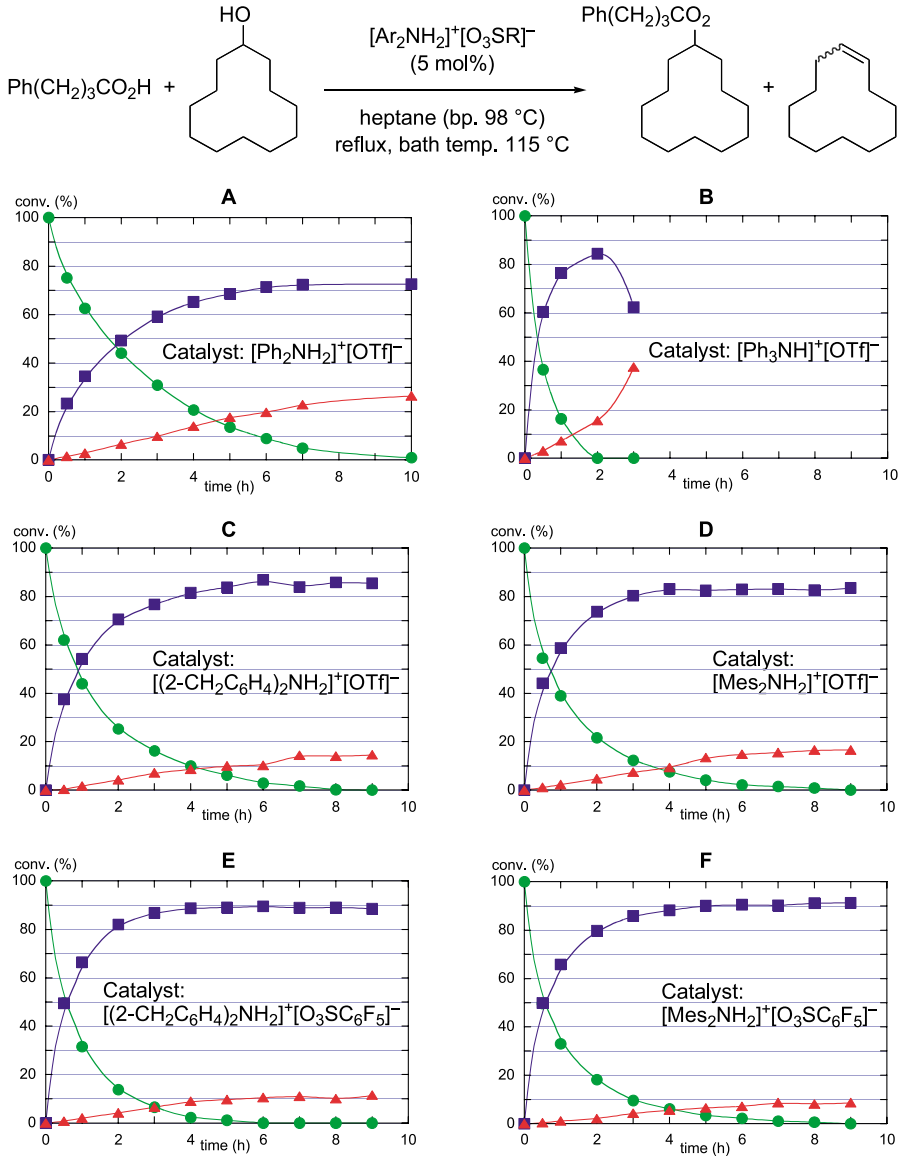


Figure 4. Ester condensation of 4-phenylbutyric acid with cyclododecanol. The ratio of cyclododecanol (green line), cyclododecyl 4-phenylbutyrate (blue line) and cyclododecene (red line) in the reaction mixture over time was evaluated by ^{1}H NMR analysis.

$[Ph_2NH_2]^+[O_3SC_6F_5]^-$. Interestingly, the most bulky catalyst $[(2,6\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ exhibited higher catalytic activity than $C_6F_5SO_3H$, and cyclododecyl 4-phenylbutyrate was obtained after 5 h in 95% yield (green line). $[(2,6\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ had the highest catalytic activity. These experimental results suggested that the hydrophobic effect due to bulky *N*-aryl groups and the *S*-pentafluorophenyl group of $[(2,6\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$, which surrounded NH_2^+ of the catalyst, synergistically accelerated the dehydrative condensation reaction, and that the hydrophobic effect was more important than the strong acidity of NH_2^+ in promoting the dehydrative reaction.[12]

To explore the generality and scope of the selective esterification catalyzed by $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (1 mol%) at 80 °C, the condensation was examined with an equimolar mixture of various structurally diverse carboxylic acids and alcohols (Table 1). 2-Unsubstituted carboxylic acids, 2-monosubstituted carboxylic acids, and sterically demanding 2,2-disubstituted carboxylic acids were smoothly condensed to produce the corresponding esters (entries 1–6). α,β-Unsaturated carboxylic acids and benzoic acids were also transformed into the corresponding esters (entries 7–11 and 22). 2-Alkoxycarboxylic acids and 2-unsubstituted carboxylic acids were very reactive substrates probably due to favorable chelation between the substrates and $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (entries 12, 13, 24, and 29–31). 4-Oxopentanoic acid was selectively esterified without a protecting ketone moiety (entries 14 and 23). $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ could be used for acid-sensitive alcohols such as benzyl alcohol, allylic alcohols, propargylic alcohols, and secondary alcohols (entries 17–28). In particular, esterification with sterically demanding alcohol 6-undecanol gave the desired esters in good yield with less than 5% of alkenes (entries 20–24). Although Lewis acidic metal salts such as Hf(IV) and Zr(IV) were not adapted to 1,2-diols due to tight chelation with metal

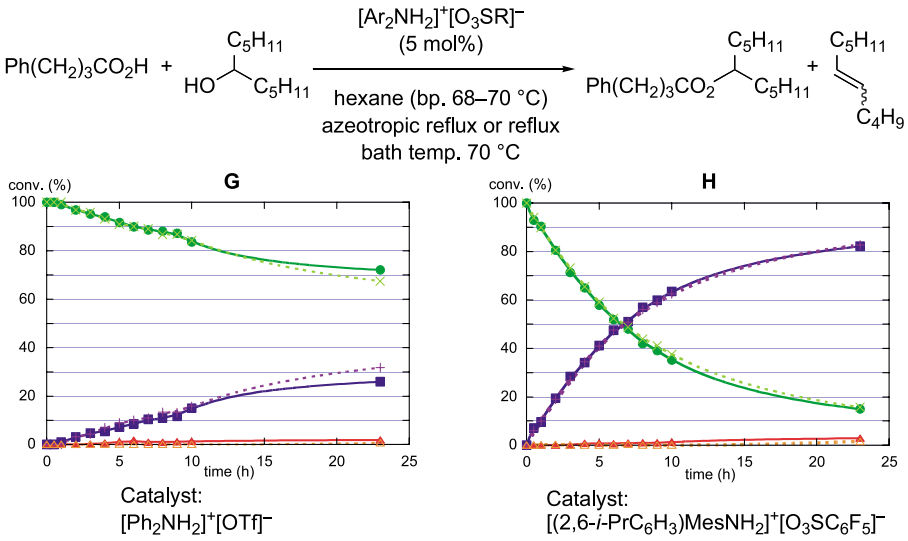


Figure 5. Ester condensation of 4-phenylbutyric acid with 6-undecanol. The catalytic activities of $[Ph_2NH_2]^+[OTf]^-$ and $[(2,6\text{-}i\text{-}Pr_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ under reflux conditions without removing water (solid lines) and azeotropic reflux conditions (broken lines) were compared. The ratio of 6-undecanol (green solid line), 6-undecyl 4-phenylbutyrate (blue solid line), and 5-undecene (red solid line) in the reaction mixture over time was evaluated by ^{1}H NMR analysis for the reaction conducted under reflux conditions without removing water (bath temperature 70 °C). The ratio of 6-undecanol (green broken line), 6-undecyl 4-phenylbutyrate (blue broken line), and 5-undecene (red broken line) in the reaction mixture over time was evaluated by ^{1}H NMR analysis for the reaction conducted under azeotropic reflux conditions.

ions,[5c] these diols were also esterified in high yield by $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (entries 26–28). Less-reactive aryl alcohols and 1-adamantanol were also esterified in high yields (entries 29–31).

Ester condensation reactions with more-reactive primary alcohols proceeded even at room temperature (22 °C) without solvents (Table 2). Most carboxylic acids were esterified with 1.1 equiv of methanol in good yield in the presence of 1 mol% of $[Mes_2NH_2]^+[O_3SC_6F_5]^-$. 1-Octanol was also reactive. As far as we know, this is the first example of an ultimate green esterification process.

One major problem associated with the use of soluble catalysts lies in recovery of the catalyst from the reaction medium. A simple solution is to immobilize the catalyst on a polymeric matrix.[13] Figure 9 describes the preparation of immobilized catalyst **2**. 4-(*N*-mesitylamino)polystyrene resin (**1**) was prepared by palladium-catalyzed cross-coupling of 4-bromopolystyrene resin cross-linked with 2% divinyl benzene (2.71 mmol Br/g, 200–400 mesh) with 2,4,6-trimethylaniline in 75% yield.[14] Compound **2** was then readily prepared in 97% yield by treating **1** with $C_6F_5SO_3H$. In contrast, an immobilized catalyst could not be prepared from **1** and TfOH since the resin decomposed with superacidic TfOH. Compound **2** was recovered by filtration and reused more than ten times as the catalyst for the direct ester condensation reaction of 4-phenylbutyric acid with octanol, and no loss of activity was observed for the recovered catalyst.

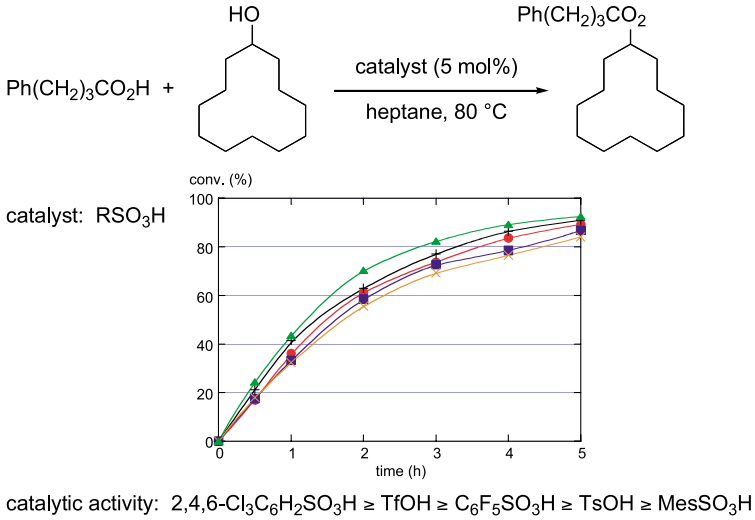
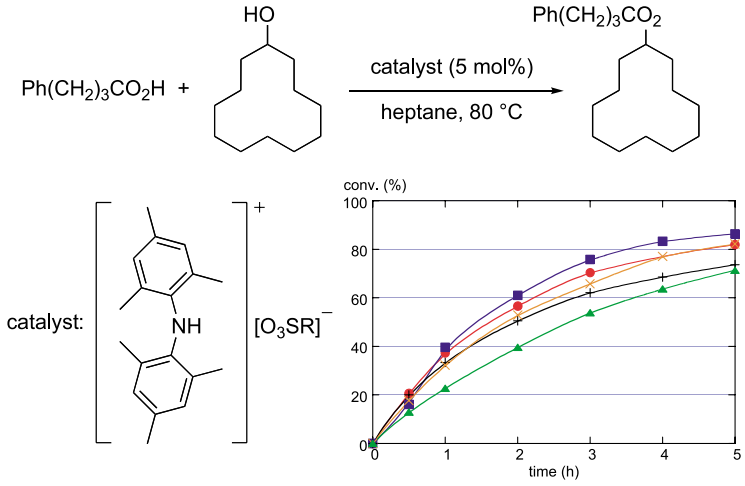


Figure 6. Ester condensation of 4-phenylbutyric acid with cyclododecanol catalyzed by various alkanesulfonic acids. The yield of cyclododecyl 4-phenylbutyrate over time was evaluated by ^{1}H NMR analysis. Green line, 2,4,6-$Cl_3C_6H_2SO_3H$; black line, TfOH; red line, $C_6F_5SO_3H$; blue line, TsOH; orange line, $MesSO_3H$.



catalytic activity: $^{-}OTs > {}^{-}O_3SC_6F_5 \approx {}^{-}O_3SMes > {}^{-}OTf > {}^{-}O_3S\text{-}2,4,6\text{-}Cl_3C_6H_2$

Figure 7. Ester condensation of 4-phenylbutyric acid with cyclododecanol catalyzed by various dimesitylammonium sulfonates. The yield of cyclododecyl 4-phenylbutyrate over time was evaluated by ^{1}H NMR analysis. Blue line, $[OTs]^-$; red line, $[O_3SC_6F_5]^-$; orange line, $[O_3SMes]^-$; black line, $[OTf]^-$; green line, $[O_3S\text{–}2,4,6\text{-}Cl_3C_6H_2]^-$.

3. Conclusion

In conclusion, the hydrophobic effect of bulky diarylammonium sulfonates activated the esterification reaction and steric hindrance suppressed the dehydrative elimination of secondary alcohols to produce alkenes. Thus, we achieved direct, catalytic ester condensation of carboxylic acids with an equimolar amount of primary alcohols without solvents at room temperature. In addition, the immobilization of bulky diarylammonium pentafluorobenzenesulfonate on a polymer support provided an efficient atom-economical esterification catalyst that could be easily recovered and reused.

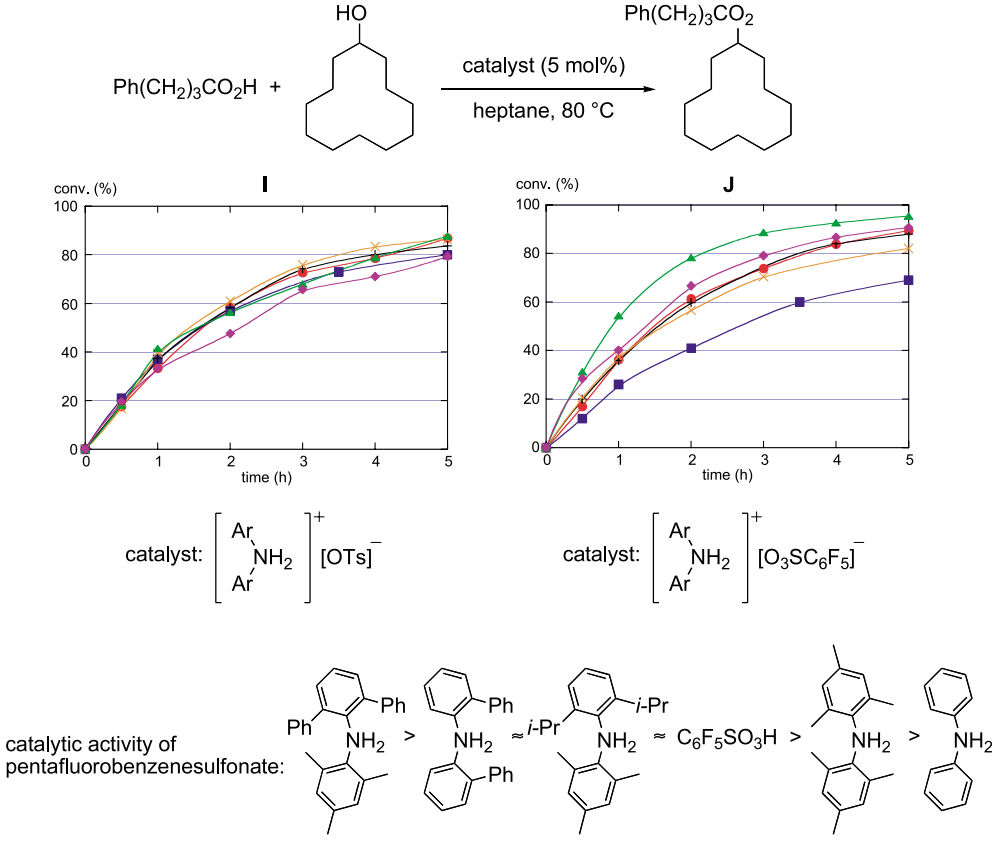
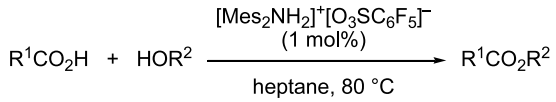
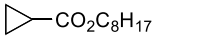
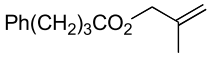
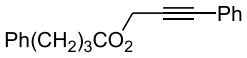
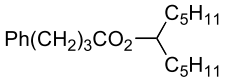
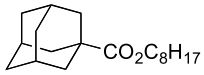
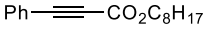
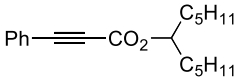
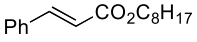
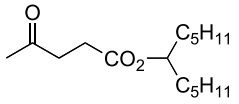
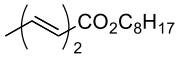
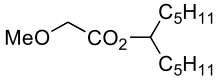
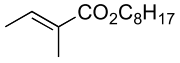
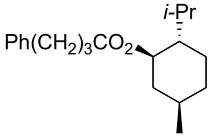
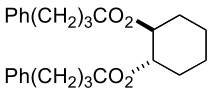
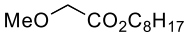
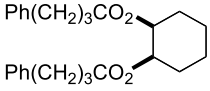
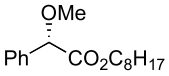
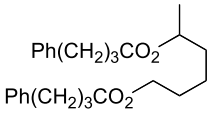
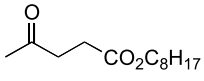
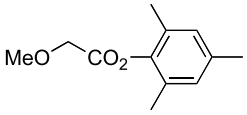
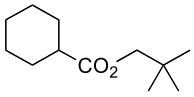
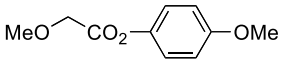
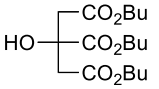
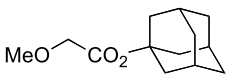


Figure 8. Ester condensation of 4-phenylbutyric acid with cyclododecanol catalyzed by various diarylammonium tosylates (graph **I**) and diarylammonium pentafluorobenzenesulfonates (graph **J**). The yield of cyclododecyl 4-phenylbutyrate over time was evaluated by ^{1}H NMR analysis. Green line, $[(2,6\text{-}PhC_6H_3)MesNH_2]^+$; purple line, $[(2\text{-}PhC_6H_4)_2NH_2]^+$; red line, $C_6F_5SO_3H$; black line, $[(2,6\text{-}i\text{-}PrC_6H_3)MesNH_2]^+$; orange line, $[Mes_2NH_2]^+$; blue line, $[Ph_2NH_2]^+$.

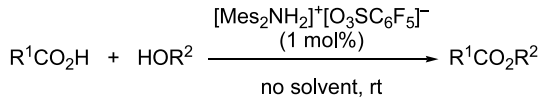
Table 1. Esterification reaction between an equimolar mixture of carboxylic acids and alcohols catalyzed by $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ [a]

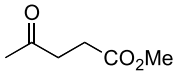
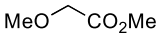
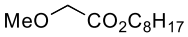
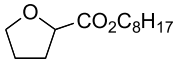
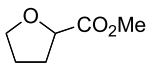
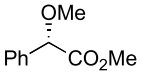


Entry	$R^1CO_2R^2$	Time (h)	Yield (%)[b]	Entry	$R^1CO_2R^2$	Time (h)	Yield (%)[b]
1	$Ph(CH_2)_3CO_2C_8H_{17}$	1	99	17	$Ph(CH_2)_3CO_2Bn$	2	95
2		8	94	18		3	>99
3	$c\text{-}C_6H_{11}CO_2C_8H_{17}$	5	98	19		24	88
4	$Et_2CHCO_2C_8H_{17}$	24	94				
5	$t\text{-}BuCO_2C_8H_{17}$	6	93	20[c]		23	83 (3)
6		7	91	21[d]		24	85 (0)
7		5	96	22[d]		30	88 (0)
8		24	96	23		24	82 (5)
9		24	91	24		4	95 (0)
10		24	90	25		10	93 (0)
11	$PhCO_2C_8H_{17}$	24	91	26[d]		48	90 (0)
12		1	99	27[e]		48	90 (0)
13		3	>99	28		24	97 (0)
14		3	98	29[f]		24	73
15		2	71	30[f]		24	99
16		24	97	31		72	92

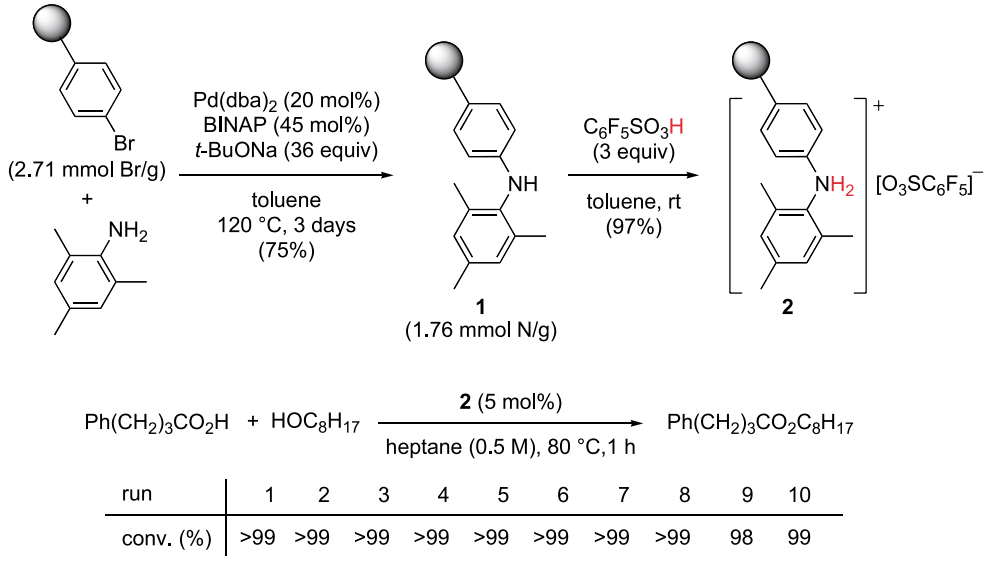
[a] Unless otherwise noted, a solution of carboxylic acids (2 mmol) and alcohols (2 mmol) in heptane (4 mL) was heated at 80 °C in the presence of $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (1 mol%).
[b] Yield of alkenes is shown in parentheses.
[c] $[(2,6\text{-}i\text{-}Pr_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ (5 mol%) was used in hexane at 70 °C (See graph **H** in Fig. 5).
[d] $[(2,6\text{-}i\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ (1 mol%) was used.
[e] $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (5 mol%) was used.
[f] $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (10 mol%) was used at 115 °C.

Table 2. Ester condensation reaction at room temperature without solvents[a]



Entry	$R^1CO_2R^2$	Time (h)	Yield (%)	Entry	$R^1CO_2R^2$	Time (h)	Yield (%)
1	$Ph(CH_2)_3CO_2C_2Me$	24	95	8		48	90
2		8	72	9[b]		48	69
3[c]		7	81				
4[b]		24	68	10		24	74
				11[b]		48	71
5		11	91				
6[c]		24	92	12		42	69
7[b]		24	82				

[a] Unless otherwise noted, a mixture of carboxylic acids (2 mmol) and alcohols (2.2 mmol) was stirred at room temperature in the presence of $[Mes_2NH_2]^+[O_3SC_6F_5]^-$ (1 mol%).
[b] $[(2,6\text{-}Ph_2C_6H_3)MesNH_2]^+[O_3SC_6F_5]^-$ (1 mol%) was used.
[c] $[Mes_2NH_2]^+[OTs]^-$ (1 mol%) was used.



run	1	2	3	4	5	6	7	8	9	10
conv. (%)	>99	>99	>99	>99	>99	>99	>99	>99	98	99

Figure 9. Preparation of polymer-supported catalyst **2** and its recovery and reuse for the ester condensation reaction.

4. Experimental

4.1. General

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^1H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or Varian INOVA-500 (500 MHz). Tetramethylsilane was used as an internal standard (δ 0.00 ppm). ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) or Varian INOVA-500 (125 MHz). Chemical shifts were recorded in ppm from the solvent resonance ($CDCl_3$ at 77.0 ppm). High-resolution mass spectral analysis (HRMS) was performed at the Chemical Instrument Room, Research Center for Material Science, Nagoya University. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. 4-Bromopolystyrene resin (2% DVB, 2.71 mmol/g) was purchased from TCI, Co., Ltd, Japan. Dimesitylamine,[15] *N*-(2,6-diisopropylphenyl)-*N*-(2,4,6-mesityl)amine,[6] bis(2-biphenyl)amine,[16] dimesitylammonium pentafluorobenzenesulfonate,[6] and *N*-(2,6-diisopropylphenyl)-*N*-(2,4,6-mesityl)ammonium pentafluorobenzenesulfonate[6] are known compounds. Other starting materials such as 2,6-diphenylaniline, 2,4,6-trimethylaniline, and iminodibenzyl are commercially available. The following obtained esters are known compounds: octyl 4-phenylbutyrate[17] (Table 1), octyl cyclohexanecarboxylate[18] (Table 1), octyl pivaloate[19] (Table 1), octyl adamantanecarboxylate[20] (Table 1), octyl cinnamoate[21] (Table 1), octyl benzoate[22] (Table 1), octyl methoxyacetate[23] (Table 1), octyl levulinate[24] (Table 1), neopentyl cyclohexanecarboxylate[12] (Table 1), benzyl 4-phenylbutyrate[25] (Table 1),

phenylpropargyl 4-phenylbutyrate[5c] (Table 1), *l*-mentyl 4-phenylbutyrate[26] (Table 1), 2,4,6-trimethylphenyl methoxyacetate[27] (Table 1), 1-adamantyl methoxyacetate[23] (Table 1), methyl 4-phenylbutyrate[28] (Table 2), methyl tetrahydrofuran-2-carboxylate[29] (Table 2), octyl tetrahydrofuran-2-carboxylate[22] (Table 2), and methyl 2-methoxyphenylacetate[30] (Table 2). The following obtained esters are commercially available: tributyl citrate (Table 1), methyl methoxyacetate (Table 2), and methyl levulinate (Table 2). The following obtained esters are known compounds, but spectroscopic and analytical data have not been reported: cyclododecyl 4-phenylbutyrate (Fig. 4), 6-undecyl 4-phenylbutyrate (Fig. 5), octyl cyclopropanecarboxylate (Table 1), octyl 2-ethylbutyrate (Table 1), octyl phenylpropiolate (Table 1), octyl (*E*,*E*)-2,4-hexadienoate (Table 1), octyl tiglate (Table 1), octyl 2-methoxyphenylacetate (Table 1), methallyl 4-phenylbutyrate (Table 1), 6-undecyl phenylpropiolate (Table 1), 6-undecyl levulinate (Table 1), 6-undecyl methoxyacetate (Table 1), *trans*-1,2-di(4-phenylbutyroxy)cyclohexane (Table 1), *cis*-1,2-di(4-phenylbutyroxy)cyclohexane (Table 1), and *p*-methoxyphenyl methoxyacetate (Table 1).

4.1.1. *N*-(2,6-diphenylphenyl)-*N*-(2,4,6-mesityl)amine. The reported method[6] for dimesitylamine was followed, but using 2,6-diphenylaniline instead of 2,4,6-trimethylaniline. IR (KBr) 3407, 1599, 1586, 1486, 1455, 1437, 1415, 1374, 1314, 1285, 1241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, $J=7.5$ Hz, 4H), 7.20 (t, $J=7.5$ Hz, 4H), 7.16–7.08 (m, 2H), 7.13 (d, $J=7.5$ Hz, 2H), 6.94 (t, $J=7.5$ Hz, 1H), 6.37 (s, 2H), 5.25 (s, 1H), 2.00 (s, 3H), 1.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.3, 137.2, 132.7, 132.2, 130.6, 130.4, 128.8, 128.6, 127.9, 126.5, 118.9, 20.4, 19.0; HRMS (FAB) calcd for $C_{27}H_{25}N$ [M^+] 363.1987, found 363.1998.

4.1.2. Dimesitylammonium tosylate. The reported method[6] for dimesitylammonium pentafluorobenzenesulfonate was followed. IR (KBr) 1608, 1484, 1401, 1227, 1148, 1124, 1035, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (br s, 2H), 7.36 (d, $J=7.5$ Hz, 2H), 7.03 (d, $J=7.5$ Hz, 2H), 6.80 (s, 4H), 2.33 (s, 3H), 2.26 (s, 6H), 2.12 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 139.0, 134.9, 131.2, 130.4, 128.8, 128.7, 126.0, 21.4, 20.6, 18.9.

4.1.3. Iminodibenzyl pentafluorobenzenesulfonate. The reported method[6] for dimesitylammonium pentafluorobenzenesulfonate was followed. IR (KBr) 1648, 1587, 1555, 1525, 1489, 1336, 1247, 1227, 1115 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.62 (br s, 2H), 7.29 (d, $J=8.0$ Hz, 2H), 7.10–6.95 (m, 6H), 3.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9 (d, $J=253$ Hz), 142.0 (d, $J=254$ Hz), 138.7, 137.3 (d, $J=253$ Hz), 131.4, 130.9, 127.2, 125.0, 120.6, 119.0, 31.7.

4.1.4. *N*-(2,6-diisopropylphenyl)-*N*-(2,4,6-mesityl)ammonium tosylate. The reported method[6] for dimesitylammonium pentafluorobenzenesulfonate was followed. IR (KBr) 1484, 1465, 1439, 1345, 1199, 1127, 1045, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (br s, 2H), 7.48 (d, $J=8.0$ Hz, 2H), 7.23 (t, $J=8.0$ Hz, 1H), 7.15 (d, $J=8.0$ Hz, 2H), 7.07 (d, $J=8.0$ Hz, 2H), 6.77 (s, 2H), 3.13 (septet, $J=7.0$ Hz, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 2.05 (s, 6H), 1.08 (d, $J=7.0$ Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 141.5, 138.8, 137.4, 135.9, 133.2, 130.6, 128.9, 128.7, 126.6, 126.1, 124.1, 28.2, 23.5, 21.4, 20.5, 19.2.

4.1.5. *N*-(2,6-diphenylphenyl)-*N*-(2,4,6-mesityl)ammonium pentafluorobenzenesulfonate. The reported method[6] for dimesitylammonium pentafluorobenzenesulfonate was followed. IR (KBr) 1648, 1525, 1488, 1306, 1246, 1227, 1115, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 2H), 7.54 (t, $J=7.5$ Hz, 1H), 7.44–7.22 (m, 12H), 6.33 (s, 2H), 2.04 (s, 3H), 1.76 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9 (d, $J=256$ Hz), 142.4 (d, $J=246$ Hz), 137.4 (d, $J=258$ Hz), 136.0, 132.5, 132.1, 131.8, 129.9, 129.2, 128.8, 117.8, 20.0, 18.6.

4.1.6. *N*-(2,6-diphenylphenyl)-*N*-(2,4,6-mesityl)ammonium tosylate. The reported method[6] for dimesitylammonium pentafluorobenzenesulfonate was followed. IR (KBr) 1599, 1584, 1486, 1455, 1436, 1427, 1239, 1180, 1120, 1072, 1028, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, $J=2.0$, 8.0 Hz, 2H), 7.38–7.06 (m, 15H), 6.37 (s, 2H), 2.40 (s, 3H), 2.00 (s, 3H), 1.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 140.6, 140.2, 137.0, 132.7, 132.1, 130.6, 130.5, 130.4, 129.1, 128.7, 128.6, 127.9, 126.5, 126.0, 119.0, 21.3, 20.3, 19.0.

4.1.7. Cyclododecyl 4-phenylbutyrate (Fig. 4). IR (neat) 1730, 1496, 1470, 1446, 1249, 1201, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H), 5.03 (m, 1H), 2.64 (t, $J=7.5$ Hz, 2H), 2.29 (t, $J=7.5$ Hz, 2H), 1.94 (quint, $J=7.5$ Hz, 2H), 1.69 (m, 2H), 1.53–1.20 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 141.5, 128.4, 128.3, 125.9, 72.0, 35.1, 34.0, 29.1, 26.7, 24.0, 23.8, 23.3, 23.2, 20.9; HRMS (FAB) calcd for $C_{22}H_{35}O_2$ [$(M+H)^+$] 331.2637, found 331.2647.

4.1.8. 6-Undecyl 4-phenylbutyrate (Fig. 5). IR (neat) 1732, 1496, 1456, 1378, 1200, 1131 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.22–7.10 (m, 3H), 4.89 (quint, $J=6.5$ Hz, 1H), 2.65 (t, $J=7.5$ Hz, 2H), 2.31 (t, $J=7.5$ Hz, 2H), 1.95 (quint, $J=7.5$ Hz, 2H), 1.56–1.42 (m, 4H), 1.35–1.10 (m, 12H), 0.87 (t, $J=7.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 141.5, 128.5, 128.3, 125.9, 74.3, 35.2, 34.1, 34.0, 31.7, 26.7, 25.0, 22.5, 14.0; HRMS (FAB) calcd for $C_{21}H_{35}O_2$ [$(M+H)^+$] 319.2637, found 319.2635.

4.1.9. Octyl cyclopropanecarboxylate (Table 1). IR (neat) 1731, 1457, 1404, 1372, 1267, 1200, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (t, $J=7.0$ Hz, 2H), 1.66–1.56 (m, 3H), 1.39–1.20 (m, 10H), 0.98 (ddd, $J=4.5$, 4.5, 7.5 Hz, 2H), 0.88 (t, $J=7.0$ Hz, 3H), 0.84 (ddd, $J=4.0$, 7.0, 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 64.6, 31.7, 29.2, 29.1, 28.6, 25.9, 22.6, 14.0, 12.8, 8.2; HRMS (FAB) calcd for $C_{12}H_{23}O_2$ [$(M+H)^+$] 199.1693, found 199.1693.

4.1.10. Octyl 2-ethylbutyrate (Table 1). IR (neat) 1735, 1460, 1383, 1269, 1229, 1177, 1148 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.08 (t, $J=7.0$ Hz, 2H), 2.19 (tt, $J=5.5$, 8.5 Hz, 1H), 1.68–1.56 (m, 4H), 1.56–1.43 (m, 2H), 1.39–1.20 (m, 10H), 0.92–0.80 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 64.1, 49.0, 31.8, 29.2, 29.2,

28.7, 25.9, 25.1, 22.6, 14.1, 11.8; HRMS (FAB) calcd for $C_{14}H_{29}O_2$ [(M+H)$^+$] 229.2168, found 229.2155.

4.1.11. Octyl phenylpropiolate (Table 1). IR (neat) 2224, 1711, 1491, 1466, 1444, 1384, 1285, 1189, 1173 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J=1.5, 7.0 Hz, 2H), 7.45 (tt, J=1.5, 7.5 Hz, 1H), 7.37 (dd, J=7.0, 7.5 Hz, 2H), 4.23 (*t*, J=7.0 Hz, 2H), 1.71 (quint, J=7.0 Hz, 2H), 1.46–1.12 (m, 10H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 132.9, 130.5, 128.5, 119.7, 86.0, 80.7, 66.2, 31.7, 29.2, 29.1, 28.4, 25.8, 22.6, 14.1; HRMS (FAB) calcd for $C_{17}H_{23}O_2$ [(M+H)$^+$] 259.1698, found 259.1689.

4.1.12. Octyl (*E*,*E*)-2,4-hexadienoate (Table 1). IR (neat) 1722, 1647, 1619, 1458, 1379, 1244, 1175, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J=10.5, 15.5 Hz, 1H), 6.19 (dd, J=10.5, 15.0 Hz, 1H), 6.13 (qd, J=6.0, 15.0 Hz, 1H), 5.77 (d, J=15.5 Hz, 1H), 4.13 (t, J=7.0 Hz, 2H), 1.85 (d, J=6.0 Hz, 3H), 1.65 (quint, J=7.0 Hz, 2H), 1.40–1.20 (m, 10H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 144.8, 139.1, 129.8, 119.1, 64.4, 31.8, 29.2, 29.2, 28.7, 25.9, 22.6, 18.6, 14.1; HRMS (FAB) calcd for $C_{14}H_{25}O_2$ [(M+H)$^+$] 225.1855, found 225.1855.

4.1.13. Octyl tiglate (Table 1). IR (neat) 1713, 1654, 1467, 1381, 1341, 1267, 1139, 1079 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (qq, J=1.5, 7.0 Hz, 1H), 4.12 (t, J=7.0 Hz, 2H), 1.83 (d, J=1.5 Hz, 3H), 1.79 (d, J=7.0 Hz, 3H), 1.66 (quint, J=7.0 Hz, 2H), 1.41–1.20 (m, 10H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 136.7, 128.8, 64.6, 31.8, 29.2, 29.2, 28.7, 26.0, 22.6, 14.3, 14.1, 12.0; HRMS (FAB) calcd for $C_{13}H_{25}O_2$ [(M+H)$^+$] 213.1855, found 213.1852.

4.1.14. Octyl 2-methoxyphenylacetate (Table 1). IR (neat) 1751, 1456, 1257, 1199, 1174, 1116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.38–7.29 (m, 3H), 4.76 (s, 1H), 4.13 (td, J=6.5, 11.0 Hz, 1H), 4.10 (td, J=6.5, 11.0 Hz, 1H), 3.41 (s, 3H), 1.61–1.51 (m, 2H), 1.33–1.12 (m, 10H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 136.3, 128.6, 128.5, 127.1, 82.6, 65.2, 57.2, 31.6, 29.0, 29.0, 28.4, 25.6, 22.6, 14.0; HRMS (FAB) calcd for $C_{17}H_{27}O_3$ [(M+H)$^+$] 279.1960, found 279.1967.

4.1.15. Methallyl 4-phenylbutyrate (Table 1). IR (neat) 1736, 1496, 1455, 1375, 1144 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H), 4.97 (s, 1H), 4.92 (s, 1H), 4.50 (s, 2H), 2.66 (t, J=7.5 Hz, 2H), 2.37 (t, J=7.5 Hz, 2H), 1.98 (quint, J=7.5 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 141.3, 140.0, 128.4, 128.3, 125.9, 112.8, 67.6, 35.1, 33.6, 26.5, 19.5; HRMS (FAB) calcd for $C_{14}H_{19}O_2$ [(M+H)$^+$] 219.1385, found 219.1383.

4.1.16. 6-Undecyl phenylpropiolate (Table 1). IR (neat) 2213, 1705, 1490, 1466, 1444, 1283, 1191, 1173, 1121 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J=1.5, 7.0 Hz, 2H), 7.44 (tt, J=1.5, 7.5 Hz, 1H), 7.37 (dd, J=7.0, 7.5 Hz, 2H), 5.04 (tt, J=5.0, 7.5 Hz, 1H), 1.69–1.51 (m, 4H), 1.44–1.16 (m, 12H), 0.89 (t, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 132.9, 130.4, 128.5, 119.8, 85.8, 81.0, 76.9, 34.0, 31.7, 25.0, 22.5, 14.0; HRMS (FAB) calcd for $C_{20}H_{29}O_2$ [(M+H)$^+$] 301.2168, found 301.2168.

4.1.17. 6-Undecyl levulinate (Table 1). IR (neat) 1725, 1458, 1418, 1362, 1208, 1184, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (quint, J=6.5 Hz, 1H), 2.74 (t, J=6.5 Hz, 2H), 2.56 (t, J=6.5 Hz, 2H), 2.19 (s, 3H), 1.57–1.43 (m, 4H), 1.36–1.16 (m, 12H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 172.5, 74.8, 38.0, 34.0, 31.7, 29.9, 28.3, 24.9, 22.5, 14.0; HRMS (FAB) calcd for $C_{16}H_{31}O_3$ [(M+H)$^+$] 271.2273, found 271.2267.

4.1.18. 6-Undecyl methoxyacetate (Table 1). IR (neat) 1753, 1732, 1458, 1379, 1283, 1195, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (quint, J=6.3 Hz, 1H), 4.01 (s, 2H), 3.45 (s, 3H), 1.62–1.46 (m, 4H), 1.36–1.20 (m, 12H), 0.878 (t, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 75.0, 69.8, 59.1, 34.0, 31.5, 24.9, 22.4, 13.9; HRMS (FAB) calcd for $C_{14}H_{29}O_3$ [(M+H)$^+$] 245.2117, found 245.2109.

4.1.19. *trans*-1,2-Di(4-phenylbutyroxy)cyclohexane (Table 1). IR (neat) 1734, 1496, 1454, 1370, 1244, 1140, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.10 (m, 10H), 4.83 (m, 2H), 2.58 (t, J=7.5 Hz, 2H), 2.57 (t, J=7.5 Hz, 2H), 2.26 (t, J=7.5 Hz, 2H), 2.25 (t, J=7.5 Hz, 2H), 2.06–1.98 (m, 2H), 1.88 (quint, J=7.5 Hz, 4H), 1.74–1.66 (m, 2H), 1.43–1.28 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 141.3, 128.4, 128.3, 125.9, 73.5, 35.0, 33.8, 30.1, 26.6, 23.3; HRMS (FAB) calcd for $C_{26}H_{33}O_4$ [(M+H)$^+$] 409.2379, found 409.2370.

4.1.20. *cis*-1,2-Di(4-phenylbutyroxy)cyclohexane (Table 1). IR (neat) 1736, 1496, 1453, 1396, 1241, 1200, 1144, 1123 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.21 (m, 4H), 7.21–7.10 (m, 6H), 5.06 (d, J=7.5 Hz, 2H), 2.63 (t, J=7.5 Hz, 4H), 2.31 (t, J=7.5 Hz, 4H), 1.93 (quint, J=7.5 Hz, 4H), 1.88–1.76 (m, 2H), 1.69–1.55 (m, 4H), 1.48–1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 141.4, 128.4, 128.3, 125.9, 70.8, 35.0, 33.8, 27.7, 26.6, 21.7; HRMS (FAB) calcd for $C_{26}H_{33}O_4$ [(M+H)$^+$] 409.2379, found 409.2390.

4.1.21. 1,5-Di(4-phenylbutyroxy)hexane (Table 1). IR (neat) 1732, 1604, 1496, 1454, 1376, 1247, 1175, 1143 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 4H), 7.20–7.05 (m, 6H), 4.91 (qt, J=6.0, 6.5 Hz, 1H), 4.05 (t, J=6.5 Hz, 2H), 2.63 (t, J=7.5 Hz, 4H), 2.30 (t, J=7.0 Hz, 2H), 2.28 (t, J=7.0 Hz, 2H), 1.94 (quint, J=7.0 Hz, 4H), 1.68–1.55 (m, 3H), 1.55–1.45 (m, 1H), 1.45–1.28 (m, 2H), 1.20 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 173.0, 141.4, 141.3, 128.4, 128.4, 128.3, 128.3, 125.9, 125.9, 70.4, 64.0, 35.4, 35.1, 35.1, 33.9, 33.5, 28.4, 26.6, 26.5, 21.8, 19.9; HRMS (FAB) calcd for $C_{26}H_{35}O_4$ [(M+H)$^+$] 411.2530, found 411.2521.

4.1.22. *p*-Methoxyphenyl methoxyacetate (Table 1). IR (neat) 1773, 1597, 1507, 1465, 1299, 1249, 1195, 1170, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J=9.3 Hz, 2H), 6.90 (d, J=9.3 Hz, 2H), 4.27 (s, 2H), 3.80 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 157.4, 143.6, 122.1, 114.5, 69.8, 59.5, 55.6; HRMS (FAB) calcd for $C_{10}H_{13}O_4$ [(M+H)$^+$] 197.0814, found 197.0818.

4.1.23. 4-(*N*-mesitylamino)polystyrene resin (1). 4-Bromopolystyrene resin (2% DVB, 2.71 mmol/g) (369 mg, 1 mmol), sodium *tert*-butoxide (3.46 g, 36 mmol), bis(dibenzylideneacetone)palladium (115 mg, 0.20 mmol) and BINAP (280 mg, 0.45 mmol) were placed in a round-bottomed flask, which was then evacuated and backfilled with nitrogen. To this mixture was added degassed toluene (20 mL) and 2,4,6-mesitylaniline (0.84 mL, 6.0 mmol) dropwise under N_2. This mixture was refluxed at 120 °C for 72 h. After the mixture was cooled, the resin was filtered and washed with THF. This resin was stirred for 0.5 h with thiocyanuric acid (532 mg, 3 mmol) in THF (10 mL) and then centrifuged. The organic layer was decanted from the resin and THF (10 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the THF layer was removed, and Et_3N (5 mL)/THF (5 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the organic layer was removed and 4 M HCl (5 mL)/1,4-dioxane (5 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the organic layer was removed and washed with DMF, and Et_3N (5 mL)/THF (5 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the organic layer was removed and H_2O (5 mL)/THF (5 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the liquid phase was removed and DMF (5 mL)/THF (5 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the organic layer was removed and THF (10 mL) was added. After 0.5 h of stirring, the sample was centrifuged, the organic layer was removed and Et_2O (10 mL) was added. After 0.5 h of stirring, the resin was filtered and dried in vacuo to give product **1** (1.76 mmol/g) as a brown solid. IR (KBr) 1510, 1484, 1452 cm^{-1}.

4.1.24. 1-Bound pentafluorobenzenesulfonic acid (2). To a mixture of **1** (1.76 mmol/g) in toluene (10 mL) was added pentafluorobenzenesulfonic acid (909 mg, 3.0 mmol), and the mixture was stirred at room temperature for 6 h. This resin was filtered and washed with toluene, hexane, and a little ether, and dried in vacuo to give **2** as a black solid (1.12 mmol/g). IR (KBr) 1488, 1226, 1115 cm^{-1}.

4.2. Experimental procedure for recovering and reusing 2

The reaction mixture, 4-phenylbutyric acid (181 mg, 1.1 mmol), 1-octanol (157 μL, 1.0 mmol), **2** (1.12 mmol NH_2^+/g; 45 mg, 0.05 mmol), and heptane (2 mL), was stirred for 1 h at 80 °C. Chloroform (1 mL) was added to the reaction mixture, which was further stirred at room temperature for 0.5 h to swell **2**. The mixture was centrifuged and the solution phase was decanted to separate **2**, which was washed twice with heptane. **2** was recovered in quantitative yield and reused for the next reaction.

Acknowledgements

Financial support for this project was provided by JSPS KAKENHI(15205021), the 21st Century COE Program 'Nature-Guided Materials Processing' of MEXT, the Iwatani Naoji Foundation, and the Sumitomo Foundation.

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Tetrahedron 62 (2006) 434–439
Tetrahedron

Acid-free, organocatalytic acetalization

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Received 13 July 2005; revised 31 August 2005; accepted 16 September 2005

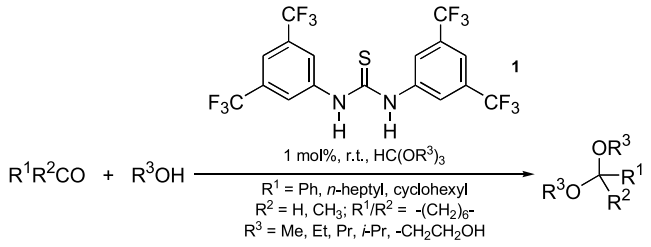
Available online 25 October 2005

Abstract—The acid-free, organocatalytic acetalization of various aldehydes and ketones with *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl] thiourea is presented. The neutral, double hydrogen bonding thiourea catalyst can be used at very low loadings of 0.01–1 mol% at room temperature to furnish the respective acetals in 65–99% yield at turnover frequencies around 600 h^{-1}. Acid-labile TBDMS-protected as well as unsaturated aldehydes can be converted efficiently into their acetals utilizing this very mild and highly practical method.

