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Tetrahedron

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Organocatalysis and New Chemical Concepts Tetrahedron Young Investigator Award David MacMillan

Guest editor: Stephen F. Martin

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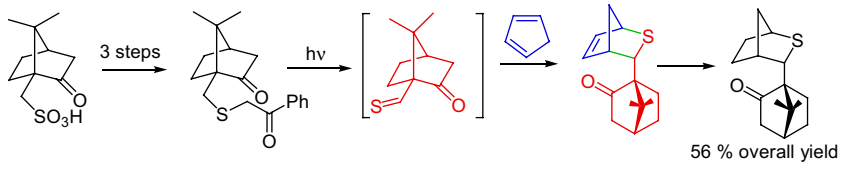
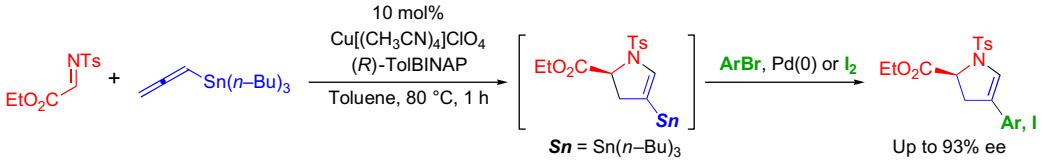
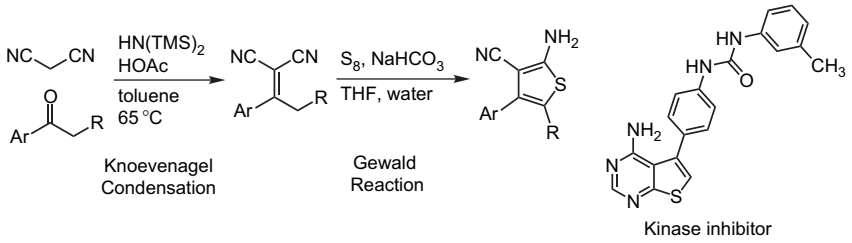
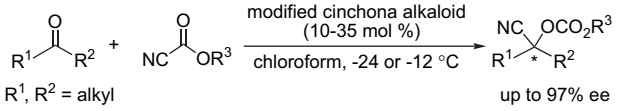
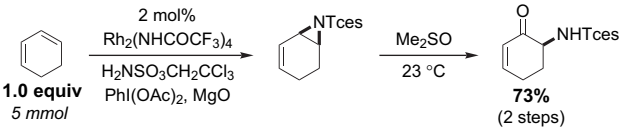
Contents

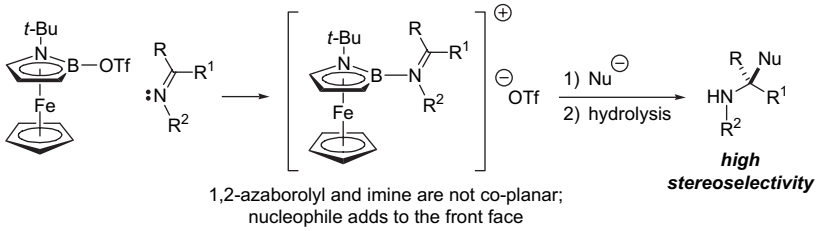


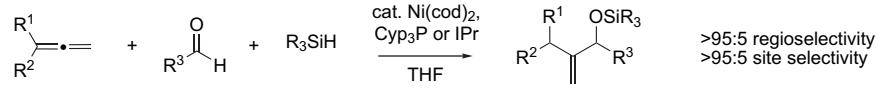


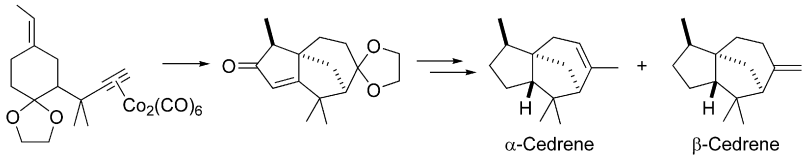


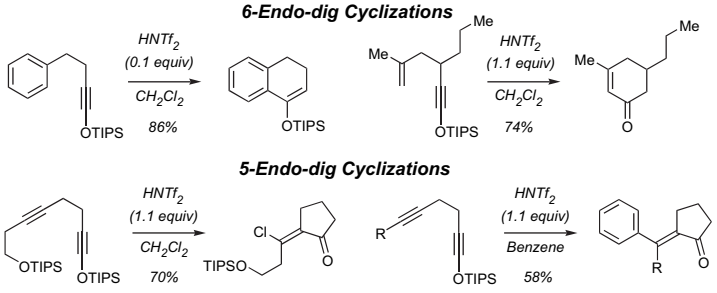


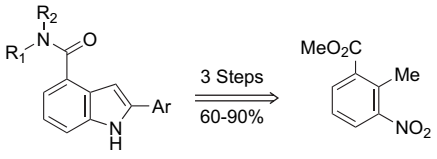


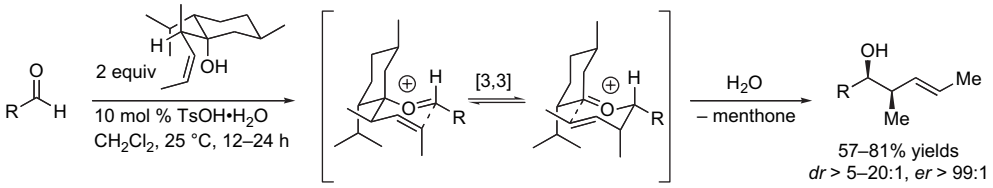


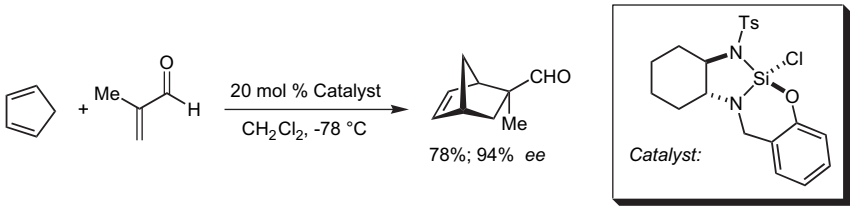


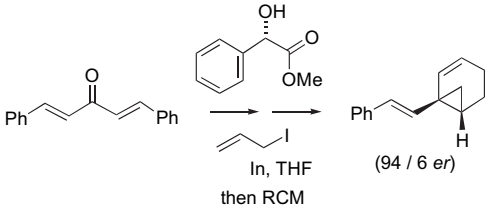




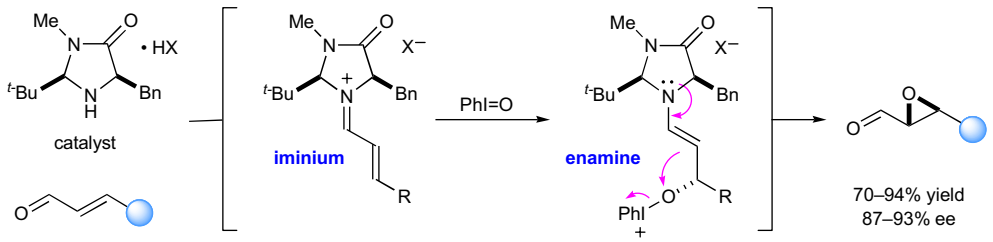


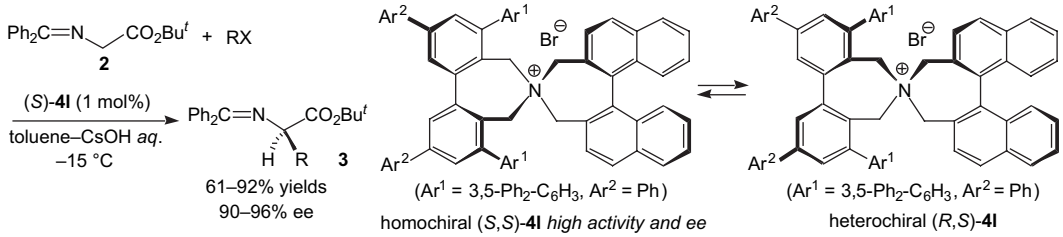


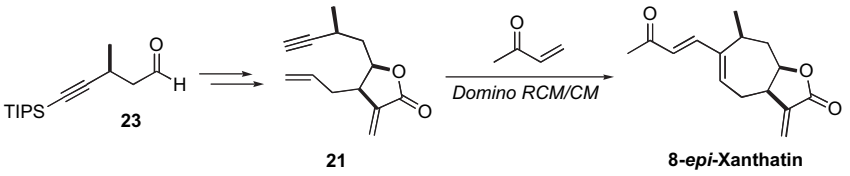


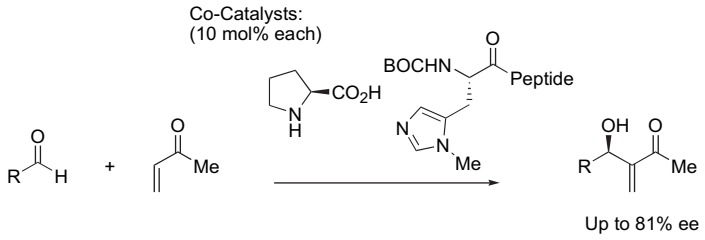


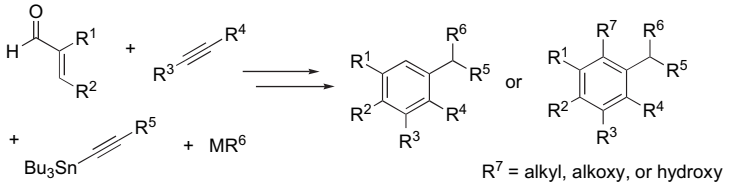
Methyl mandelate has been identified as a simple and inexpensive stoichiometric asymmetric modifier for the homoallyl-cyclopropanation of dibenzylideneacetone. Subsequent Ru-cat. RCM provides rapid entry to enantiomerically enriched 1-styryl-norcarene.

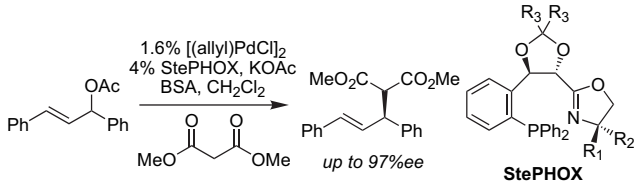


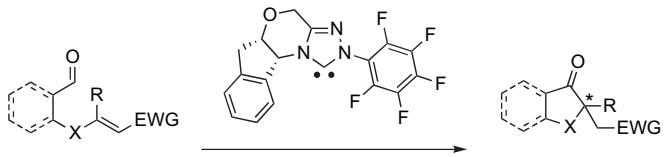


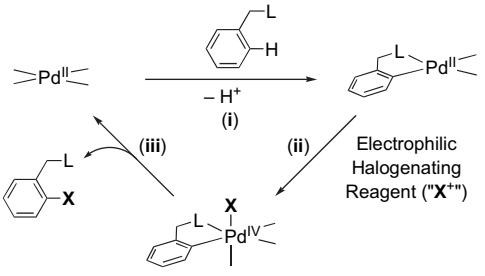


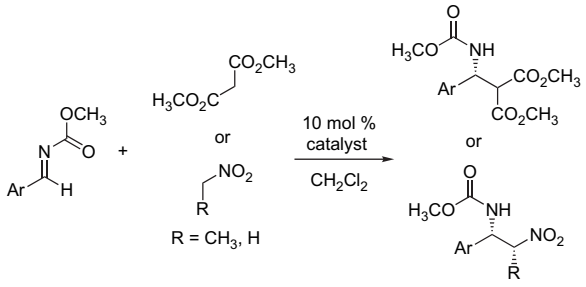


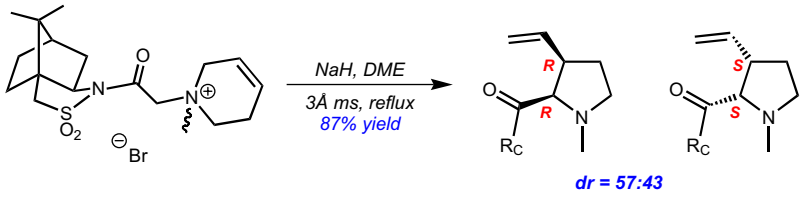


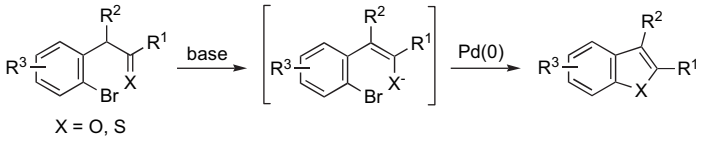












OTHER CONTENT

*Corresponding author
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COVER

The graphic illustrates three components which are essential for the success of the iminium catalyzed epoxidation reported in 'Enantioselective organocatalytic epoxidation using hypervalent iodine reagents'. First (a) the defined architecture of activated iminium species derived from the imidazolidinone catalyst **1** that enables high levels of enantioselectivity in a number of organic transformations. Second (b) the need for the slow release of iodosobenzene from an iminoiodinane source under aqueous conditions to ensure optimal levels of catalyst efficiency in the reported epoxidation, and last (c) the compatibility of organic catalysts with air and water.

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Preface

Tetrahedron Young Investigator Award

Last year the Executive Board of Editors for Tetrahedron Publications announced that the inaugural recipients of the Tetrahedron Young Investigator Awards were Professors David W. MacMillan and Laura Kiessling in recognition of their exceptional creativity and dedication in the respective fields of organic synthesis and bioorganic and medicinal chemistry. Professors MacMillan and Kiessling presented their award addresses at the Tetrahedron Symposium that was held in Bordeaux, France in June of 2005. Separate Symposia-in-Print were organized to honor both awardees.

This special Symposium-in-Print entitled 'Organocatalysis and New Chemical Concepts' was organized for Professor MacMillan, who will become a Professor of Chemistry at Princeton University in September of 2006. Professor MacMillan was born in 1968 in Bellshill, Scotland. He received his undergraduate degree in chemistry at the University of Glasgow, where he worked with the late Dr. Ernest Colvin. In 1990, David left the UK to begin his doctoral studies under the direction of Professor Larry Overman at the University of California, Irvine. During this time Dave focused on the development of new reaction methodologies directed toward the total synthesis of marine metabolites. In 1996, Dave moved to a postdoctoral position with Professor David Evans at Harvard University where his studies centered on enantioselective catalysis. Dave began his independent career at the University of California, Berkeley in July of 1998 before moving to the California Institute of Technology in June of 2000. In 2004, Professor MacMillan became the Earle C. Anthony Chair in Chemistry at Caltech. Despite a self-professed 'love for Caltech and California', Dave will relocate to Princeton University in September of this year to become the Barton Hepburn Chair of Organic Synthesis and Director of the new Merck Center for Catalysis at Princeton University.

The papers collected in this special Symposium-in-Print are provided by a large representation of the pioneers of reaction engineering and complex target synthesis in the modern era. Collectively, this special issue spans the realm of organic synthesis with contributions in the important areas of metal catalysis (Rh, Ni, Pd), organocatalysis (iminium-, acyl anion-, phase-transfer-, Brønsted acid-, nucleophilic catalysis), C–H bond functionalization, ligand design, pharmacophore synthesis, heterocycle construction, new catalytic methods for natural product synthesis (norcarene, xanthatin, cedrone), as well as the introduction of a new activation mode for enantioselective catalysis that relies upon Si-centered strain release. Professor MacMillan has asked me to extend his deepest gratitude and appreciation to all of the contributors for their substantial efforts in helping to create this unique issue.

It is clear that David MacMillan has been a pioneer in changing the face of organic chemistry. He has made innovative contributions to the general area of catalysis, particularly organic catalysis, and has inspired the work of others in developing this and other new chemical concepts. These are the kinds of achievements that the Tetrahedron Young Investigator Award is proud to recognize.

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A practical synthesis of a [2.2.1] bicyclic chiral sulfide for asymmetric transformations

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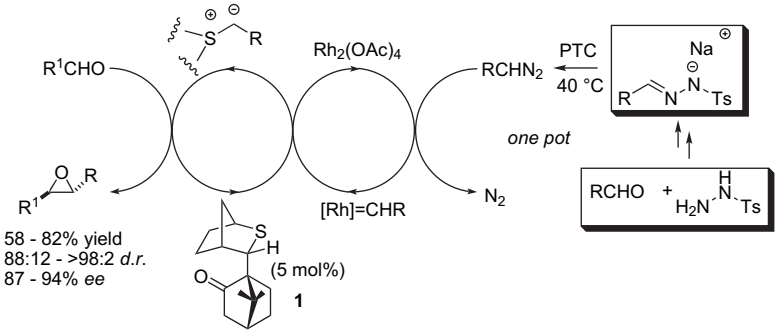
This paper is dedicated to Professor David MacMillan, the rising star of our generation

Abstract—A substantially improved synthesis of synthetically useful chiral sulfide **1** is described. Starting from (+)-10-camphorsulfonic acid, the chiral sulfide was synthesised on large scale in five steps and 56% overall yield. Significant improvements include the use of Bu_3P in place of Ph_3P for the reduction of the chlorosulfonyl group to the thiol, allowing removal of phosphine oxide by aqueous extraction and improvements in the photochemistry using either a modified batch reactor or a single pass continuous flow reactor.

1. Introduction

Sulfur ylides are extremely useful carbon nucleophiles in organic synthesis.[1] They are mostly used for two types of reactions: three-membered ring formation (epoxidation, cyclopropanation or aziridination) and rearrangement reactions.[2] In the first class of reactions the sulfur ylide reacts with an electrophilic carbon atom (of a carbonyl group, imine or an activated carbon–carbon double bond) followed by elimination of the sulfide to give a strained three-membered ring. We have developed a new catalytic process in which tosyl hydrazone salts couple with carbonyl compounds to give epoxides with control over relative and absolute stereochemistry in high yield (Scheme 1). The reaction is mediated by sub-stoichiometric quantities of a chiral sulfide (5 mol %) and rhodium acetate (0.5 mol %).[3] The process shows good substrate scope but with many catalytic process limitations. As a result of these limitations, we have developed a stoichiometric epoxidation protocol, which is highly efficient and enantioselective and shows very broad substrate scope.[4]

The catalytic process has been extended to the synthesis of cyclopropanes and aziridines (Scheme 2).[5] The practicality of these processes has been demonstrated in the synthesis of a number of biologically important targets (CDP 840,[5] prelactone B,[6] taxol side chain,[7] and the anti-hypertensive agent (+)-LY354740[8]) involving each class of three-membered ring compounds with almost complete control of chirality.



Scheme 1. Catalytic cycle for epoxide formation with in situ generation of diazocompounds.

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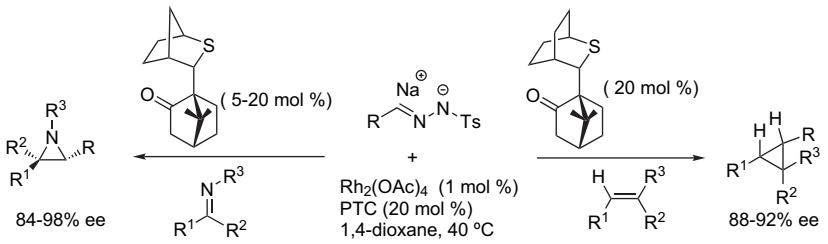
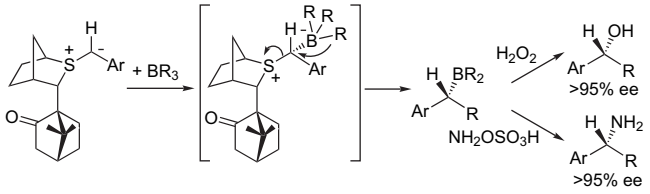


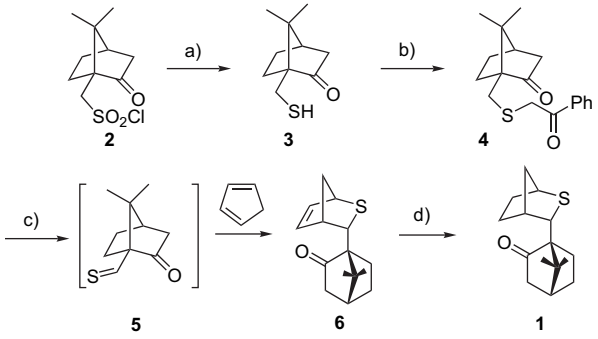
Scheme 2. Catalytic asymmetric synthesis of cyclopropanes and aziridines with in situ generation of diazocompounds.

New and useful reactions of chiral sulfur ylides with organoboranes have also been developed and high levels of enantioselectivity have been achieved (Scheme 3).[9]



Scheme 3. Asymmetric synthesis of chiral organoboranes using sulfur ylides.

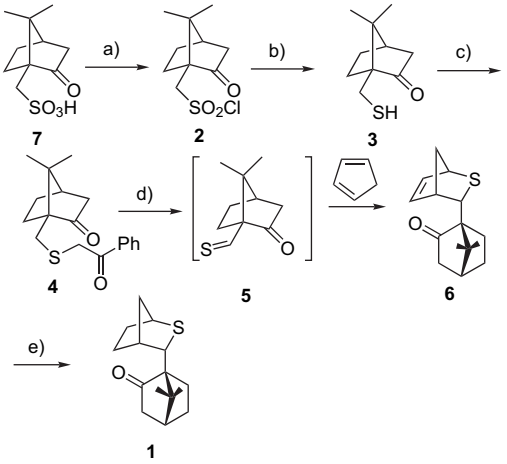
Having developed these useful asymmetric processes, a facile large-scale synthesis of sulfide **1** was sought. Although **1** had been previously prepared in four high yielding steps from camphorsulfonyl chloride (Scheme 4), this process could only be used to prepare **1** on a 5–10 g scale.[10]



Reagents and conditions:
a) PPh_3 (4 equiv.), 1,4-dioxane/H_2O (4:1), reflux, 1 h, 82%.
b) $PhCOCH_2Cl$ (1.1 equiv.), K_2CO_3 (5 equiv.), THF, reflux, 20 h, 82%.
c) cyclopentadiene (20 equiv.), CH_2Cl_2, 20 °C, 16 h, 70%, 20:1 diastereoselectivity.
d) H_2, 1.7% PdS/C, EtOH, r.t., 83%.

Scheme 4. Original protocol for the synthesis of chiral sulfide **1**.[10]

This is a consequence of limitations that arose in two of the key steps: the reduction of camphorsulfonyl chloride, which was limited by the large quantities of triphenylphosphine oxide by-product that must be removed and the photolysis-Diels–Alder reaction, which was limited by the power output of the lamp used. Each step, and in particular these two, was therefore studied in order to find the optimal conditions, with specific attention directed towards finding reaction conditions that could be performed easily on a large scale. The final optimised route is shown in Scheme 5 and is discussed in detail below.



Reagents and conditions:
a) PCl_5 (1.4 equiv.), 4 h, 0 °C ⟶ r.t., 96%.
b) PBu_3 (3 equiv.), 1,4-dioxane/H_2O (4:1), reflux, 15 h, 98%.
c) $PhCOCH_2Cl$ (1.0 equiv.), $NaHCO_3$ (2 equiv.), DMF, r.t., 5 h,100%.
d) cyclopentadiene (40 equiv.), CH_2Cl_2, –20 °C, continuous flow reactor.
e) H_2, 3% Pd/C, EtOH, r.t., 18 h, 59% (two steps).

Scheme 5. Improved synthesis of chiral sulfide **1**.

2. Results and discussion

Initially, the synthesis of the sulfide is started from the commercially available (+)-10-camphorsulfonyl chloride. However, this reagent is rather expensive (£196/100 g, Aldrich) and often contained impurities including (+)-10-camphorsulfonic acid **7**, which had to be removed. We therefore considered starting from (+)-10-camphorsulfonic acid (£33.70/100 g, Aldrich). Following the method reported by Vandewalle and co-workers,[11] (+)-10-camphorsulfonic acid **7** was efficiently converted to the corresponding sulfonyl chloride **2** by phosphorous pentachloride at 0 °C under solvent free conditions (Scheme 5). Recrystallisation of the chloride was necessary before continuing to the next step as the impure material gave significantly reduced yields in the next step (70% cf. 90% with pure material).

The next step of the synthesis was the formation of thiol **3** by reduction of camphorsulfonyl chloride with 4 equiv of triphenylphosphine according to the literature protocol.[10,12] While this reaction worked well giving the thiol **3** in good yield, an unappealing aspect of this procedure was the removal of a large quantity of triphenylphosphine oxide, which was often non-trivial. Therefore, an alternative phosphine was sought that resulted in a water-soluble phosphine oxide thus making it easier to remove. Both trimethylphosphine and tri-*n*-butylphosphine met this requirement although tri-*n*-butylphosphine was chosen, not least because

trimethylphosphine is a sternutator. Interestingly, the water solubility of tri-*n*-butylphosphine oxide has been shown to be greater at low temperature and so extraction was performed using ice cold water.[13] Substituting tri-*n*-butylphosphine for triphenylphosphine under identical conditions (note: the solution was degassed before addition of phosphine) gave the thiol in 85% yield after ice-water extraction and column chromatography. Since only 3 equiv of the phosphine are formally required, we tested the reduction under the reduced loading and this reaction proved very efficient (98%). It could be performed on large scale and unlike the use of 4 equiv, required no chromatographic purification. In the alkylation of thiol **3** with α-chloroacetophenone, it was found that the generation of undesired by-products could be minimised by using DMF in place of the previously employed THF. The use of DMF allowed the reaction to proceed smoothly at an ambient temperature over a shorter time scale and ultimately led to an overall cleaner reaction. The use of a weaker base in this alkylation step also allowed the reaction to proceed more smoothly, so the original base K_2CO_3 was replaced by $NaHCO_3$. The efficient alkylation of the thiol was thus achieved using 1 equiv of α-chloroacetophenone, followed by a simple purifying work-up procedure and removal of solvent in vacuo gave material of sufficient purity for the next transformation (Scheme 5).

2.1. Optimisation of batch photochemical reactor process

While there are a variety of methods available for the generation of thioaldehydes,[14] the photochemical generation of thioaldehydes from phenacyl sulfides, as described by Vedejs and co-workers, is the key step in this synthetic sequence. This method involves the irradiation of a solution of phenacyl sulfide using a sun lamp, in the presence of an excess of cyclopentadiene (Scheme 4).[14a] A copper sulfate bath was used to filter out light of wavelengths below 320 nm, which are believed to cause undesirable secondary photochemical reactions, and the reaction temperature was maintained at 20 °C with the aid of a crystostat. The reaction needs to be degassed since oxygen can sequester the radical intermediates[14a] and this was achieved by simply repeating the procedure of putting the cooled solution (−78 °C) under vacuum (about 15 mbar) followed by charging the vessel with nitrogen twice.

Perhaps the biggest obstacle for the scale up of this reaction is the output of the lamp, since this does not change when the amount of material that is to be photolysed is increased. Ordinarily this would simply require increased reaction times to allow sufficient light to enter the system and thus complete the reaction. However, cyclopentadiene slowly dimerises over time and so prolonged reaction times are not acceptable. Therefore the efficiency of the lamp was examined. It was found that the phenacyl sulfide **4** had two peaks in its UV spectrum (ca. 280 nm and 300 nm). The absorption at ca. 280 nm was attributed to the π–π* transition of the carbonyl group on the camphor moiety and the absorption at ca. 300 nm was assigned to the π–π* transition of the carbonyl that was to be excited. However the spectral output of the lamp (Osram Ultra-Vitalux 300 W sun lamp) was discovered to be very broad and quite weak and therefore not well suited to this reaction, as only a small percentage

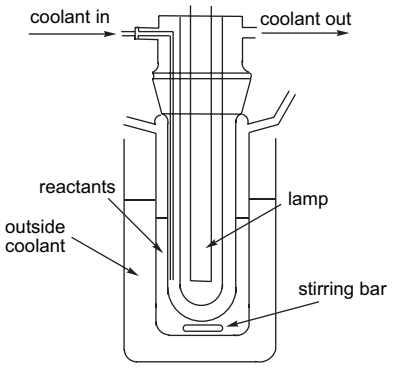


Figure 1. The batch photochemical reactor.

of the relatively weak output was able to excite the molecule into the triplet state. Therefore, a lamp with a higher output in the desired wavelength range was sought. The use of a 125 W mercury arc lamp in a Vycor immersion well provided a suitable alternative (no copper sulfate bath used due to lamp set up—see Fig. 1). Under these conditions the reaction was significantly faster and the product was obtained in similar yield and diastereoselectivity to the original conditions. This allowed 18.2 g of **4** to be processed in a single batch carried out in neat cyclopentadiene (20 equiv). However, the mercury lamp generated a large amount of heat and efficient cooling of the reaction vessel was required to achieve good stereocontrol (Fig. 1). This was carried out by using a circulating coolant on the inner wall and cryostatic cooling to the outer wall, with both set at −10 °C. The reaction was monitored by ^{1}H NMR and it was found that at this temperature good diastereoselectivity (~20:1) was observed. Without internal cooling, the reaction temperature is significantly higher and lower diastereoselectivity (6:1) was obtained, resulting in more difficult downstream problems for separating the diastereomers.

2.2. A single pass, continuous flow photochemical reactor

The use of the batch reactor for this photochemical reaction had certain limitations associated with it that were difficult to overcome and made further scale up inefficient. Most notably, the reaction mixture in the batch reactor is unevenly irradiated. This problem is emphasised when using large volumes of reactant solution, as diffusion in the narrow well is inefficient even with rapid stirring, resulting in reduced yields and increased by-product formation. This problem was overcome by the use of a single pass, continuous flow, Vycor reactor as described by Booker-Milburn and co-workers[15] (Fig. 2).

This consists of three layers of UV transparent tubing (fluorinated ethenepropylene (FEP), 2.7 mm i.d.×3.1 mm o.d.) wound around a traditional cooled immersion well containing a 400 W mercury lamp (Fig. 2b). The reaction solution could then be driven around the reactor through the use of a common HPLC pump (Fig. 2c) and the irradiation time could be defined by the flow rate. This system would then allow large volumes of reaction solution to be processed continuously. The cooling of the reaction solution was efficiently achieved by passing cooled ethylene glycol/water

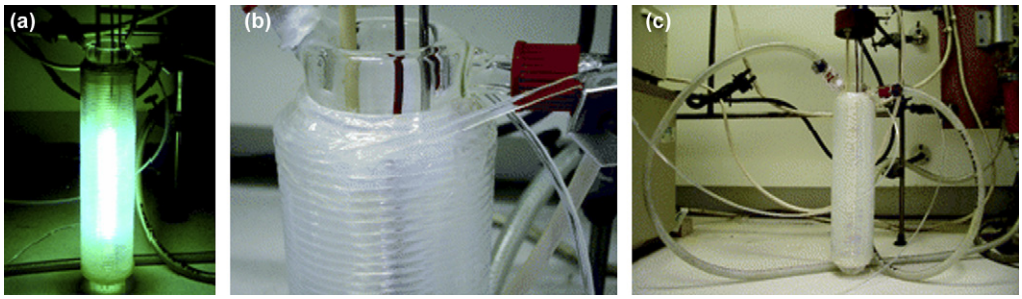


Figure 2. (a) A Vycor/FEP continuous flow chemical reactor. (b) Close-up of FEP tubing (2.7 mm i.d.×3.1 mm o.d.). (c) Attached to water supply and HPLC pump.

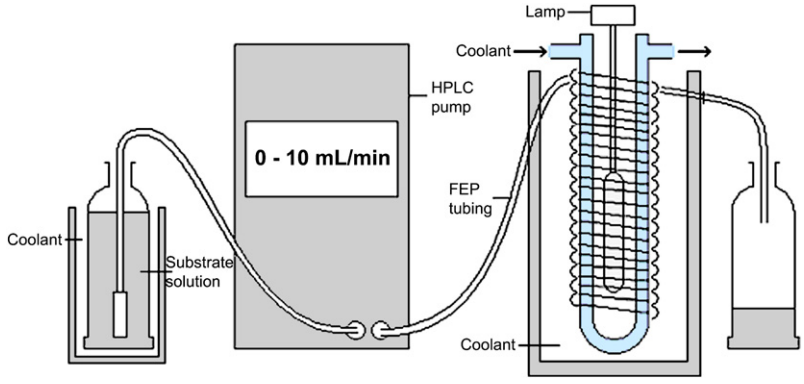
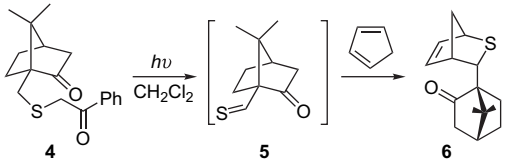


Figure 3. The single pass, continuous flow photochemical reactor.

(1:1) solution at temperature of −5 to −20 °C through the immersion well. In addition to this, the submersion of the entire reactor in an immersion bath of cooled ethylene glycol/water (1:1) solution ensured that the reaction temperature was well maintained. A schematic representation of the continuous flow photochemical reaction is shown in Figure 3.

The optimisation of this process was achieved by exploring how variations in flow rate, acylsulfide concentration, equivalents of cyclopentadiene and temperature affected both the reaction yield and the diastereoselectivity.[16] It was discovered that reducing the sulfide concentration from 0.4 to 0.2 M increased the yield from 43 to 59% (Table 1, entries 1 vs 2). Increasing the equivalents of cyclopentadiene was also shown to have a positive effect on both the yield and diastereoselectivity (Table 1, entries 2 vs 3). Reducing the temperature of the immersion bath from −5 to −20 °C was shown to have a positive effect on the yield, though no change in diastereoselectivity was observed (Table 1, entries 3 vs 4). Finally, a further increase in the amount of cyclopentadiene used (40 equiv) was shown to increase the yield

Table 1. Optimisation of the continuous flow photolysis of sulfide **4**



Entry	Flow rate (ml/min)	Sulfide concn (M)	Cyclopentadiene (equiv)	Internal temp (°C)	External temp (°C)	Yield (%)[a]	d.r.[b]
1	4	0.4	10	−20	−5	43[c]	9:1
2	4	0.2	10	−20	−5	59	10:1
3	4	0.2	20	−20	−5	67	11:1
4	4	0.2	20	−20	−20	72	11:1
5	2[d]	0.2	40	−20	−20	82	11:1
6	2	0.12	40	−20	−20	75	10:1

[a] Yield is calculated by ^{1}H NMR.
[b] Diastereoselectivity is calculated by HPLC using a Discovery® HS C18 568523-U column 25 cm×4.6 mm, 5 μm eluting with a flow rate of 1 mL/min with a gradient of water acetonitrile: 0–25 min from 5 to 95% acetonitrile, 25–27 min 95% acetonitrile, 27–37 min from 95 to 5% acetonitrile, 37–42 min 5% acetonitrile (t_{rminor}: 24.34 min, t_{rmajor}: 24.82 min).
[c] Starting material (25%) was recovered.
[d] A reduced flow rate of 2 mL/min was required as the high viscosity of the solution would not allow the pump to achieve a greater flow rate.

further (Table 1, entries 4 vs 5). A reduced flow rate of 2 mL/min was required when using these conditions due to the high viscosity of the reaction solution, which would not allow the pump system to achieve a greater flow rate. It was considered that on a large scale the problem of viscosity could be circumvented by reducing the concentration of the sulfide in combination with the reduced flow rate, thus giving a more practical set of optimised conditions (Table 1, entry 6). The final large scale (38 g of substrate) optimised conditions for the photolysis of sulfide **4** are shown in Table 1, entry 6 and gave a reaction yield of 75% with a 10:1 d.r.

Throughout this study it proved very difficult to separate the acetophenone by-product from the cycloadduct following the photolysis process, so the crude material was filtered through a short silica plug, and then taken onto the final hydrogenation step. Although initially the pre-poisoned catalyst PdS/C was used, it was found that the reactive double bond could be just as easily reduced using (10%) Pd/C (3 mol % Pd used). Following hydrogenation, the solvent and acetophenone were removed under reduced pressure (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad and the partially purified product recrystallised from pentane, to give the sulfide **1** as a white crystalline solid of >95% d.r.

3. Conclusions

We have developed a practical five-step synthesis of sulfide **1** in 56% overall yield from camphorsulfonic acid. The acid is extremely cheap and readily available in both enantiomeric forms. This practical synthesis of the chiral sulfide not only allows the organocatalytic reaction, which utilises the sulfide to be run on a large scale but also allows the stoichiometric reactions to be run on moderate scale.

4. Experimental

4.1. (+)-10-Camphorsulfonyl chloride (2)[11]

Based on the procedure of Vandewalle and co-workers,[11] (+)-10-Camphorsulfonic acid **7** (100.0 g, 0.43 mol) was placed in a 1 L round-bottomed flask with a gas outlet tube leading to a saturated $NaHCO_3$ trap (as HCl is produced in the reaction). The flask was cooled in a large ice bath and PCl_5 solid (124.0 g, 0.60 mol) was added portion wise. The mixture was agitated manually using a glass rod to initiate the liquefication of the mixture, before being stirred magnetically. After 1 h the cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then slowly poured portion wise into a 2 L separating funnel that was approximately 50% filled with crushed ice. After addition of each portion the separating funnel was thoroughly shaken before further material was added. Once addition of the reaction mixture to the separating funnel was complete, CH_2Cl_2 (500 mL) was added, and the separating funnel was shaken. CH_2Cl_2 layer was removed and the aqueous material was re-extracted with CH_2Cl_2 (2×200 mL). The combined organic fractions were then dried with $MgSO_4$ and the solvent was removed under reduced pressure to afford an off-white crystalline solid. This solid was then recrystallised from petrol to afford the product as white crystalline flakes (104.1 g, 96%). Mp 66–67 °C (hexane) [lit.[17] 67–68 °C (heptane)]; R_f 0.42 (20% EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.15 (3H, s), 1.49 (1H, ddd, J=13.0, 9.5 and 4.0 Hz), 1.78 (1H, ddd, J=14.0, 9.5, and 5.0 Hz), 1.99 (1H, d, J=18.5 Hz), 2.05–2.15 (1H, m), 2.17 (1H, $t_{(app.)}$, J=4.5 Hz), 2.40–2.52 (2H, m), 3.73 (1H, d, J=14.5 Hz), 4.31 (1H, d, J=14.5 Hz).

4.2. 7,7-Dimethyl-1-(sulfanylmethyl)bicyclo[2.2.1]-heptan-2-one (3)[10]

4.2.1. Method A: reduction using triphenylphosphine.[10] (+)-(10)-Camphorsulfonyl chloride **2** (14.0 g, 0.06 mmol) and triphenylphosphine (63.3 g, 0.24 mol) were refluxed in a mixture of H_2O (50 mL) and 1,4-dioxane (200 mL) for 1 h. The reaction mixture was allowed to cool to rt and was extracted with petrol (200 mL and 4×100 mL). The combined organic extracts were washed with H_2O (2×100 mL), saturated aqueous NaCl (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil, which was purified by flash chromatography (3% EtOAc in petrol) to give thiol **3** as a white crystalline solid (9.1 g, 82%). Mp 63–64 °C (EtOAc/petrol) [lit.[18] 65–66 °C]; R_f 0.22 (5% EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.02 (3H, s), 1.36–1.43 (1H, m), 1.67–1.75 (1H, m), 1.88–2.04 (4H, m), 2.09 (1H, $t_{(app.)}$, J=5.0 Hz), 2.29–2.42 (2H, m), 2.87 (1H, dd, J=13.5 and 7.0 Hz).

4.2.2. Method B: reduction using tri-*n*-butylphosphine. A solution of (+)-(10)-camphorsulfonyl chloride **2** (50.0 g, 0.2 mol) in 1,4-dioxane (380 mL) was degassed by bubbling N_2 through it for 10 min. Meanwhile, a mixture of H_2O (190 mL) and 1,4-dioxane (380 mL) in a 2 L 3-necked round-bottomed flask fitted with two heat resistant septa, a reflux condenser and a large magnetic stirrer bar was degassed in the same way. After 10 min tri-*n*-butylphosphine (150 mL, 0.6 mol) was added to the H_2O/dioxane mixture via syringe, giving a biphasic solution. This was followed rapidly by the addition of the degassed camphorsulfonyl chloride solution via cannula, which resulted in a monophasic solution. The reaction mixture was then stirred and heated to reflux for 15 h. The reaction mixture was then allowed to cool to rt and transferred to a 5 L separating funnel, where it was partitioned between petrol (1 L) and ice cold H_2O (1 L). The aqueous layer was removed and extracted with petrol (3×500 mL), the total volume of these organic extracts was then reduced to 300 mL and the colourless solution was then washed with ice cold H_2O (3×500 mL) and the solvent evaporated to give a white crystalline solid. The initial petrol layer was washed with ice cold H_2O (3×500 mL) and then evaporated to give a yellow crystalline mass. This was then washed with petrol to give a white crystalline solid. The organic washings were then evaporated to dryness and filtered through a short silica plug (eluent 5% EtOAc in petrol) collecting all fractions that stained a $KMnO_4$ plate. After evaporation of the appropriate fractions, the white crystalline solid obtained was combined with the other solids obtained to give **3** as white crystalline solid (36.0 g, 98%).

4.3. (+)-7,7-Dimethyl-1-{[(2-oxo-2-phenylethyl)-sulfanyl]methyl}bicyclo[2.2.1]heptan-2-one (4)[10]

Using an improved procedure of Vedejs and co-workers,[19] into a solution of **3** (30.0 g, 0.163 mol) and α-chloroacetophenone (1.0 equiv, 25.2 g, 0.163 mol) in DMF (100 mL) was added $NaHCO_3$ (2 equiv, 27.4 g, 0.326 mol). After 5 h the reaction was monitored by either HPLC or ^{1}H NMR to look for complete consumption of the α-chloroacetophenone. If all was consumed the reaction mixture was then diluted with diethyl ether, filtered and washed with diethyl ether. The solution was washed with water (3×100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **4** as a pale yellow oil (49.3 g, 100%) that was of sufficient purity to use in the subsequent reaction. If any α-chloroacetophenone remained (lachrymator!), then commercial aqueous ammonia solution (35%, 40 mL) was added and the reaction mixture stirred for 1 h, then cooled in an ice bath and carefully acidified by the portion wise addition of aqueous HCl (1 M). The solution was then diluted with diethyl ether (500 mL) and extracted with aqueous HCl (3×100 mL), water (1×100 mL) and dried over $MgSO_4$. Diethyl ether was removed and the resulting dark orange oil dissolved in ethanol (100 mL) and treated with activated charcoal (5.0 g), then heated to 50 °C for 1 h, allowed to cool, then filtered through Celite and the solvent removed under reduced pressure to afford **4** as a pale yellow oil (49.3 g, 100%) that was of sufficient purity to use in the subsequent reaction. $[\alpha]_D^{21}$ +6.5 (*c* 20, CH_2Cl_2); R_f 0.37 (15% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, s), 1.03 (3H, s), 1.28–1.41 (1H, m), 1.52 (1H, dd, *J*=12.5 and 3.0 Hz), 1.85 (1H, d, *J*=18.0 Hz), 1.90–2.01 (2H, m), 2.06 (1H, $t_{(app.)}$, *J*=4.0 Hz), 2.34 (1H, ddd, *J*=18.0, 4.7 and 2.3 Hz), 2.57 (1H, d, *J*=13.1 Hz), 2.87 (1H, d, *J*=13.1 Hz), 3.87 (2H, s), 7.47 (2H, t, *J*=8.0 Hz), 7.57 (1H, t, *J*=8.0 Hz), 7.98 (2H, d, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.2, 26.8, 26.9, 29.4, 39.6, 43.0, 43.5, 47.8, 61.1, 128.6, 128.7, 133.3, 135.4, 194.6, 217.2.

4.4. General procedure for large-scale photolysis using a batch reactor

The solution of phenacyl sulfide **4** (18.2 g, 60 mmol) and freshly distilled cyclopentadiene (80.0 g, 20 equiv) in a 125 mL Vycor immersion well was cooled in dry ice-acetone. The cooled solution was degassed by repeating the procedure of putting the solution under vacuum (about 15 mbar) followed by charging the vessel with nitrogen twice. The degassed solution was photolysed at −10 °C with a 125 W medium pressure mercury lamp for 9 h (monitored by ^{1}H NMR) *with simultaneous cooling of both the inside and outside walls of the reaction vessel* (Fig. 1). The reaction mixture was then transferred to a round-bottomed flask and the excess cyclopentadiene (51.1 g) was collected under reduced pressure (20 mbar); this could then be recycled if desired. The sulfide was then isolated by passing the crude reaction mixture through a short silica plug (150 g of silica gel), eluting first with petrol to remove the cyclopentadiene dimers until the yellow front line reaches the bottom of the column. The petrol fractions were then discarded and the product and acetophenone were eluted from the silica plug using 2.5% ethyl acetate/petrol, monitoring by TLC (R_f=0.45 [product], 0.43 [acetophenone], 5% ethyl acetate/petrol) to ensure all of the product is collected. The solvent was then removed under reduced pressure to give the partially purified product as a pale yellow oil (65% yield by ^{1}H NMR, using the stoichiometrically produced acetophenone as an internal standard, and 20:1 d.r.), which was dissolved in EtOH (~40 mL) and 10% Pd/C (3.0% based on the Diels–Alder product) was added. The mixture was stirred under a hydrogen atmosphere (7.0 bar) for 18 h (monitored by ^{1}H NMR) and the Pd/C was removed by filtration through a Celite® pad. The solvent and acetophenone (the by-product of the photolysis) were removed under vacuum (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad eluting with 2% ethyl acetate/petrol, to remove the coloured impurities. The crude product was then recrystallised from pentane to afford the sulfide **1** as a white solid (8.21 g, 54%, >95% d.r.). Mp 60–62 °C (MeOH) [lit.[10] 60–62 °C (MeOH)]; $[\alpha]_D^{25}$ +35.9 (*c* 19.5, CH_2Cl_2) [lit.[10] $[\alpha]_D^{25}$ +39.3 (*c* 1.0, MeOH)]; R_f 0.36 (4% EtOAc in petrol); IR ($CDCl_3$) 3025, 2950, 1760, 1230 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s), 0.96 (3H, s), 1.32–2.08 (11H, m), 2.38 (1H, ddd, *J*=18.2, 4.8 and 3.1 Hz), 2.52–2.66 (1H, m), 3.24–3.32 (1H, br), 3.60 (1H, m), 3.64–3.71 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.6, 21.4, 23.5, 24.4, 27.6, 35.2, 41.3, 42.4, 44.0, 44.7, 45.0, 49.3, 49.9, 62.6, 217.6; MS (EI): *m/z* (%): 250 (85) [M^+], 209 (52), 194 (49) 181 (100); HRMS (EI) (*m/z*) calculated for $C_{15}H_{22}SO$ 250.1391, found 250.1401.

4.5. General procedure for large-scale photolysis using a continuous flow reactor

To a solution of ketosulfide **4** (38 g, 0.126 mol) in CH_2Cl_2 (630 mL) at −20 °C was added freshly distilled cyclopentadiene (420 mL, 5.04 mol) and the reaction mixture degassed for 10 min by the passing of N_2 through the solution. The continuous flow reactor (Fig. 3) was set with the internal and the external cooling systems at −20 °C (ethylene glycol/water 1:1). The 400 W mercury lamp was switched on and degassed CH_2Cl_2 (20 mL) was pumped through the Vycor, three-layer continuous flow reactor at a flow rate of 2 mL/min. The reaction mixture was then pumped through the reactor at a flow rate of 2 mL/min, with collection of the product in a large conical flask. Once the whole solution had passed through the reactor, the tubing was washed with CH_2Cl_2 (350 mL) using the same flow rate. The reaction solution and tube wash were then combined and transferred to a round-bottomed flask and the solvent and cyclopentadiene were removed under reduced pressure (20 mbar). The sulfide was then isolated by passing the crude reaction mixture through a short silica plug (250 g of silica gel), eluting first with petrol to remove the cyclopentadiene dimers until the yellow front line reaches the bottom of the column. The petrol fractions were then discarded and the product was eluted from the silica plug using 2.5% ethyl acetate/petrol, monitoring by TLC (R_f = 0.45 [product], 0.43 [acetophenone], 5% ethyl acetate/petrol) to ensure all of the product is collected. The solvent was then removed under reduced pressure to give the partially purified product as a pale yellow oil (75% yield by ^{1}H NMR, using the stoichiometrically produced acetophenone as an internal standard, and 10:1 d.r. by HPLC), which was dissolved in EtOH (~80 mL) and 10% Pd/C (2.6 g, 2.0 mol % based on sulfide

4 and 3.0% based on the Diels–Alder product) was added. The mixture was stirred under a hydrogen atmosphere (7.0 bar) for 18 h (monitored by ^{1}H NMR) and the Pd/C was removed by filtration through a Celite® pad. The solvent and acetophenone (the by-product of the photolysis) were removed under vacuum (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad eluting with 2% ethyl acetate/petrol to remove the coloured impurities. The crude product was then recrystallised from pentane to afford the sulfide **1** as white solid (18.6 g, 59%, >95% d.r.).

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16. This study was carried out on medium scale (~1.5 g of sulfide per reaction) due to constraints on the availability of starting material. Table 1, entries 1–5 represent medium scale trial reactions. Table 1, entry 6 represent the conditions and results for the 38 g, large scale reaction.
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One-pot synthesis of chiral dehydroproline esters: [3+2]-type cycloaddition reaction of allenylstannane and α-imino ester

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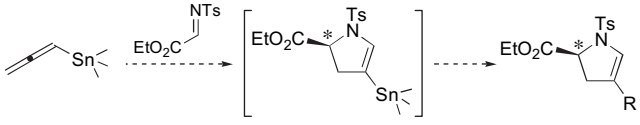
Abstract—An enantioselective [3+2]-type cycloaddition of allenylstannane and α-imino ester was developed. Synthetic utility of the 4-stannyldehydroproline ester intermediate was demonstrated: iodine oxidation and Stille coupling reaction of the intermediate afforded optically active 4-iodo- and 4-aryldehydroproline esters in good yields and in high ees, respectively.

1. Introduction

Development of the novel synthetic method of proline and its derivatives in optically pure form is an important objective because they play key roles as chiral sources in synthetic organic chemistry. For instance, chiral diamines and amino alcohols (prolinols), prepared from optically active proline are efficient ligands for asymmetric aldol reactions,[1a] alkylation of aldehydes,[1b] and Michael addition reactions.[1c] Chiral oxazaborolidine, prepared from optically active prolinols, are useful catalysts for asymmetric borane reduction of ketones[1d] and Diels–Alder reactions.[1e–h] Parent proline and its substituted form have lately emerged as an efficient chiral organocatalysts.[2] Prolines have, thus, found increasing synthetic utility as chiral catalysts in addition to chiral building blocks.

Previously, we reported [3+2]-type cycloaddition reactions of allenylsilanes with α-imino ester, and we could obtain 4-silylated dehydroproline esters in an enantioselective manner.[3] This result encouraged us to examine the [3+2]-type cycloaddition reactions of allenylstannane and α-imino ester (Scheme 1): in analogy to the chemistry of the allenylsilanes,[3,4] it is expected that allenylstannane also undergoes [3+2]-type cycloaddition with α-imino ester.[5] The resulting 4-stannylated dehydroproline ester would be a useful synthetic intermediate for the preparation of optically active 4-substituted dehydroproline esters because C–Sn bond is more reactive than the corresponding C–Si bond.[6]



Scheme 1. Our approach to optically active dehydroproline esters.

Based on the consideration, we studied (1) the cycloaddition reaction of allenylstannane and α-imino ester and (2) functionalization of the resulting [3+2]-type cycloadduct.[7]

2. Results and discussion

2.1. Cycloaddition reaction of allenylstannane and α-imino ester

At the outset, we studied the reaction of α-imino ester **1** and allenyl(tributyl)stannane **2** (Scheme 2). Compounds **1** and **2** were heated in the presence of $[Cu(MeCN)_4]ClO_4$ and (*R*)-TolBINAP (10 mol % each). After stirring for 5 h, we could obtain chiral dehydroproline ester **3** in 66% yield and 56% ee. Compound **3** is a protonolysis product of the expected stannyldehydroproline ester **4**.

This result is in clear contrast to our enantioselective propargylation reaction:[8,9] in the presence of 1 mol % of the catalyst at −30 °C, **1** reacted with **2** to give (*S*)-homopropargylamine **5** in 96% yield and 86% ee. It is found that propargylation product was obtained under mild conditions and that [3+2]-type cycloaddition product was obtained under more harsh conditions.

We found that the product distribution of the cycloadduct(s) and the propargylation product was also dependent on the

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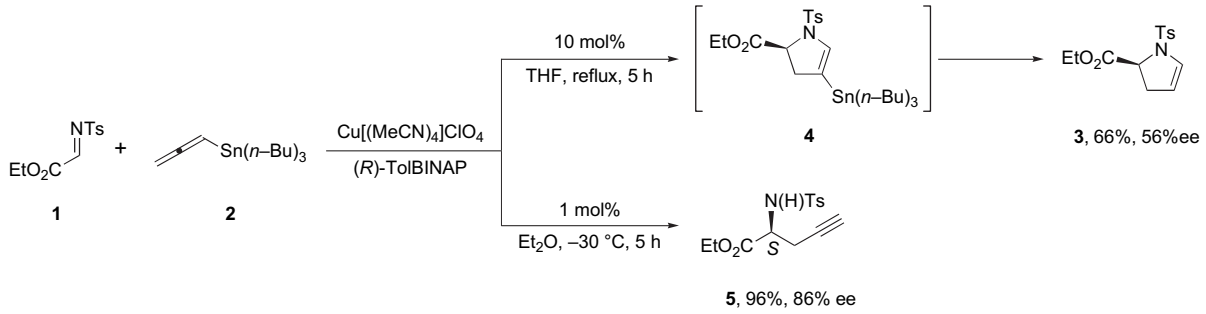
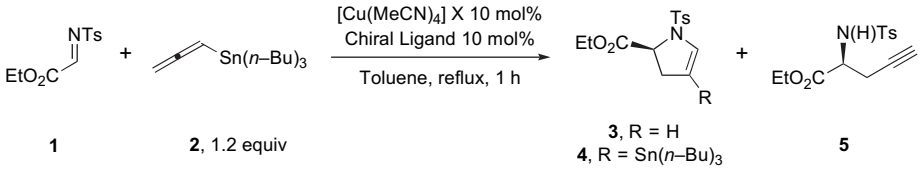


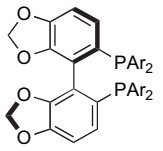
Scheme 2. [3+2]-Type cycloadditions of **1** and **2**.

Table 1. Ligand effect



Entry	Chiral ligand	X	**3**+**4** (%) (**3**/**4**), ee of **3** (%)[a]	**5** (%)[a,b]
1	(*R*)-TolBINAP	ClO_4	86 (91/9), 71	—
2	(*R*)-TolBINAP	BF_4	93 (63/37), 84	—
3	(*R*)-TolBINAP	PF_6	78 (87/13), 85	—
4	(*R*)-SEGPHOS	ClO_4	64 (66/34), 81	—
5	(*R*)-SEGPHOS	BF_4	9 (100/0), 70	55
6	(*R*)-SEGPHOS	PF_6	Trace (—), —	58, 63% ee
7	(*R*)-DM–SEGPHOS	ClO_4	26 (46/54), 72	56, 70% ee
8	(*R*)-DTBM–SEGPHOS	ClO_4	Trace (—), —	70

[a] The ee values of **3** and **5** were determined by chiral HPLC analysis.
[b] The ee values were not determined unless otherwise indicated.



Ar=Ph for (*R*)-SEGPHOS
Ar=(3,5-Me_2)C_6H_3 for (*R*)-DM-SEGPHOS
Ar=(3,5-*t*–Bu_2)(4-MeO)C_6H_2 for (*R*)-DTBM-SEGPHOS

nature of the phosphine ligand employed (Table 1). When **1** and **2** (1.2 equiv) were refluxed in toluene for 1 h in the presence of (*R*)-TolBINAP and cuprous salt ([Cu(MeCN)$_4$]ClO_4, –BF_4, –PF_6) (10 mol % each), cycloadducts (**3** and survived **4**) were obtained in good yields and propargylation product **5** was not obtained at all (Entries 1–3).[10] However, when (*R*)-SEGPHOS was used, **5** was produced by means of the BF_4 and PF_6 salts (Entries 5 and 6). When (*R*)-DM-SEGPHOS was used as a chiral ligand, **5** was formed preferentially even in the case of ClO_4 salt (Entry 7). Use of (*R*)-DTBM-SEGPHOS gave **5** as an essentially sole product (Entry 8). It seems that electron-donating ligand gives homopropargylamine **5** preferentially.

The structure of **4** was characterized spectroscopically. ^1H and ^{13}C NMR spectra were consistent with the structure of the expected 4-stannyldehydroproline ester. The isotope pattern of observed fragment ion ($M^+-C_4H_9$, $C_{22}H_{34}NO_4SSn$), in particular, was in complete agreement with its computer simulation (Fig. 1).

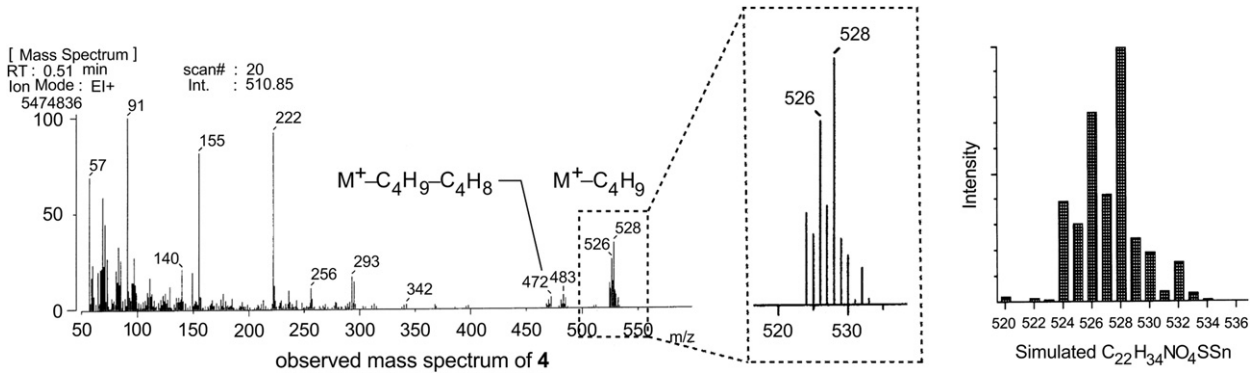


Figure 1. Mass spectrum of stannyldehydroproline **4**.

Table 2. Temperature and reaction time[a]

Entry	Temp	Time (h)	ee of **3** (%)[b]	**3**+**4** (%) (Ratio)	**5** (%)
1	Reflux	1	71	86 (91/9)	—
2	Reflux	5 min	89	45 (56/44)	39
3	80 °C	5	77	87 (66/34)	—
4	80 °C	3	82	82 (63/37)	—
5	80 °C	1	91	65 (55/45)	—
6	80 °C	0.5	94	25 (84/16)	61

[a] **1**/**2**/[Cu(MeCN)$_4$]ClO$_4$/(*R*)-TolBINAP=1/1.2/0.1/0.1, toluene.
[b] The ee values were determined by chiral HPLC analysis.

We optimized the reaction conditions by means of the [Cu(MeCN)$_4$]ClO$_4$/(*R*)-TolBINAP system. High ee values were achieved by carrying out the reaction at lower temperature and that prolonging the reaction time decreased the ee values (Table 2): the value of 71% ee (**3**) obtained by refluxing **1** and **2** for 1 h in toluene (Entry 1) increased up to 91% ee by carrying out the reaction in an oil bath of 80 °C (Entry 5).[11] When the reaction was allowed to proceed longer, the ee value decreased gradually (Entries 1, 2, and 3–6).

Besides, we could obtain considerable amount of **5** when the reaction was quenched in a short period of time (Entries 2 and 6). This propargylation product disappeared by prolonged time, and cycloaddition products were obtained.

In analogy to the silicon analogues,[4a–c] we initially surmised that this reaction proceeded by a migratory cyclization mechanism (left, in Scheme 3): allenylstannane **2** undergoes copper(I)-catalyzed nucleophilic addition with the α-imino ester **1**, giving a β-carbocation intermediate **6**. **6** undergoes C–Sn bond cleavage under mild conditions (e.g., in Scheme 2) to give stannylamide intermediate **7**, which is readily hydrolyzed to furnish homopropargylamine **5**. On the other hand, stannyl moiety of **6** undergoes 1,2-migration under more harsh conditions and simultaneous cyclization gives the stannyldehydroproline ester **4** and its protonolysis product **3**.

However, this mechanism is apparently inconsistent with the fact that we could obtain considerable amount of **5** in a short period of time, and after prolonging reaction time, we could obtain **3** and **4**, instead (Table 2)—regeneration of **6** from **7** is highly unlikely.

We thus rejected the migratory cyclization mechanism and adopted a sequential propargylation–cyclization mechanism (right, in Scheme 3): **6**, generated from **1** and **2**, undergoes rapid C–Sn bond cleavage to give **7**.[12] **7** is a resting intermediate and the subsequent copper(I)-catalyzed cyclization gives the stannyldehydroproline ester **4** probably via copper(I)-alkyne π complex.[13] On the other hand, when the reaction is carried out under mild conditions or quenched in a short period of time, the resting **7** is hydrolyzed during work-up to give **5**.[14] Use of electron-donating ligand retards the electrophilic cyclization process and also results in the formation of **5** (Table 1). Prolonged reaction time decreased enantioselectivity, indicating that **7** (and/or **4**) readily racemize(s) under the reaction conditions.[15]

We suppose that the absolute stereochemistry of the cycloadducts **3** and **4** is *S* because our enantioselective propargylation reaction afforded (*S*)-**5** (Scheme 1)[8] and enantioselective [3+2]-type cyclization of **1** and allenylsilanes afforded silyldehydroproline esters of *S* isomers.[3a] *Re* face of **1** might be shielded by pseudoequatorial tolyl group on copper(I)/(*R*)-TolBINAP/**1** complex (Fig. 2).

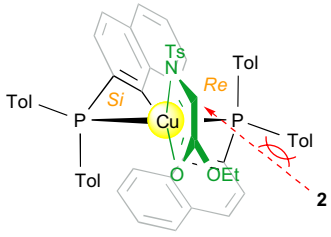
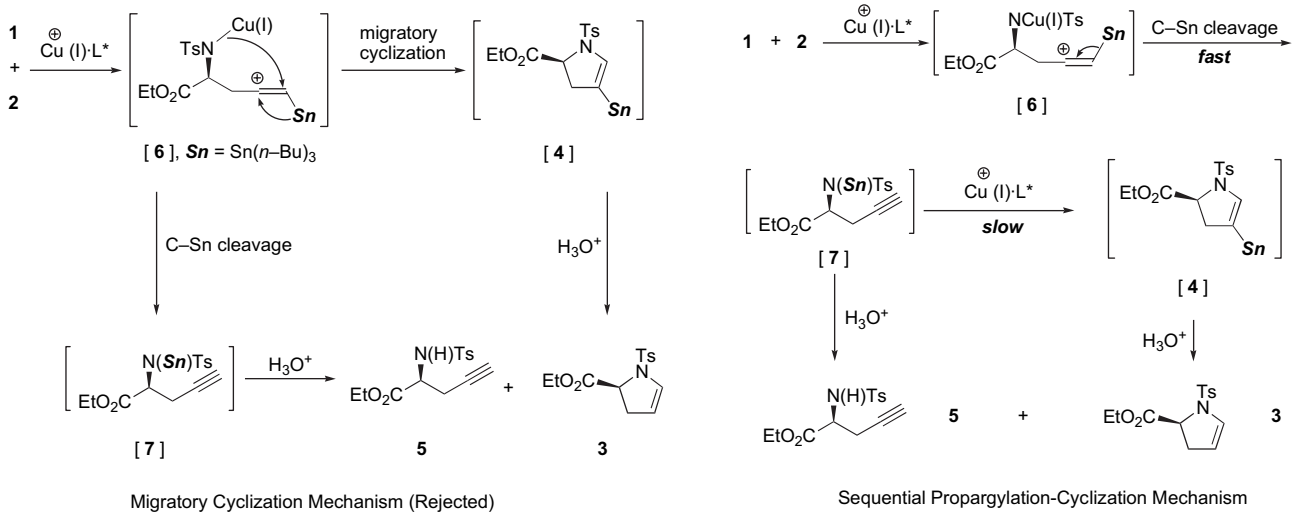


Figure 2. Working hypothesis of *Si*-face selective attack.

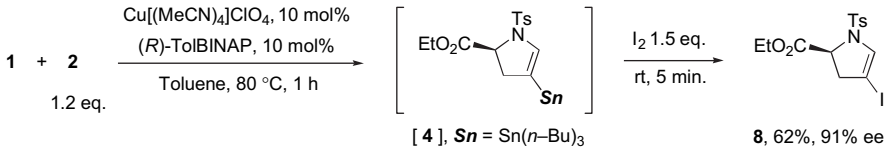
2.2. Functionalization of 4—iodine oxidation

The stannyldehydroproline ester **4** appeared to be an electron-rich, and thus reactive alkenylstannane. We expected

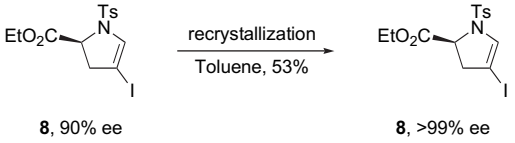


Scheme 3. Reaction mechanisms.

that **4** was a useful intermediate for synthesis of chiral dehydroproline ester derivatives: after **1** and **2** (1.2 equiv) were stirred for 1 h at 80 °C in the presence of $[Cu(MeCN)_4]ClO_4$ and (*R*)-TolBINAP (10 mol %, each), the resulting mixture containing **4** was treated with iodine (I_2, 1.5 equiv) at room temperature in the same flask. The iodine was consumed quite rapidly and reductive work-up with aqueous $Na_2S_2O_3$ gave 4-iododehydroproline ester **8** in 62% yield and 91% ee (Scheme 4). It should be noted that one recrystallization of **8** (90% ee) from toluene dramatically improved the ee value (Scheme 5). The minor enantiomer was not detected by chiral HPLC analysis and it is estimated that optical purity is >99% ee.



Scheme 4. Synthesis of chiral 4-iododehydroproline **8**.



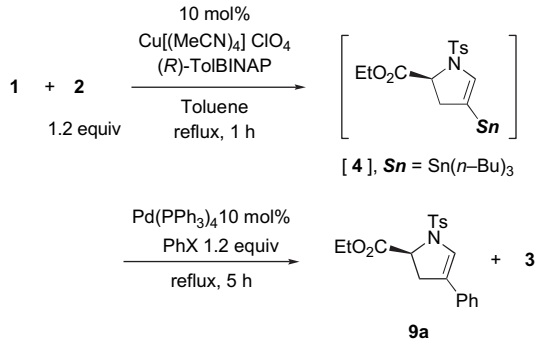
Scheme 5. Recrystallization of **8**.

2.3. Functionalization of 4—Stille coupling reaction

Three-component coupling was also accomplished by application of the Stille coupling reaction to **4** (Table 3). Stannyldehydroproline **4**, generated from **1** and **2** (toluene, reflux, 1 h), was subsequently treated with 1.2 equiv of iodo- or bromobenzene and 10 mol % of $Pd(PPh_3)_4$ in the same flask. After refluxing for 5 h, 4-phenylated dehydroproline ester **9a** was obtained in good yields (Entries 1 and 2). Chlorobenzene, phenyl trifluoromethanesulfonate, $[Cu(MeCN)_4]BF_4$, and $[Cu(MeCN)_4]PF_6$ gave disappointing results (Entries 3–6).

We could synthesize various 4-arylated dehydroproline esters in good yields and in high ees by the three-component coupling reaction, using aryl bromides particularly bearing electron-withdrawing group on their aromatic rings (Table 4).

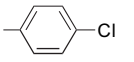
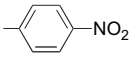
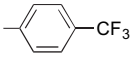
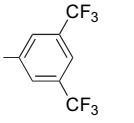
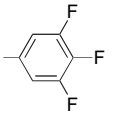
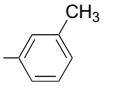
Table 3. Stille-type phenylation of **4**



Entry	PhX	**9a** (%), ee (%)[a]	**3** (%), ee (%)[a]
1	PhI	76, 78	20, 78
2	PhBr	81, 81	15, 85
3	PhCl	—	76, 75
4	PhOTf	—	80, 75
5[b]	PhI	4[d]	22, 72
6[c]	PhI	6[d]	41, 75

[a] The ee values were determined by chiral HPLC analysis.
[b] $Cu[(MeCN)_4]BF_4$ was employed.
[c] $Cu[(MeCN)_4]PF_6$ was employed.
[d] The ee values were not determined.

Table 4. Three-component synthesis of **9**[a]

Entry	Ar	**9** (%), ee (%)[b]	**3** (%), ee (%)[b]
1	Ph	62, 90 (**9a**)	20, 91
2		46, 93 (**9b**)	20, 93
3		80, 84 (**9c**)	13, 87
4		66, 90 (**9d**)	18, 92
5		43, 84 (**9e**)	20, 91
6		68, 87 (**9f**)	18, 72
7		34, 74 (**9g**)	24, 92

[a] **1/2**/$[Cu(MeCN)_4]ClO_4$/(*R*)-TolBINAP=1/1.2/0.1/0.1, toluene, 80 °C, 1 h; then ArBr (1.2 equiv), $Pd(PPh_3)_4$ (10 mol %), reflux, 5 h.
[b] The ee values were determined by chiral HPLC analysis.

3. Conclusion

We have developed a novel enantioselective [3+2]-type cycloaddition reactions of allenylstannane and α-imino ester. The reaction could be rationalized by a sequential propargylation–cyclization mechanism. Synthetic utility of the stannyldehydroproline ester intermediate was demonstrated; iodine oxidation and Stille coupling reaction afforded

optically active 4-iodo- and 4-aryldehydroproline esters in good yields and in high ees, respectively.

4. Experimental

4.1. General

NMR spectra were recorded on an Unity Inova-400 instrument (Varian Japan Ltd, 400 MHz for ^{1}H, 100 MHz for ^{13}C) and JNM-Al300 instrument (JEOL, 300 MHz for ^{1}H, 75 MHz for ^{13}C) using $CDCl_3$ as a solvent. Chemical shifts (δ) for ^{1}H were referenced to tetramethylsilane (δ=0.00 ppm) as an internal standard. Chemical shifts (δ) for ^{13}C were referenced to a solvent signal ($CDCl_3$, δ=77.00 ppm). IR spectra were recorded on FTIR-8600PC instrument (Shimadzu Co.) using $CHCl_3$ as a solvent. Elemental analysis (EA) was carried out on EA1110 instrument (Amco Inc.). Mass spectra (MS) were recorded on JMS-AX505HA instrument (JEOL). Specific rotation was recorded on SEPA-300 instrument (HORIBA, Ltd).

4.1.1. Preparation of the starting materials. α-Imino ester **1** was prepared according to the literature[16] $[Cu(MeCN)_4]PF_6$ was prepared according to the literature,[17] and its ClO_4 and BF_4 analogues were prepared by its modification. Allenyl(tributyl)stannane **2** was prepared by the following procedure: to a flask containing magnesium (0.44 g, 18 mmol), lead dibromide (0.33 g, 0.90 mmol), tetrahydrofuran (30 mL), and chloro(tributyl)stannane was added propargyl bromide (2.14 g, 18 mmol) over 5 min and the mixture was heated carefully. The mixture was stirred for 1 h at ambient temperature, quenched with saturated aqueous ammonium chloride, filtered through a pad of Celite®, and the residue was washed with ethyl acetate. Products were extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate. Solvents were evaporated under vacuum and purification by column chromatography (SiO_2, Hexane) gave allenyl(tributyl)stannane **2** (4.35 g, 88%).

4.1.2. Synthesis of 3 and 4 (Entry 5, Table 2). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (6.5 mg, 0.020 mmol) and (*R*)-TolBINAP (14.9 mg, 0.022 mmol) were added **1** (51.1 mg, 0.20 mmol in 0.8 mL toluene) and **2** (79.0 mg, 0.24 mmol in 0.7 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. The resulting mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The crude mixture was put on a silica gel (2 cm×30 cm) and a mixed eluent (Hexane/AcOEt=10/1, 150 mL) was passed through the SiO_2 column to remove non-polar stannane residue and then fractions containing **3** (21.4 mg, 36% yield, 91% ee) and **4** (33.8 mg, 29% yield) were collected (Hexane/AcOEt=8/1). The ee value of **3** was determined by chiral HPLC analysis (Daicel Chiralpak, AD-H, Hexane/EtOH=5/1).

4.1.3. Synthesis of 8 (Scheme 4). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (4.7 mg, 0.014 mmol) and (*R*)-TolBINAP (11.2 mg, 0.016 mmol) were added **1** (38.3 mg, 0.15 mmol in 0.5 mL toluene) and **2** (59.2 mg, 0.18 mmol in 0.5 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. To the resulting mixture were added iodine (I_2, 57.1 mg, 0.23 mmol in 1.0 mL toluene) at room temperature, and after 5 min, saturated aqueous sodium thiosulfate was added. Products were extracted with ethyl acetate and combined organic layers were dried over anhydrous sodium sulfate. Purification by column chromatography (SiO_2, Hexane/AcOEt=8/1) gave **8** (101.9 mg, 62% yield, 91% ee). The ee value of **8** was determined by chiral HPLC analysis (Daicel Chiralpak, AS-H, Hexane/*i*-PrOH=5/1).