1. Introduction

Acetals are masked carbonyl derivatives that are important intermediates in synthetic as well as carbohydrate chemistry. They often are the synthetic targets themselves; acetals are one of the most frequently used protecting groups[1] for aldehydes and ketones against the attack of nucleophiles, organometallic reagents, oxidants, and basic reagents, for example, in synthetic carbohydrate,[2] steroid,[3] and pharmaceutical chemistry.[4] As the reaction of an alcohol with a carbonyl compound is thermodynamically disfavored and reversible, catalytic activation is practically always required; this is traditionally the domain of Lewis- and Brønsted acids. The only exceptions are acetalizations in the presence of $LiBF_4$,[5] ionic liquids (only aldehydes),[6] and NBS[7,8] as well as tetrabutylammonium tribromide (TBATB),[9] which, however, also generate acids (in case of NBS and TBATB) or suffer from a lack of generality. It would be highly desirable to develop a general acid-free method so that acid-labile substrates (e.g., carrying silyl groups or unsaturation) can also be acetalized. Since such a method apparently does not exist, we set out to develop an acid-free route to acetalization utilizing neutral, double hydrogen-bonding organocatalysis.[10,11]

The selective activation of carbonyl groups by Brønsted and Lewis acids is a milestone achievement of modern chemistry that relies on the principle that coordination lowers the orbital energies, thereby activating the functional group towards nucleophilic attack. However, these types of reactions often require overstoichiometric amounts of the 'catalyst' because the product still contains a basic moiety that binds the Lewis acid.[12] Hence, catalytic turnover may be hampered by product inhibition that derives from the fact that many of the highly electron-deficient Lewis acids bind basic sites too strongly. Much progress has been made by using weaker Lewis acids[13] such as the lanthanides that retain activity even in water.[14] On the other hand, the simplest catalyst, the proton, which often works best, is not tolerated in many interesting C–-X-bond forming reactions, as the required nucleophiles may be rapidly deactivated under acidic conditions. It is therefore attractive to design catalysts that are capable of 'partial protonation' by means of hydrogen-bonding for the activation of compounds with Lewis basic sites. This is generally feasible when a reaction proceeds under general acid catalysis where the catalyst stabilizes the transition state (TS) by hydrogen bonding. As nucleophilic additions to carbonyl compounds are often accompanied by a substantial increase in negative charge on the carbonyl atom in the TS, it can be preferentially stabilized. As we were able to show recently the similarities between the double-hydrogen bonding ability of a series of electron-deficient thiourea derivatives such as *N*,*N*′-bis[3,5-bis(trifluoro-methyl)phenyl]thiourea (**1**) and traditional Lewis acid catalysis,[10] we hoped that **1** would also catalyze the acetalization of a variety of aldehydes and ketones (Scheme 1).



Scheme 1.

Keywords: Acetalization; Organocatalysis; Protective groups; Turnover.
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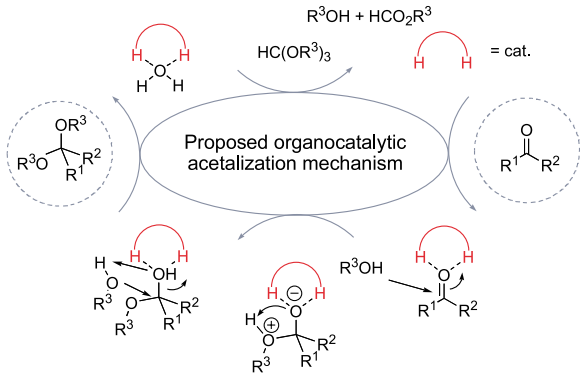
doi:10.1016/j.tet.2005.09.079

The reasoning behind this idea is that during the acetalization there will also be an increase of negative charge on the carbonyl oxygen that can then be stabilized by double hydrogen-bonding (Scheme 2).



Scheme 2.

2. Results and discussion

Our experiments with benzaldehyde (**2**) and ethanol as well as 1,2-ethanediol as the alcohol components cleanly gave the respective acetals in excellent yields at a catalyst loading of only 1 mol% (Table 1) at room temperature. Considering that typical acetalizations with strong acids are carried out in, for instance, refluxing toluene for azeotropic water removal (see below, Section 4.6), we were very pleased with the high activity of catalysts **1** in this reaction. The application of this protocol to other aromatic (e.g., **4**–**8**) but also simple aliphatic aldehydes (**9** and **10**) worked equally well and resulted in the respective acetals in excellent yields. The considerably less reactive ketones (e.g., **11**–**13**) can also be acetalized in good yields but, as expected, at considerably longer reaction times. All uncatalyzed reactions run in parallel under otherwise identical conditions gave no product within the time required for completion of the catalyzed transformation. Even after 1 week, the uncatalyzed reactions generally gave $<1\%$ of the respective acetals. The scale-up in preparative (20 mmol) experiments (noted in parentheses in Table 1) is also excellent and makes this reaction synthetically useful; the catalyst loading can be reduced routinely to 0.01 mol%, which still gives high yields at marginally extended reaction times.

The current reaction operates, to the best of our knowledge, at the lowest catalyst loadings for an organocatalytic reaction reported to date (0.01 mol%). Hence, turnover is significant enough to express it in terms of turnover number (TON) and, better, turnover frequency (TOF). For the acetalization of **4** and **10** we find TOFs of 632 h^{-1} (TON = 9800) and 577 h^{-1} (TON = 9700), respectively.

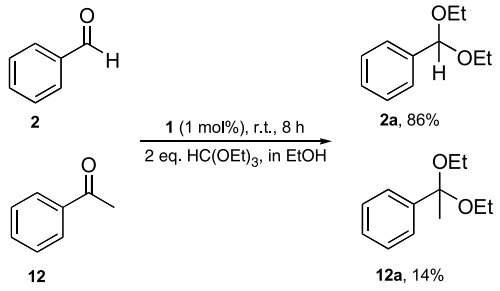
Thus far, the only limitation of our protocol concerns the acetalization of electron-rich *p*-tolylbenzaldehyde (**8**), which required very long reaction times owing to the low

Table 1. Organocatalytic acetalization of aryl as well as alkyl aldehydes and ketones with **1** at room temperature

Carbonyl compound	Mol% **1**	Alcohol[a,b]	*t* (h)[c]	Acetal (%)[d,e]
Benzaldehyde (**2**)	1	A	10	98 (94)
2	1	B	9.2	99 (92)
p-Fluorobenzaldehyde (**3**)	1	A	11.3	97
p-Chlorobenzaldehyde (**4**)	1	A	13 (3)	98 (95)
4	1	B	11.5 (2.5)	98 (87)
4	0.1	A	13.8	97
4	0.01	A	15.5	98
4	0.001	A	—	—
4	1	C	13.5	98
4	1	D	11	98
4	1	E	16	98
p-Bromobenzaldehyde (**5**)	1	A	21.5	98
p–CF_3-benzaldehyde (**6**)	1	A	7.5	97
Phenylacetaldehyde (**7**)	1	A	10.3	97
p-Tolylaldehyde (**8**)	1	A	250	71
8	1	B	250	76
Cyclohexanecarbaldehyde (**9**)	1	A	13.2	98 (89)
9	1	B	12.8	97 (88)
Octanal (**10**)	1	A	14.3 (4.3)	97 (91)
10	0.1	A	15.5	97
10	0.01	A	16.8	97
10	0.001	A	—	—
10	1	B	11.8 (3.8)	98 (89)
Cyclohexanone (**11**)	1	A	98	69 (61)
11	1	B	92	72 (63)
Acetophenone (**12**)	1	A	93	71 (62)
12	1	B	92	74 (65)
p-Chloroacetophenone (**13**)	1	A	94	71
13	1	B	91	65

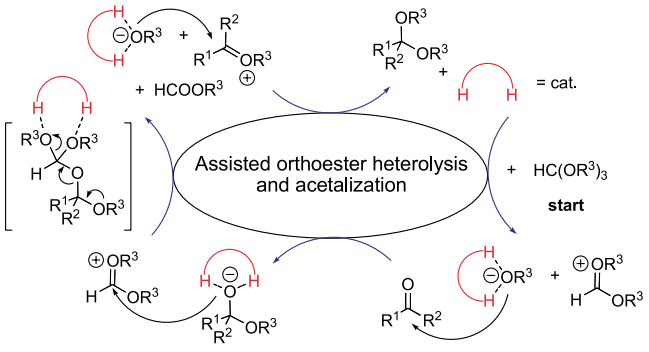
[a] Using alcohol A (ethanol), B (1,2-ethanediol), C (methanol), D (propanol), E (2-propanol, with dry THF as co-solvent).
[b] For each experiment alkyl orthoformate $HC(OR^3)_3$ (Schemes 2 and 4) was used, R depends on the alcohol (see Section 4).
[c] Reaction times of comparative experiments using 1 mol% *p*-toluenesulfonic acid monohydrate as catalyst under otherwise indentical conditions given in parentheses.
[d] Yield (GC).
[e] Preparative experiment (20 mmol scale, in parentheses), isolated yield of NMR-pure product.

reactivity of **8**; this high sensitivity to electronic effects is also apparent in the series of *p*-halogen-substituted benzaldehydes (**3**–**5**). The significant difference in reaction times of aldehydes and ketones translates approximately into the observed chemoselectivity in a competition experiment between benzaldehyde (**2**) and acetophenone (**12**): after 8 h we detect an acetal product mixture of 6.1:1 (NMR) in favor of the acetal of **2** with ethanol; a shorter reaction times (and non-quantitative conversion) gave higher chemoselectivity (Scheme 3).



Scheme 3.

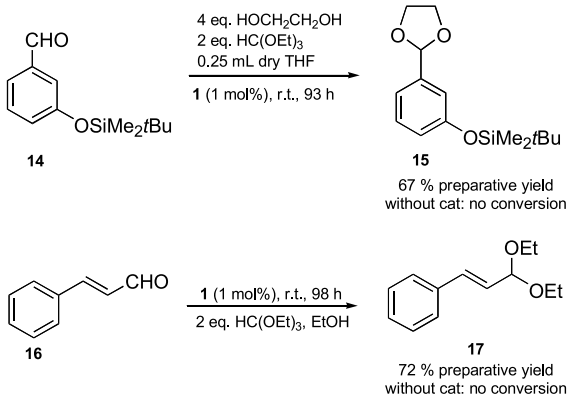
Our current mechanistic proposal for the organocatalytic acetalization of aldehydes and ketones (Scheme 2) begins with the coordination of **1** to the carbonyl group (binding and activation), followed by the nucleophilic attack of the first mole of alcohol. Increased binding to the incipient zwitterion emphasizes the notion of preferential stabilization through partial protonation by means of double hydrogen bonding (general acid catalysis). The catalyst also aids in activating the hydroxide as a formally rather poor leaving group by assisting proton transfer from the second mole of catalyst during nucleophilic attack onto the hemiacetal. This step is remarkable as it emphasizes the role of **1** as a partial proton donor because the key step in acid-catalyzed acetalizations is the protonation of the hydroxy function to produce water in the final S_N1 displacement with a second mole of alcohol.[15] Finally, **1** is released from the cycle by water removal with orthoformate. One problem of this proposal (Scheme 2) is the formal S_N2-like substitution of the OH group (with concomittant proton transfer) of the hemiacetal. A mechanistic alternative would be the thiourea-assisted heterolysis of the orthoester followed by the rapid attack of the alcoholate onto the carbonyl compound as outlined in Scheme 4.



Scheme 4.

Evidence for this mechanistic proposal comes from our attempts to perform thioacetalization reactions, which are also accelerated in the presence of our catalysts **1** in the absence of $HC(OEt)_3$. Addition of the orthoester only gave the normal diethyl acetal although the thiols are much better nucleophiles. Clearly, the full mechanistic elucidation of this reaction requires more elaborate studies that are under way in our laboratories and will be reported in full in due course.

The practicality of our acid-free acetalization is further exemplified (Scheme 5) with the acetalization of TBDMS-protected aldehyde **14**, which is acid-sensitive and reacts rather sluggish under alternative conditions (e.g., in the presence of 2 mol% NBS[8] or in refluxing cyclohexane (80 °C) with higher catalyst ($InCl_3$) loading[16] of 5 mol%): acetal **15** is formed in 67% preparative yield; there is no reaction without catalyst over the same period of time. The clean conversion of *trans*-cinnamic aldehyde to the acetal **17** also emphasizes the synthetic usefulness of this acid-free conversion.



Scheme 5.

3. Conclusions

In summary, we have successfully extended the principle of double-hydrogen bonding organocatalysis as provided by hydrogen-bonding thiourea derivative **1** to the acetalization of various aliphatic and aromatic carbonyl compounds. The scope of our high-yielding acid-free acetalization includes saturated, aromatic as well as unsaturated aldehydes and ketones, and proceeds at the highest turnover frequencies (around 600 h^{-1}) reported for an organocatalytic reaction to date (catalyst loadings down to 0.01 mol%). Comparative experiments using *p*-toluenesulfonic acid monohydrate as a traditional catalyst still are faster by a factor of 4–5 for some representative carbonyl substrates under otherwise identical conditions but this protocol is obviously not applicable to acid-sensitive substrates for which our approach works well. We currently focus on the elucidation of the reaction mechanism, the acetalization of unsaturated ketones, and enantioselective acetalizations.

4. Experimental

4.1. General information

All chemicals were purchased from Aldrich, Acros Organics, and Lancaster in the highest purity available;

for all syntheses and experiments dry chemicals were used; methanol and ethanol were dried according to the usual literature procedures using magnesium and sodium/diethyl phthalate, respectively; propanol, isopropanol, and 1,2-ethandiol were distilled once over a 20 cm Vigreux column; alkyl orthoformates were distilled twice over a 20 cm column filled with Raschig rings; THF and triethylamine were freshly distilled from Na/benzophenone; all dry chemicals were stored until use under argon atmosphere over new molecular sieve 3 Å (alcohols), 4 Å (alkyl orthoformates), and sodium (THF, triethylamine). Solid aldehydes were dried over Sicapent™ in a desiccator and were used without further purification; to remove traces of benzoic acid all liquid aldehydes were purified by vacuum destillation over a 10 cm Vigreux column directly before use. Column chromatography was performed on activated basic Al_2O_3 (50–200 microns; Acros Organics). All experiments were carried out in oven-dried and flame-dried glassware (Schott DURAN), all equipment was dry, including syringes, pipettes, and cannulas.

For progress monitoring of acetalizations GC-analysis was performed with Carlo Erba instruments 5300 equipped with a 10 m OV 101 column using N_2 as carrier gas; *T*-program standard 100–250 °C, heating rate 15 °C/min, injector and detector (FID) 250 °C; time-dependent conversion in percent was determined from integral ratio of educt and product signals; retention times of the products were detected by analyzing the pure acetals (reference compounds); ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer using TMS as the internal standard; chemical shift values are given in ppm. IR spectra were measured with a Bruker IFS 25 spectrometer; HRMS was performed with a Sectorfield-MS: Finnigan MAT 95, CHN-Analysis were obtained from a Carlo Erba 1106 (balance: Mettler Toledo UMX-2); the melting point (corrected) of **1** was determined with a BÜCHI SMP-20; pH-value of a representative organocatalyzed reaction was measured with a portable HANNA HI 8314 pH meter.

4.1.1. Synthesis of organocatalyst *N,N′*-bis[3,5-bis(trifluoromethyl)phenyl]thiourea. For large-scale preparation the synthesis of **1** followed a modified literature protocol.[17] In an oven-dried 1000 mL three-necked flask equipped with thermometer, addition funnel, gas inlet, and magnetic stirring bar a mixture of 3,5-bis(trifluoromethyl)aniline (23.39 g, 100 mmol) and triethylamine (16.57 mL, 119 mmol) in THF (720 mL) was prepared. Under argon atmosphere a mixture of thiophosgene (3.29 mL, 43 mmol) in THF (70 mL) was added dropwise to the stirred solution at −5–0 °C. After addition, the yellow suspension (a white solid precipitated) was allowed to stir at room temperature After 24 h the bulk of solvent was removed in a rotary evaporator under reduced pressure, the concentrated brown-colored residue was added to water (450 mL), and the aqueous layer was extracted with diethyl ether (2× 150 mL). The combined organic layers were washed with brine (1×80 mL) and dried over sodium sulfate. After filtration and evaporation of the solvent the red-brown solid crude product was purified by recrystallization from chloroform once, and the resulting slightly yellow solid, was dissolved in a minimum amount of diethyl ether to be re-precipitated by addition of *n*-hexane as a nearly colorless solid that was dried over Sicapent™ in a desiccator to obtain spectroscopically pure thiourea derivative **1** (36.1 g, 72 mmol, 84%). Concentrating the mother liquor to a minimum volume and cooling in an ice box afforded an additional amount (2.9 g, 5.8 mmol) of **1**. Mp 172–173 °C; X-ray data,[18] IR (KBr): 3207, 3050, 2987, 1555, 1467, 1376, 1326, 1289, 1181, 1133, 930, 891, 714, 701, 684; ^1H NMR (400 MHz, [d_4] methanol): δ=7.33–7.27 (m, 6H), 7.68 (s, 2H), ^{13}C NMR (100 MHz, [d_4] methanol): δ= 120.47 (CH), 123.17 (C_q), 125.87 (CH), 132.67 (C_q), 142.51 (C_q), 182.20 (C=S); HRMS calcd $C_{17}H_8N_2SF_{12}$: 500.0216; found: 500.0210; CHN-analysis: calcd C 40.81, H 1.61, N 5.60; found C 40.69, H 1.65, N 5.68.

4.2. Organocatalytic synthesis of acyclic acetals from aldehydes and ketones

In a flame-dried 10 mL one-necked flask tightly sealed with a plastic plug a mixture of 2 mmol freshly distilled carbonyl compound, 0.5 mL (8.6 mmol) dry ethanol, 0.66 mL (4 mmol) dry triethyl orthoformate, and 10 mg (1 mol%) organocatalyst **1** was magnetically stirred (~900 rpm, stirring bar: 1 cm) at room temperature. The progress of the homogenous reaction was monitored by GC analysis. After completion of the reaction a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, the resulting mixture was extracted with CH_2Cl_2 (3×5 mL), the collected organic layers were washed with water (1× 5 mL) and finally dried over anhydrous Na_2SO_4. Evaporation of solvent in a rotary evaporator under reduced pressure furnished almost pure products. Further purification was achieved by column chromatography through a column of basic Al_2O_3 (20 cm×1.5 cm, ~35 g) with *n*-hexane/ethyl acetate (5/1) as eluent to afford the corresponding diethyl acetal spectroscopically pure in good to excellent yields.

4.3. Organocatalytic synthesis of cyclic acetals from aldehydes and ketones

In a flame-dried 10 mL one-necked flask tightly sealed with a plastic plug a mixture of 2 mmol freshly distilled carbonyl compound, 0.45 mL (8 mmol) dry 1,2-ethandiol, 0.66 mL (4 mmol) dry triethyl orthoformate, 0.25 mL dry THF, and 10 mg (1 mol%) organocatalyst **1** was magnetically stirred (~900 rpm) until completion of the reaction (GC-analysis), the reaction mixture was worked up according to the procedure described for acyclic acetals to gave pure 1,3-dioxolanes in good to excellent yields.

Acyclic and cyclic acetals were identified by comparison of their NMR, IR, and GC co-injection of authentic samples (reference compounds) synthesized by established procedures.

4.4. Synthesis of reference compounds

4.4.1. Synthesis of dimethyl and diethyl acetals. A mixture of freshly distilled carbonyl compound (0.06 mol), dry methanol (20 mL) or ethanol, trimethyl orthoformate, and triethyl orthoformate (0.09 mol), respectively, and

p-toluenesulfonic acid monohydrate (150 mg) was stirred in an argon atmosphere at room temperature for 24 h (ketones were refluxed for 12 h). The acid was neutralized by dropwise addition of a saturated aqueous solution of sodium carbonate, the organic layer was separated und washed with an aqueous solution of sodium hydrogen sulfite (5 mL, 20%), and dried over sodium sulfate. After evaporation of the solvent the crude product was distilled over a 10 cm Vigreux column (in case of benzaldehyde **2** a 20 cm column was used) under reduced pressure to furnish the pure acetals in yields ranging from 64–81%.

4.5. Synthesis of dipropyl and diisopropyl acetal of 4

Dipropyl and diisopropyl acetals of *p*-chlorobenzaldehyde **4** were synthesized by refluxing a solution of the aldehyde (4.21 g, 30 mmol), *p*-toluenesulfonic acid monohydrate (200 mg), tripropyl orthoformate (8.56 g, 45 mmol) and triisopropyl orthoformate (8.56 g, 45 mmol), respectively, in the corresponding dry alcohol (6 mL) for 12 h in an argon atmosphere. The reaction mixture was neutralized with an aqueous solution of sodium carbonate, the aqueous layer was extracted with diethyl ether (once 5 mL), and after drying with sodium carbonate, the solvent was removed. Vacuum destillation over a 10 cm Vigreux column afforded at 131–133 °C (~10 mbar) pure *p*-chlorobenzaldehyde dipropyl acetal (4.6 g, 19.0 mmol, 63%) and at 120–122 °C (~10 mbar) *p*-chlorobenzaldehyde diisopropyl acetal (4.8 g, 19.8 mmol, 66%), respectively.

4.5.1. *p*-Chlorobenzaldehyde dipropyl acetal. Colorless liquid, IR (neat): ν=2964, 2937, 2877, 1490, 1339, 1205, 1090, 1067, 1042, 1016, 809; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.95 (t, 3H, J=7.5 Hz), 1.58–1.67 (m, 2H, J=7.4 Hz), 3.38–3.36 (m, 2H), 5.5 (s, 1H), 7.27–7.34 (m, 2H), 7.37–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.7 (CH_3), 22.9 (CH_2), 66.9 (CH_2), 100.7 (CH), 128.1 (CH), 128.2 (CH), 133.9 (C_q), 137.7 (C_q); HRMS calcd $C_{13}H_{19}ClO_2$ 242.1074; found: 242.1091; CHN-analysis: calcd C 64.32, H 7.89; found C 64.54, H 8.16.

4.5.2. *p*-Chlorobenzaldehyde diisopropyl acetal. Colorless liquid, IR (neat): ν=2973, 2931, 1599, 1491, 1466, 1381, 1324, 1295, 1204, 1180, 1126, 1089, 1075, 1035, 1015, 943, 833, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.13–1.19 (m, 6H), 3.85–3.94 (m, 1H, J=6 Hz), 5.03 (s, 1H), 7.27–7.34 (m, 2H), 7.37–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.4 (CH_3), 23.0 (CH_3), 67.9 (CH), 98.5 (CH), 128.1 (CH), 128.2 (CH), 133.8 (C_q), 139.0 (C_q); HRMS calcd $C_{13}H_{19}ClO_2$ 242.1074; found: 242.1086; CHN-analysis: calcd C 64.32, H 7.89; found C 64.47, H 8.09.

4.6. Synthesis of 1,3-dioxolanes as reference compounds

In a oven-dried 50 mL one-necked flask equipped with a water separator and a reflux condenser a mixture of 0.1 mol of the corresponding freshly distilled carbonyl compound, 7.45 g (0.12 mol) 1,2-ethandiol, 30 mL toluene, and 150 mg *p*-toluenesulfonic acid monohydrate were magnetically stirred and refluxed until no more water separated. For work-up the reaction mixture was poured into an aqueous saturated solution of $NaHCO_3$ (20 mL), the organic layer was washed with water (2×15 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent in a rotary evaporator under reduced pressure the crude products were purified by vacuum destillation over a 10 cm Vigreux column to afford colorless liquids; the yields ranged from 67 to 85%. Spectral data were identical to those reported in the literature.

The acid-labile aldehyde **14** incorporating the TBDMS-group was prepared by a straightforward literature procedure (yield:79%).[19]

4.7. Analytical methodology

All analytical reaction mixtures of the acetalizations were prepared in clean (for cleaning glass flasks were stored for 8 h in a KOH/*iso*-propanol bath, washed intensively with water, demineralized water, and acetone, successively), oven-dried (5 h) and flame-dried 10 mL (for 2 mmol scale; 25 and 250 mL flasks for larger scale) one-necked glass flasks were tightly sealed with a plastic plug. Two millimoles of the respective carbonyl compound (for catalyst loading of 0.1 and 0.01 mol% a 20 mmol scale was used, for 0.001 mol% 200 mmol scale) and organocatalysts **1** (various loadings: 1.0 [10 mg/2 mmol], 0.1 [10 mg/20 mmol], 0.01 [1 mg/20 mmol], and 0.001 mol% [1 mg/200 mmol scale] relative to the carbonyl compound) were weighted out directly into the flasks and were dissolved in 2 equiv of the corresponding alkyl orthoformate and alcohol (methanol, ethanol, propanol, and isopropanol, respectively) by intensive stirring (900 rpm) with a new magnetic stirring bar wrapped with plastics (size: 0.8 cm for 2 mmol, 1.4 cm for larger scale experiment); stirring was continued until completion of the reaction. The volume of the alcohol was adjusted relative the volume of alkyl orthoformate, to keep total volume constant (1.16 mL) making all experiments comparable to each other (Table 2). For the formation of cyclic acetals 2 mmol of carbonyl compound, 4 equiv 1,2-ethandiol, 2 equiv triethyl orthoformate, and 0.25 mL THF as cosolvent were mixed; all reactions were carried out at room temperature (25 °C); the reaction time measurements started with the addition of the alcohol, that served as reagent as well as solvent; the volumes were measured with 1 and 2 mL pipettes. Every mixture containing catalyst was prepared twice, and for detection of catalytic efficiency all experiments were accompanied by a parallel control experiment under same conditions, but without catalyst. Samples (0.8–1.2 μL; volume depended on progress of reaction) were taken directly from the stirred homogenous reaction mixture by a Hamilton syringe (10 μL) and were injected immediately to record the GC chromatogram. The course of each acetalization was monitored by integrating the educt/product ratio. Signals were assigned by injecting

Table 2. Volumes of orthoformates (2 equiv/4 mmol) and alcohols for 2 mmol scale experiments

Orthoformate	Volume (mL)	Alcohol	Volume (mL)
Trimethyl	0.44	Methanol	0.72
Triethyl	0.66	Ethanol	0.50
Tri-*n*-propyl	0.87	1-Propanol	0.29
Triisopropyl	0.87	2-Propanol	0.29

the starting material and reference compound; in case of the acetalization of **14** and **16** reference compounds **15** and **17** were not prepared, so completion of the reaction was indicated by disappearance of starting material, yield was obtained by preparative work-up, product identification by NMR and IR. Comparative experiments using 1 mol% (4 mg) *p*-toluenesulfonic acid monohydrate were accomplished in 2 mmol scale and ran under the same conditions (alcohol, orthoformate, room temperature) as described in the details given in Table 1).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SPP1179). This article is dedicated to Eva Kotke on the occasion of her 60th birthday.

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Tetrahedron
Tetrahedron 62 (2006) 440–456

$[HP(HNCH_2CH_2)_3N]NO_3$: an efficient homogeneous and solid-supported promoter for aza and thia-Michael reactions and for Strecker reactions

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Received 1 July 2005; revised 6 September 2005; accepted 16 September 2005

Available online 21 November 2005

Abstract—In the presence of a catalytic amount of an azaphosphatrane nitrate salt, amines and thiols react readily with Michael acceptors. The salt is also an efficient promoter for the one pot synthesis of α-amino and α-amidonitriles. By anchoring the salt to Merrifield Resin, a reusable heterogeneous catalyst is obtained for these reactions. Evidence is presented for catalysis being attributable solely to the NO_3^- ion.

1. Introduction

The Michael conjugate addition reaction has been a useful tool for organic, medicinal, and biochemists for several decades.[1] This transformation is an efficient and commonly used route to the formation of C–C,[2] C–O,[3] C–N,[4] and C–S[5] bonds and it facilitates, for example, the synthesis of important amino alcohols and versatile intermediates for a large number of natural products,[6] heterocycles,[7] peptides,[8] and chiral auxiliaries.[9] Protected β-amino carbonyl compounds and β-thiocarbonyl compounds can also be prepared via aza-Michael and thia-Michael reactions, respectively.[10]

Michael reactions are facilitated homogeneously by protic acid catalysts,[11] base catalysts,[2a,c,3] or Lewis acid catalysts.[4,5] Recently, bismuth nitrate[4b] and also palladium tetrafluoroborate and chloride complexes[4f] have been reported to catalyze the production of β-amino and β-thio carbonyl compounds in the presence of α,β-unsaturated ketones.

α-Aminonitriles, often synthesized by a Strecker reaction,[12] are highly useful synthons for the synthesis of α-amino acids[13] and nitrogen and sulfur-containing heterocycles[14] such as imidazoles and thiadiazoles. Acyclic α-amidonitriles[15] are versatile synthons for the synthesis of diverse heterocyclic compounds,[16] and they are normally prepared by acylation of an α-aminonitrile.[15b,c,16,17a–e,18,19] Strecker reactions are generally carried out in aqueous solution with a variety of cyanide ion sources, including trimethylsilyl cyanide (TMSCN),[17] which appears to be most useful and also relatively safe.

A variety of homogeneous catalysts containing Lewis acidic metal ions have been reported for the Strecker reaction.[15b,c,16b,17e,18a,c,e] The Strecker reaction is also known to proceed via the nucleophilic addition of cyanide to an imine in the absence of a catalyst, albeit with long reaction times (2–3 days).[19] Many of the reported methodologies for this reaction involve the use of relatively expensive reagents, extended reaction times and/or tedious work-up procedures leading to the generation of considerable amounts of waste, which in a substantial number of instances is toxic.

By contrast with α-aminonitriles, few reports were found describing the preparation of α-amidonitriles.[15] These two-step methods require relatively long reaction times and relatively tedious work-up procedures that generate comparatively large quantities of toxic waste.[15]

Catalysts bound to cross-linked polystyrene solid supports are well known and have been utilized for a myriad of organic transformations.[20] Azaphosphatrane **1a** supported on crosslinked polystyrene has been shown to be an effective procatalyst in dehydrohalogenations and debrominations with NaH.[21] Acylation of alcohols has been achieved using polymer-supported iminoproazaphosphatrane **2**.[22]

Keywords: Homogeneous; Heterogeneous; Catalysis; Michael reactions; Nitrate; Azaphosphatrane; Promoter.
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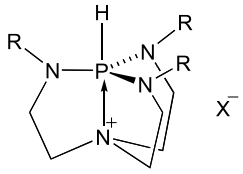
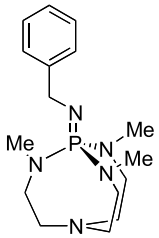
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.117

Polymer-supported catalysts are also known to catalyze Michael reaction such as acids,[23] cinchona alkaloids,[24] catalytic lithium and aluminum ions complexed by a ligand linked to the polymer,[2b] or fluoride ion.[25] Unfortunately, these catalysts have only been tested on a small number of amines. Moreover, repeated recycling of these polymers was either not discussed or the polymer mounted catalysts required periodic reactivation.

Although resin bound catalysts for the Strecker reaction are known, such catalysts either involve the use of toxic metals[26] or of multistep syntheses.[27]



	R	X
1a	H	Cl^-
1b	H	NO_3
1c	H	CF_3CO_2
1d	H	CF_3CO_3
1e	Me	NO_3
1f	Me_2CHCH_2	Cl
1g	Me_2CHCH_2	NO_3



2

Our interest in thia and aza-Michael reactions was piqued by the efficacy of bismuth nitrate as a catalyst and particularly by the apparent co-catalytic role of the nitrate ion.[4b] To ensure that the nitrate ion in our experiments would be essentially free of Lewis acid–Lewis base interactions with its counter cation, in contrast to the likelihood of such interactions between the bismuth(III) cation and nitrate ion, we chose to investigate the nitrate salts of three aza-phosphatranes, namely, **1b**,**e** and **1g** because of the opportunity for positive charge delocalization in the azaphosphatrane cations. Here, we report the synthesis of these salts and compare their efficiencies as catalysts with previously synthesized **1c**,**d**, and **1f**[28] for the aza and thia-Michael reactions of amines and thiols at room temperature with α,β-unsaturated ketones, α,β-unsaturated esters and α,β-unsaturated nitriles. We also report here a simple one-pot three-component protocol for the preparation of a variety of α-aminonitriles using **1b**[28] as a promoter in reactions wherein nitrate ion is demonstrated to be the catalytically active species. A one-pot four-component coupling method for the synthesis of α-amidonitriles using **1b** is also reported.

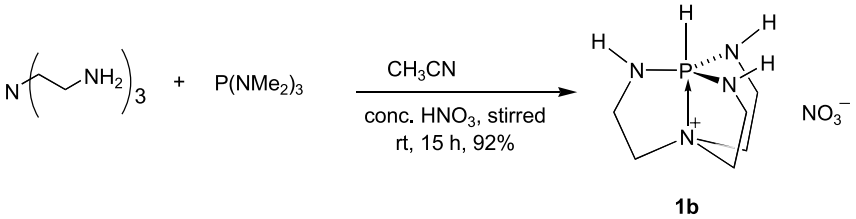
2. Results and discussion

2.1. Homogeneously catalyzed Michael reactions

Initially, we attempted to use the deprotonated form of **1e** [i.e., $P(MeNCH_2CH_2)_3N$] as a base catalyst for the aza-Michael reaction of aniline with methyl vinyl ketone, but to no avail. We found, however, that although 10 mol% of the chloride salt **1f** gave no detectable yield of product in this reaction, 10 mol% of the nitrate salts **1e** and **1g** afforded a 78 and a 72% product yield after 30 h at room temperature, respectively. Because **1b** is considerably easier and cheaper to synthesize than **1e** or **1g**, we continued our investigations with **1b**, which was prepared from commercially available starting materials in a single step as shown in Scheme 1.

When we screened the trifluoroacetate and triflate salts of **1b** (**1c** and **1d**, respectively) in the reaction of aniline with methyl vinyl ketone under the aforementioned conditions, the reactions were quite slow, furnishing product yields of 70 and 72% after 40 h using **1c** and after 48 h using **1d**, respectively. We also tested 10 mol% solution concentrations of HNO_3, $NaNO_3$, $NaNO_3$ in the presence of 15-crown-5, CAN, $Bu_4N(NO_3)$, 1-butyl-3-methylimidazolium chloride, and 1-ethyl-3-methylimidazolium nitrate in this reaction, all of which provided unimpressive yields of 40, 32, 20, 0, 30, 45, and 50%, respectively, after 40 h. We attribute these poor results to anion–cation interactions that significantly exceed those experienced with the cation in **1b** wherein the positive charge is very well delocalized among the phosphorus and the four nitrogens as can be envisioned in the five resonance structures that can be drawn.

In the presence of 10 mol% of **1b**, reactions of methyl vinyl ketone with the anilines in Table 1 (entries 1–5) gave reasonable to good yields, except for relatively poorly nucleophilic 3-nitroaniline, which contains the strongly electron withdrawing nitro group. With morpholine and the acceptors shown in entries 6–10 in Table 1, the corresponding aza-Michael products were realized in good to excellent yields. Piperidine and 1-aminonaphthalene when reacted with methyl vinyl ketone, gave good yields of the expected aza-Michael reaction product (Table 1, entries 10 and 11) although the reaction involving 1-aminonaphthalene



1b

Scheme 1. Synthesis of **1b**.

required warming to 50 °C to accelerate the reaction. Benzylamine and piperonylamine also participated well in the aza-Michael reaction, giving the anticipated products in excellent yields (entries 12 and 13 in Table 1).

Thiophenol when allowed to react with a variety of acceptors in the presence of 10 mol% of **1b**, afforded the corresponding thia-Michael reaction products in excellent yields after 40 h at room temperature (Table 2, entries 1–4).

Table 1. Room temperature aza-Michael reactions in the presence of **1b** as a promoter[a]

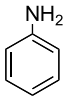
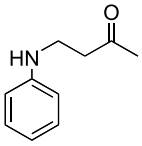
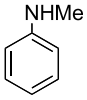
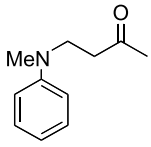
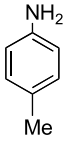
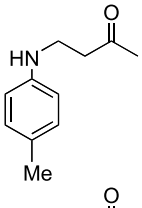
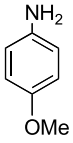
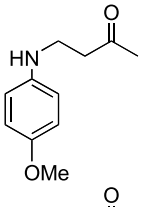
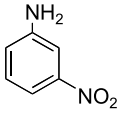
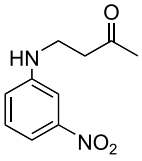
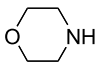
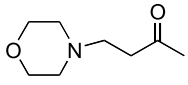
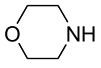
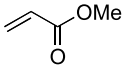
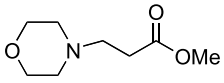
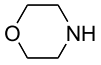
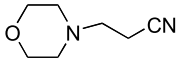
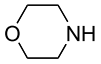
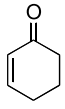
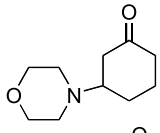
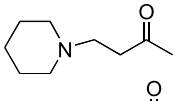
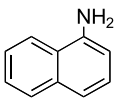
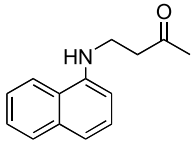
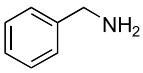
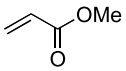
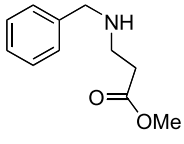
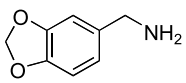
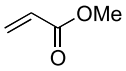
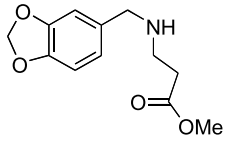
Entry	Donor	Acceptor	Time (h)	Product	Yield w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. yield (%)[c]
1			30		NR	78	80–90[4f]
2			40			68	–[d]
3			40			83	73[10g]
4			40			84	76[10g]
5			50		NR	27	–[e]
6			20		40	90	87–88[4g,k]
7			20		50	86	91[4g]
8			20		45	98	82[4g]
9			20			85	60[4j]
10			20		40	88	87–90[4e,l]
11			20			85[f]	–[e]
12			48		70	98	60–70[4g,h,l]

Table 1 (*continued*)

Entry	Donor	Acceptor	Time (h)	Product	Yield w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. yield (%)[c]
13			48		60	96	–[g]

[a] Conditions: amine (2.0 mmol), acceptor (2.5 mmol), **1b** (10 mol%) and CH_3CN (3 mL).
[b] Isolated yields.
[c] Literature yields.
[d] This compound was reported earlier in Ref. 7b, but no yield was given.
[e] New compound.
[f] Heated at 50 °C.
[g] Although this compound has been reported and characterized,[4m] its yield and NMR spectral data were not given.

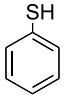
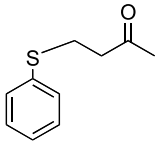
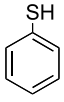
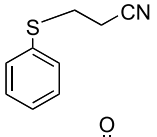
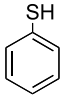
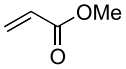
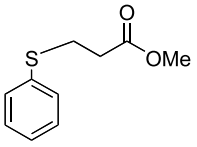
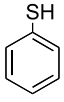
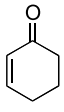
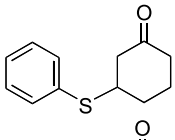
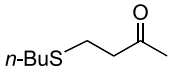
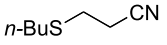
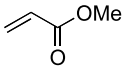
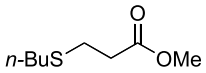
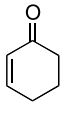
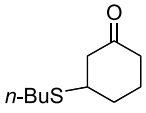
Butanethiol also provided thia-Michael products in excellent yields after 48 h (Table 2, entries 5–8).

Our protocol is simple and of good scope, giving product yields that are better in 12 of the 17 reactions for which literature yields could be found (as seen in Tables 1 and 2). In three additional instances among those 17 cases, the yields realized with **1b** were about the same as the maximum yield found in the literature, and in only one case was the yield roughly the same as the minimum literature yield.

2.2. Homogeneously catalyzed Strecker reactions

For the Strecker reaction, we initially examined **1c** and **1d** as promoters (20 mol%) for the three-component model reaction employing benzaldehyde, aniline, and TMSCN in acetonitrile at room temperature for 12 h. Although the

Table 2. Room temperature thia-Michael reactions promoted by 1b[a]

Entry	Donor	Acceptor	Time (h)	Product	w/o cat. (%)[b]	Yield w/**1b** (%)[b]	Lit. Yield (%)[c]
1			40			95	66–72[5a,c]
2			40		30	98	92[5a]
3			40		20	98	92[5a]
4			40			94	65–92[4b,5a]
5	*n*-BuSH		48			90	70[5a]
6	*n*-BuSH		48			98	88[5a]
7	*n*-BuSH		48		NR	99	90[5a]
8	*n*-BuSH		48			93	73[4b]

[a] Conditions: thiol (2.0 mmol), acceptor (2.5 mmol), **1b** (10 mol%) and CH_3CN (3 mL).
[b] Isolated yields.
[c] Literature yields.

Table 3. Room temperature preparation of α-aminonitriles using **1b** as a promoter[a]

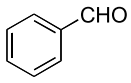
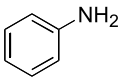
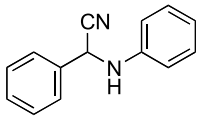
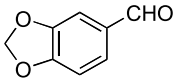
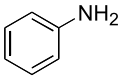
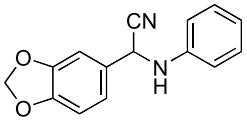
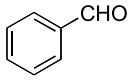
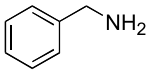
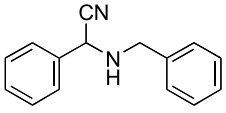
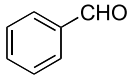
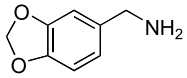
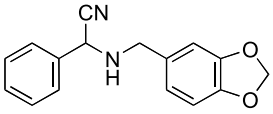
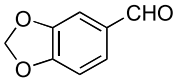
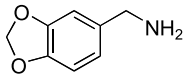
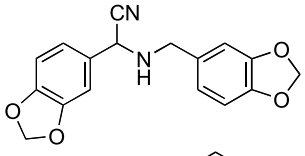
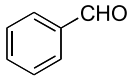
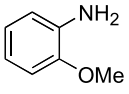
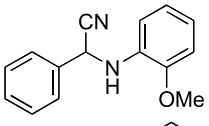
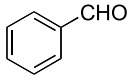
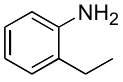
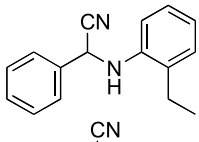
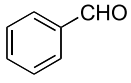
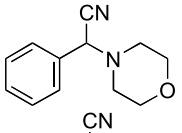
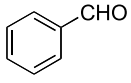
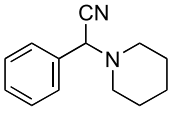
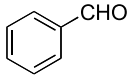
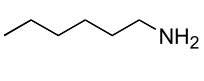
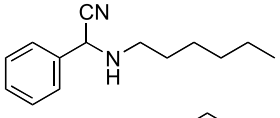
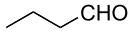
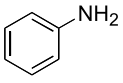
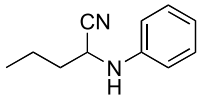
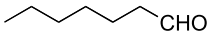
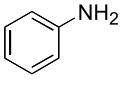
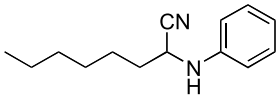
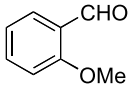
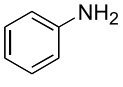
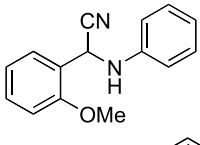
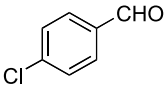
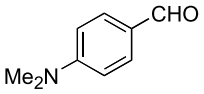
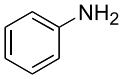
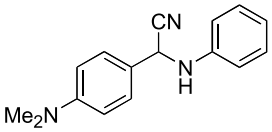
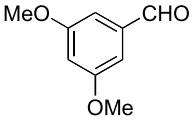
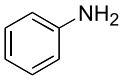
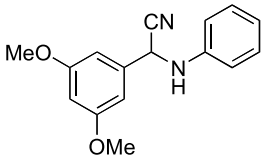
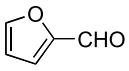
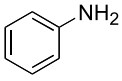
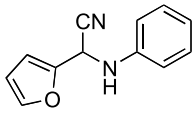
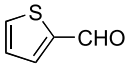
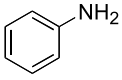
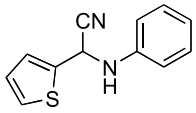
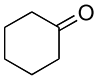
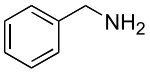
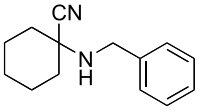
Entry	Aldehyde	Amine	Product	Time (h)	% Yield w/**1b**[b]	Lit. Yield (%)[c]
1				12	94	75–92[d, 15b16a,d]
2				15	91	97[15b]
3				12	90	73–96[d, 15a,b]
4				8	93	–[e]
5				12	90	–[e]
6				15	92	–[f, 15a,c]
7				15	90	–[e]
8				8	98	82[d, 15b]
9				15	98	78[d, 16c]
10				15	92	83[d, 17f]
11				25	82	75[15a]
12				25	80	–[e]
13				12	88	74[15a]
14				15	90	75–91[d, 15a,16a]

Table 3 (*continued*)

Entry	Aldehyde	Amine	Product	Time (h)	% Yield w/**1b**[b]	Lit. Yield (%)[c]
15				15	88	97[15b]
16				25	85	–[e]
17				15	93	94[15c]
18				20	95	97[15c]
19				15	82	66[d, 15b]

[a] Conditions: aldehyde or ketone (1.0 mmol), amine (1.0 mmol), TMSCN (1.2 mmol), **1b** (20 mol%) and CH_3CN (3 mL).
[b] Isolated yields.
[c] Literature yields.
[d] Three-component coupling reaction.
[e] New compound.
[f] The yield was reported as quantitative.

yields were disappointing (75 and 60%, respectively) the same reaction with 20 mol% of **1b** provided a 94% yield of the desired product. The use of dichloromethane as a solvent in this reaction gave a poor yield (40%) in a very slow (12 h) reaction probably owing to incomplete solution of **1b**.

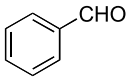
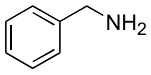
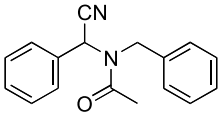
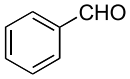
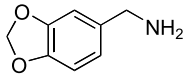
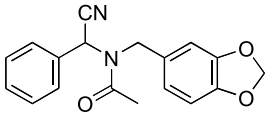
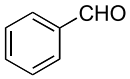
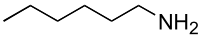
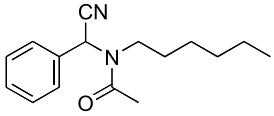
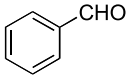
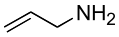
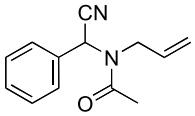
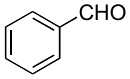
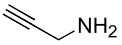
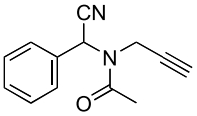
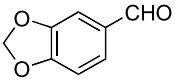
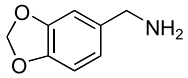
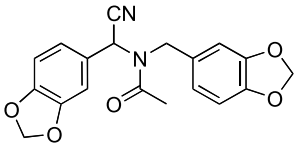
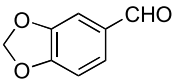
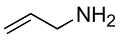
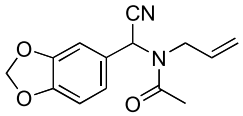
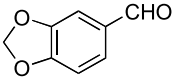
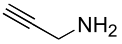
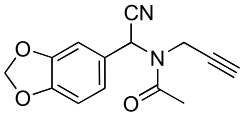
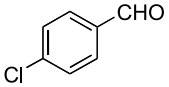
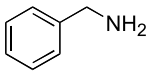
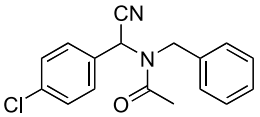
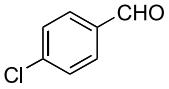
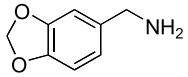
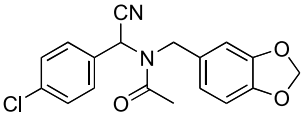
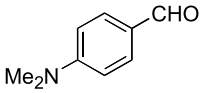
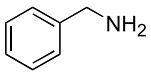
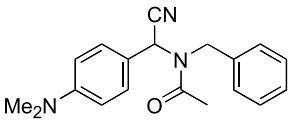
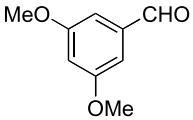
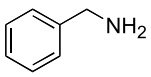
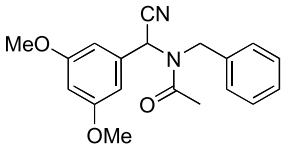
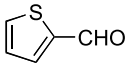
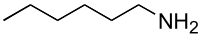
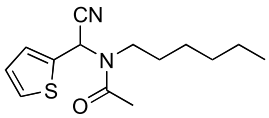
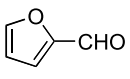
Benzaldehyde (1.0 mmol) reacted with a variety of amines (1.0 mmol) in the presence of 20 mol% of **1b** and TMSCN (1.2 mmol) in CH_3CN to give excellent product yields (Table 3, entries 1, 3, 4, 6–10). Secondary amines (Table 3, entries 8 and 9) reacted relatively quickly to give 98% product yields and *n*-hexylamine (entry 10) also gave a high yield of product of 83%. Piperonal reacted with amines, giving the corresponding α-aminonitrile in excellent yield (entries 2 and 5). Aliphatic aldehydes also reacted well with aniline, affording good product yields (entries 11 and 12). Aniline reacted with substituted aromatic aldehydes, affording 85–90% product yields (entries 13–16) and the heterocycles in entries 17 and 18 gave a 93 and 95% yield of desired product, respectively. Reactions of the type reported here are very sluggish without promoter **1b**, as was shown for the reaction in entry 1, in which case, 3 days were necessary to achieve a 90% product yield.

To our knowledge, only two reports of Strecker-type reactions with ketones appear in the literature.[17b,29] In one case $InCl_3$ was the catalyst for cyclohexanones[17b] and in the second, elevated pressure in the absence of a catalyst was employed for aliphatic and aromatic ketones.[29] Although the reaction of acetophenone with aniline and TMSCN in the presence of 20 mol% of **1b** at room temperature gave no detectable product after 25 h, the reaction of cyclohexanone with benzylamine and TMSCN under the same conditions gave an 82% product yield after 15 h (entry 19).

From Table 3 it is seen that, of the literature yields reported for three-component reactions (entries 1, 3, 8–10, 14, and 19), our protocol delivers a substantially higher yield in four of the seven cases, and yields that are near or at the upper end of the literature range in the other three cases. In the remaining entries in which literature yields were reported for perhaps less risky two-step syntheses (entries 2, 6, 8, 11, 13, and 15–18) our one-pot methodology produced higher yields in three of the nine cases, very comparable yields in two cases and lower yields in four instances.

For the four-component one-pot synthesis of α-amidonitriles, we employed 20 mol% of **1b**, benzaldehyde (1.0 mmol), benzylamine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol), and acetic anhydride (1.0 mmol). After 20 h at room temperature, a 40% yield (based on benzaldehyde) of the coupling product was realized. Increasing the quantity of acetic anhydride to 1.5 mmol improved the product yield to only 60%. After further attempts to increase the yield by changing relative concentrations of the reactants, we found that a mixture of 30 mol% of **1b**, benzaldehyde (1.0 mmol), benzylamine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol), and acetic anhydride (2.0 mmol) stirred at room temperature for 25 h gave a good yield (82%) of product (entry 1 in Table 4). We also observed that after addition of the TMSCN, it was advantageous to quickly add the acetic anhydride in order to

Table 4. Room temperature preparation of α-amidonitriles using **1b** as a promoter and acetic anhydride as the acetylating reagent[a]

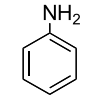
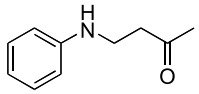
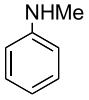
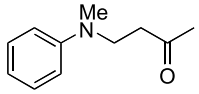
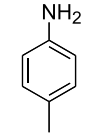
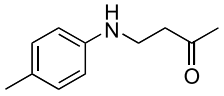
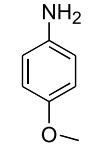
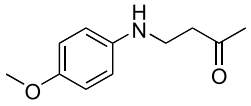
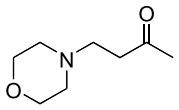
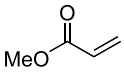
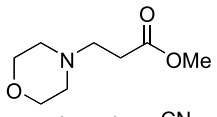
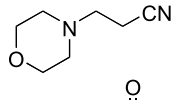
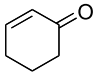
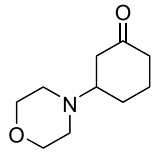
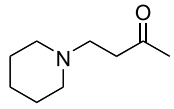
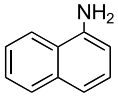
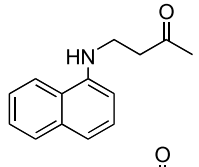
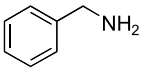
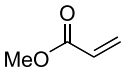
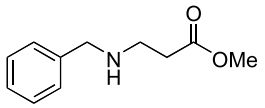
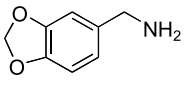
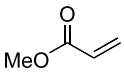
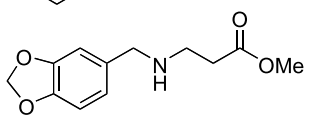
Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)[b]
1				25	82
2				25	84
3				25	85
4				30	86
5				35	60
6				25	70
7				35	73
8				35	50
9				25	74
10				25	76
11				30	65
12				25	80
13				25	75
14				30	72

[a] Conditions: aldehyde (1.0 mmol), amine (1.0 mmol), TMSCN (1.2 mmol), $(CH_3CO)_2O$ (2.0 mmol), **1b** (30 mol%) and CH_3CN (3 mL).
[b] Isolated yields. None of the products in Table 4 have been described in the literature.

avoid decreased yields. Substituting acetyl chloride for acetic anhydride gave no detectable amount of product. Using 30 mol% of the commercially available catalysts $InCl_3$ or $Bi(NO_3)_3$ gave only acylated amine.

Stirring a mixture of benzaldehyde, **1b**, an amine, TMSCN and acetic anhydride as specified in Table 4 gave product yields ranging from 60–86% yields as shown in entries 1–5 of this table. Extending this chemistry to reactions of a variety of aryl aldehydes with different amines, 50–80% yields of the corresponding coupling products were realized (Table 4, entries 6–12). The relatively low yields obtained in the case of propargylamine may be due to side reactions associated with its reactivity with the aldehyde and/or with acetic anhydride. The heterocycles in entries 13 and 14 gave in each case reasonable product yields. Although none of the products in Table 4 were found in the literature, the yields for the 14 products listed in this table are good (80–86%) in

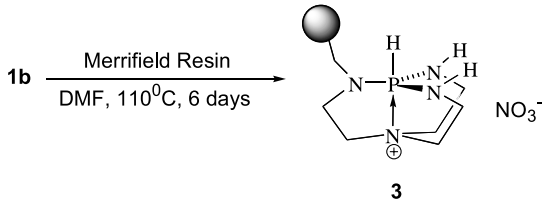
Table 5. Room temperature aza-Michael reaction in the presence of **3** as a promoter

Entry[a]	Donor	Acceptor	Product	Yield (%)
1				80
2[b]				70
3[b]				92
4[b]				92
5				99
6				99
7				82
8				89
9				99
10[b]				84
11				95
12				99

[a] Conditions: amine (1.5 mmol), acceptor (1.9 mmol), **3** (10 mol%) and CH_3CN (2 mL). Reactions were run for 24 h at room temperature.
[b] Reaction temperature was 60 °C.

five instances, moderate (60–75%) in eight cases and modest in only one (50%).

A drawback of our four-component methodology is that no coupling product stemming from aniline as a reagent was detected. This result may be attributed to steric hindrance provided by the phenyl group. Thus, our protocol is effective, however, with benzyl amine (entries 1, 9, 11, and 12 in Table 4).



Scheme 2. Synthesis of **3**.

2.3. Heterogeneously catalyzed Michael reactions

We reported the synthesis of the triflate salt of a polymer-bound azaphosphatrane several years ago[21] and we synthesized **3** by an analogous route (Scheme 2). Our conditions for the nitrate-catalyzed Michael additions are mild (Tables 5 and 6). It is seen in Table 5 that electron neutral (entries 1 and 2) and electron rich anilines (entries 3 and 4) react readily with methyl vinyl ketone, but higher temperatures are sometimes needed for sterically hindered or electron rich anilines (Table 5, entries 2–4). Aliphatic amines also react with various Michael acceptors (Table 5, entries 5–9) providing the desired products in very good to excellent yields. 1-Aminonaphthalene, on the other hand, required a reaction temperature of 60 °C to afford a product yield (Table 5, entry 10) comparable to other products in this table. The same reaction at room temperature produced only a 30% yield. Benzylic amines (Table 5 entries 11 and 12) also react cleanly to give the desired products in excellent yields.

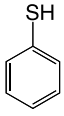
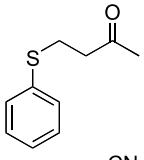
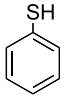
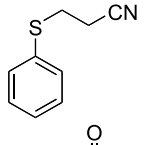
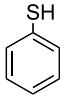
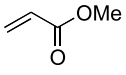
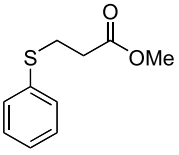
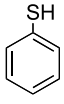
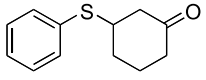
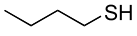
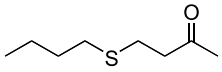
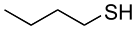
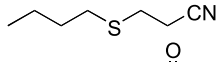
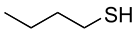
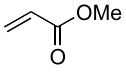
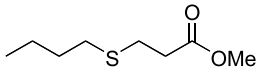
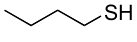
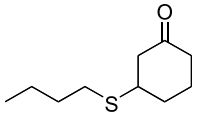
Upon extending our protocol to thiols, excellent yields of products were found in all cases (Table 6). It should also be noted that no electrophilic substitution was observed when an aromatic thiol was employed as the Michael donor (Table 6, entries 1–4).

Workup is simplified in many cases because column chromatography can be avoided. In cases where there are no aromatic groups on the amine, the polymeric catalyst is filtered from the reaction mixture, and washed well to remove any remaining traces of products and starting materials. After removal of the volatile compounds and solvent on a vacuum line, the desired products are NMR pure.

2.4. Heterogeneously catalyzed Strecker reactions

Results of the Strecker-type reactions promoted by **3** are

Table 6. Room temperature thia-Michael reactions promoted by **3**

Entry[a]	Donor	Acceptor	Product	Yield (%)
1				99
2				99
3				99
4				99
5				99
6				99
7				99
8				99

[a] Conditions: thiol (1.5 mmol), acceptor (1.9 mmol), **3** (10 mol%) and CH_3CN (2 mL). Reactions were run for 48 h at room temperature.

Table 7. Room temperature preparation of α-aminonitriles using **3** as a promoter

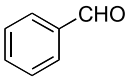
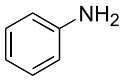
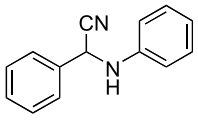
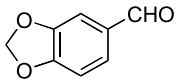
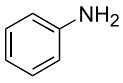
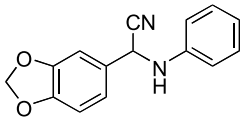
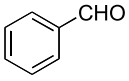
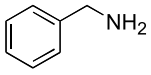
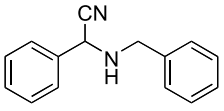
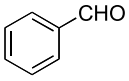
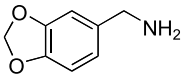
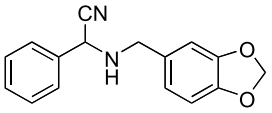
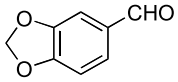
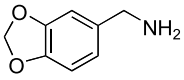
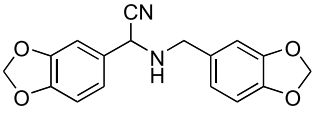
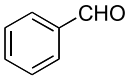
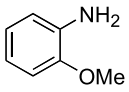
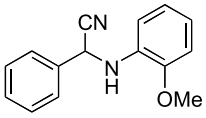
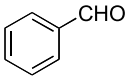
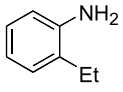
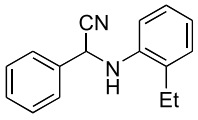
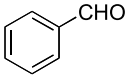
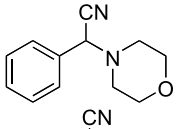
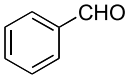
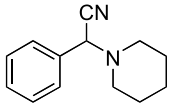
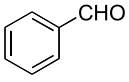
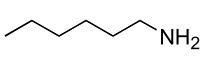
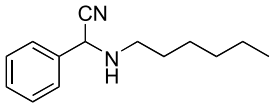
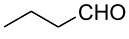
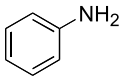
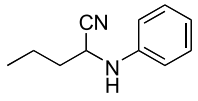
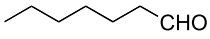
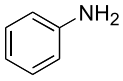
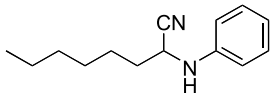
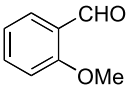
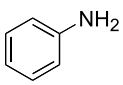
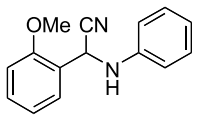
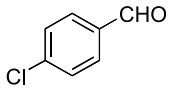
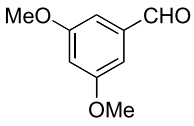
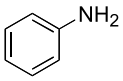
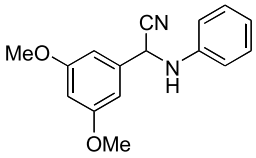
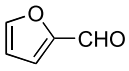
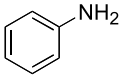
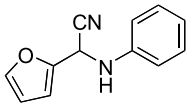
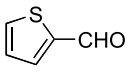
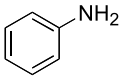
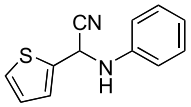
Entry[a]	Aldehyde	Amine	Product	Time	Yield (%)
1				12	99
2				15	99
3				12	99
4				8	99
5				12	99
6				15	99
7				15	99
8				8	99
9				15	99
10				15	99
11				25	90
12				25	90
13				12	99
14				15	99
15				15	97

Table 7 (*continued*)

Entry[a]	Aldehyde	Amine	Product	Time	Yield (%)
16				25	89
17				15	95
18				20	99

[a] Conditions: aldehyde or ketone (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), **3** (20 mol%) and CH_3CN (2 mL).

summarized in Table 7. The isolated yields are seen to be excellent in all cases, and both aromatic and aliphatic amines react well. The same cannot be said for aromatic and aliphatic aldehydes. While aromatic aldehydes were willing participants in the reaction, the reactions with aliphatic aldehydes proved sluggish (Table 7 entries 11 and 12). Moreover, the yields in these reactions, while impressive, are slightly lower than those achieved with the various benzaldehydes tested.

Because we observed excellent results for the synthesis of Reissert compounds homogeneously promoted by **1b** (Table 4) we decided to extend that work with the utilization of the heterogeneous catalyst **3**, the results of which are contained in Table 8. Benzaldehyde willingly participated in this reaction, giving products with various amines in 80–90% yield (Table 8, entries 1–5). Other functionalized benzaldehdyes gave products in varying yields (Table 8, entries 6–12). It is not clear why low product yields were obtained in a few cases (Table 8, entries 8 and 12). Heterocycles gave the desired coupling products in modest to good yield (Table 8, entries 13–14).

2.5. Catalyst re-usability

The re-usability of polymer-bound nitrate salt **3** was evaluated in the Michael addition of aniline to methyl vinyl ketone as a model system. We found that when precautions were taken to avoid moisture, polymer **3** can be recycled up to 20 times without loss of activity. However, when water (1 equiv based on the amine) was added, the amount of desired product isolated decreased sharply after four cycles. It is likely that hydroxide ion formed in the reaction of the amine with the water allows nitrate ion to be exchanged from the cationic polymer resin into the reaction solution. The catalytic activity of **3** is easily recovered, however, by washing the nitrate-depleted resin with aqueous sodium nitrate.

Furthermore, we found that resin bound azaphosphatrane nitrate catalyst **3** can be recycled 20 times with no loss of catalytic activity in the three component coupling of purified benzaldehyde, aniline, and trimethylsilylcyanide. However, when the benzaldehyde and aniline were taken from previously opened bottles exposed to air, the resin recycled only 11 times. The 12th reaction required twice as much time to achieve a similar yield as the previous 11 uses of the catalyst. The 13th cycle failed to give any product after 24 h. The catalyst can be reactivated, however, upon treatment with 3 M aqueous sodium nitrate. The reactivated catalyst behaved identically to a freshly prepared sample.

When we tested the re-usability of polymer-bound promoter **3** a second time in the four-component coupling reaction of benzaldehyde, benzylamine, TMSCN, and acetic anhydride the isolated product yield dropped from 90 to 73%. We conjectured that the water and acetate ion side products in the reaction displaced nitrate ion from **3**, thereby decreasing its effectiveness in the reaction. These problems were easily overcome by a simple washing of the polymer with aqueous sodium nitrate. The regenerated polymer then behaved identically to a fresh sample in the reaction.

2.6. Mechanistic considerations

Representative reactions chosen from Tables 1 and 2, when carried out under the same conditions in the absence of catalyst **1b**, either produced no detectable amount of product or gave substantially lower product yields. To compare the efficacy of **1b** with $Bi(NO_3)_3$, we also carried out the reaction in entry 1 of Table 1 with the latter salt, albeit with only 3.3 mol% in order to maintain 10 mol% of nitrate ion concentration in the reaction mixture. The product yield in that reaction (80%) was close to the 78% yield realized with **1b**. This result suggests (a) that the bismuth ion is not active as a catalyst whereas nitrate is, (b) that the bismuth ion is as active as naked nitrate (and that the nitrate is completely inactivated owing to anion–cation interactions), or (c) that the situation is somewhere between these two extremes (a more likely scenario in our view).

We have also performed a competition experiment between aniline and benzylamine, which showed that the nucleophilicity of the amine plays an important role in this reaction. Here, we observed that methyl acrylate reacted selectively with benzylamine to give the desired product in nearly quantitative yield while aniline was recovered unreacted.

To investigate whether or not the P– and N– bonds in **1b**

Table 8. Room temperature preparation of α-amidonitriles using **3** as a promoter and acetic anhydride as the acetylating reagent

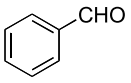
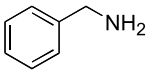
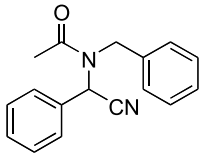
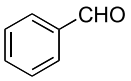
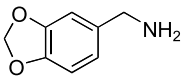
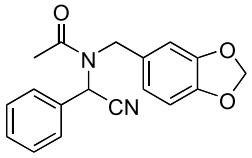
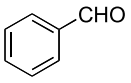
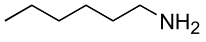
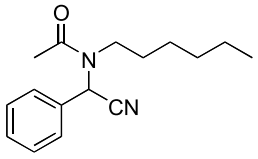
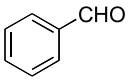
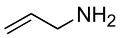
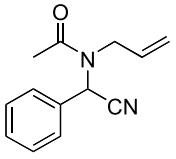
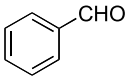
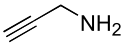
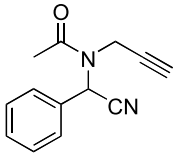
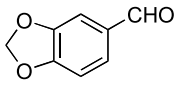
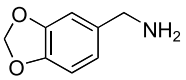
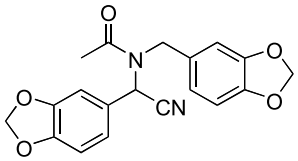
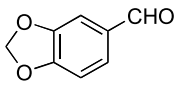
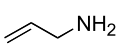
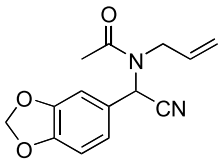
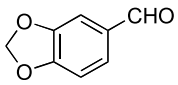
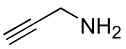
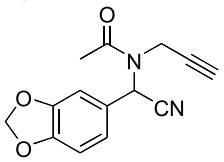
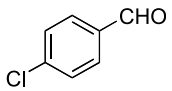
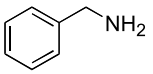
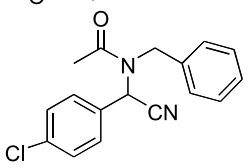
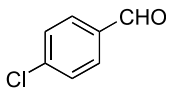
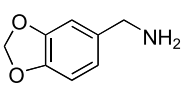
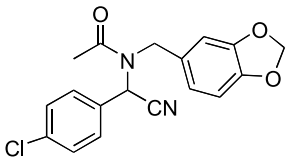
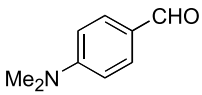
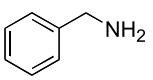
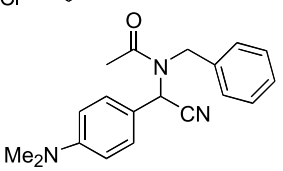
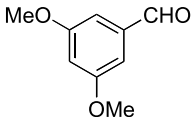
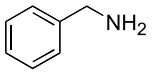
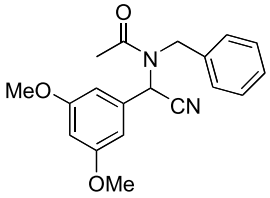
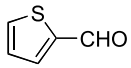
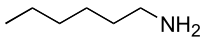
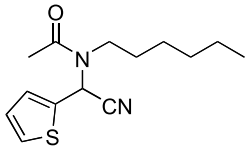
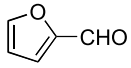
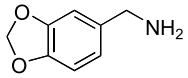
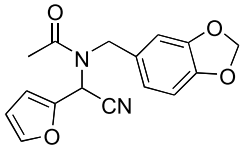
Entry[a]	Aldehyde	Amine	Product	Time (h)	Yield (%)
1				25	90
2				25	90
3				25	89
4				30	80
5				35	80
6				25	60
7				35	71
8				35	29
9				25	90
10				25	90
11				30	80

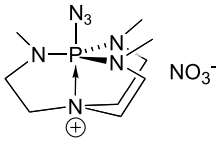
Table 8 (*continued*)

Entry[a]	Aldehyde	Amine	Product	Time (h)	Yield (%)
12				25	29
13				25	47
14				30	80

[a] Conditions: aldehyde (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), $(CH_3CO)_2O$ (3.0 mmol), **3** (30 mol%) and CH_3CN (2 mL).

play a role in the reaction, we utilized nitrate salt **4**.[30] This salt behaved identically when used in place of **1b** in the Michael addition of aniline to methyl vinyl ketone. Since **4** contains no groups that might be deprotonated to produce nitric acid in situ, we can rule out dissociation of **1b** in solution to produce an active catalytic species.

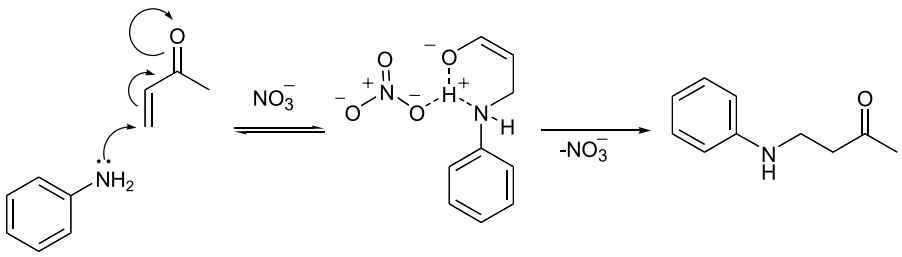
The results taken in toto prompt us to propose the mechanism in Scheme 3. Initially, the amine adds to the electron deficient carbon atom of the Michael acceptor and nitrate ion in this case acts as a 'proton shuttle', utilizing hydrogen bonding to facilitate transfer of the proton from nitrogen to oxygen.



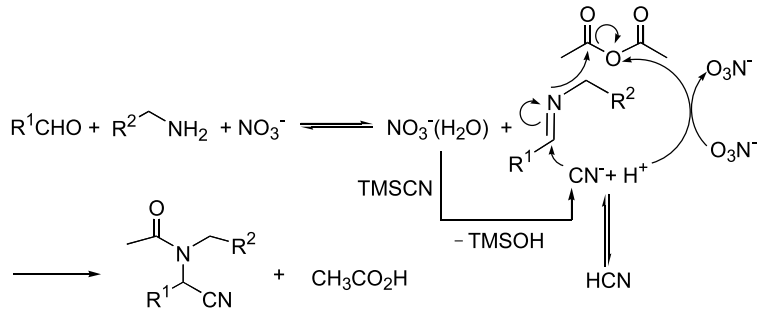
4

In order to gain an idea regarding how the three-component reactions described here are accelerated by **1b**, a mixture of benzaldehyde (0.1 mmol) and aniline (0.1 mmol) in CD_3CN (0.7 mL) was monitored by ^1H NMR spectroscopy for a period of 12 h at room temperature with and without 20 mol% of **1b** present. It was found that imine formation is 14 times faster in the presence of **1b** than in its absence. The same monitoring experiment was carried out for the reaction of TMSCN (0.100 mmol, 13.3 μL) with H_2O (0.100 mmol, 1.80 μL) in CD_3CN (0.7 mL) in the absence and presence of **1b** (20 mol%). Here, we observed that the peak position of TMSCN disappeared too quickly compared with product resonances, thus precluding a conclusion. However, when a solution of *N*-benzylidene aniline (1 mmol), TMSCN (1.2 mmol) and 20 mol% of **1b** in 3 mL of acetonitrile was stirred at room temperature for 12 h, a 94% yield of the expected product was obtained. When the same reaction was carried out in the absence of promoter, a 50% yield of the product was obtained. From these experiments it is clear that **1b** promoted both imine formation and cyanide addition.

Other nitrate ion sources (20 mol%) were also tested in a model reaction of benzaldehyde, aniline, and TMSCN. Both sodium nitrate and 1,1,3,3-tetramethylguanidinium nitrate were ineffective, a result that can be attributed to the observed incomplete solution of these salts. When 15-crown-5 was added to the sodium nitrate, an 89% yield of the desired product was isolated, suggesting that effective inhibition of anion–cation interactions is important. The somewhat higher yield (94% in entry 1 of Table 3) indicates that this inhibition is somewhat stronger for **1b**. CAN proved to be completely ineffective, giving a large number



Scheme 3. Proposed mechanism of nitrate-catalyzed aza and thia-Michael reactions.



Scheme 4. Proposed mechanism of four-component coupling reactions catalyzed by **1b**.

of spots on TLC. Tetrabutylammonium nitrate was only mildly efficacious, permitting isolation of a 49% yield of product.

On the basis of the foregoing observations, we suggest that the nitrate ion acts as a proton shuttle in these transformations (Scheme 4) and that the nitrate ion is rendered quite 'naked' by delocalization of the positive charge among the four nitrogens and the phosphorus atom in the cation of **1b**. It may be noted that this cation is relatively modest in size compared with a $[Na(15\text{-crown-}5)]^+$ or a $[NBu_4]^+$ species, for example.

3. Conclusion

We have developed a novel and efficient azaphosphatrane nitrate catalyst that operates at room temperature in nearly all cases for not only aza and thia-Michael reactions, but also for Strecker and four-component coupling reactions. When bound to a solid support, this catalyst shows excellent catalytic activity at room temperature in the above reactions, and it is also recyclable. Investigations are currently underway of the catalytic activity of other anions that behave as strong bases in non-aqueous solvents[31] and which are rendered 'naked' by cations of the phosphatrane type.

4. Experimental

4.1. General considerations

All reactions were conducted under argon. All solvents were collected from a Grubbs-type two column solvent purification system and kept under 4 Å molecular sieves. NMR spectrometers employed were a Varian VXR-300 for ^1H and ^{13}C spectra and a Varian VXR-400 for ^{31}P spectra. Standards for the NMR spectra were TMS (^1H, internal), 85% H_3PO_4 (^{31}P, external). High-resolution mass spectra were recorded on a KRATOS MS-50 spectrometer. Silica gel (Baker, 40–140 mesh) was used for column chromatography. All chemicals were purchased from Aldrich or Fisher.

4.2. Preparation of 1b

HMPT (10 mmol) was added to an ice-cold acetonitrile (25 mL) solution of tris(2-aminoethyl)amine (10 mmol) under argon and the mixture was stirred at room temperature for 30 min. A solution of HNO_3 [concd HNO_3 (69%) 12 mmol] in acetonitrile (5 mL) was slowly added to the reaction mixture and the byproduct Me_2NH was allowed to escape while stirring at room temperature for 15 h. The solvent was distilled under vacuum and the residue was washed with ether and dried under vacuum to afford the solid product.

4.3. Preparation of 1e and 1g

To a stirred solution of $P(MeNCH_2CH_2)_3N$ or $P(i\text{-}BuNCH_2CH_2)_3N$ (1 mmol) in acetonitrile (5 mL) was added HNO_3 [concd HNO_3 (69%) 1.5 mmol, 0.1 mL] drop wise very slowly. After stirring the solution at room temperature for 6 h, the solvent was removed under vacuum and the residue was washed with hexane and then ether. The residue was dried under vacuum to afford the solid product in 95% (**1e**) and 94% (**1g**) yields, respectively.

4.4. General procedure for aza and thia-Michael reactions promoted by 1b

To a stirred acetonitrile (3 mL) solution of **1b** (10 mol%) was added an amine or thiol (2 mmol) followed by stirring at room temperature under argon. An acceptor (2.5 mmol) was added to the reaction mixture followed by stirring at room temperature for 20–50 h (see Tables 1 and 2). The solvent was evaporated to dryness and the product was purified by chromatography over silica gel using 5% ether-in-hexane for Table 2, entries 1 and 3; 10% ether-in-hexane for Table 2, entries 2 and 4–8; 20% ether-in-hexane for Table 1, entries 1, 2, 5, and; 50% ether-in-hexane for Table 1, entries 3 and 4; and ether for Table 1, entries 6–10, 12, and 13 as eluent. ^1H and/or ^{13}C NMR data are reported for known compounds in the literature references and our corresponding data compared well.

4.5. General procedure for the synthesis of α-amino-nitriles promoted by 1b

A mixture of **1a** (20 mol%), aldehyde (1.0 mmol), amine (1.0 mmol), and trimethylsilyl cyanide (1.2 mmol) was stirred in acetonitrile (3 mL) under argon at room temperature for 8–25 h. The solvent was evaporated to dryness and the product was purified by silica gel column chromatography using 5% ether-in-hexane for Table 3 entries 1, 2, 6, 7, 9–12, 14, and 19; 10% ether-in-hexane for Table 2, entries 3, 4, 13, and 15–18; 20% ether-in-hexane for Table 2, entry 5; and 25% ether-in-hexane for Table 2,

entry 8 as eluents. ^{1}H and/or ^{13}C NMR data are reported for known compounds in the literature references and our corresponding data compared well.

4.6. General procedure for the synthesis of α-amido-nitriles promoted by 1b

A mixture of **1a** (30 mol%), aldehyde (1.0 mmol), amine (1.0 mmol), trimethylsilyl cyanide (1.2 mmol), and acetic anhydride (2.0 mmol) in acetonitrile (3 mL) was stirred under argon at room temperature for 25–35 h. The reaction mixture was evaporated to dryness and the product was purified by column chromatography over silica gel using 50% ether-in-hexane for Table 2 entries 1–5, and 7–14 and ether for Table 3, entry 6 as eluent.

4.7. General procedure for Michael addition promoted by 3

The Michael donor (1.5 mmol) the acceptor (2.25 mmol) and acetonitrile (2 mL) were combined and then the mixture was added to **3** whose catalyst capacity was calculated from the phosphorus elemental analysis (1.98 mmol/g). The weight of **3** used was 106 mg (10 mol% based on the Michael donor). The reaction mixture was stirred and after the conditions in the Tables 5 and 6 had been met, the polymer was filtered off and washed with ~10 mL of acetonitrile. The solvent and volatiles were then removed from the acetonitrile solution under reduced pressure (~40 μmHg). Products were then subjected to column chromatography on silica gel where necessary to give the pure compound.

For the re-use of **3**, the procedure in the previous paragraph was followed for an aniline/MVK/**3** mixture, which was stirred for 24 h at room temperature. Stirring was then stopped, the solution was allowed to settle and then the supernatant was decanted by cannula and the polymer was washed with ~10 mL of acetonitrile. Another aniline/MVK mixture was then cannulated into the polymer catalyst and the procedure repeated.

4.8. General procedure for the Strecker-type reaction promoted by 3

The catalyst (20 mol% based on the aldehyde and amine) was weighed into a 10 mL round bottomed flask. The aldehyde (1.5 mmol), amine (1.5 mmol), and TMSCN (1.8 mmol) were premixed in acetonitrile (2 mL) and cannulated into the flask containing the catalyst. The reaction was then stirred magnetically at room temperature until the conditions in Table 7 had been met. The catalyst was then filtered off and washed with ~10 mL of acetonitrile. The product was purified by a short path silica gel column using mixtures of 5–25% ether in hexane as the eluent. Exact solvent mixtures are given in Section 4.5.

For the re-use of **3**, the procedure for the experiment in the previous paragraph was followed. After the reaction time indicated in Table 7 for a benzaldehyde/aniline/TMSCN reaction mixture, stirring was stopped and the polymer was allowed to settle. The supernatant was then carefully cannulated off, and a new mixture of starting materials was cannulated in. The experiment was then repeated. The product was purified as described in the preceding paragraph.

4.9. General procedure for four component coupling promoted by 3

The catalyst (30 mol% based on the aldehyde and amine) was weighed into a 10 mL round bottomed flask. The aldehyde (1.5 mmol), amine (1.5 mmol), TMSCN (1.8 mmol), and acetic anhydride (3.0 mmol) were pre-mixed in acetonitrile (2 mL) and cannulated into the flask with the catalyst. The reaction was then stirred magnetically at room temperature until the conditions in Table 8 had been met. The catalyst was then filtered off and washed with ~10 mL of acetonitrile. The product was then purified by a short path silica gel column using solvent mixtures given in Section 4.6.

For the re-use of **3**, the procedure in the previous paragraph was followed. After the reaction time indicated in Table 7 for a benzaldehyde/aniline/TMSCN/acetic anhydride reaction mixture, stirring was stopped and the polymer was allowed to settle. The supernatant was then carefully cannulated off, and a new mixture of starting materials was cannulated in. The experiment was then repeated. The product was purified as described in the previous paragraph.

4.10. Reactivation of 3

Samples of used **3** from previous experiments (approximately 500 mg) were combined into a 100 mL flask followed by the addition of 30 mL of a 3 M aqueous sodium nitrate solution. The suspension was stirred for 2 h at room temperature and filtered. The polymer was washed with water, 3 M sodium nitrate, water, methanol, THF, and ether (~20 mL each). The polymer was then dried under reduced pressure at room temperature for 24 h.

Acknowledgements

We thank the National Science Foundation for a grant that supported this research, Aldrich for generous gifts of research samples, and Professor George Kraus for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.117.

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Tetrahedron 62 (2006) 457–460

Phosphine-catalyzed one-pot synthesis of cyclopentenes from electron-deficient allene, malononitrile and aromatic aldehydes

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Received 30 May 2005; revised 24 August 2005; accepted 9 September 2005

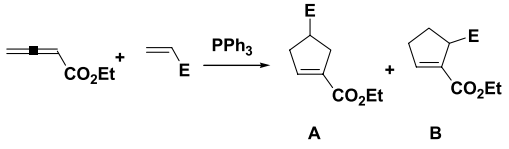
Available online 12 October 2005

Abstract—A three component reaction of aryl aldehydes and malononitrile with ethyl 2,3-butadienoate catalyzed by triphenylphosphine has been developed. The reaction furnishes highly functionalized cyclopentenes in moderate to good yields in a one-pot process.

1. Introduction

The efficient synthesis of highly functionalized cyclopentenes is a challenging area in methodological studies.[1] Among them, the [3+2] annulation reaction attracts the chemists' interest mostly due to its advantage of forming several bonds in a single operation. To our knowledge, there are many kinds of [3+2] annulation reactions: for example, transition metal catalyzed,[2] anionic,[3] cationic,[4] and free radical mediated.[5] Our group first reported that tertiary phosphines can catalyze the [3+2] annulation reaction between electron-deficient olefins and 2,3-butadinenoate.[6] Many annulation reactions using tertiary phosphines as catalysts were reported recently.[7]

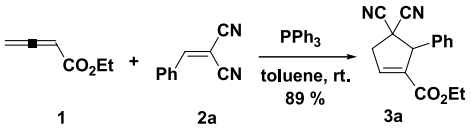
While the annulation reactions using tertiary phosphines as catalysts are well developed, as far as we know, only terminal alkenes can be used in the phosphine catalyzed [3+2] reaction except those for the intramolecular annulation reaction (or dual activated olefin such as diethyl fumarate or diethyl maleate). Also, a pair of regioisomers (Scheme 1, the ratio of **A** to **B** is 80 to 20) were produced in almost every case.[6b] Here, we wish to report our recent results of the reaction of β-substituted olefins in the phosphine catalyzed [3+2] reaction leading to cyclopentene derivatives regioselectively and the development of a one-pot variant.



Scheme 1.

2. Results and discussion

In order to increase the reactivity of the olefin, β-substituted olefins with two electron-withdrawing groups at the α-olefin carbon atom were used to test its reactivity. The reaction of ethyl 2,3-butadienoate (**1**) and 2-benzylidenemalononitrile (**2**) were first examined in the presence of triphenylphosphine in toluene at room temperature. Fortunately, in contrast to the reaction of the terminal olefins,[6b] the reaction is highly regioselective yielding only one cyclopentene derivative as the product in high yield (Scheme 2).



Scheme 2.

With this successful result in hand, we were encouraged to modify the reaction to make it more convenient. It was reported that compound **2a** can be synthesized in the presence of 20 mol% of triphenylphosphine (Scheme 3).[8] It occurred to us that a three component reaction in one-pot might be possible if benzaldehyde, malononitrile and ethyl

Keywords: Phosphine; Cyclopentenes; Malononitrile; Aromatic aldehydes; Electron-deficient allene.
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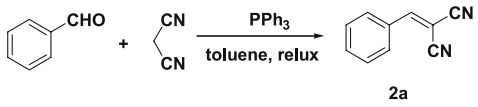
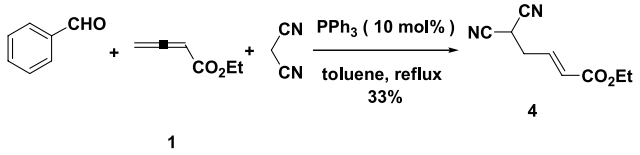
doi:10.1016/j.tet.2005.09.100



Scheme 3.

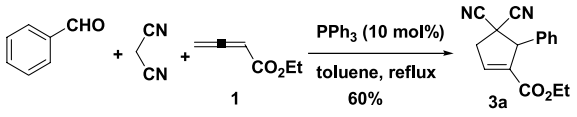
2,3-butadienoate were reacted together in the presence of triphenylphosphine.

When benzaldehyde, malononitrile and ethyl 2,3-butadienoate were heated with 10 mol% of triphenylphosphine in toluene under reflux, (*E*)-ethyl 5,5-dicyanopent-2-enoate (**4**), which may result from the γ-addition of the malononitrile to the ethyl 2,3-butadienoate,[9] was isolated in 33% yield (Scheme 4). It implies that the γ-addition of the malononitrile to the 2,3-butadienoate is faster than that of the condensation of the benzaldehyde and the malononitrile.



Scheme 4.

Now, the difficulty facing us is how to suppress the γ-addition reaction thus making the condensation reaction between the benzaldehyde and the malononitrile to occur first. It was suggested that the condensation reaction between the benzaldehyde and the malononitrile may occur first if a low concentration of 2,3-butandienoate (**1**) was used. Thus, we tried the reaction by heating under reflux benzaldehyde and malononitrile in the presence of triphenylphosphine in toluene first, followed by adding 2,3-butandienoate with a syringe pump over a period of 3 h. To our delight, the expected three component coupling product **3a** was obtained in 60% yield (Scheme 5).

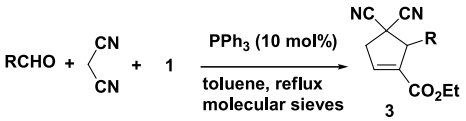


Scheme 5.

Although the result is inspiring, the yield is lower than that from the direct reaction of compounds **1** and **2a**. Considering that an equivalent of water formed during the condensation reaction might represent the drawback of the reaction, the reaction was tried in the presence of molecular sieves. To our surprise, the yield of the reaction increased from 60 to 86%. This result is as good as that of the reaction employing compounds **1** and **2a**. With this result in hand, other aldehydes were studied as shown in Table 1.

All the aromatic aldehydes reacted smoothly under these conditions with good yields (Table 1, entries 1–8). Unfortunately, this reaction cannot be used for aliphatic aldehydes. When butyraldehyde was employed, no [3+2] product was detected (Table 1, entry 9).

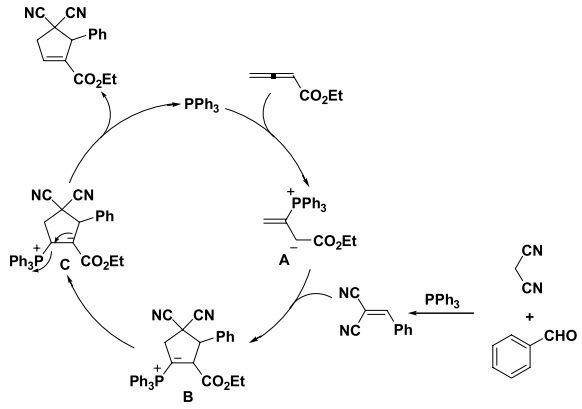
Table 1. The reaction of various aldehydes in the triphenylphosphine catalysed one-pot annulation reaction[a]



Entry	R	Product	Yield(%)[b]
1	Ph	**3a**	86
2	*p*-$MeOC_6H_4$	**3b**	56
3	*p*-FC_6H_4	**3c**	76
4	*p*-ClC_6H_4	**3d**	78
5	α-Naphthyl	**3e**	69
6	2-Pyridyl	**3f**	53
7	2-Furyl	**3g**	74
8	Cinnamyl	**3h**	26
9	*n*-Propyl	—	—

[a] Malononitrile (1 mmol) and aldehyde (1.2 mmol) were heated under reflux in toluene in the presence of triphenylphosphine and 3 Å molecular sieves for 10 min, then compound **1** (1 mmol, 1 M toluene solution) was added via a syringe pump over a period of 3 h.
[b] Isolated yields.

A possible mechanism for this one-pot catalytic reaction is shown in Scheme 6. First, nucleophilic attack of triphenylphosphine to the β-position of ethyl 2,3-butadienoate yields a dipolar intermediate **A**. Nucleophilic attack of the dipolar intermediate **A** to the 2-benzylidenemalononitrile, which was formed in the reaction condition followed by an intramolecular conjugate addition to give ylide intermediate **B**. After a proton transfer to form **C**, elimination of triphenylphosphine occurs to complete the catalytic cycle.



Scheme 6. Mechanism of the reaction.

In summary, we found that 2-benzylidenemalononitrile could react with ethyl 2,3-butadienoate in the presence of catalytic triphenylphosphine to yield cyclopentene derivatives with high regioselectivity. Based on this discovery, a one-pot reaction of three components (aryl aldehyde, malononitrile and 2,3-butadienoate) under the catalysis of triphenylphosphine was developed to yield cyclopentene derivatives with high yield and regioselectivity.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were obtained on a Varian

EM-360 at 300 and 75 MHz, respectively. The mass spectra were run using a Hewlett–Packard MS-Engine 5989A instrument. Infrared spectra were recorded on a Bio-Rad FTS-185 machine. 2-Benzylidenemalononitrile was prepared according to literature.[8]

3.2. Reaction of 2-benzylidenemalononitrile with ethyl 2,3-butadienoate

Ethyl 2,3-butadienoate (25 mg, 0.22 mmol) and 2-benzylidenemalononitrile in toluene (2 mL) was stirred in the presence of triphenylphosphine (5 mg, 0.02 mmol) at 15 °C. The reaction was monitored by TLC. The mixture was subjected to column chromatography on silica gel (ethyl acetate/petroleum ether=1:4) to give **3a** as an oil (53 mg, yield 89%). IR (KBr): ν 2990, 2251, 1715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.42–7.39 (m, 3H), 7.23–7.20 (m, 2H), 6.99–6.97 (m, 1H), 4.80 (d, J=0.9 Hz, 1H), 4.14–4.10 (m, 2H), 3.42–3.40 (m, 2H), 1.15 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.92, 138.06, 137.11, 133.10, 129.32, 129.15, 127.74, 116.48, 113.29, 61.10, 59.90, 43.42, 39.96, 13.78. MS (EI) *m/z*: 266 (M^+), 221, 115 (100). HRMS (ESI) *m/z*: Calcd for $C_{16}H_{14}N_2O_2Na^+$ $[M+Na]^+$: 289.0953. Found: 289.0930.

3.3. One-pot reaction in the absence of molecular sieves

3.3.1. One-pot reaction without syringe pump. To a stirred refluxing solution of malononitrile (44 mg, 0.67 mmol) and triphenylphosphine (18 mg, 0.068 mmol) in toluene (0.5 mL) under argon was added ethyl 2,3-butadienoate (68 mg, 0.61 mmol) and benzaldehyde (78 mg, 0.73 mmol) in toluene (1.5 mL). After the solution had been stirred for 3 h, the mixture was subjected to column chromatography on silica gel (ethyl acetate/petroleum ether=1:5) to give (*E*)-ethyl 5,5-dicyanopent-2-enoate (**4**) as an oil (36 mg, yield 33%). IR (KBr): ν 2987, 2918, 2260, 1719, 1663 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.86 (dt, J=15.6, 7.2 Hz, 1H), 6.24 (q, J=7.2 Hz, 2H), 6.12 (dt, J=15.6, 1.2 Hz, 1H), 3.92 (t, J=6.6 Hz, 1H), 2.92 (td, J=7.2, 1.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 164.84, 137.09, 127.85, 111.57, 61.01, 32.88, 22.06, 14.10. MS (EI) *m/z*: 179 (M^++H), 133 (100), 68. Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.29; H, 5.63; N, 16.11.

3.3.2. One-pot reaction with syringe pump. A stirred solution of malononitrile (90 mg, 1.36 mmol) and benzaldehyde (120 mg, 1.13 mmol) with triphenylphosphine (36 mg, 0.14 mmol) in toluene (1.5 mL) was heated under reflux for 10 min. Then ethyl 2,3-butadienoate (158 mg, 1.41 mmol) was added as a 1 M toluene solution during 3 h with a syringe pump. The mixture was allowed to stir under reflux for an additional hour before it was subjected to column chromatography on silica gel (ethyl acetate/petroleum ether=1:4). Compound **3a** was obtained as an oil (226 mg, yield 60%).

3.4. One-pot reaction in the presence of molecular sieve

3.4.1. Typical procedure for the synthesis of ethyl 4,4-dicyano-5-phenyl-cyclopent-1-enecarboxylate (3a) using the one-pot reaction of malononitrile, benzaldehyde and 2,3-butadienoate. Malononitrile (65 mg, 0.98 mmol), benzaldehyde (120 mg, 1.13 mmol) and triphenylphosphine (27 mg, 0.10 mmol) were heated under reflux in 2 ml of toluene in the presence of 3 Å molecular sieves (427 mg) for 10 min. Ethyl 2,3-butadienoate (114 mg, 1.02 mmol) was added in as a 1 M toluene solution during 3 h with a syringe pump. Then the mixture was allowed to stir under reflux for an additional hour. The reaction mixture was subjected to column chromatography on silica gel (ethyl acetate/petroleum ether=1:4) to give **3a** as an oil (225 mg, yield 86%).

3.4.2. Ethyl 4,4-dicyano-5-(*p*-methoxylphenyl)-cyclopent-1-enecarboxylate (3b). Yield: 56%; oil. IR (KBr): ν 2984, 2253, 1717 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.14 (d, J=9.0 Hz, 2H), 6.99–6.90 (m, 3H), 4.77 (s, 1H), 4.16–4.08 (m, 2H), 3.80 (s, 3H), 3.39–3.37 (m, 2H), 1.47 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.04, 160.16, 137.63, 137.39, 128.96, 125.49, 116.61, 114.52, 113.44, 61.16, 59.38, 55.16, 43.27, 40.09, 13.88. MS (EI) *m/z*: 296 (M^+), 250, 145 (100). HRMS (ESI) *m/z*: Calcd for $C_{17}H_{16}N_2O_3Na^+$ $[M+Na]^+$: 319.1059. Found: 319.1040.

3.4.3. Ethyl 4,4-dicyano-5-(*p*-flurophenyl)-cyclopent-1-enecarboxylate (3c). Yield: 76%; oil. IR (KBr): ν 2986, 2252, 1719 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.24–7.17 (m, 2H), 7.14–7.09 (m, 2H), 6.99–6.97 (m, 1H), 4.80 (s, 1H), 4.19–4.10 (m, 2H), 3.42–3.40 (m, 2H), 1.17 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 164.66, 161.81, 138.23, 136.96, 129.66, 129.55, 116.36, 116.27, 116.07, 113.26, 61.19, 59.14, 43.30, 39.90, 13.77. MS (EI) *m/z*: 284 (M^+), 238, 133 (100). Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.53; H, 4.60; N, 9.83.

3.4.4. Ethyl 4,4-dicyano-5-(*p*-chlorophenyl)-cyclopent-1-enecarboxylate (3d). Yield: 78%; oil. IR (KBr): ν 2985, 1718 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H), 7.00–6.98 (m, 1H), 4.78 (d, J=0.9 Hz, 1H), 4.19–4.07 (m, 2H), 3.41–3.39 (m, 2H), 1.17 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.84, 138.38, 136.99, 135.49, 132.28, 129.56, 129.19, 116.24, 113.21, 61.41, 59.35, 43.54, 39.90, 13.92. MS (EI) *m/z*: 300 (M^+), 254, 84 (100). HRMS (ESI) *m/z*: Calcd for $C_{16}H_{14}N_2O_2Cl^+$ $[M+H]^+$: 301.0744. Found: 301.0740.

3.4.5. Ethyl 4,4-dicyano-5-(α-naphthyl)-cyclopent-1-enecarboxylate (3e). Yield: 69%; oil. IR (KBr): ν 3079, 2986, 2253, 1711 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.16 (d, J=8.7 Hz, 1H), 7.93 (d, J=8.7 Hz, 1H), 7.89 (d, J=8.7 Hz, 1H), 7.69 (dt, J=7.5, 1.2 Hz, 1H), 7.58 (t, J=7.5 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.19 (d, J=7.5 Hz, 1H), 7.10–7.07 (m, 1H), 5.72 (s, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.56–3.39 (m, 2H), 1.07 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.01, 138.39, 137.21, 134.18, 131.58, 130.13, 129.84, 129.24, 127.33, 126.38, 125.01, 124.17, 122.59, 116.87, 113.24, 61.22, 54.69, 44.25, 38.94. MS (EI) *m/z*: 316 (M^+), 287, 165 (100). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.00; H, 5.07; N, 8.86.