4.1.4. Synthesis of 9a (Entry 1, Table 4). To a toluene solution (0.5 mL) containing $[Cu(MeCN)_4]ClO_4$ (6.5 mg, 0.020 mmol) and (*R*)-TolBINAP (14.9 mg, 0.022 mmol) were added **1** (51.9 mg, 0.20 mmol in 0.8 mL toluene) and **2** (79.0 mg, 0.24 mmol in 0.7 mL toluene) successively. The solution was stirred in an oil bath of 80 °C for 1 h. To the resulting mixture were added $Pd(PPh_3)_4$ (23.3 mg, 0.020 mmol) and bromobenzene (37.7 mg, 0.24 mmol in 1 mL of toluene) at room temperature and the solution was refluxed for 5 h. The resulting mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The crude mixture was put on a silica gel (2 cm×30 cm) and a mixed eluent (Hexane/AcOEt=10/1, 150 mL) was passed through the SiO_2 column to remove non-polar stannane residue. Fractions containing the products were collected (Hexane/AcOEt=5/1, 200 mL) and purification by preparative TLC (SiO_2, toluene/MeCN=5/1) gave **9a** (45.8 mg, 62% yield, 90% ee) and **3** (11.7 mg, 20%, 91% ee). The ee values of **9a** and **3** were determined by chiral HPLC analysis (Daicel Chiralcel, OD-H, Hexane/*i*-PrOH=5/1 for **9a**).

4.1.5. Compound data.

4.1.5.1. (*S*)-1-Tosyl-4,5-dehydroproline ethyl ester (3). ^{1}H NMR δ=1.31 (3H, t, *J*=7.2 Hz), 2.44 (3H, s), 2.65 (1H, ddt, *J*=16.4, 7.2, 2.4 Hz), 2.78 (1H, ddt, *J*=16.4, 11.2, 2.4 Hz), 4.23 (1H, dd, *J*=11.2, 7.2 Hz), 4.25 (2H, q, *J*=7.2 Hz), 5.07 (1H, dt, *J*=4.4, 2.4 Hz), 6.37 (1H, dt, *J*=4.4, 2.4 Hz), 7.33 (2H, d, *J*=8.2 Hz), 7.70 (2H, d, *J*=8.2 Hz); ^{13}C NMR δ=14.0, 21.6, 35.2, 60.2, 61.7, 109.6, 127.7, 129.7, 130.4, 133.4, 144.2, 170.9; IR $\overline{\nu}$=1016, 1169, 1362, 1734, 1749, 3022 cm^{-1}; EA Calcd for $C_{14}H_{17}NO_4S$: C 56.93, H 5.80, N 4.74, S 10.86%; Found: C 56.78, H 5.87, N 4.71, S 10.98%; $[\alpha]_D^{27}$ −443.10 (*c* 1.00, $CHCl_3$, 91% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_R=16.91 min, t_S=21.43 min).

4.1.5.2. (*S*)-1-Tosyl-4-tributylstannyl-4,5-dehydroproline ethyl ester (4). ^{1}H NMR δ=0.85–0.91 (15H, m), 1.23–1.32 (9H, m), 1.38–1.44 (6H, m), 2.43 (3H, s), 2.68 (1H, ddd, *J*=16.2, 7.4, 2.0 Hz), 2.81 (1H, ddd, *J*=16.2, 10.8, 2.0 Hz), 4.11 (1H, dd, *J*=10.8, 7.4 Hz), 4.24 (2H, q, *J*=7.2 Hz), 6.18 (1H, t, *J*=2.0 Hz), 7.31 (2H, d, *J*=8.2 Hz), 7.68 (2H, d, *J*=8.2 Hz); ^{13}C NMR δ=9.5, 13.6, 14.1, 21.5, 27.1, 28.9, 41.9, 60.5, 61.5, 119.4, 127.7, 129.6, 133.5, 134.8, 143.9, 171.5; IR $\overline{\nu}$=1167, 1205, 1225, 1356, 1734, 1749, 3017, 3022 cm^{-1}; MS (DI) Isotope pattern of fragment ion ($M^+-C_4H_9$, $C_{22}H_{34}NO_4SSn$) was in complete agreement with its computer simulation (see text).

4.1.5.3. Ethyl (*S*)-2-tosylamino-4-pentynoate (5). ^{1}H NMR δ=1.17 (3H, t, *J*=7.2 Hz), 2.03 (1H, t, *J*=2.6 Hz), 2.42 (3H, s), 2.65 (1H, ddd, *J*=16.8, 5.2, 2.6 Hz), 2.72

(1H, ddd, J=16.8, 4.4, 2.6 Hz), 4.02–4.11 (3H, m), 5.43 (1H, d, J=8.4 Hz), 7.30 (2H, d, J=8.0 Hz), 7.75 (2H, d, J=8.0 Hz); ^{13}C NMR δ=13.9, 21.5, 24.1, 54.0, 62.2, 72.2, 127.2, 129.7, 136.9, 143.8, 169.5; IR $\overline{\nu}$=1018, 1094, 1163, 1229, 1371, 1740, 3013 cm^{-1}; EA Calcd for $C_{14}H_{17}NO_4S$: C 56.93, H 5.80, N 4.74, S 10.86%; Found: C 57.10, H 5.82, N 4.53, S 10.64%; $[\alpha]_D^{26}$ +15.20 (c 1.00, $CHCl_3$, 67% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=42.46 min, t_S=36.14 min).

4.1.5.4. (*S*)-4-Iodo-1-tosyl-4,5-dehydroproline ethyl ester (8). ^{1}H NMR δ=1.30 (3H, t, J=7.2 Hz), 2.45 (3H, s), 2.82 (1H, ddd, J=16.2, 7.2, 2.0 Hz), 2.97 (1H, ddd, J=16.2, 11.2, 2.0 Hz), 4.25 (2H, q, J=7.2 Hz), 4.27 (1H, dd, J=11.2, 7.2 Hz), 6.53 (1H, t, J=2.0 Hz), 7.36 (2H, d, J=8.2 Hz), 7.70 (2H, d, J=8.2 Hz); ^{13}C NMR δ=14.1, 21.8, 44.4, 61.1, 62.1, 67.9, 127.6, 129.8, 132.9, 135.3, 144.5, 169.7; IR $\overline{\nu}$=1099, 1169, 1296, 1364, 1734, 3032 cm^{-1}; EA Calcd for $C_{14}H_{16}INO_4S$: C 39.92, H 3.83, N 3.33, S 7.61%; Found: C 39.98, H 3.74, N 3.31, S 7.58%; $[\alpha]_D^{27}$ −175.80 (c 1.00, $CHCl_3$, >99% ee, Daicel Chiralpak AS-H, Hexane/*i*-PrOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_S=36.73 min).

4.1.5.5. (*S*)-4-Phenyl-1-tosyl-4,5-dehydroproline ethyl ester (9a). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.42 (3H, s), 2.98 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.15 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.28 (2H, q, J=7.2 Hz), 4.37 (1H, dd, J=11.6, 7.2 Hz), 6.85 (1H, t, J=1.8 Hz), 7.21 (1H, t, J=6.4 Hz), 7.23 (2H, d, J=7.8 Hz), 7.26–7.35 (4H, m), 7.74 (2H, d, J=7.8 Hz); ^{13}C NMR δ=14.1, 21.6, 35.8, 60.6, 61.9, 122.7, 124.7, 124.8, 127.3, 127.6, 128.6, 129.9, 132.9, 133.4, 144.3, 170.8; IR $\overline{\nu}$=1167, 1205, 1227, 1362, 1734, 1749, 3024 cm^{-1}; EA Calcd for $C_{20}H_{21}NO_4S$: C 64.67, H 5.70, N 3.77, S 8.63%; Found: C 64.80, H 5.62, N 3.59, S 8.46%; $[\alpha]_D^{26}$ −41.30 (c 1.00, $CHCl_3$, 90% ee, Daicel Chiralcel OD-H, Hexane/*i*-PrOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=21.96 min, t_S=34.47 min).

4.1.5.6. (*S*)-4-(4-Chlorophenyl)-1-tosyl-4,5-dehydroproline ethyl ester (9b). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.43 (3H, s), 2.95 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.14 (1H, ddd, J=15.6, 11.4, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.39 (1H, dd, J=11.4, 7.2 Hz), 6.84 (1H, t, J=1.8 Hz), 7.14 (2H, d, J=8.4 Hz), 7.26 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.73 (2H, d, J=8.4 Hz); ^{13}C NMR δ=14.1, 21.6, 35.8, 60.6, 62.0, 121.4, 125.4, 125.8, 127.6, 128.8, 130.0, 131.5, 132.9, 133.4, 144.5, 170.6; IR $\overline{\nu}$=1096, 1167, 1211, 1362, 1495, 1636, 1734, 2359, 3017 cm^{-1}; EA Calcd for $C_{20}H_{20}ClNO_4S$: C 59.18, H 4.97, N 3.45, S 7.90%; Found: C 58.99, H 4.83, N 3.20, S 7.70%; $[\alpha]_D^{25}$ −17.37 (c 0.95, $CHCl_3$, 93% ee, Daicel Chiralpak AD-H, Hexane/*i*-PrOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=51.82 min, t_S=56.96 min).

4.1.5.7. (*S*)-4-(4-Nitrophenyl)-1-tosyl-4,5-dehydroproline ethyl ester (9c). ^{1}H NMR δ=1.32 (3H, t, J=7.2 Hz), 2.44 (3H, s), 3.04 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.26 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.49 (1H, dd, J=11.6, 7.2 Hz), 7.09 (1H, t, J=1.8 Hz), 7.33 (2H, d, J=8.6 Hz), 7.36 (2H, d, J=8.6 Hz), 7.76 (2H, d, J=8.6 Hz), 8.15 (2H, d, J=8.6 Hz); ^{13}C NMR δ=14.0, 21.6, 35.6, 60.7, 62.1, 119.8, 124.1, 124.8, 127.6, 129.1, 130.1, 133.6, 139.7, 144.8, 146.2, 170.2; IR $\overline{\nu}$=1169, 1205, 1225, 1344, 1518, 1734, 3024 cm^{-1}; EA Calcd for $C_{20}H_{20}N_2O_6S$: C 57.68, H 4.84, N 6.73, S 7.70%; Found: C 57.72, H 4.93, N 6.79, S 7.60%; $[\alpha]_D^{25}$ +42.35 (c 1.00, $CHCl_3$, 84% ee, Daicel Chiralcel OD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=350 nm, t_R=63.20 min, t_S=53.82 min).

4.1.5.8. (*S*)-1-Tosyl-4-(4-trifluoromethylphenyl)-4,5-dehydroproline ethyl ester (9d). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.43 (3H, s), 3.00 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.20 (1H, ddd, J=15.6, 11.4, 2.0 Hz), 4.27 (2H, q, J=7.0 Hz), 4.43 (1H, dd, J=11.4, 7.2 Hz), 6.97 (1H, s), 7.30 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.0 Hz), 7.53 (2H, d, J=8.6 Hz), 7.75 (2H, d, J=8.0 Hz); ^{13}C NMR δ=14.0, 21.6, 35.7, 60.6, 62.0, 120.9, 124.7, 125.6 (q, $^3J_{C-F}$=3.8 Hz), 127.1, 127.6, 127.9 (q, $^1J_{C-F}$=285 Hz), 129.0 (q, $^2J_{C-F}$=33 Hz), 123.0, 133.5, 136.5, 144.6, 170.5; IR $\overline{\nu}$=1130, 1169, 1209, 1325, 1616, 1749, 2359, 3018 cm^{-1}; EA Calcd for $C_{21}H_{20}NO_4S$: C 57.40, H 4.59, N 3.19, S 7.30%; Found: C 57.47, H 4.37, N 3.28, S 7.12%; $[\alpha]_D^{24}$ −26.90 (c 1.00, $CHCl_3$, 90% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=65.07 min, t_S=56.22 min).

4.1.5.9. (*S*)-4-[3,5-Bis(trifluoromethyl)phenyl]-1-tosyl-4,5-dehydroproline ethyl ester (9e). ^{1}H NMR δ=1.33 (3H, t, J=7.2 Hz), 2.44 (3H, s), 3.03 (1H, ddd, J=15.6, 7.2, 1.8 Hz), 3.27 (1H, ddd, J=15.6, 11.6, 1.8 Hz), 4.27 (2H, q, J=7.2 Hz), 4.49 (1H, dd, J=11.6, 7.2 Hz), 7.06 (1H, s), 7.36 (2H, d, J=8.6 Hz), 7.59 (2H, s), 7.68 (1H, s), 7.77 (2H, d, J=8.6 Hz); ^{13}C NMR δ=14.0, 21.6, 35.6, 60.5, 62.2, 119.2, 120.1–120.5 (m), 124.2, 127.6, 128.3, 130.1, 132.0 (q, $^2J_{C-F}$=33 Hz), 133.6, 135.3, 144.8, 170.2; IR $\overline{\nu}$=1142, 1169, 1184, 1281, 1369, 1634, 1749, 3032 cm^{-1}; EA Calcd for $C_{22}H_{19}F_6NO_4S$: C 52.07, H 3.77, N 2.76, S 6.32%; Found: C 52.30, H 3.76, N 2.50, S 6.57%; $[\alpha]_D^{24}$ −42.90 (c 1.00, $CHCl_3$, 84% ee, Daicel Chiralpak AD-H, Hexane/EtOH=50/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=30.72 min, t_S=23.26 min).

4.1.5.10. (*S*)-1-Tosyl-4-(3,4,5-trifluorophenyl)-4,5-dehydroproline ethyl ester (9f). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.44 (3H, s), 2.91 (1H, ddd, J=15.6, 7.2, 1.6 Hz), 3.11 (1H, ddd, J=15.6, 11.6, 1.6 Hz), 4.26 (2H, q, J=7.0 Hz), 4.42 (1H, dd, J=11.6, 7.2 Hz), 6.80 (2H, dd, J=6.4, 8.4 Hz), 6.82 (1H, s), 7.35 (2H, d, J=8.4 Hz), 7.74 (2H, d, J=8.4 Hz); ^{13}C NMR δ=14.1, 21.6, 35.7, 60.5, 62.1, 108.6 (dd, $^2J_{C-F}$=15 Hz, $^3J_{C-F}$=6.8 Hz), 119.4–119.6 (m), 127.0, 127.6, 129.7, 130.0, 133.5, 138.8 (d, $^1J_{C-F}$=252 Hz), 144.7, 151.3 (d, $^1J_{C-F}$=236 Hz), 170.3; IR $\overline{\nu}$=1016, 1169, 1205, 1227, 1533, 1734, 1749, 3017, 3024 cm^{-1}; EA Calcd for $C_{20}H_{18}F_3NO_4S$: C 56.46, H 4.26, N 3.29, S 7.54%; Found: C 56.28, H 4.29, N 3.30, S 7.54%; $[\alpha]_D^{26}$ −64.05 (c 1.00, $CHCl_3$, 87% ee, Daicel Chiralpak AD-H, Hexane/EtOH=5/1, Flow rate 0.7 mL/min, UV=228 nm, t_R=25.56 min, t_S=18.11 min).

4.1.5.11. (*S*)-4-(3-Tolyl)-1-tosyl-4,5-dehydroproline ethyl ester (9g). ^{1}H NMR δ=1.32 (3H, t, J=7.0 Hz), 2.32 (3H, s), 2.42 (3H, s), 2.96 (1H, ddd, J=15.8, 7.1, 1.8 Hz), 3.14 (1H, ddd, J=15.8, 11.5, 1.8 Hz), 4.27 (2H, q,

J=7.0 Hz), 4.35 (1H, dd, J=11.5, 7.1 Hz), 6.84 (1H, t, J=1.8 Hz), 7.01–7.05 (2H, m), 7.16–7.24 (2H, m), 7.32 (2H, d, J=8.1 Hz), 7.73 (2H, d, J=8.1 Hz); ^{13}C NMR δ=14.1, 21.4, 21.6, 35.9, 60.6, 61.9, 121.8, 122.8, 124.7, 125.4, 127.6, 128.2, 128.5, 129.9, 132.8, 133.4, 138.2, 144.3, 170.8; IR $\bar{\nu}$=1092, 1167, 1362, 1734, 3018 cm^{-1}; EA Calcd for $C_{21}H_{23}NO_4S$: C 65.43, H 6.01, N 3.63, S 8.32%; Found: C 65.24, H 5.95, N 3.61, S 8.17%; $[\alpha]_D^{27}$ −19.04 (c 0.99, $CHCl_3$, 74% ee, Daicel Chiralpak AS-H, Hexane/EtOH=5/1, Flow rate 0.5 mL/min, UV=228 nm, t_R=23.22 min, t_S=18.28 min).

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10. Compound **3** was not observed just after concentration of the reaction mixture (^{1}H NMR analysis). Partial protonolysis of the cycloadduct **4** took place on silica gel during purification. Compounds **3** and **4** were isolated and total yields are indicated in Table 1 for clarity.
11. The ee value was not improved further by carrying out the reaction in an oil bath of 60 °C (93% ee) and the yield of **3** miserably decreased to 13%.
12. We suppose that weaker C–Sn bond is responsible for this fast process.
13. In the presence of the copper(I) catalyst, **5** (69% ee) underwent cyclization to give 18% yield of **3** (83% ee) and 82% recovery of **5** (62% ee) (10 mol % of $[Cu(MeCN)_4]ClO_4$, 10 mol % (*R*)-TolBINAP, toluene, 80 °C, 5 h). For Pd(0)-catalyzed cyclization of methyl ester corresponding to **5** see: Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *39*, 5081; We also treated **5** with *n*-BuLi/*n*-Bu_3SnCl in THF at –78 °C and then attempted Cu(I)-catalyzed cyclization. Indeed, **3** was obtained, but in 3% yield.
14. When the catalyst loading was lowered to 1 mol %, the cyclization did not take place to give homopropargylamine **5** exclusively in 75% yield, 64% ee (toluene, reflux, 1 h).
15. It was confirmed that dehydroproline ester **3** did not racemize under the reaction conditions. Compound **3** of 83% ee afforded 91% recovery of **3** with 83% ee even after 5 h stirring (10 mol % of $[Cu(MeCN)_4]ClO_4$, 10 mol % (*R*)-TolBINAP, toluene, and 80 °C).
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New conditions for the synthesis of thiophenes via the Knoevenagel/Gewald reaction sequence. Application to the synthesis of a multitargeted kinase inhibitor

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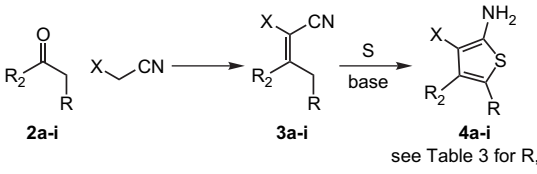
This paper is dedicated to Professor David MacMillan on the occasion of his receipt of the Tetrahedron *Young Investigator Award*

Abstract—Novel conditions have been developed for the preparation of substituted 2-aminothiophenes employing the Knoevenagel condensation followed by the Gewald reaction. The benefits of these conditions are their mildness, and the ease of product isolation. Thus, the Knoevenagel condensation is run in the presence of hexamethyldisilazane and acetic acid, which combine to perform the roles of desiccant, and catalyst. The Gewald reaction is performed with inorganic base in THF/water, which suppresses byproduct formation. This process has been employed in the total synthesis of a multitargeted kinase inhibitor.

1. Introduction

2-Aminothiophenes have demonstrated a broad spectrum of uses, including pharmaceuticals, dyes, and agrochemical applications.[1] Conceptually, the simplest and most convergent preparation of this class of compounds is the condensation of ketones with an activated nitrile and elemental sulfur, which was first described in 1960s by Gewald and co-workers.[2] Although a one-pot procedure is well-established, the two-step procedure in which an α,β-unsaturated nitrile is first prepared by Knoevenagel condensation of a ketone or aldehyde with an activated acetonitrile, followed by base-promoted reaction with sulfur, has generally been found to result in higher yields (Eq. 1).[1]



2a-i **3a-i** **4a-i**
see Table 3 for R, R_2

(1)

Thienopyrimidine **1** is a multitargeted receptor tyrosine kinase inhibitor, which demonstrates potent antitumor activity;[3] retrosynthetically, its heterocyclic core arises via condensation of 2-aminothiophene **4a** with formamide to form the pyrimidine ring (Scheme 1). Knoevenagel condensation of 4′-nitroacetophenone (**2a**) with malononitrile, followed by Gewald reaction with sulfur forms this aminothiophene in a concise fashion. Initial attempts to accomplish the synthesis of 2-aminothiophene **4a** employing standard literature conditions[1] provided poor yields for both the Knoevenagel and Gewald reactions and resulted in complicated mixtures that were difficult to purify. In this paper, we describe new conditions for both the Knoevenagel and Gewald reactions and their application in the synthesis of **1**. In addition, we describe the extension of these conditions to other substrates.

2. Results and discussion

2.1. Knoevenagel condensation

Literature preparation[4] of **3a** and similar ylidene compounds involves mixing of ketone, malononitrile, and a catalyst (e.g., ammonium acetate) in benzene or toluene (Eq. 2). The mixture is then warmed to reflux and water is removed via azeotropic distillation employing a Dean–Stark apparatus.

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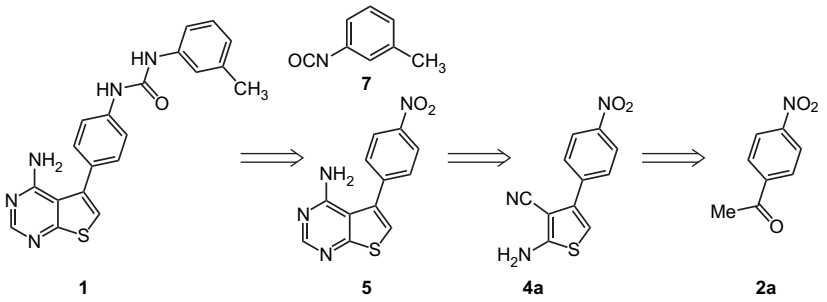
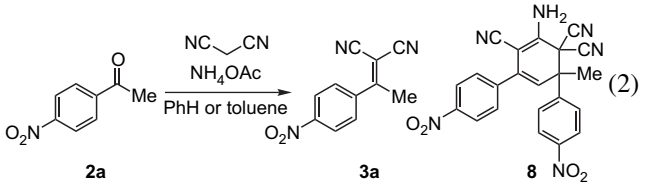


Scheme 1. Retrosynthesis of kinase inhibitor **1**.

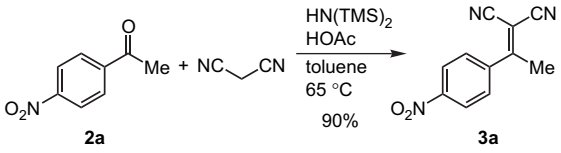


(2)

Ylidene **3a** is thermally unstable, hydrolytically sensitive, and decomposes in the presence of weak bases (i.e., sodium bicarbonate). This instability is most likely due to the combination of an unhindered enolizable methyl group and an electron withdrawing nitro-substituted aromatic ring. Analogous compounds derived from acetophenone or 4′-nitropropiophenone are much less prone to degradation. At the elevated temperatures required for azeotropic distillation, dimerization to form adduct **8** was significant; this dimerization resulted in highly variable yields of ylidene **3a** ranging from 10–70% (Eq. 2). Using lower boiling solvents such as THF or EtOAc resulted in even more ylidene dimerization. In addition, ylidene **3a** isolated by silica gel chromatography from these standard Knoevenagel reaction conditions was an unstable oil, which dimerized to **8** upon standing.

Lowering the reaction temperature to ~60 °C in toluene did show promise; however, the reaction stalled (~50% conversion); longer reaction times resulted only in significant dimerization. Isolated ylidene **3a** hydrolyzes to starting ketone **2a** under mild acidic conditions (LiH_2PO_4, THF/water) indicating that the condensation reaction is reversible, and that the removal of the water is necessary to drive the reaction to completion. Addition of inorganic desiccants ($MgSO_4$, Na_2SO_4, 4 Å molecular sieves) at 60 °C failed to improve the reaction. On the other hand, an organic desiccant, namely trimethylsilyl acetate (TMSOAc,[5] 1.5 equiv relative to ketone) afforded full conversion with only 5% dimerization in 6 h at 60 °C (toluene, NH_4OAc).

Aside from increasing the yield of the reaction, the significant decrease in ylidene dimerization under these conditions was surprising. Postulating that buffering of the reaction by acetic acid was responsible, the Knoevenagel reaction was attempted using acetic acid as solvent.[6] Without added TMSOAc the reaction stalled at around 80% conversion after 6 h at 65 °C, but the level of ylidene dimer **8** remained low (~2%). Addition of TMSOAc (Eq. 3) afforded 100% conversion in 6 h with ~1.5% dimer **8** at 65 °C. Hexamethyldisilazane (HMDS) could also be used to generate in situ not only the TMSOAc, but also the NH_4OAc promoter for the reaction (Eq. 3).[7] Thus simple premixing of HMDS (1.2 equiv relative to ketone) with acetic acid[8] prior to addition of 4′-nitroacetophenone (**2a**) and malononitrile (2.0 equiv), followed by warming to 65 °C affords 97% conversion in 5 h with ~1% dimer **8**. Following aqueous workup, crystallization from toluene/heptane afforded 90% yield of ylidene crystals, which were stable at ambient conditions for at least three months.



(3)

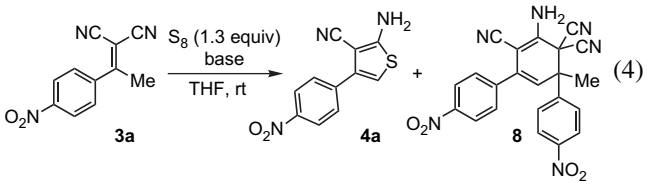
2.2. Gewald reaction

Classical conditions for the Gewald thiophene synthesis involve the reaction of ylidene and sulfur with an organic base (i.e., triethylamine, morpholine) in ethanol or dimethyl formamide (DMF). In the case of ylidene **3a** these conditions afforded mostly dimer **8** with thiophene **4a** as a minor component of the reaction mixture. A brief solvent screen (toluene, ethanol, tetrahydrofuran, DMF) for the reaction (using morpholine as base) identified tetrahydrofuran (THF) as showing the highest reactivity and selectivity toward product formation although the reaction still contained a significant amount of dimer **8** (30–40%).

A base screen in THF at ambient temperature next showed that inorganic bases are preferred to organic (Table 1). Aqueous sodium carbonate showed the highest reactivity and selectivity; in the absence of water, sodium carbonate provided almost no reaction. Careful monitoring of the sodium carbonate reaction showed that the reaction was mildly exothermic and complete upon mixing of the base. Continued exploration of inorganic bases highlighted aqueous $NaHCO_3$ as a superior base for the preparation of thiophene **4a**. In the optimized procedure, 1 equiv of $NaHCO_3$ in water is added to a stirring mixture of sulfur and ylidene in THF; the reaction is complete at the end of the addition. The reverse addition protocol did not offer any benefit to product purity and gave non-reproducible results.

The effect of temperature on the impurity profile of the reaction was also investigated. Four different reaction temperatures were investigated under otherwise identical conditions (Table 2). Cooling the reaction to 5 °C slowed the rate of product formation significantly while comparatively increasing the rate of ylidene dimerization. Increasing the reaction

Table 1. Gewald reaction base screen (Eq. 4)[a]

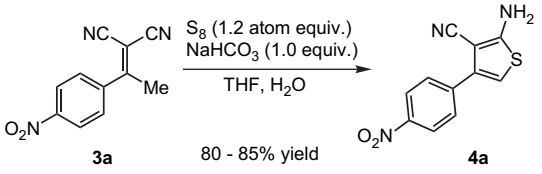


(4)

Base	HPLC PA%[b] **3a**	HPLC PA%[b] **4a**	HPLC PA%[b] **8**
Morpholine[c]	5.0	39.5	35.1
Pyridine[c]	71.8	0.5	1.7
i-Pr_2NH[c]	ND	64.4	14.7
Et_3N[c]	0.1	59.1	17.9
KOt-Bu[c]	1	35.1	6.1
Na_2CO_3[c]	88.5	3.2	2.1
Na_2CO_3 (aq)[d]	0.7	86.3	4.1
$NaHCO_3$ (aq)[d]	ND	91.2	1.6
K_2CO_3 (aq)[d]	0.6	69.5	2.6
K_3PO_4 (aq)[d]	0.5	80.7	2.1
NaOH (aq)[d]	0.5	66.2	2.5

[a] Base was added in one portion to sulfur and **3a** suspended in THF (10 mL/g **3a**). Reaction samples were analyzed by HPLC.
[b] Peak area percent of each component. ND=not detected.
[c] Monitored after 120 min.
[d] Monitored after 10 min.

temperature, while affording no appreciable increase in reaction rate, appeared to decrease the relative rate of dimer formation. At 60 °C there was no detectable formation of dimer **8**, however, the reaction generated new unidentified impurities. Therefore, the optimal reaction temperature was determined to be 35–40 °C. Following the reaction, the product was crystallized from a THF/EtOH/water mixture to provide aminothiophene **4a** in 80–85% isolated yield (Eq. 6).



(6)

Based upon the mechanism proposed by Gewald and others, the reaction should be catalytic in base.[1,9] Indeed, if substoichiometric $NaHCO_3$ (0.2 equiv) is employed the reaction goes to completion although with a slightly poorer purity profile. HPLC analysis of the reactions with stoichiometric versus catalytic $NaHCO_3$, showed that while dimer **8** is generated in both cases, prolonged stirring at 35 °C in the presence of 1.0 equiv of $NaHCO_3$ significantly degrades it to a secondary byproduct, which is easier to remove during the crystallization of desired product **4a**.

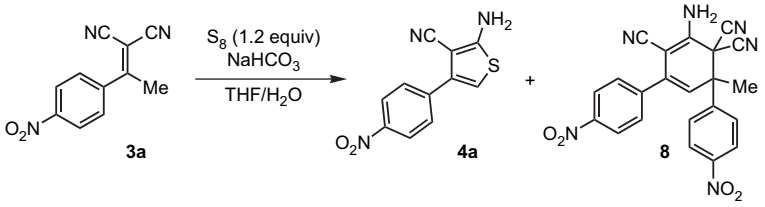
Using the optimized reaction conditions from the experiments described above, the thermochemical profile of the reaction was monitored with a MultiMax™ system (Fig. 1).[10] The initial endotherm arises from simple mixing of the sodium bicarbonate solution with THF. HPLC monitoring of the reaction mixture during the endotherm period showed that little reaction occurred (<10% PA **4a**). Most of the reaction occurs during the exotherm, with the majority of the reaction (>85% PA **4a**) complete once T_{max} is reached.

An interesting trend was observed in the temperature profile when the addition time was varied between 15 and 90 min. With the slower addition rates of 60 and 90 min, the initial endotherm (due to mixing) was followed by a return of internal temperature to the jacket temperature of 35 °C for a brief period of time, followed by the exotherm. As noted above, the reaction is complete prior to complete addition of the base solution. Samples of reaction mixtures pulled during the plateau period between endo- and exotherm events showed little reaction occurring. From these reactions we determined the amount of bicarbonate solution that had been added at the onset of the exotherm event to be 0.173 and 0.178 equiv of $NaHCO_3$, respectively. At this time, the underlying mechanism of this effect is not readily apparent, although a base-mediated reorganization of S_8 to a more reactive sulfur species may be implicated.[11]

2.3. Other substrates

This two-step procedure for the synthesis of 2-aminothiophenes was applied to other substrates.[12] As can be seen in Table 3, thiophenes with both electron rich (entries 2 and 7) and electron poor (entries 3–6) phenyl rings at the 4-position are prepared successfully. In addition, a 4-heterocycle-

Table 2. Temperature screen for the Gewald reaction (Eq. 5)[a]



(5)

Temperature,[b] °C	Assay yield%[c] **4a**	HPLC PA%[d] **8**
5	55	16
22	94	1.4
39	94	0.4
60	92	0

[a] Ylidene **3a** and sulfur (1.2 atom equiv) were suspended in THF at the specified temperature. $NaHCO_3$ solution was added over 30 s.
[b] Internal temperature at start of $NaHCO_3$ addition.
[c] Reaction yield determined by HPLC assay in relative to a standard.
[d] Peak area percent of each component.

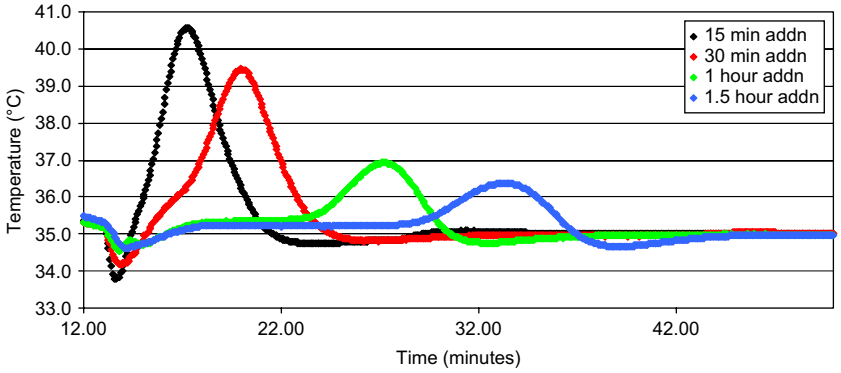
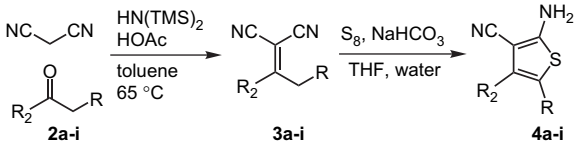


Figure 1. Temperature profiles of Gewald reaction at different $NaHCO_3$ addition rates.

Table 3. Application of the Knoevenagel and Gewald conditions to other substrates (Eq.7)



(7)

Entry	Ketone	R_2	R	Ylidene, yield%	Thiophene, yield%
1	**2a**	4-NO_2Ph	H	**3a**, 90	**4a**, 80
2	**2b**	Ph	H	**3b**, 82	**4b**, 40 (96)
3	**2c**	3-NO_2-Ph	H	**3c**, 83 (88)	**4c**, 81
4	**2d**	4-$MeSO_2$Ph	H	**3d**, 76	**4d**, 58 (96)
5	**2e**	4-BrPh	H	**3e**, 86	**4e**, 73 (96)
6	**2f**	2,6-F_2Ph	H	**3f**, 64 (73)	**4f**, 58 (98)
7	**2g**	4-MeOPh	H	**3g**, 82	**4g**, 80
8	**2h**	2-Thiophene	H	**3h**, 56	**4h**, 46 (100)
9	**2i**	Ph	Ph	**3i**, 80	**4i**, 78 (99)

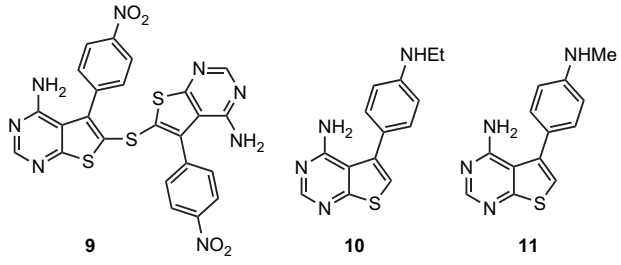
Numbers in parentheses represent assay yields prior to isolation.[13]

substituted derivative (entry 8) as well as a 5-substituted thiophene (entry 9) is accessible using this methodology.

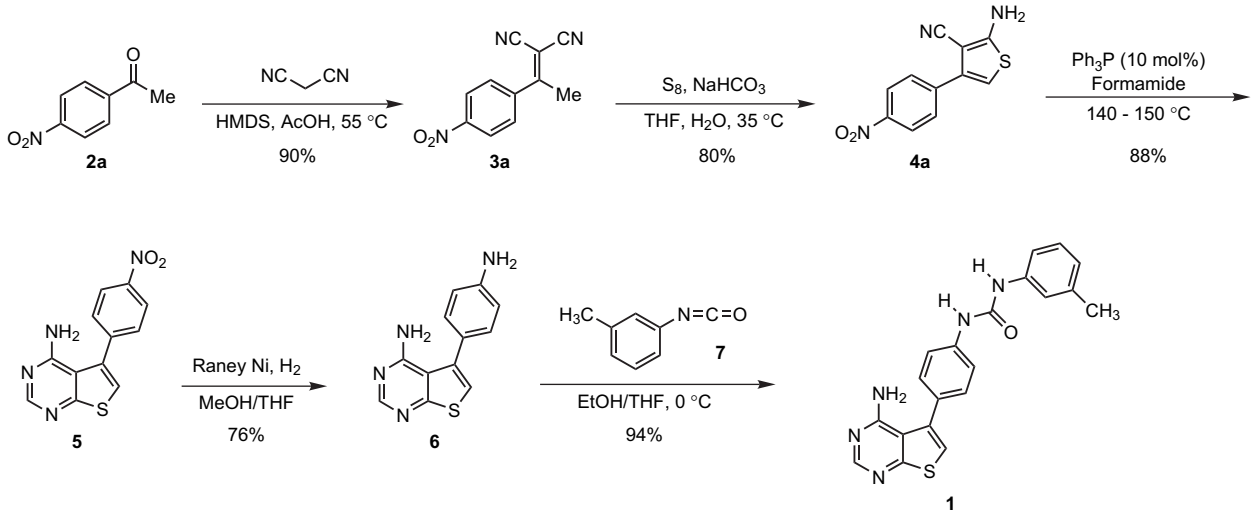
2.4. Synthesis of thienopyrimidine 1

The two-step synthesis of 2-aminothiophenes was employed in the context of a synthesis of thienopyrimidine **1** (Scheme 2). As discussed above, thiophene **4a** was prepared in 72% yield over two steps from 4′-nitroacetophenone. This set the stage for a highly convergent synthesis in which the isocyanate was added in the final step.