3.4.6. Ethyl 4,4-dicyano-5-(2-pyridyl)-cyclopent-1-enecarboxylate (3f). Yield: 53%; oil. IR (KBr): ν 2986, 2253, 1719 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.66 (dd, J=4.7, 1.8 Hz, 1H), 8.30 (d, J=2.4 Hz, 1H), 7.58–7.54 (m, 1H),

7.39–7.27 (m, 1H), 7.04–7.02 (m, 1H), 4.81 (d, $J=2.1$ Hz, 1H), 4.18–4.09 (m, 2H), 3.44 (d, $J=2.1$ Hz, 2H), 1.17 (t, $J=7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.53, 150.56, 149.04, 138.86, 136.21, 135.48, 129.87, 123.76, 115.87, 113.08, 61.32, 57.48, 43.53, 39.79, 13.74. MS (EI) *m/z*: 267 (M^+), 238, 194 (100). HRMS (MALDI) *m/z*: Calcd for $C_{15}H_{14}N_3O_2^+$ $[M+H]^+$: 268.1086. Found: 268.1078.

3.4.7. Ethyl 4,4-dicyano-5-(2-furyl)-cyclopent-1-enecarboxylate (3g). Yield 74%; oil. IR (KBr): ν 2986, 2231, 2253, 1717 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.43 (t, $J=1.5$ Hz, 1H), 6.94–6.92 (m, 1H), 6.40 (d, $J=1.5$ Hz, 2H), 4.91 (s, 1H), 4.25–4.08 (m, 2H), 3.54–3.31 (m, 2H), 1.24 (t, $J=7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.58, 146.81, 143.66, 138.76, 134.59, 115.93, 112.84, 110.84, 110.12, 61.11, 53.18, 43.32, 38.41, 13.77. MS (EI) *m/z*: 256 (M^+), 210, 155 (100). HRMS (MALDI) *m/z*: Calcd for $C_{14}H_{12}N_2NaO_3^+$ $[M+Na]^+$: 279.0746. Found: 279.0750.

3.4.8. Ethyl 4,4-dicyano-5-cinnamyl-cyclopent-1-enecarboxylate (3h). Yield: 26%; oil. IR (KBr): ν 3650, 2985, 2252, 1714 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.43–7.39 (m, 2H), 7.37–7.29 (m, 3H), 6.86–6.84 (m, 1H), 6.72 (d, $J=15.6$ Hz, 1H), 6.11 (dd, $J=15.6$ Hz, 5.7 Hz, 1H), 4.36 (dd, $J=9.0$, 1.2 Hz, 1H), 4.28–4.16 (m, 2H), 3.36–3.35 (m, 2H), 1.27 (t, $J=7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.00, 137.66, 136.80, 136.59, 135.40, 128.62, 128.59, 126.86, 121.17, 116.06, 113.54, 61.23, 56.74, 42.90, 39.17, 14.02. MS (EI) *m/z*: 292 (M^+), 246, 218 (100). HRMS (EI) *m/z*: Calcd for $C_{18}H_{16}N_2O_2$ $[M]^+$: 292.1212. Found: 292.1230.

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Tetrahedron
Tetrahedron 62 (2006) 461–475

Aza-Baylis–Hillman reaction of *N*-tosylated imines with β-substituted α,β-unsaturated esters

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Received 8 May 2005; revised 25 August 2005; accepted 9 September 2005

Available online 5 October 2005

Abstract—Aza-Baylis–Hillman reaction of *N*-tosylated imines with β-substituted α,β-unsaturated esters can take place under mild reaction conditions to give the corresponding Baylis–Hillman adducts in moderate to excellent yields.

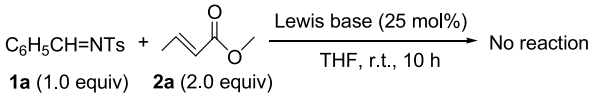
1. Introduction

The Baylis–Hillman reaction, one of the most economical and important carbon–carbon bond-forming reactions,[1] has undergone remarkable progress recently in the areas of shortening reaction time, extending the scope of the substrates, asymmetric catalysis, and mechanistic studies.[2] However, the reaction has traditionally suffered from low reaction rates and limited substrate scope, which has significantly restricted its further applications. Due to their low reactivity, β-substituted electron deficient olefins were less explored as Michael acceptors for the reaction. In the previous studies, we found that β-substituted enones or enals can react with *N*-tosylated imines in the presence of tertiary phosphine promoters.[3] It is well known that enones and enals usually have higher reactivity than α,β-unsaturated esters in the Baylis–Hillman reaction, while the products derived from α,β-unsaturated esters are more versatile in further transformations.[4] Thus, we wanted to know whether β-substituted α,β-unsaturated esters are also suitable substrates for the aza-Baylis–Hillman reaction. Herein, we wish to report the aza-Baylis–Hillman reactions of *N*-tosylated imines **1** with several β-substituted α,β-unsaturated esters under mild conditions.

2. Result and discussion

The aza-Baylis–Hillman reaction of methyl crotonate **2a** with *N*-benzylidene-4-methylbenzenesulfonamide **1a** was first examined. To our disappointment, no reaction took place at all in the presence of various Lewis bases such as the tertiary amines DABCO, DMAP, DBU, or tertiary phosphines such as PPh_3, PBu_3, PPh_2Me, $PPhMe_2$, PMe_3 in THF at room temperature for 10 h (Scheme 1).

Thus, we attempted to investigate other crotonates in the reaction. It is well-known that the addition of the phosphorus enolate to an imine is believed to be the rate-determining step for the aza-Baylis–Hillman reaction. Therefore, stabilization of the enolate species would shift the equilibrium forward to accelerate the reaction rate. In fact, Chen and co-workers have reported that structural variants of acrylates can affect the reactivity significantly. For example, phenyl acrylate or α-naphthyl acrylate has higher reactivity than methyl acrylate for the reaction with aldehydes under the same conditions.[5] Enlightened by these findings, we next utilized vinyl crotonate instead of methyl crotonate to examine whether the vinyl group could stabilize the enolate and subsequently produce the corresponding Baylis–Hillman adduct. The reaction of vinyl crotonate **2b** with *N*-benzylidene-4-methylbenzenesulfonamide **1a** was first examined as well. Indeed the reaction did take place in the presence of $PPhMe_2$, giving the corresponding aza-Baylis–Hillman adduct **3a** in 68% yield as a mixture of *E*- and *Z*-isomers (*E*/*Z* 92:8) (Table 1, entry 6). Then, the Lewis base and solvent effects were carefully examined. The results are presented in Table 1. As can be



Scheme 1.

Keywords: *N*-tosylated imine; Aza-Baylis–Hillman reaction; β-substituted activated olefins; Lewis base.
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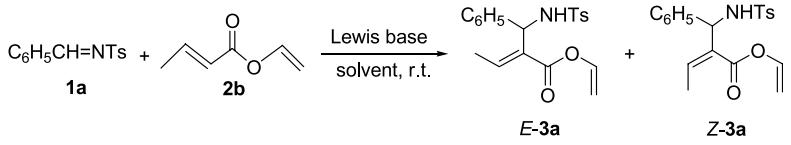
doi:10.1016/j.tet.2005.09.058

Table 1. The aza-Baylis–Hillman reaction of vinyl crotonate **2b** (2.0 equiv) with *N*-benzylidene-4-methylbenzenesulfonamide **1a** (1.0 equiv) in the presence of 25 mol% of Lewis base



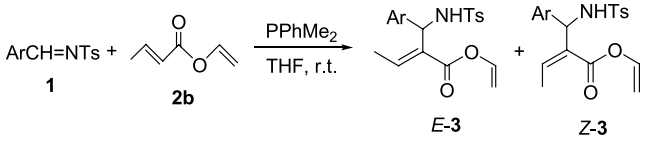
Entry	Lewis base	Solvent	Time (h)	Yield of **3a** (*E*/*Z*)[a]
1	DABCO	THF	24	—[b]
2	DMAP	THF	24	—[b]
3	DBU	THF	30	37 (88:12)
4	PPh_3	THF	24	—[b]
5	PPh_2Me	THF	24	—[b]
6	$PPhMe_2$	THF	6	68 (92:8)
7	PBu_3	THF	3	50 (81:19)
8	PMe_3	THF	4	36 (88:12)
9	$PPhMe_2$	Toluene	12	62 (90:10)
10	$PPhMe_2$	CH_3CN	5	41 (90:10)
11	$PPhMe_2$	CH_2Cl_2	7	58 (90:10)
12	$PPhMe_2$	Et_2O	6	62 (86:14)
13	$PPhMe_2$	DMF	4	Trace

[a] Isolated yields.
[b] No reaction.

seen from Table 1, the weak Lewis base catalysts (25 mol%) such as DABCO, DMAP, Ph_3P, and PPh_2Me did not show catalytic abilities for the reaction (Table 1, entries 1, 2, 4, and 5). Of the catalysts examined, $PPhMe_2$ is the best. Using $PPhMe_2$ as the catalyst, the solvent effects were screened (Table 1, entries 6 and 9–13). We found that THF was the solvent of choice.

Under the optimized reaction conditions as shown in entry 6 of Table 1, we next carried out the aza-Baylis–Hillman reaction of **2b** with several other aromatic *N*-tosylated imines **1**. The results are summarized in Table 2. As can be seen from Table 2, the substituents on the benzene ring of **1** significantly affected the reaction rates. For *N*-tosylated imines with electron-withdrawing groups on the benzene ring, the reactions were complete within 3 h to give the adduct **3** in moderate to good yields (Table 2, entries 1–5). However, for *N*-tosylated imines **1g** or **1h** bearing an electron-donating group on the benzene ring, the reaction required a prolonged reaction time to give the corresponding products in moderate yields under the same conditions (Table 2, entries 6 and 7). In all these cases, the addition products **3** were obtained as *E*/*Z* mixtures in which isomers *E*-**3** were the major products.

Table 2. The aza-Baylis–Hillman reaction of vinyl crotonate **2b** (2.0 equiv) with other *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of $PPhMe_2$



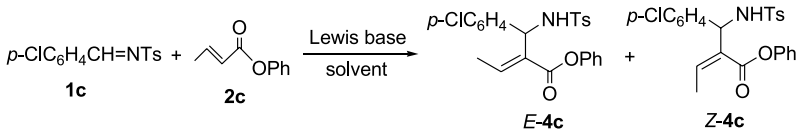
Entry	Ar	Time (h)	Yield of **3** (%) (*E*/*Z*)[a]
1	*p*-FC_6H_4 **1b**	3	**3b**, 67 (84:16)
2	*p*-ClC_6H_4 **1c**	3	**3c**, 68 (84:16)
3	*p*-BrC_6H_4 **1d**	3	**3d**, 74 (82:18)
4	*p*-$NO_2C_6H_4$ **1e**	3	**3e**, 67 (84:16)
5	*m*-$NO_2C_6H_4$ **1f**	3	**3f**, 62 (83:17)
6	*p*-MeC_6H_4 **1g**	22	**3g**, 79 (91:9)
7	*p*-$MeOC_6H_4$ **1h**	48	**3h**, 44 (73:27)

[a] Isolated yields.

Encouraged by the above good results in the aza-Baylis–Hillman reaction of vinyl crotonate with *N*-tosylated imines, we anticipated that phenyl crotonate **2c** might be a better Michael acceptor for this type of aza-Baylis–Hillman reaction. Therefore, the reaction of phenyl crotonate **2c** with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1c** was performed to screen the Lewis bases and the solvents. The results are presented in Table 3. Similarly, it was found that $PPhMe_2$ was the best catalyst and THF was the solvent of choice (Table 1, entries 1–12). The Michael acceptor of but-2-enoic acid phenyl ester **2c** is alcoholized in methanol (Table 1, entry 13). Moreover, the use of molecular sieves 4 Å (50 mg for 0.25 mmol of **1c**) as the additives to prevent the decomposition of *N*-tosylated imine **1c** due to ambient moisture did not improve the yield of **4c** (Table 3, entry 15). In addition, using hydroquinone (5 mg for 0.25 mmol of **1c**) as a radical inhibitor or carrying out the reaction at lower temperature did not result in higher yields of **4c** (Table 3, entries 16 and 17). Thus, the best reaction conditions are using $PPhMe_2$ as the catalyst in THF at room temperature. Under the optimized reaction conditions, we next carried out the aza-Baylis–Hillman reaction of **2c** with several other aromatic *N*-tosylated imines **1**. The results are summarized in Table 4. As can be seen from Table 4, the similar substituent effect on *N*-tosylated imines **1** as described above is observed for this reaction. In all these cases, the addition products **4** were obtained as *E*/*Z* mixtures in which isomers *E*-**4** were the major products. It seems to us that phenyl crotonate **2c** almost has the similar reactivities as vinyl crotonate **2b** as Michael acceptor in the reactions.

Since vinyl crotonate and phenyl crotonate were both applicable for this type of aza-Baylis–Hillman reaction, we further employed α-naphthyl crotonate to the reaction under the above optimum reaction conditions. The results are

Table 3. The aza-Baylis–Hillman reaction of phenyl crotonate **2c** (2.0 equiv) with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1c** (1.0 equiv) in the presence of 25 mol% of Lewis base



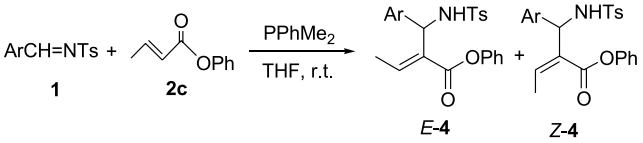
Entry	Lewis base	Temperature (°C)	Solvent	Time (h)	Yield of **4c** (*E*/*Z*)[a]
1	DABCO	rt	THF	24	—[b]
2	DMAP	rt	THF	24	—[b]
3	DBU	rt	THF	5	25 (81:19)
4	PPh_3	rt	THF	24	—[b]
5	PPh_2Me	rt	THF	24	—[b]
6	$PPhMe_2$	rt	THF	3	80 (82:18)
7	PBu_3	rt	THF	25	18 (84:16)
8	PMe_3	rt	THF	7	19 (90:10)
9	$PPhMe_2$	rt	Toluene	24	38 (87:13)
10	$PPhMe_2$	rt	CH_3CN	5	45 (80:20)
11	$PPhMe_2$	rt	CH_2Cl_2	18	63 (88:12)
12	$PPhMe_2$	rt	Et_2O	6	51 (83:17)
13	$PPhMe_2$	rt	MeOH	2	—[c]
14	$PPhMe_2$	rt	DMF	4	Trace
15[d]	$PPhMe_2$	rt	THF	5	70 (81:19)
16[e]	$PPhMe_2$	rt	THF	5	57 (81:19)
17	$PPhMe_2$	0 °C	THF	6	55 (89:11)

[a] Isolated yields.
[b] No reaction.
[c] But-2-enoic acid phenyl ester was alcoholized.
[d] Molecular sieves 4 Å was added.
[e] Hydroquinone was added.

summarized in Table 5. As can be seen from Table 5, the yields of **5** are higher than those of **3** and **4** presumably because the naphthyl group can stabilize the in situ formed enolate intermediate in Baylis–Hillman reaction better than the phenyl group or vinyl group.

On the other hand, on the basis of the above results, we expected that sulfur could be better than oxygen to stabilize the resulting enolate intermediate. To test this hypothesis, but-2-enethioic acid *S*-phenyl ester was employed as the Michael acceptor for the reaction under the above established optimum conditions. To our disappointment, the reaction led to the formation of many by-products, and the corresponding aza-Baylis–Hillman products **6** were only obtained in moderate yields as the *E*-configuration. The results are shown in Table 6. To explore the by-products formed, we performed the reaction on larger scales. We found that when *N*-tosylated imine **1d** was utilized as the substrate, one of the by-products **7d** could be recrystallized from the complicated mixture and the structure was identified by X-ray diffraction (Fig. 1).[6]

Table 4. The aza-Baylis–Hillman reaction of phenyl crotonate **2c** (2.0 equiv) with other *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of $PPhMe_2$



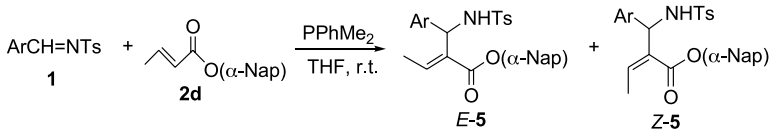
Entry	Ar	Time (h)	Yield of **4** (%) (*E*/*Z*)[a]
1	C_6H_5 **1a**	10	**4a**, 77 (74:26)
2	*p*-FC_6H_4 **1b**	7	**4b**, 49 (78:22)
3	*p*-BrC_6H_4 **1d**	7	**4d**, 58 (79:21)
4	*p*-$NO_2C_6H_4$ **1e**	4	**4e**, 57 (78:22)
5	*m*-$NO_2C_6H_4$ **1f**	5	**4f**, 77 (74:26)
6	*p*-MeC_6H_4 **1g**	22	**4g**, 72 (90:10)
7	*p*-$MeOC_6H_4$ **1h**	216	**4h**, 44 (70:30)

[a] Isolated yields.

We speculated that but-2-enethioic acid *S*-phenyl ester **2e** partially decomposed to the corresponding crotonic acid and benzenethiol (PhSH) by trace amounts of water under the reaction conditions because the Michael acceptor **2e** can be more easily hydrolyzed by ambient water than **2c** in any sense. Then, the newly formed benzenethiol underwent Michael addition to the aza-Baylis–Hillman products **6** to give **7**. Since by-products **7** have three chiral centers, there will be four diastereomers. The other diastereomers and the aza-Baylis–Hillman product with *Z*-configuration could not be isolated by flash chromatography. Therefore, at the present stage, we could not identify all of these by-products. To minimize the yields of the by-products, we reduced the amount of the Michael acceptor **2e** to 1 equiv in this reaction. Indeed higher yields of the corresponding aza-Baylis–Hillman products **6** were obtained in most cases although a prolonged reaction time was required. The results are summarized in Table 7.

In a previous paper, we proposed a mechanistic explanation for the formation of *Z*- and *E*-isomeric mixtures in the aza-Baylis–Hillman reaction of β-substituted enones or enals with *N*-tosylated imines in the presence of tertiary phosphines.[3] The formation of *Z*- and *E*-isomeric mixtures was thought to occur during the formation of the adducts. As can be seen, the stereoselectivities are not very good for these above aza-Baylis–Hillman reactions. We attempted to improve the stereoselectivities or convert the *Z*- and

Table 5. The aza-Baylis–Hillman reaction of α-naphthyl crotonate **2d** (2.0 equiv) with *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of $PPhMe_2$



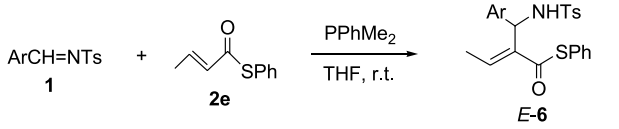
Entry	Ar	Time (h)	Yield of **5** (%) (*E*/*Z*)[a]
1	C_6H_5 **1a**	10	**5a**, 88 (87:13)
2	*p*-FC_6H_4 **1b**	5	**5b**, 78 (94:6)
3	*p*-ClC_6H_4 **1c**	5	**5c**, 91 (86:14)
4	*p*-BrC_6H_4 **1d**	4	**5d**, 85 (83:17)
5	*p*-$NO_2C_6H_4$ **1e**	2	**5e**, 78 (83:17)
6	*m*-$NO_2C_6H_4$ **1f**	2	**5f**, 63 (79:21)
7	*p*-MeC_6H_4 **1g**	23	**5g**, 75 (83:17)
8	*p*-$MeOC_6H_4$ **1h**	120	**5h**, 60 (73:27)

[a] Isolated yields.

E-isomeric mixtures to the product with only *E*-configuration. First, we wondered if the adducts could reach a *Z*- and *E*-isomeric equilibrium under the reaction conditions. To test this possibility, we added 25 mol% of $PPhMe_2$ to a THF solution of **4a** with *E*-configuration. After 10 h, **4a** was isolated in 96% yield as mixtures *E*- and *Z*-isomers (*E*/*Z* 77:23) (Scheme 2).

Thus, the isomerization of the adducts might occur through two different pathways. First, the adduct **4a** might undergo nucleophilic attack by $PPhMe_2$ to form the enolate species, which could be isomerized and then the elimination occurred to give the *E*- and *Z*-isomeric mixtures of **4a** (pathway 1). The other pathway might be that the above aza-Baylis–Hillman reaction was a reversible reaction, the

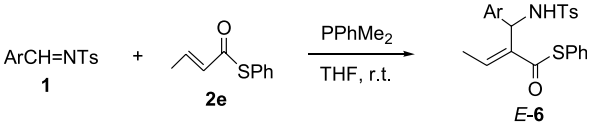
Table 6. The aza-Baylis–Hillman reaction of but-2-enethioic acid *S*-phenyl ester **2e** (2.0 equiv) with *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of $PPhMe_2$



Entry	Ar	Time (h)	Yield of **6** (%) [a]
1	C_6H_5 **1a**	2	**6a**, 60
2	*p*-FC_6H_4 **1b**	2	**6b**, 47
3	*p*-ClC_6H_4 **1c**	5	**6c**, 41
4	*p*-BrC_6H_4 **1d**	5	**6d**, 41
5	*p*-$NO_2C_6H_4$ **1e**	2	**6e**, 32
6	*m*-$NO_2C_6H_4$ **1f**	2	**6f**, 36
7	*p*-MeC_6H_4 **1g**	22	**6g**, 62
8	*p*-$MeOC_6H_4$ **1h**	120	**6h**, 25

[a] Isolated yields and only *E*-isomer was obtained.

Table 7. The aza-Baylis–Hillman reaction of but-2-enethioic acid *S*-phenyl ester **2e** (1.0 equiv) with *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of $PPhMe_2$



Entry	Ar	Time (h)	Yield of **6** (%)[a]
1	C_6H_5 **1a**	10	**6a**, 63
2	*p*-FC_6H_4 **1b**	8	**6b**, 57
3	*p*-ClC_6H_4 **1c**	10	**6c**, 51
4	*p*-BrC_6H_4 **1d**	10	**6d**, 50
5	*p*-$NO_2C_6H_4$ **1e**	3	**6e**, 54
6	*m*-$NO_2C_6H_4$ **1f**	2	**6f**, 51
7	*p*-MeC_6H_4 **1g**	34	**6g**, 55
8	*p*-$MeOC_6H_4$ **1h**	144	**6h**, 57

[a] Isolated yields and only *E*-isomer was obtained.

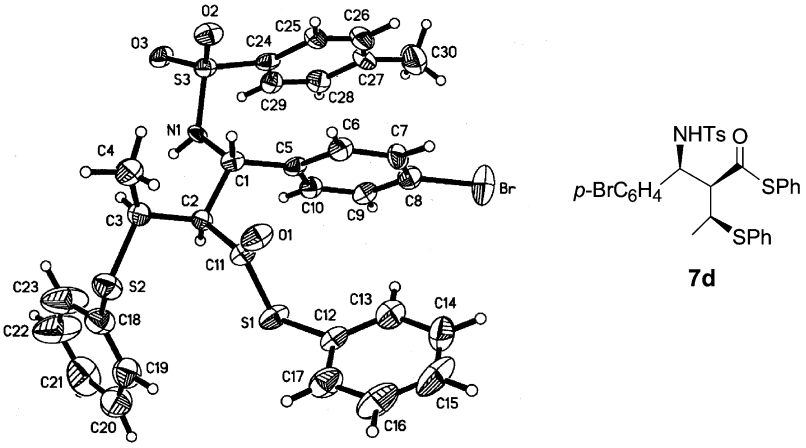
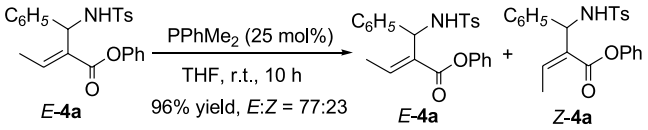
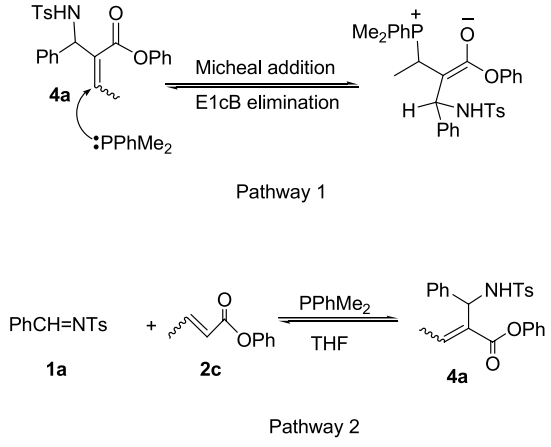


Figure 1. Crystal structure of one isomer of **7d**.



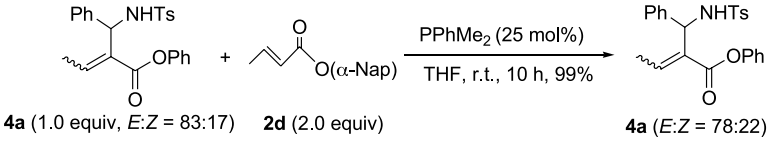
Scheme 2.

adduct **4a** underwent a retro reaction to give phenyl crotonate **2c** and the imine **1a** under the catalysis of $PPhMe_2$. Then, the aza-Baylis–Hillman reaction of newly created phenyl crotonate **2c** with the imine **1a** occurred to give the *E*- and *Z*-isomeric mixtures of **4a** (pathway 2). Careful monitoring the course of the reaction shown in Scheme 2 by TLC revealed that neither the phenyl crotonate **2c** nor the imine **1a** was observed. Thus, we hypothesized that the reaction was not reversible. This presumption was further confirmed by a control experiment. To a THF solution of a *E*- and *Z*-isomeric mixtures of **4a** (1 equiv) and α-naphthyl crotonate **2d** (2 equiv) was added 25 mol% of $PPhMe_2$, after 10 h only **4a** was recovered in 99% isolated yield as a *E*- and *Z*-isomeric mixtures and none of adduct **5a**, derived from the Baylis–Hillman reaction of α-naphthyl crotonate **2d** with imine **1a**, was detected (Scheme 3). Therefore, this type of aza-Baylis–Hillman reaction is not a reversible reaction and the adducts may be isomerized via the rotation of the single bonds in their enolate formation process under the reaction conditions. In summary, the *E*- and *Z*-isomeric mixtures were formed either during the course of the formation of the adducts in above Baylis–Hillman reaction or by the *E*- and *Z*-isomeric equilibrium of the products under the reaction conditions.

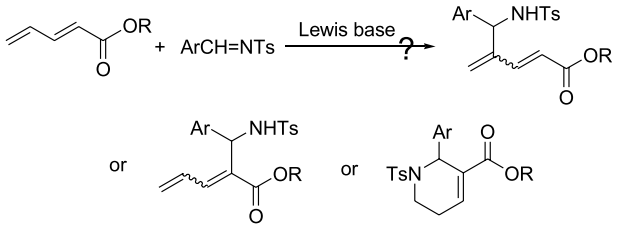


Since *N*-tosylated imines do have high reactivity as electrophile in the Baylis–Hillman reaction with crotonates, we further examined whether *N*-tosylated imines could also react with 2,4-pentadienoic esters to give different regioselective adducts or the cyclized products (Scheme 4).

To test this hyhothesis, we adopted 2,4-pentadienoic phenyl ester **2f** as the activated olefin and used the reaction of



Scheme 3.



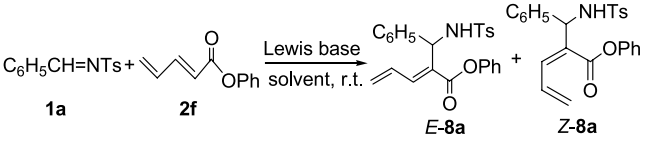
Scheme 4.

N-tosylated imine **1a** with **2f** as a model to screen various catalysts and solvents in a similar way as that described above, the results are summarized in Table 8 as entries 1–13. DABCO was found to be the best catalyst and CH_3CN was the best solvent in this reaction (Table 8, entry 11).

Under the optimized reaction conditions, other *N*-tosylated imines can also react with **2f** to give the corresponding adducts **8** in moderate to good yields (Table 9, entries 1–7). The reaction position of **2f** is exclusively at the α-position to the carbonyl group and no cyclized products or other regioisomers were detected. The structure of *E*-**8d** was confirmed by X-ray diffraction (Fig. 2).[7]

In conclusion, several β-substituted α,β-unsaturated esters can undergo the aza-Baylis–Hillman reaction with *N*-tosylated imines under mild conditions in the presence of phosphine or nitrogen Lewis base promoter, giving the adducts in major *E*-form in moderate to excellent yields. Further transformations of the aza-Baylis–Hillman reaction products is under investigation in our laboratory.

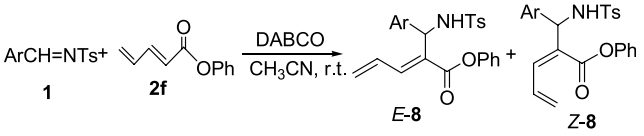
Table 8. The aza-Baylis–Hillman reaction of penta-2,4-dienoic acid phenyl ester **2f** (1.5 equiv) with *N*-benzylidene-4-methylbenzenesulfonamide **1a** (1.0 equiv) in the presence of 25 mol% of Lewis base



Entry	Lewis base	Solvent	Time (h)	Yield of **8a** (%) (*E*/*Z*)[a]
1	DABCO	THF	24	59 (69:31)
2	DMAP	THF	24	—[b]
3	DBU	THF	24	—[b]
4	PPh_2Me	THF	24	—[b]
5	$PPhMe_2$	THF	24	—[b]
6	PMe_3	THF	24	—[b]
7	PBu_3	THF	24	Trace
8	PPh_3	THF	24	—[b]
9	DABCO	CH_2Cl_2	24	20 (87:13)
10	DABCO	Et_2O	24	30 (92:8)
11	DABCO	CH_3CN	24	90 (88:12)
12	DABCO	DMF	24	64 (63:37)
13	DABCO	PhMe	24	33 (81:19)

[a] Isolated yields.
[b] No reaction occurred.

Table 9. The aza-Baylis–Hillman reaction of penta-2,4-dienoic acid phenyl ester **2f** (1.5 equiv) with other *N*-tosylated imines **1** (1.0 equiv) in the presence of 25 mol% of DABCO



Entry	Ar	Time (h)	Yield of **8** (%) (*E*/*Z*)[a]
1	*p*-FC_6H_4 **1b**	20	**8b**, 67 (79:21)
2	*p*-ClC_6H_4 **1c**	24	**8c**, 62 (85:15)
3	*p*-BrC_6H_4 **1d**	24	**8d**, 68 (86:14)
4	*p*-$NO_2C_6H_4$ **1e**	6	**8e**, 78 (89:11)
5	*m*-$NO_2C_6H_4$ **1f**	7	**8f**, 75 (85:15)
6	*p*-MeC_6H_4 **1g**	48	**8g**, 55 (86:14)
7	*p*-$MeOC_6H_4$ **1h**	120	**8h**, 32 (77:23)

[a] Isolated yields.

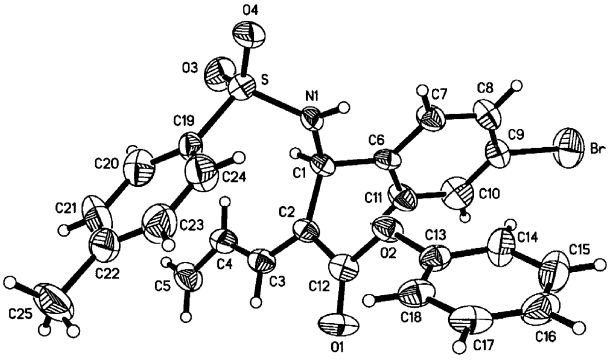


Figure 2. Crystal structure of adduct *E*-**8d**.

3. Experimental

3.1. General remarks

Unless otherwise stated, all reactions were carried out under argon atmosphere. All solvents were purified by distillation. $PPhMe_2$ was obtained from Aldrich Chem. Co. and used without purification. All *N*-tosylated imines[8] and crotonates[9] were prepared according to the literature. Infrared spectra were measured on a Perkin-Elmer 983 spectrometer. ^1H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by an Ion Spec 4.7 Tesla FTMS mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo-Erba 1106 analyzer. Melting points were obtained by means of a micro melting point apparatus and are uncorrected.

3.1.1. Penta-2,4-dienoic acid phenyl ester (2f). A new compound prepared according to the literature[10]: a colorless liquid; IR ($CHCl_3$) ν 1736 (C=O), 1641, 1493, 1306, 1265, 1216, 1194, 1163, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 5.58 (1H, d, J=9.9 Hz), 5.70 (1H, d, J=16.8 Hz), 6.11 (1H, d, J=15.6 Hz), 6.48–6.69 (1H, m), 7.07–7.14 (2H, m), 7.21–7.26 (1H, m), 7.37–7.50 (3H, m). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 121.2, 121.5, 125.7, 126.6, 129.4, 134.5, 146.5, 150.6, 165.2. MS (EI) *m*/*e* 174 (M^+, 18.00), 81 (M^+-93, 100). HRMS calcd for $C_{11}H_{10}O_2Na^+$ requires 197.0573, found 197.0578.

3.2. Typical reaction procedure for $PPhMe_2$-catalyzed aza-Baylis–Hillman reaction of vinyl crotonate with *N*-benzylidene-4-methylbenzenesulfonamide

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide **1a** (65 mg, 0.25 mmol) and $PPhMe_2$ (9 μL, 0.06 mmol) in THF (1.0 mL) at room temperature was added vinyl crotonate **2b** (60 μL, 0.5 mmol) and the reaction mixture was further stirred at room temperature. The reaction was monitored by TLC. When the *N*-tosylated imine disappeared, the solvent was removed under reduced pressure and the residue was purified by a flash chromatography (SiO_2, EtOAc/petroleum ether 1:6) to yield **3a** (63 mg, 68%). The pure *E*-isomer of **3a** can be isolated by flash chromatography, but the pure *Z*-isomer of **3a** is very difficult to be isolated and is obtained along with small amount of the *E*-isomer. The ratio of the two isomers is obtained based on ^1H NMR spectroscopic data. The configuration of *E*-isomer of **3a** is confirmed by its 2D NOESY spectrum (see Supporting information).

3.2.1. *E*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3a). A white solid: mp 86–88 °C; IR ($CHCl_3$) ν 1709 (C=O), 1644, 1495, 1450, 1336, 1302, 1250, 1163, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.88 (3H, d, J=7.5 Hz, Me), 2.38 (3H, s, Me), 4.55 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.80 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.64 (1H, d, J=10.5 Hz), 6.23 (1H, d, J=10.5 Hz), 7.00 (1H, q, J=7.5 Hz, –CH=), 7.09 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.19–7.28 (7H, m, Ar), 7.65–7.68 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.5, 21.4, 53.1, 98.0, 125.7, 126.9, 127.4, 128.4, 129.3, 130.1, 137.9, 138.5, 140.6, 142.9, 143.3, 162.7. MS (EI) *m*/*e* 328 (M^+-43, 95.36), 157 (M^+-214, 100). Anal. Calcd for $C_{20}H_{21}NO_4S$ requires C, 64.67; H, 5.70; N, 3.77%. Found: C, 64.81; H, 5.62; N, 3.82%.

3.2.2. *Z*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3a). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.92 (3H, d, J=7.2 Hz, Me), 2.40 (3H, s, Me), 4.55 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.79 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.23 (1H, d, J=9.3 Hz), 5.65 (1H, d, J=9.3 Hz), 6.31 (1H, q, J=7.2 Hz, –CH=), 7.09 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.16–7.26 (7H, m, Ar), 7.66–7.69 (2H, m, Ar).

3.2.3. *E*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3b). A white solid: mp 82–84 °C; IR ($CHCl_3$) ν 1710 (C=O), 1644, 1509, 1337, 1302, 1162, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.88 (3H, d, J=7.2 Hz, Me), 2.40 (3H, s, Me), 4.57 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.81 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.60 (1H, d, J=10.5 Hz), 6.20 (1H, d, J=10.5 Hz), 6.92–6.98 (2H, m, Ar), 7.00 (1H, q, J=7.5 Hz, –CH=), 7.10 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.21–7.25 (4H, m, Ar), 7.66 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.5, 21.4, 52.6, 98.1, 115.2 (1C, d, J_{C-F}=21.8 Hz), 126.8, 127.5 (1C, d, J_{C-F}=8.4 Hz), 129.3, 129.9, 134.3 (1C, d, J_{C-F}=3.4 Hz), 137.8, 140.5, 143.1,

143.4, 162.0 (1C, d, J_{C-F}=246.6 Hz), 162.6. MS (EI) *m/e* 346 (M^+−43, 84.94), 234 (M^+−155, 100). Anal. Calcd for $C_{20}H_{20}FNO_4S$ requires C, 61.68; H, 5.18; N, 3.60%. Found: C, 61.69; H, 5.20; N, 3.59%.

3.2.4. *Z*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3b). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 4.57 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.80 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.19 (1H, d, J=10.5 Hz), 6.20 (1H, d, J=10.5 Hz), 6.28 (1H, q, J=7.5 Hz, –CH=), 6.90–7.25 (7H, m, Ar), 7.66 (2H, d, J=8.7 Hz, Ar).

3.2.5. *E*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3c). A white solid: mp 105–107 °C; IR ($CHCl_3$) ν 1710 (C=O), 1645, 1492, 1338, 1302, 1161, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.87 (3H, d, J=7.2 Hz, Me), 2.39 (3H, s, Me), 4.56 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.81 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.59 (1H, d, J=10.5 Hz), 6.22 (1H, d, J=10.5 Hz), 7.00 (1H, q, J=7.2 Hz, –CH=), 7.08 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.17–7.24 (6H, m, Ar), 7.65 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.5, 21.4, 52.7, 98.2, 126.8, 127.2, 128.6, 129.4, 129.8, 133.3, 137.1, 137.7, 140.5, 143.2, 143.4, 162.6. MS (EI) *m/e* 362 (M^+−43, 49.50), 91 (M^+−314, 100). Anal. Calcd for $C_{20}H_{20}ClNO_4S$ requires C, 59.18; H, 4.97; N, 3.45%. Found: C, 59.10; H, 4.92; N, 3.40%.

3.2.6. *Z*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3c). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 4.57 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.80 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.18 (1H, d, J=10.2 Hz), 5.59 (1H, d, J=10.5 Hz), 6.28 (1H, q, J=7.2 Hz, –CH=), 7.15 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.20–7.26 (6H, m, Ar), 7.65 (2H, d, J=8.4 Hz, Ar).

3.2.7. *E*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3d). A white solid: mp 101–103 °C; IR ($CHCl_3$) ν 1709 (C=O), 1644, 1488, 1337, 1302, 1162, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.87 (3H, d, J=7.5 Hz, Me), 2.38 (3H, s, Me), 4.56 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.81 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.57 (1H, d, J=10.5 Hz), 6.24 (1H, d, J=10.5 Hz), 7.00 (1H, q, J=7.5 Hz, –CH=), 7.08 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.11–7.15 (2H, m, Ar), 7.19–7.22 (2H, m, Ar), 7.37 (2H, d, J=8.7 Hz, Ar), 7.64 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.5, 21.4, 52.7, 98.2, 121.4, 126.8, 127.6, 129.4, 129.8, 131.5, 137.7, 137.8, 140.5, 143.2, 143.4, 162.5. MS (EI) *m/e* 406 (M^+−43, 47.94), 91 (M^+−358, 100). Anal. Calcd for $C_{20}H_{20}BrNO_4S$ requires C, 53.34; H, 4.48; N, 3.11%. Found: C, 53.34; H, 4.26; N, 3.02%.

3.2.8. *Z*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3d). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 4.56 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.81 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.15 (1H, d, J=9.6 Hz), 5.68 (1H, d, J=9.6 Hz), 6.28 (1H, q, J=7.5 Hz, –CH=), 7.05–7.14 (3H, m, Ar), 7.24 (2H, d, J=8.1 Hz, Ar), 7.34–7.39 (2H, m, Ar), 7.65 (2H, d, J=8.4 Hz, Ar).

3.2.9. *E*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3e). A white solid: mp 93–95 °C; IR ($CHCl_3$) ν 1710 (C=O), 1645, 1522, 1348, 1162, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.92 (3H, d, J=7.2 Hz, Me), 2.40 (3H, s, Me), 4.59 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.83 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.69 (1H, d, J=10.5 Hz), 6.27 (1H, d, J=10.5 Hz), 7.07 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.08 (1H, q, J=7.5 Hz, –CH=), 7.24 (2H, d, J=8.1 Hz, Ar), 7.44 (2H, d, J=8.7 Hz, Ar), 7.67 (2H, d, J=8.1 Hz, Ar), 8.12 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.8, 98.5, 123.6, 126.8, 126.8, 129.5, 129.5, 137.6, 140.4, 143.8, 144.0, 146.1, 147.2, 162.4. MS (EI) *m/e* 373 (M^+−43, 100), 155 (M^+−261, 40.26). Anal. Calcd for $C_{20}H_{20}N_2O_6S$ requires C, 57.68; H, 4.84; N, 6.73%. Found: C, 57.72; H, 4.91; N, 6.72%.

3.2.10. *Z*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3e). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 4.60 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.82 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.25 (1H, d, J=9.9 Hz), 5.80 (1H, d, J=9.9 Hz), 6.32 (1H, q, J=7.5 Hz, –CH=), 7.07 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.27 (2H, d, J=8.1 Hz,, Ar), 7.43 (2H, d, J=8.4 Hz, Ar), 7.67 (2H, d, J=8.1 Hz, Ar), 8.10 (2H, d, J=8.4 Hz, Ar).

3.2.11. *E*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3f). A white solid: mp 135–137 °C; IR ($CHCl_3$) ν 1710 (C=O), 1645, 1533, 1351, 1162, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.5 Hz, Me), 2.40 (3H, s, Me), 4.60 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.85 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.69 (1H, d, J=10.5 Hz), 6.24 (1H, d, J=10.5 Hz), 7.09 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.11 (1H, q, J=7.5 Hz, –CH=), 7.24 (2H, d, J=8.4 Hz, Ar), 7.48 (1H, t, J=8.1 Hz, Ar), 7.68 (3H, d, J=8.4 Hz, Ar), 8.00 (1H, s, Ar), 8.09 (1H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.6, 98.5, 120.8, 122.5, 126.8, 129.4, 129.5, 129.5, 132.1, 137.5, 140.4, 141.0, 143.7, 144.1, 148.3, 162.4. MS (EI) *m/e* 373 (M^+−43, 100), 155 (M^+−261, 86.75). Anal. Calcd for $C_{20}H_{20}N_2O_6S$ requires C, 57.68; H, 4.84; N, 6.73%. Found: C, 57.68; H, 4.88; N, 6.64%.

3.2.12. *Z*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid vinyl ester (3f). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.2 Hz, Me), 2.40 (3H, s, Me), 4.59 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.83 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.27 (1H, d, J=10.2 Hz), 5.92 (1H, d, J=10.2 Hz), 6.37 (1H, q, J=7.2 Hz, -CH=), 7.09 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.25 (2H, d, J=8.1 Hz, Ar), 7.42–7.50 (1H, m, Ar), 7.67 (3H, d, J=8.1 Hz, Ar), 8.01 (1H, s, Ar), 8.05–8.09 (1H, m, Ar).

3.2.13. *E*-2-[(4-methylphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid vinyl ester (3g). A white solid: mp 110–111 °C; IR ($CHCl_3$) ν 1711 (C=O), 1645, 1421, 1337, 1303, 1161, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.88 (3H, d, J=6.9 Hz, Me), 2.29 (3H, s, Me), 2.39 (3H, s, Me), 4.55 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.83 (1H, dd, J=1.8, 14.1 Hz, H_2C=), 5.60 (1H, d, J=10.5 Hz), 6.16 (1H, d, J=10.5 Hz), 6.98 (1H, q, J=6.9 Hz, –CH=), 7.06–7.15 (5H, m, Ar), 7.21 (2H,

d, J=8.7 Hz, Ar), 7.66 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.4, 20.9, 21.4, 52.9, 97.8, 125.6, 126.8, 129.1, 129.3, 130.1, 135.4, 137.1, 137.9, 140.5, 142.7, 143.2, 162.6. MS (EI) *m/e* 342 (M^+-43, 24.68), 230 (M^+-155, 100). Anal. Calcd for $C_{21}H_{23}NO_4S$ requires C, 65.43; H, 6.01; N, 3.63%. Found: C, 65.54; H, 6.02; N, 3.58%.

3.2.14. *Z*-2-[(4-methylphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid vinyl ester (3g). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.91 (3H, d, J=7.2 Hz, Me), 2.28 (3H, s, Me), 2.41 (3H, s, Me), 4.55 (1H, dd, J=1.8, 6.6 Hz, H_2C=), 4.80 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.19 (1H, d, J=9.0 Hz), 5.57 (1H, d, J=9.0 Hz), 6.31 (1H, q, J=7.2 Hz, –CH=), 7.06–7.15 (5H, m, Ar), 7.23–7.26 (2H, m, Ar), 7.65–7.68 (2H, m, Ar).

3.2.15. *E*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid vinyl ester (3h). A colorless solid: mp 141–142 °C; IR ($CHCl_3$) ν 1711 (C=O), 1645, 1512, 1337, 1302, 1250, 1160, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.87 (3H, d, J=7.2 Hz, Me), 2.38 (3H, s, Me), 3.75 (3H, s, Me), 4.55 (1H, dd, J=1.8, 6.0 Hz, H_2C=), 4.80 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.58 (1H, d, J=10.8 Hz), 6.18 (1H, d, J=10.8 Hz), 6.77–6.82 (2H, m, Ar), 6.97 (1H, q, J=7.2 Hz, –CH=), 7.10 (1H, dd, J=6.0, 13.8 Hz, H_2C=), 7.18–7.22 (4H, m, Ar), 7.65 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.5, 21.4, 52.7, 55.2, 97.9, 113.8, 126.9, 127.0, 129.3, 130.2, 130.4, 137.9, 140.6, 142.6, 143.2, 158.8, 162.7. MS (EI) *m/e* 358 (M^+-43, 7.52), 246 (M^+-155, 100). Anal. Calcd. for $C_{21}H_{23}NO_5S$ requires C, 62.82; H, 5.77; N, 3.49%. Found: C, 62.88; H, 5.76; N, 3.46%.

3.2.16. *Z*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid vinyl ester (3h). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 3.76 (3H, s, Me), 4.56 (1H, dd, J=1.8, 6.3 Hz, H_2C=), 4.81 (1H, dd, J=1.8, 13.8 Hz, H_2C=), 5.18 (1H, d, J=9.6 Hz), 5.55 (1H, d, J=9.6 Hz), 6.30 (1H, q, J=7.2 Hz, –CH=), 6.74–6.79 (2H, m, Ar), 7.08 (2H, d, J=8.1 Hz, Ar), 7.09 (1H, dd, J=6.3, 13.8 Hz, H_2C=), 7.23–7.26 (2H, m, Ar), 7.67 (2H, d, J=8.7 Hz, Ar).

3.3. Typical reaction procedure for $PPhMe_2$-catalyzed aza-Baylis–Hillman reaction of phenyl crotonate with *N*-(3-chlorobenzylidene)-4-methylbenzenesulfonamide

To a solution of *N*-(3-chlorobenzylidene)-4-methylbenzene-sulfonamide **1c** (75 mg, 0.25 mmol) and $PPhMe_2$ (9 μL, 0.06 mmol) in THF (1.0 mL) at room temperature was added phenyl crotonate **2c** (78 μL, 0.5 mmol) and the reaction mixture was further stirred at room temperature. The reaction was monitored by TLC. When the *N*-tosylated imine disappeared, the solvent was removed under reduced pressure and the residue was purified by a flash chromatography (SiO_2, EtOAc/petroleum ether 1:6) to yield **4c** (91 mg, 80%). The pure *E*-isomer of **4c** can be isolated by flash chromatography, but the pure *Z*-isomer of **4c** is very difficult to be isolated and is obtained along with small amount of the *E*-isomer. The ratio of the two isomers is obtained based on ^{1}H NMR spectroscopic data. The configuration of *E*-isomer of **4c** is confirmed by its 2D NOESY spectrum (see Supporting information).

3.3.1. *E*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4a). A white solid: mp 113–115 °C; IR ($CHCl_3$) ν 1713 (C=O), 1598, 1493, 1194, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.97 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 5.73 (1H, d, J=10.2 Hz), 6.24 (1H, d, J=10.2 Hz), 6.81–6.84 (2H, m, Ar), 7.12–7.35 (11H, m, Ar), 7.71 (2H, d, J= 7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.4, 53.2, 121.3, 125.8, 125.9, 126.9, 127.4, 128.4, 129.3, 129.4, 130.8, 138.2, 138.7, 142.9, 143.2, 150.0, 164.4. MS (EI) *m/e* 328 (M^+-93, 100), 260 (M^+-161, 47). Anal. Calcd for $C_{24}H_{23}NO_4S$ requires C, 68.39; H, 5.50; N, 3.32%. Found: C, 68.40; H, 5.54; N, 3.16%.

3.3.2. *Z*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4a). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.97 (3H, d, J=7.5 Hz, Me), 2.40 (3H, s, Me), 5.33 (1H, d, J=9.3 Hz), 5.68 (1H, d, J=9.3 Hz), 6.37 (1H, q, J=7.5 Hz, –CH=), 6.66–6.70 (2H, m, Ar), 7.14–7.32 (10H, m, Ar), 7.71 (2H, d, J=8.4 Hz, Ar).

3.3.3. *E*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4b). A white solid: mp 107–108 °C; IR ($CHCl_3$) ν 1713 (C=O), 1599, 1509, 1193, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 5.69 (1H, d, J=10.2 Hz), 6.25 (1H, d, J=10.2 Hz), 6.83–6.86 (2H, m, Ar), 6.92–6.98 (2H, m, Ar), 7.11–7.36 (8H, m, Ar), 7.70 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.5, 52.8 (1C, d, J_{C-F}=0.8 Hz), 115.3 (1C, d, J_{C-F}=22.0 Hz), 121.3, 126.0, 126.9, 127.5, 127.6, 129.4 (1C, d, J_{C-F}=5.0 Hz), 130.7, 134.5 (1C, d, J_{C-F}=3.3 Hz), 138.1, 143.0, 143.4, 150.0, 162.1 (1C, d, J=251.3 Hz), 164.4. MS (EI) *m/e* 439 (M^+, 0.55), 91 (M^+-348, 100). Anal. Calcd for $C_{24}H_{22}FNO_4S$ requires C, 65.59; H, 5.05; N, 3.19%. Found: C, 65.45; H, 5.07; N, 2.90%.

3.3.4. *Z*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4b). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 5.30 (1H, d, J=9.6 Hz), 5.78 (1H, d, J=9.6 Hz), 6.33 (1H, d, J=7.2 Hz, –CH=), 6.70–6.74 (2H, m, Ar), 6.92–6.98 (2H, m, Ar), 7.11–7.36 (7H, m, Ar), 7.70 (2H, d, J=8.4 Hz, Ar).

3.3.5. *E*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4c). A white solid: mp 124–125 °C; IR ($CHCl_3$) ν 1713 (C=O), 1593, 1492, 1193, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 5.68 (1H, d, J=10.5 Hz), 6.25 (1H, d, J=10.5 Hz), 6.82–6.86 (2H, m, Ar), 7.12–7.37 (10H, m, Ar), 7.67–7.71 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.8, 121.3, 126.0, 126.9, 127.3, 128.6, 129.4, 129.5, 130.4, 133.3, 137.3, 138.0, 143.2, 143.4, 149.9, 164.3. MS (EI) *m/e* 455 (M^+, 0.34), 91 (M^+-364, 100). Anal. Calcd for $C_{24}H_{22}ClNO_4S$ requires C, 63.22; H, 4.86; N, 3.07%. Found: C, 63.44; H, 4.94; N, 2.94%.

3.3.6. *Z*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4c). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.2 Hz, Me),

2.40 (3H, s, Me), 5.28 (1H, d, J=9.6 Hz), 5.85 (1H, d, J=9.6 Hz), 6.33 (1H, q, J=7.2 Hz, –CH═), 6.72–6.75 (2H, m, Ar), 7.14–7.35 (10H, m, Ar), 7.67–7.71 (2H, m, Ar).

3.3.7. *E*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4d). A white solid: mp 117–120 °C; IR ($CHCl_3$) ν 1716 (C═O), 1592, 1488, 1193, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=6.9 Hz, Me), 2.41 (3H, s, Me), 5.66 (1H, d, J=10.5 Hz), 6.24 (1H, d, J=10.5 Hz), 6.82–6.87 (2H, m, Ar), 7.12–7.41 (10H, m, Ar), 7.67–7.71 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.9, 121.3, 121.4, 126.0, 126.9, 127.7, 129.4, 129.5, 130.5, 131.5, 137.9, 138.0, 143.2, 143.5, 150.0, 164.3. MS (EI) *m/e* 500 (M^++1, 1.86), 91 (M^+−408, 100). Anal. Calcd for $C_{24}H_{22}BrNO_4S$ requires C, 57.60; H, 4.43; N, 2.80%. Found: C, 57.54; H, 4.44; N, 2.46%.

3.3.8. *Z*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4d). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 5.26 (1H, d, J=9.6 Hz), 5.80 (1H, d, J=9.6 Hz), 6.33 (1H, q, J=7.2 Hz, –CH═), 6.70–6.74 (2H, m, Ar), 7.10–7.40 (9H, m, Ar), 7.68 (2H, d, J=8.7 Hz, Ar).

3.3.9. *E*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4e). A colorless solid: mp 150–152 °C; IR ($CHCl_3$) ν 1713 (C═O), 1598, 1523, 1493, 1193, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.00 (3H, d, J=7.5 Hz, Me), 2.42 (3H, s, Me), 5.77 (1H, d, J=10.5 Hz), 6.31 (1H, d, J=10.5 Hz), 6.83–6.86 (2H, m, Ar), 7.18–7.36 (6H, m, Ar), 7.47 (2H, d, J=8.7 Hz, Ar), 7.71 (2H, d, J=8.4 Hz, Ar), 8.12 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.8, 21.5, 53.0, 121.2, 123.7, 126.2, 126.8, 126.8, 129.4, 129.6, 130.1, 137.8, 143.8, 144.0, 146.3, 147.1, 149.8, 164.1. MS (EI) *m/e* 466 (M^+, 0.17), 91 (M^+−375, 100). Anal. Calcd for $C_{24}H_{22}N_2O_6S$ requires C, 61.79; H, 4.75; N, 6.00%. Found: C, 61.91; H, 4.81; N, 5.96%.

3.3.10. *Z*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4e). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.99 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 5.36 (1H, d, J=9.9 Hz), 5.99 (1H, d, J=9.9 Hz), 6.39 (1H, q, J=7.2 Hz, –CH═), 6.73–6.76 (2H, m, Ar), 7.18–7.36 (5H, m, Ar), 7.47 (2H, d, J=8.7 Hz, Ar), 7.71 (2H, d, J=8.4 Hz, Ar), 8.12 (2H, d, J=8.7 Hz, Ar).

3.3.11. *E*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4f). A white solid: mp 143–145 °C; IR ($CHCl_3$) ν 1713 (C═O), 1593, 1532, 1351, 1193, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.01 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 5.77 (1H, d, J=10.5 Hz), 6.33 (1H, d, J=10.5 Hz), 6.85–6.88 (2H, m, Ar), 7.20–7.36 (6H, m, Ar), 7.46 (1H, t, J=7.8 Hz, Ar), 7.71–7.73 (3H, m, Ar), 8.06–8.09 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.8, 21.5, 52.8, 120.8, 121.2, 122.5, 126.1, 126.8, 129.4, 129.5, 129.6, 130.0, 132.2, 137.8, 141.2, 143.7, 144.2, 148.3, 149.9, 164.2. MS (EI) *m/e* 466 (M^+, 0.50), 373 (M^+−93, 100). Anal. Calcd for $C_{24}H_{22}N_2O_6S$ requires C, 61.79; H, 4.75; N, 6.00%. Found: C, 61.79; H, 4.68; N, 5.87%.

3.3.12. *Z*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4f). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.01 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 5.38 (1H, d, J=9.9 Hz), 5.78 (1H, d, J=9.9 Hz), 6.42 (1H, q, J=7.5 Hz, –CH═), 6.76–6.79 (2H, m, Ar), 7.17–7.40 (5H, m, Ar), 7.46 (1H, t, J=8.1 Hz, Ar), 7.67–7.74 (3H, m, Ar), 8.04–8.07 (2H, m, Ar).

3.3.13. *E*-2-[(4-methylphenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4g). A white solid: mp 144–146 °C; IR ($CHCl_3$) ν 1713 (C═O), 1593, 1493, 1336, 1193, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, d, J=7.2 Hz, Me), 2.29 (3H, s, Me), 2.40 (3H, s, Me), 5.69 (1H, d, J=10.5 Hz), 6.23 (1H, d, J=10.5 Hz), 6.82–6.85 (2H, m, Ar), 7.06–7.34 (10H, m, Ar), 7.70 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 20.9, 21.4, 53.1, 121.3, 125.7, 125.9, 126.9, 129.1, 129.3, 129.3, 130.9, 135.6, 137.1, 138.2, 142.7, 143.2, 150.1, 164.5. MS (EI) *m/e* 342 (M^+−93, 59.586), 171 (M^+−264, 100). Anal. Calcd for $C_{25}H_{25}NO_4S$ requires C, 68.94; H, 5.79; N, 3.22%. Found: C, 68.89; H, 5.72; N, 3.10%.

3.3.14. *Z*-2-[(4-methylphenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4g). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.97 (3H, d, J=7.2 Hz, Me), 2.30 (3H, s, Me), 2.41 (3H, s, Me), 5.29 (1H, d, J=9.3 Hz), 5.62 (1H, d, J=9.3 Hz), 6.37 (1H, q, J=7.2 Hz, –CH═), 6.69–6.73 (2H, m, Ar), 7.00–7.38 (9H, m, Ar), 7.71 (2H, d, J=8.4 Hz, Ar).

3.3.15. *E*-2-[(4-methoxyphenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4h). A white solid: mp 129–131 °C; IR ($CHCl_3$) ν 1713 (C═O), 1598, 1493, 1251, 1193, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, d, J=7.2 Hz, Me), 2.41 (3H, s, Me), 3.76 (3H, s, Me), 5.67 (1H, d, J=10.5 Hz), 6.23 (1H, d, J=10.5 Hz), 6.79–6.86 (4H, m, Ar), 7.12 (1H, q, J=7.2 Hz, –CH═), 7.17–7.25 (5H, m, Ar), 7.30–7.36 (2H, m, Ar), 7.70 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.5, 52.9, 55.2, 113.8, 121.3, 125.9, 126.9, 127.1, 129.3, 129.4, 130.7, 130.8, 138.2, 142.6, 143.2, 150.1, 158.8, 164.5. MS (EI) *m/e* 451 (M^+, 0.24), 91 (M^+−360, 100). Anal. Calcd for $C_{25}H_{25}NO_5S$ requires C, 66.50; H, 5.58; N, 3.10%. Found: C, 66.28; H, 5.50; N, 3.04%.

3.3.16. *Z*-2-[(4-methoxyphenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid phenyl ester (4h). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.96 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 3.87 (3H, s, Me), 5.28 (1H, d, J=9.0 Hz), 5.62 (1H, d, J=9.0 Hz), 6.36 (1H, q, J=7.2 Hz, –CH═), 6.72–6.81 (3H, m, Ar), 7.13 (2H, d, J=8.7 Hz, Ar), 7.25–7.34 (6H, m, Ar), 7.71 (2H, d, J=8.1 Hz, Ar).

3.4. Typical reaction procedure for $PPhMe_2$-catalyzed aza-Baylis–Hillman reaction of α-naphthyl crotonate with *N*-benzylidene-4-methylbenzenesulfonamide

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide **1a** (65 mg, 0.25 mmol) and $PPhMe_2$ (9 μL, 0.06 mmol) in THF (1.0 mL) at room temperature was added α-naphthyl crotonate **2d** (92 μL, 0.5 mmol) and the

reaction mixture was further stirred at room temperature. The reaction was monitored by TLC. When the *N*-tosylated imine disappeared, the solvent was removed under reduced pressure and the residue was purified by a flash chromatography (SiO_2, EtOAc/petroleum ether 1:5) to yield **5a** (104 mg, 88%). The pure *E*-isomer of **5a** can be isolated by flash chromatography, but the pure *Z*-isomer of **5a** is very difficult to be isolated and is obtained along with small amount of the *E*-isomer. The ratio of the two isomers is obtained based on ^{1}H NMR spectroscopic data. The configuration of *E*-isomer of **5a** is confirmed by its 2D NOESY spectrum (see Supporting information).

3.4.1. *E*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5a). A white solid: mp 115–116 °C; IR ($CHCl_3$) ν 1716 (C=O), 1643, 1599, 1335, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.03 (3H, d, J=7.5 Hz, Me), 2.41 (3H, s, Me), 5.83 (1H, d, J=10.5 Hz), 6.29 (1H, d, J=10.5 Hz), 6.98–7.01 (1H, m, Ar), 7.22–7.48 (12H, m, Ar), 7.68–7.76 (3H, m, Ar), 7.82 (1H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.8, 21.5, 53.2, 117.9, 120.8, 125.2, 125.8, 126.2, 126.4, 126.4, 126.5, 126.9, 127.5, 128.0, 128.6, 129.5, 131.0, 134.5, 138.3, 138.7, 142.9, 143.3, 146.0, 164.7. MS (EI) *m/e* 471 (M^+, 0.35), 173 (M^+-298, 100). Anal. Calcd for $C_{28}H_{25}NO_4S$ requires C, 71.32; H, 5.34; N, 2.97%. Found: C, 71.28; H, 5.15; N, 2.90%.

3.4.2. *Z*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5a). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.05 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 5.44 (1H, d, J=10.2 Hz), 5.83 (1H, d, J=10.2 Hz), 6.50 (1H, q, J=7.2 Hz, –CH=), 6.84–6.88 (2H, m, Ar), 7.22–7.42 (10H, m, Ar), 7.67–7.74 (4H, m, Ar).

3.4.3. *E*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5b). A white solid: mp 110–113 °C; IR ($CHCl_3$) ν 1716 (C=O), 1600, 1509, 1161, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.02 (3H, d, J=7.5 Hz, Me), 2.42 (3H, s, Me), 5.78 (1H, d, J=10.5 Hz), 6.29 (1H, d, J=10.5 Hz), 6.96–7.02 (3H, m, Ar), 7.25–7.50 (9H, m, Ar), 7.70–7.74 (3H, m, Ar), 7.83 (1H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.8, 115.4 (1C, d, J_{C-F}= 21.4 Hz), 117.9, 120.7, 125.2, 126.2, 126.4, 126.4, 126.5, 126.9, 127.6, 127.7, 128.0, 129.5, 130.8, 134.5 (1C, d, J_{C-F}=2.9 Hz), 138.1, 143.0, 143.4, 145.9, 162.1 (1C, d, J= 246.3 Hz), 164.6. MS (EI) *m/e* 489 (M^+, 1.47), 144 (M^+- 345, 100). Anal. Calcd for $C_{28}H_{24}FNO_4S$ requires C, 68.69; H, 4.94; N, 2.86%. Found: C, 68.64; H, 4.98; N, 2.76%.

3.4.4. *Z*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5b). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.05 (3H, d, J=7.2 Hz, Me), 2.43 (3H, s, Me), 5.40 (1H, d, J=9.9 Hz), 5.78 (1H, d, J=9.9 Hz), 6.47 (1H, q, J=7.2 Hz), 6.88–7.04 (3H, m, Ar), 7.26–7.50 (8H, m, Ar), 7.69–7.80 (3H, m, Ar), 7.81 (1H, d, J=8.4 Hz, Ar).

3.4.5. *E*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5c). A white solid: mp 146–148 °C; IR ($CHCl_3$) ν 1716 (C=O), 1599, 1491, 1336, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.04 (3H, d, J=7.2 Hz, Me), 2.43 (3H, s, Me), 5.77 (1H, d, J=10.5 Hz), 6.27 (1H, d, J=10.5 Hz), 7.01 (1H, d, J=7.2 Hz, Ar), 7.23–7.51 (11H, m, Ar), 7.72 (3H, d, J=8.1 Hz, Ar), 7.84 (1H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.8, 117.9, 120.6, 125.2, 126.2, 126.4, 126.4, 126.5, 126.8, 127.3, 128.0, 128.7, 129.5, 130.6, 133.4, 134.5, 137.4, 138.1, 143.2, 143.5, 145.9, 164.5. MS (EI) *m/e* 505 (M^+, 2.09), 144 (M^+-361, 100). Anal. Calcd for $C_{28}H_{24}ClNO_4S$ requires C, 66.46; H, 4.78; N, 2.77%. Found: C, 66.47; H, 4.80; N, 2.71%.

3.4.6. *Z*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5c). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.04 (3H, d, J=7.5 Hz, Me), 2.43 (3H, s, Me), 5.38 (1H, d, J=9.6 Hz), 5.77 (1H, d, J=9.6 Hz), 6.46 (1H, d, J=7.5 Hz, –CH=), 6.85–6.92 (2H, m, Ar), 7.25–7.42 (9H, m, Ar), 7.69–7.74 (3H, m, Ar), 7.81 (1H, d, J=8.4 Hz, Ar).

3.4.7. *E*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5d). A white solid: mp 152–153 °C; IR ($CHCl_3$) ν 1715 (C=O), 1599, 1338, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.04 (3H, d, J=7.2 Hz, Me), 2.44 (3H, s, Me), 5.75 (1H, d, J=10.5 Hz), 6.25 (1H, d, J=10.5 Hz), 7.00–7.03 (1H, m, Ar), 7.20–7.51 (11H, m, Ar), 7.72 (3H, d, J=7.8 Hz, Ar), 7.84 (1H, d, J=7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 52.8, 117.9, 120.6, 121.5, 125.1, 126.2, 126.4, 126.4, 126.4, 126.8, 127.7, 128.0, 129.5, 130.6, 131.6, 134.5, 137.9, 138.0, 143.2, 143.5, 145.9, 164.5. MS (EI) *m/e* 549 (M^+, 1.13), 144 (M^+-405, 100). Anal. Calcd for $C_{28}H_{24}BrNO_4S$ requires C, 61.09; H, 4.39; N, 2.54%. Found: C, 61.16; H, 4.38; N, 2.46%.

3.4.8. *Z*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5d). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.02 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 5.37 (1H, d, J=9.6 Hz), 5.88 (1H, d, J=9.6 Hz), 6.45 (1H, d, J=7.2 Hz, -CH=), 6.84 (1H, d, J=8.4 Hz, Ar), 6.91 (1H, d, J=7.8 Hz, Ar), 7.17–7.50 (10H, m, Ar), 7.72 (3H, d, J=7.8 Hz, Ar), 7.80 (1H, d, J= 8.4 Hz, Ar).

3.4.9. *E*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5e). A white solid: mp 118–120 °C; IR ($CHCl_3$) ν 1720 (C=O), 1598, 1515, 1247, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.08 (3H, d, J=7.5 Hz, Me), 2.43 (3H, s, Me), 5.86 (1H, d, J=10.5 Hz), 6.33 (1H, d, J=10.5 Hz), 7.00 (1H, d, J=7.2 Hz, Ar), 7.27–7.52 (9H, m, Ar), 7.70–7.75 (3H, m, Ar), 7.84 (1H, d, J=8.4 Hz, Ar), 8.13 (2H, d, J= 8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 15.0, 21.5, 53.0, 117.9, 120.4, 123.7, 125.2, 126.3, 126.4, 126.5, 126.5 (2C), 126.9, 128.1, 129.6, 130.3, 134.5, 37.9, 143.8, 144.0, 145.8, 146.3, 147.2, 164.4. MS (EI) *m/e* 516 (M^+, 0.19), 144 (M^+-372, 100). Anal. Calcd for $C_{28}H_{24}N_2O_6S$ requires C, 65.10; H, 4.68; N, 5.42%. Found: C, 65.06; H, 4.67; N, 5.28%.

3.4.10. *Z*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5e). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.09 (3H, d, J=7.2 Hz,

Me), 2.43 (3H, s, Me), 5.46 (1H, d, J=9.6 Hz), 6.00 (1H, d, J=9.6 Hz), 6.52 (1H, q, J=7.2 Hz, –CH═), 6.89 (1H, d, J=7.5 Hz, Ar), 7.03 (1H, d, J=7.8 Hz, Ar), 7.28–7.55 (7H, m, Ar), 7.71–7.75 (3H, m, Ar), 7.82 (1H, d, J=8.4 Hz, Ar), 8.16 (2H, d, J=8.7 Hz, Ar).

3.4.11. *E*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5f). A white solid: mp 128–129 °C; IR ($CHCl_3$) ν 1716 (C═O), 1599, 1532, 1351, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.08 (3H, d, J=7.5 Hz, Me), 2.43 (3H, s, Me), 5.85 (1H, d, J=10.2 Hz), 6.36 (1H, d, J=10.2 Hz), 7.00–7.03 (1H, m, Ar), 7.28–7.30 (2H, m, Ar), 7.38–7.50 (6H, m, Ar), 7.70–7.84 (5H, m, Ar), 8.07–8.10 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 15.0, 21.5, 52.78, 117.9, 120.5, 120.7, 122.6, 125.2, 126.4, 126.4, 126.5, 126.6, 126.8, 128.1, 129.6, 129.9, 132.3, 134.5, 137.8, 141.2 (2C), 143.8, 144.4, 145.8, 148.3, 164.4. MS (EI) *m/e* 373 (M^+−143, 3.33), 144 (M^+−372, 100). Anal. Calcd for $C_{28}H_{24}N_2O_6S$ requires C, 65.10; H, 4.68; N, 5.42%. Found: C, 64.82; H, 4.62; N, 5.31%.

3.4.12. 2-[(3-Nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5f). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.10 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 5.46 (1H, d, J=9.9 Hz), 6.08 (1H, d, J=9.9 Hz), 6.54 (1H, q, J=7.2 Hz, –CH═), 6.93 (1H, d, J=7.5 Hz, Ar), 7.12 (1H, d, J=8.4 Hz, Ar), 7.26–7.51 (6H, m, Ar), 7.70–7.85 (5H, m, Ar), 8.09–8.13 (2H, m, Ar).

3.4.13. *E*-2-[(4-methylphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5g). A yellow solid: mp 145–147 °C; IR ($CHCl_3$) ν 1716 (C═O), 1599, 1512, 1420, 1336, 1160, 1122 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.02 (3H, d, J=7.2 Hz, Me), 2.32 (3H, s, Me), 2.41 (3H, s, Me), 5.78 (1H, d, J=10.2 Hz), 6.25 (1H, d, J=10.2 Hz), 7.00 (1H, d, J=7.2 Hz, Ar), 7.10 (2H, d, J=7.8 Hz, Ar), 7.22–7.48 (9H, m, Ar), 7.68–7.75 (3H, m, Ar), 7.81 (1H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.0, 21.5, 53.1, 118.0, 120.9, 125.2, 125.8, 126.1, 126.3, 126.4, 126.6, 126.9, 128.0, 129.3, 129.4, 131.1, 134.5, 135.7, 137.2, 138.3, 142.7, 143.3, 146.0, 164.7. MS (EI) *m/e* 485 (M^+, 3.50), 171 (M^+−314, 100). HRMS calcd for $C_{29}H_{27}NO_4SNa^+$ requires 508.1553, found 508.1548.

3.4.14. *Z*-2-[(4-methylphenyl)-(toluene-4-sulfonyla-mino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5g). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.03 (3H, d, J=6.9 Hz, Me), 2.35 (3H, s, Me), 2.40 (3H, s, Me), 5.41 (1H, d, J=9.0 Hz), 5.71 (1H, d, J=9.0 Hz), 6.48 (1H, q, J=6.9 Hz, –CH═), 6.86–6.90 (1H, m, Ar), 7.06–7.48 (10H, m, Ar), 7.64–7.76 (4H, m, Ar).

3.4.15. *E*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5h). A white solid: mp 92–93 °C; IR ($CHCl_3$) ν 1713 (C═O), 1600, 1511, 1250, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.03 (3H, d, J=6.9 Hz, Me), 2.43 (3H, s, Me), 3.79 (3H, s, Me), 5.77 (1H, d, J=10.2 Hz), 6.25 (1H, d, J=10.2 Hz), 6.82–6.85 (2H, m, Ar), 7.02 (1H, d, J=7.8 Hz, Ar), 7.26–7.50 (9H, m, Ar), 7.70–7.75 (3H, m, Ar), 7.84 (1H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.4, 52.8, 55.2, 113.9, 117.9, 120.8, 125.1, 126.1, 126.3, 126.3, 126.5, 126.8, 127.0, 127.9, 129.4, 130.6, 130.9, 134.4, 138.2, 142.6, 143.2, 145.9, 158.9, 164.7. MS (EI) *m/e* 501 (M^+, 0.72), 187 (M^+−314, 100). Anal. Calcd for $C_{29}H_{27}NO_5S$ requires C, 69.44; H, 5.43; N, 2.79%. Found: C, 69.44; H, 5.46; N, 2.70%.

3.4.16. *Z*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enoic acid naphthalen-1-yl ester (5h). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.04 (3H, d, J=7.2 Hz, Me), 2.43 (3H, s, Me), 3.81 (3H, s, Me), 5.40 (1H, d, J=9.0 Hz), 5.66 (1H, d, J=9.0 Hz), 6.49 (1H, q, J=7.2 Hz, –CH═), 6.83–6.91 (4H, m, Ar), 7.19–7.30 (5H, m, Ar), 7.36–7.45 (2H, m, Ar), 7.68–7.82 (4H, m, Ar).

3.5. Typical reaction procedure for $PPhMe_2$-catalyzed aza-Baylis–Hillman reaction of but-2-enethioic acid *S*-phenyl ester with *N*-benzylidene-4-methylbenzenesulfonamide

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide **1a** (65 mg, 0.25 mmol) and $PPhMe_2$ (9 μL, 0.025 mmol) in THF (1.0 mL) at room temperature was added but-2-enethioic acid *S*-phenyl ester **2e** (85 μL, 0.5 mmol) and the reaction mixture was further stirred at room temperature. The reaction was monitored by TLC. When the *N*-tosylated imine disappeared, the solvent was removed under reduced pressure and the residue was purified by a flash chromatography (SiO_2, EtOAc/petroleum ether 1:6) to yield **6a** (66 mg, 60%). The reaction gave many by-products and only the *E*-isomer of **6a** was obtained as a pure form. The configuration of *E*-isomer of **6a** is confirmed by its 2D NOESY spectrum (see Supporting information).

3.5.1. *E*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6a). A colorless solid: mp 138–140 °C; IR ($CHCl_3$) ν 1657 (C═O), 1599, 1494, 1415, 1335, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.92 (3H, d, J=6.9 Hz, Me), 2.40 (3H, s, Me), 5.62 (1H, d, J=10.2 Hz), 6.16 (1H, d, J=10.2 Hz), 7.03 (1H, q, J=6.9 Hz, –CH═), 7.18–7.26 (9H, m, Ar), 7.35–7.38 (3H, m, Ar), 7.65 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.5, 54.0, 125.9, 126.7, 126.9, 127.4, 128.4, 129.1, 129.4, 129.6, 134.9, 138.0, 138.2, 138.9, 140.8, 143.2, 191.9. MS (EI) *m/e* 328 (M^+−109, 45.09), 157 (M^+−280, 100). Anal. Calcd for $C_{24}H_{23}NO_3S_2$ requires C, 65.88; H, 5.30; N, 3.20%. Found: C, 65.76; H, 5.04; N, 3.14%.

3.5.2. *E*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6b). A colorless solid: mp 123–124 °C; IR ($CHCl_3$) ν 1656 (C═O), 1604, 1509, 1420, 1336, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.91 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 5.57 (1H, d, J=10.2 Hz), 6.14 (1H, d, J=10.2 Hz), 6.92 (2H, q, J=8.4 Hz, Ar), 7.03 (1H, q, J=7.2 Hz, –CH═), 7.17–7.25 (6H, m, Ar), 7.38–7.40 (3H, m, Ar), 7.64 (2H, d, J=7.5 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.5, 53.6, 115.3 (1C, d, J_{C-F}=21.6 Hz), 126.5, 126.9, 127.7 (1C, d, J_{C-F}=8.3 Hz), 129.2, 129.4, 129.7, 134.0 (1C, d, J_{C-F}=5.6 Hz), 134.9, 137.9, 138.8, 140.9, 143.4, 161.6 (1C, d, J=246.3 Hz), 192.1. MS (EI) *m/e* 346 (M^+−109, 14.18), 91 (M^+−364,

100). Anal. Calcd for $C_{24}H_{22}FNO_3S_2$ requires C, 63.27; H, 4.87; N, 3.07%. Found: C, 63.30; H, 4.83; N, 3.02%.

3.5.3. *E*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6c). a colorless solid: mp 160–161 °C; IR ($CHCl_3$) ν 1656 (C=O), 1598, 1491, 1418, 1337, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.93 (3H, d, J=6.9 Hz, Me), 2.42 (3H, s, Me), 5.57 (1H, d, J=10.2 Hz), 6.14 (1H, d, J=10.2 Hz), 7.05 (1H, q, J=6.9 Hz, –CH=), 7.14–7.27 (8H, m, Ar), 7.37–7.41 (3H, m, Ar), 7.64 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 53.6, 126.5, 126.9, 127.4, 128.6, 129.2, 129.5, 129.7, 133.3, 135.0, 136.9, 137.9, 138.7, 141.1, 143.4, 192.0. MS (EI) *m/e* 362 (M^+-109, 37.80), 91 (M^+-380, 100). Anal. Calcd for $C_{24}H_{22}ClNO_3S_2$ requires C, 61.07; H, 4.70; N, 2.97%. Found: C, 60.88; H, 4.66; N, 2.88%.

3.5.4. *E*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6d). A colorless solid: mp 161–163 °C; IR ($CHCl_3$) ν 1656 (C=O), 1598, 1487, 1417, 1337, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.92 (3H, d, J=6.9 Hz, Me), 2.42 (3H, s, Me), 5.54 (1H, d, J=10.2 Hz), 6.14 (1H, d, J=10.2 Hz), 7.04 (1H, q, J=6.9 Hz, –CH=), 7.09 (2H, d, J=8.1 Hz, Ar), 7.22–7.26 (4H, m, Ar), 7.32–7.40 (5H, m, Ar), 7.64 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.7, 21.5, 53.6, 121.4, 126.4, 126.8, 127.7, 129.2, 129.4, 129.7, 131.5, 134.9, 137.4, 137.8, 138.6, 141.1, 143.4, 192.0. MS (EI) *m/e* 406 (M^+-109, 2.78), 91 (M^+-424, 100). Anal. Calcd for $C_{24}H_{22}BrNO_3S_2$ requires C, 55.81; H, 4.29; N, 2.71%. Found: C, 55.90; H, 4.30; N, 2.74%.

3.5.5. *E*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6e). A yellow solid: mp 199–201 °C; IR ($CHCl_3$) ν 1655 (C=O), 1523, 1421, 1348, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.97 (3H, d, J=7.2 Hz, Me), 2.43 (3H, s, Me), 5.67 (1H, d, J=10.2 Hz), 6.17 (1H, d, J=10.2 Hz), 7.13 (1H, q, J=7.2 Hz, –CH=), 7.22–7.28 (4H, m, Ar), 7.38–7.42 (5H, m, Ar), 7.67 (2H, d, J=8.4 Hz, Ar), 8.09 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.9, 21.5, 53.6, 123.7, 126.0, 126.8, 129.3, 129.6, 129.8, 134.9, 137.7, 138.2 (2C), 141.8, 143.7, 145.9, 147.1, 192.0. MS (EI) *m/e* 373 (M^+-109, 55.60), 91 (M^+-391, 100). Anal. Calcd for $C_{24}H_{22}N_2O_5S_2$ requires C, 59.73; H, 4.60; N, 5.81%. Found: C, 59.43; H, 4.51; N, 5.68%.

3.5.6. *E*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6f). A yellow solid: mp 105–107 °C; IR ($CHCl_3$) ν 1655 (C=O), 1532, 1414, 1352, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.00 (3H, d, J=7.2 Hz, Me), 2.43 (3H, s, Me), 5.67 (1H, d, J=10.2 Hz), 6.16 (1H, d, J=10.2 Hz), 7.15 (1H, q, J=7.2 Hz, –CH=), 7.24–7.28 (4H, m, Ar), 7.38–7.48 (4H, m, Ar), 7.65–7.69 (3H, m, Ar), 7.95 (1H, s, Ar), 8.07 (1H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.8, 21.5, 53.4, 120.9, 122.5, 126.1, 126.8, 129.2, 129.5, 129.6, 129.8, 132.2, 134.9, 137.6, 138.1, 140.8, 142.0, 143.7, 148.2, 192.1. MS (EI) *m/e* 482 (M^+, 0.73), 91 (M^+-391, 100). Anal. Calcd for $C_{24}H_{22}N_2O_5S_2$ requires C, 59.73; H, 4.60; N, 5.81%. Found: C, 59.81; H, 4.70; N, 5.62%.

3.5.7. *E*-2-[(4-methyphenyl)-(toluene-4-sulfonylamino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6g). A yellow solid: mp 156–158 °C; IR ($CHCl_3$) ν 1657 (C=O), 1513, 1479, 1418, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, d, J=7.2 Hz, Me), 2.26 (3H, s, Me), 2.40 (3H, s, Me), 5.58 (1H, d, J=10.2 Hz), 6.14 (1H, d, J=10.2 Hz), 7.01 (1H, q, J=7.2 Hz, –CH=), 7.03 (2H, d, J=6.9 Hz, Ar), 7.11 (2H, d, J=8.1 Hz, Ar), 7.20–7.26 (4H, m, Ar), 7.36–7.38 (3H, m, Ar), 7.65 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 20.9, 21.4, 53.9, 125.8, 126.7, 126.9, 129.0, 129.1, 129.3, 129.5, 134.9, 135.2, 137.0, 138.0, 139.0, 140.7, 143.1, 191.8. MS (EI) *m/e* 343 (M^+-108, 92.49), 65 (M^+-386, 100). Anal. Calcd for $C_{25}H_{25}NO_3S_2$ requires C, 66.49; H, 5.58; N, 3.10%. Found: C, 66.42; H, 5.55; N, 3.10%.

3.5.8. *E*-2-[(4-methoxylphenyl)-(toluene-4-sulfonyl-amino)-methyl]-but-2-enethioic acid *S*-phenyl ester (6h). A yellow solid: mp 120–122 °C; IR ($CHCl_3$) ν 1656 (C=O), 1598, 1512, 1441, 1424, 1335, 1250, 1178, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.91 (3H, d, J=7.2 Hz, Me), 2.42 (3H, s, Me), 3.82 (3H, s, Me), 5.57 (1H, d, J=10.5 Hz), 6.12 (1H, d, J=10.5 Hz), 6.77 (2H, d, J=8.7 Hz, Ar), 7.01 (1H, q, J=7.2 Hz, –CH=), 7.14 (2H, d, J=8.1 Hz, Ar), 7.22–7.28 (4H, m, Ar), 7.38–7.40 (3H, m, Ar), 7.65 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.6, 21.5, 53.7, 55.2, 113.8, 126.8, 126.9, 127.2, 129.1, 129.4, 129.6, 130.3, 135.0, 138.0, 139.1, 140.5, 143.2, 158.8, 192.0. MS (EI) *m/e* 358 (M^+-109, 36.27), 187 (M^+-280, 100). Anal. Calcd for $C_{25}H_{25}NO_4S_2$ requires C, 64.21; H, 5.39; N, 3.00%. Found: C, 63.92; H, 5.42; N, 3.12%.

3.5.9. (2*S*,3*R*)-*S*-phenyl 2-((*R*)-(4-bromophenyl)(4-methylphenylsulfonamido)methyl)-3-(phenylthio)butanethioate and (2*R*,3*S*)-*S*-phenyl 2-((*S*)-(4-bromophenyl)(4-methylphenylsulfonamido)methyl)-3-(phenylthio)butanethioate (7d). A white solid: mp 191–193 °C; IR ($CHCl_3$) ν 3213, 3020, 2400, 1679, 1583, 1479, 1440, 1338, 1216, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.42 (3H, d, J=7.2 Hz, Me), 2.36 (3H, s, Me), 3.20 (1H, dd, J=9.9, 2.4 Hz), 3.69 (1H, dq, J=2.4, 7.2 Hz), 4.92 (1H, dd, J=9.9, 6.0 Hz), 6.37 (1H, d, J=6.0 Hz), 6.88 (2H, d, J=8.4 Hz, Ar), 6.96–6.99 (2H, m, Ar), 7.05 (2H, d, J=7.8 Hz, Ar), 7.21 (2H, d, J=8.7 Hz, Ar), 7.28–7.45 (8H, m, Ar), 7.55–7.58 (2H, m, Ar). ^{13}C NMR ($(CD_3)_2SO$, 75.44 MHz) δ 20.7, 21.2, 43.6, 56.9, 63.0, 120.5, 126.1, 126.3, 127.1, 128.8, 129.0, 129.2, 129.7, 129.9, 130.5, 132.0, 133.7, 135.3, 137.1, 138.1, 142.0, 194.7. MS (EI) *m/e* 516 (M^+-109, 2.59), 130 (M^+-495, 100). Anal. Calcd. for $C_{30}H_{28}NBrO_3S_3$ requires C, 57.50; H, 4.50; N, 2.24%. Found: C, 57.40; H, 4.57; N, 2.22%.

3.6. Typical reaction procedure for DABCO-catalyzed aza-Baylis–Hillman reaction of 2,4-pentadienoic phenyl ester with *N*-benzylidene-4-methylbenzenesulfonamide

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide **1a** (65 mg, 0.25 mmol) and DABCO(7 mg, 0.06 mmol) in CH_3CN (1.0 mL) at room temperature was

added penta-2,4-dienoic acid phenyl ester **2f** (64 μL, 0.375 mmol) and the reaction mixture was further stirred at room temperature. The reaction was monitored by TLC. When the *N*-tosylated imine disappeared, the solvent was removed under reduced pressure and the residue was purified by a flash chromatography (SiO_2, EtOAc/petroleum ether 1:6) to yield **8a** (98 mg, 90%). The pure *E*-isomer of **8a** can be isolated by flash chromatography, but the pure *Z*-isomer of **8a** is very difficult to be isolated and is obtained along with small amount of the *E*-isomer. The ratio of the two isomers is obtained based on ^{1}H NMR spectroscopic data.

3.6.1. *E*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8a). A colorless solid: mp 154–155 °C; IR ($CHCl_3$) ν 3021, 1713 (C=O), 1493, 1343, 1216, 1193, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.41 (3H, s, Me), 5.74 (1H, d, J=10.2 Hz), 5.80 (1H, d, J=16.5 Hz), 5.86 (1H, d, J=10.5 Hz), 6.81 (2H, d, J=7.5 Hz, Ar), 6.88 (1H, ddd, J=16.5, 10.8, 10.5 Hz), 7.21–7.37 (12H, m, Ar), 7.69 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.7, 121.3, 125.8, 126.0, 127.0, 127.4, 128.2, 128.5, 129.3, 129.4, 129.5, 130.5, 138.0, 138.5, 142.9, 143.3, 149.9, 164.8. MS (EI) *m/e* 433 (M^+, 0.39), 340 (M^+-93, 47.42), 91 (M^+-342, 100). Anal. Calcd for $C_{25}H_{23}NO_4S$ requires C, 69.26; H, 5.35; N, 3.23%. Found: C, 69.23; H, 5.30; N, 3.09%.

3.6.2. *Z*-2-[phenyl-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8a). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 5.38 (1H, d, J=8.7 Hz), 5.51–5.63 (3H, m), 6.63–6.68 (3H, m), 7.15–7.33 (11H, m, Ar), 7.73 (2H, d, J=6.3 Hz, Ar).

3.6.3. *E*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8b). A white solid: mp 155–156 °C; IR ($CHCl_3$) ν 3286, 3021, 1716 (C=O), 1626, 1592, 1508, 1494, 1420, 1340, 1216, 1195, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.41 (3H, s, Me), 5.74–5.84 (3H, m), 6.20 (1H, d, J=10.5 Hz), 6.79–7.00 (5H, m), 7.20–7.37 (8H, m, Ar), 7.67 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.2, 115.3 (1C, d, J_{C-F}=21.8 Hz), 121.2, 126.1, 127.0, 127.6 (1C, d, J_{C-F}=8.1 Hz), 128.0, 129.4, 129.5, 129.8, 130.3, 134.3 (1C, d, J_{C-F}=3.0 Hz), 137.9, 143.0, 143.4, 149.9, 162.1 (1C, d, J_{C-F}=246.4 Hz), 164.8. MS (EI) *m/e* 451 (M^+, 0.05), 91 (M^+-360, 100). Anal. Calcd for $C_{25}H_{22}FNO_4S$ requires C, 66.50; H, 4.91; N, 3.10%. Found: C, 66.52; H, 4.92; N, 3.06%.

3.6.4. *Z*-2-[(4-fluorophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8b). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 5.34 (1H, d, J=9.0 Hz), 5.50–5.57 (2H, m), 5.66 (1H, d, J=9.0 Hz), 6.60 (1H, d, J=10.8 Hz), 6.70–6.73 (2H, m), 6.94–7.00 (2H, m), 7.13–7.37 (8H, m, Ar), 7.71 (2H, d, J=8.7 Hz, Ar).

3.6.5. *E*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8c). a white solid: mp 153–155 °C; IR ($CHCl_3$) ν 3276, 3024, 1716 (C=O), 1628, 1591, 1492, 1422, 1341, 1217, 1194, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.41 (3H, s, Me), 5.74–5.84 (3H, m), 6.19 (1H, d, J=10.5 Hz), 6.79–6.91 (3H, m), 7.20–7.24 (7H, m, Ar), 7.32–7.37 (3H, m, Ar), 7.67 (2H, d, J=8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.3, 121.2, 126.1, 127.0, 127.3, 127.8, 128.6, 129.4, 129.5, 130.0, 130.3, 133.4, 137.2, 137.8, 143.1, 143.5, 149.9, 164.7. MS (EI) *m/e* 374 (M^+-93, 5.29), 91 (M^+-376, 100). Anal. Calcd for $C_{25}H_{22}ClNO_4S$ requires C, 64.16; H, 4.74; N, 2.99%. Found: C, 63.98; H, 4.52; N, 2.84%.

3.6.6. *Z*-2-[(4-chlorophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8c). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 5.32 (1H, d, J=9.3 Hz), 5.52–5.58 (2H, m), 5.67 (1H, d, J=9.3 Hz), 6.60 (1H, d, J=10.8 Hz), 6.72–6.76 (2H, m), 7.14–7.35 (10H, m, Ar), 7.71 (2H, d, J=7.8 Hz, Ar).

3.6.7. *E*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8d). A white solid: mp 155–156 °C; IR ($CHCl_3$) ν 3273, 3023, 1714 (C=O), 1628, 1590, 1489, 1421, 1340, 1217, 1193, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.42 (3H, s, Me), 5.74–5.85 (3H, m), 6.19 (1H, d, J=10.8 Hz), 6.78–6.91 (3H, m), 7.16–7.41 (10H, m, Ar), 7.66 (2H, d, J=8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.3, 121.3, 121.5, 126.2, 127.0, 127.6, 127.8, 129.4, 129.5, 130.0, 130.3, 131.6, 137.7, 137.8, 143.2, 143.5, 149.9, 164.7. MS (EI) *m/e* 418 (M^+-93, 9.08), 91 (M^+-420, 100). Anal. Calcd for $C_{25}H_{22}BrNO_4S$ requires C, 58.60; H, 4.33; N, 2.73%. Found: C, 58.62; H, 4.26; N, 2.68%.

3.6.8. *Z*-2-[(4-bromophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8d). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 5.30 (1H, d, J=9.6 Hz), 5.52–5.58 (2H, m), 5.65 (1H, d, J=9.6 Hz), 6.60 (1H, d, J=10.8 Hz), 6.72–6.76 (2H, m), 7.12–7.42 (10H, m, Ar), 7.70 (2H, d, J=8.1 Hz, Ar).

3.6.9. *E*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8e). A white solid: mp 144–145 °C; IR ($CHCl_3$) ν 3020, 1712 (C=O), 1599, 1524, 1493, 1420, 1349, 1216, 1192, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.42 (3H, s, Me), 5.80–5.92 (3H, m), 6.24 (1H, d, J=10.5 Hz), 6.80–6.93 (3H, m), 7.22–7.51 (8H, m, Ar), 7.67–7.70 (2H, m, Ar), 8.14 (2H, d, J=8.7 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.5, 121.1, 123.6, 126.2, 126.8, 126.9, 127.3, 129.4, 129.6, 130.0, 130.8, 137.6, 143.7, 143.7, 146.1, 147.2, 149.8, 164.5. MS (EI) *m/e* 478 (M^+, 0.05), 91 (M^+-387, 100). Anal. Calcd for $C_{25}H_{22}N_2O_6S$ requires C, 62.75; H, 4.63; N, 5.85%. Found: C, 62.68; H, 4.71; N, 5.55%.

3.6.10. *Z*-2-[(4-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8e). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 5.40 (1H, d, J=9.6 Hz), 5.56–5.64 (2H, m), 5.90 (1H, d, J=9.6 Hz), 6.61 (1H, d, J=11.1 Hz), 6.74–6.76 (2H, m), 7.19–7.51 (8H, m, Ar), 7.72 (2H, d, J=8.7 Hz, Ar), 8.15 (2H, d, J=8.7 Hz, Ar).

3.6.11. *E*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8f). A

white solid: mp 142–143 °C; IR ($CHCl_3$) ν 3223, 3025, 1713 (C═O), 1591, 1530, 1493, 1419, 1351, 1268, 1247, 1217, 1193, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.42 (3H, s, Me), 5.82–5.92 (3H, m), 6.27 (1H, d, J= 10.2 Hz), 6.81–6.94 (3H, m), 7.20–7.26 (3H, m, Ar), 7.33–7.38 (2H, m, Ar), 7.43–7.52 (2H, m, Ar), 7.68–7.75 (3H, m, Ar), 8.06–8.12 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.2, 120.8, 121.2, 122.6, 126.2, 126.9, 127.1, 129.4, 129.5, 129.6, 130.0, 130.8, 132.1, 137.6, 141.1, 143.7, 143.9, 148.2, 149.8, 164.6. MS (EI) *m/e* 478 (M^+, 0.13), 91 (M^+-387, 100). Anal. Calcd for $C_{25}H_{22}N_2O_6S$ requires C, 62.75; H, 4.63; N, 5.85%. Found: C, 62.85; H, 4.51; N, 5.84%.

3.6.12. *Z*-2-[(3-nitrophenyl)-(toluene-4-sulfonylamino)-methyl]-penta-2,4-dienoic acid phenyl ester (8f). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39 (3H, s, Me), 5.40 (1H, d, J=9.6 Hz), 5.58–5.65 (2H, m), 5.88 (1H, d, J= 9.6 Hz), 6.65 (1H, d, J=11.1 Hz), 6.77–6.80 (2H, m), 7.20–7.35 (6H, m, Ar), 7.46–7.52 (1H, m, Ar), 7.70–7.73 (3H, m, Ar), 8.06–8.12 (2H, m, Ar).

3.6.13. *E*-2-[(toluene-4-sulfonylamino)-*p*-tolyl-methyl]-penta-2,4-dienoic acid phenyl ester (8g). A colorless solid: mp 157–158 °C; IR ($CHCl_3$) ν 3020, 1713 (C═O), 1592, 1514, 1493, 1419, 1351, 1216, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.30 (3H, s, Me), 2.41 (3H, s, Me), 5.71–5.84 (3H, m), 6.18 (1H, d, J=10.5 Hz), 6.81–6.93 (3H, m), 7.08 (2H, d, J=7.8 Hz, Ar), 7.17–7.23 (5H, m, Ar), 7.31–7.36 (3H, m, Ar), 7.68 (2H, d, J=7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 20.9, 21.5, 53.5, 121.3, 125.7, 126.0 (2C), 127.0, 128.4, 129.2, 129.3, 129.4, 130.6, 135.5, 137.2, 138.0, 142.8, 143.2, 150.0, 164.8. MS (EI) *m/e* 354 (M^+-93, 11.76), 91 (M^+-356, 100). Anal. Calcd for $C_{26}H_{25}NO_4S$ requires C, 69.78; H, 5.63; N, 3.13%. Found: C, 69.78; H, 5.77; N, 3.10%.

3.6.14. *Z*-2-[(toluene-4-sulfonylamino)-*p*-tolyl-methyl]-penta-2,4-dienoic acid phenyl ester (8g). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.31 (3H, s, Me), 2.40 (3H, s, Me), 5.34 (1H, d, J=9.0 Hz), 5.50–5.56 (3H, m), 6.66 (1H, d, J=11.4 Hz), 6.71 (2H, d, J=8.4 Hz), 7.06–7.33 (10H, m, Ar), 7.72 (2H, d, J=8.4 Hz, Ar).

3.6.15. *E*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-penta-2,4-dienoic acid phenyl ester (8h). A white solid: mp 128–129 °C; IR ($CHCl_3$) ν 3020, 1713 (C═O), 1512, 1342, 1250, 1216, 1194, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 3.77 (3H, s, Me), 5.70–5.82 (3H, m), 6.20 (1H, d, J=10.5 Hz), 6.79–6.85 (5H, m), 7.20–7.23 (5H, m, Ar), 7.30–7.36 (3H, m, Ar), 7.66–7.69 (2H, m, Ar). ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.5, 53.3, 55.2, 113.8, 121.3, 126.0, 127.0, 127.8, 128.3, 129.3, 129.4, 129.4, 129.7, 130.5, 138.0, 142.7, 143.2, 150.0, 158.9, 164.8. MS (EI) *m/e* 370 (M^+-93, 5.53), 91 (M^+-372, 100). Anal. Calcd for $C_{26}H_{25}NO_5S$ requires C, 67.37; H, 5.44; N, 3.02%. Found: C, 67.12; H, 5.42; N, 3.02%.