Condensation with formamide was accomplished at elevated temperatures to effect conversion to nitropyrimidine **5** in 88% yield.[14] In early experiments the sulfur-linked dimer **9** was observed in varying amounts. A small amount of triphenylphosphine (10 mol %) added to the reaction mixture was sufficient to scavenge residual sulfur from the Gewald reaction, providing an effective control of this impurity.



Previous reports have detailed the use of formamidine acetate as an effective reagent for the conversion of amino nitriles to pyrimidines.[15] While the use of this reagent (4 equiv) in formamide did permit the reaction to be run at lower temperatures (~125 °C), we observed evolution of CO and NH_3 during the course of the reaction. In the absence of



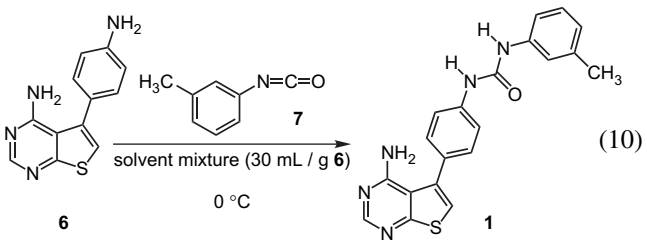
Scheme 2. Synthesis of thienopyrimidine **1**.

formamidine acetate, the thermal decomposition of formamide itself was not significant at <160 °C.

Hydrogenation of the nitro group to the corresponding aniline **6** was accomplished over Raney nickel in THF/MeOH, in 76% yield. The choice of methanol as the alcohol co-solvent was based on the formation of *N*-ethyl derivative **10** (1–2%) when EtOH was employed, presumably via an oxidation to acetaldehyde/reductive alkylation mechanism.[16] When methanol was employed, less than 0.5% of *N*-alkylated product **11** was observed.

The final step required acylation of aniline **6** with 3-tolylisocyanate **7**. There are two reactive amine sites, although the aniline (N_1) proved more reactive than the aminopyrimidine (N_2), overacylation to form bis-acyl **12** (Eq. 8) was observed. Under standard conditions (3:1 CH_2Cl_2/THF, 1.0 equiv isocyanate, 0 °C to rt),[3] from which the product precipitated early in the reaction, 3% of this impurity was formed at 99% conversion (HPLC peak area% levels at 265 nm). We expected that thienopyrimidine **1** reacted with residual isocyanate **7** at the end of the reaction and reasoned that an alternate, sacrificial nucleophile might be added to the mixture, which would not interfere with acylation of the aniline nitrogen, but would compete with overacylation of **1** (Eq. 8) to furnish an easily removable side-product (Eq. 9).

Table 4. Solvent effects in isocyanate acylation (Eq. 10)[a]

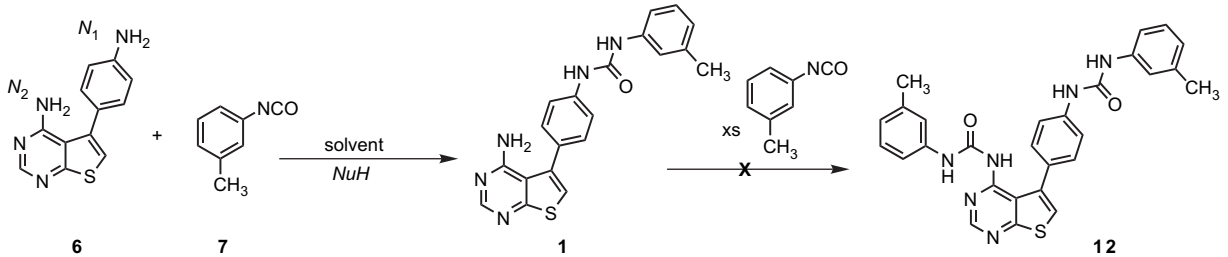


(10)

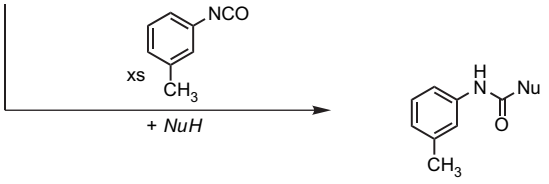
Entry	Solvent mixture	Isocyanate **7**, equiv	**6**, HPLC PA%[b]	**1**, HPLC PA%[b]	**12**, HPLC PA%[b]
1	THF/EtOH (2:1)	1.0	2.2	97.1	0.2
2	THF/EtOH (2:1)	1.25	0.2	98.7	0.4
3	THF/MeOH (2:1)	1.25	0.4	98.8	0.2
4	THF/MeOH (2:1)	1.5	0.1	98.4	0.4
5	CH_2Cl_2/THF (3:1)[c]	0.5	19.4	78.4	1.1
6	THF/EtOH (2:1)	0.625	13.9	85.6	0.08

[a] Isocyanate **7** was added dropwise to a mixture of **6** in the solvent mixture (30 mL/g **6**) over ~5 min, maintaining the temperature at <2 °C. Reactions were assayed after 2 h.
[b] Reactions were analyzed by HPLC at 265 nm.
[c] Reaction was run at 0 °C for 2 h, then warmed to rt for 2 h.

a sacrificial nucleophile of intermediate reactivity between that of the two amines of aniline **6**, so that excess isocyanate **7** is destroyed before it overacylates the product (even



(8)



(9)

Alcohols react with isocyanates at a slower rate and possibly via a slightly different mechanism than do amines.[17] Due to the inherent low nucleophilicity of the aminopyrimidine, an alcohol might serve as an additive with the desired effect. When ethanol was added to a reaction in THF (2:1 THF/EtOH, 1.0 equiv isocyanate **7**, 0 °C), we observed good conversion to **1** (2.2% remaining **6**), with <0.2% overacylated impurity **12** (Table 4, entry 1). Both MeOH and EtOH in THF required extra isocyanate **7** to attain high levels of conversion (<0.4% remaining **6**), but a smaller excess was required with EtOH (1.25 equiv vs 1.5 equiv in MeOH for >99.8% conversion). Stirring overnight at ambient temperature did not significantly affect impurity levels. The product was crystallized from EtOH in 94% isolated yield.

Our results indicate that the alcohol co-solvent is playing two roles in the acylation reaction. First, it functions as with 1.25 equiv of isocyanate **7**, only 0.4% of **12** is formed). However, the lower levels of bis-acyl **12** even at incomplete conversion (entries 5 and 6) indicate that the alcohol is also affecting the relative reactivities of the two nitrogen atoms, perhaps by selective hydrogen bonding.[18]

In conclusion, we have described new reaction conditions for the Knoevenagel condensation and Gewald thiophene synthesis by which 4′-nitroacetophenone (**2a**) is converted to 2-aminothiophene **4a** in 72% yield via crystalline intermediates. This methodology has been extended to the use of other alkyl aryl and alkyl heterocyclic ketones, where it has also proven effective. Finally, we have applied this in the context of a synthesis of multitargeted kinase inhibitor **1**, which was prepared in 45% overall yield through five steps.

3. Experimental

3.1. Knoevenagel condensation

Hexamethyldisilazane (1.2 equiv) was added to acetic acid (0.67 mL/mmol ketone **2**) at a rate to maintain the internal temperature at or below 74 °C. (*Caution—this addition is very exothermic*!) The HMDS/acetic acid mixture is added to a solution of ketone **2** and malononitrile (2 equiv) in acetic acid (0.33 mL/mmol). After reaction completion, the mixture is cooled to ambient temperature with chilled toluene (1.67 mL/mmol, at 0 °C) and diluted with water (1.33 mL/mmol). The aqueous layer was separated and extracted with toluene (0.67 mL/mmol). The combined organic extracts were washed four times with water and dried over $MgSO_4$. The products **3** were isolated by crystallization or chromatography.

3.1.1. 2-[1-(4-Nitrophenyl)ethylidene]-malononitrile (3a). Reaction run using 4′-nitroacetophenone (10.00 g, 60.6 mmol). Crystallization with heptane (93 mL) provided 11.49 g (89.0%) of yellow crystalline **3a**. Mp=87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.69 (ddd, J=9.09, 2.40, 2.23 Hz, 2H), 8.36 (dt, J=9.16, 2.28 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 87.6, 111.5, 111.5, 124.1, 128.1, 141.2, 149.1, 172.3 ppm; MS (APCI+) m/z 212.0 (M−H); Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.69; H, 3.30; N, 19.74.

3.1.2. 2-[1-(Phenyl)ethylidene]-malononitrile (3b). Reaction run using acetophenone (9.7 mL, 83 mmol). Crystallization with heptane provided 11.48 g (82.3%) of white crystalline **3b**. Mp=94.5–95.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 7.31 (m, 5 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 84.6, 112.5, 112.5, 127.0, 128.8, 131.9, 135.5, 174.9 ppm; MS (APCI+) m/z 167.1 (M−H); Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.24; H, 4.47; N, 16.81.

3.1.3. 2-[1-(3-Nitrophenyl)ethylidene]-malononitrile (3c). Reaction run using 3′-nitroacetophenone (10.00 g, 60.6 mmol). Crystallization with heptane (93 mL) provided 10.76 g (83.4%) of yellow crystalline **3c**. Mp=99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 7.74 (t, J=8.03 Hz, 1H), 7.89 (ddd, J=7.75, 1.78, 1.03 Hz, 1H), 8.36 (t, J=1.85 Hz, 1H), 8.40 (ddd, J=8.23, 2.13, 1.03 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 87.4, 111.5, 111.6, 122.1, 126.1, 130.3, 132.6, 136.9, 148.0, 171.9 ppm; MS (APCI+) m/z 212.1 (M−H); Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.04; H, 3.10; N, 19.37.

3.1.4. 2-[1-(4-Methylsulfonylphenyl)ethylidene]-malononitrile (3d). Reaction run using 4′-methylsulfonylacetophenone (10.00 g, 50.5 mmol). The product crystallized during the reaction. After drying, the solids were stirred in ethanol (50 mL) and filtered. Drying in vacuo provided 9.47 g (76.2%) of crystalline **3d**. Mp=138.5–139.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.11 (s, 3H), 7.69 (d, J=8.37 Hz, 2H), 8.08 (d, J=8.37 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 44.5, 87.3, 111.6, 111.7, 128.0, 140.6, 143.1, 172.8 ppm; MS (APCI+) m/z 245.1 (M−H); Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.41; H, 3.78; N, 11.45.

3.1.5. 2-[1-(4-Bromophenyl)ethylidene]-malononitrile (3e). Reaction run using 4′-bromoacetophenone (10.00 g, 50.3 mmol). Crystallization with heptane (88 mL) provided 10.55 g (86.0%) of yellow crystalline **3e**. Mp=93.5–94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.23 (ddd, J=8.89, 2.47, 2.23 Hz, 2H), 7.46 (ddd, J=8.89, 2.47, 2.23 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 85.1, 112.2, 112.3, 126.8, 128.5, 132.1, 134.2, 173.3 ppm; MS (APCI+) m/z 247.0; Anal. Calcd for $C_{11}H_7BrN_2$: C, 53.47; H, 2.86; N, 11.34. Found: C, 53.26; H, 2.87; N, 11.19.

3.1.6. 2-[1-(2,6-Difluorophenyl)ethylidene]-malononitrile (3f). Reaction run using of 2′,6′-difluoroacetophenone (10.21 g, 65.4 mmol). Crystallization with heptane (100 mL) provided 8.48 g (63.5%) of yellow crystalline **3f**. Mp=80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 3H), 7.22 (dd, J=8.51, 7.96 Hz, 2H), 7.65 (tt, J=8.51, 6.38 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 91.4, 110.9, 111.0, 112.1, 112.1, 112.1, 112.3, 112.3, 112.3, 113.3, 113.5, 113.7, 132.8, 132.9, 133.0, 156.7, 156.8, 159.2, 159.3, 165.3 ppm; MS (APCI+) m/z 203.0 (M−H); Anal. Calcd for $C_{11}H_6F_2N_2$: C, 64.71; H, 2.96; N, 13.72. Found: C, 64.47; H, 2.83; N, 13.78.

3.1.7. 2-[1-(4-Methoxyphenyl)ethylidene]-malononitrile (3g). Reaction run using 4′-methoxyacetophenone (2.89 g, 19.3 mmol). Crystallization with heptane (30 mL) provided 3.14 g (82.3%) of yellow crystalline **3g**. Mp=79.5–80.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3H), 4.15 (s, 3H), 7.26 (ddd, J=9.43, 3.16, 2.64 Hz, 2H), 7.88 (ddd, J=9.50, 3.09, 2.64 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 81.9, 113.1, 113.4, 114.2, 127.6, 129.5, 162.6, 173.4 ppm; MS (APCI+) m/z 197.1 (M−H); Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.38; H, 4.78; N, 14.07.

3.1.8. 2-[1-(2-Thiophene-yl)ethylidene]-malononitrile (3h). Reaction run using 2-acetylthiophene (8.5 mL, 78.9 mmol). At the end of the reaction, ethanol (60 mL) was added and the mixture was filtered. After drying the solids were stirred in ethanol (45 mL) and filtered. Drying in vacuo provided 7.67 g (56%) of crystalline **3h**. Mp=87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3H), 7.24 (dd, J=4.87, 4.19 Hz, 1H), 7.77 (dd, J=4.94, 0.82 Hz, 1H), 8.04 (dd, J=4.05, 0.75 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 78.7, 113.3, 113.8, 128.8, 133.2, 134.1, 137.9, 162.1 ppm; MS (APCI+) m/z 173.0 (M−H); Anal. Calcd for $C_9H_6N_2S$: C, 62.05; H, 3.47; N, 16.08. Found: C, 60.66; H, 2.99; N, 15.84.

3.1.9. 2-[1-(Phenyl)benzylidene]-malononitrile (3i). Reaction run using deoxybenzoin (10.01 g, 51.0 mmol). Crystallization with heptane (100 mL) provided 9.98 g (80.0%) of white crystalline **3i**. Mp=78.7–79.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 2H), 7.10 (dd, J=7.20, 2.26 Hz, 2H), 7.28 (m, 3H), 7.49 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 85.4, 112.4, 112.6, 127.5, 128.7, 131.6, 133.9, 134.4, 176.9 ppm; Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.27; H, 4.78; N, 11.33.

3.2. Gewald reaction

Ylidene **3** and elemental sulfur (1.2 atom equiv) are suspended in tetrahydrofuran (10 mL/g **3**) and warmed to an

internal temperature of 35 °C. A solution of sodium bicarbonate (1.0 equiv in 5 mL of water/g **3**) is added over ~1 h. The mixture is stirred at 35 °C for approximately 30 min before the solution is transferred to a separatory funnel and washed with 12.5% aqueous NaCl and 25% aqueous NaCl. The products **4** were isolated by crystallization.

3.2.1. 2-Amino-4-phenyl-3-thiophenecarbonitrile (4b). Reaction run using 2-[1-(phenyl)ethylidene]-malononitrile (**3b**, 2 g, 11.9 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 15 mL of toluene yielded 0.93 g (40% yield) of the desired product as a white solid. Mp= 102.3–105.1 °C (lit.[19] 100–102 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48–7.56 (m, 2H), 7.38–7.44 (m, 2H), 7.30–7.36 (m, 1H), 7.23 (s, 2H), 6.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 137.9, 133.9, 128.1, 127.3, 126.4, 116.2, 104.7, 82.9 ppm. MS (ESI+) *m/z* 201 (M+H); Anal. Calcd for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found: C, 65.96; H, 3.84; N, 13.95.

3.2.2. 2-Amino-4-(3-nitrophenyl)-3-thiophenecarbonitrile (4c). Reaction run using 2-[1-(3-nitrophenyl)ethylidene]-malononitrile (**3c**, 2.51 g, 11.8 mmol). Crystallization from 25 mL of toluene yielded 2.34 g (81%) of the desired product. Mp=194–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (t, *J*=2.1 Hz, 1H), 8.19 (ddd, *J*=8.2, 2.3, 1.0 Hz, 1H), 7.99 (ddd, *J*=7.7, 1.8, 1.0 Hz, 1H), 7.72 (t, *J*=8.0 Hz, 1H), 7.38 (s, 2H), 6.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 147.4, 135.20, 135.17, 132.7, 129.8, 122.0, 120.7, 115.9, 106.9, 82.2 ppm; MS (ESI+) *m/z* 246 (M+H), 263 (M+NH$_4$), 268 (M+Na); Anal. Calcd for $C_{11}H_7N_3O_2S$: C, 53.87; H, 2.88; N, 17.13. Found: C, 53.85; H, 2.64; N, 17.03.

3.2.3. 2-Amino-4-(4-methanesulfonylphenyl)-3-thiophenecarbonitrile (4d). Reaction run using 2-[1-(4-methanesulfonylphenyl)ethylidene]-malononitrile (**3d**, 1.4 g, 5.7 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 22 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 10 mL toluene yielded 0.91 g (58%) of the desired product. Mp=195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, *J*=8.5 Hz, 2H), 7.78 (d, *J*=8.5 Hz, 2H), 7.36 (s, 2H), 6.73 (s, 1H), 3.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 139.2, 138.6, 136.1, 127.2, 126.9, 115.9, 107.2, 82.3, 43.4 ppm; MS (ESI+) *m/z* 279 (M+H), 296 (M+NH$_4$), 301 (M+Na); HRMS (ESI FTMS) Calcd for $C_{12}H_{11}N_2O_2S_2$ (M+H): 279.0256. Found: 279.0256.

3.2.4. 2-Amino-4-(4-bromophenyl)-3-thiophenecarbonitrile (4e). Reaction run using 2-[1-(4-bromophenyl)ethylidene]-malononitrile (**3e**, 1.98 g, 8.03 mmol). HPLC assay following the reaction indicated a 96% yield. Crystallization from 17 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 17 mL toluene yielded 1.67 g (73%) of the desired product. Mp=190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, *J*=8.5 Hz, 2H), 7.47 (d, *J*=8.7 Hz, 2H), 7.28 (s, 2H), 6.58 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 136.5, 133.1, 131.1, 128.4, 120.6, 116.0, 105.3, 82.5 ppm; MS (APCI+) *m/z* 279, 281 (M+H); Anal. Calcd for $C_{11}H_7BrN_2S$: C, 47.33; H, 2.53; N, 10.04. Found: C, 47.02; H, 2.25; N, 9.78.

3.2.5. 2-Amino-4-(2,6-difluorophenyl)-3-thiophenecarbonitrile (4f). Reaction run using 2-[1-(2,6-difluorophenyl)ethylidene]-malononitrile (**3f**, 2.0 g, 9.8 mmol). HPLC assay following the reaction indicated a 98% yield. Crystallization from 32 mL of 2:1:1 water/EtOH/THF, followed by crystallization from 20 mL toluene yielded 1.35 g (58%) of the desired product. Mp=143.6–145.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (tt, *J*=8.4, 6.6 Hz, 1H), 7.27 (s, 2H), 7.19 (t, *J*=8.0 Hz, 2H), 6.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 160.1 (1/2 of doublet), 157.7 (1/2 of doublet), 130.2 (t), 124.5, 115.1, 111.6, 111.3, 109.7, 84.5 ppm; MS (ESI+) *m/z* 237 (M+H); HRMS (ESI FTMS) Calcd for $C_{11}H_7F_2N_2S$ (M+H): 237.0293. Found: 237.0289.

3.2.6. 2-Amino-4-(4-methoxyphenyl)-3-thiophenecarbonitrile (4g). Reaction run using 2-[1-(4-methoxyphenyl)-ethylidene]-malononitrile (**3g**, 1.98 g, 8.03 mmol). Crystallization from 28 mL of 2:1:1 water/EtOH/THF, followed by trituration in 15 mL toluene yielded 1.39 g (80%) of the desired product. Mp=164–166.5 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J*=8.9 Hz, 2H), 7.18 (s, 2H), 6.97 (d, *J*=8.9 Hz, 2H), 6.39 (s, 1H), 3.77 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 158.3, 137.6, 127.6, 126.5, 116.3, 113.6, 103.3, 83.1, 55.1 ppm; MS (APCI+) *m/z* 231 (M+H); Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.40; H, 4.29; N, 12.05.

3.2.7. 2-Amino-4-(2-thienyl)-3-thiophenecarbonitrile (4h). Reaction run using 2-[1-(2-thienyl)ethylidene]-malononitrile (**3h**, 2.00 g, 11.5 mmol). HPLC assay following the reaction indicated a 100% yield. Crystallization from 23 mL toluene yielded 1.09 g (46%) of the desired product. Mp=110–112 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, *J*=5.1, 1.2 Hz, 1H), 7.34 (dd, *J*=3.6, 1.2 Hz, 1H), 7.30 (s, 2H), 7.09 (dd, *J*=5.1, 3.6 Hz, 1H), 6.54 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 135.8, 130.5, 127.3, 124.9, 123.7, 116.0, 104.1, 82.2 ppm; MS (ESI+) *m/z* 207 (M+H); HRMS (ESI FTMS) Calcd for $C_9H_7N_2S_2$: 207.0045. Found: 207.0039; Anal. Calcd for $C_9H_6N_2S_2$: C, 52.40; H, 2.93; N, 13.58. Found: C, 51.45; H, 2.64; N, 13.20.

3.2.8. 2-Amino-4,5-diphenyl-3-thiophenecarbonitrile (4i). Reaction run using 2-[1-(phenyl)benzylidene]-malononitrile (**3i**, 1.20 g, 4.9 mmol). HPLC assay following the reaction indicated a 99% yield. Crystallization from 62 mL of 4:1:1 water/EtOH/THF, followed by trituration with 15 mL toluene yielded 1.06 g (78%) of the desired product. Mp=203–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (s, 2H), 7.29–7.38 (m, 2H), 7.10–7.26 (m, 6H), 7.02 (ddd, *J*=6.4, 1.7, 1.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 134.1, 133.7, 132.4, 128.8, 128.1, 127.6, 127.4, 126.4, 118.8, 115.7, 86.6 ppm; MS (ESI+) *m/z* 277 (M+H); Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14. Found: C, 74.23; H, 4.25; N, 10.19.

3.3. Scale up of multitargeted kinase inhibitor 1

3.3.1. 2-[1-(4-Nitrophenyl)ethylidene]-malononitrile (3a). *Caution*: *malononitrile is highly toxic and readily absorbed through the skin*!

A round bottomed flask was charged with acetic acid (6 L), malononitrile [2.6 kg], and 4′-nitroacetophenone (3.0 kg).

To a separate flask was charged acetic acid (12 L) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (3.55 kg) was added at a rate to maintain the internal temperature at or below 45 °C. *Caution*: *the addition of HMDS to acetic acid is very exothermic*!

The contents of the first flask were transferred to the acetic acid/HMDS mixture and rinsed with acetic acid (300 mL). The contents were warmed to 55 °C±10 °C for 9 h 35 min, then the heat source was turned off. The reaction was rapidly cooled by charging pre-chilled toluene (30 L, chilled to 0 °C) to the flask. The reaction solution was then extracted with water (23.9 L). The aqueous layer was back-extracted with toluene (12 L). The combined organic layers were then repeatedly washed with water (4×24 L) to remove acetic acid and malononitrile. After drying over magnesium sulfate, the toluene solution was concentrated in vacuo to approximately four volumes (mL/g) and the mixture was seeded and the reaction was stirred for 15 min. Heptane (29.25 L) was added over 4.5 h and the slurry was stirred overnight. The slurry was then filtered and was washed with 6 L of heptane and the product was dried in a vacuum oven at room temperature for 8 h, to yield 3.486 kg (90.0% yield) of the desired product.

3.3.2. 2-Amino-4-(4-nitrophenyl)-3-thiophenecarbonitrile (4a). Ylidene **3a** (3300 g), sulfur (599.0 g), and tetrahydrofuran (29.4 kg) were charged to a flask. The reaction contents were warmed to an internal temperature of approximately 35 °C. The reaction mixture was charged with 7.0 kg of 7.3% aqueous $NaHCO_3$ over a period of approximately 50 min maintaining the reaction temperature below 65 °C. An additional 10.8 kg of the sodium bicarbonate solution was added to the reaction mixture at a rate, which maintained the reaction temperature above 30 °C. The reaction mixture was maintained at 35 °C for 30 min post addition time. The heat source was turned off and the reaction mixture was cooled to approximately 30 °C. NaCl solution (14.3 kg, 12.5%) was added in one portion to the reaction mixture, which was stirred for 10 min and then the layers were separated and the organics were washed with an additional 15.3 kg of the 12.5% NaCl solution. The layers were separated and the organics were washed with 25% NaCl solution (13.0 kg). The organics were concentrated in vacuo to a volume of approximately four volumes relative to theoretical yield of the product. At this point the mixture is warmed to an internal temperature of 60 °C and ethyl alcohol (14.5 L) added at such a rate to maintain internal temperature of 60 °C. After seeding, 23.2 L of water was added over approximately 5 h while maintaining 60 °C, then the slurry was cooled overnight. The slurry was filtered and the solids were dried in vacuo at 60 °C.

In order to remove sulfur, the solids product were removed from the vacuum oven and then charged into a flask. Toluene (28.6 kg) was charged and the slurry was stirred for approximately 1 h and then filtered. The filter cake was rinsed twice with toluene (5.7 kg) and then dried in vacuo at 60 °C to yield 3.04 kg (80.0% isolated yield) of the desired product **4a**. Mp=202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J=9.1 Hz, 2H), 7.80 (d, J=8.9 Hz), 7.40 (s, 2H), 6.82 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 146.0, 140.0, 135.5, 127.3, 123.5, 115.8, 108.0, 82.0 ppm; MS (APCI−) m/z 244 (M−H); HRMS (ESI FTMS) Calcd for $C_{11}H_8N_3O_2S$ (M+H): 246.0332. Found: 246.0327.

3.3.3. 4-Amino-5-(4-nitrophenyl)-thieno[2,3-*d*]pyrimidine (5). To a round bottomed flask were charged thiophene **4a** (2850 g, 11.62 mol), triphenylphosphine (243.8 g, 0.9296 mol), and formamide (48.6 kg). The reaction mixture was warmed to an internal temperature of 145–150 °C. *NOTE: This reaction has been shown to generate carbon monoxide and ammonia due to decomposition of formamide above 150 °C*. After 4 h 20 min the heating mantle was turned off and the reaction mixture allowed to cool to room temperature and stirred overnight. To the orange suspension was added 42.6 L of water and the reaction mixture stirred at room temperature for 1 h. The suspension was filtered and washed with water (3×14.3 L). The filter cake was then washed with acetone in portions until the filtrate was pale yellow (5×5.8 L). Thienopyrimidine **5** was dried in vacuo at 60–70 °C to yield 2.792 kg (88.2%) of an orange solid. Mp>225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.32 (d, J=8.9 Hz, 2H), 7.71 (d, J=8.9 Hz, 2H), 7.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.6, 153.3, 146.5, 141.4, 132.6, 129.5, 123.4, 122.4, 111.8 ppm; MS (ESI+) m/z 273 (M+H), 227 (M+H−NO_2); Anal. Calcd for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.58. Found: C, 52.66; H, 2.57; N, 20.52.

3.3.4. 4-Amino-5-(4-aminophenyl)-thieno[2,3-*d*]pyrimidine (6). A slurry of nitrothienopyrimidine **5** (2.8 kg) in 32 kg of tetrahydrofuran and 29 kg of methanol was added to a mixture of Raney nickel (2.7 kg) and water (0.7 kg). The slurry was rinsed with 32 kg tetrahydrofuran then hydrogenated at 40 psi. After the reaction is complete, the reaction mixture is filtered the filter cake is rinsed with 13.5 kg of tetrahydrofuran. After distilling to about 12 L, 15 kg of EtOH is added and reconcentrated twice. Water (36 kg) is added over 1 h. The product was isolated by filtration, washed with 20.6 kg of water and dried in a vacuum oven at 55 °C to yield 1.894 kg (76%) of the desired aminothienopyrimidine **6**. Mp=185–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.25 (s, 1H), 7.09 (d, J=8.4 Hz, 2H), 6.66 (d, J=8.5 Hz, 2H), 5.37 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 157.8, 153.0, 148.4, 135.1, 129.1, 121.9, 118.5, 113.4, 113.0 ppm; MS (ESI+) m/z 243 (M+H); Anal. Calcd for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12. Found: C, 59.60; H, 3.97; N, 22.96.

3.3.5. *N*-[4-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-phenyl]-*N*′-(3-methylphenyl)urea (1). To a solution of aniline **6** (45.7 g, 189 mmol) in 450 mL of ethyl alcohol and 900 mL of THF at 0 °C was added 3-methylphenylisocyanate (30 mL, 240 mmol) at such a rate to maintain the temperature ≤2 °C. The addition required 6 min. Following the addition, the reaction mixture was stirred in an ice/water bath for 2 h, then warmed to ambient for 2 h. The reaction mixture was concentrated, then washed twice with 200 mL EtOH to remove THF. The product was filtered and washed with 300 mL EtOH, then dried at 60 °C to yield 66.6 g (94% yield) of the product as a white solid. Mp=227–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.27 (s, 3H) 6.78 (d, J=7.27 Hz, 1H) 7.15 (t, J=7.75 Hz, 1H) 7.24 (d, J=8.65 Hz, 1H) 7.30 (s, 1H) 7.37 (d, J=8.51 Hz, 2H) 7.40 (s, 1H) 7.59

(d, J=8.65 Hz, 2H) 8.32 (s, 1H) 8.64 (s, 1H) 8.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 157.7, 153.1, 151.8, 139.4, 138.9, 137.4, 134.2, 128.9, 128.3, 128.1, 122.2, 119.7, 118.3, 117.8, 115.0, 112.7, 21.3 ppm; Anal. Calcd for $C_{20}H_{12}N_5OS$: C, 63.98; H, 4.56; N, 18.65. Found: C, 64.24; H, 4.35; N, 18.42.

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Enantioselective cyanocarbonation of ketones with chiral base

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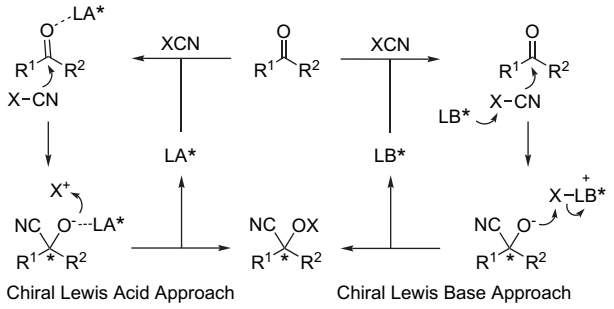
Abstract—A highly enantioselective cyanocarbonation of dialkyl ketones catalyzed by commercially available and easily recyclable cinchona alkaloid derivatives has been developed. The reaction provides a useful approach for the enantioselective construction of tetrasubstituted carbon stereocenters. Mechanistic studies have been carried out to shed light on the origin of the catalytic activity of the cinchona alkaloid and the asymmetric induction step.

1. Introduction

The asymmetric construction of molecules with tetrasubstituted carbon stereocenters is fundamentally important and represents a great challenge in organic synthesis.[1] A conceptually direct and attractive approach is to transform prochiral ketones to chiral building blocks each containing an *O*-substituted quaternary stereocenter by catalytic asymmetric C–C bond formation. The realization of this approach requires the development of chiral catalysts that are effective in promoting a C–C bond forming reaction involving a relatively weak electrophile and in discriminating the two enantiotopic faces of the sterically hindered ketone functionality. Achieving synthetically useful enantioselectivity with unconjugated aliphatic ketones is particularly challenging since the two alkyl substituents of ketone closely resemble each other both electronically and sterically.

The asymmetric cyanation of ketones, an important reaction for the creation of chiral tetrasubstituted carbon stereocenters via asymmetric C–C bond formation, produces versatile chiral cyanohydrins, which can be easily converted to many synthetically useful building blocks such as α-hydroxy acids, α-hydroxy aldehydes (or ketones), and β-aminoalcohols.[2] In principle, the catalytic asymmetric cyanation of ketones can be promoted by two fundamentally different mechanisms involving either a chiral Lewis acid that activates the electrophilic ketone or a chiral Lewis base that activates the nucleophilic cyanating agent (Scheme 1),[3] and in the recent years great breakthroughs have been made with both approaches for the highly enantioselective cyanation of various ketones.[4,5]



Scheme 1. Conceptual chemical catalyst-promoted asymmetric cyanation of ketones.

In this article we describe in detail the synthetic and mechanistic studies of the first highly enantioselective cyanation of ketones catalyzed by chiral Lewis bases.[6] We embarked on the development of a chiral amine-catalyzed cyanation of ketone for both conceptual and practical considerations. In light of the lack of a precedent, the successful development of a highly enantioselective cyanation of ketone with a chiral amine would introduce a conceptually new strategy to this area of research. As most organic functionalities are Lewis basic in nature, a chiral amine-catalyzed reaction may provide the advantage of excellent functional group tolerance. Moreover, the switch of its solubility between aqueous and organic phases corresponding to its protonated and free base form renders a chiral amine catalyst easy to be separated from most organic compounds and subsequently to be recycled. Finally, a catalytic asymmetric reaction with a chiral organic catalyst provides certain advantage in terms of environmental friendliness as well as applicability for pharmaceutical manufacturing.

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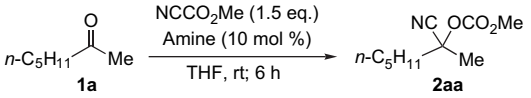
2. Results and discussion

2.1. Tertiary amine-catalyzed cyanocarbonation of ketones

The first obstacle to overcome in the development of a chiral Lewis base-catalyzed cyanation was the establishment of an efficient amine-catalyzed cyanation of ketones. In 1999, Poirier and co-workers described the synthesis of racemic tertiary cyanohydrin carbonate **2** in good yield by the addition of 5–10 equiv of methyl cyanoformate (**4**, R^3=Me) to ketone **1** in the presence of 20 equiv of diisopropylamine (**3**, R^4=^{i}Pr) (Scheme 2).[7] The use of secondary amine **3** and alkyl cyanoformate **4** in a large excess amount hinted at the existence of a decomposition reaction involving these two reagents. We postulated that the reaction proceeded through the mechanism outlined in Scheme 2, which provided a rational for the decomposition of the alkyl cyanoformate **4** and the secondary amine **3**. The acyl ammonium intermediates **5** and **6**, derived from amine **3** and alkyl cyanoformate **4**, could undergo deprotonation by another molecule of **3** to irreversibly form carbamate **7**. According to this postulation, we envisaged that these two decomposition pathways could be eliminated by employing a tertiary amine, in lieu of a secondary amine, to mediate the cyanocarbonation. Additionally, if our rationale was correct, not only a catalytic cyanocarbonation with tertiary amine could be developed, but also such a reaction should require a drastically reduced amount, if not 1 equiv, of alkyl cyanoformate **4**.

With these expectations we began to investigate the use of a tertiary amine to promote the cyanocarbonation of ketones. Although Poirier and co-workers reported that excess NEt_3 was even much less effective than diisopropylamine in promoting the conversion of ketone **1** to cyanohydrin carbonate **2**, we observed that the cyanocarbonation of 2-heptanone with 10 mol % of NEt_3 and 1.5 equiv of methyl cyanoformate in THF at 25 °C proceeded in 38% conversion (Table 1), thereby demonstrating that the cyanocarbonation of a ketone with alkyl cyanoformate **4** could be realized with a catalytic amount of a tertiary amine. It should be noted that the same reaction with 10 mol % of diisopropylamine, a secondary amine, proceeded in only 3.0% conversion. While pyridine, a weaker base, failed to catalyze this transformation, other tertiary amines, such as DABCO and DBU, were found to give significantly higher conversion than that by NEt_3 (Table 1).[8]

Table 1. Organic amine-catalyzed cyanocarbonation of 2-heptanone (**1a**)

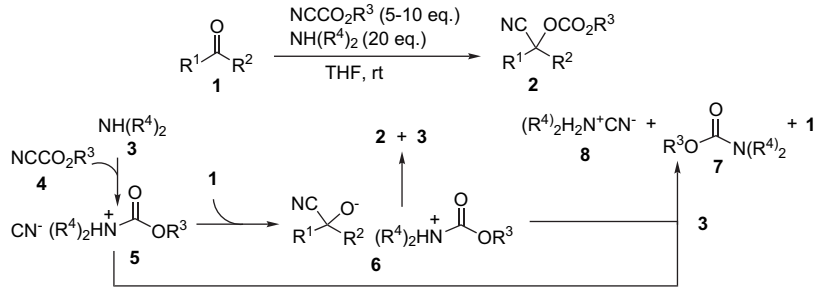


Amine	^{i}Pr$_2$NH	Pyridine	NEt_3	Quinuclidine	DABCO	DBU
Conv. (%)[a]	3.0	0.0	38	37	84	98

[a] Determined by GC using dodecane as an internal standard.

2.2. Chiral Lewis base-catalyzed asymmetric cyanocarbonation of ketones

Encouraged by our success in establishing a tertiary amine-catalyzed cyanocarbonation of ketones, we next focused on the development of an enantioselective variant with a tertiary chiral amine. The promising catalytic activity of DABCO and our discovery in 2000 that certain commercially available modified cinchona alkaloids (Fig. 1) are highly efficient



Scheme 2. Decomposition of secondary amines to carbamates **7**.