3.6.16. *Z*-2-[(4-methoxyphenyl)-(toluene-4-sulfonyl-amino)-methyl]-penta-2,4-dienoic acid phenyl ester (8h). ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39 (3H, s, Me), 3.78 (3H, s, Me), 5.34 (1H, d, J=8.7 Hz), 5.49–5.56 (3H, m), 6.63–6.84 (5H, m), 7.12 (2H, d, J=8.4 Hz, Ar), 7.16–7.34 (6H, m, Ar), 7.72 (2H, d, J=8.4 Hz, Ar).

Acknowledgements

We thank the State Key Project of Basic Research (Project 973) (no. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (203900502, 20025206, and 20272069).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.058. X-ray crystal data of **7d** and *E*-**8d**. NOESY spectra of **3a**, **4c**, **5a**, and **6a**.

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6. The crystal data of **7d** has been deposited in CCDC with number 240685. Empirical formula: $C_{30}H_{28}NO_3S_3Br$; formula weight: 626.62; temperature: 293(2) K; crystal dimensions: 0.385×0.283×0.177 mm; crystal system: triclinic; space group: *P*-1; unit cell dimensions: $a=10.353(2)$ Å, $b=11.438(2)$ Å, $c=14.385(4)$ Å, $\alpha=81.009(6)°$, $\beta=69.480(4)°$, $\gamma=72.047(4)°$, $V=1515.4(6)$ Å^3; $Z=2$; $D_{calcd}=1.373$ mg/m^3; $F_{000}=644$; Final *R* indices [$I>2\sigma(I)$]: $R_1=0.0582$, $R_2=0.1185$.
7. The crystal data of *E*-**8d** has been deposited in CCDC with number 240686. Empirical formula: $C_{25}H_{22}NO_4SBr$; formula weight: 512.41; temperature: 293(2) K; crystal dimensions: 0.505×0.123×0.052 mm; crystal system: monoclinic; space group: *P*(2)1/*c*; unit cell dimensions: $a=12.644(2)$ Å, $b=20.783(4)$ Å, $c=9.8450(17)$ Å, $\alpha=90°$, $\beta=112.145(4)°$, $\gamma=90°$, $V=2396.2(7)$ Å^3; $Z=4$; $D_{calcd}=1.420$ mg/m^3; $F_{000}=1048$; final *R* induces [$I>2\sigma(I)$]: $R_1=0.0412$, $R_2=0.0579$.
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A Practical, efficient, and atom economic alternative to the Wittig and Horner–Wadsworth–Emmons reactions for the synthesis of (*E*)-α,β-unsaturated esters from aldehydes

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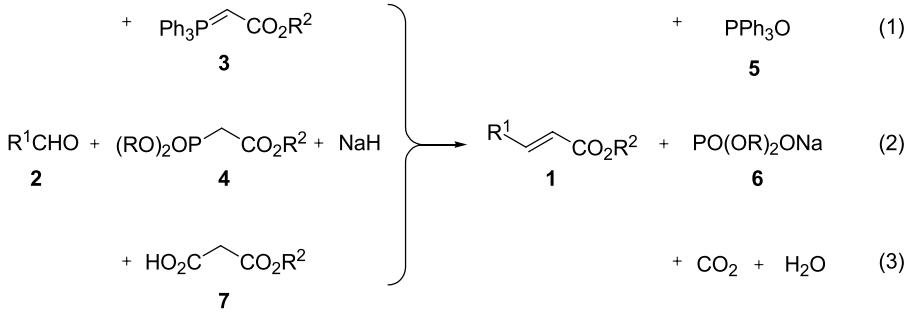
Received 7 July 2005; revised 8 September 2005; accepted 16 September 2005

Available online 20 October 2005

Abstract—We describe a highly efficient new methodology for the synthesis of (*E*)-α,β-unsaturated esters from aldehydes. In our DMAP-catalyzed reaction, both aromatic as well as aliphatic aldehydes furnish the desired products highly regio- and stereoselectively if treated with commercially available or synthetically easily accessible malonic acid half ester. A large scale application in the synthesis of *p*-methoxycinnamates, which are of use as sunscreen ingredients, is described.

1. Introduction

The synthesis of α,β-unsaturated esters **1** from aldehydes **2** is regularly required and a variety of methods have been developed for this transformation.[1,2,3] Because the classical Claisen-type aldol condensation of esters with aldehydes is limited to non-enolizable aldehydes, Wittig- (Eq. 1) or Horner–Wadsworth–Emmons-reactions (Eq. 2) using carbalkoxymethylene triphenylphosphoranes **3** or trialkylphosphonoacetates **4**, respectively, are commonly used alternatives and both high yields and (*E*)-stereoselectivities are typically obtained. A significant limitation, however, in particular concerning large scale applications, is the modest atom economy of these reactions. In the Wittig reaction, triphenylphosphine oxide **5** is a stoichiometric by-product and has to be removed chromatographically only to be disposed.[4] The Horner–Wadsworth–Emmons variant has the advantage of producing a water-soluble phosphate salt **6** as the by-product, which can be removed via aqueous extraction. This variant, however, typically requires the use of a strong base such as sodium hydride and, as in the Wittig reaction stoichiometric by-product formation can challenge waste-management. The decarboxylative Knoevenagel-type reaction of malonic acid half esters **7** with aldehydes to give α,β-unsaturated esters (Eq. 3) is another alternative yet rarely used process.[5] Because only water and carbon dioxide are produced as by-products, this reaction has a significantly improved atom economy. In addition, half-esters of



malonates **7** are as inexpensive as the corresponding phosphorous-based reagents (e.g., **3** and **4**) and can also be obtained easily from even less expensive dialkyl malonates.[6]

Keywords: (*E*)-Stereoselectivity; α,β-Unsaturated esters; Doebner–Knoevenagel reaction; DMAP-catalysis.
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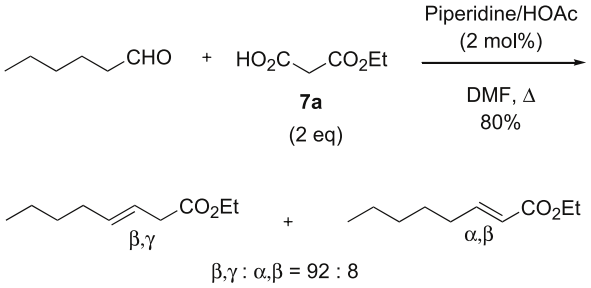
doi:10.1016/j.tet.2005.09.081

While advantageous in principle, the Knoevenagel (or Doebner–Knoevenagel) reaction variant is much less frequently used. Among the main reasons are the generally required reaction conditions, which include using a larger excess of the malonic half ester, catalysis with piperidine in pyridine as the solvent, and elevated temperatures (typically pyridine/reflux). In addition, (*E*)- versus (*Z*)-selectivity varies. The most important drawback, however, results form the fact that in the reaction with enolizable aldehydes, not α,β- but rather β,γ-unsaturated esters (or their mixtures) are commonly obtained.[7]

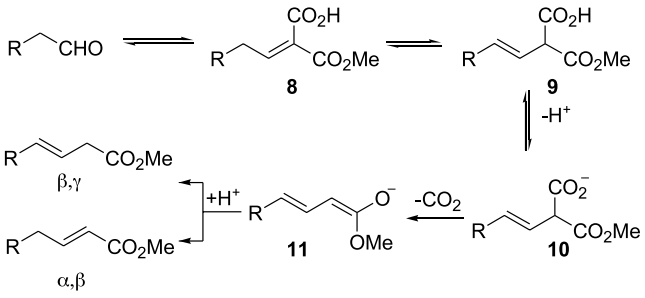
In the context of several other projects we realized the need for a clean, by-product-free, and reliably selective methodology for the production of α,β-unsaturated esters from aldehydes. A desirable feature of such a process would be applicability to large scale production and no requirement for heating or strong bases. We set up a study aimed at overcoming the disadvantages of the traditional Claisen-aldol, Wittig, Horner–Wadsworth–Emmons, and Knoevenagel reactions. Here, we report the full details of our investigation, which resulted in the development of a practical and highly efficient synthesis of α,β-unsaturated esters from aldehydes.[8]

At the onset, we identified the low α,β- versus β,γ-selectivity in the reaction of aliphatic and unbranched aldehydes with malonic acid half esters as the primary issue to be addressed in our studies. Surprisingly, it has been found that under standard Knoevenagel conditions the thermodynamically less stable β,γ-isomer usually dominates. For example, treating *n*-hexanal with ethyl hydrogen malonate **7a** in the presence of piperidinium acetate results in the selective formation of the β,γ-unsaturated ester (Eq. 4).[7b]



(4)

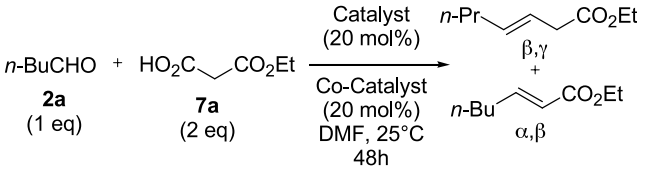
Mechanistic studies by Corey led to the proposal that the reaction in pyridine proceeds via decarboxylation of intermediate **10** to give the dienolate **11**. Its protonation occurs irreversibly at the more reactive α-position resulting in the predominant generation of the β,γ-unsaturated ester (Eq. 5).[9]



(5)

We reasoned that if a catalyst was used that in contrast to pyridine would be able to establish an equilibrium between the β,γ- and the α,β-isomer, the latter should be favoured thermodynamically. In addition, we envisioned alternative mechanistic modes of the decarboxylation, such as conjugate addition of a Lewis basic catalyst to Knoevenagel product **8**, followed by a decarboxylative elimination. Thus, screening alternative catalysts seemed attractive to us.

We decided to initiate our study with a screen of several different amine catalysts in the presence of various base co-catalysts for the reaction of *n*-pentanal **2a** with half ester **7a** (for selected examples see Eq. 6, Table 1). Most combinations led to mixtures of α,β- and β,γ-isomer in various ratios, the β,γ-isomer typically dominating. Remarkably, however, in reactions where we used DMAP as the co-catalyst, the selectivity shifted towards the desired α,β-isomer, independent of the amine catalyst. Moreover, when DMAP was used alone, only the α,β-isomer was formed and gratifyingly with high diastereoselectivity (*E*:*Z*=95:5).



(6)

After further optimization studies, we established reaction conditions that could be used with a large variety of aliphatic aldehydes (Eq. 7, Table 2). Thus, upon treating

Table 1. Screening of catalyst combinations

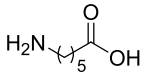
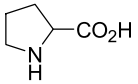
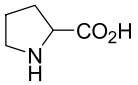
Entry	Catalyst	Co-catalyst	Yield	α,β:β,γ (GC)
1		$NaHCO_3$	60	1:5
2		Na_2CO_3	50	1:3
3		DMAP	80	10:1
4	DMAP	—	91	>20:1

Table 2. Synthesis of α,β-unsaturated esters from aliphatic aldehydes

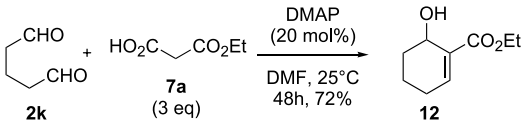
Entry	R	Yield	*E*:*Z* (GC)
1[a]	**a**	91	95:5
2[a]	**b**	95	96:4
3[a]	**c**	92	95:5
4[a]	**d**	91	95:5
5[a]	**e**	91	98:2
6	**f**	96	>99:1
7	**g**	92	98:2
8[b]	**h**	91	>99:1
9	**i**	92	>99:1
10	**j**	92	94:6

[a] Reaction at 10 °C.
[b] Piperidine as co-catalyst (10 mol%).

aliphatic aldehydes **2** with ethyl hydrogen malonate (**7a**, 1.5 equiv) in the presence of DMAP (10 mol%) at rt or below, in DMF, the corresponding α,β-unsaturated esters **1** were obtained with high yields, essentially complete α,β-selectivities, and also highly (*E*)-stereoselective.[10] An aqueous extraction was sufficient to obtain the products in excellent purities and chromatographic purification of the products was generally not required. The reaction proceeds efficiently with both simple unbranched aliphatic aldehydes (entries 1–4), branched aldehydes (entries 6–8), and also with an α-trisubstituted aldehyde (entry 9). Ketones are tolerated in the reaction at least as long as an aldehyde is also present such as in keto aldehyde **2e** (entry 5). This substrate readily undergoes an intramolecular base-catalyzed aldolization but under our reaction conditions this intramolecular process is completely suppressed and only the desired olefination occurs.[11] Despite the initially mildly acidic reaction conditions, aliphatic acetals are preserved in the process (entry 10).[12]

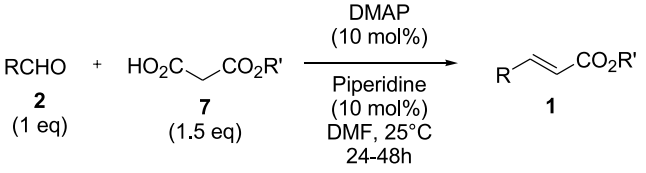
(7)

Not unexpectedly, a tandem olefination, Morita–Baylis–Hilmann reaction to hydroxyl ester **12** was observed with dialdehyde **2k** even when an excess of malonate **7a** was used (Eq. 8).[13]



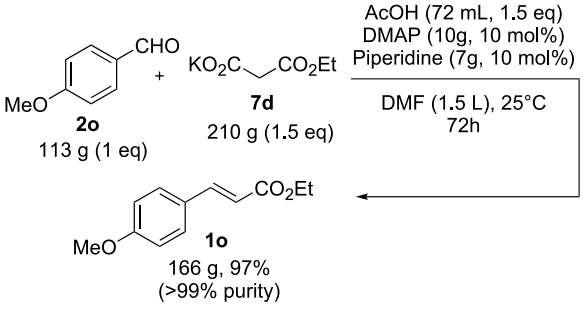
(8)

Aromatic aldehydes can also be used under our reaction conditions. However, the reaction times are generally somewhat longer. Gratifyingly, we found that the reaction rate could be significantly increased when we added piperidine (10 mol%) as co-catalyst. These conditions could be applied to a number of different aromatic and heteroaromatic aldehydes (Eq. 9, Table 3). In general, (*E*)/(*Z*)-selectivities are excellent exceeding 99:1 (by GC and NMR). In addition to ethyl esters (R^2=Et), both *tert*-butyl (R^2=*t*-Bu, entry 2) and benzyl esters (R^2=Bn, entry 3) can be obtained with comparable efficiency. As expected, rates are generally faster with electron poor aldehydes (entries 8, 11–13) and can be relatively slow with electron rich aromatic aldehydes such as *p*-hydroxybenzaldehyde (entry 9). *p*-Terephtalaldehyde **2v** and isophthalaldehyde **2w** in the presence of 3 equiv of malonate **7** gave the expected bis-enoates **1v** and **1w** in good yield (entries 13 and 4).



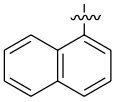
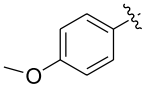
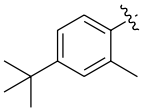
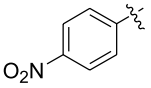
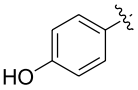
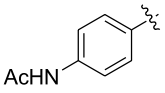
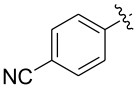
(9)

The synthesis of *p*-methoxyethylcinnamate (**1o**, entry 6) has been scaled up to illustrate the practicability of our process (Eq. 10).[14] In this reaction, we generated malonate **7a** in situ from the even less expensive potassium salt **7d** with acetic acid. Transesterification of cinnamate **1o** with 2-ethyl hexanol or isoamyl alcohol gave industrially relevant cinnamates **13** and **14**, UV-light absorbing ingredients of commercially available sunscreens (Eq. 11).



(10)

Table 3. Synthesis of α,β-unsaturated esters from aromatic aldehydes

Entry	R	R′	Yield	*E*:*Z* (GC)
1		Et (**a**)	92	>99:1
2		*t*-Bu (**b**)	87	>99:1
3		Bn (**c**)	96	>99:1
	l			
4		Et	92	>99:1
	m			
5		Et	91	>99:1
	n			
6		Et	99	>99:1
	o			
7		Et	89	>99:1
	p			
8		Et	86	>99:1
	q			
9[a]		Et	90	>99:1
	r			
10[a]		Et	92	>99:1
	s			
11		Et	94	>99:1
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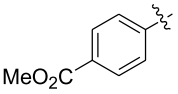
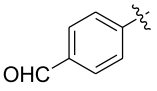
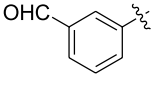
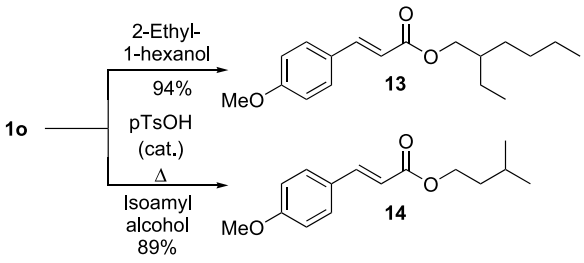
12		Et	92	>99:1
	u			
13[b]		Et	93	>99:1
	v			
14[b]		Et	93	>99:1
	w			

[a] Reaction time (168 h).
[b] bis-Enoate was obtained using 3 equiv of halfester.



(11)

In summary, we have developed a new synthesis of α,β-unsaturated esters from aldehydes. Our reaction is mild, efficient, catalytic, practical, (atom-)economic, and highly α,β-regio-, and (*E*)-stereoselective. The reaction tolerates various functional groups and can be used with both aliphatic and aromatic aldehydes. Future studies in our laboratory will focus on exploring the full scope of this reaction and of related decarboxylative carbon–carbon bond forming reactions.[15]

2. Experimental

2.1. General procedure for the reaction with the malonic acid monoethyl ester (7a)

4-Dimethylaminopyridine (24.4 mg, 0.20 mmol) was dissolved in 5 mL of DMF. The malonic acid half ester (3.00 mmol) followed by the aldehyde (2.00 mmol) were added, and the reaction was stirred at 10 °C or rt until the aldehyde was consumed.[16] The mixture was extracted with Et_2O and the organic layer was washed successively with NH_4Cl, water, $NaHCO_3$, and once again with water. After drying (Na_2SO_4) and filtering, all volatiles were evaporated in vacuo yielding, without any further purification, the pure α,β-unsaturated ester in the reported yields.

2.2. Scale up for *p*-methoxyethylcinnamate (1o)

4-Dimethylaminopyridine (10 g, 81.9 mmol) was dissolved in DMF (1.5 L). The potassium salt of the malonic acid half ester (**7d**, 210.1 g, 1234.4 mmol) followed by *p*-anisaldehyde (**2o**, 113.0 g, 829.0 mmol) were added. This suspension was stirred at 10 °C and acetic acid (72.2 mL, 1262.4 mmol) and piperidine (7 g, 82.2 mmol) were added dropwise consecutively. The mixture was stirred at rt until the aldehyde was consumed (72 h). After the standard aqueous work (see above) and recrystallization from ethanol, 165.8 g (803.9 mmol, 97%) of ester **1o** was obtained as white needles.

2.2.1. Transesterification of *p*-methoxyethylcinnamate (1o) with 2-ethyl-1-hexanol. *p*-Methoxyethylcinnamate **1o** (24.8 g, 120.3 mmol) and *p*-TsOH (2.3 g, 12.1 mmol) were dissolved in 2-ethyl-1-hexanol (223.0 g, 1712.3 mmol). The resulting solution was heated overnight to reflux. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The organics were dried (Na_2SO_4) and concentrated in vacuo to give ester **13** (32.8 g, 113 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 6H, J=7.3 Hz), 1.30–1.44 (m, 8H); 1.64–1.67 (m, 1H), 3.84 (s, 3H), 4.11 (d, 2H, J=5.8 Hz), 6.31 (d, 1H, J=15.9 Hz), 6.91 (d, 2H, J=6.8 Hz), 7.48 (d, 2H, J=6.8 Hz), 7.63 (d, 1H, J=15.9 Hz). ^{13}C NMR δ11.0, 14.1, 23.0, 23.9, 29.0, 30.5, 38.9, 55.4, 66.8, 114.3, 115.9, 127.3, 129.7, 144.2, 161.3, 167.6.

2.2.2. Transesterification of *p*-methoxyethylcinnamate (1o) with isoamyl alcohol. *p*-Methoxyethylcinnamate **1o** (101 g, 489.7 mmol) and *p*-TsOH (5.3 g, 27.9 mmol) were dissolved in isoamyl alcohol (432.1 g, 4901.9 mmol). The resulting solution was heated overnight to reflux. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The organics were dried (Na_2SO_4) and concentrated in vacuo to give isoamylester **14** (108.4 g, 436.5 mmol, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 6H, J=6.7 Hz), 1.58–1.63 (m, 4H), 1.71–1.77 (m, 1H), 3.80 (s, 3H), 4.23 (t, 2H, J=6.7 Hz), 6.30 (d, 1H, J=15.9 Hz), 6.91 (d, 2H, J=8.6 Hz), 7.49 (d, 2H, J=8.6 Hz), 7.63 (d, 1H, J=15.9 Hz). ^{13}C NMR δ 22.5, 25.1, 37.5, 55.4, 63.1, 114.3, 115.8, 129.7, 144.2, 161.3, 167.4.

2.2.3. Ethyl-(*E*)-3-phenyl-2-propenoate (1l–a). Colourless oil (325.3 mg, 1.85 mmol, 92%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[17]

2.2.4. *tert*-Butyl-(*E*)-3-phenyl-2-propenoate (1l–b). Colourless oil (354.6 mg, 1.74 mmol, 87%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[18]

2.2.5. Benzyl-(*E*)-3-phenyl-2-propenoate (1l–c). Colourless oil (456.8 mg, 1.92 mmol, 96%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[19]

2.2.6. Ethyl-(*E*)-3-(1-naphthalenyl)-2-propenoate (1m). Colourless oil (417.1 mg, 1.84 mmol, 92%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[20]

2.2.7. Ethyl-(*E*)-3-(2-furanyl)-2-propenoate (1n). Colourless oil (302.1 mg, 1.82 mmol, 91%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[21]

2.2.8. Ethyl-(*E*)-3-(4-methoxyphenyl)-2-propenoate (1o). Colourless needles (408.1 mg, 1.98 mmol, 99%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[17]

2.2.9. Ethyl-(*E*)-3-(2-methyl-4-*tert*-butylphenyl)-2-propenoate (1p). Colourless oil (437.1 mg, 1.77 mmol, 89%, *E*:*Z*>99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.28 (t, 3H, J=7.1 Hz), 2.33 (s, 3H); 4.21 (q, 2H, J=7.1 Hz), 6.30 (d, 1H, J=15.9 Hz), 7.07 (d, 1H, J=8.0 Hz), 7.24 (dd, 1H, J=8.0, 2 Hz), 7.49 (d, 1H, J=2 Hz), 7.91 (d, 1H, J=15.9 Hz). ^{13}C NMR δ 13.9, 18.8, 30.9, 34.1, 60.1, 118.6, 122.9, 124.0, 126.9, 130.2, 132.0, 142.6, 148.8, 166.0.

2.2.10. Ethyl-(*E*)-3-(4-nitrophenyl)-2-propenoate (1q). Pale-yellow needles (378.8 mg, 1.71 mmol, 86%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[22]

2.2.11. Ethyl-(*E*)-3-(4-hydroxyphenyl)-2-propenoate (1r). Colourless oil (346.0 mg, 1.8 mmol, 90%, *E*:*Z*>99:1). The NMR data is in accordance with the lit.[23]

2.2.12. Ethyl-(*E*)-3-(4-acetamidophenyl)-2-propenoate (1s). Pale-yellow needles (427.6 mg, 1.83 mmol, 92%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[24]

2.2.13. Ethyl-(*E*)-3-(4-cyanophenyl)-2-propenoate (1t). Colourless oil (379.5 mg, 1.89 mmol, 94%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[25]

2.2.14. Ethyl-(*E*)-3-(4-acetoxyphenyl)-2-propenoate (1u). White needles (429.2 mg, 1.83 mmol, 92%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[22]

2.2.15. Bis-ethyl-(*E*)-3,3′-(1,4-phenylene)-2-propenoate (1v). White needles (510.8 mg, 1.86 mmol, 93%, *E*:*Z*>99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 6H, J=7.1 Hz), 4.21 (q, 4H, J=7.1 Hz), 6.39 (d, 2H, J=15.9 Hz), 7.47 (s, 4H), 7.59 (d, 2H, J=15.9 Hz). ^{13}C NMR δ 14.7, 61.0, 119.8, 128.9, 136.5, 143.8, 167.1.

2.2.16. Bis-ethyl-(*E*)-3,3′-(1,3-phenylene)-2-propenoate (1w). White needles (511.4 mg, 1.86 mmol, 93%, *E*:*Z*>99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 6H, J=7.1 Hz), 4.27 (q, 4H, J=7.1 Hz), 6.47 (d, 2H, J=16.0 Hz), 7.41 (dd, 1H, J=7.5 Hz), 7.54 (d, 2H, J=7.5 Hz), 7.65 (t, 1H, J=7.5 Hz), 7.68 (d, 2H, J=16.0 Hz). ^{13}C NMR δ 14.3, 60.6, 119.3, 127.6, 129.4, 129.5, 135.2, 143.6, 166.7.

2.2.17. Ethyl-(*E*)-2-heptenoate (1a). Colourless oil (284.0 mg, 1.82 mmol, 91%, *E*:*Z*=95:5). NMR data is in accordance with the lit.[26]

2.2.18. Ethyl-(*E*)-2-nonenoate (1b). Colourless oil (350.9 mg, 1.90 mmol, 95%, *E*:*Z*=96:4). NMR data is in accordance with the lit.[27]

2.2.19. Ethyl-(*E*)-5-methyl-2-hexenoate (1c). Colourless oil (287.3 mg, 1.84 mmol, 92%, *E*:*Z*=95:5). NMR data is in accordance with the lit.[28]

2.2.20. Ethyl-(*E*)-5-phenyl-2-pentenoate (1d). Colourless oil (370.1 mg, 1.81 mmol, 91%, *E*:*Z*=95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, J=7.1 Hz), 2.43–2.48 (m, 2H), 2.67–2.72 (m, 2H), 4.10 (q, 2H, J=7.1 Hz), 5.78 (d, 1H, J=15.6 Hz), 6.90 (dt, 1H, J=15.6 Hz), 7.10–7.14 (m, 3H), 7.17–7.23 (m, 2H). ^{13}C NMR δ 15.3, 35.0, 35.5, 61.3, 123.0, 127.2, 129.4, 129.6, 141.9, 149.1, 167.7.

2.2.21. Ethyl-(*E*)-8-oxo-2-nonenoate (1e). Colourless oil (360.6 mg, 1.82 mmol, 91%, *E*:*Z*=98:2). NMR data is in accordance with the lit.[29]

2.2.22. Ethyl-(*E*)-4-methyl-2-pentenoate (1f). Colourless oil (273.2 mg, 1.92 mmol, 96%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[28]

2.2.23. Ethyl-(*E*)-3-cyclohexyl-2-propenoate (1g). Colourless oil (335.4 mg, 1.84 mmol, 92%, *E*:*Z*=98:2). NMR data is in accordance with the lit.[22]

2.2.24. Ethyl-(*E*)-4,4-diphenyl-2-butenoate (1h). Colourless oil (483.1 mg, 1.81 mmol, 91%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[22]

2.2.25. Ethyl-(*E*)-4,4-dimethyl-2-pentenoate (1i). Colourless oil (286.5 mg, 1.83 mmol, 92%, *E*:*Z*>99:1). NMR data is in accordance with the lit.[28]

2.2.26. Ethyl-(*E*)-6,6-dimethoxy-2-hexenoate (1j). Colourless oil (373.1 mg, 1.85 mmol, 92%, *E*:*Z*=94:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, J=7.1 Hz), 1.66–1.71 (m, 2H), 2.17–2.22 (m, 2H), 3.25 (s, 6H), 4.12 (q, 2H, J=7.1 Hz), 4.30 (t, 1H, J=5.6 Hz), 5.78 (d, 1H, J=15.6 Hz), 6.89 (dt, 1H, J=15.6 Hz). ^{13}C NMR δ 13.9, 26.9, 30.5, 52.5, 59.8, 103.3, 121.3, 147.7, 166.2.

Acknowledgements

Generous gifts of chemicals by Degussa and general support of our work by Lanxess is most gratefully acknowledged. We thank Kathrin Wobser, Hendrik van Thienen, and Pedro Llamas Galilea for technical assistance.

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A [3,3]-sigmatropic process catalysed by acetate. The decarboxylative Claisen rearrangement

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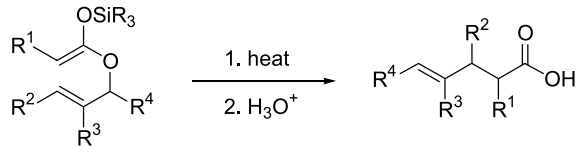
Received 15 June 2005; revised 30 August 2005; accepted 16 September 2005

Available online 14 October 2005

Abstract—Allylic tosylacetates and tosylmalonates undergo acetate-catalysed decarboxylative Claisen rearrangement in the presence of *N*,*O*-bis(trimethylsilyl)acetamide. The homoallylic sulfones formed in these transformations correspond to the products of regiospecific allylation of sulfone-stabilised carbanions. A mechanistic rationale is proposed.

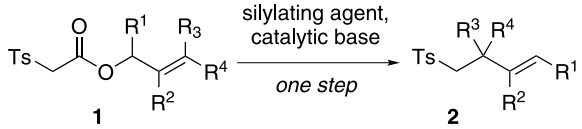
1. Introduction

The Claisen rearrangement enjoys widespread use as a key strategy-level transformation in organic synthesis.[1] The power of the process stems from (i) its ability to deliver new carbon–carbon bonds with regiospecific allylic transposition from simple derivatives of alcohol precursors; (ii) ease of substrate synthesis; (iii) high levels of stereoslectivity, which may be predicted largely on the basis of well-established trends; and (iv) compatibility with a wide range of functionality, which makes it amenable to application in total synthesis. Following the discovery of the Claisen rearrangement in 1912, several variations have been devised, which augment the original process in terms of reaction conditions and product functionality. Arguably the most versatile of these is the Ireland–Claisen rearrangement, in which silyl ketene acetals derived from allylic carboxylic esters provide rearranged carboxylic acids on hydrolysis of the initial silyl ester products (Scheme 1).[2] This variant is characterised by the mildness of the conditions used for the rearrangement step, which often takes place at ambient or sub-ambient temperature, and by the ready availability of the substrates from allylic alcohol and carboxylic acid starting materials.



Scheme 1. The Ireland–Claisen rearrangement.

In 1991 Davidson and co-workers reported the Ireland–Claisen rearrangement of a highly substituted allylic α-phenylsulfonylacetate ester-derived substrate.[3] They generated the requisite sulfonyl-substituted silyl ketene acetal using the standard lithium diisopropylamide-TMSCl conditions, and carried out decarboxylation post-rearrangement by heating the product acid under weakly basic conditions. Following repeated failures in our own laboratory to repeat the standard rearrangement step on structurally different tosylacetate substrates, we uncovered alternative conditions using silylating agent and catalytic, weak base, which effect rearrangement and decarboxylation to give homoallylic sulfones **2** in a single step directly from the allylic α-tolylsulfonylacetate esters **1** (Scheme 2). We term this process a decarboxylative Claisen rearrangement[4] (dCr) reaction; this paper describes our results in full.[5]



Scheme 2.

Keywords: Acetate-catalysed; Claisen rearrangement; Decarboxylation; Regiospecific allylation.
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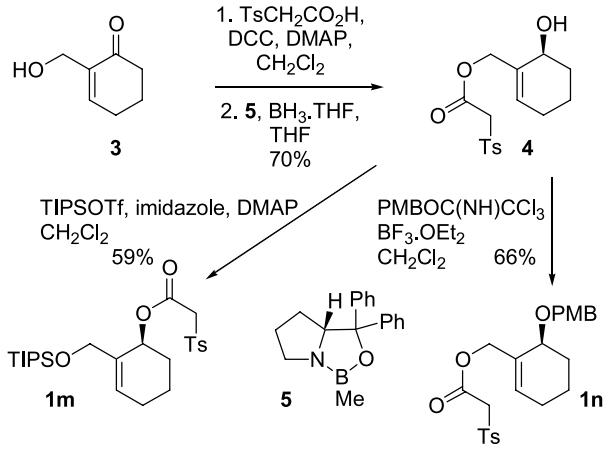
doi:10.1016/j.tet.2005.09.073

2. Results and discussion

2.1. Acetate-catalysed dCr reactions of simple allylic tosylacetates

Most of the tosylacetate ester substrates **1** required for our study were easily prepared by combining allylic alcohols and commercially available[6] tosylacetic acid in the presence of DCC and DMAP.[7] Substrates **1m** and **1n** were made from 2-hydroxymethyl-2-cyclohexenone **3**[8] according to the sequence depicted in Scheme 3. Thus, tosylacetylation of **3** followed by enantioselective reduction using (+)-(*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine **5** in conjunction with $BH_3\cdot THF$[9] gave secondary alcohol **4** in high yield and 82% ee as evidenced by ^1H NMR analysis of the derived Mosher esters. Attempted triisopropylsilyl (TIPS) protection of the alcohol in **4** led to tosylacetyl migration and silylation of the primary alcohol, providing substrate **1m** in 59% yield. Compound **4** was more straightforwardly alkylated to give the 4-methoxybenzyl (PMB) derivative **1n** in 66% yield using 4-methoxybenzyl trichloroacetimidate in conjunction with $BF_3\cdot OEt_2$.[10]



Scheme 3.

Following work by Poli[11] and by Trost[12] on palladium(0)-catalysed allylation reactions involving arylsulfonylacetate esters we examined the use of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) in conjunction with potassium acetate. We established that heating of **1** with one equivalent of BSA and 10 mol% KOAc in toluene at 110 °C overnight (conditions A) gave homoallylic sulfone products **2** in good to excellent yields. Little or no diminution in yield was observed when the dCr reactions were carried out using microwave irradiation in the presence (conditions B) or absence (conditions C) of solvent (Table 1).

The data in Table 1 demonstrate the dCr reaction to be compatible with a wide range of substrate structure and functionality. Notably, the transformation worked well irrespective of allylic geometry (compare entries 1 and 2) and level of substitution (entries 5 and 6), and delivered homoallylic sulfones possessing quaternary centres in high yields (entries 7, 8, 11). Reactions of cyclic, chiral substrates (entries 9, 10, 12, 13) were usually completely diastereoselective (but see entry 14), and in one instance an acyclic substrate possessing a heteroatom-bearing stereocentre adjacent to but outside the pericyclic array reacted with high selectivity (entry 16), though the major diastereoisomer has yet to be assigned. Yields for the two silyl ether-containing substrates (entries 13 and 16) were significantly lower than those for all other substrates, and this may reflect competing acetate-induced desilylation taking place under the thermal conditions of the rearrangement.

Subsequent to the initial phase of our investigation it occurred to us that the acetate-catalysed rearrangement process might equally be viable in the presence of sub-stoichiometric quantities of BSA as well as of potassium acetate. This idea was based on the notion that acetate ions might catalyse trimethylsilyl transfer from the presumed initial silyl ester rearrangement product to **1**, generating further silyl ketene acetal substrate and rendering the reaction catalytic in silylating agent. Therefore, we subsequently investigated a modification of the dCr reaction using 10 mol% each of BSA and KOAc. In all cases studied the yields of **2** were comparable with those obtained in the stoichiometric reactions (Table 2).

2.2. Mechanistic considerations

As alluded to above, we propose a catalytic cycle for the dCr reactions of **1** in which acetate functions as a silyl transfer reagent. The cycle is initiated through the generation of **6**, the silyl ketene acetal derivative of **1**. This could in principle take place through the reversible combination of BSA and KOAc, giving the conjugate base of *N*-trimethylsilyl-acetamide and TMSOAc; the former species effects deprotonation of **1**, and the resulting enolate is silylated by TMSOAc. Alternatively, **1** undergoes direct proton-silyl exchange with BSA, giving *N*-trimethylsilylacetamide and the ketene acetal. Support for the involvement of the latter pathway comes from the observation that heating of **1a** with BSA alone gave in 49% yield the carboxylic acid **8**, the product of rearrangement but not decarboxylation. Once formed, silyl ketene acetal **6** undergoes [3,3]-sigmatropic rearrangement to the silyl ester **7**, which is intercepted by acetate to give the derived carboxylate anion and regenerated TMSOAc. Decarboxylation gives the conjugate base of product **2**, which can then abstract a proton either directly from **1**, or from *N*-trimethylsilylacetamide, in which case the conjugate base of *N*-trimethylsilylacetamide effects deprotonation of **1** prior to silylation by TMSOAc in the next cycle. The proposed mechanisms are depicted in Scheme 4.

Evidence to support the mechanistic proposals depicted in Scheme 4 was obtained from the following observations. Heating of toluene solutions of **1a** in the presence of potassium acetate alone (0.1, 0.5, 1.0 equiv) resulted in quantitative recovery of starting material. Replacing BSA with Me_3SiOAc, $Me_3SiOSiMe_3$ or $(Me_3Si)_2NH$ likewise resulted in complete recovery of starting material, and the same outcome was observed when *N*-trimethylsilyl-acetamide was used instead of BSA. In contrast, substitution of KOAc with Et_3N, DBU or pyrrolidine resulted in formation of acid **8** in yields of 70, 56 and 63%, respectively. As stated above, treatment of **1a** with BSA

Table 1. Acetate-catalysed decarboxylative Claisen rearrangement reactions of **1**: stoichiometric BSA

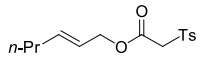
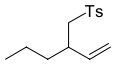
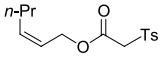
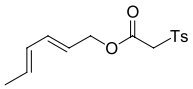
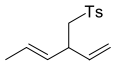
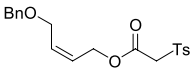
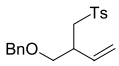
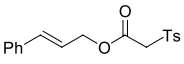
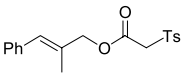
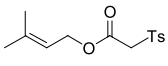
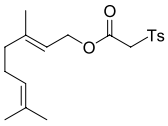
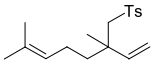
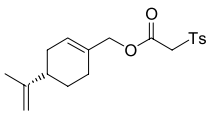
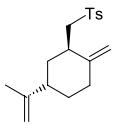
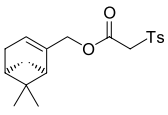
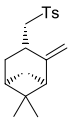
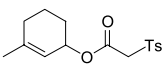
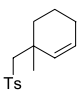
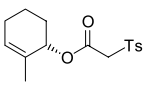
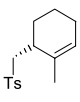
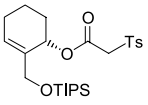
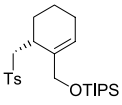
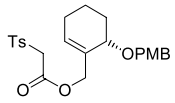
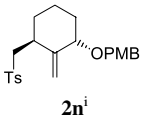
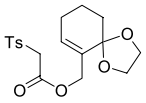
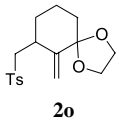
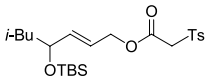
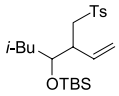
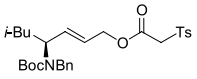
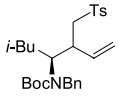
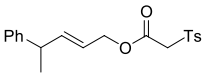
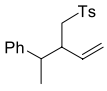
Entry	Substrate	Product	Yield (%)		
			Conditions A[a]	Conditions B[b]	Conditions C[c]
1	 **1a**	 **2a**	80	81	92
2	 **1b**	**2a**	92	—	59
3	 **1c**	 **2c**	90	81	—
4	 **1d**	 **2d**	77	—	58
5	 **1e**	 **2e**	74	—	—
6	 **1f**	 **2f**	88	—	72
7	 **1g**	 **2g**	88	—	—
8	 **1h**[d]	 **2h**	83	89	83
9	 **1i**	 **2i**	89	67	80
10	 **1j**	 **2j**	81	—	80
11	 **1k**[e]	 **2k**	86	—	74
12	 **1l**[f]	 **2l**	87	—	—
13	 **1m**[g]	 **2m**	55[h]	—	—

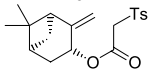
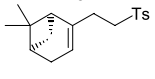
Table 1 (*continued*)

Entry	Substrate	Product	Yield (%)		
			Conditions A[a]	Conditions B[b]	Conditions C[c]
14	 **1n**[g]	 **2n**[i]	64	—	—
15	 **1o**	 **2o**	86	—	—
16	 **1p**[e]	 **2p**[j]	62	—	—
17	 **1q**	 **2q**[k]	74	18	67
18	 **1r**[e]	 **2r**[l]	63	—	—

[a] Conditions A: BSA (1 equiv), KOAc (0.1 equiv), PhMe, reflux, 16 h.
[b] Conditions B: BSA (1 equiv), KOAc (0.1 equiv), PhMe, microwave irradiation (150 °C [250 W]), 3 min.
[c] Conditions C: BSA (1 equiv), KOAc (0.1 equiv), no solvent, microwave irradiation (150 °C [250 W]), 3 min.
[d] See Ref. 13.
[e] Racemic substrate.
[f] Substrate had 84% ee by Mosher ester analysis of precursor alcohol.
[g] Substrate had 82% ee by Mosher ester analysis of precursor alcohol **4**.
[h] Yield based on 29% recovered **1m**.
[i] Product was formed as a 3:1 mixture of *anti* and *syn* diastereoisomers (major isomer shown).
[j] Product was formed as a 7:1 mixture of diastereoisomers (not assigned).
[k] Product was formed as a 1:1 mixture of diastereoisomers.
[l] Product was formed as a 3:2 mixture of diastereoisomers (not assigned).

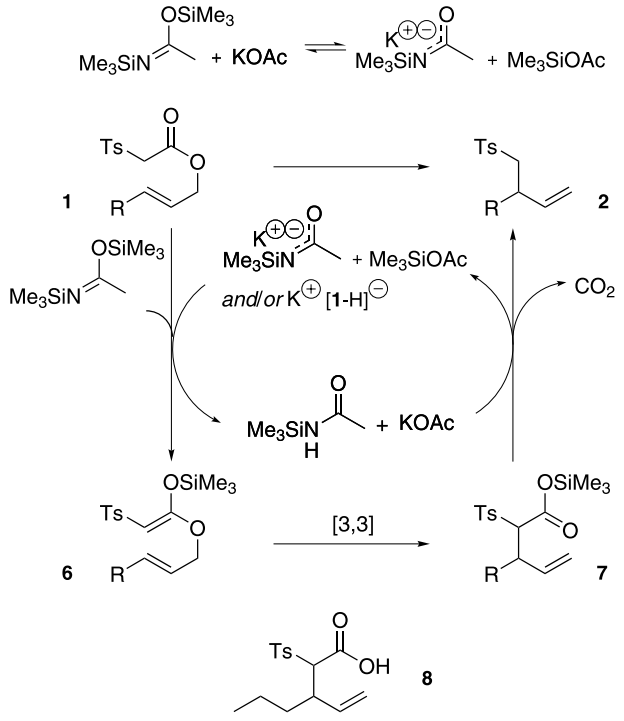
alone (1.1 equiv) in toluene under reflux gave **8** in 49% yield; evidently silyl ketene acetal formation and rearrangement, but not decarboxylation take place under these conditions, pointing to the key, catalytic role of acetate ion in the silyl transfer step. Use of Me_3SiOTf or *t*-$BuMe_2SiOTf$ together with DBU gave **2a** in respective yields of 15 and 28%, whilst combinations of Me_3SiCl and DBU again gave **8**. Lastly, exposure of **1a** to a mixture containing *N*-trimethylsilylacetamide, *t*-BuLi and Me_3-SiOAc gave **2a** in 67% yield; replacing *t*-BuLi with KH in this modified reaction gave the same product in a yield of 51%. These results strongly suggest that whilst the catalytic cycle requires acetate, the manner of its generation is less important.

Table 2. Acetate-catalysed decarboxylative Claisen rearrangement reactions of **1**: sub-stoichiometric BSA

Entry	Substrate	Product	Yield (%)	
			Conditions A[a]	Conditions B[b]
1	**1a**	**2a**	88	94
2	**1e**	**2e**	92	85
3	**1h**	**2h**	75	87
4	**1j**	**2j**	98	93
5	 **1s**	 **2s**	91	87

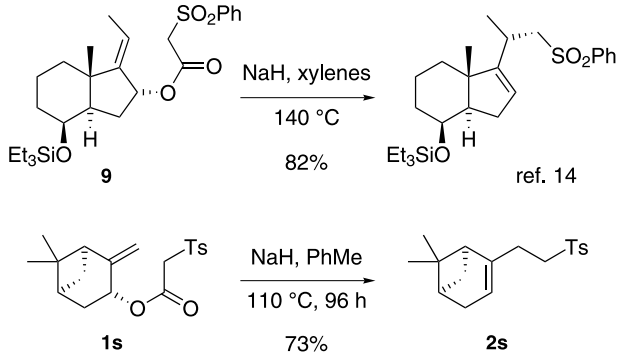
[a] Conditions A: BSA (0.1 equiv), KOAc (0.1 equiv), PhMe, reflux, 15 h.
[b] Conditions B: BSA (0.1 equiv), KOAc (0.1 equiv), PhMe, microwave irradiation (150 °C [250 W]), 3 min.

Whilst this work was in progress a report[14] appeared from the laboratory of Posner of a related transformation of allylic tosylacetate **9**, in which exposure to strong base under thermal conditions effected [3,3]-sigmatropic rearrangement and decarboxylation in situ. This reaction was described as a Carroll-type process,[15] in which the substrate was rendered reactive by formation of its conjugate base. That our acetate-catalysed dCr reaction is distinct mechanistically from the Carroll reaction is evidenced by the failure of **1a** to react in the presence of acetate alone, demonstrating that both nucleophile/base and silylating agent are necessary for the catalytic cycle to be viable. In our hands, substrate **1s** did undergo rearrangement



Scheme 4.

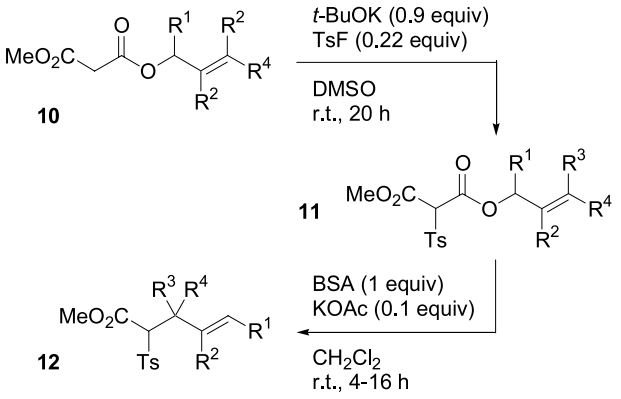
and decarboxylation to give **2s** in good yield when exposed to NaH in toluene under reflux over a 4-day period (Scheme 5).



Scheme 5.

2.3. dCr Reactions of allylic methyl tosylmalonates

With the efficiency and scope of the dCr reaction of simple allylic tosylacetates established, our attention was turned to the development of modified substrates. It was anticipated that addition of an electron-withdrawing group at the ester α-position would enhance reactivity, such that ambient-temperature reactions would be attainable. This was an attractive goal in view of our longer-term plan to realise high levels of selectivity in the reactions of acyclic, chiral substrates related to **1p**, **1q**, and **1r**. Methoxycarbonyl was chosen as the electron-withdrawing auxiliary group. Substrates **11** were readily prepared from methyl malonate[16] in generally good yields by DCC–MAP-mediated esterification with allylic alcohols to give mixed malonates **10**,[5b] followed by tosylation using *t*-BuOK–TsF in DMSO. Four equivalents of the anion of **10** with respect to TsF were required for acceptable levels of conversion; unconsumed malonate was usually recoverable in good yield.[17,18] Treatment of **11** with one equiv BSA and 0.1 equiv KOAc in CH_2Cl_2 at rt during reaction times ranging from 4 to 16 h resulted in generally high-yielding dCr reactions, providing the products **12** of formal regiospecific allylation of methyl tosylacetate. The reactions of all substrates other than **11a** and **11e** gave rise to mixtures of diastereoisomers on account of the additional α-stereocentre in the products.[19] The dCr reactions of chiral substrates showed the diastereoselectivities for new C–C bond formation expected on the basis of simple steric considerations. The synthesis and dCr reactions of **11** are depicted in Scheme 6 and the results summarised in Table 3.



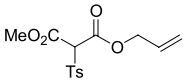
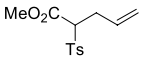
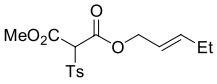
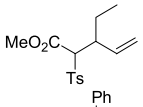
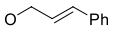
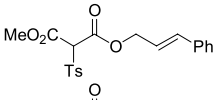
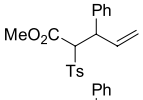
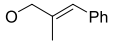
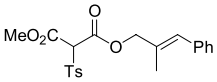
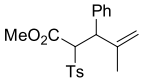
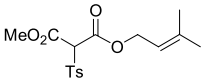
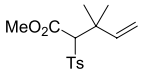
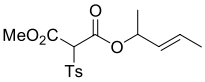
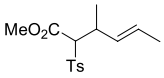
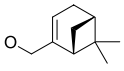
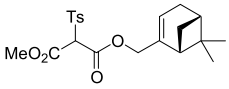
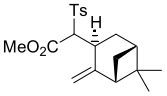
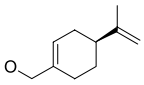
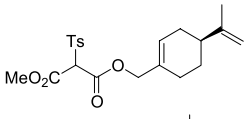
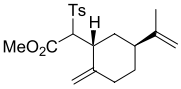
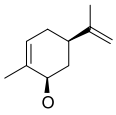
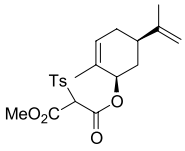
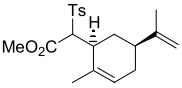
Scheme 6.

The reduction in minimum temperature required for the acetate-catalysed dCr reactions of these modified substrates to occur is striking. Also noteworthy was the observation that these room-temperature transformations took place with similar efficiencies but significantly more rapidly when the BSA–OAc reagent system was substituted with DBU–TBDMSOTf.[5b] In the dCr reactions of tosylacetates **1** DBU–TBDMSOTf was markedly inferior to BSA–OAc, and combinations of BSA and Et_3N gave rearrangement but no decarboxylation.[5a] We have interpreted[5b] these findings in terms of an alternative dCr reaction mechanism for malonate substrates **11**, in which the ketene acetals formed in the [3,3]-sigmatropic rearrangement step undergo decarboxylation by a mechanism not requiring acetate, involving silatropic rearrangement[23] in a formal retro-ene reaction. Formation of the silyl ketene acetal derivatives of the isolated products **12** in this way would consume BSA, consistent with the finding that the use of sub-stoichiometric quantities of BSA resulted in incomplete conversion of **11**.

3. Conclusions

In summary, we have uncovered an acetate-catalysed variant of the Claisen rearrangement reaction, which allows regiospecific allylation of sulfone-substituted carbon moieties.[24] To our knowledge, this is the first example of a ketene acetal formation-Claisen rearrangement sequence, which utilises sub-stoichiometric amounts of base and

Table 3. Synthesis and dCr reactions of allylic methyl tosylmalonates **11**

Entry	10		11			12		
	OR	Substrate	Structure		Yield[a]	Structure		Yield
1		**10a**		**11a**	67 (79)		**12a**[b]	62
2		**10b**		**11b**	60 (65)		**12b**	74
3		**10c**		**11c**	70 (74)		**12c**[c]	81
4		**10d**		**11d**	56 (99)		**12d**	59
5		**10e**		**11e**	90 (91)		**12e**	80
6		**10f**		**11f**	79 (83)		**12f**	88
7		**10g**		**11g**	78 (99)		**12g**	72
8		**10h**		**11h**	81 (100)		**12h**	45
9		**10i**		**11i**	74 (66)		**12i**	19

[a] See Ref. 20.
[b] See Ref. 21.
[c] See Ref. 22.

silylating agent. Addition of an electron-withdrawing group to the sulfone-substituted carbon atom results in significant acceleration of the acetate-catalysed tandem process such that the reactions proceed at rt. We are presently applying this chemistry in the synthesis of pyridines, phenols, and alkaloid natural products, and have investigated diastereoselective dCr reactions of the sulfoximine analogues of **1**.[25] The results of these studies will be the subject of future reports from this laboratory.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on either Jeol GX-270a, DRX 300, DRX 400 or Aspect 500 spectrometers, using residual isotopic solvents as internal reference. Infra-red spectra were measured on a Mattson 5000 FTIR spectrometer. Mass spectra were recorded using VG 707E or VG Autospec Q instruments. Accurate masses were determined using the Autospec Q instrument at Imperial College. Elemental combustion analyses were performed in the Imperial College microanalytical laboratory. Melting points were measured on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Chromatography refers to flash chromatography on BDH (40–63 μM) silica gel. Analytical thin-layer chromatography was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light and/or acidic ammonium molybdate(IV), acidic vanillin, ethanolic potassium permanganate or acidic 3,5-dinitrophenylhydrazine solutions. Standard solvents were distilled under nitrogen; Et_2O and THF from sodium-benzophenone ketyl, CH_2Cl_2 and MeCN from calcium hydride and PhMe from sodium. Petrol refers to petroleum ether bp 40–60 °C. Other solvents and reagents were used as received or purified before use according to standard procedures.[26] All reactions were performed under an atmosphere of nitrogen unless stated otherwise.

4.1.1. Preparation of (*S*)-6-hydroxycyclohexen-1-ylmethyl tosylacetate (4). To a stirred solution of 2-hydroxymethyl-2-cyclohexenone **3**[8] (494 mg, 3.9 mmol) in CH_2Cl_2 (53 mL) was added a solution of DCC (892 mg, 4.33 mmol, 1.1 equiv) in CH_2Cl_2 (11 mL) and tosylacetic acid (927 mg, 4.33 mmol), the solution stirred for 5 min and DMAP (48 mg, 0.39 mmol) added. The cloudy reaction mixture was stirred at rt for 24 h, filtered through Celite, the pad washed with EtOAc (10 mL) and the organic layers washed with 1 M $KHSO_4$ (50 mL), saturated $NaHCO_3$

(50 mL) and brine (50 mL). The organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by chromatography (60% EtOAc/petrol) to give 6-oxocyclohexen-1-ylmethyl tosylacetate (1.01 g, 80%) as a colourless solid; mp 134–136 °C; R_f 0.27 (60% EtOAc/petrol); ν_{max} (CH_2Cl_2) 2936, 2888, 1742, 1672, 1453, 1327, 1272, 1150, 1118, 815, 646 cm^{-1}; δ_H (270 MHz) 7.67 (2H, d, J=8.0 Hz, *ortho*-ArH), 7.24 (2H, d, J=8.0 Hz, *meta*-ArH), 6.58 (1H, t, J=4.0 Hz, C=CH), 4.76 (2H, d, J=1.0 Hz, CH_2O), 4.10 (2H, s, CH_2SO_2), 2.46–2.39 (4H, m, ring CH_2), 2.41 (3H, s, CH_3), 2.00–1.92 (2H, m, ring CH_2); δ_C (67.5 MHz) 197.6 (C=C–*C*=O), 162.2 (OC=O), 149.4 (C=*C*H), 145.4 (*C*=CH), 135.8 (*para*-Ar), 133.2 (*ipso*-Ar), 129.9 (*meta*-Ar), 128.4 (*ortho*-Ar), 62.8 (CH_2O), 60.9 (CH_2SO_2), 37.9 (CH_2CH_2C=O), 25.7 (ring CH_2), 22.5 (ring CH_2), 21.7 (CH_3); *m/z* (CI) 340 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 340.1219. $C_{16}H_{18}O_5S$ requires $[M+NH_4]^+$, 340.1219) (found: C, 59.69; H, 5.84. $C_{16}H_{18}O_5S$ requires C, 59.61; H, 5.84%). To a stirred solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (1 M in PhMe; 31 μl, 0.03 mmol) in THF (0.2 mL) at 0 °C was added BH_3·THF (1 M in THF; 200 μl, 0.20 mmol) and the solution stirred for 5 min before dropwise addition of a solution of 6-oxocyclohexen-1-ylmethyl tosylacetate (100 mg, 0.31 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C. The reaction was stirred at 0 °C for 10 min, H_2O (0.5 mL) added and reaction mixture partitioned between brine (5 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, the aqueous phase further extracted with CH_2Cl_2 (10 mL), the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (60% EtOAc/petrol) gave the ester **4** (87 mg, 87%) as a colourless oil; R_f 0.28 (60% EtOAc/petrol); $[\alpha]_D^{25}$ −28.5 (*c* 2.5, $CHCl_3$); ν_{max} (film) 3528, 3456, 2934, 2867, 1732, 596, 1441, 1323, 1304, 1150, 1085, 812, 729, 644 cm^{-1}; δ_H (270 MHz) 7.77 (2H, d, J=8.0 Hz, *ortho*-ArH), 7.33 (2H, d, J=8.0 Hz, *meta*-ArH), 5.85 (1H, t, J=3.5 Hz, C=CH), 4.79 (1H, d, J=12.0 Hz, CH_2O), 4.47 (1H, d, J=12.0 Hz, CH_2O), 4.11 (1H, m, C*H*OH), 4.09 (2H, s, CH_2SO_2), 2.44 (3H, s, CH_3), 2.29 (1H, br s, OH), 2.15–1.82 (2H, m, ring CH_2), 1.80–1.49 (4H, m, ring CH_2); δ_C (67.5 MHz) 162.5 (C=O), 145.6 (*C*=CH), 135.7 (*para*-Ar), 134.0 (*ipso*-Ar), 132.2 (C=*C*H), 130.0 (*meta*-Ar), 128.5 (*ortho*-Ar), 68.6 (CH_2O), 64.9 (*C*HOH), 61.2 (CH_2SO_2), 31.6 (CH_2CHOH), 25.4 (ring CH_2), 21.8 (CH_3), 18.1 (ring CH_2); *m/z* (CI) 342 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 342.1378. $C_{16}H_{20}O_5S$ requires $[M+NH_4]^+$, 342.1375) (found: C, 58.95; H, 6.03. $C_{16}H_{20}O_5S$ requires C, 59.24; H, 6.21%).

4.1.2. (*S*)-2-methyl-2-cyclohexenol. To a stirred solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (1 M in PhMe; 1.38 mL, 1.38 mmol) in THF (9 mL) at 0 °C was added borane–THF complex (1 M in THF; 9.04 mL, 9.04 mmol) and the solution stirred for 5 min before addition of a solution of 2-methyl-2-cyclohexenone (1.53 g, 13.89 mmol) in THF (37 mL) at 0 °C via cannula. The reaction was stirred at 0 °C for 2 min, H_2O (20 mL) slowly added and the reaction mixture partitioned between brine (100 mL) and CH_2Cl_2 (200 mL). The organic layers were separated, the aqueous phase further extracted with CH_2Cl_2 (200 mL), the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (20% EtOAc/petrol) gave (*S*)-2-methyl-2-cyclohexenol (1.22 g, 79%) as a colourless oil; R_f 0.27 (20% EtOAc/petrol); $[\alpha]_D^{25}$ −40.0 (*c* 0.1, $CHCl_3$); ν_{max} (film) 3563, 3523, 3386, 3060, 2989, 2923, 1469, 1452, 1284, 1242, 1227, 1161, 1030 cm^{-1}; δ_H (270 MHz) 5.52 (1H, br s, C=CH), 3.97 (1H, br s, C*H*OH), 3.17 (1H, q, J=7.5 Hz, OH), 2.10–1.83 (2H, m, ring CH_2), 1.81–1.32 (4H, m, ring CH_2), 1.77 (3H, s, Me); δ_C (125.8 MHz) 135.2 (*C*=CH), 125.4 (C=*C*H), 68.4 (CHOH), 32.2 (CH_2CHOH), 25.4 (CH_3), 20.6 (ring CH_2), 18.1 (ring CH_2); *m/z* (CI) 130 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 130.1227. $C_7H_{12}O$ requires $[M+NH_4]^+$, 130.1231).

4.2. Standard procedure for preparation of 1 by tosylacetylation of allylic alcohols

To a solution of allylic alcohol (2.00 mmol, 1.0 equiv) in dichloromethane (10 mL) was added 4-(dimethylamino)-pyridine (24.3 mg, 0.20 mmol, 0.1 equiv) followed by a solution of 1,3-dicyclohexylcarbodiimide (453 mg, 2.20 mmol, 1.1 equiv) in dichloromethane (2 mL). After 5 min tosylacetic acid (471 mg, 2.20 mmol, 1.1 equiv) was added and the reaction stirred at rt for 15 h. The crude mixture was filtered, and the precipitate washed with EtOAc (10 mL). The solution was then washed with aqueous $KHSO_4$ (1 M; 10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (EtOAc/petrol) yielded tosylacetates **1**.

4.2.1. Spectroscopic data for 1a. Yield 94%; R_f 0.16 (20% EtOAc/petrol); ν_{max} (film) 2960, 2932, 2874, 1740 (C=O), 1598, 1455, 1399, 1379, 1326 (SO_2), 1304, 1154 (SO_2), 1086, 971, 725, 646 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.64 (2H, d, J=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.17 (2H, d, J=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.61–5.44 (1H, m, H-3), 5.31–5.16 (1H, m, H-2), 4.31 (2H, dd, J=6.5, 1.0 Hz, CH_2-1), 3.98 (2H, s, CH_2–SO_2–Ar-CH_3), 2.25 (3H, s, SO_2–Ar-CH_3), 1.88–1.73 (2H, m, CH_2-4), 1.29–1.11 (2H, m, CH_2-5), 0.71 (3H, t, J=7.5 Hz, CH_3-6); δ_C (67.5 MHz, $CDCl_3$) 162.3 (C=O), 145.2 (*para* SO_2–*Ar*-CH_3), 137.1 (*ipso* SO_2–*Ar*-CH_3), 136.0 (C-3), 129.5 (*meta* SO_2–*Ar*-CH_3), 128.5 (*ortho* SO_2–*Ar*-CH_3), 123.8 (C-2), 66.6 (C-1), 60.9 (*C*H_2–SO_2–Ar-CH_3), 34.1 (C-4), 21.8 (C-5), 21.5 (SO_2–Ar-*C*H_3), 13.5 (C-6); *m/z* (CI) 314 $[M+NH_4]^+$, 232, 174, 160, 82 (found: $[M+NH_4]^+$, 314.1431. $C_{15}H_{20}O_4S$ requires $[M+NH_4]^+$, 314.1426) (found: C, 60.83; H, 6.85. $C_{15}H_{20}O_4S$ requires C, 60.79; H, 6.80%).

4.2.2. Spectroscopic data for 1b. Yield 85%; R_f 0.22 (25% EtOAc/petrol); ν_{max} (film) 3006, 2959, 2933, 2872, 1735 (C=O), 1599, 1455, 1359, 1328 (SO_2), 1284, 1153 (SO_2), 1085, 972, 813, 731, 647 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.76 (2H, d, J=8.5 Hz, *ortho* SO_2–*Ar*-CH_3), 7.30 (2H, d, J=8.5 Hz, *meta* SO_2–*Ar*-CH_3), 5.66–5.50 (1H, m, H-3), 5.42–5.28 (1H, m, H-2), 4.57 (2H, d, J=7.0 Hz, CH_2-1), 4.06 (2H, s, CH_2–SO_2–Ar-CH_3), 2.39 (3H, s, SO_2–Ar-CH_3), 2.04–1.91 (2H, m, CH_2-4), 1.41–1.23 (2H, m, CH_2-5), 0.83 (3H, t, J=7.5 Hz, CH_3-6); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C=O), 145.4 (*para* SO_2–*Ar*-CH_3), 136.2 (C-3), 135.8 (*ipso* SO_2–*Ar*-CH_3), 129.9 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 122.3 (C-2), 61.9 (C-1), 61.1 (*C*H_2–SO_2–Ar-CH_3), 29.5 (C-4), 22.5 (C-5), 21.7 (SO_2–Ar-*C*H_3), 13.7 (C-6); *m/z* (CI) 610 $[2M+NH_4]^+$, 314 $[M+NH_4]^+$, 288,

248, 82 (found: $[M+NH_4]^+$, 314.1425. $C_{15}H_{20}O_4S$ requires $[M+NH_4]^+$, 314.1426).

4.2.3. Spectroscopic data for 1c. Yield 83%; R_f 0.14 (20% EtOAc/petrol); ν_{max} (film) 3009, 2944, 2882, 1741 (C=O), 1661, 1597, 1328 (SO_2), 1276, 1151 (SO_2), 1085, 992, 814, 727, 647, 609 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73 (2H, d, J=8.5 Hz, *ortho* SO_2–*Ar*-CH_3), 7.27 (2H, d, J=8.5 Hz, *meta* SO_2–*Ar*-CH_3), 6.17–6.03 (1H, m, H-3), 5.99–5.84 (1H, m, H-4), 5.74–5.57 (1H, m, H-2), 5.46–5.31 (1H, m, H-5), 4.48 (2H, d, J=6.5 Hz, CH_2-1), 4.04 (2H, s, CH_2–SO_2–Ar-CH_3), 2.36 (3H, s, SO_2–Ar-CH_3), 1.69 (3H, d, J=6.5 Hz, CH_3-6); δ_C (67.5 MHz, $CDCl_3$) 162.3 (C=O), 145.4 (*para* SO_2–*Ar*-CH_3), 136.0 (*ipso* SO_2–*Ar*-CH_3), 131.9 (C-2), 130.3 (C-4), 129.9 (*meta* SO_2–*Ar*-CH_3), 128.6 (C-3, *ortho* SO_2–*Ar*-CH_3), 122.3 (C-5), 66.6 (C-1), 61.1 (*C*H_2–SO_2–Ar-CH_3), 21.7 (SO_2–Ar-*C*H_3), 18.2 (C-6); *m/z* (CI) 312 $[M+NH_4]^+$, 188, 98, 821 (found: $[M+NH_4]^+$, 312.1278. $C_{15}H_{18}O_4S$ requires $[M+NH_4]^+$, 312.1270) (found: C, 61.31; H, 6.07. $C_{15}H_{18}O_4S$ requires C, 61.20; H, 6.16%).

4.2.4. Spectroscopic data for 1d. Yield 96%; R_f 0.09 (20% EtOAc/petrol); ν_{max} (film) 3030, 2931, 2860, 1741 (C=O), 1597, 1495, 1454, 1398, 1327 (SO_2), 1282, 1149 (SO_2), 1086, 1018, 968, 814, 735, 700, 646, 607 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.77 (2H, d, J=8.5 Hz, *ortho* SO_2–*Ar*-CH_3), 7.36–7.19 (7H, m, *meta* SO_2–*Ar*-CH_3, Ph), 5.84–5.72 (1H, m, H-3), 5.59–5.47 (1H, m, H-2), 4.61 (2H, d, J=7.0 Hz, CH_2-1), 4.45 (2H, s, CH_2-Ph), 4.07 (2H, s, CH_2–SO_2–Ar-CH_3), 4.04 (2H, dd, J=6.5, 1.0 Hz, CH_2-4), 2.38 (3H, s, SO_2–Ar-CH_3); δ_C (67.5 MHz, $CDCl_3$) 162.4 (C=O), 145.5 (*para* SO_2–*Ar*-CH_3), 138.0 (*ipso* Ph), 135.8 (*ipso* SO_2–*Ar*-CH_3), 131.9 (C-3), 129.9 (*meta* SO_2–*Ar*-CH_3), 128.6 (*meta* Ph), 128.5 (*ortho* Ph), 127.8 (*para* Ph), 127.7 (*ortho* SO_2–*Ar*-CH_3), 125.4 (C-2), 72.5 (*C*H_2-Ph), 65.7 (C-4), 62.0 (C-1), 61.0 (*C*H_2–SO_2–Ar-CH_3), 21.8 (SO_2–Ar-*C*H_3); *m/z* (CI) 392 $[M+NH_4]^+$, 375 $[M+H]^+$, 322, 238, 161, 108, 91 (found: $[M+NH_4]^+$, 392.1531. $C_{20}H_{22}SO_5$ requires $[M+NH_4]^+$, 392.1532) (found: C, 64.28; H, 5.77. $C_{20}H_{22}O_5S$ requires C, 64.15; H, 5.92%).

4.2.5. Spectroscopic data for 1e. Yield 94%; R_f 0.11 (20% EtOAc/petrol); mp 55–56 °C; ν_{max} (film) 3058, 3028, 2945, 1741 (C=O), 1597, 1448, 1327 (SO_2), 1275, 1149 (SO_2), 1084, 966, 814, 744, 692, 646 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.79 (2H, d, J=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.41–7.23 (7H, m, *meta* SO_2–*Ar*-CH_3, Ph), 6.59 (1H, d, J=16.0 Hz, H-3), 6.12 (1H, dt, J=16.0, 6.5 Hz, H-2), 4.72 (2H, dd, J=6.5, 1.0 Hz, CH_2-1), 4.12 (2H, s, CH_2–SO_2–Ar-CH_3), 2.37 (3H, s, SO_2–Ar-CH_3); δ_C (67.5 MHz, $CDCl_3$) 171.0 (C=O), 145.2 (*para* SO_2–*Ar*-CH_3), 135.5 (*ipso* SO_2–*Ar*-CH_3, *ipso* Ph), 129.9 (*meta* SO_2–*Ar*-CH_3, *meta* Ph), 128.7 (*ortho* SO_2–*Ar*-CH_3, *ortho* Ph), 128.4 (C-3), 126.7 (*para* Ph), 121.7 (C-2), 66.7 (C-1), 61.2 (*C*H_2–SO_2–Ar-CH_3), 21.7 (SO_2–Ar-*C*H_3); *m/z* (CI) 348 $[M+NH_4]^+$, 194, 174, 134, 117 (found: $[M+NH_4]^+$, 348.1272. $C_{18}H_{18}SO_4$ requires $[M+NH_4]^+$, 348.1270) (found: C, 65.50; H, 5.55. $C_{18}H_{18}SO_4$ requires C, 65.43; H, 5.49%).

4.2.6. Spectroscopic data for 1f. Yield 88%; R_f 0.14 (20% EtOAc/petrol); ν_{max} (film) 3024, 2979, 2943, 1741 (C=O), 1598, 1492, 1446, 1398, 1327 (SO_2), 1279, 1151 (SO_2), 1086, 1026, 985, 814, 750, 727, 700, 642, 607 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.79 (2H, d, J=8.5 Hz, *ortho* SO_2–*Ar*-CH_3), 7.37–7.14 (7H, m, *meta* SO_2–*Ar*-CH_3, Ph), 6.42 (1H, s, H-3), 4.60 (2H, s, CH_2-1), 4.15 (2H, s, CH_2–SO_2–Ar-CH_3), 2.32 (3H, s, SO_2–Ar-CH_3), 1.77 (3H, d, J=1.0 Hz, CH_3-3′); δ_C (67.5 MHz, $CDCl_3$) 162.4 (C=O), 145.5 (*para* SO_2–*Ar*-CH_3), 136.8 (C-2), 135.9 (*ipso* SO_2–*Ar*-CH_3), 131.6 (*ipso* Ph), 130.0 (*meta* SO_2–*Ar*-CH_3), 129.5 (*meta* Ph), 129.0 (*para* Ph), 128.6 (*ortho* SO_2–*Ar*-CH_3), 128.3 (*ortho* Ph), 127.1 (C-3), 71.9 (C-1), 61.1 (*C*H_2–SO_2–Ar-CH_3), 21.7 (SO_2–Ar-*C*H_3), 15.5 (C-3′); *m/z* (CI) 362 $[M+NH_4]^+$, 188, 116, 108 (found: $[M+NH_4]^+$, 362.1430. $C_{19}H_{20}SO_4$ requires $[M+NH_4]^+$, 362.1426) (found: C, 66.38; H, 5.70. $C_{19}H_{20}SO_4$ requires C, 66.26; H, 5.85%).

4.2.7. Spectroscopic data for 1g. Yield 85%; ν_{max} (film) 3028, 2973, 2938, 1732 (C=O), 1597, 1387, 1326 (SO_2), 1151 (SO_2), 1085, 959, 814, 726 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.78 (2H, d, J=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.25 (2H, d, J=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.14 (1H, tsept, J=7.0, 1.0 Hz, H-2), 4.50 (2H, d, J=7.5 Hz, CH_2-1), 4.03 (2H, s, CH_2–SO_2–Ar-CH_3), 2.36 (3H, s, SO_2–Ar-CH_3), 1.68 (3H, s, CH_3-4), 1.59 (3H, s, CH_3-4′); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C=O), 145.3 (*para* SO_2–*Ar*-CH_3), 140.6 (C-3), 135.7 (*ipso* SO_2–*Ar*-CH_3), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 117.4 (C-2), 63.0 (C-1), 61.0 (*C*H_2–SO_2–Ar-CH_3), 25.7 (C-4), 21.7 (SO_2–Ar-*C*H_3), 18.0 (C-4′); *m/z* (CI) 300 $[MNH_4]^+$, 232, 188, 139, 108, 86 (found: $[MNH_4]^+$, 300.1269. $C_{14}H_{18}O_4S$ requires $[MNH_4]^+$, 300.1262).

4.2.8. Spectroscopic data for 1h. Yield 85%; R_f 0.23 (20% EtOAc/petrol); ν_{max} (film) 2966, 2925, 2858, 1739 (C=O), 1668, 1597, 1448, 1379, 1329 (SO_2), 1280, 1151 (SO_2), 1086, 960, 814, 727, 648 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.78 (2H, d, J=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.32 (2H, d, J=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.19 (1H, dt, J=7.0, 1.0 Hz, H-2), 5.07–4.97 (1H, m, H-6), 4.56 (2H, d, J=7.0 Hz, CH_2-1), 4.06 (2H, s, CH_2–SO_2–Ar-CH_3), 2.42 (3H, s, SO_2–Ar-CH_3), 2.09–1.93 (4H, m, CH_2-4, CH_2-5), 1.64 (3H, d, J=0.5 Hz, CH_3-8), 1.63 (3H, d, J=1.0 Hz, CH_3-8), 1.56 (3H, s, CH_3-4′); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C=O), 145.4 (*para* SO_2–*Ar*-CH_3), 143.7 (*ipso* SO_2–*Ar*-CH_3), 135.9 (C-3), 132.0 (C-7), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.7 (*ortho* SO_2–*Ar*-CH_3), 123.6 (C-6), 117.1 (C-2), 63.1 (C-1), 61.1 (*C*H_2–SO_2–Ar-CH_3), 39.6 (C-4), 26.3 (C-8), 25.7 (C-5), 21.8 (SO_2–Ar-*C*H_3), 17.8 (C-8), 16.5 (C-4′); *m/z* (CI) 368 $[M+NH_4]^+$, 232, 188, 154, 137 (found: $[M+NH_4]^+$, 368.1886. $C_{19}H_{26}SO_4$ requires $[M+NH_4]^+$, 368.1896) (found: C, 65.28; H, 7.56. $C_{19}H_{26}SO_4$ requires C, 65.11; H, 7.48%); in agreement with published data.[13]

4.2.9. Spectroscopic data for 1i. Yield 95%; R_f 0.19 (20% EtOAc/petrol); $[\alpha]_D^{23}$ −36.5 (*c* 1.07, $CHCl_3$); ν_{max} (film) 2924, 2839, 1739 (C=O), 1644, 1598, 1452, 1436, 1327 (SO_2), 1276, 1151 (SO_2), 1085, 968, 888, 813, 728, 641 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.80 (2H, d, J=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.35 (2H, d, J=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.71 (1H, d, J=4.0 Hz, H-2), 4.77–4.65 (2H, m, H-6′), 4.45 (2H, s, CH_2-2′), 4.09 (2H, s, CH_2–SO_2–Ar-CH_3), 2.44 (3H, s, SO_2–Ar-CH_3), 2.21–1.38 (7H, m, H-4, CH_2-3, CH_2-5, CH_2-6), 1.72 (3H, m, CH_3-6″); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C=O), 156.8 (C-5′), 149.4 (C-1), 145.3 (*para* SO_2–*Ar*-CH_3), 131.6 (*ipso* SO_2–*Ar*-CH_3),

129.9 (*meta* SO_2–*Ar*-CH_3), 128.7 (*ortho* SO_2–*Ar*-CH_3), 127.4 (C-2), 109.0 (C-6′), 70.4 (C-2′), 61.1 (CH_2–SO_2–Ar-CH_3), 40.7 (C-4), 30.5 (C-5), 27.3 (C-3), 26.3 (C-6), 21.8 (SO_2–Ar-CH_3), 20.8 (C-6″); *m/z* (CI) 366 $[M+NH_4]^+$, 232, 188, 135, 108 (found: $[M+NH_4]^+$, 366.1727. $C_{19}H_{24}O_4S$ requires $[M+NH_4]^+$, 366.1739) (found: C, 65.69; H, 7.06. $C_{19}H_{24}SO_4$ requires C, 65.49; H, 6.94%).

4.2.10. Spectroscopic data for 1j. Yield 80%; R_f 0.28 (20% EtOAc/petrol); $[\alpha]_D^{20}-10.7$ (*c* 1.5, $CHCl_3$); ν_{max} (film) 3020, 2976, 2933, 1739 (C=O), 1522, 1427, 1330 (SO_2), 1279, 1216, 1151 (SO_2), 1086, 1045, 930, 771, 669 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.82 (2H, d, *J*=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.33 (2H, d, *J*=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.49–5.46 (1H, m, H-3), 4.41 (2H, d, *J*=1.5 Hz, CH_2-1), 4.07 (2H, s, CH_2–SO_2–Ar-CH_3), 2.42 (3H, s, SO_2–Ar-CH_3), 2.39–1.94 (5H, m, H-4_{eq}, H-5, H-7, CH_2-8), 1.23 (3H, s, CH_3-7′), 1.08 (1H, d, *J*=8.5 Hz, H-4_{ax}), 0.73 (3H, s, CH_3-7″); δ_C (67.5 MHz, $CDCl_3$) 162.5 (C=O), 145.4 (*para* SO_2–*Ar*-CH_3), 141.9 (C-2), 135.9 (*ipso* SO_2–*Ar*-CH_3), 129.9 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 122.8 (C-3), 68.9 (C-1), 61.1 (CH_2–SO_2–Ar-CH_3), 43.5 (C-5), 40.6 (C-7), 38.0 (C-6), 31.5 (C-4), 31.3 (C-8), 26.1 (C-7′), 21.8 (SO_2–Ar-CH_3), 21.0 (C-7″); *m/z* (CI) 366 $[M+NH_4]^+$, 212, 135 (found: $[M+NH_4]^+$, 366.1746. $C_{19}H_{24}SO_4$ requires $[M+NH_4]^+$, 366.1739) (found: C, 65.30; H, 6.73. $C_{19}H_{24}O_4S$ requires C, 65.49; H, 6.94%).

4.2.11. Spectroscopic data for 1k. Yield 61%; R_f 0.32 (20% EtOAc/petrol); ν_{max} (film) 2937, 2868, 1732 (C=O), 1672, 1597, 1448, 1398, 1381, 1327 (SO_2), 1277, 1151 (SO_2), 1117, 1086, 920, 893, 813, 719, 646 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.69 (2H, d, *J*=8.0 Hz, *ortho* SO_2–*Ar*-CH_3), 7.24 (2H, d, *J*=8.0 Hz, *meta* SO_2–*Ar*-CH_3), 5.27–5.18 (1H, m, H-2), 5.10–5.02 (1H, m, H-1), 3.98 (2H, s, CH_2–SO_2–Ar-CH_3), 2.32 (3H, s, SO_2–Ar-CH_3), 1.79–1.37 (6H, m, CH_2-4, CH_2-5, CH_2-6), 0.90 (3H, m, CH_3-4′); δ_C (67.5 MHz, $CDCl_3$) 162.2 (C=O), 145.2 (*para* SO_2–*Ar*-CH_3), 142.1 (C-3), 135.9 (*ipso* SO_2–*Ar*-CH_3), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 118.8 (C-2), 71.0 (C-1), 61.2 (CH_2–SO_2–Ar-CH_3), 29.8 (C-6), 27.5 (C-4), 23.7 (C-5), 21.6 (SO_2–Ar-CH_3), 18.5 (C-4′); *m/z* (CI) 326 $[M+NH_4]^+$, 188, 172, 145, 128, 112, 95 (found: $[M+NH_4]^+$, 326.1429. $C_{16}H_{20}SO_4$ requires $[M+NH_4]^+$, 326.1426).

4.2.12. Spectroscopic data for 1l. Yield 95%; R_f 0.23 (20% EtOAc/petrol); $[\alpha]_D^{25}-68.9$ (*c* 4.7, $CHCl_3$); ν_{max} (film) 2937, 2866, 1734, 1664, 1597, 1454, 1329, 1275, 1155, 1086, 987, 814, 719 cm^{-1}; δ_H (270 MHz) 7.76 (2H, d, *J*=8.0 Hz, *meta*-Ar), 7.31 (2H, d, *J*=8.0 Hz, *ortho*-Ar), 5.64 (1H, br s, C=CH), 5.14 (1H, t, *J*=4.0 Hz, CHOCO), 4.05 (2H, s, CH_2SO_2), 2.43 (3H, s, $ArCH_3$), 2.06–1.85 (2H, m, ring CH_2), 1.68–1.62 (2H, m, ring CH_2), 1.55 (3H, d, *J*=1.5 Hz, CH=CCH_3), 1.49–1.34 (2H, m, ring CH_2); δ_C (67.5 MHz) 162.4 (C=O), 145.4 (*C*=CH), 136.0 (*para*-Ar), 130.6 (*ipso*-Ar), 129.9 (C=*C*H), 129.8 (*meta*-Ar), 128.6 (*ortho*-Ar), 73.1 (*C*HOCO), 61.3 (CH_2SO_2), 28.6 (ring CH_2), 25.1 (ring CH_2), 21.7 (CH_3), 20.5 (C=*C*CH_3), 17.9 (ring CH_2); *m/z* (CI) 326 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 326.1432. $C_{16}H_{20}O_4S$ requires $[M+NH_4]^+$, 326.1426); (found: C, 62.45; H, 6.34. $C_{16}H_{20}O_4S$ requires C, 62.31; H, 6.54%).

4.2.13. Preparation of (*S*)-2-(triisopropylsilyloxymethyl)cyclohex-2-enyl tosylacetate (1m). To a stirred solution of alcohol **4** (130 mg, 0.40 mmol) in CH_2Cl_2 (1.4 mL) was added TIPSOTf (128 μl, 0.48 mmol) and imidazole (55 mg, 0.80 mmol) and the reaction mixture stirred at rt for 16 h. DMAP (10 mg, 0.08 mmol) was added, the reaction mixture stirred for 40 h and further TIPSOTf (128 μl, 0.48 mmol) added. The reaction mixture was stirred for a further 2 h, partitioned between CH_2Cl_2 (20 mL) and 1 M HCl (10 mL), the organic layers separated and then washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (20% Et_2O/petrol) gave the title ester **1m** (190 mg, 59%) as a colourless oil; q0.14 (20% Et_2O/petrol); $[\alpha]_D^{25}-33.2$ (*c* 4.8, $CHCl_3$); ν_{max} (film) 2942, 2908, 2865, 1735, 1462, 1331, 1303, 1273, 1159, 1085, 812, 684 cm^{-1}; δ_H (270 MHz) 7.79 (2H, d, *J*=8.0 Hz, *ortho*-ArH), 7.32 (2H, d, *J*=8.0 Hz, *meta*-ArH), 6.00 (1H, m, C=CH), 5.33 (1H, t, *J*=3.5 Hz, CHOCO), 4.08 (2H, d, *J*=1.5 Hz, CH_2OSi), 4.05 (2H, s, CH_2SO_2), 2.46 (3H, s, $ArCH_3$), 2.12–1.42 (6H, m, ring CH_2), 1.06–0.93 (21H, m, TIPS); δ_C (67.5 MHz) 162.2 (C=O), 145.3 (*C*=CH), 136.0 (*para*-Ar), 134.2 (*ipso*-Ar), 129.9 (Ar), 128.6 (Ar), 128.4 (C=*C*H), 69.5 (*C*HOCO), 64.3 (CH_2OSi), 61.3 (CH_2SO_2), 28.3 (ring CH_2), 24.7 (ring CH_2), 21.7 ($ArCH_3$), 18.1 ($CH(CH_3)_2$), 17.8 (ring CH_2), 12.0 ($CH(CH_3)_2$); *m/z* (CI) 481 $[M+H]^+$ (found: $[M+H]^+$, 481.2435. $C_{25}H_{40}O_5SSi$ requires $[M+H]^+$, 481.2444) (found: C, 62.69; H, 8.05. $C_{25}H_{40}O_5SSi$ requires C, 62.46; H, 8.39%).

4.2.14. Preparation of (*S*)-6-(4-methoxybenzyloxy)cyclohexen-1-ylmethyl tosylacetate (1n). To a stirred suspension of NaH (60% w/w in mineral oil; 150 mg, 3.8 mmol) in Et_2O (40 mL) was added a solution of *p*-methoxybenzyl alcohol (5.2 g, 37.6 mmol) in Et_2O (35 mL), the resultant cloudy orange mixture stirred for 30 min at rt, cooled to 0 °C and trichloroacetonitrile (3.8 mL, 37.6 mmol) added. The reaction mixture was allowed to warm to rt over 4 h, concentrated under reduced pressure and petrol (50 mL) and MeOH (0.16 mL, 4.0 mmol) added. The suspension was filtered through Celite and concentrated under reduced pressure to give the crude imidate (10.5 g, 100%) as a yellow oil. To a stirred solution of the crude imidate (65 mg, 0.23 mmol) in hexane (0.37 mL) was added a solution of alcohol **4** (50 mg, 0.15 mmol) in CH_2Cl_2 (0.19 mL), the solution cooled to 0 °C and $BF_3{\cdot}OEt_2$ (0.6 μl) added. The reaction mixture was allowed to warm to rt over 16 h, filtered through a pad of Celite and the pad washed with 1:2 CH_2Cl_2/hexane (10 mL). The organic layers were washed with saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by chromatography (20% EtOAc/petrol) to give the title ether **1n** (45 mg, 66%) as a colourless oil; R_f 0.40 (40% EtOAc/petrol); $[\alpha]_D^{25}-4.3$ (*c* 4.6, $CHCl_3$); ν_{max} (film) 2935, 2864, 1738, 1612, 1599, 1514, 1326, 1247, 1153, 1083, 816 cm^{-1}; δ_H (270 MHz) 7.76 (2H, d, *J*=8.5 Hz, *ortho*-$ArSO_2$), 7.34 (2H, d, *J*=8.0 Hz, *meta*-$ArSO_2$), 7.23 (2H, d, *J*=8.0 Hz, *meta*-$ArOCH_3$), 6.84 (2H, d, *J*=8.0 Hz, *ortho*-$ArOCH_3$), 5.87 (1H, t, *J*=3.5 Hz, C=CH), 4.70 (1H, d, *J*=10.5 Hz, CH_2OCO), 4.54 (1H, d, *J*=11.0 Hz, CH_2Ar), 4.43 (1H, d, *J*=12.0 Hz, CH_2OCO), 4.33 (1H, d, *J*=11.0 Hz, CH_2Ar), 4.00 (1H, d, *J*=14.0 Hz, CH_2SO_2), 3.95 (1H, d, *J*=14.0 Hz, CH_2SO_2), 3.86 (1H, br s, C*H*OCH_2Ar), 3.78 (3H, s, OCH_3),

2.43 (3H, s, $ArCH_3$), 2.13–1.86 (3H, m, ring CH_2), 1.78–1.49 (3H, m, ring CH_2); δ_C (125.8 MHz) 162.2 (C=O), 159.1 (*ipso*-$ArOCH_3$), 145.2 (*C*=CH), 135.8 (*para*-$ArSO_2$), 132.4 (C=*C*H), 132.3 and 130.7 (*ipso*-$ArSO_2$ and *para*-$ArOCH_3$), 129.8 (ArH), 129.6 (Ar), 128.5 (Ar), 113.7 (*ortho*-$ArOCH_3$), 70.8 (CH_2Ar), 70.7 (*C*$HOCH_2Ar$), 67.7 (*C*H_2OCO), 60.9 (CH_2SO_2), 55.2 (OCH_3), 26.9 (ring CH_2), 25.2 (ring CH_2), 21.6 ($ArCH_3$), 17.7 (ring CH_2); *m/z* (CI) 462 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 462.1936. $C_{24}H_{28}O_6S$ requires $[M+NH_4]^+$, 462.1950) (found: C, 65.11; H, 6.16. $C_{24}H_{28}O_6S$ requires C, 64.84; H, 6.39%).

4.2.15. Spectroscopic data for 1o. Yield 65%; R_f 0.28 (40% EtOAc/petrol); ν_{max} (film) 2929, 2852, 1741, 1328, 1288, 1153, 1084, 912, 733 cm^{-1}; δ_H (270 MHz) 7.81 (2H, d, $J=8.0$ Hz, *ortho*-Ar), 7.34 (2H, d, $J=8.0$ Hz, *meta*-Ar), 5.97 (1H, tt, $J=4.0$, 1.0 Hz, C=CH), 4.61 (2H, d, $J=1.0$ Hz, CH_2OC=O), 4.09 (2H, s, CH_2SO_2), 3.94 (4H, s, OCH_2CH_2O), 2.44 (3H, s, CH_3), 2.08–2.01 (2H, m, ring CH_2), 1.77–1.70 (4H, m, ring CH_2); δ_C (125.8 MHz) 162.5 (C=O), 145.2 (*C*=CH), 135.9 (*para*-Ar), 134.9 (C=*C*H), 131.9 (*ipso*-Ar), 129.8 (*meta*-Ar), 128.6 (*ortho*-Ar), 105.2 (OCO), 65.1 (OCH_2CH_2O), 64.5 (CH_2OCO), 61.0 (CH_2SO_2), 33.4 (ring CH_2), 25.3 (ring CH_2), 21.6 (CH_3), 20.2 (ring CH_2); *m/z* (CI) 384 $[M+NH_4]^+$, 367 $[M+H]^+$ (found: $[M+H]^+$, 367.1215. $C_{18}H_{22}O_6S$ requires $[M+H]^+$, 367.1216) (found: C, 58.94; H, 5.99. $C_{18}H_{22}O_6S$ requires C, 59.00; H, 6.05%).

4.2.16. Spectroscopic data for 1p. Yield 78%; ν_{max} (film) 2967, 2856, 1744 (C=O), 1664, 1331 (SO_2), 1154 (SO_2), 1085, 1000, 903, 836 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.81 (2H, d, $J=8.0$ Hz, *ortho* SO_2–*Ar*-CH_3), 7.34 (2H, d, $J=8.0$ Hz, *meta* SO_2–*Ar*-CH_3), 5.72 (1H, ddt, $J=15.0$, 7.0, 1.0 Hz, H-3), 5.57 (1H, dtd, $J=15.0$, 6.0, 1.0 Hz, H-2), 4.54 (2H, d, $J=6.0$ Hz, C*H*$_2$-1), 4.13 (1H, q, $J=7.0$ Hz, H-4), 4.09 (2H, s, C*H*$_2$–SO_2–Ar-CH_3), 2.43 (3H, s, SO_2–Ar-C*H*$_3$), 1.66 (1H, apparent septet, $J=7.0$ Hz, H-6), 1.40 (1H, dt, $J=13.5$, 7.0 Hz, H-5), 1.25–1.15 (1H, m, H-5), 0.88 (3H, d, $J=7.0$ Hz, C*H*$_3$-7), 0.87 (3H, d, $J=7.0$ Hz, C*H*$_3$-7′), 0.86 (9H, s, Si–*t*Bu), 0.01 (3H, s, Si–Me), −0.02 (3H, s, Si–Me); δ_C (67.5 MHz, $CDCl_3$) 162.3 (C=O), 145.4 (*para* SO_2–*Ar*-CH_3), 140.0 (C-3), 135.5 (*ipso* SO_2–*Ar*-CH_3), 129.9 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 121.6 (C-2), 70.8 (C-1), 66.3 (C-4), 61.0 (*C*H_2–SO_2–Ar-CH_3), 47.3 (C-5), 25.9 (Si–C–*C*H_3), 24.1 (C-6), 23.2 (C-7), 22.5 (C-7), 21.7 (SO_2–Ar-*C*H_3), 18.2 (Si–*C*–CH_3), −4.1 (Si–*C*H_3), −4.7 (Si–*C*H_3); *m/z* (CI) 472 $[MNH_4]^+$, 318, 241, 188, 109 (found: $[MNH_4]^+$, 472.2552. $C_{23}H_{38}O_5SSi$ requires $[MNH_4]^+$, 472.2553).

4.2.17. Spectroscopic data for 1q. Yield 85%; R_f 0.38 (30% EtOAc/petrol); $[\alpha]_D^{28}$ −18.5 (*c* 1.08, $CHCl_3$); ν_{max} (film) 2959, 2934, 2871, 1744 (C=O ester), 1688 (C=O Boc), 1453, 1329 (SO_2), 1159 (SO_2), 1086, 973, 814, 734, 702, 646 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.80 (2H, d, $J=8.0$ Hz, *ortho* SO_2–*Ar*-CH_3), 7.35 (2H, d, $J=8.0$ Hz, *meta* SO_2–*Ar*-CH_3), 7.25–7.11 (5H, m, Ph), 5.68–5.60 (1H, m, H-3), 5.59–5.35 (1H, m, H-2), 4.78–4.56 (1H, m, H-4), 4.47 (2H, d, $J=6.0$ Hz, C*H*$_2$-1), 4.31 (2H, s, C*H*$_2$-Ph), 4.07 (2H, s, C*H*$_2$–SO_2–Ar-CH_3), 2.44 (3H, s, SO_2–Ar-C*H*$_3$), 1.64–1.26 (12H, m, C*H*$_2$-5, H-6, 3×C–*H*$_3$), 0.86 (3H, s, C*H*$_3$-7), 0.75 (3H, s, C*H*$_3$-7′); δ_C (67.5 MHz, $CDCl_3$) 162.2 (C=O ester), 155.8 (C=O Boc), 145.3 (*para* SO_2–*Ar*-CH_3), 139.7 (*ipso* Ph, *ipso* SO_2–*Ar*-CH_3), 135.9 (C-3), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.6 (*meta* Ph), 128.3 (*ortho* Ph), 127.4 (*ortho* SO_2–*Ar*-CH_3), 126.8 (*para* Ph), 124.2 (C-2), 80.0 (O–*C*–CH_3), 66.1 (C-1), 60.9 (*C*H_2–SO_2–Ar-CH_3), 55.8 (C-4), 47.7 (*C*H_2-Ph), 41.3 (C-5), 28.4 (3×O—*C*H_3), 24.6 (C-6), 22.6 (C-7), 22.5 (C-7′), 21.7 (SO_2–Ar-*C*H_3); *m/z* (CI) 547 $[M+NH_4]^+$, 530 $[M+H]^+$, 491, 430, 337, 276, 216, 174, 139, 109 (found: $[M+H]^+$, 530.2576. $C_{29}H_{39}NO_6S$ requires $[M+H]^+$, 530.2576) (found: C, 65.67; H, 7.30; N, 2.55. $C_{29}H_{39}NO_6S$ requires C, 65.76; H, 7.42; N, 2.64%).

4.2.18. Spectroscopic data for 1r. Yield 79%; ν_{max} (film) 3083, 3060, 3003, 2875, 1740 (C=O), 1598, 1494, 1453, 1396, 1382, 1328 (SO_2), 1305, 1150 (SO_2), 1085, 815, 649 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.79 (2H, d, $J=8.5$ Hz, *ortho* SO_2–*Ar*-CH_3), 7.38–7.13 (7H, m, *meta* SO_2–*Ar*-CH_3, Ph), 5.92 (1H, ddt, $J=15.5$, 6.5, 1.0 Hz, H-3), 5.49 (1H, dtd, $J=15.5$, 6.5, 1.5 Hz, H-2), 4.53 (2H, d, $J=6.5$ Hz, C*H*$_2$-1), 4.07 (2H, s, C*H*$_2$–SO_2–Ar-CH_3), 3.47 (1H, quin, $J=6.5$ Hz, H-4), 2.40 (3H, s, SO_2–Ar-C*H*$_3$), 1.34 (3H, d, $J=6.5$ Hz, C*H*$_3$-5); δ_C (67.5 MHz, $CDCl_3$) 162.3 (C=O), 145.5 (*para* SO_2–*Ar*-CH_3), 144.8 (*ipso* Ph), 141.7 (*ipso* SO_2–*Ar*-CH_3), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.7 (*meta* Ph), 128.6 (*ortho* SO_2–*Ar*-CH_3, *ortho* Ph), 127.2 (*para* Ph), 126.4 (C-2), 121.5 (C-3), 66.8 (C-1), 61.1 (*C*H_2–SO_2–Ar-CH_3), 42.0 (C-4), 21.8 (SO_2–Ar-*C*H_3), 20.9 (C-5); *m/z* (CI) 376 $[MNH_4]^+$, 350, 232, 188, 145, 118 (found: $[MNH_4]^+$, 376.1580. $C_{20}H_{22}SO_4$ requires $[MNH_4]^+$, 376.1583).