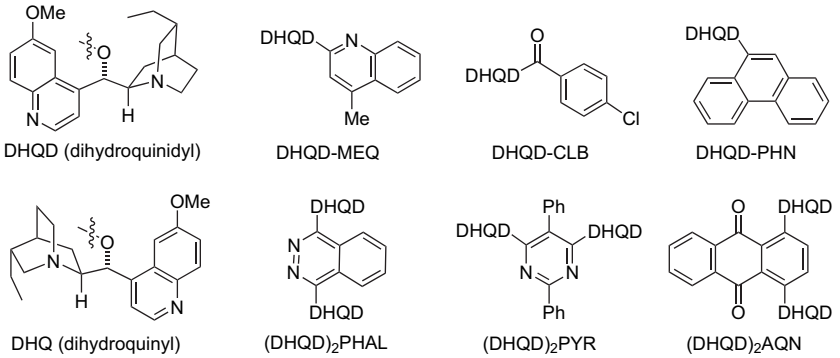


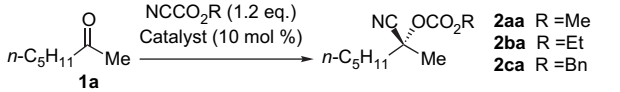
Figure 1. Structures of commercially available modified cinchona alkaloids.

catalysts for enantioselective alcoholysis of cyclic anhydrides[9] immediately attracted us to the possibility of using cinchona alkaloid to realize a highly enantioselective cyanocarbonation of ketones.

The catalyst screening studies were conducted via the asymmetric cyanocarbonation of 2-heptanone (**1a**) with 1.2 equiv of methyl cyanoformate and 10 mol % of the chiral amine catalyst in $CHCl_3$ at 25 °C. As shown in Table 2, DHQD-PHN and $(DHQD)_2AQN$ provided the highest ee (27%, entries 4 and 7), and the latter gave a higher conversion. With $(DHQD)_2AQN$ as the catalyst, the enantioselectivity of the asymmetric cyanocarbonation of 2-heptanone (**1a**) can be improved from 27 to 40% ee by employing ethyl cyanoformate and performing the reaction at −24 °C (entry 17, Table 2). The substitution of ethyl cyanoformate with benzyl cyanoformate and the employment of other common organic solvents such as dichloromethane, ether, toluene, and acetonitrile resulted in deteriorated enantioselectivity for the asymmetric cyanocarbonation of 2-heptanone (**1a**).

Under the optimized reaction condition, the $(DHQ)_2AQN$-catalyzed asymmetric cyanocarbonation of 2-heptanone (**1a**) provided the corresponding tertiary cyanohydrin carbonate in 53% yield and 64% ee (entry 3, Table 3), and the $(DHQ)_2AQN$-catalyzed reaction of 2-butanone provided the product in 51% yield and 41% ee (entry 4, Table 3). Although such enantioselectivity obtained with these α-unbranched methyl alkyl ketones was not synthetically useful, these results were very encouraging considering that these ketones are especially difficult substrates for enantioselective nucleophilic additions, as a chiral catalyst must discriminate efficiently the methyl vs ethyl or *n*-pentyl groups in order to achieve high enantioselectivity. We were pleased to observe that the enantioselectivity improved significantly with dialkyl ketones bearing two alkyl groups that are significantly different from each other in terms of steric bulk. As summarized in Table 3, a variety of acyclic and cyclic dialkyl ketones, both α-substituted and α,α-disubstituted, were transformed to the corresponding tertiary cyanohydrin carbonates in good to excellent enantioselectivity and in synthetically useful yield with DHQD-PHN and $(DHQD)_2AQN$ (Table 3). The enantioselective cyanation of the sterically hindered α,α-disubstituted ketones has been reported previously only once with pinacolone (**1g**) using an enzymatic method.[10] Particularly noteworthy is that, for the first time, a catalytic asymmetric cyanation of a cyclic ketone is realized with excellent enantioselectivity (entries 14, 15, 19, and 20, Table 3). To our knowledge, highly enantioselective cyanation of cyclic ketones remains extremely rare.[4g] The reaction, catalyzed by a chiral base catalyst, readily tolerated acid-sensitive functionality, which is illustrated by the successful enantioselective cyanocarbonation of acyclic and cyclic ketones bearing either an acetal or ketal functionality (entries 9, 11, 12, 16–18, and 21, Table 3).

Table 2. Screening studies on the catalysts, solvents, alkyl cyanoformates, and temperature[a]



Entry	R	Catalyst	Solvent	*T* (°C)	Conv. (%)[b]	ee (%)[c,d]
1	Me	Quinidine	$CHCl_3$	25	66	2.6
2	Me	DHQD-CLB	$CHCl_3$	25	63	17
3	Me	DHQD-MEQ	$CHCl_3$	25	85	17
4	Me	DHQD-PHN	$CHCl_3$	25	83	27
5	Me	$(DHQD)_2PHAL$	$CHCl_3$	25	80	22
6	Me	$(DHQD)_2PYR$	$CHCl_3$	25	86	11
7	Me	$(DHQD)_2AQN$	$CHCl_3$	25	94	27
8	Me	$(DHQD)_2AQN$	CH_2Cl_2	25	96	23
9	Me	$(DHQD)_2AQN$	CCl_4	25	98	20
10	Me	$(DHQD)_2AQN$	PhMe	25	95	14
11	Me	$(DHQD)_2AQN$	Et_2O	25	86	17
12	Me	$(DHQD)_2AQN$	THF	25	54	6.9
13	Me	$(DHQD)_2AQN$	EtOAc	25	84	11
14	Me	$(DHQD)_2AQN$	CH_3CN	25	95	22
15	Et	$(DHQD)_2AQN$	$CHCl_3$	25	97	32
16	Bn	$(DHQD)_2AQN$	$CHCl_3$	25	97	26
17	Et	$(DHQD)_2AQN$	$CHCl_3$	−24	96	40

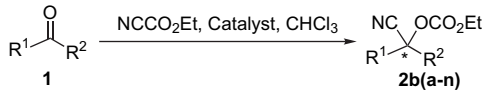
[a] The reaction was performed by treatment of 2-heptanone (0.20 mmol) with alkyl cyanoformate (1.2 equiv) and catalyst (10 mol %) in solvent (0.20 mL).
[b] Determined by GC using dodecane as an internal standard.
[c] Determined by chiral GC and HPLC analysis.
[d] The absolute configuration of the major enantiomer was determined to be *R* by acidic hydrolysis of the product (see Section 4 for the details).

The modified cinchona alkaloid-catalyzed asymmetric cyanocarbonation proceeded cleanly to consistently afford the chiral tertiary cyanohydrin carbonates in greater than 95% yield based on converted ketones (Table 3). The reactions were usually quenched after 2–7 days when they reached a conversion greater than 50% to provide the desired products in 51–99% isolated yields. It should be noted that the catalyst loading could be reduced substantially without any significant adverse effect on the enantioselectivity and yield of the reaction. For example, the nearly quantitative yield and excellent ee obtained from the cyanocarbonation of ketone **1l** (entry 17, Table 3) using 20 mol % catalyst can also be realized by using 10 mol % catalyst (entry 18, Table 3). These results have been successfully reproduced in a 10 mmol scale reaction from which the catalyst, DHQD-PHN, was recovered quantitatively using a simple extractive procedure. Although an extended reaction time was required with a reduced catalyst loading, the reaction can be carried out by simply allowing the reaction mixture in a vial to stand in a freezer without stirring and any special precaution to exclude moisture and air. Modified cinchona alkaloids derived from quinine and quinidine have been shown to furnish highly enantioselective access to both enantiomers of the tertiary cyanohydrin carbonates (Table 3).[11]

2.3. Chemical transformations of chiral tertiary cyanohydrin carbonates

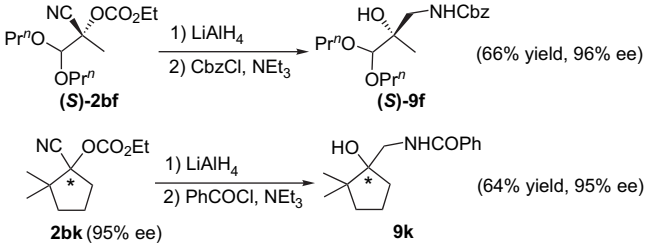
Cyanohydrin carbonates are more stable than their corresponding cyanohydrins toward acidic or basic conditions. However, the two functional groups, cyano and carbonate, of cyanohydrin carbonate can undergo useful chemical transformations under appropriate conditions. For example, $LiAlH_4$ reduces the optically active cyanohydrin carbonates (**2bf** and **2bk**) to the synthetically and biologically important chiral β-aminoalcohols without any deterioration in ee (Scheme 3).

Table 3. Catalytic asymmetric cyanocarbonation of dialkyl ketones with modified cinchona alkaloids[a,b]



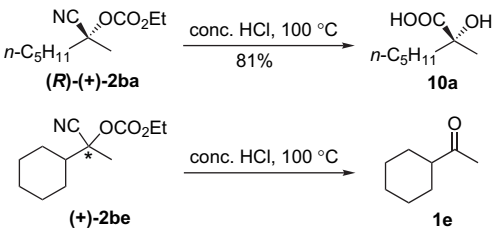
Entry	Substrate	Catalyst (mol %)	Temp (°C)	Time (days)	Conv.[c] (%)	Yield[d] (%)	ee[e](%)
1		(DHQD)$_2$AQN (20)	−24	0.5	56	54	59
2	**1a**, R=*n*-C_5H_{11}	(DHQD)$_2$AQN (20)	−24	2.5	96	93	40
3		(DHQ)$_2$AQN (15)	−24	6	55	53	64[f]
4	**1b**, R=Et	(DHQ)$_2$AQN (10)	−24	5	—	51	41
5		(DHQD)$_2$AQN (10)	−24	4	—	54	59
6	**1c**, R=Me	(DHQ)$_2$AQN (15)	−24	6	—	51	76[f]
7	**1d**, R=Allyl	(DHQ)$_2$AQN (20)	−24	2	57	54	81
8	**1e**, R=$(CH_2)_5$	(DHQ)$_2$AQN (20)	−24	2	55	52	87
9	**1f**, R=O^{n}Pr	DHQD-PHN (30)	−24	4	90	86	96[g]
10	**1g**, R=Me	(DHQD)$_2$AQN (30)	−24	5	58	55	88
11	**1h**, R=OMe	DHQD-PHN (35)	−24	4	67	63	85
12	**1i**, R=OEt	DHQD-PHN (35)	−12	4	68	65	90
13	**1j**	(DHQD)$_2$AQN (10)	25	3	—	66	74
14		(DHQ)$_2$AQN (15)	−24	4	79	76	95
15	**1k**, R=Me	(DHQD)$_2$AQN (15)	−24	2	68	66	97[f]
16		DHQ-PHN (30)	−24	4	83	80	95
17	**1l**, R=OEt	DHQD-PHN (20)	−24	3	97	96	93[f]
18		DHQD-PHN (10)	−24	7	100	99	94
19		(DHQ)$_2$AQN (30)	−12	5	56	53	92
20	**1m**, R=Me	(DHQD)$_2$AQN (20)	−24	4	65	62	91[f]
21	**1n**, R=OEt	DHQD-PHN (35)	−12	5	82	78	96

[a] The reaction was performed by treatment of the ketone (0.20 mmol) with ethyl cyanoformate (1 equiv for entries 3–6, 15; 1.5 equiv for entries 1, 2, 7, 8; 2.0 equiv for entries 9, 10, 13, 20; 3.0 equiv for the other entries) and catalyst in chloroform (0.20 mL for entries 9–21; 0.30 mL for entries 1, 2, 7, 8; 0.40 mL for entries 3–6).
[b] The catalyst was recovered in quantitative yield.
[c] Determined by GC using dodecane as an internal standard.
[d] Isolated yields.
[e] The ee of the product was determined by chiral GC and HPLC analysis.
[f] The opposite enantiomer is generated.
[g] The absolute configuration of the major enantiomer was determined to be *S* (see Section 4 for the details).



Scheme 3. Conversion of chiral tertiary cyanohydrin carbonates to β-amino-alcohol derivatives.

In the presence of a strong acid a simple cyanohydrin carbonate such as (*R*)-(+)-**2ba** was hydrolyzed to give the corresponding α-hydroxy acid (Scheme 4). However, the acidic hydrolysis of β-substituted cyanohydrin carbonate



Scheme 4. Acidic hydrolysis of cyanohydrin carbonates.

(+)-**2be** under the same condition was dominated by the decomposition of the starting material to generate the corresponding ketone **1e**.

2.4. Mechanistic considerations

While the enantioselective cyanocarbonation of unconjugated ketones was found to proceed very cleanly, the ee of the product (cyanohydrin carbonate **2**) generated from reactions with simple dialkyl ketones such as **1a** started to decrease noticeably when the conversion of the reaction proceeded over 55% (comparing entries 1 and 2 of Table 3, also see Fig. 2). This made it necessary to stop the reactions with simple dialkyl ketones well before they reached completion, resulting in the generation of the optically active cyanocarbonates **2** in modest yet still useful yield (Table 3). Interestingly, this ee variation is significantly less pronounced in a reaction employing α,α-dialkoxy cyclic and acyclic ketone such as **1f**, **1h**, **1i**, **1l**, and **1n**, and the corresponding highly enantioenriched cyanohydrin carbonates could be isolated in good to excellent yield. This ee variation of the product has to be accounted for by any proposed reaction mechanism.

Illustrated in Scheme 5 is a mechanism proposed to explain the origin of the enantioselectivity of the modified cinchona alkaloid-catalyzed cyanocarbonation. In principle, the

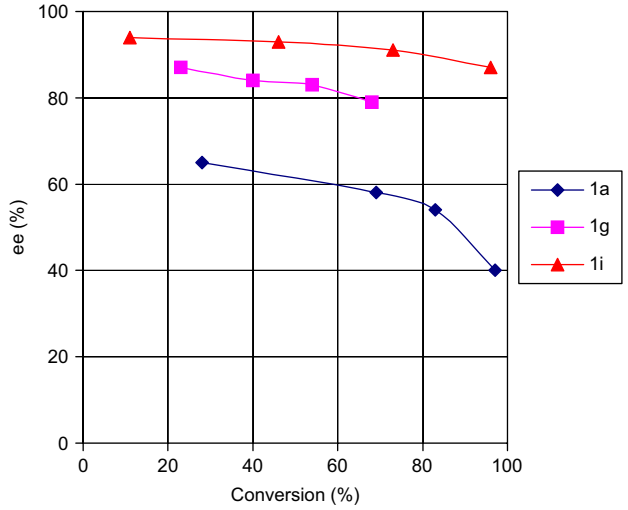
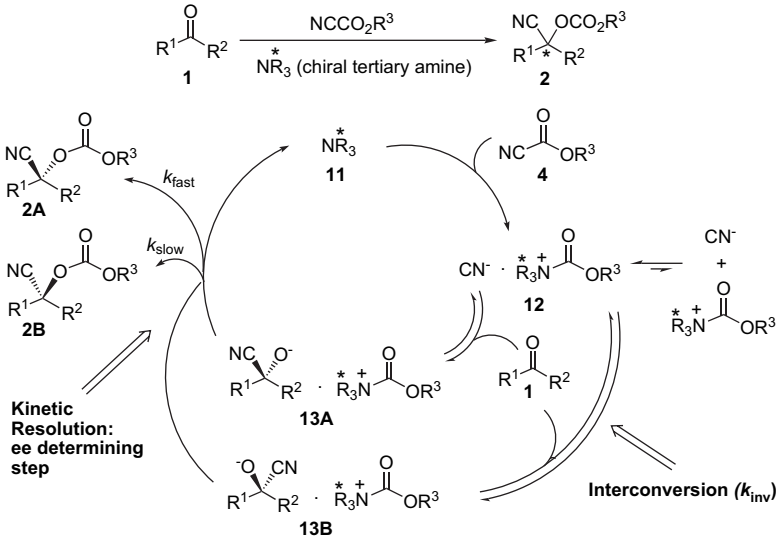


Figure 2. The ee of the product vs the conversion in the modified cinchona alkaloid-catalyzed asymmetric cyanocarbonation of ketones **1a**, **1g**, and **1i**.

asymmetric induction may arise from the enantioselective addition of the cyanide, as part of a chiral ion complex **12**, to ketone **1**. The ee deterioration of cyanocarbonate **2**, however, is difficult to be accounted for by such a mechanism, as it is highly unlikely that the ee deterioration as described above is due to either side reactions or catalyst decompositions, given that the reaction proceeded in excellent yield and the cinchona alkaloid catalysts could be recycled in nearly quantitative yield at the end of the reaction. On the other hand, the unusual ee deterioration of the cyanohydrin carbonate **2** could be explained by an alternative mode of asymmetric induction invoking a dynamic kinetic resolution[12] of intermediates **13A** and **13B**. Conceivably, the two diastereomeric complexes **13A** and **13B**, while undergoing interconversion between each other through ketone **1**, could undergo transfer of the alkoxycarbonyl group from the *N*-acyl ammonium to the alkoxide at different rate, thereby generating product **2** in optically active form via a kinetic resolution of **13A** and **13B**. According to this model, the significant drop in ee observed with simple dialkyl ketones is because the rate of the interconversion between **13A** and **13B**, involving retrocyanation of **13** and cyanation of **1**, is not significantly faster than that of the kinetic resolution step.[13] Increasing the rate of the interconversion between **13A** and **13B** should lead to a reduction in the extent of the ee drop, a phenomenon observed in the reaction with α,α-dialkoxy ketones. The electron-withdrawing dialkoxy group presumably activated the ketone toward nucleophilic attack by CN^-, thereby increasing the rate of the interconversion step. This in turn lessened the decline in the ee of the product **2** as the reaction proceeded to high conversion.

We have found that certain ketone cyanohydrin such as **14** is stable enough to be isolated. This raised the possibility of quenching the modified cinchona alkaloid-catalyzed cyanocarbonation with an alcohol to trap intermediates **13A** and **13B** by protonation of the alkoxide ions (Fig. 3). According to the proposed mechanism outlined in Scheme 5 and assuming that the protonation is much faster than the interconversion between **13A** and **13B**, the er (enantiomer ratio) of cyanohydrin **14** should reflect the dr (diastereomer ratio) of intermediates **13A** and **13B**. Consequently, if the high enantioselectivity is due to efficient kinetic resolution of **13A** and **13B**, the ee of cyanohydrin **14** should be significantly lower than that of the cyanocarbonate **2**. On the other hand, if the asymmetric induction occurred in the step of cyanation of ketone **1**, the ee values of **14** and **2** should closely match each other. In a modified cinchona alkaloid-catalyzed cyanocarbonation of pinacolone (**1g**) in chloroform, the reaction mixture was treated with methanol and the resulting mixture was then subjected to GC analysis under conditions that allowed determination of ee values of both **14** and **2bg**. As shown by the GC chromatograms in Figure 3, the ee of cyanohydrin **14** is much lower than that of the cyanocarbonation product **2bg** (21 vs 83% ee). This result provided an experimental evidence to support the mechanistic proposal that the ee determination step in the cinchona alkaloid-catalyzed cyanocarbonation of pinacolone (**1g**) is the dynamic kinetic resolution of the putative intermediates **13Ag** and **13Bg** via asymmetric transfer of the alkoxycarbonyl group.



Scheme 5. A proposed catalytic cycle for a tertiary chiral amine-catalyzed asymmetric cyanocarbonation of ketones.

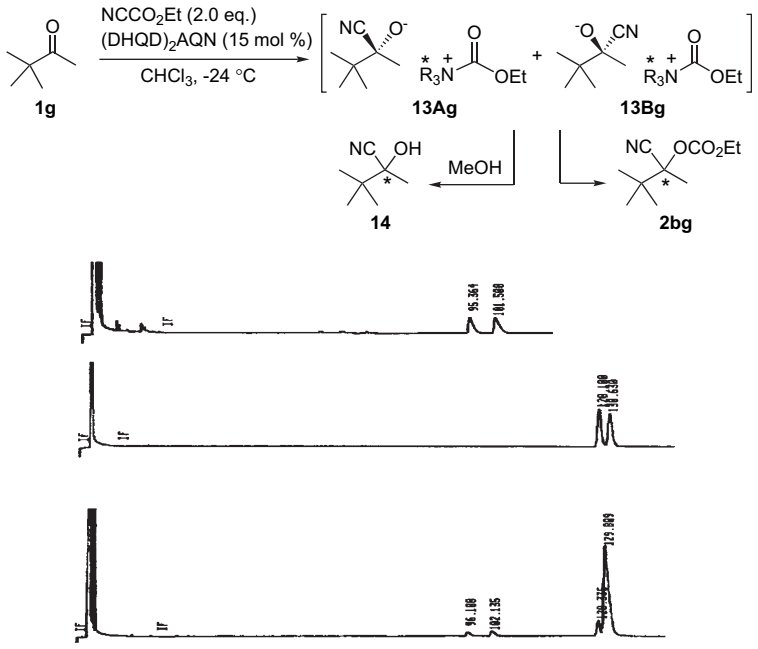


Figure 3. Chiral GC chromatograms (the retention time was expressed in minutes): top, racemic **14**; middle, racemic **2bg**; bottom, reaction mixture of the $(DHQD)_2AQN$-catalyzed asymmetric cyanocarbonation of pinacolone (**1g**) quenched at 54% conversion.

3. Conclusion

The development of the first highly enantioselective cyanocarbonation of prochiral ketones promoted by a chiral base catalyst is documented.[14] Importantly, the reaction complements known enzyme- and transition metal-based methods in substrate scope via its unique ability to promote highly enantioselective cyanocarbonation of sterically hindered simple dialkyl ketones. Additional desirable features of the reaction are the utilization of easily accessible and fully recyclable cinchona alkaloid catalysts and the employment of a simple experimental protocol that is insensitive to either air or moisture. These features should render the reaction a useful catalytic entry for the asymmetric synthesis of tertiary cyanohydrin derivatives via prochiral ketones. The reaction is conceptually interesting as the first efficient asymmetric cyanation of simple ketones realized with a chiral Lewis base approach. Mechanistic studies provided experimental evidence to shed significant light on the asymmetric induction step, in which the modified cinchona alkaloid acts as a chiral nucleophilic catalyst. These mechanistic studies in combination with those revealing cinchona alkaloids as highly efficient chiral general base catalysts underscore their remarkable ability to function as versatile yet efficient chiral organic catalysts for a wide variety of asymmetric transformations.[5b,15]

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to $SiMe_4$ signal. Low-resolution mass spectra for all the new compounds were recorded on a Hewlett–Packard 5989A GC–MS, and exact mass spectra on a VG 7070 high resolution mass spectrometer. Infrared spectra were recorded on a Perkin–Elmer FTIR Spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett–Packard 6890 Series instrument equipped with a split mode capillary injection system, a flame ionization detector, using a HP-5 GC column or a GC column with chiral stationary phase [gamma cyclodextrin trifluoroacetyl (30 m×0.25 mm) or HP chiral (20% permethylated B-cyclodextrin, 30 m×0.25 mm)]. All the GC analyses of chiral cyanohydrin carbonates were carried out with both a crude reaction sample and a sample purified by silica gel chromatography. High pressure liquid chromatography (HPLC) analyses were performed on a Hewlett–Packard 1100 Series instrument equipped with an isostatic pump, using a Daicel Chiralpak AS (250×4.6 mm), AD (250×4.6 mm) or Hypersil SI (200×4.6 mm) column. UV detection was monitored at 254 or 220 nm.

Unless otherwise mentioned, ketones, alkyl cyanoformates, and catalysts were purchased from Aldrich (Milwaukee) and used without further purification. Ketone **1e** was prepared via oxidation of 1-cyclohexylethanol with PCC. Ketones **1d**,[16] **1f**,[17] and **1i**,[18] were prepared according to the literature. Ketones **1l** and **1n** were prepared using a modified literature procedure[19] as described below. Chloroform was distilled over K_2CO_3 before use.

4.2. Preparation of 2,2-diethoxycyclopentanone (1l)

To a solution of *p*-toluenesulfonic acid (150 mg) and cyclopentanone (16.8 g, 200 mmol) in ethanol (50 mL) was added triethyl orthoformate (32.6 g, 220 mmol). A vigorous reaction ensued which caused ebullition, after which the reaction solution was heated at reflux for 15 min. Then another

portion of *p*-toluenesulfonic acid (200 mg) was added, and the reaction mixture was fractionated to give 1-ethoxycyclopentene (68–70 °C/80 mmHg, 14.5 g, 65%) as a colorless oil.

To a solution of 1-ethoxycyclopentene (2.24 g, 20.0 mmol) in ethanol (40 mL) at 0 °C was added dropwise a solution of *m*CPBA (4.00 g, 22.0 mmol) in ethanol (40 mL) over 1 h. The mixture was allowed to warm to room temperature and stirred for 20 min. The mixture was neutralized with saturated aqueous $NaHCO_3$. Ethanol was removed under reduced pressure and the residue was extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated to give crude 2,2-diethoxycyclopentanol.

To a solution of pyridine (19.0 g, 240 mmol) in dichloromethane (300 mL) at room temperature (cooled with water bath) was added CrO_3 (12.0 g, 120 mmol). The mixture was stirred for 15 min and the crude 2,2-diethoxycyclopentanol was added dropwise. After stirring for an additional 15 min at room temperature, ether (300 mL) was added and the mixture was stirred vigorously for 5 min. The mixture was filtered through a pad of silica gel and the filtrate was concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:100) to give 2,2-diethoxycyclopentanone (**1l**) (2.53 g, 74% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 6H), 1.79–1.88 (m, 2H), 1.98 (t, J=6.6 Hz, 2H), 2.23 (t, J=7.3 Hz, 2H), 3.42–3.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 16.8, 34.2, 34.9, 58.3, 100.6, 210.2; IR (neat) ν 2977, 1756, 1444, 1392, 1199 cm^{-1}; MS (NH_3/CI) m/z 190 (M+NH_4^+), 173 (MH^+), 144 (M−CO), 127 (M−OEt); HRMS (NH_3/CI) calcd for $C_9H_{17}O_3$ (MH^+) 173.1178, found 173.1175.

4.3. Preparation of 2,2-diethoxycyclohexanone (1n)

This compound was prepared in 60% yield (three steps) following the same procedure employed for 2,2-diethoxycyclopentanone. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.4 Hz, 6H), 1.71–1.82 (m, 4H), 1.92–1.96 (m, 2H), 2.47–2.51 (m, 2H), 3.37–3.45 (m, 2H), 3.48–3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 22.2, 27.7, 36.5, 40.3, 57.2, 101.0, 207.6; IR (neat) ν 2976, 1736, 1446, 1390, 1159 cm^{-1}; MS (NH_3/CI) m/z 204 (M+NH_4^+), 187 (MH^+), 158 (M−CO), 141 (M−OEt); HRMS (NH_3/CI) calcd for $C_{10}H_{19}O_3$ (MH^+) 187.1334, found 187.1331.

4.4. General procedure for the preparation of racemic cyanohydrin carbonates

To a stirred mixture of ketone (0.50 mmol) and alkyl cyanoformate (1.5–3.0 equiv) at room temperature (cooled with water bath) was slowly added DABCO or DBU (20 mol %). The reaction was monitored by either GC or TLC. The mixture was allowed to stand for 1.5–24 h and then diluted with ether. The resulting mixture was washed successively with 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give the desired racemic cyanohydrin carbonate in good to excellent yield.

4.5. Screening studies on the catalysts

To a stirred solution of 2-heptanone (**1a**) (23 mg, 0.20 mmol) in chloroform (0.20 mL) at room temperature was added the modified cinchona alkaloid (10 mol %), dodecane (2–4 μL, as the internal standard), and methyl cyanoformate (20 mg, 0.24 mmol). The mixture was allowed to stand for 31 h, then added aqueous HCl (1 N, 2.0 mL), and extracted with ether (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give (*R*)-2-methoxycarboxy-2-methylheptanenitrile (**2aa**) as a colorless oil. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 80 °C, 4 min, 5 °C/min to 110 °C, t (major)=23.5 min, t (minor)=26.2 min]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=6.8 Hz, 3H), 1.29–1.39 (m, 4H), 1.44–1.62 (m, 2H), 1.78 (s, 3H), 1.85–1.94 (m, 1H), 1.98–2.06 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 23.6, 24.6, 31.4, 39.8, 55.4, 74.5, 118.6, 153.4.

4.6. Screening studies on the solvents and alkyl cyanoformates

The procedure for the screening studies on the catalysts was used while employing a different solvent or alkyl cyanoformate. The ee of (*R*)-2-benzyloxycarboxy-2-methylheptanenitrile [(*R*)-**2ca**] was determined with chiral HPLC [Daicel Chiralpak OD, isopropanol/hexane 10:90, 0.50 mL/min, λ=220 nm; for a $(DHQD)_2AQN$-catalyzed reaction, t (major)=13.2 min, t (minor)=11.7 min]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=7.2 Hz, 3H), 1.27–1.39 (m, 4H), 1.41–1.61 (m, 2H), 1.76 (s, 3H), 1.86–1.96 (m, 1H), 1.98–2.08 (m, 1H), 5.18 (s, 2H), 7.31–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 23.5, 24.5, 31.3, 39.6, 74.5, 76.9, 118.5, 128.7, 128.8, 128.9, 134.6, 152.7.

4.7. General procedure for the asymmetric catalytic cyanocarbonation of ketones

To a stirred solution of ketone (0.20 mmol) in chloroform (0.20–0.40 mL) at the temperature indicated in Table 3 was added the modified cinchona alkaloid (10–35 mol %), dodecane (2–4 μL), and ethyl cyanoformate (1.0–3.0 equiv). The resulting mixture was allowed to stand at that temperature in a freezer without stirring. When the reaction reached the conversion indicated in Table 3 as determined by GC, aqueous HCl (1 N, 2.0 mL) was added to the reaction mixture. The mixture was extracted with ether (10 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:400–1:100) to give the chiral cyanohydrin carbonate.

To the aqueous layer was added K_2CO_3 to adjust the pH value of the solution to 9–11. The resulting mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the recovered catalyst, which is ^{1}H NMR ($CDCl_3$, 400 M) pure, in quantitative yield.

4.7.1. (*R*)-(+)-2-Ethoxycarboxy-2-methylheptanenitrile [(*R*)-(+)-2ba]. The ee was determined with chiral GC

[gamma cyclodextrin trifluoroacetyl, 110 °C, 4 min, 0.10 °C/min to 112 °C; for a $(DHQD)_2AQN$-catalyzed reaction, *t* (major)=19.8 min, *t* (minor)=20.5 min]. Colorless oil; 59% ee; $[\alpha]_D^{25}$ +16.2 (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J*=7.0 Hz, 3H), 1.35 (t, *J*=7.2 Hz, 3H), 1.29–1.40 (m, 4H), 1.44–1.63 (m, 2H), 1.78 (s, 3H), 1.86–1.94 (m, 1H), 1.98–2.06 (m, 1H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.4, 23.6, 24.5, 31.4, 39.7, 64.8, 74.3, 118.6, 152.7; IR (neat) ν 2950, 1759, 1468, 1371, 1265 cm^{-1}; MS (EI) *m/z* 214 (MH^+), 187 (M−CN); HRMS (EI) calcd for $C_{11}H_{20}NO_3$ (MH^+) 214.1443, found 214.1441.

4.7.2. (−)-2-Ethoxycarboxy-2-methylbutanenitrile [(−)-2bb]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 4.0 min, 0.10 °C/min to 85 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=43.4 min, *t* (minor)=42.0 min]. Colorless oil; 41% ee; $[\alpha]_D^{25}$ −8.0 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J*=7.2 Hz, 3H), 1.34 (t, *J*=7.2 Hz, 3H), 1.77 (s, 3H), 1.97 (dt, *J*=21.0, 7.2 Hz, 1H), 2.10 (dt, *J*=21.0, 7.2 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 14.2, 24.0, 35.0, 64.8, 74.8, 118.5, 152.7; IR (neat) ν 2985, 1758, 1465, 1371, 1263 cm^{-1}; MS (EI) *m/z* 172 (MH^+), 145 (M−CN); HRMS (CH_4/CI) calcd for $C_8H_{14}NO_3$ (MH^+) 172.0974, found 172.0975.

4.7.3. (−)-2-Ethoxycarboxy-2,3-dimethylbutanenitrile [(−)-2bc]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 100 °C, 25.0 min, 1.0 °C/min to 105 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=21.1 min, *t* (minor)=20.6 min]. Colorless oil; 76% ee; $[\alpha]_D^{25}$ −17.6 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J*=6.8 Hz, 3H), 1.14 (d, *J*=6.4 Hz, 3H), 1.34 (t, *J*=7.2 Hz, 3H), 1.75 (s, 3H), 2.19–2.29 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.6, 17.0, 21.1, 36.6, 64.6, 78.0, 117.8, 152.7; IR (neat) ν 2981, 1757, 1467, 1372, 1264 cm^{-1}; MS (EI) *m/z* 186 (MH^+), 159 (M−CN); HRMS (EI) calcd for $C_9H_{16}NO_3$ (MH^+) 186.1130, found 186.1126.

4.7.4. (−)-2-Ethoxycarboxy-2-methyl-3-(2-propenyl)-5-hexenenitrile [(−)-2bd]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 110 °C, 4 min, 0.10 °C/min to 114 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=36.8 min, *t* (minor)=38.1 min]. Colorless oil; 81% ee; $[\alpha]_D^{25}$ −25.4 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H), 1.79 (s, 3H), 2.18–2.29 (m, 3H), 2.32–2.41 (m, 1H), 2.44–2.54 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 5.05–5.15 (m, 4H), 5.73–5.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.3, 33.4, 34.1, 45.5, 64.9, 77.4, 117.6, 117.7, 118.3, 135.6, 135.6, 152.6; IR (neat) ν 3080, 2983, 1759, 1642, 1444, 1371, 1260 cm^{-1}; MS (CH_4/CI) *m/z* 238 (MH^+), 211 (M−CN); HRMS (CH_4/CI) calcd for $C_{13}H_{20}NO_3$ (MH^+) 238.1443, found 238.1450.

4.7.5. (−)-2-Cyclohexyl-2-ethoxycarboxy-propionitrile [(−)-2be]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 4 min, 0.10 °C/min to 124 °C; for a $(DHQ)_2AQN$-catalyzed reaction, *t* (major)=35.1 min, *t* (minor)=36.9 min]. Colorless oil; 87% ee; $[\alpha]_D^{25}$ −25.5 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.12–1.31 (m, 5H), 1.34 (t, *J*=7.2 Hz, 3H), 1.67–1.74 (m, 1H), 1.75 (s, 3H), 1.82–1.92 (m, 4H), 1.99–2.06 (m, 1H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.6, 25.9, 26.0, 27.0, 27.3, 46.0, 64.8, 77.8, 118.2, 152.8; IR (neat) ν 2936, 1757, 1454, 1371, 1267 cm^{-1}; MS (EI) *m/z* 226 (MH^+); HRMS (EI) calcd for $C_{12}H_{20}NO_3$ (MH^+) 226.1443, found 226.1450.

4.7.6. (*S*)-(+)-2-Ethoxycarboxy-2-methyl-3,3-dipropoxypropionitrile [(*S*)-(+)-2bf]. The ee and absolute configuration were determined after transforming this compound to its corresponding β-aminoalcohol derivative **9f** (vide infra). Colorless oil; 96% ee (DHQD-PHN-catalyzed reaction); $[\alpha]_D^{25}$ +14.6 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.2 Hz, 3H), 0.97 (t, *J*=7.2 Hz, 3H), 1.34 (t, *J*=7.0 Hz, 3H), 1.58–1.72 (m, 4H), 1.76 (s, 3H), 3.48–3.55 (m, 1H), 3.61–3.66 (m, 1H), 3.70–3.82 (m, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 4.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 14.3, 18.5, 23.1, 23.2, 65.1, 72.4, 72.9, 75.7, 102.0, 117.5, 152.7; IR (neat) ν 2968, 1760, 1466, 1372, 1267 cm^{-1}; MS (CH_4/CI) *m/z* 274 (MH^+); HRMS (CH_4/CI) calcd for $C_{13}H_{24}NO_5$ (MH^+) 274.1654, found 274.1659.

4.7.7. (+)-2-Ethoxycarboxy-2,3,3-trimethylbutyronitrile [(+)-2bg]. The ee was determined with chiral GC [20% permethylated B-cyclodextrin, 60 °C, 4 min, 0.10 °C/min to 75 °C; for a $(DHQD)_2AQN$-catalyzed reaction, *t* (major)=124.3 min, *t* (minor)=126.6 min]. Colorless oil; 88% ee; $[\alpha]_D^{25}$ +36.0 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.34 (t, *J*=7.2 Hz, 3H), 1.76 (s, 3H), 4.25 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.1, 24.8, 38.8, 64.8, 80.5, 118.2, 153.0; IR (neat) ν 2981, 1760, 1469, 1372, 1266 cm^{-1}; MS (EI) *m/z* 200 (MH^+), 173 (M−CN); HRMS (EI) calcd for $C_{10}H_{18}NO_3$ (MH^+) 200.1287, found 200.1287.