4.2.19. Spectroscopic data for 1s. Yield 73%; R_f 0.22 (20% EtOAc/petrol); mp 79–82 °C; $[\alpha]_D^{26}$ −14.4 (*c* 0.97, $CHCl_3$); ν_{max} (film) 2970, 2935, 2870, 1736 (C=O), 1597, 1331 (SO_2), 1273, 1153 (SO_2), 1086, 975, 813, 714, 640 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.71 (2H, d, $J=8.0$ Hz, *ortho* SO_2–*Ar*-CH_3), 7.25 (2H, d, $J=8.0$ Hz, *meta* SO_2–*Ar*-CH_3), 5.42 (1H, d, $J=7.5$ Hz, H-3′), 4.91 (1H, s, H-3′), 4.77 (1H, s, H-1), 4.03 (2H, s, C*H*$_2$–SO_2–Ar-CH_3), 2.35 (1H, s, H-3), 2.34 (3H, s, SO_2–Ar-C*H*$_3$), 2.27–2.10 (2H, m, C*H*$_2$-4), 1.84–1.75 (1H, m, H-6′$_{eq}$), 1.57 (1H, dd, $J=15.5$, 4.0 Hz, H-6′$_{ax}$), 1.22 (1H, d, $J=10.0$ Hz, H-5), 1.16 (3H, s, C*H*$_3$-7), 0.54 (3H, s, C*H*$_3$-7); δ_C (67.5 MHz, $CDCl_3$) 161.9 (C=O), 148.9 (C-2), 145.3 (*para* SO_2–*Ar*-CH_3), 135.9 (*ipso* SO_2–*Ar*-CH_3), 129.8 (*meta* SO_2–*Ar*-CH_3), 128.6 (*ortho* SO_2–*Ar*-CH_3), 115.3 (C-3′), 70.8 (C-1), 61.4 (*C*H_2–SO_2–Ar-CH_3), 50.5 (C-3), 40.5 (C-6), 39.3 (C-5), 32.6 (C-6′), 27.4 (C-4), 25.8 (C-7), 21.9 (C-7), 21.7 (SO_2–Ar-*C*H_3); *m/z* (CI) 366 $[M+NH_4]^+$, 317, 303, 188, 152, 135, 108 (found: $[M+NH_4]^+$, 366.1726. $C_{19}H_{24}SO_4$ requires $[M+NH_4]^+$, 366.1739) (found: C, 65.45; H, 7.08. $C_{19}H_{24}SO_4$ requires C, 65.49; H, 6.94).

4.3. Standard procedure for dCr reaction of 1

Conventional thermal conditions: BSA (16.6 mL, 0.07 mmol, 0.1 equiv) and KOAc (6.6 mg, 0.07 mmol, 0.1 equiv) were added to a solution of ester **1** (0.7 mmol, 1 equiv) in dry toluene (5 mL; ca. 0.14 M), and the resulting mixture was heated at 110 °C for 15 h. Concentration under reduced pressure and chromatography (EtOAc/petrol) gave sulfone **2**.

Microwave conditions: KOAc (0.1 equiv) was added to a microwave vial followed by tosylacetate **1** (1 equiv), BSA (0.1 or 1 equiv) and toluene (1 mL; ca. 0.3 M). The mixture was heated at 150 °C (250 W) for 3 min. Concentration under reduced pressure and chromatography (EtOAc/petrol) gave sulfone **2**.

4.4. Spectroscopic data for dCr reaction products 2

Spectroscopic data for the dCr reaction products **2a**, **2c**–**2k**, **2p**–**2r** may be found in the Supporting information in Ref. 5a: http://www.wiley-vch.de/contents/jc_2002/2005/z462023_s.pdf.

4.4.1. Spectroscopic data for 2l. R_f 0.36 (20% EtOAc/petrol); mp 62–64 °C; $[\alpha]_D^{25}+54.1$ (*c* 3.4, $CHCl_3$); ν_{max} (film) 3035, 2929, 2863, 2837, 1597, 1448, 1311, 1300, 1147, 1088, 817, 752 cm^{-1}; δ_H (500 MHz) 7.80 (2H, dt, $J=$ 8.5, 2.0 Hz, *ortho*-Ar), 7.34 (2H, dd, $J=8.5$, 0.5 Hz, *meta*-Ar), 5.46–5.44 (1H, m, C=CH), 3.11 (1H, ddd, $J=14.5$, 2.0, 0.5 Hz, CH_2SO_2), 3.04 (1H, dd, $J=14.5$, 9.5 Hz, CH_2SO_2), 2.51–2.46 (1H, m, C*H*CH_2SO_2), 2.44 (3H, s, $ArCH_3$), 1.94–1.90 (2H, m, ring CH_2), 1.88–1.83 (1H, m, ring CH_2), 1.71–1.66 (1H, m, ring CH_2), 1.57–1.53 (1H, m, ring CH_2), 1.49–1.48 (3H, m, CH=CC*H*$_3$), 1.46–1.42 (1H, m, ring CH_2); δ_C (125.8 MHz) 144.5 (*C*=CH), 136.9 (*para*-Ar), 132.9 (*ipso*-Ar), 129.8 (*meta*-Ar), 127.9 (*ortho*-Ar), 125.1 (C=*C*H), 58.4 (CH_2SO_2), 33.6 (*C*HCH_2SO_2), 27.2 (ring CH_2), 24.9 (ring CH_2), 21.6 (CH_3), 21.5 (CH_3), 17.7 (ring CH_2); *m/z* (CI) 282 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 282.1532 $C_{15}H_{20}O_2S$ requires $[M+NH_4]^+$, 282.1528); 265 $[M+H]^+$ (found: $[M+H]^+$, 265.1270. $C_{15}H_{20}O_2S$ requires $[M+H]^+$, 265.1262) (found: C, 67.94; H, 7.48. $C_{15}H_{20}O_2S$ requires C, 68.14; H, 7.62%).

4.4.2. Spectroscopic data for 2m. R_f 0.42 (40% Et_2O/petrol); $[\alpha]_D^{25}+12.0$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 2940, 2891, 1733, 1598, 1461, 1312, 1150, 1086, 882, 759, 686 cm^{-1}; δ_H (500 MHz) 7.79 (2H, d, $J=8.0$ Hz, *ortho*-ArH), 7.34 (2H, d, $J=8.0$ Hz, *meta*-ArH), 5.74 (1H, br s, C=CH), 3.92 (2H, s, CH_2OSi), 3.39 (1H, dd, $J=14.5$, 2.0 Hz, CH_2SO_2), 3.10 (1H, dd, $J=14.5$, 10.0 Hz, CH_2SO_2), 2.69 (1H, m, C*H*CH_2SO_2), 2.44 (3H, s, $ArCH_3$), 2.01–1.98 (3H, m, ring CH_2), 1.62–1.55 (3H, m, ring CH_2), 1.10–0.94 (21H, m, TIPS); δ_C (125.8 MHz) 144.4 (*para*-Ar), 137.2 (*ipso*-Ar), 136.7 (*C*=CH), 129.8 (*meta*-ArH), 127.9 (*ortho*-ArH), 125.6 (C=*C*H), 66.1 (CH_2OSi), 58.5 (CH_2SO_2), 30.4 (*C*HCH_2SO_2), 26.7 (ring CH_2), 24.6 (ring CH_2), 21.6 ($ArCH_3$), 18.0 (CH(*C*H$_3$)$_2$ and ring CH_2), 12.0 (*C*H$(CH_3)_2$); *m/z* (CI) 437 $[M+H]^+$ (found: $[M+H]^+$, 437.2547. $C_{24}H_{40}O_3SSi$ requires $[M+H]^+$, 437.2545).

4.4.3. Spectroscopic data for 2n. R_f 0.22 (20% EtOAc/petrol); ν_{max} (film) 2924, 2850, 1612, 1512, 1456, 1301, 1248, 1147, 1086, 1034, 818 cm^{-1}; *m/z* (CI) 418 $[M+NH_4]^+$ (found: $[M+NH_4]^+$, 418.2049. $C_{23}H_{28}O_4S$ requires $[M+NH_4]^+$, 418.2052).

Major, anti-diastereoisomer. δ_H (270 MHz) 7.78 (2H, d, $J=8.0$ Hz, *ortho*-$ArSO_2$), 7.30 (2H, d, $J=8.0$ Hz, *meta*-$ArSO_2$), 7.16 (2H, d, $J=8.5$ Hz, *meta*-$ArOCH_3$), 6.85 (2H, d, $J=8.5$ Hz, *ortho*-$ArOCH_3$), 4.90 (1H, s, C=CH_2), 4.70 (1H, s, C=CH_2), 4.26 (1H, d, $J=11.5$ Hz, CH_2Ar), 4.09 (1H, d, $J=11.5$ Hz, CH_2Ar), 3.87 (1H, m, C*H*OCH_2), 3.80 (3H, s, OCH_3), 3.42 (1H, dd, $J=14.0$, 4.5 Hz, CH_2SO_2), 3.08 (1H, dd, $J=14.0$, 8.0 Hz, CH_2SO_2), 2.96 (1H, m, C*H*CH_2SO_2) 2.41 (3H, s, $ArCH_3$), 2.18–2.11 (2H, m, ring CH_2), 1.95–1.45 (4H, m, ring CH_2); δ_C (125.8 MHz) 159.0 (*ipso*-$ArOCH_3$), 148.9 (*C*=CH_2), 144.5 (*para*-$ArSO_2$), 137.0 (*ipso*-$ArSO_2$), 130.7 (*para*-$ArOCH_3$), 129.9 (Ar), 129.1 (Ar), 127.9 (Ar), 113.7 (Ar), 108.9 (C=*C*H_2), 79.0 (*C*HOCH_2Ar), 69.1 (OCH_2Ar), 58.6 (CH_2SO_2), 55.2 (OCH_3), 36.7 (*C*HCH_2SO_2), 34.2 (ring CH_2), 33.6 (ring CH_2), 21.6 ($ArCH_3$), 20.6 (ring CH_2).

Minor, syn-diastereoisomer. δ_H (270 MHz) 7.74 (2H, d, $J=$ 8.0 Hz, *ortho*-$ArSO_2$), 7.32 (2H, d, $J=8.0$ Hz, *meta*-$ArSO_2$), 7.19 (2H, d, $J=8.5$ Hz, *meta*-$ArOCH_3$), 6.82 (2H, d, $J=8.5$ Hz, *ortho*-$ArOCH_3$), 4.97 (1H, s, C=CH), 4.78 (1H, s, C=CH_2), 4.46 (1H, d, $J=12.5$ Hz, CH_2OAr), 4.28 (1H, d, $J=11.5$ Hz, CH_2OAr), 3.79 (3H, s, OCH_3), 3.73 (1H, m, C*H*OCH_2), 3.41 (1H, dd, $J=14.0$, 4.5 Hz, CH_2SO_2), 3.29 (1H, dd, $J=14.0$, 8.0 Hz, CH_2SO_2), 2.86 (1H, m, C*H*CH_2SO_2), 2.44 (3H, s, $ArCH_3$), 1.95–1.42 (6H, m, ring CH_2); δ_C (125.8 MHz) 158.9 (*ipso*-$ArOCH_3$), 147.6 (*C*=CH_2), 144.4 (*para*-$ArSO_2$), 137.4 (*ipso*-$ArSO_2$), 130.6 (*para*-$ArOCH_3$), 129.8 (Ar), 128.9 (Ar), 127.8 (Ar), 113.7 (Ar), 109.6 (C=*C*H_2), 79.0 (*C*HOCH_2Ar), 69.8 (OCH_2Ar), 59.1 (CH_2SO_2), 55.2 (OCH_3), 36.7 (*C*HCH_2SO_2), 33.9 (ring CH_2), 32.8 (ring CH_2), 21.6 ($ArCH_3$), 19.4 (ring CH_2).

4.4.4. Spectroscopic data for 2o. R_f 0.15 (20% EtOAc/petrol); ν_{max} (film) 2937, 2889, 1302, 1288, 1192, 1147, 1089, 1049, 1020, 922, 895, 818, 756 cm^{-1}; δ_H (270 MHz) 7.76 (2H, d, $J=8.5$ Hz, *ortho*-Ar), 7.34 (2H, d, $J=8.0$ Hz, *meta*-Ar), 5.11 (1H, s, C=CH_2), 4.70 (1H, s, C=CH_2), 3.93–3.75 (4H, m, OCH_2CH_2O), 3.39 (1H, dd, $J=14.0$, 5.0 Hz, CH_2SO_2), 3.18 (1H, dd, $J=14.0$, 8.0 Hz, CH_2SO_2), 3.04 (1H, m, C*H*CH_2SO_2), 2.43 (3H, s, CH_3), 1.96–1.36 (6H, m, ring CH_2); δ_C (125.8 MHz) 147.2 (*C*=CH_2), 144.4 (*para*-Ar), 137.3 (*ipso*-Ar), 129.8 (*meta*-Ar), 127.9 (*ortho*-Ar), 108.4 (C=*C*H_2), 108.0 (OCO), 64.3 (OCH_2CH_2O), 58.9 (CH_2SO_2), 37.3 (*C*HCH_2SO_2), 36.8 (ring CH_2), 32.5 (ring CH_2), 21.6 (CH_3), 21.2 (ring CH_2); *m/z* (CI) 340 $[M+NH_4]^+$, 323 $[M+H]^+$ (found: $[M+H]^+$, 323.1317. $C_{17}H_{22}O_4S$ requires $[M+H]^+$, 323.1313).

4.4.5. Spectroscopic data for 2s. R_f 0.33 (20% EtOAc/petrol); mp 54–55 °C; $[\alpha]_D^{24}+24.7$ (*c* 1.03, $CHCl_3$); ν_{max} (film) 2983, 2918, 2833, 1599, 1444, 1315 (SO_2), 1302, 1272, 1226, 1149 (SO_2), 1088, 912, 814, 733, 653 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.72 (2H, d, $J=8.0$ Hz, *ortho* SO_2–*Ar*-CH_3), 7.30 (2H, d, $J=8.0$ Hz, *meta* SO_2–*Ar*-CH_3), 5.18–5.11 (1H, m, H-3), 3.08–2.97 (2H, m, C*H*$_2$-4′), 2.38 (3H, s, SO_2–Ar-C*H*$_3$), 2.33–2.22 (3H, m, H-1, C*H*$_2$-3′), 2.16–2.07 (1H, m, H-6′), 2.03–1.94 (1H, m, H-6′), 1.90–1.81 (1H, m, H-5), 1.23–1.12 (1H, m, H-4_{eq}), 1.18 (3H, s, C*H*$_3$-7), 1.00 (1H, d, $J=8.5$ Hz, H-4_{ax}), 0.70 (3H, s, C*H*$_3$-7); δ_C (67.5 MHz, $CDCl_3$) 144.8 (*para* SO_2–*Ar*-CH_3), 144.0 (C-2), 136.2 (*ipso* SO_2–*Ar*-CH_3), 130.0 (*meta* SO_2–*Ar*-CH_3), 128.2 (*ortho* SO_2–*Ar*-CH_3), 118.5 (C-3), 54.6 (C-4′), 45.6 (C-1), 40.7 (C-5), 38.1 (C-6), 31.6 (C-4), 31.3 (C-6′), 29.8 (C-3′), 26.2 (C-7), 21.7 (SO_2–Ar-*C*H$_3$), 21.2 (C-7); *m/z* (CI) 322 $[M+NH_4]^+$, 305 $[M+H]^+$, 149, 105 (found: $[M+NH_4]^+$, 322.1838. $C_{18}H_{24}SO_2$ requires $[M+NH_4]^+$,

322.1841) (found: C, 71.04; H, 8.20. $C_{18}H_{24}SO_2$ requires C, 71.01; H, 7.95).

4.5. Standard procedure for tosylation of 10

To a solution ($\geq$2 M) of allylic methyl malonates **10a–i** (4.5 equiv) in DMSO was added very slowly, at rt and under N_2, potassium *tert*-butoxide (4 equiv of a 1 M solution in THF). The reaction was then stirred for 15 min before the addition of tosyl fluoride (1 equiv). After 20 h of stirring at rt, the mixture was poured into aqueous HCl (10%), extracted twice with ether and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel (25–50% EtOAc/petrol) of the residual mixture gave recovered excess allylic methyl malonates **10a–i**, followed by the desired allylic methyl tosylmalonates **11a–i**.

4.6. Standard procedure for dCr reaction of 11

To solutions of tosylmalonates **11a–11i** in CH_2Cl_2 were added, at rt and under N_2, BSA (1 equiv) and KOAc (0.1 equiv). After stirring for 4–16 h, the reaction mixtures were concentrated under reduced pressure. Chromatography on silica gel afforded the decarboxylated rearranged products **12a–i**.

4.7. Spectroscopic data for dCr reaction products 12

Spectroscopic data for the dCr reaction products **12a–12i** may be found in the Supporting information in Ref. 5b: http://pubs.acs.org/subscribe/journals/orlef7/suppinfo/ol047577w/ol047577wsi20041220_092954.pdf.

Acknowledgements

We thank EPSRC (postdoctoral research associateship to D. B. [grant GR/N31412]; DTA Studentship to D. M. M.; quota Studentship to A. J. W. S.), GlaxoSmithKline (additional funding of Studentship to D. M. M.) and the European Community Human Potential program (Marie Curie Individual Fellowship to F. G. [contract number HPMT-CT-2002-02015]) for support.

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Tetrahedron 62 (2006) 496–502
Tetrahedron

Highly selective formation of propargyl- and allenyltrichlorosilanes and their regiospecific addition to various types of aldehydes: preparation of both allenic and homopropargylic alcohols

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Received 23 April 2005; revised 3 August 2005; accepted 31 August 2005

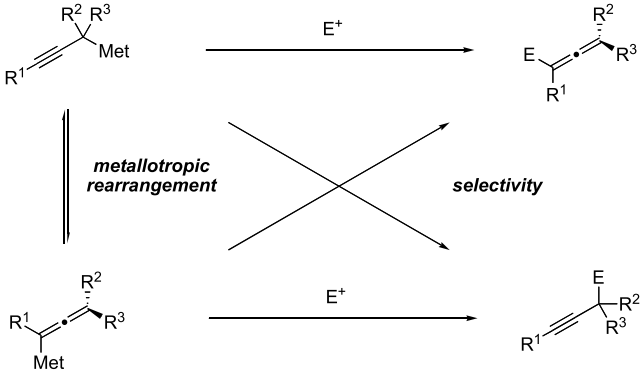
Available online 28 September 2005

Abstract—The highly selective preparation of propargyl- and allenyltrichlorosilanes via metal-catalyzed silylation of propargyl chloride has been developed. These trichlorosilyl nucleophiles were then shown to add to various types of aldehydes to afford the corresponding allenic and homopropargylic alcohols, respectively, in high yields with complete regiospecificity. Remarkably, these carbon–carbon bond-forming reactions simply proceeded in *N*,*N*-dimethylformamide (DMF) without using any metal catalysts.

1. Introduction

Functionalized allenes and alkynes such as allenic and homopropargylic alcohols have proved to be extremely versatile, key intermediates in modern organic synthesis,[1] for example, in coupling reactions,[2] ene–yne metathesis[3] and formation of heterocycles.[4] Carbon–carbon bond-forming reactions such as the regiospecific addition of propargyl and allenyl nucleophiles to aldehydes provide very attractive routes to these types of compounds.[1] However, drawbacks concerning the use of propargyl and allenyl metal derivatives are potential metallotropic rearrangement[5] between these species and non-regiospecific addition to electrophiles resulting in formation of product mixtures (Scheme 1).[6] Moreover, accessibility to these propargyl and allenyl nucleophiles is highly substrate-dependent.[5,6,7]

Additionally, because of recent demands for safe and environmentally benign organic synthesis, the use of organometallic nucleophiles or metal catalysts is sometimes undesirable, especially for large-scale synthesis. In this context,[8] we recently reported that neutral (non-ionic)



Scheme 1. Potential metallotropic rearrangement and selectivity problem.

Lewis bases such as *N*,*N*-dimethylformamide (DMF), sulfoxides or phosphine oxides promote the nucleophilic addition of allyl- and crotyltrichlorosilanes to aldehydes,[9] imines[10] and *N*-acylhydrazones (Scheme 2).[11]

Remarkably, all these reactions proceeded without using any metal catalysts since these non-ionic Lewis bases, which are defined as neutral coordinate-organocatalysts (*NCO*s),[12] are able to activate the trichlorosilyl nucleophiles by coordination to the silicon atom resulting in the formation of highly reactive hypervalent silicon species. Previously, we also reported selective preparation of both propargyl- and allenyltrichlorosilanes starting from the same corresponding propargyl halides.[13a] Their

Keywords: Propargyltrichlorosilane; Allenyltrichlorosilane; Regiospecific addition; Homopropargylic alcohols; Allenic alcohols; Carbon–carbon bond-forming reaction.
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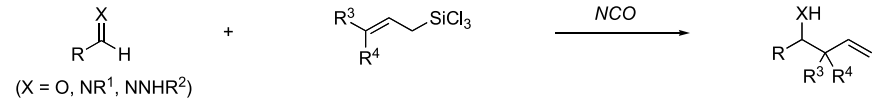
doi:10.1016/j.tet.2005.08.114



Scheme 2. *NCO*-mediated additions of allyl- and crotyltrichlorosilanes to aldehydes,[9] imines,[10] and *N*-acylhydrazones.[11]

nucleophilic addition to several aldehydes in order to form the corresponding allenic and homopropargylic alcohols, respectively, was also described. However, selectivities, yields and substrate scope still remained to be improved. Herein, we report a more practical and greatly improved protocol for the silylation of propargyl chloride resulting in significantly enhanced selectivities. Moreover, the nucleophilic, regiospecific addition of both propargyl- and allenyltrichlorosilanes to various types of aldehydes afforded the corresponding allenic or homopropargylic alcohols exclusively.

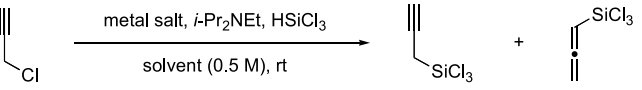
2. Results and discussion

The preparation of propargyl and allenyl organometallics from the corresponding propargyl halides typically requires stoichiometric amounts of metals.[5–7] In contrast, our procedure needs only a catalytic amount of a metal salt together with an amine base and trichlorosilane. In the literature, it has been reported that propargyl chloride reacts with trichlorosilane in the presence of triethylamine and copper(I) chloride under thermal conditions (THF, 60 °C, 12 h) to give a mixture of propargyltrichlorosilane (**2**) and allenyltrichlorosilane (**3**; ratio **2**:**3**=86:14).[14] It is also known that the distillation of a mixture of compounds **2** and **3** provokes (further) isomerization towards product **3** (ratio **2**:**3**=33:67).[13a] We wanted to reinvestigate the silylation procedure of propargyl chloride based on our previous work in order to develop a more practical protocol and improve selectivities for trichlorosilanes **2** and **3** (Table 1).

The initial solvent screening revealed that the silylation proceeded efficiently only in non-polar solvents such as diethyl ether (EE) or *t*-butyl methyl ether (TBME). On the other hand, in acetonitrile or propionitrile the reaction was sluggish, whereas in dichloromethane (DCM), tetrahydrofuran (THF) or *N*,*N*-dimethylformamide (DMF) the silylation scarcely proceeded. In our previous work, a slight excess of the amine base with respect to trichlorosilane in a solvent mixture by using a copper(I) catalyst was necessary to obtain a high selectivity in favor of product **2** (Table 1, entry 1). We found that under similar conditions in EE as a sole solvent the reaction was faster, but less selective (entry 2). We, therefore, reinvestigated the silylation conditions and after extensive optimization, it was found that a slight excess of trichlorosilane with respect to Hünig's base in EE afforded propargyltrichlorosilane (**2**) exclusively (entry 3). Even more significantly, only 1 mol% CuCl was sufficient to catalyze the transformation while maintaining exceptional selectivity (entry 4). Previously, we found that the Ni(II)-catalyzed formation of allenyltrichlorosilane (**3**) as the major product (moderate to good selectivities) was highly solvent- and temperature-dependent (entries 5 and 6). However, with our newly optimized protocol just by switching from Cu(I) to Ni(II), the exclusive formation of trichlorosilane **3** was observed (entry 7). Here again, it is noted that only 1 mol% of the Ni(II) catalyst was sufficient to promote this highly selective silylation (entry 8).

Next, we turned our attention towards the use of in situ prepared trichlorosilyl nucleophiles **2** and **3** in the reaction with aldehydes in DMF for the synthesis of both allenic and homopropargylic alcohols. We have previously demonstrated that allyltrichlorosilane regiospecifically reacts with various aldehydes in DMF without metal catalysis to afford the corresponding homoallylic alcohols in high yields.[9] In these reactions, DMF might coordinate to the silicon atom

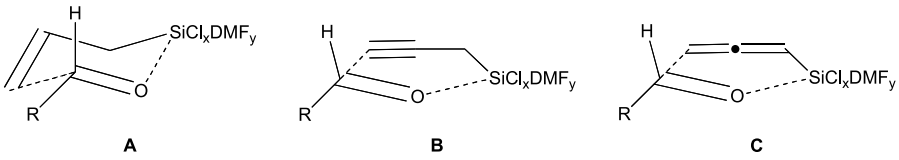
Table 1. Optimization of the selective silylation of propargyl chloride (**1**)



1 **2** **3**

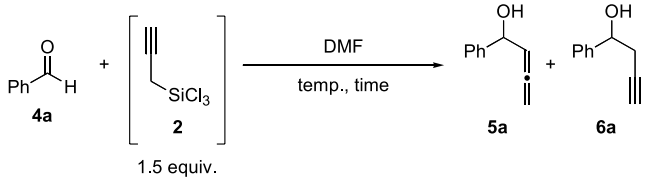
Entry	Metal salt (mol%)	*i*-Pr_2NEt (equiv)	$HSiCl_3$ (equiv)	Solvent[a]	Time (h)	Conversion (%)[b]	Ratio **2**:**3**[b]
1[c]	CuCl (3)	1.0	1.1	EE/EtCN	12	nd	94:6
2	CuCl (5)	2.0	1.5	EE	6–8	>95	85:15
3	CuCl (5)	2.0	2.2	EE	6	>99	>99:1
4	CuCl (1)	2.0	2.2	EE	12	>99	>99:1
5[c]	NiL_2 (3)[d]	1.1	1.0	THF[e]	12	nd	3:>97
6[c]	$Ni(acac)_2$ (3)	1.1	1.0	EE	n.d	nd	9:91
7	$Ni(acac)_2$ (5)	2.0	2.2	EE	6	>99	1:>99
8	$Ni(acac)_2$ (1)	2.0	2.2	EE	12	>99	1:>99

[a] EE=diethyl ether.
[b] Determined by ^1H NMR analysis by aliquot dilution in $CDCl_3$.
[c] Ref. 13a.
[d] L=PhC(O)CH=C(O)Ph.
[e] The reaction was carried out under reflux.



Scheme 3. Assumed transition states of the reactions between various trichlorosilanes and aldehydes.[9,13a]

Table 2. DMF-mediated allenylation of benzaldehyde (**4a**) with in situ prepared propargyltrichlorosilane (**2**)



Entry	DMF (M)	Temperature (°C)	Time (h)	Yield (%)	Ratio **5a**:**6a**[a]
1[b]	0.25	0	12	60	91:9
2	0.5	10	12–48	55–63	>99:1
3	0.4	10	24	72	>99:1
4	0.2	10	24	80–84	>99:1
5	0.1	10	24	83–89	>99:1
6	0.1	0	24	92	>99:1
7[c]	0.1	0	24	80	>99:1

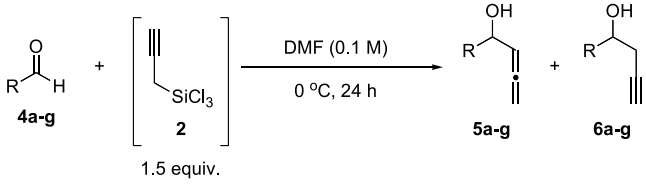
[a] Determined by ^{1}H NMR analysis of the isolated material.
[b] Best previously data published by our group: 1.2 equiv of **2** were used (see Ref. 13a).
[c] Three equivalents of in situ prepared propargyltrichlorosilane (**2**) were used.

of the allyltrichlorosilane resulting in the formation of a highly reactive hypervalent silicon species, which in turn smoothly adds to aldehydes via a supposed cyclic transition state **A** (Scheme 3). We assumed that the same kind of intermediates could be formed with trichlorosilyl nucleophiles **2** and **3** and these transition states **B** and **C** are represented in Scheme 3.[†,13a]

We first examined the conditions for the reaction between in situ prepared propargyltrichlorosilane (**2**) and benzaldehyde (**4a**) as a model substrate, the results are shown in Table 2.

The allenylation proceeded smoothly in DMF at 10 °C with moderate yields (entry 2), which are in the same range as our previous result (entry 1). Whilst the selectivity was lower previously (entry 1), now exclusive formation of allenic alcohol **5a** was observed (entry 2). Further optimization revealed the importance of the amount of DMF; with gradually increasing amounts of DMF, which is considered to be both solvent and an *NCO*, the yields were significantly improved to 89% (entries 3–5). This improvement might be attributed to both a more homogenous reaction mixture and more efficient activation of nucleophile **2** by DMF.[‡] Finally, conducting the reaction at 0 °C provided the highest yield (92%, entry 6), whereas the use of 3 equiv of nucleophile **2** (instead of 1.5 equiv) was less efficient, probably a solubility issue (entry 7). It is, however, remarkable that in all cases allenic alcohol **5a** was the single product; no trace of homopropargylic alcohol **6a** could be detected.[§]

Table 3. DMF-mediated allenylation of various aldehydes **4** with in situ prepared propargyltrichlorosilane (**2**)



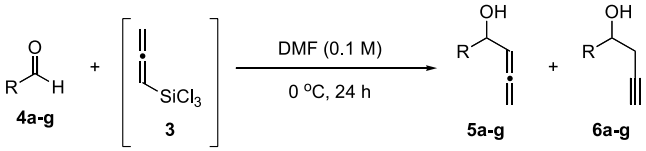
Entry	Substrate **4**: R	Yield (%)	Ratio **5**:**6**[a]
1	**4a**: Ph	92	>99:1
2	**4b**: 4-MeOC$_6$H$_4$	88	>99:1
3	**4c**: 3-Furyl	55	>99:1
4	**4d**: *n*-Octyl	80	>99:1
5	**4e**: *c*-Hexyl	61	>99:1
6	**4f**: PhCH$_2$CH$_2$	90	>99:1
7	**4g**: (*E*)-*n*-PrCH=CH	79	>99:1

[a] Determined by ^{1}H NMR analysis of the isolated material.

Next, we extended the optimized allenylation conditions to various aldehydes, the results are represented in Table 3.

[†] In these supposed S_E2' type additions, propargyltrichlorosilane (**2**) and allenyltrichlorosilane (**3**) would convert aldehydes into the corresponding allenic and homopropargylic alcohols, respectively.
[‡] It should be pointed out that the same reaction carried out in a non-coordinating solvent such as EE or DCM (instead of DMF), under otherwise identical conditions, proceeded only scarcely (yields <5%), thereby underlining the crucial role of DMF.
[§] In this context, it is important to mention that we carried out a control experiment with benzaldehyde (**4a**) by using a solution of **2** obtained after vacuum transfer at low temperature (instead of the supernatant from in situ preparation of **2**, that might contain a trace of Cu(I)). Since we observed that the reaction proceeded smoothly (even though the yield was slightly lower) while maintaining the exclusive regiospecificity, it can be considered that a trace amount of the metal salt (potentially present) does not affect the reaction outcome.

Table 4. DMF-mediated propargylation of various aldehydes **4** with in situ prepared allenyltrichlorosilane (**3**)



Entry	Substrate **4**: R	Yield (%)	Ratio **5**:**6**[a]
1	**4a**: Ph	90	1:>99
2	**4b**: 4-MeO–C_6H_4	78	1:>99
3	**4c**: 3-Furyl	65	1:>99
4	**4d**: *n*-Octyl	79	1:>99
5	**4e**: *c*-Hexyl	56	1:>99
6	**4f**: $PhCH_2CH_2$	72	1:>99
7	**4g**: (*E*)-*n*-propyl–CH=CH	70	1:>99

[a] Determined by ^{1}H NMR analysis of the isolated material.

We were delighted to find that a wide range of substrates tolerated the optimized reaction conditions. Aromatic aldehydes **4a**,**b** and aliphatic aldehyde **4f**, containing an aromatic moiety, were excellent substrates (88–92% yield, entries 1,2 and 6). On the other hand, heteroaromatic aldehyde **4c** and the branched sterically demanding aliphatic aldehyde **4e** gave lower yields (entries 3 and 5). Finally, aliphatic aldehyde **4d** and α,β-unsaturated substrate **4g** proved to be very reactive under the conditions employed providing high yields of the desired products (79–80% yields, entries 4 and 7). It is notable that in all cases the allenylation reactions proceeded with complete regiospecificity; allenic alcohols **5a**–**g** were found to be the single products and no traces of the corresponding homopropargylic alcohols **6a**–**g** could be observed.

We then examined the substrate generality concerning the propargylation of several aldehydes. We employed the optimized allenylation conditions, and simply used in situ prepared allenyltrichlorosilane (**3**) instead of nucleophile **2** (Table 4).

As was the case in the previous allenylation study, several aldehydes were reactive towards propargylation with trichlorosilyl nucleophile **3**. Benzaldehyde (**4a**) proved to be the best substrate providing the corresponding homopropargylic alcohol **6a** exclusively in 90% yield (entry 1). Although the sterically hindered compound **4e** gave a little lower yield (entry 5), all other aldehydes were found to give the corresponding homopropargylic alcohols **6** in good yields (entries 2–4, 6, and 7). In all cases, the reactions proceeded with complete regiospecificity.[¶] This remarkable regiospecificity in both the allenylation and the propargylation of various aldehydes with trichlorosilyl nucleophiles **2** and **3** might be explained by the approach of the silanes and aldehydes shown in Scheme 3.

[¶] As in the earlier study, a control experiment with benzaldehyde (**4a**) by using a solution of **3** obtained after vacuum transfer at low temperature (instead of the supernatant from in situ preparation of **3**, that might contain a trace of Ni(II)), revealed comparable reactivity along with the same exceptional regiospecificity. This confirms that a trace amount of Ni(II), potentially present, does not influence the course of the reaction.

3. Conclusion

In summary, the highly selective preparation of both propargyl- and allenyltrichlorosilanes via metal-catalyzed silylation of propargyl chloride has been developed. These trichlorosilyl nucleophiles proved to add regiospecifically to various types of aldehydes to afford the corresponding allenic and homopropargylic alcohols, respectively, in high yields. Remarkably, these organocatalytic carbon–carbon bond-forming reactions simply proceeded in *N*,*N*-dimethylformamide (DMF) without using any metal catalysts.

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-LA300 or JNM-LA400 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS; $\delta=0$ ppm) and $CDCl_3$ ($\delta=77.0$ ppm) served as internal standards for ^{1}H NMR and for ^{13}C NMR, respectively. 1,2,4,5-Tetrachlorobenzene was used as internal standard for monitoring, with time, by ^{1}H NMR analysis the in situ preparation of trichlorosilanes **2** and **3**. IR spectra were measured with a JASCO FT/IR-610 infrared spectrometer. High-resolution electrospray ionization mass spectroscopy analysis HRMS (ESI) was carried out using a Bruker Daltonics BioTOF II mass spectrometer. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin layer chromatography (PTLC) was carried out using Wakogel B-5F. All reactions were conducted under an argon atmosphere in dried glassware. Dry diethylether (EE) was purchased from Wako Co. Ltd and was used without distillation; dry *N*,*N*-dimethylformamide (DMF) was purchased from Wako Co. Ltd and was used after distillation from barium(II) oxide. 3-Chloroprop-1-yne (**1**) and *N*,*N*-diisopropylethylamine were purchased from Tokyo Kasei Kogyo Co. Ltd and were used after distillation. Trichlorosilane was purchased from Tokyo Kasei Kogyo Co. Ltd and was used without distillation. Copper(I) chloride and bis(2,4-pentanedionato)nickel(II) were dried at 50 °C under vacuum for 12 h before transfer into a glovebox. All other solvents and reagents were purified and dried according to standard procedures.

4.2. Procedure for the selective in situ preparation of trichlorosilanes 2 and 3

To a stirred suspension of dry copper(I) chloride (10.0 mg, 100 μmol, 5 mol%) or dry bis(2,4-pentanedionato)nickel(II) (25.7 mg, 100 μmol, 5 mol%) in dry EE (4 mL, 0.5 M) at room temperature were added dropwise *N*,*N*-diisopropylethylamine (680 μL, 4.0 mmol, 2.0 equiv), 3-chloroprop-1-yne (**1**; 143 μL, 2.0 mmol, 1.0 equiv) and trichlorosilane (445 μL, 4.4 mmol, 2.2 equiv), successively. The mixture was stirred at room temperature for 6 h and the product ratios **2**:**3** were determined by ^{1}H NMR analysis of an aliquot diluted with $CDCl_3$. Under the indicated optimized conditions, compound **1** was completely consumed (>99% conversion) and exclusive formation of propargyltrichlorosilane (**2**; by using CuCl) or allenyltrichlorosilane (**3**; by

using $Ni(acac)_2$) was observed (~75% NMR yield, >99:1 ratios for each isomer).

4.3. Procedure for the selective synthesis of allenic alcohols 5 or homopropargylic alcohols 6

The supernatant solution of in situ prepared trichlorosilanes **2** or **3** (1.5 equiv) in EE was added dropwise via a syringe to stirred solutions of the corresponding aldehydes **4a–g** (1.0 equiv) in DMF (0.1 M with respect to aldehydes **4a–g**) at 0 °C. The mixtures were stirred at 0 °C for 24 h, and quenched by dropwise addition of aq HCl (1 M, 1 mL per 0.5 mmoL of used nucleophile **2** or **3**). After stirring at 0 °C for an additional 30 min, the mixtures were warmed to room temperature and extracted with EE (three times, after addition of H_2O). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered and concentrated in vacuo. The residues were purified by preparative thin-layer chromatography (PTLC; eluant: *n*-hexane/ethyl acetate 5:1–15:1) to afford the corresponding allenic alcohols **5a–g** (by using nucleophile **2**) or the corresponding homopropargylic alcohols **6a–g** (by using nucleophile **3**) exclusively.

4.4. Analytical data for the synthesized compounds

4.4.1. Trichloro(prop-2-ynyl)silane (2).[13a,d] ^1H NMR ($CDCl_3$) δ 2.10 (t, $J=3.3$ Hz, 1H), 2.44 (d, $J=3.3$ Hz, 2H).

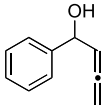
2

4.4.2. Trichloro(propa-1,2-dienyl)silane (3).[13a,d] ^1H NMR ($CDCl_3$) δ 4.91 (d, $J=6.9$ Hz, 2H), 5.35 (t, $J=6.9$ Hz, 1H).

3

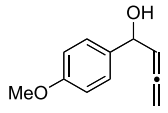
4.5. Allenic alcohols 5a–g

4.5.1. 1-Phenylbuta-2,3-dien-1-ol (5a).[13a,d,16] Colorless oil; ^1H NMR ($CDCl_3$) δ 2.09 (br s, 1H), 4.86 (ddd, $J=1.0$, 2.5, 6.4 Hz, 2H), 5.21 (dt, $J=2.5$, 6.4 Hz, 1H), 5.38 (dt, $J=6.4$, 6.8 Hz, 1H), 7.20–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 71.9, 78.2, 95.2, 126.1, 127.8, 128.5, 142.8, 207.1; IR (neat) 3399, 3030, 1955, 1677, 1494, 1451, 1360, 1264, 1187, 1025, 852, 700 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{10}O$ $[M+H]^+$: *m/z* 147.0810, found: *m/z* 147.0814.



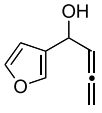
5a

4.5.2. 1-(4-Methoxyphenyl)buta-2,3-dien-1-ol (5b).[16] Pale yellow oil; ^1H NMR ($CDCl_3$) δ 2.12 (br s, 1H), 3.80 (s, 3H), 4.87–4.92 (m, 2H), 5.18 (s, 1H), 5.40 (dt, $J=6.5$, 6.8 Hz, 1H), 6.85 (d, $J=8.7$ Hz, 2H), 7.29 (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.4, 71.8, 78.1, 95.3, 113.9, 127.2, 135.0, 159.1, 206.9; IR (neat) 3402, 2837, 1955, 1610, 1589, 1514, 1247, 1174, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}O_2$ $[M+H]^+$: *m/z* 177.0916, found: *m/z* 177.0915.



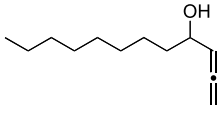
5b

4.5.3. 1-(Furan-3-yl)buta-2,3-dien-1-ol (5c). Pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.98 (br s, 1H), 4.84–4.90 (m, 2H), 5.19 (s, 1H), 5.38 (q, $J=6.5$ Hz, 1H), 6.40 (d, $J=1.0$ Hz, 1H), 7.37 (s, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 67.9, 78.0, 95.1, 107.8, 128.1, 139.0, 143.1, 206.5; IR (neat) 3380, 2907, 1957, 1497, 1451, 1000, 867 cm^{-1}; HRMS (ESI) calcd for $C_8H_8O_2$ $[M+H]^+$: *m/z* 137.0603, found: *m/z* 137.0602.



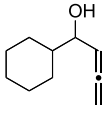
5c

4.5.4. Dodeca-1,2-dien-4-ol (5d).[13a] Colorless oil; ^1H NMR ($CDCl_3$) δ 0.81 (t, $J=6.6$ Hz, 3H), 1.23–1.85 (m, 15H), 4.07–4.15 (m, 1H), 4.78 (dd, $J=2.3$, 6.4 Hz, 2H), 5.17 (q, $J=6.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.8, 25.5, 29.2, 29.5, 29.9, 32.0, 37.6, 70.0, 77.6, 95.0, 206.7; IR (neat) 3334, 2929, 1956, 1464, 1005, 841 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{22}O$ $[M+H]^+$: *m/z* 183.1749, found: *m/z* 183.1748.



5d

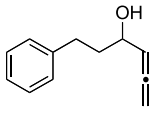
4.5.5. 1-Cyclohexylbuta-2,3-dien-1-ol (5e).[13d] Colorless oil; ^1H NMR ($CDCl_3$) δ 0.87–1.26 (m, 10H), 1.30–1.47 (m, 1H), 1.67 (s, 1H), 3.87 (ddd, $J=2.1$, 6.4, 6.8 Hz, 1H), 4.74 (dd, $J=2.1$, 6.8 Hz, 2H), 5.14 (dt, $J=6.4$, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.6, 28.7, 44.0, 74.1, 77.5, 93.4, 207.2; IR (neat) 3360, 2924, 1955, 1453, 1015, 836, 700 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}O$ $[M+H]^+$: *m/z* 153.1279, found: *m/z* 153.1279.



5e

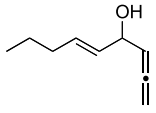
4.5.6. 1-Phenylhexa-4,5-dien-3-ol (5f).[13a,d] Colorless oil; ^1H NMR ($CDCl_3$) δ 1.69 (br s, 1H), 1.82 (dt, $J=6.9$, 7.8 Hz,

2H), 2.67 (dt, J=4.4, 7.8 Hz, 2H), 4.08–4.15 (m, 1H), 4.80 (dd, J=2.5, 6.8 Hz, 2H), 5.20 (dt, J=6.4, 6.8 Hz, 1H), 7.11–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.7, 39.0, 68.9, 77.8, 94.7, 125.9, 128.4, 128.5, 141.8, 207.1; IR (neat) 3384, 2928, 1955, 1716, 1454, 849, 700 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}O$ $[M+H]^+$: m/z 175.1123, found: m/z 175.1125.



5f

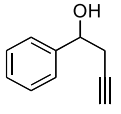
4.5.7. (*E*)-Nona-1,2,5-trien-4-ol (5g). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J=7.0 Hz, 3H), 1.36 (q, J=7.0 Hz, 2H), 1.89–2.05 (m, 3H), 4.83 (dd, J=2.5, 6.0 Hz, 2H), 5.28 (dt, J=2.5, 6.0 Hz, 1H), 5.59 (dd, J=6.3, 15.7 Hz, 1H), 5.70–5.78 (m, 1H), 5.99 (dt, J=6.6, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.2, 35.3, 71.6, 78.2, 95.3, 129.0, 135.4, 207.0; IR (neat) 3365, 3011, 2891, 1952, 1498, 1453, 1003, 844, 703 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}O$ $[M+H]^+$: m/z 139.1123, found: m/z 139.1120.



5g

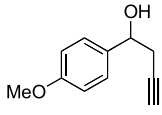
4.6. Homopropargylic alcohols 6a–g

4.6.1. 1-Phenylbut-3-yn-1-ol (6a).[13a,15] Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.01 (t, J=2.7 Hz, 1H), 2.25 (br s, 1H), 2.58 (dd, J=2.7, 6.3 Hz, 2H), 4.81 (t, J=6.3 Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.5, 71.0, 72.3, 80.6, 125.7, 128.0, 128.5, 142.4; IR (neat) 3294, 3032, 2913, 2118, 1668, 1625, 1494, 1453, 1048, 756, 700 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{10}O$ $[M+H]^+$: m/z 147.0810, found: m/z 147.0815.



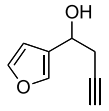
6a

4.6.2. 1-(4-Methoxyphenyl)but-3-yn-1-ol (6b).[15] Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.96 (t, J=2.5 Hz, 1H), 2.48–2.64 (m, 3H), 3.71 (s, 3H), 4.74 (t, J=6.4 Hz, 1H), 6.79 (d, J=8.9 Hz, 2H), 7.24 (d, J=8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.5, 55.7, 71.2, 72.4, 80.4, 113.8, 126.9, 135.2, 159.4; IR (neat) 3443, 3290, 2959, 2919, 2832, 2110, 1603, 1245, 1026, 800 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}O_2$ $[M+H]^+$: m/z 177.0916, found: m/z 177.0918.



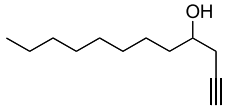
6b

4.6.3. 1-(Furan-3-yl)but-3-yn-1-ol (6c). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.90 (br s, 1H), 2.02 (d, J=2.3 Hz, 1H), 2.58–2.60 (m, 2H), 4.78 (t, J=6.2 Hz, 1H), 6.38 (d, J=1.0 Hz, 1H), 7.33 (s, 1H), 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$) 28.3, 65.3, 71.2, 80.3, 108.4, 127.3, 139.4, 143.4; IR (neat) 3400, 3308, 2111, 1450, 750, 695 cm^{-1}; HRMS (ESI) calcd for $C_8H_8O_2$ $[M+H]^+$: m/z 137.0603, found: m/z 137.0612.



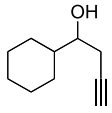
6c

4.6.4. Dodec-1-yn-4-ol (6d).[13a] Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J=6.4 Hz, 3H), 1.19–1.70 (m, 14H), 1.98 (t, J=2.5 Hz, 1H), 2.15–2.41 (m, 3H), 3.70 (tt, J=5.7, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 25.6, 27.2, 28.8, 29.2, 29.8, 31.8, 36.0, 69.7, 70.5, 81.0; IR (neat) 3330, 2940, 2108, 1455, 828, 700 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{22}O$ $[M+H]^+$: m/z 183.1749, found: m/z 183.1750.



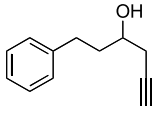
6d

4.6.5. 1-Cyclohexylbut-3-yn-1-ol (6e). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95–1.82 (m, 12H), 1.98 (t, J=2.3 Hz, 1H), 2.32 (dd, J=2.3, 6.0 Hz, 2H), 4.77–4.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.6, 28.6, 29.2, 45.4, 70.8, 72.9, 81.6; IR (neat) 3365, 2919, 2109, 1450, 1022, 839, 715 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}O$ $[M+H]^+$: m/z 153.1279, found: m/z 153.1277.



6e

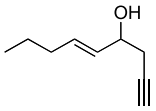
4.6.6. 1-Phenylhex-5-yn-3-ol (6f).[13a] Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.78–1.89 (m, 2H), 1.99 (br s, 1H), 2.05 (t, J=2.5 Hz, 1H), 2.27–2.45 (m, 2H), 2.61–2.83 (m, 2H), 3.78 (tt, J=5.7, 12.0 Hz, 1H), 7.11–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1, 31.9, 37.5, 69.0, 71.2, 80.5, 126.0, 128.2, 128.4, 141.5; IR (neat) 3385, 2920, 2115, 1710, 1451, 833, 699 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}O$ $[M+H]^+$: m/z 175.1123, found: m/z 175.1124.



6f

4.6.7. (*E*)-Non-5-en-1-yn-4-ol (6g). Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J=7.2 Hz, 3H), 1.33 (q, J=7.2 Hz, 2H), 1.87–2.10 (m, 3H), 1.98 (t, J=2.7 Hz, 1H), 2.37 (dd,

J=2.7, 6.0 Hz, 2H), 4.18 (dt, J=6.0, 6.4 Hz, 1H), 5.47 (dd, J=6.4, 15.4 Hz, 1H), 5.64 (dt, J=6.4, 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.1, 29.4, 35.2, 71.1, 72.5, 80.6, 129.1, 133.7; IR (neat) 3370, 3011, 2889, 2107, 1498, 1456, 1004, 840, 709 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}O$ [M+H]$^+$: m/z 139.1123, found: m/z 139.1123.



6g

Acknowledgements

Financial support was provided by ERATO, Japan Science and Technology Agency (JST). U. S. is indebted to ERATO, JST, for a postdoctoral fellowship.

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