4.7.8. (+)-3,3-Dimethoxy-2-ethoxycarboxy-2-methylbutyronitrile [(+)-2bh]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 120 °C, 10.0 min, 0.1 °C/min to 123 °C; for a DHQD-PHN-catalyzed reaction, *t* (major)=26.0 min, *t* (minor)=25.3 min]. Colorless oil; $[\alpha]_D^{25}$ +41.8 (*c* 2.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H), 1.53 (s, 3H), 1.83 (s, 3H), 3.42 (s, 3H), 3.44 (s, 3H), 4.26 (q, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 16.9, 19.8, 51.4, 65.1, 78.9, 102.0, 117.8, 152.5; IR (neat) ν 2984, 1760, 1454, 1372, 1265 cm^{-1}; MS (EI) *m/z* 232 (MH^+), 200 (M−OMe); HRMS (CH_4/CI) calcd for $C_{10}H_{18}NO_5$ (MH^+) 232.1185, found 232.1174.

4.7.9. (+)-3,3-Diethoxy-2-ethoxycarboxy-2-methylbutyronitrile [(+)-2bi]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 100 °C, 4 min, 0.10 °C/min to 106 °C; for a DHQD-PHN-catalyzed reaction, *t* (major)=48.3 min, *t* (minor)=46.7 min]. Colorless oil; 90% ee; $[\alpha]_D^{25}$ +34.5 (*c* 2.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.24 (m, 6H), 1.34 (t, *J*=7.0 Hz, 3H), 1.54 (s, 3H), 1.83 (s, 3H), 3.63–3.72 (m, 4H), 4.25 (q, *J*=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.6, 17.9, 19.7, 59.0, 59.1, 64.9, 79.2, 101.6, 118.0, 152.6; IR (neat) ν 2982, 1759, 1446, 1372, 1263 cm^{-1}; MS (CH_4/CI) *m/z* 260 (MH^+), 214 (M−OEt);

HRMS (CH_4/CI) calcd for $C_{12}H_{22}NO_5$ (MH^+) 260.1498, found 260.1502.

4.7.10. 2-Ethoxycarboxy-2-(adamantan-1-yl)propionitrile (2bj). The ee was determined after transforming this compound to its corresponding β-aminoalcohol derivative **9j** (vide infra). White solid; 74% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.0 Hz, 3H), 1.66–1.84 (m, 15H), 2.08–2.11 (m, 3H), 4.24 (q, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 17.7, 28.2, 36.0, 36.6, 39.9, 64.7, 80.9, 117.8, 153.1.

4.7.11. (−)-1-Ethoxycarboxy-2,2-dimethylcyclopentanecarbonitrile [(−)-2bk]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 90 °C, 4 min, 0.10 °C/min to 100 °C; for a $(DHQ)_2AQN$-catalyzed reaction, t (major)=87.5 min, t (minor)=91.7 min]. Colorless oil; 95% ee; $[\alpha]_D^{25}$ −15.8 (c 1.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.21 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.63–1.92 (m, 4H), 2.33–2.42 (m, 1H), 2.51–2.60 (m, 1H), 4.19–4.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.6, 21.5, 25.1, 35.3, 36.7, 47.6, 65.0, 84.8, 117.7, 153.3; IR (neat) ν 2974, 1760, 1470, 1372, 1276 cm^{-1}; MS (EI) m/z 212 (MH^+); HRMS (EI) calcd for $C_{11}H_{18}NO_3$ (MH^+) 212.1287, found 212.1297.

4.7.12. (−)-2,2-Diethoxy-1-ethoxycarboxycyclopentanecarbonitrile [(−)-2bl]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 95 °C, 4 min, 0.05 °C/min to 104 °C; for a DHQ-PHN-catalyzed reaction, t (major)=150.6 min, t (minor)=158.3 min]. White solid, mp 74–75 °C; 95% ee; $[\alpha]_D^{25}$ −32.1 (c 2.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J=7.0 Hz, 3H), 1.24 (t, J=7.0 Hz, 3H), 1.33 (t, J=7.1 Hz, 3H), 1.68–1.75 (m, 2H), 1.82–1.90 (m, 1H), 2.08–2.15 (m, 1H), 2.39–2.57 (m, 2H), 3.54–3.62 (m, 2H), 3.71–3.86 (m, 2H), 4.25 (q, J=7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.3, 18.1, 30.5, 35.9, 57.5, 58.8, 65.1, 79.2, 109.3, 117.1, 152.7; IR ($CHCl_3$) ν 3019, 1757, 1423, 1221 cm^{-1}; MS (CH_4/CI) m/z 271 (M^+); HRMS (CH_4/CI) calcd for $C_{13}H_{21}NO_5$ (M^+) 271.1420, found 271.1424.

4.7.13. (−)-1-Ethoxycarboxy-2,2-dimethylcyclohexanecarbonitrile [(−)-2bm]. The ee was determined by chiral GC [gamma cyclodextrin trifluoroacetyl, 115 °C, 4 min, 0.10 °C/min to 121 °C; for a $(DHQ)_2AQN$-catalyzed reaction, t (major)=51.1 min, t (minor)=54.0 min]. Colorless oil; 92% ee; $[\alpha]_D^{25}$ −15.5 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.48–1.68 (m, 6H), 2.11–2.21 (m, 1H), 2.30–2.40 (m, 1H), 4.25 (q, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.4, 21.6, 22.7, 25.2, 29.1, 35.7, 38.2, 64.7, 81.2, 117.7, 152.8; IR (neat) ν 2939, 1755, 1458, 1371, 1261 cm^{-1}; MS (EI) m/z 226 (MH^+); HRMS (EI) calcd for $C_{12}H_{20}NO_3$ (MH^+) 226.1443, found 226.1448.

4.7.14. (+)-2,2-Diethoxy-1-ethoxycarboxycyclohexanecarbonitrile [(+)-2bn]. The ee was determined with chiral GC [gamma cyclodextrin trifluoroacetyl, 105 °C, 4 min, 0.05 °C/min to 113 °C; for a DHQD-PHN-catalyzed reaction, t (major)=145.9 min, t (minor)=143.6 min]. Colorless oil; 96% ee; $[\alpha]_D^{25}$ +26.0 (c 2.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.0 Hz, 3H), 1.25 (t, J=7.0 Hz, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.44–1.62 (m, 4H), 1.78–1.96 (m, 2H), 2.24–2.34 (m, 1H), 2.42–2.52 (m, 1H), 3.62 (q, J=7.0 Hz, 2H), 3.72–3.82 (m, 2H), 4.26 (q, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 15.4, 15.6, 20.4, 21.4, 30.2, 32.2, 57.3, 57.9, 64.9, 99.5, 117.4, 152.4; IR (neat) ν 2979, 1758, 1447, 1371, 1258 cm^{-1}; MS (CH_4/CI) m/z 286 (MH^+), 285 (M^+), 240 (M−OEt); HRMS (CH_4/CI) calcd for $C_{14}H_{23}NO_5$ (M^+) 285.1576, found 285.1564.

4.8. A 10 mmol-scale synthesis of (+)-2,2-diethoxy-1-ethoxycarboxycyclopentanecarbonitrile [(+)-2bl]

To a stirred solution of 2,2-diethoxycyclopentanone (1.72 g, 10.0 mmol) and DHQD-PHN (502 mg, 1.00 mmol) in chloroform (10 mL) at −24 °C was added dropwise ethyl cyanoformate (2.97 g, 30.0 mmol). After the mixture was allowed to stand at −24 °C in a freezer for 7 days, aqueous HCl (1 N, 20 mL) was added. The resulting mixture was stirred vigorously for 2 min and then extracted with ether (50 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:100) to give the cyanohydrin carbonate (2.69 g, 99%, 94% ee) as a white solid. This compound was also obtained in 87% yield and 97% ee simply by recrystallizing the residue in hexane.

To the aqueous layer was added K_2CO_3 to adjust the pH value of the solution to 9–11. The resulting mixture was extracted with ethyl acetate (50 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the recovered catalyst DHQD-PHN, which is ^{1}H NMR ($CDCl_3$, 400 M) pure, in quantitative yield.

4.9. Transformation of cyanohydrin carbonate (−)-2bk to β-aminoalcohol derivative 9k

To a solution of (−)-**2bk** (95% ee, 20 mg, 0.095 mmol) in ether (0.50 mL) at room temperature was added $LiAlH_4$ (18 mg, 0.47 mmol). The mixture was stirred for 2 h, and then added water (three drops) and ether (5.0 mL). The resulting mixture was dried over Na_2SO_4, filtered, and to the filtrate was added benzoyl chloride (25 mg, 0.18 mmol) and triethylamine (36 mg, 0.36 mmol). After being stirred at room temperature for 2 h, the mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:20–1:10) to give amide **9k** (13 mg, 63%) as a white solid. The ee of **9k** was determined to be 95% with chiral HPLC [Daicel Chiralpak AS, isopropanol/hexane 5:95, 1.0 mL/min, t (major)=33.9 min, t (minor)=43.2 min]. Mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.06 (s, 3H), 1.45–1.53 (m, 1H), 1.60–1.84 (m, 4H), 1.91–2.00 (m, 1H), 2.22 (br s, 1H), 3.44 (dd, J=13.8, 4.4 Hz, 1H), 3.68 (dd, J=13.8, 7.0 Hz, 1H), 6.69 (br s, 1H), 7.39–7.44 (m, 2H), 7.49 (t, J=7.2 Hz, 1H), 7.78 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 22.3, 24.7, 36.1, 39.5, 44.8, 45.2, 84.1, 127.1, 128.7, 131.6, 134.8, 168.4; MS (NH_3/CI) m/z 248 (MH^+), 230 (M−OH); HRMS (NH_3/CI) calcd for $C_{15}H_{22}NO_2$ (MH^+) 248.1651, found 248.1660.

4.10. Transformation of cyanohydrin carbonate (*S*)-(+)-2bf to β-aminoalcohol derivative (*S*)-9f

Cyanohydrin carbonate (*S*)-(+)-**2bf** (prepared from a DHQD-PHN-catalyzed reaction, 14 mg, 0.050 mmol) was reduced to its corresponding β-aminoalcohol with $LiAlH_4$ using the same procedure as described above. To the solution of crude β-aminoalcohol in ether (5 mL) was added benzyl chloroformate (17 mg, 0.10 mmol) and triethylamine (20 mg, 0.20 mmol). The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by silica gel column chromatography (acetone/hexane 1:40) to give carbamate (*S*)-**9f** (12 mg, 66%) as a colorless oil. The ee of (*S*)-**9f** was determined to be 96% [HPLC conditions: Daicel Chiralpak AD+Hypersil SI, isopropanol/hexane 1:99, 0.5 mL/min, *t* (major)=91.7 min, *t* (minor)=103.3 min]. (*S*)-**9f** can also be obtained from (*S*)-(+)-2-trimethylsiloxy-2-methyl-3,3-dipropoxypropionitrile[5b] employing the same sequences, so the absolute configuration was determined to be *S*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.4 Hz, 6H), 1.17 (s, 3H), 1.58–1.68 (m, 4H), 2.45 (s, 1H), 3.30–3.36 (m, 2H), 3.43–3.50 (m, 2H), 3.71–3.79 (m, 2H), 4.24 (s, 1H), 5.11 (s, 2H), 5.25–5.30 (m, 1H), 7.39–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 20.7, 23.4, 46.7, 65.6, 66.9, 72.8, 72.8, 74.1, 107.8, 127.2, 128.2, 128.7, 136.9, 157.2.

4.11. Transformation of cyanohydrin carbonate 2bj to β-aminoalcohol derivative 9j

This transformation was accomplished by employing the above sequences. The ee was determined to be 74% with chiral HPLC [Daicel Chiralpak OD, isopropanol/hexane 20:80, 0.50 mL/min, λ=254 nm; *t* (major)=13.4 min, *t* (minor)=12.0 min]. White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.62–1.76 (m, 12H), 2.01–2.07 (m, 3H), 3.45 (dd, *J*=13.4, 3.0 Hz, 1H), 3.67 (dd, *J*=13.4, 8.0 Hz, 1H), 6.58–6.62 (m, 1H), 7.41–7.52 (m, 3H), 7.78–7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 28.7, 34.6, 36.4, 37.2, 39.1, 44.7, 76.8, 127.1, 128.8, 131.6, 134.9, 168.6.

4.12. Acidic hydrolysis of (*R*)-(+)-2ba

To a concentrated aqueous hydrochloric acid (5 mL) was added (*R*)-(+)-**2ba** (59% ee, 82 mg, 0.38 mmol). The mixture was stirred at room temperature overnight and then heated under reflux for 5 h. After being cooled down to room temperature, the mixture was extracted with ethyl acetate (3×5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (ether/hexane 1:1) to give (*R*)-(−)-2-hydroxy-2-methylheptanoic acid (**10a**) (50 mg, 81%). The absolute configuration of (+)-**2ba** was determined to be *R* by comparing the specific rotation {$[\alpha]_D^{25}$ −5.4 (*c* 1.60, $CHCl_3$)} with that reported in literature {$[\alpha]_D^{25}$ −9.4 (*c* 0.35, $CHCl_3$), 98% ee}.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.15–1.36 (m, 5H), 1.42–1.53 (m, 1H), 1.47 (s, 3H), 1.62–1.72 (m, 1H), 1.75–1.84 (m, 1H), 6.60 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 23.4, 26.0, 32.0, 40.1, 75.0, 181.7.

Acknowledgements

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Rh-catalyzed alkene oxidation: a highly efficient and selective process for preparing *N*-alkoxysulfonyl aziridines

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Abstract—Unique alkoxysulfonyl aziridine heterocycles were prepared through selective intra- and intermolecular alkene oxidation reactions. These methods are general and perform efficiently at low Rh-catalyst loadings (1–2 mol %) with only a slight excess of an inexpensive commercial oxidant, $PhI(OAc)_2$. For intermolecular processes, trichloroethylsulfamate was identified as a novel and markedly effective N-atom source, allowing reactions to be conducted with limiting amounts of the olefin substrate. The aziridine products submit to facile, nucleophilic ring opening; these processes are regioselective and can be used to prepare polyfunctionalized amines, including α-aminoketones via the direct addition of Me_2SO.

1. Introduction

The versatility of aziridines as precursors to amine derivatives drives the development of preparative methods for this unique class of heterocycles.[1,2] Catalytic nitrogen atom transfer to alkenes is a particularly appealing strategy for the generation of aziridines because of the ready availability of olefinic starting materials and the direct nature of such a process. For this reason, intensive efforts by numerous labs have taken aim at the problem of alkene aziridination.[3] These studies have identified Cu-based catalysts as the most universal for promoting oxidation with hypervalent iodoimine-derived reagents of the general form $PhI{=}NSO_2Ar$. Nevertheless, the vast majority of reported protocols for effecting nitrene transfer employ multiple equivalents of the starting alkene, and thus the application of these processes has been largely relegated to simple, inexpensive substrates.[4] In our lab, alkoxysulfonamides (sulfamate esters) were found to be exceptional substrates for Rh-catalyzed C–H amination reactions (Fig. 1).[5] Related studies have further revealed the effectiveness of sulfamate esters for synthesizing aziridines

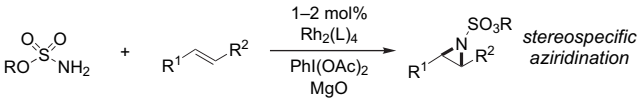

Figure 1. Rh-catalyzed oxidation affords *N*-alkoxysulfonyl aziridines.

in both intra- and intermolecular processes.[5b,6,7] Our methods thus make available a large and diverse set of alkoxysulfonyl-substituted aziridine products. In this report, we describe in detail the preparation and electrophilic reactivity of these novel compounds.

2. Results and discussion

2.1. Intra- and intermolecular aziridination

Interest in developing selective methods for alkene aziridination followed from our discovery that sulfamate esters were excellent substrates for Rh-catalyzed intramolecular C–H amination.[5a] Given the greater reactivity of π-bonds compared with σ-C–H centers toward chemical oxidants, we assumed that the Rh-mediated conditions would likely promote cyclization of homoallyl-derived sulfamates. Such expectations were indeed realized when homoallyl ester **1** was mixed with 2 mol % $Rh_2(oct)_4$, $PhI(OAc)_2$, and MgO to give the corresponding bicyclic aziridine **2** in 83% yield (Fig. 2). This unusual heterocycle is remarkably stable to chromatographic purification, and yet sufficiently reactive for ring opening under ambient conditions with common nucleophiles (vide infra). Following an empirical screen of different Rh complexes, the tetra-trifluoroacetamide adduct,

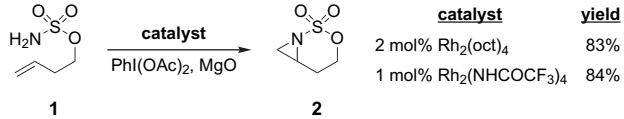

Figure 2. Intramolecular aziridination gives a novel bicyclic heterocycle.

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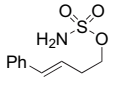
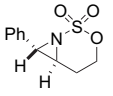
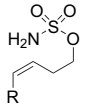
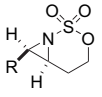
$Rh_2(NHCOCF_3)_4$, was found to be the catalyst of choice for effecting aziridine reactions across a varied spectrum of substituted starting materials.[8] In most cases, as little as 1 mol % of catalyst is needed to mediate the intramolecular aziridination event. Contemporaneous with these findings, others have delineated analogous processes for sulfamate-mediated aziridination using Cu- and Ru-based catalysts.[3g,9]

A number of differentially configured achiral and chiral unsaturated sulfamates have been prepared to map the scope of this aziridination process. Using standard conditions that employ 1–2 mol % $Rh_2(NHCOCF_3)_4$ and 1.1 equiv of commercial $PhI(OAc)_2$, substrates containing either *E*- or *Z*-alkenyl units are oxidized smoothly (Table 1). A notable feature of the Rh-catalyzed reaction follows from these collective data: *E*-olefins afford exclusively *trans* aziridines; conversely, *Z*-olefins give cis products. Stereospecificity is an invariant property of this Rh-mediated π-bond oxidation whether the reaction is performed in an intra- or intermolecular fashion. As seen in Table 1, cis-substituted vinylsilanes, α,β-unsaturated phosphonates, and conjugated enynes all engage in this process, giving single diastereomeric products (entry 2). These stable, heteroatom-substituted aziridines are rather unusual structural motifs, access to which is not readily apparent in the absence of this method.

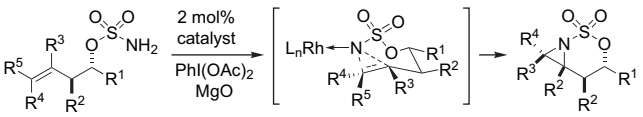
Table 1. Intramolecular reactions of achiral sulfamates

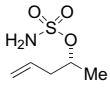
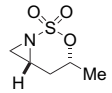
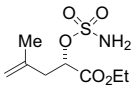
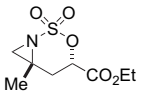
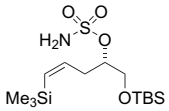
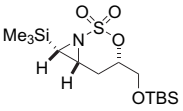
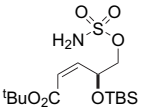
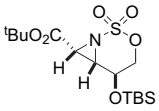
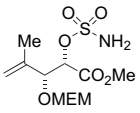
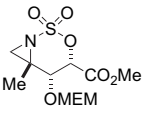
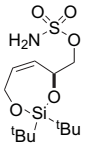
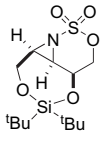
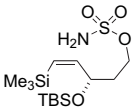
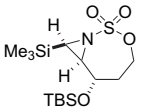
Entry[a]	Substrate	Product		% Yield
1				72
2			R = $SiPh_3$ = P(O)OEt_2 = –C≡C$SiiPr_3$	83 62 74

[a] All reactions conducted with 1–2 mol % $Rh_2(NHCOCF_3)_4$ in CH_2Cl_2 between 0 and 23 °C.

Our optimized conditions for intramolecular olefin aziridination can be employed with chiral sulfamate derivatives to give products with satisfactory levels of diastereocontrol. Several examples of such reactions are highlighted in Table 2. In these entries, product diastereoselectivities range from modest to high across a number of structurally dissimilar starting materials. While only moderate stereocontrol was noted for sulfamates prepared from secondary alcohols (entries 1 and 2, entry 3 being an exception), a sharp increase in diastereoselectivity was recorded for substrates containing a stereogenic element at the β-site (entries 4 and 5). These studies, along with previous work from our lab, have led us to propose a stereochemical model to account for the observed sense of induction.[5b] In brief, the recorded data are consistent with an aziridination event proceeding through a chair-like transition state that minimizes gauche and $A_{1,3}$-type interactions. It is interesting to note, however, that seven-membered ring oxathiazepane-fused aziridines (entry 7) can also be generated with useful levels of diastereocontrol. The scope of this latter finding has not been explored in full.[3f,10]

Table 2. Diastereoselective reactions of chiral sulfamates



Entry[a]	Substrate	Major product	Selectivity[b]	% Yield
1			4:1	84
2			4:1	92
3			15:1	69
4			20:1	87
5			20:1	82
6			20:1	61
7			10:1	66[c]

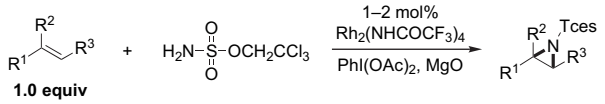
[a] Reactions conducted with 2 mol % $Rh_2(oct)_4$ in CH_2Cl_2 at 23 °C.
[b] Product diastereoselectivity determined by integration of the ^1H NMR of the unpurified reaction mixture.
[c] Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$.

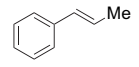
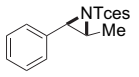
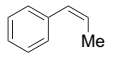
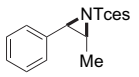
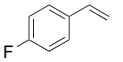
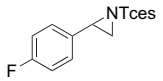
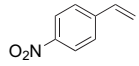
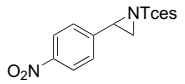
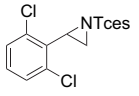
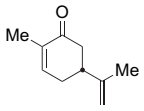
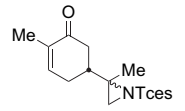
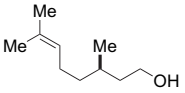
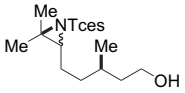
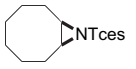
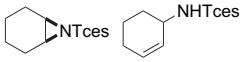
Our ability to oxidize alkenes in an intramolecular process with both high efficiency and chemoselectivity motivated the advancement of a related intermolecular protocol.[6] Identifying an N-functionalized starting material that itself would not undergo intramolecular C–H insertion was a prerequisite to the successful execution of this aim. In practice, use of the terminal oxidant $PhI(OAc)_2$ for aziridination offers a salient advantage by enabling the choice of any number of sulfonamide and/or carbamate derivatives as the N-atom source. This point is noteworthy, as previous aziridination methods that rely on $ArSO_2N{=}IPh$-type reagents are strictly limited to a small number of sulfonamide materials.[2,11] Accordingly, after screening a collection of aryl- and alkylsulfonamides, we identified 2,2,2-trichloroethylsulfamate ($TcesNH_2$) as the most effective reagent for Rh-catalyzed intermolecular amination reactions. The decision to utilize $TcesNH_2$ followed from a number of considerations, which included: (1) its ease and low cost of preparation from trichloroethanol;[12] (2) crystallinity and shelf-stability; and (3) the potential to

cleave the Tces-group from the product aziridine under mild reducing conditions (i.e., Zn). Later studies have shown that it is also the fastest nitrogen source to react under our conditions, a fact that may be responsible for its superior performance.[13]

Initial experiments using *trans*-β-methylstyrene as a test substrate in combination with $TcesNH_2$, $PhI(OAc)_2$, MgO, and 1 mol % $Rh_2(NHCOCF_3)_4$ afforded an 85% yield of the desired aziridine (Table 3, entry 1). Importantly, no product from competing allylic insertion, a problem encountered with other Rh(II) catalysts, was obtained. A second distinguishing characteristic of this process is its efficacy with only *a single equivalent of the olefinic substrate*. This feature is of paramount importance in the context of complex molecule synthesis, but is more the exception than the rule for previously reported catalytic aziridination methods. We have observed comparable results in reactions with a host of different aryl- and aliphatic alkenes applied as the limiting reagent. Of added note, the reactive nitrene-like oxidant can discriminate between electronically dissimilar olefins and, as would be expected for an electrophilic oxidant, the isopropylidene moiety in carvone is preferentially modified (entry 6). Although most styrenyl alkenes display exceptional performance under the Rh-catalyzed conditions, electron-deficient 2,6-dichlorostyrene (entry 5) presents a daunting test and in this case the product yield is reduced. By employing a larger number of equivalents of this alkene (i.e., 3 equiv), however, the aziridine can be generated in 77% yield (2 mol % catalyst). Finally, it should be noted that cyclopentene and cyclohexene (entry 9) are problematic substrates and fail to give even modest amounts of the corresponding aziridines. Allylic C–H insertion is also found to be competitive in these cases. Similar difficulties functionalizing both alkenes have been encountered using other transition metal-based aziridination methods.[3a,14] The inability to form either product in higher yield under our conditions is rather surprising, and lacks an obvious explanation at this time.

Table 3. A method for intermolecular olefin aziridination



Entry[a]	Substrate	Product	% Yield
1			85
2			85
3			91
4			71
5			40
6			85[b]
7			70[b]
8			82
9			15[c]

[a] Reactions conducted with 1 mol % $Rh_2(NHCOCF_3)_4$ in C_6H_5Cl from –10 to 23 °C.
[b] Product isolated as a 1:1 diastereomeric mixture.
[c] Isolated yield for each of the two products.

Knowledge of the scope of the Rh-mediated aziridination process coupled with a desire to showcase further its utility for synthesis gave us cause to explore reactions with glycal-based substrates.[15] Oxidation of such materials provides direct entry into value-added 2-amino sugars masked with a readily removable trichloroethoxysulfonyl (Tces) unit. By using Zn deprotection under non- or mildly acidic conditions, access to *N*-sulfated amino sugars, common structural units in heparins and in complex cell-surface carbohydrates, is also possible.[16] Much to our satisfaction, when 1 equiv of commercial tri-*O*-acetyl-D-glucal was subjected to oxidation (2 mol % catalyst), complete formation of the C2-aminated product occurred (Fig. 3). The product in this case is not the fused bicycle, but instead the 1,2-acetoxy-Tces-amine, presumed to result from in situ aziridine ring opening with AcOH. Although MgO is needed as a scavenger for AcOH, it is kinetically slow to remove the acid from solution; as such, the labile aziridine is displaced to give the anomeric acetate. We have observed similar patterns of reactivity with electron-rich aryl and strained aziridines, such as those derived from *p*-methoxystyrene and indene, respectively. Ring opening of the aziridine aside, the efficiency of this reaction to give the alkoxysulfonamide product using a limiting amount of triacetyl glucal is unprecedented, thus this method should find application in carbohydrate synthesis.

2.2. Nucleophilic ring openings of alkoxysulfonyl aziridines

In undertaking studies to advance our amination chemistry, we wished to examine systematically the electrophilic reactivity of these unusual alkoxysulfonylated strained heterocycles. Prior work by Dauban and Dodd, in accord with our own findings, indicated that the 6,3-bicyclic aziridines formed through intramolecular reactions ring open to favor the seven-membered oxathiazepane dioxide product

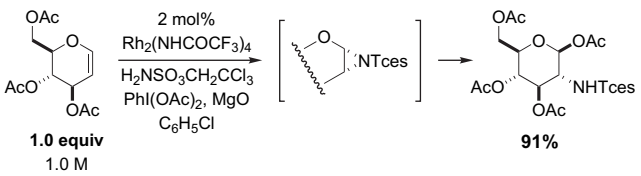


Figure 3. Glycal oxidation gives a sulfated 2-amino sugar in protected form.

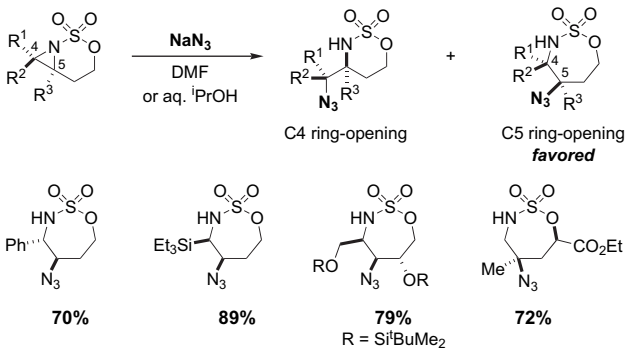


Figure 4. Regioselective nucleophilic opening favors seven-membered ring product.

(Fig. 4).[5b,9] We have found subsequently that substitution on the bicyclic framework does not adversely affect regioselectivity in these S_N2 processes. Regiocontrol in the ring opening of alkoxysulfonylaziridines was investigated using a small collection of differentially substituted starting materials and NaN_3 as the nucleophile. As a general rule, azide attack occurs with a strong preference to displace the C5–N bond giving the corresponding oxathiazepane. Substrates that displayed lower selectivity and afforded small amounts of the 6-membered oxathiazinane contained groups that strongly enhance electrophilicity at the C4 position (e.g., vinyl and alkynyl).

X-ray crystallography has provided some insight for understanding the high regioselectivity observed in these S_N2 reactions (Fig. 5).[17] Analysis of the ORTEP diagram of phenyl-substituted aziridine **3** shows only a very slight, albeit statistically discernible, variation between the C4–N (1.491 Å) and the C5–N bond lengths (1.497 Å). While this difference is biased in a way that is consistent with the observed regioselectivity for ring opening, it is so small that we presume other factors must be at play. An X-ray structure of the highly crystalline seven-membered azide product has led us to consider an alternative proposal. In comparing the starting material and product ORTEPs, it appears that minimal conformational reorganization occurs upon C5–N bond cleavage. Alternatively, nucleophilic attack at the C4 position would give the oxathiazinane product in a twist boat-like arrangement with the benzyl substituent aligned pseudo-axially. A large conformational change is then needed for the product to interconvert into its preferred chair-like structure. Presumably, such torsional strain energy is manifest in the transition state for C4 attack, thus disfavoring it as compared to azide addition at C5. A second possible

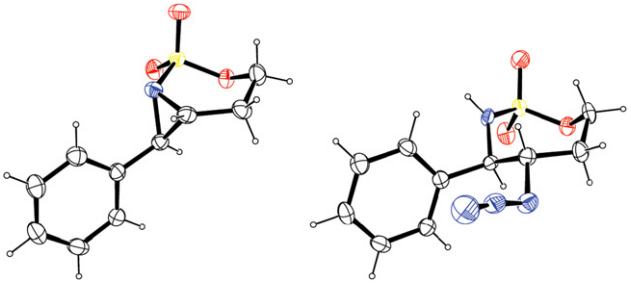


Figure 5. X-ray structures of bicyclic aziridine **3** and the azide-opened product.

explanation for the observed C5 regioselectivity follows from frontier molecular orbital theory. Density functional calculations (B3LYP/6-31G*) on the parent bicyclic aziridine **2** indicate that the coefficient of the LUMO orbital is substantially greater at C5 than at C4 (Fig. 6).[18] Similar observations are noted for the calculated structures of the LUMO+ orbital on **2** and for related alkyl-substituted aziridines of this type. Although the underlying factors biasing the shape of the LUMO and LUMO+ orbitals are unclear, such computational data are consistent with our experimental findings and the strong preference for these unusual heterocycles to ring open at the C5 center.

Regioselective ring opening of bicyclic aziridines such as **3** is observed with nucleophiles other than azide ion (Fig. 7). Oxygen- and sulfur-derived agents such as MeOH, H_2O, and PhSH are effective for the internal opening of alkoxysulfonyl aziridines to give oxathiazepane products, analogous to the results of Dauban and Dodd.[9] When H_2O and PhSH were employed, neither acid nor base was necessary for the reactions to proceed to completion, a fact that is demonstrative of the exceptional reactivity of these aziridinyl heterocycles.

The product oxathiazepanes are valuable precursors to polysubstituted amine derivatives. As with other cyclic sulfamates, the seven-membered heterocycles are susceptible to nucleophilic displacement of the C–O bond to give ring-opened products.[5a,19] Such reactions are possible using N–H or *N*-alkyl derived starting materials; however, the facility by which this S_N2 process occurs can be greatly improved if the N-center is first acylated (Fig. 8). This behavior is analogous to that observed for six-membered oxathiazinanes. Accordingly, *N*-Boc functionalization of **5** enables the subsequent addition of NaCN to give the diastereochemically-pure acyclic amine **7**. Thus, in four steps from a starting homoallylic alcohol, access to diverse product libraries of highly functionalized amines can be achieved.

Given the marked electrophilic reactivity of the intramolecular aziridine products, we expected that trichloroethoxysulfonyl aziridines synthesized through intermolecular olefin amination would display a similar propensity for ring

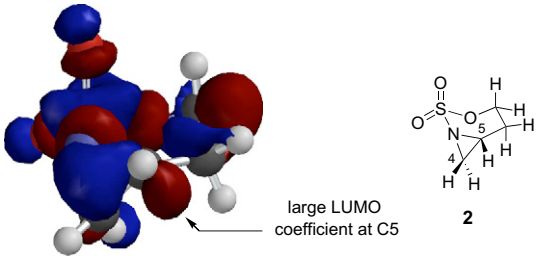


Figure 6. B3LYP/6-31G* calculated LUMO of unsubstituted bicyclic aziridine **2**.

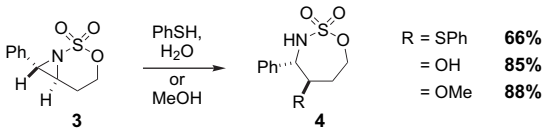


Figure 7. Ring opening occurs selectively with disparate nucleophiles.

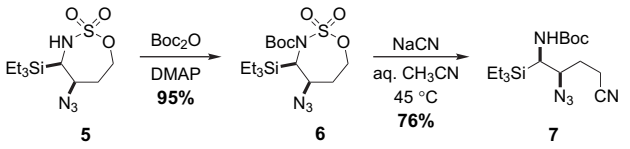
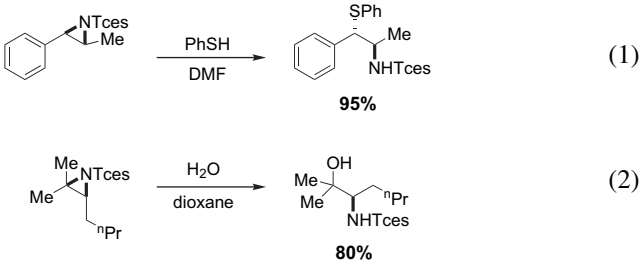


Figure 8. Activation and ring opening of seven-membered oxathiazepane.

opening. Nucleophiles such as PhSH, H_2O, NaN_3, and $BnNH_2$ do indeed react smoothly with these materials to give 1,2-difunctionalized amine products (Eqs. 1 and 2).[6] In the case of phenyl-substituted aziridines, a clear bias exists for opening at the benzylic position, and a single diastereomeric alkoxysulfonamide is formed. Similarly, trisubstituted aziridines are observed to open regioselectively and with absolute stereocontrol. As demonstrated previously, the trichloroethoxysulfonyl group may be removed from these products with a mild reducing agent such as Zn/Cu couple followed by acid treatment to cleave the sulfated amine. Consequently, this aziridination protocol should enjoy use in complex, multi-step synthesis due to the overall efficiency of the process (i.e., limiting amounts of alkene) and the ease by which the free amine can be liberated from the ring-opened product.



With the aim of employing an aziridination strategy in the context of a natural product synthesis, we required a direct method for converting *N*-alkoxysulfonyl aziridines to the corresponding α-aminoketones. Hiyama has shown that phenyl-substituted *N*-acylaziridines undergo oxidative ring opening in DMSO to give *N*-acyl-α-aminoketones, albeit at high temperatures (120 °C) and under long reaction times (Fig. 9).[20,21] In addition, application of this process typically leads to mixtures of regioisomeric products. Ring opening by the solvent followed by intramolecular deprotonation and elimination of Me_2S has been postulated as the mechanism for this transformation.

The ability of trichloroethoxysulfonyl aziridines to undergo facile displacement with common nucleophiles suggested that oxidative opening with DMSO would indeed be feasible (Fig. 10). Remarkably, the reaction of **8** in DMSO ensued with reasonable speed at 23 °C to give a single ketone product. As with other nucleophilic reactions of styrenyl-derived aziridines, DMSO addition is regioselective and furnishes

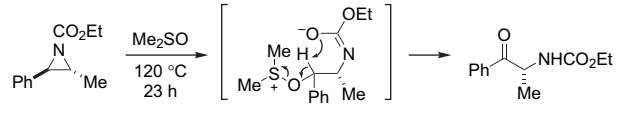
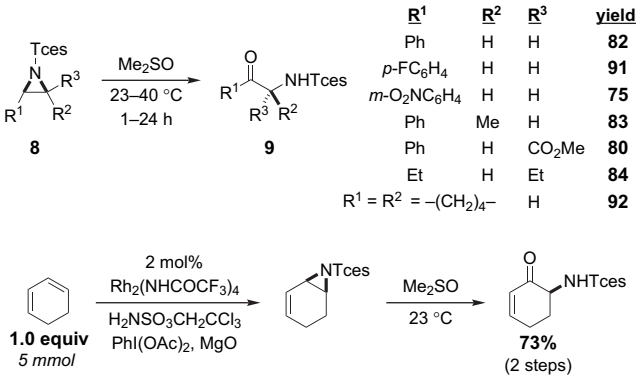


Figure 9. Hiyama's DMSO-promoted oxidative ring opening affords an α-aminoketone.[20]

the corresponding aryl ketones. Both aryl- and alkyl-substituted aziridines undergo smooth displacement by DMSO solvent at temperatures ranging from 23–40 °C. As no additional reagents are required to effect this reaction, the products may be easily obtained from a simple extractive work-up; yields in all cases exceed 75%. Taking advantage of this new protocol in combination with an effective aziridination method, we have found that 1,3-cyclohexadiene can be converted in a two-step sequence to a useful α-amino enone derivative. The intermediate vinylaziridine is generated quantitatively, but is unstable to both chromatography and crystallization. By simply stirring the unpurified aziridine in DMSO, the easily isolable, aminated product is obtained. Overall, the high performance of both reaction steps and low catalyst load (2 mol %) has enabled this transformation to be conducted with 5 mmol of cyclohexadiene, furnishing >1 g of crystalline aminoketone product.



R¹	R²	R³	yield
Ph	H	H	82
p-FC_6H_4	H	H	91
m-$O_2NC_6H_4$	H	H	75
Ph	Me	H	83
Ph	H	CO_2Me	80
Et	H	Et	84
$R^1 = R^2 = -(CH_2)_4-$		H	92

Figure 10. Tces-aziridines undergo facile ring opening with Me_2SO.

Selective oxidation of olefins to aziridines is a particularly appealing strategy for assembling functionally complex amines and amine derivatives. We have described a Rh-catalyzed process for effecting such chemistry in both intra- and intermolecular contexts. In the latter method, unparalleled efficiency with limiting amounts of the starting alkene is noted across a range of dissimilar substrates. When combined with the versatility of the alkoxysulfonylated azacycles for subsequent ring opening reactions, these processes should find great value in synthesis.

3. Experimental

3.1. General

All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Dichloromethane, benzene, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were dried by passage under 12 psi of N_2 through two columns containing activated alumina. In addition, DMSO was also stored over 3 Å molecular sieves. *N*,*N*-Dimethyl acetamide (DMA) was dried over 4 Å molecular

sieves and used without further purification. All other solvents (^{i}PrOH and C_6H_5Cl) were used as received from commercial suppliers. Chlorosulfonyl isocyanate was obtained from Acros Chemicals, transferred via cannula to a Schlenk flask, and stored at –20 °C. Triethylamine was distilled from CaH_2 prior to use. Light magnesium oxide was flame dried under reduced pressure (~15 Torr). (Diacetoxy)iodobenzene was recrystallized from $CHCl_3$ and dried in vacuo (~1 Torr). Chromatographic purification of products was accomplished using forced-flow chromatography on EM Science Geduran silica gel 60 (40–63 μm). Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution.

3.2. Instrumentation

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Mercury-400 operating at 400 and 100 MHz or a Varian Inova-500 operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; m, multiplet), integration, and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded on a Thermo-Nicolet IR300 spectrometer using NaCl salt plates and are reported in terms of frequency of absorption. High-resolution mass spectra were obtained from the Mass Spectrometry Facility, University of California at San Francisco, supported by the NIH Division of Research and Resources, the High-Resolution Mass Spectrometry Facility, University of California at Riverside, and the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University. Diffraction data were collected at the UC Berkeley CHEXRAY facility on Bruker-Siemens SMART and APEX diffractometers (λ=0.71073 Å, graphite monochromator). The structures were solved by direct methods (SIR-2002) and refined using Fourier techniques (SHELXL-97).

3.3. General procedures

3.3.1. Alcohol sulfamoylation. Formic acid (0.70 mL, 18 mmol, 1.5 equiv) was added dropwise to neat $ClSO_2NCO$ (1.6 mL, 18 mmol, 1.5 equiv) at 0 °C with rapid stirring. Vigorous gas evolution was observed during the addition process and within 5 min the mixture solidified. To the solid mass was then added 9.2 mL of CH_3CN, and the resulting solution was stirred for 1 h at 0 °C and 8 h at 23 °C. The reaction was cooled to 0 °C and a solution of the alcohol (12.3 mmol) and pyridine (1.1 mL, 13.5 mmol, 1.1 equiv) in DMA was added dropwise via cannula. After stirring for 3 h at 23 °C, the solution was diluted with 25 mL of Et_2O and transferred to a separatory funnel with 25 mL of H_2O. The ethereal layer was collected washed successively with 1×25 mL of H_2O and 1×25 mL of saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (conditions given below) afforded the desired sulfamate ester. Product yields range from 75–90%.

3.3.2. Intramolecular aziridination. To a solution of sulfamate (4.96 mmol) in 50 mL of CH_2Cl_2 were added sequentially MgO (460 mg, 11.4 mmol, 2.3 equiv) and 1–2 mol % $Rh_2(NHCOCF_3)_4$.[22] The mixture was cooled to 0 °C and a single portion of $PhI(OAc)_2$ (2.08 g, 6.45 mmol, 1.3 equiv) was added. The orange suspension was allowed to warm slowly to 23 °C over 2 h. After 6 h at 23 °C, during which time the colored mixture faded to a pale yellow, the reaction was filtered through a small pad of Celite. The flask and filter cake were washed thoroughly with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. Purification by chromatography on silica gel (conditions given below) afforded the desired bicyclic aziridine product.

3.3.3. Intermolecular aziridination. To a solution of $Cl_3CCH_2OSO_2NH_2$ (251 mg, 1.1 mmol, 1.1 equiv) in 2.0 mL of C_6H_5Cl were added sequentially olefin (1.0 mmol, 1.0 equiv), MgO (93 mg, 2.3 mmol, 2.3 equiv), and $Rh_2(NHCOCF_3)_4$ (6 mg, 10 μmol, 0.01 equiv).[22] The resulting purple mixture was cooled to −10 °C (s-CO_2/ethylene glycol bath) and a single portion of $PhI(OAc)_2$ (420 mg, 1.3 mmol, 1.3 equiv) was added. Immediately following the addition of $PhI(OAc)_2$, the suspension turned orange. This mixture was allowed to warm slowly to 23 °C over 3 h. After 5 h at 23 °C, during which time the colored mixture faded to pale yellow, the reaction was diluted with 10 mL of CH_2Cl_2 and filtered through a small pad of Celite. The flask and filter cake were washed thoroughly with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The isolated material was purified by chromatography on silica gel (conditions given below) to afford the desired aziridine.

3.4. Characterization data for substrates and products

3.4.1. Compounds from Table 1.

3.4.1.1. Entry 1, *trans*-styrenyl sulfamate. Purified by chromatography on silica gel (3:2 hexanes/EtOAc); white solid: TLC R_f=0.45 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 4H), 7.28–7.24 (m, 1H), 6.53 (d, 1H, J=16.0 Hz), 6.19 (dt, 1H, J=16.0, 7.0 Hz), 5.02 (br s, 2H), 4.32 (t, 2H, J=6.5 Hz), 2.68 (qd, 2H, J=6.5, 2.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.8, 133.3, 128.6, 127.5, 126.1, 124.0, 70.4, 32.4 ppm; IR (thin film) ν 3415, 3315, 1536, 1362, 1181, 933 cm^{-1}; HRMS (ES^{+}) calcd for $C_{10}H_{13}NO_3S$ 227.0616 found 250.0516 (MNa^{+}).

3.4.1.2. Entry 1, *trans*-phenyl aziridine. Reaction performed with 1 mol % $Rh_2(NHCOCF_3)_4$. Purified by chromatography on silica gel (90:10:1 CH_2Cl_2/EtOAc/Et_3N); white solid (72%): TLC R_f=0.42 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5H), 4.77 (ddd, 1H, J=12.5, 7.5, 6.0 Hz), 4.55 (ddd, 1H, J=12.5, 6.5, 6.5 Hz), 3.90 (d, 1H, J=4.0 Hz), 3.28 (ddd, 1H, J=6.5, 4.5, 2.5 Hz), 2.51 (dq, 1H, J=15.0, 6.0 Hz), 2.41 (dtd, 1H, J=17.0, 7.0, 2.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.1, 128.7 (2), 126.2, 68.9, 50.5, 47.6, 18.7 ppm; IR (thin film) ν 1366, 1186, 1051, 878, 783 cm^{-1}; HRMS (ES^{+}) calcd for $C_{10}H_{11}NO_3S$ 225.0460 found 248.0352 (MNa^{+}).

3.4.1.3. Entry 2, *cis*-triphenylsilyl sulfamate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc); white solid: TLC R_f=0.32 (7:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.57 (m, 6H), 7.45–7.36 (m, 9H), 6.69 (dt, 1H, J=14.4, 7.2 Hz), 6.21 (dt, 1H, J=14.0, 1.4 Hz), 4.52 (br s, 2H), 3.96 (t, 2H, J=6.6 Hz), 2.36 (qd, 2H, J=6.8, 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.4, 135.7, 134.8, 129.6, 128.0, 127.9, 69.7, 33.3 ppm; IR (thin film) ν 3391, 3291, 3067, 1607, 1427, 1365, 1182, 1109, 928, 700 cm^{-1}; HRMS (ES^-) calcd for $C_{22}H_{23}NO_3SSi$ 409.1168 found 408.1102 (M^+-H).

3.4.1.4. Entry 2, *cis*-triphenylsilyl aziridine. Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$. Purified by chromatography on silica gel (7:3 hexanes/EtOAc); white solid (83%): TLC R_f=0.13 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.67 (m, 6H), 7.35–7.18 (m, 9H), 4.51 (td, 1H, J=11.6, 4.4 Hz), 3.72 (ddd, 1H, J=8.4, 6.8, 4.0 Hz), 3.64 (ddd, 1H, J=11.6, 7.0, 2.0 Hz), 2.88 (d, 1H, J=6.8 Hz), 2.39–2.28 (m, 1H), 2.13–2.05 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.2, 132.2, 130.1, 127.8, 69.4, 43.6, 37.0, 18.7 ppm; IR (thin film) ν 3070, 3050, 3014, 1428, 1370, 1182, 1110, 1049, 973, 895, 796 cm^{-1}; HRMS (ES^-) calcd for $C_{22}H_{21}NO_3SSi$ 407.1011 found 406.0938 (M^+-H).

3.4.1.5. Entry 2, *cis*-diethoxyphosphoryl sulfamate. Purified by chromatography on silica gel (98:2 Et_2O/MeOH); colorless oil: TLC R_f=0.34 (97:3 Et_2O/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (ddt, 1H, J_{HP}=52.2 Hz, J_{HH}=13.0, 3.8 Hz), 5.92 (br s, 2H), 5.76 (ddt, 1H, J_{HP}=18.0 Hz, J_{HH}=12.8, 1.2 Hz), 4.31 (t, 2H, J=6.2 Hz), 4.08 (dq, 4H, J_{HP}=7.2 Hz, J_{HH}=7.2 Hz), 3.04–2.97 (m, 2H), 1.32 (t, 6H, J=7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.0 (d, J_{CP}=3.8 Hz), 119.9 (d, J_{CP}=182.0 Hz), 68.8 (d, J_{CP}=3.0 Hz), 62.0 (d, J_{CP}=5.4 Hz), 30.1 (d, J_{CP}=8.4 Hz), 16.3 (d, J_{CP}=6.8 Hz) ppm; IR (thin film) ν 3337, 2985, 1629, 1574, 1367, 1226, 1178, 1021, 968, 775 cm^{-1}; HRMS (ES^+) calcd for $C_8H_{18}NO_6PS$ 287.0592 found 310.0478 (MNa^+).

3.4.1.6. Entry 2, *cis*-diethoxyphosphoryl aziridine. Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$. Purified by chromatography on silica gel (24:1 Et_2O/MeOH); colorless oil (62%): TLC R_f=0.21 (24:1 Et_2O/MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.80 (ddd, 1H, J=11.6, 10.6, 4.6 Hz), 4.70 (ddd, 1H, J=11.6, 7.0, 3.2 Hz), 4.35–4.25 (m, 2H), 4.18 (dq, 2H, J=8.0, 7.2 Hz), 3.47 (dtd, 1H, J=8.0, 6.4, 4.0 Hz), 2.89–2.79 (m, 1H), 2.74 (t, 1H, J=5.8 Hz), 2.17 (dddd, 1H, J=14.8, 8.2, 4.6, 3.2 Hz), 1.39–1.33 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.6, 64.4 (d, J_{CP}=6.1 Hz), 62.4 (d, J_{CP}=6.8 Hz), 43.0, 38.8 (d, J_{CP}=184.3 Hz), 16.4 (d, J_{CP}=6.1 Hz), 16.3 (d, J_{CP}=6.0 Hz), 16.2 (d, J_{CP}=3.0 Hz) ppm; IR (thin film) ν 2986, 2915, 1376, 1256, 1187, 1053, 1025, 937, 804 cm^{-1}; HRMS (ES^-) calcd for $C_8H_{16}NO_6PS$ 285.0436 found 284.0349 (M^+-H).

3.4.2. Compounds from Table 2.

3.4.2.1. Entry 1, pentenyl sulfamate. Purified by chromatography on silica gel (3:1 hexanes/EtOAc); colorless oil: TLC R_f=0.30 (7:3 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79 (ddt, 1H, J=16.4, 10.8, 7.2 Hz), 5.18–5.15 (m, 1H), 5.13 (t, 1H, J=1.2 Hz), 4.98 (br s, 2H), 4.73 (sext, 1H, J=6.2 Hz), 2.48 (dddt, 1H, J=14.4, 7.2, 6.0, 1.2 Hz), 2.41 (dddt, 1H, J=14.4, 7.2, 6.0, 1.2 Hz), 1.41 (d, 3H, J=6.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.5, 118.9, 80.3, 40.7, 20.1 ppm; IR (thin film) ν 3378, 3289, 3082, 2982, 2938, 1644, 1558, 1359, 1181, 918 cm^{-1}; HRMS (ES^+) calcd for $C_5H_{11}NO_3S$ 165.0460 found 183.0800 (MNH_4^+).

3.4.2.2. Entry 1, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Purified by chromatography on silica gel (1:1 hexanes/EtOAc); white solid (84%, 4:1 ds). *Major diastereomer*: TLC R_f=0.28 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.07 (dqd, 1H, J=11.0, 6.5, 4.5 Hz), 3.19 (dddd, 1H, J=5.0, 3.2 Hz), 2.57 (dd, 1H, J=5.4, 0.6 Hz), 2.43–2.40 (m, 1H), 2.30 (ddd, 1H, J=14.4, 8.2, 4.6 Hz), 1.93 (ddd, 1H, J=14.4, 10.8, 3.2 Hz), 1.42 (d, 3H, J=6.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.6, 40.8, 35.8, 26.3, 21.3 ppm; IR (thin film) ν 2988, 2931, 1366, 1187, 971, 863, 798 cm^{-1}; HRMS (ES^+) calcd for $C_5H_9NO_3S$ 163.0303 found 181.0653 (MNH_4^+). *Minor diastereomer*: TLC R_f=0.21 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59 (dqd, 1H, J=11.4, 6.2, 4.3 Hz), 3.13 (dddd, 1H, J=5.2, 1.5 Hz), 2.86 (dd, 1H, J=5.0, 1.8 Hz), 2.61 (ddd, 1H, J=5.4, 2.0, 0.6 Hz), 2.43 (ddd, 1H, J=15.4, 11.4, 4.0 Hz), 2.29 (ddd, 1H, J=15.4, 4.2, 1.6 Hz), 1.46 (d, 3H, J=6.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.2, 40.9, 32.8, 26.1, 21.4 ppm; IR (thin film) ν 2923, 2851, 1361, 1184, 1023, 870, 800 cm^{-1}.

3.4.2.3. Entry 2, ethylpentenoate sulfamate. Purified by chromatography on silica gel (97:3 CH_2Cl_2/EtOAc); colorless oil: TLC R_f=0.22 (97:3 CH_2Cl_2/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.49 (br s, 2H), 5.01 (t, 1H, J=6.5 Hz), 4.87 (s, 1H), 4.81 (s, 1H), 4.22 (q, 2H, J=7.1 Hz), 2.57 (d, 2H, J=6.7 Hz), 1.76 (s, 3H), 1.27 (t, 3H, J=7.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 138.9, 115.0, 77.5, 62.2, 40.0, 22.1, 14.0 ppm; IR (thin film) ν 3374, 3280, 3082, 2984, 1741, 1654, 1560, 1376, 1186, 1054, 929, 781 cm^{-1}; HRMS (EI) calcd for $C_8H_{15}NO_5S$ 237.0671 found 237.0676 (M^+).

3.4.2.4. Entry 2, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Purified by chromatography on silica gel (7:3 hexanes/EtOAc); white solid (92%, 4:1). *Major diastereomer*: TLC R_f=0.46 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.14 (t, 1H, J=7.4 Hz), 4.26 (q, 2H, J=7.1 Hz), 2.76 (s, 1H), 2.48 (dd, 1H, J=15.0, 7.0 Hz), 2.41 (dd, 1H, J=15.1, 8.0 Hz), 2.38 (s, 1H), 1.47 (s, 3H), 1.29 (t, 3H, J=7.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 76.0, 62.7, 48.2, 41.3, 25.9, 25.2, 14.0 ppm; IR (thin film) ν 2985, 1755, 1446, 1379, 1302, 1191, 1085, 1026, 946, 892, 830 cm^{-1}; HRMS (EI) calcd for $C_8H_{13}NO_5S$ 235.0514 found 235.0546 (M^+). *Minor diastereomer*: TLC R_f=0.29 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84 (dd, 1H, J=10.8, 6.4 Hz), 4.28 (q, 2H, J=7.1 Hz), 2.95 (d, 1H, J=2.1 Hz), 2.65–2.48 (m, 3H), 1.46 (s, 3H), 1.29 (t, 3H, J=7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 74.2, 62.6, 47.6, 39.2, 26.2, 24.4, 14.0 ppm; IR (thin film) ν 2985, 1758, 1371, 1306, 1185, 1076, 1029, 890, 784 cm^{-1}; HRMS (EI) calcd for $C_8H_{13}NO_5S$ 235.0514 found 235.0518 (M^+).

3.4.2.5. Entry 3, pentenylsilane sulfamate. Purified by chromatography on silica gel (13% EtOAc/hexanes); white solid: TLC R_f=0.40 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (dt, 1H, J=14.5, 7.0 Hz), 5.74 (d, 1H, J=14.0 Hz), 4.97 (br s, 2H), 4.69 (ddd, 1H, J=12.8, 6.3, 4.5 Hz), 3.85–3.80 (m, 2H), 2.61–2.50 (m, 2H), 0.93 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.2, 133.8, 84.3, 65.2, 34.9, 25.8, 18.3, 0.1, −5.4, −5.5 ppm; IR (thin film) ν 3368, 3290, 2955, 2931, 2858, 1609, 1363, 1251, 1186, 1128, 933, 837, 779 cm^{-1}; HRMS (ES$^-$) calcd for $C_{14}H_{33}NO_4SSi_2$ 367.1669 found 366.1591 (M^+−H).

3.4.2.6. Entry 3, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Reaction performed with 2 mol % $Rh_2(oct)_4$. Purified by chromatography on silica gel (13% EtOAc/hexanes); white solid (69%, 15:1 ds): TLC R_f=0.33 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.88 (ddt, 1H, J=9.8, 5.4, 4.4 Hz), 3.79 (dd, 1H, J=11.4, 4.2 Hz), 3.75 (dd, 1H, J=11.6, 4.0 Hz), 3.46 (q, 1H, J=6.8 Hz), 2.18–2.10 (m, 2H), 1.95 (d, 1H, J=7.2 Hz), 0.89 (s, 9H), 0.27 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.2, 64.1, 43.7, 40.3, 25.8, 21.6, 18.3, −0.8, −5.4, −5.5 ppm; IR (thin film) ν 2950, 2929, 2858, 1360, 1256, 1174, 972, 843, 776 cm^{-1}.

3.4.2.7. Entry 4, *tert*-butyl ester sulfamate. Purified by chromatography on silica gel (5:14:1 hexanes/CH_2Cl_2/Et_2O); colorless oil: TLC R_f=0.25 (5:14:1 hexanes/CH_2Cl_2/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.06 (dd, 1H, J=11.6, 3.6 Hz), 5.80 (dd, 1H, J=11.6, 1.6 Hz), 5.56 (dddd, 1H, J=7.6, 6.0, 3.6, 1.6 Hz), 5.03 (br s, 2H), 4.28 (dd, 1H, J=11.0, 3.6 Hz), 4.19 (dd, 1H, J=10.8, 6.0 Hz), 1.48 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 146.3, 123.0, 81.5, 73.8, 67.7, 28.0, 25.7, 18.1, −4.8, −4.9 ppm; IR (thin film) ν 3369, 3284, 2955, 2931, 2858, 1710, 1369, 1254, 1186, 1113, 1001, 836 cm^{-1}; HRMS (ES$^+$) calcd for $C_{15}H_{31}NO_6SSi$ 381.1641 found 404.1539 (MNa^+).

3.4.2.8. Entry 4, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Purified by chromatography on silica gel (7% EtOAc/hexanes); white solid (87%, 20:1 ds): TLC R_f=0.20 (19:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82–4.77 (m, 1H), 4.58 (dd, 1H, J=11.4, 9.0 Hz), 4.41 (dd, 1H, J=11.4, 6.6 Hz), 3.25–3.21 (m, 2H), 1.51 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 84.4, 73.6, 56.1, 50.9, 42.2, 27.7, 25.5, 17.9, −4.9, −5.0 ppm; IR (thin film) ν 2955, 2859, 1737, 1385, 1257, 1192, 1111, 995, 842, 788 cm^{-1}; HRMS (ES$^+$) calcd for $C_{15}H_{29}NO_6SSi$ 379.1485 found 402.1363 (MNa^+).

3.4.2.9. Entry 5, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Purified by chromatography on silica gel (11:9 hexanes/EtOAc); white solid (82%, 20:1 ds): TLC R_f=0.16 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.30 (d, 1H, J=2.7 Hz), 4.78 (d, 1H, J=7.3 Hz), 4.73 (d, 1H, J=7.3 Hz), 4.39 (d, 1H, J=2.8 Hz), 3.83 (s, 3H), 3.68–3.60 (m, 2H), 3.60–3.48 (m, 2H), 3.37 (s, 3H), 2.88 (s, 1H), 2.42 (s, 1H), 1.64 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 95.0, 79.9, 71.3, 69.5, 68.0, 59.0, 54.6, 53.1, 38.6, 24.0 ppm; IR (thin film) ν 2933, 1773, 1387, 1196, 1024, 828, 690 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{19}NO_8S$ 325.0831 found 250.0389 (M^+−O(CH_2)OCH_3).

3.4.2.10. Entry 6, dioxasilylcycloheptene sulfamate. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid: TLC R_f=0.22 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79–5.72 (m, 1H), 5.61 (ddt, 1H, J=12.0, 3.6, 1.8 Hz), 5.12–5.08 (m, 1H), 4.84 (br s, 2H), 4.71 (dq, 1H, J=17.2, 2.8 Hz), 4.51 (ddt, 1H, J=17.2, 4.0, 2.0 Hz), 4.24 (dd, 1H, J=10.2, 5.8 Hz), 4.21 (dd, 1H, J=9.8, 5.0 Hz), 1.04 (s, 9H), 1.03 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.1, 128.0, 73.9, 69.4, 64.2, 27.7, 21.3, 21.0 ppm; IR (thin film) ν 3370, 3291, 2935, 2859, 1560, 1473, 1364, 1185, 1116, 1000, 826 cm^{-1}; HRMS (ES$^-$) calcd for $C_{13}H_{27}NO_5SSi$ 337.1379 found 336.1301 (M^+−H).

3.4.2.11. Entry 6, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(oct)_4$ at 23 °C. Purified by chromatography on silica gel (15% EtOAc/hexanes); white solid (61%, 20:1 ds): TLC R_f=0.42 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92–4.86 (m, 2H), 4.55 (dd, 1H, J=12.8, 1.6 Hz), 4.47 (dd, 1H, J=12.0, 10.8 Hz), 4.37 (dd, 1H, J=12.2, 6.2 Hz), 3.56 (t, 1H, J=6.4 Hz), 3.21 (dt, 1H, J=10.6, 6.2 Hz), 1.06 (s, 9H), 1.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 77.8, 63.2, 58.9, 48.3, 45.3, 27.2, 27.0, 21.4, 20.8 ppm; IR (thin film) ν 2930, 2858, 1472, 1371, 1257, 1182, 1063, 1010, 900, 787 cm^{-1}; HRMS (ES$^-$) calcd for $C_{13}H_{25}NO_5SSi$ 335.1223 found 358.1119 (M^+−H).

3.4.2.12. Entry 7, bicyclic aziridine. Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$ at 23 °C. Purified by chromatography on silica gel (9:1 hexanes/Et_2O); white solid (66%, 10:1 ds): TLC R_f=0.48 (4:1 hexanes/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (td, 1H, J=12.2, 1.8 Hz), 4.33 (ddd, 1H, J=12.2, 4.0, 3.0 Hz), 4.18 (ddd, 1H, J=10.2, 8.4, 2.4 Hz), 2.80 (dd, 1H, J=8.8, 3.2 Hz), 2.30 (d, 1H, J=7.2 Hz), 2.31–2.22 (m, 1H), 1.97 (dq, 1H, J=14.8, 2.2 Hz), 0.89 (s, 9H), 0.29 (s, 9H), 0.11 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.5, 69.2, 49.1, 43.9, 38.7, 25.6, 17.8, −0.7, −3.6, −3.9 ppm; IR (thin film) ν 2953, 2931, 2857, 1355, 1253, 1165, 1105, 954, 837 cm^{-1}; HRMS (ES$^-$) calcd for $C_{14}H_{31}NO_4SSi_2$ 365.1512 found 364.1432 (M^+−H).

3.4.3. Products from Table 3.

3.4.3.1. Entry 3, *p*-fluorophenyl aziridine. Purified by chromatography on silica gel (9:1 hexanes/EtOAc); white solid (91%): TLC R_f=0.52 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.28 (m, 2H), 7.12–7.07 (m, 2H), 4.89 (d, 1H, J=11.0 Hz), 4.83 (d, 1H, J=11.0 Hz), 3.88 (dd, 1H, J=7.0, 4.5 Hz), 3.11 (d, 1H, J=7.5 Hz), 2.62 (d, 1H, J=4.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.2 (d, J_{CF}=248.8 Hz), 129.9 (d, J_{CF}=3.1 Hz), 128.6 (d, J_{CF}=8.0 Hz), 116.2 (d, J_{CF}=22.1 Hz), 93.0, 79.9, 42.4, 37.8 ppm; IR (thin film) ν 1515, 1382, 1182, 1011, 841, 784 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_9Cl_3FNO_3S$ 346.9353 found 346.9353 (MNa^+).

3.4.3.2. Entry 5, 2,6-dichlorophenyl aziridine. Purified by chromatography on silica gel (9:1 hexanes/EtOAc);

white solid (40%): TLC R_f=0.51 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.35 (m, 2H), 7.28 (dd, 1H, J=7.0, 8.5 Hz), 4.94 (d, 1H, J=11.0 Hz), 4.90 (d, 1H, J=11.0 Hz), 4.02 (dd, 1H, J=7.5, 5.0 Hz), 3.26 (dd, 1H, J=7.5, 1.0 Hz), 2.84 (dd, 1H, J=5.0, 1.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.2, 130.4, 129.5, 128.8, 92.9, 79.7, 41.3, 36.7 ppm; IR (thin film) ν 1433, 1385, 1184, 1011, 781 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_8Cl_5NO_3S$ 396.8667 found 419.8576 (MNa^+).

3.4.3.3. Entry 6, carvone aziridine. Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (85%, 1:1 ds): TLC R_f=0.21 (3:1 hexanes/EtOAc). Higher R_f diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.75 (d, 1H, J=6.0 Hz), 4.78 (s, 2H), 2.72 (s, 1H), 2.58–2.49 (m, 1H), 2.49 (s, 1H), 2.42 (dt, 1H, J=18.5, 5.0 Hz), 2.36–2.27 (m, 2H), 2.11–2.03 (m, 1H), 1.78 (s, 3H), 1.62 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 143.6, 135.7, 93.0, 79.4, 50.9, 42.5, 41.9, 40.1, 27.7, 15.6, 14.8 ppm; IR (thin film) ν 1672, 1366, 1179, 1012, 853, 781 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{16}Cl_3NO_4S$ 374.9866 found 397.9758 (MNa^+).

3.4.3.4. Entry 7, citronellol aziridine. Purified by chromatography on silica gel (9:1 CH_2Cl_2/EtOAc); colorless oil (70%, 1:1 ds): TLC R_f=0.33 (9:1 CH_2Cl_2/EtOAc). Data reported for the mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.77–4.70 (m, 4H), 3.72–3.60 (m, 4H), 2.84–2.82 (m, 2H), 1.62 (s, 6H), 1.66–1.24 (m, 14H), 1.32 (s, 6H), 0.90 (d, 3H, J=6.4 Hz), 0.89 (d, 3H, J=6.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 93.14, 93.13, 79.1, 60.64, 60.57, 55.02, 54.90, 51.9, 51.7, 39.45, 39.39, 34.1, 34.0, 29.1, 28.9, 25.2, 25.1, 21.0, 20.5, 20.4, 19.4 ppm; IR (thin film) ν 3315, 1364, 1177, 1016, 868, 777 cm^{-1}; HRMS (ES$^+$) calcd for $C_{12}H_{22}Cl_3NO_4S$ 381.0335 found 404.0248 (MNa^+).

3.4.3.5. Entry 9, cyclohexene aziridine. Purified by chromatography on silica gel (10:1 hexanes/EtOAc); white solid (15%): TLC R_f=0.61 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.80 (s, 2H), 3.14–3.09 (m, 2H), 2.02–1.84 (m, 4H), 1.51–1.39 (m, 2H), 1.35–1.24 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 93.1, 79.3, 42.0, 22.6, 19.2 ppm; IR (thin film) ν 2943, 1367, 1181, 1016, 784 cm^{-1}; HRMS (ES$^+$) calcd for $C_8H_{12}Cl_3NO_3S$ 306.9603 found 329.9506 (MNa^+).

3.4.3.6. Entry 9, cyclohexenyl amine. Purified by chromatography on silica gel (10:1 hexanes/EtOAc); white solid (15%): TLC R_f=0.54 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93 (dtd, 1H, J=10.0, 3.6, 1.6 Hz), 5.72 (ddt, 1H, J=10.0, 4.4, 2.4 Hz), 4.70 (br d, 1H, J=8.0 Hz), 4.63 (s, 2H), 4.14–4.06 (m, 1H), 2.10–1.94 (m, 3H), 1.80–1.60 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.7, 126.0, 93.4, 78.1, 50.4, 29.7, 24.5, 19.1 ppm; IR (thin film) ν 3304, 2945, 1431, 1364, 1183, 855 cm^{-1}; HRMS (ES$^+$) calcd for $C_8H_{12}Cl_3NO_3S$ 306.9603 found 329.9503 (MNa^+).

3.4.4. Experimental protocols from Figures 3, 4, 7, and 8.

3.4.4.1. β-1,3,4,6-Tetraacetyl-2-*N*-trichloroethoxysulfonyl glucosamine. Reaction performed with 2 mol % $Rh_2(NHCOCF_3)_4$ at 1.0 M substrate concentration. Purified by chromatography on silica gel (2:1 hexanes/EtOAc); white solid (91%): TLC R_f=0.43 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.19 (d, 1H, J=9.5 Hz), 5.71 (d, 1H, J=8.5 Hz), 5.21 (t, 1H, J=9.5 Hz), 5.07 (t, 1H, J=10.0 Hz), 4.62 (d, 1H, J=11.5 Hz), 4.58 (d, 1H, J=11.0 Hz), 4.26 (dd, 1H, J=12.5, 4.5 Hz), 4.09 (dd, 1H, J=12.5, 2.0 Hz), 3.88 (ddd, 1H, J=10.0, 4.5, 2.0 Hz), 3.76 (q, 1H, J=9.5 Hz), 2.19 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 170.7, 169.7, 169.4, 93.2, 91.9, 78.5, 72.5, 72.4, 67.9, 61.4, 57.8, 21.0, 20.8, 20.7, 20.5 ppm; IR (thin film) ν 3262, 1755, 1369, 1218, 1079, 1043 cm^{-1}; HRMS (ES$^+$) calcd for $C_{16}H_{22}Cl_3NO_{12}S$ 556.9928 found 579.9823 (MNa^+).

3.4.4.2. *trans*-5-Azido-4-phenyl-[1,2,3]-oxathiazepane-2,2-dioxide. To a solution of 7-phenyl-3-oxa-2-thia-1-azabicyclo[4.1.0]heptane-2,2-dioxide (53 mg, 0.25 mmol) in 1.25 mL of DMF was added NaN_3 (20 mg, 0.31 mmol, 1.2 equiv). The solution was stirred for 35 min then transferred to a separatory funnel containing 10 mL of EtOAc and 10 mL of H_2O. The organic phase was collected and washed with an additional 1×10 mL of H_2O. The aqueous portions were combined and extracted with 1×10 mL of EtOAc. The collective organic extracts were washed with 1×10 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (2:1 hexanes/EtOAc) afforded the desired product as a white solid (47 mg, 70%): TLC R_f=0.57 (1:1 hexanes/EtOAc); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.45–7.35 (m, 5H), 6.57 (br s, 1H), 4.46–4.34 (m, 2H), 4.24 (d, 1H, J=10.5 Hz), 3.99 (td, 1H, J=10.5, 4.5 Hz), 2.41 (dtd, 1H, J=15.5, 4.5, 1.0 Hz), 2.17–2.10 (m, 1H); ^{13}C NMR (CD_3CN, 125 MHz) δ 139.2, 129.8, 129.4, 128.3, 68.1, 64.5, 61.2, 35.3 ppm; IR (thin film) ν 3284, 2104, 1338, 1174, 758 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_{12}N_4O_3S$ 268.0630 found 291.0526 (MNa^+).

3.4.4.3. 4-Phenyl-5-(phenylthio)-[1,2,3]-oxathiazepane-2,2-dioxide. To a solution of aziridine **3** (53 mg, 0.25 mmol) in 2.5 mL of DMF was added neat PhSH (27 μL, 0.26 mmol, 1.05 equiv). The solution was stirred for 2 h then transferred to a separatory funnel with 10 mL of EtOAc and 10 mL of H_2O. The organic layer was collected and washed with 1×10 mL of H_2O. The aqueous layers were combined and extracted with 1×10 mL of EtOAc. The collective organic fractions were then washed with 1×10 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (3:1 hexanes/EtOAc) furnished the desired product as a white solid (55 mg, 66%): TLC R_f=0.70 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.29 (m, 5H), 7.25–7.19 (m, 3H), 7.18–7.14 (m, 2H), 5.30 (br d, 1H, J=8.5 Hz), 4.47–4.34 (m, 3H), 3.71 (td, 1H, J=10.5, 4.0 Hz), 2.46 (dt, 1H, J=16.0, 4.0 Hz), 2.39–2.30 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 133.5, 132.5, 129.1, 129.0, 128.7, 128.1, 127.2, 69.2, 61.4, 52.7, 36.2 ppm; IR (thin film) ν 3284, 1346, 1178, 944, 752 cm^{-1}; HRMS (ES$^+$) calcd for $C_{16}H_{17}NO_3S_2$ 335.0650 found 358.0547 (MNa^+).

3.4.4.4. 5-Hydroxy-4-phenyl-[1,2,3]-oxathiazepane-2,2-dioxide. To a solution of aziridine **3** (53 mg, 0.25 mmol)

in 1.67 mL of DMF was added 0.8 mL of H_2O. The solution was stirred for 60 h then all volatiles were removed in vacuo (~1 Torr). Purification of the solid residue by chromatography on silica gel (3:2 EtOAc/hexanes) afforded the desired product as a white solid (52 mg, 85%): TLC R_f=0.14 (1:1 hexanes/EtOAc); ^{1}H NMR (CH_3CN, 500 MHz) δ 7.44–7.33 (m, 5H), 6.40 (br d, 1H, J=10.4 Hz), 4.46–4.30 (m, 2H), 4.13 (t, 1H, J=10.4 Hz), 4.00 (dddd, 1H, J=9.6, 9.6, 5.2, 5.2 Hz), 3.01 (d, 1H, J=5.6 Hz), 2.32 (dtd, 1H, J=15.2, 4.4, 1.2 Hz), 2.14–2.02 (m, 1H) ppm; ^{13}C NMR (CD_3CN, 125 MHz) δ 140.0, 129.4, 128.7, 128.5, 72.8, 68.2, 62.8, 38.3 ppm; IR (thin film) ν 3456, 3279, 1341, 1177, 1051, 759 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_{13}NO_4S$ 243.0565 found 266.0471 (MNa^+).

3.4.4.5. 5-Methoxy-4-phenyl-[1,2,3]-oxathiazepane-2,2-dioxide. To a solution of aziridine **3** (53 mg, 0.25 mmol) in 2.5 mL of MeOH was added *p*-toluenesulfonic acid monohydrate (2 mg, 10 μmol, 0.04 equiv). The contents were stirred for 5 h, transferred to a separatory funnel with 10 mL of EtOAc, and washed with 2×10 mL of H_2O. The aqueous layers were combined and extracted with 1×10 mL of EtOAc. The collective organic fractions were washed with 1×10 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (3:1 hexanes/EtOAc) gave the desired product as a white solid (46 mg, 72%): TLC R_f=0.70 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45–7.40 (m, 2H), 7.39–7.34 (m, 1H), 7.33–7.28 (m, 2H), 4.72 (d, 1H, J=11.0 Hz), 4.55 (td, 1H, J=11.5, 2.5 Hz), 4.49 (ddd, 1H, J=11.5, 5.5, 1.5 Hz), 4.46 (d, 1H, J=3.0 Hz), 3.87 (tt, 1H, J=11.0, 3.0 Hz), 3.38 (s, 3H), 2.11–2.01 (m, 1H), 1.33–1.27 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.3, 128.8, 128.4, 126.4, 83.3, 71.7, 60.3, 57.7, 22.1 ppm; IR (thin film) ν 3255, 1410, 1359, 1190, 780 cm^{-1}; HRMS (ES$^+$) calcd for $C_{11}H_{15}NO_4S$ 257.0722 found 280.0622 (MNa^+).

3.4.4.6. *N*-(*tert*-Butoxycarbonyl)-2-azido-4-cyano-1-triethylsilylbutanamine. To a solution of *N*-Boc oxathiazepane (800 mg, 1.96 mmol) in 14 mL of CH_3CN was added an aqueous solution of NaCN (193 mg, 3.92 mmol, 2.0 equiv) in 6 mL of H_2O. The flask was sealed and the contents heated at 45 °C for 36 h. The reaction mixture was cooled to 23 °C and poured into a separatory funnel containing 50 mL of H_2O and 5 mL of aqueous 1 M HCl (*note*: appropriate caution must be taken when working up the reaction as HCN is generated). The aqueous layer was extracted with 4×25 mL of EtOAc. The combined organic extracts were washed with 1×30 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the solid residue by chromatography on silica gel (14:1 hexanes/EtOAc) gave the desired product as a white solid (530 mg, 76%). TLC R_f=0.32 (7:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.46 (br d, 1H, J=10.4 Hz), 3.60 (td, 1H, J=7.2, 1.7 Hz), 3.40 (dd, 1H, J=10.4, 2.0 Hz), 2.65 (dt, 1H, J=17.2, 7.4 Hz), 2.58 (dt, 1H, J=17.2, 6.6 Hz), 2.04–1.88 (m, 2H), 1.42 (s, 9H), 0.99 (t, 9H, J=7.8 Hz), 0.67 (q, 6H, J=7.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 118.7, 79.8, 62.8, 40.7, 28.2, 27.0, 14.2, 7.3, 2.4 ppm; IR (thin film) ν 2957, 2878, 2100, 1703, 1494, 1366, 1243, 1167, 1011 cm^{-1}; HRMS (ES$^+$) calcd for $C_{16}H_{31}N_5O_2Si$ 353.2247 found 376.2148 (MNa^+).

3.5. General protocol for oxidative ring opening of Tces-aziridines

Aziridine (0.25 mmol) was dissolved in DMSO and stirred until TLC analysis indicated the complete consumption of starting material (1–24 h). The solution was transferred to a separatory funnel with 10 mL of EtOAc and washed with 2×10 mL of H_2O. The aqueous layers were combined and extracted with 1×10 mL of EtOAc. The collective organic fractions were then washed with 1×10 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (as indicated below) furnished the desired ketone.

3.5.1. Characterization data for products from Figure 10.

3.5.1.1. (2-Oxo-2-phenylethyl)sulfamic acid 2,2,2-trichloroethyl ester. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (82%): TLC R_f=0.23 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (dd, 2H, J=6.4, 1.5 Hz), 7.67 (tt, 1H, J=7.2, 1.2 Hz), 7.55–7.50 (m, 2H), 6.05 (br t, 1H, J=4.4 Hz), 4.72 (d, 2H, J=4.4 Hz), 4.67 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.0, 134.8, 133.4, 129.2, 128.0, 93.2, 78.3, 49.2 ppm; IR (thin film) ν 3285, 1694, 1371, 1183, 857 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_{10}Cl_3NO_4S$ 344.9396 found 367.9292 (MNa^+).

3.5.1.2. [2-(4-Fluorophenyl)-2-oxo-ethyl]sulfamic acid 2,2,2-trichloroethyl ester. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (91%): TLC R_f=0.31 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02–7.96 (m, 2H), 7.24–7.18 (m, 2H), 5.99 (t, 1H, J=4.0 Hz), 4.69 (d, 2H, J=4.4 Hz), 4.67 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.5, 166.6 (d, J_{CF}=258.7 Hz), 130.8 (d, J_{CF}=10.0 Hz), 129.9 (d, J_{CF}=3.0 Hz), 116.5 (d, J_{CF}=22.1 Hz), 93.2, 78.4, 49.1 ppm; IR (thin film) ν 3270, 1687, 1597, 1408, 1236, 1181, 861 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_9Cl_3FNO_4S$ 362.9302 found 385.9196 (MNa^+).

3.5.1.3. [2-(3-Nitrophenyl)-2-oxo-ethyl]sulfamic acid 2,2,2-trichloroethyl ester. Reaction performed at 0.1 M in olefin substrate. Purified by chromatography on silica gel (2:1 hexanes/EtOAc); yellow solid (75%): TLC R_f=0.22 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.78 (t, 1H, J=2.0 Hz), 8.53 (ddd, 1H, J=8.0, 2.0, 1.0 Hz), 8.28 (ddd, 1H, J=7.5, 2.5, 1.5 Hz), 7.78 (t, 1H, J=7.5 Hz), 5.90 (t, 1H, J=4.5 Hz), 4.78 (d, 2H, J=4.5 Hz), 4.70 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.4, 148.6, 134.6, 133.4, 130.6, 128.9, 122.9, 93.2, 78.5, 49.6 ppm; IR (thin film) ν 3303, 1705, 1534, 1353, 1183, 1086, 858 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_9Cl_3N_2O_6S$ 389.9247 found 412.9153 (MNa^+).

3.5.1.4. (1-Methyl-2-oxo-2-phenylethyl)sulfamic acid 2,2,2-trichloroethyl ester. Reaction performed at 40 °C. Purified by chromatography on silica gel (5:1 hexanes/EtOAc); white solid (83%): TLC R_f=0.24 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97–7.94 (m, 2H), 7.64 (tt, 1H, J=6.8, 1.2 Hz), 7.54–7.49 (m, 2H), 6.27 (br d, 1H, J=7.6 Hz), 5.20 (quint, 1H, J=7.2 Hz), 4.68 (d, 1H, J=10.8 Hz), 4.54 (d, 1H, J=10.8 Hz), 1.55 (d, 3H, J=7.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.5, 134.5, 132.9, 129.1, 128.8, 93.1, 78.1, 54.4, 20.5 ppm; IR (thin film) ν

3290, 1687, 1369, 1186, 973, 854 cm^{-1}; HRMS (ES^+) calcd for $C_{11}H_{12}Cl_3NO_4S$ 358.9553 found 381.9462 (MNa^+).

3.5.1.5. 3-Oxo-3-phenyl-2-(2,2,2-trichloroethoxysulfonylamino)propionic acid methyl ester. Purified by chromatography on silica gel (3:1 hexanes/EtOAc); white solid (80%): TLC R_f=0.49 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10–8.06 (m, 2H), 7.68 (tt, 1H, J=7.2, 1.2 Hz), 7.56–7.51 (m, 2H), 6.48 (d, 1H, J=8.8 Hz), 5.84 (d, 1H, J=8.4 Hz), 4.69 (d, 1H, J=10.8 Hz), 4.64 (d, 1H, J=10.8 Hz), 3.76 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.4, 166.1, 135.2, 133.0, 129.6, 129.1, 93.0, 78.4, 60.5, 53.8 ppm; IR (thin film) ν 3276, 1753, 1690, 1449, 1377, 1242, 1187, 858 cm^{-1}; HRMS (ES^+) calcd for $C_{12}H_{12}Cl_3NO_6S$ 402.9451 found 425.9340 (MNa^+).

3.5.1.6. (1-Ethyl-2-oxo-butyl)sulfamic acid 2,2,2-trichloroethyl ester. Purified by chromatography on silica gel (6:1 hexanes/EtOAc); colorless oil (84%): TLC R_f=0.17 (9:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.89 (d, 1H, J=7.5 Hz), 4.64 (d, 1H, J=10.5 Hz), 4.57 (d, 1H, J=10.5 Hz), 4.29 (ddd, 1H, J=6.0, 6.0, 4.5 Hz), 2.63 (dq, 1H, J=18.0, 7.5 Hz), 2.51 (dq, 1H, J=18.0, 7.5 Hz), 2.04 (dddd, 1H, J=15.0, 15.0, 7.5, 5.0 Hz), 1.74 (sept, 1H, 7.0 Hz), 1.13 (t, 3H, J=7.0 Hz), 0.96 (t, 3H, J=7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.9, 93.2, 78.0, 62.8, 32.8, 25.2, 8.7, 7.5 ppm; IR (thin film) ν 3285, 2978, 1721, 1373, 1188, 1008, 858 cm^{-1}; HRMS (ES^+) calcd for $C_8H_{14}Cl_3NO_4S$ 324.9709 found 347.9613 (MNa^+).

3.5.1.7. (2-Oxo-cyclohexyl)sulfamic acid 2,2,2-trichloroethyl ester. Purified by chromatography on silica gel (4:1 hexanes/EtOAc); white solid (92%): TLC R_f=0.22 (4:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.98 (br d, 1H, J=4.5 Hz), 4.62 (d, 1H, J=11.0 Hz), 4.58 (d, 1H, J=11.0 Hz), 4.18–4.12 (m, 1H), 2.73–2.67 (m, 1H), 2.62 (ddddd, 1H, J=14.0, 2.5, 2.5, 2.5, 2.5 Hz), 2.40 (ddd, 1H, J=13.5, 6.5, 1.0 Hz), 2.20–2.13 (m, 1H), 1.98–1.92 (m, 1H), 1.82–1.72 (m, 1H), 1.71–1.54 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.3, 93.2, 78.2, 61.4, 40.7, 35.9, 27.4, 23.8 ppm; IR (thin film) ν 3302.86, 2918, 1720, 1374, 1184, 1020, 858 cm^{-1}; HRMS (ES^+) calcd for $C_8H_{12}Cl_3NO_4S$ 322.9553 found 345.9445 (MNa^+).

3.5.1.8. 5-(2,2,2-Trichloroethoxysulfonylamino)cyclohex-2-enone. To a solution of $Cl_3CCH_2OSO_2NH_2$ (1.25 g, 5.5 mmol, 1.1 equiv) in 10.0 mL of C_6H_5Cl were added sequentially 1,3-cyclohexadiene (5.0 mmol), MgO (460 mg, 11.5 mmol, 2.3 equiv), and $Rh_2(NHCOCF_3)_4$ (64 mg, 0.10 mmol, 0.02 equiv). The purple mixture was cooled to −10 °C (s-CO_2/ethylene glycol bath) and $PhI(OAc)_2$ (210 mg, 0.65 mmol, 1.3 equiv) was added in a single portion. After 40 min of stirring at −10 °C, the reaction was warmed to 23 °C. The reaction was stirred for 1 h then diluted with 30 mL of CH_2Cl_2 and filtered through a pad of Celite. The flask and filter cake were washed thoroughly with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure. The isolated material was dissolved in 25 mL of DMSO and the mixture was stirred for 12 h. The solution was transferred to a separatory funnel with 100 mL of EtOAc and washed with 2×100 mL of H_2O. The aqueous washes were combined and extracted with 1×100 mL of EtOAc. The collective organic fractions were washed with 1×50 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (3:1 hexanes/EtOAc) yielded the desired product as a white solid (1.29 g, 73%). TLC R_f=0.54 (1:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10–7.05 (m, 1H), 6.14 (ddd, 1H, J=10.0, 3.0, 1.0 Hz), 6.08 (br d, 1H, J=3.0 Hz), 4.66 (d, 1H, J=11.0 Hz), 4.62 (d, 1H, J=10.5 Hz), 4.19 (ddd, 1H, J=14.0, 5.0, 3.5 Hz), 2.73–2.67 (m, 1H), 2.66–2.51 (m, 2H), 2.01–1.92 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.9, 152.4, 127.2, 93.2, 78.3, 58.7, 30.3, 25.6 ppm; IR (thin film) ν 3291, 1687, 1389, 1185, 1020, 859 cm^{-1}; HRMS (ES^+) calcd for $C_8H_{10}Cl_3NO_4S$ 320.9396 found 343.9288 (MNa^+).

Acknowledgements

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The synthesis of an enantiopure planar-chiral Lewis acid complex via kinetic resolution and its application in stereoselective additions to imines

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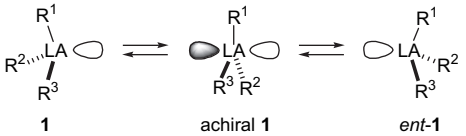
Abstract—This report describes the synthesis and an application of a new planar-chiral Lewis acid based on a 1,2-azaborolyl framework. The enantiopure complex is generated through an intriguing kinetic resolution by a chiral nucleophile. Imines bind in excellent yield to the planar-chiral 1,2-azaborolyl, furnishing crystallographically characterizable adducts that adopt the conformation that had been anticipated on the basis of steric considerations. Nucleophiles add with high stereoselectivity to these complexes, with the predicted sense of asymmetric induction.

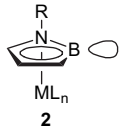
1. Introduction

Chiral Lewis acids have become widely used tools in asymmetric synthesis.[1] For most of the designs that have been described, the Lewis-acidic atom is not stereogenic, although there are a number of noteworthy exceptions to this generalization.[2] Designs in which the Lewis-acidic site is stereogenic may benefit from the close proximity of the asymmetric environment to the site of reaction; on the other hand, the issue of stereochemical lability may arise (e.g., Eq. 1).

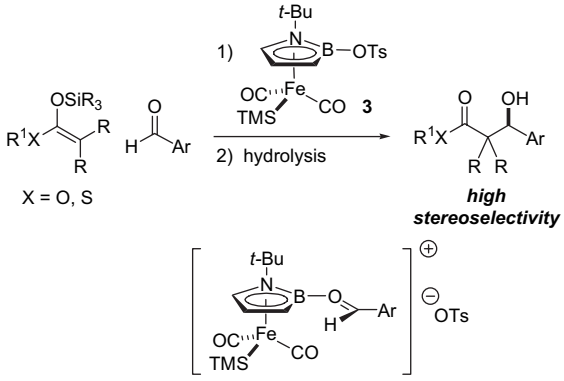


(1)

Several years ago, we initiated a program directed towards the synthesis of planar-chiral Lewis acids (for an illustrative example based on a 1,2-azaborolyl framework, see **2**).[3] This design circumvents the aforementioned complication of configurational lability at the Lewis-acidic site (Eq. 1).



As part of an earlier investigation, we described the first application of such planar-chiral Lewis acids in asymmetric synthesis, specifically, Mukaiyama aldol reactions mediated by an (η^5-1,2-azaborolyl)iron complex (Eq. 2).[3b,4–6] In these processes, a π interaction between the Lewis acid and the aldehyde organizes and activates the adduct for a stereoselective nucleophilic addition.



(2)

In this report, we add a new dimension to the use of these planar-chiral Lewis acids in asymmetric synthesis. In particular, we demonstrate their effectiveness in mediating stereoselective additions to imines through a substrate–Lewis acid adduct that is conformationally distinct from reactions of aldehydes (Eq. 3 vs Eq. 2).

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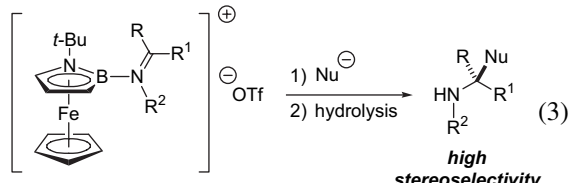
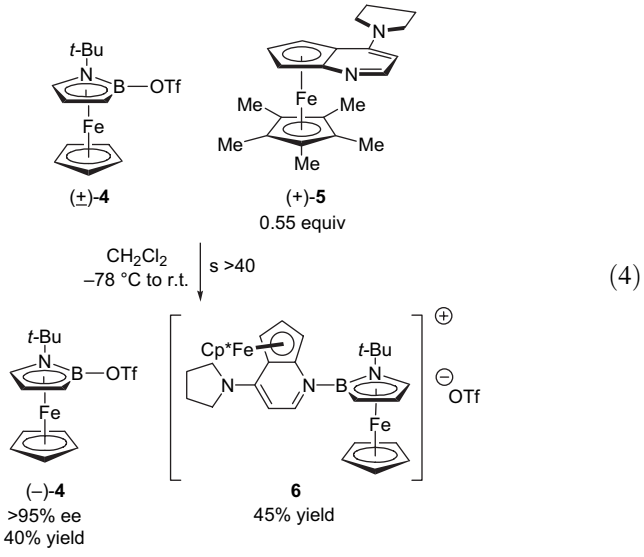


1,2-azaborolyl and imine are not co-planar; nucleophile adds to the front face

2. Results and discussion

In our study of the Mukaiyama aldol reaction, we generated enantiopure Lewis acid complex **3** by resolving a precursor via preparative chiral HPLC. In parallel with that investigation, we were exploring the chemistry of 1,2-azaborolyl analogues of ferrocene (e.g., **4** in Eq. 4).[4a] Rather than relying on chromatographic resolution of these adducts, we decided to examine the possibility that they might be separated via kinetic resolution by an enantiopure Lewis base. Specifically, we hypothesized that a planar-chiral DMAP derivative (e.g., **5**[7]) might be effective.



We were pleased to determine that this strategy is indeed viable. Thus, DMAP derivative (+)-**5** reacts with high selectivity for (+)-**4** to generate complex **6** (selectivity factor >40),[8] thereby allowing unreacted (−)-**4** to be isolated in excellent ee (Eq. 4).[9] The structure of **6** has been confirmed by X-ray crystallography (Fig. 1), which nicely illustrates how the planar chirality of the Lewis acid and the Lewis base impact upon the atropisomer preference of the adduct (FeCp* and *t*-Bu groups avoid each other). To the best of our knowledge, this is the first 1,2-azaborolyl complex that bears a neutral ligand on boron.

In the case of azaborolyl–aldehyde complexes, we had anticipated that a co-planar geometry would be preferred (Eq. 2). On the other hand, we predicted that, for azaborolyl–imine adducts, the co-planar conformation would be destabilized

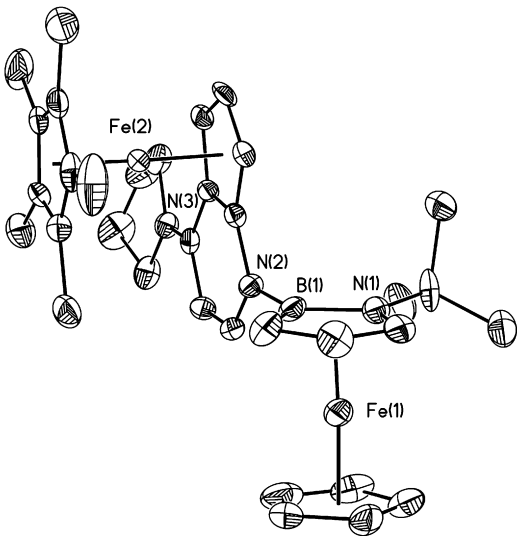
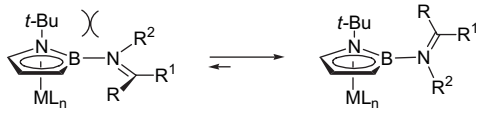


Figure 1. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of complex **6**. For the sake of clarity, the triflate counterion has been omitted.

by steric interactions,[10] leading to preferential population of the 'perpendicular' geometry (Eq. 5).



azaborolyl and imine are co-planar

azaborolyl and imine are not co-planar ("perpendicular" geometry)

Reaction of (−)-**4** with imines furnishes isolable azaborolyl–imine complexes in excellent yield (Eq. 6). An X-ray crystallographic study supports our suggestion that the perpendicular conformation should be preferred (Fig. 2).

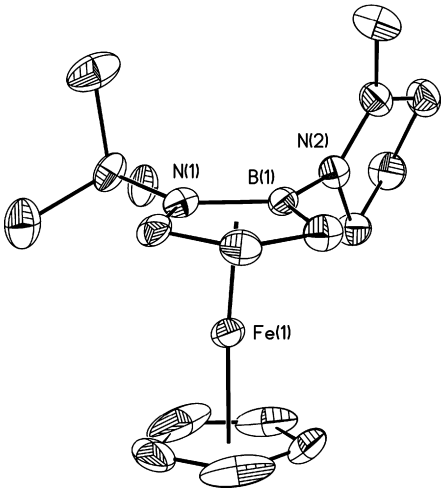
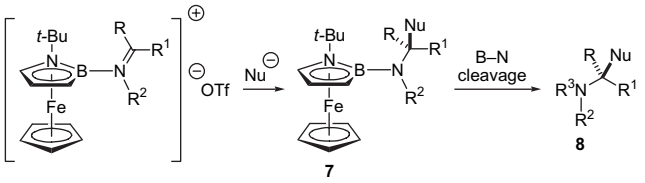
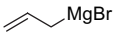
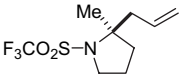
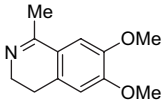
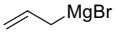
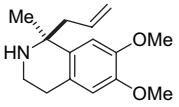
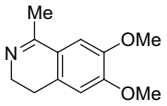
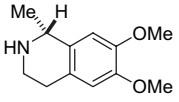


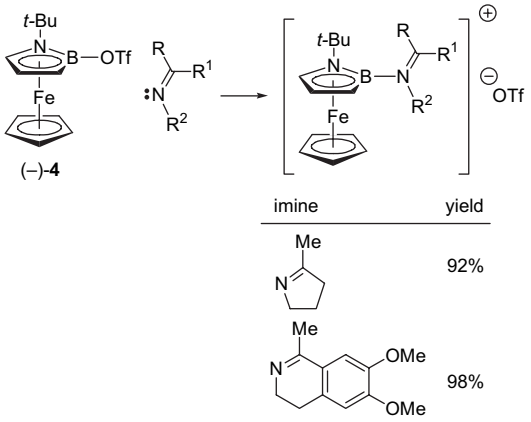
Figure 2. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of an azaborolyl-(2-methyl-1-pyrroline) complex. For the sake of clarity, the triflate counterion has been omitted.

Table 1. Stereoselective additions to planar-chiral azaborolyl–imine complexes



Entry	Imine	Nu	**7** Yield (%); de (%)[a]	**8**	
1			96; >90		94% ee[b]
2			83; 87		86% ee[c]
3		$LiBHEt_3$	69; 86		87% ee[c]

[a] Determined by ^1H NMR.
[b] Determined by chiral GC.
[c] Determined by chiral HPLC.



Just as the co-planar geometry of a planar-chiral azaborolyl–aldehyde complex provides an effective asymmetric environment for stereoselective addition reactions (Eq. 2), we anticipated that the perpendicular orientation of an azaborolyl–imine adduct would also furnish good selectivity, due to blockage of one face by the bulky *tert*-butyl substituent (Fig. 2).[11] Gratifyingly, this expectation has been fulfilled: additions of nucleophiles to azaborolyl–imine complexes do indeed proceed with high levels of stereoinduction (Table 1). For example, reaction with allylmagnesium bromide affords a quaternary stereocenter in good yield and ≥86% ee (entries 1 and 2).[12] Furthermore, addition of $LiBHEt_3$ occurs with high stereoselection to produce 1*R*-(+)-salsolidine,[13] a naturally occurring tetrahydroisoquinoline alkaloid (entry 3). The sense of induction is consistent with our prediction.

In conclusion, we have described a synthesis and an application of a new planar-chiral Lewis acid. The complex is generated in enantiopure form through an intriguing kinetic resolution by a chiral nucleophile. Imines bind in excellent yield to the planar-chiral 1,2-azaborolyl, furnishing crystallographically characterizable adducts that adopt the conformation that had been anticipated on the basis of steric considerations. Nucleophiles add with high stereoselectivity to these complexes, with the predicted sense of asymmetric induction. This study thus adds a new dimension to the use of planar-chiral azaborolyls in asymmetric synthesis, complementing our earlier investigation of additions to aldehydes, which proceed through an orthogonal transition-state geometry, also with good stereoselectivity. Efforts to develop catalyzed transformations are underway.

3. Experimental

All oxygen- and moisture-sensitive manipulations were carried out under an inert atmosphere using either standard Schlenk techniques or a glove box.

1,2-Azaborolyl complex **4**[4a] and DMAP derivative (+)-**5**[14] were prepared according to literature procedures. THF, Et_2O, CH_2Cl_2, and toluene were purified by passage through a neutral alumina column under argon. All other chemicals and solvents were purchased from Aldrich or Strem and used as received.

Silica gel (230–400 mesh; SiliCycle) was heated under vacuum in a 200 °C sand bath for 12 h. Flash chromatography was performed with this pre-treated silica gel under an inert atmosphere.

^{11}B NMR spectra were recorded on a Varian Unity 300 or on a Varian Unity 500 spectrometer at ambient temperature. ^{31}P NMR spectra and ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer with complete proton decoupling at ambient temperature. All chemical shifts

are referenced to an external standard: ^{19}F NMR to trifluoroacetic anhydride (δ −78), ^{31}P NMR to 85% H_3PO_4 (δ 0), and ^{11}B NMR to boron trifluoride diethyl etherate (δ 0).

Kinetic resolution of (±)-4 by (+)-5 (Eq. 4). A solution of (+)-**5** (263 mg, 0.699 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise to a −78 °C solution of (±)-**4** (497 mg, 1.27 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was kept at −78 °C for 2 h, and then it was allowed to warm to rt over 7 h. The CH_2Cl_2 was then removed under vacuum until a volume of ~6 mL was reached, at which time pentane (14 mL) was carefully layered on top of the reaction mixture in order to induce crystallization. After 48 h, dark purple crystals of complex **6** had formed, leaving an orange mother liquor. The solid was washed with Et_2O (~20 mL) and dried under vacuum (483 mg, 45%). Crystals suitable for X-ray analysis were grown from a CH_2Cl_2/pentane solution.

Compound 6 (Eq. 4). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.08 (d, $^3J_{HH}$=7.0 Hz, 1H), 6.18 (d, $^3J_{HH}$=7.0 Hz, 1H), 5.47 (s, 1H), 4.71 (d, $^3J_{HH}$=4.0 Hz, 1H), 4.46 (s, 5H), 4.16 (d, $^3J_{HH}$=2.5 Hz, 1H), 4.02 (t, $^3J_{HH}$=2.5 Hz, 1H), 3.98–3.78 (m, 3H), 3.74–3.69 (m, 2H), 3.70 (d, $^3J_{HH}$=5.0 Hz, 1H), 2.19–2.31 (m, 4H), 1.70 (s, 15H), 0.88 (s, 9H). Only one diastereomer was detected.

^{13}C NMR (125 MHz, CD_2Cl_2): δ 163.6, 150.3, 107.6, 95.8, 81.2, 77.4, 73.3, 72.4, 70.4, 69.2, 67.0, 66.1, 59.3 (br), 56.3, 52.0, 51.7, 30.7, 26.7, 25.1, 10.1.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 13.9.

FTIR (thin film) 3113, 2978, 2909, 1576, 1551, 1512, 1457, 1411, 1370, 1321, 1273, 1239, 1150, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{34}H_{45}BN_3Fe_2$ (M^+) 618.2400, found 618.2371.

$[\alpha]_D$ −60 (*c* 0.050, CH_2Cl_2; >95% de).

Mp 135–145 °C (decomposition).

Compound (−)-4 (Eq. 4). The orange mother liquor was filtered through an acrodisc and then concentrated to dryness. This material was purified by column chromatography (pentane → 50% pentane/CH_2Cl_2), which furnished (−)-**4** as an orange oil (199 mg, 40%).

The spectral data for (−)-**4** are identical to those reported for (±)-**4**.[4a]

$[\alpha]_D$ −500 (*c* 0.50, CH_2Cl_2; >95% ee).

General procedure for derivatization to determine the ee of (η^5-1,2-azaborolyl)iron complexes (e.g., 4). In a glove box, a vial was charged with racemic (η^5-1-*tert*-butyl-2-chloro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron[4a] (18.6 mg, 0.0670 mmol), (*S*)-(−)-α-methyl-2-naphthalenemethanol (13.8 mg, 0.0800 mmol), and sodium hydride (4.8 mg, 0.20 mmol). THF (0.6 mL) was added, and the reaction mixture was stirred at rt for 22 h. As the reaction proceeded, the color of the mixture gradually changed from orange to red. At the conclusion of the reaction, pentane was added, and the resulting mixture was filtered through an acrodisc (washed with pentane) and concentrated under vacuum. The desired product was isolated by flash chromatography (pentane → 50% pentane/CH_2Cl_2), which furnished the desired product as a red oil (25.3 mg, 91%). The ^{1}H NMR resonances of the two diastereomers of this 1:1 mixture are well distinguished from one another.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.08 (s, 1H), 7.98 (app. t, $^3J_{HH}$=8.5 Hz, 2H), 7.91 (d, $^3J_{HH}$=7.5 Hz, 1H), 7.84–7.80 (m, 5H), 7.56–7.43 (m, 5H), 5.41 (q, $^3J_{HH}$=6.5 Hz, 1H), 5.29 (q, $^3J_{HH}$=6.0 Hz, 1H), 5.13 (s, 1H), 5.08 (s, 1H), 4.19 (s, 5H), 4.07–4.03 (m, 2H), 3.74 (s, 5H), 2.57–2.51 (m, 2H), 1.89 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.59 (d, $^3J_{HH}$=7.0 Hz, 3H), 1.35 (s, 9H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 144.7, 144.5, 134.0, 133.9, 133.4, 133.1, 128.34, 128.33, 128.32, 128.23, 128.20, 128.1, 126.5, 126.4, 126.0, 125.9, 125.5, 125.1, 124.8, 124.1, 76.0, 75.5, 69.0, 68.9, 68.6, 68.5, 68.4, 68.3, 54.4, 54.3, 41.4 (br, 2C), 30.0, 29.9, 26.0, 25.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 17.1.

FTIR (thin film) 3056, 2972, 2927, 1464, 1437, 1424, 1399, 1385, 1366, 1329, 1269, 1238, 1213, 1085 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{28}BNFeO$ (M^+) 413.1608, found 413.1614.

Determination of the ee of (−)-4 (Eq. 4). The ee was determined through ^{1}H NMR analysis of its (*S*)-(−)-α-methyl-2-naphthalenemethanol derivative, which was prepared according to the general procedure: >95% ee.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.83–7.80 (m, 4H), 7.55–7.53 (m, 1H), 7.47–7.42 (m, 2H), 5.41 (q, $^3J_{HH}$=6.5 Hz, 1H), 5.11 (s, 1H), 4.18 (s, 5H), 4.05 (d, $^3J_{HH}$=4.0 Hz, 1H), 2.54 (d, $^3J_{HH}$=4.5 Hz, 1H), 1.87 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.33 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 144.7, 133.9, 133.1, 128.3, 128.2, 128.1, 126.4, 125.9, 124.8, 124.1, 75.5, 68.9, 68.6, 68.5, 54.4, 41.4 (br), 30.0, 25.9.

^{11}B NMR (96 MHz, CD_2Cl_2): δ 17.1.

FTIR (thin film) 3056, 2973, 1424, 1400, 1386, 1366, 1329, 1268, 1239, 1085 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{28}BNFeO$ (M^+) 413.1608, found 413.1625.

$[\alpha]_D$ −500 (*c* 0.10, CH_2Cl_2; >95% de).

Recovery of (+)-5 (Ref. 9). In a glove box, a vial was charged with a solution of (−)-**6** (64 mg, 0.083 mmol) in CH_2Cl_2 (0.65 mL). TBAF (1.0 M solution in THF; 92 μL, 0.092 mmol) was added, and then the progress of the reaction was monitored by ^{11}B NMR. Complete conversion was achieved within 3 h, during which time the reaction mixture changed from blue-purple to burgundy (the color of (+)-**5**). The reaction mixture was concentrated under vacuum

and then purified by silica gel chromatography (ethyl acetate → ethyl acetate/Et_3N). The first compound to elute was (+)-(η^5-1-*tert*-butyl-2-fluoro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron:[4a] orange solid, 17 mg (78%), $[\alpha]_D$ +160 (*c* 0.31, CH_2Cl_2; >95% ee), mp 47–49 °C. The second, burgundy-colored fraction contained (+)-**5**, which was contaminated with a tetrabutylammonium-containing impurity. Pure (+)-**5** was obtained after aqueous extraction (water/Et_2O) and flash chromatography (ethyl acetate → ethyl acetate/Et_3N) (29.5 mg, 94%).

Determination of the ee of (+)-(η^5-1-*tert*-butyl-2-fluoro-1,2-azaborolyl)(η^5-cyclopentadienyl)iron (Ref. 9). The ee was determined through ^{1}H NMR analysis of its (*S*)-(−)-α-methyl-2-naphthalenemethanol derivative, which was prepared according to the general procedure: >95% ee.

Eq. 6 (2-methyl-1-pyrroline complex). In a glove box, a vial was charged with a solution of (−)-**4** (40.0 mg, 0.102 mmol) in CH_2Cl_2 (1.2 mL). 2-Methyl-1-pyrroline (15 μL, 0.153 mmol) was added via a syringe. The reaction mixture was allowed to sit at rt for 7 h. Pentane was carefully layered on top of the reaction mixture to induce crystallization. The desired complex crystallized as an orange solid (44.7 mg, 92%). Crystals suitable for X-ray analysis were grown from a CH_2Cl_2/hexanes solution.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 5.41 (s, 1H), 5.08–5.02 (m, 1H), 4.92–4.87 (m, 1H), 4.61 (d, $^3J_{HH}$=4.0 Hz, 1H), 4.40 (s, 5H), 3.51 (d, $^3J_{HH}$=3.5 Hz, 1H), 3.44–3.39 (m, 2H), 2.56–2.51 (m, 1H), 2.42–2.32 (m, 1H), 2.34 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 201.8, 73.3, 73.1, 70.6, 67.5, 59.1 (br), 56.4, 42.3, 30.8, 21.1, 20.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 10.8.

FTIR (thin film) 3094, 2975, 1641, 1374, 1265, 1224, 1156, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{26}BN_2Fe$ (M^+) 325.1533, found 325.1524.

$[\alpha]_D$ −230 (*c* 0.10, CH_2Cl_2; >95% ee).

Mp 185–187 °C.

Eq. 6 (6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline complex). In a glove box, a vial was charged with a solution of (−)-**4** (50.0 mg, 0.128 mmol) in CD_2Cl_2 (0.9 mL) and then 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[15] (52.4 mg, 0.255 mmol). The reaction mixture was stirred at rt for 2 h and then at 70 °C for 19 h, after which time ^{1}H NMR indicated that the reaction was complete. The reaction mixture was cooled to rt, and then Et_2O was carefully layered on top of the reaction mixture in order to induce crystallization. The resulting solid was recrystallized from Et_2O/CH_2Cl_2 (79.6 mg, 103% yield, 95% purity according to ^{1}H NMR).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.23 (s, 1H), 6.98 (s, 1H), 5.50 (s, 1H), 5.12–5.06 (m, 1H), 4.98–4.90 (m, 1H), 4.65 (d, $^3J_{HH}$=3.5 Hz, 1H), 4.43 (s, 5H), 4.03 (s, 3H), 3.91 (s, 3H), 3.38 (d, $^3J_{HH}$=4.5 Hz, 1H), 3.31–3.26 (m, 2H), 2.58 (s, 3H), 1.30 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 181.4, 157.9, 149.4, 134.5, 120.4, 112.4, 111.3, 72.9, 72.6, 70.9, 57.8 (br), 57.3, 57.0, 56.5, 55.6, 31.0, 26.7, 24.1.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 14.0.

FTIR (thin film) 3063, 2980, 2943, 2841, 1605, 1550, 1523, 1467, 1430, 1387, 1345, 1265, 1223, 1153, 1068, 1031 cm^{-1}.

HRMS (ESI) calcd for $C_{24}H_{32}BN_2O_2Fe$ (M^+) 447.1901, found 447.1916.

$[\alpha]_D$ −450 (*c* 0.020, CH_2Cl_2; >95% ee).

Mp 120–125 °C (decomposition).

Table 1, entry 1. In a glove box, a vial was charged with a solution of the 2-methyl-1-pyrroline complex (39.3 mg, 0.0829 mmol) in CH_2Cl_2 (2.1 mL). This solution was cooled to −35 °C, and then allylmagnesium bromide (1.0 M solution in Et_2O; 91 μL, 0.091 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 2 h, and then it was warmed to rt. Pentane was added, the reaction mixture was filtered through an acrodisc, and the filtrate was concentrated under vacuum. The resulting residue was then purified by flash chromatography (pentane/Et_2O/Et_3N), which furnished the desired product as an orange oil (29.0 mg, 96%). ^{1}H NMR analysis indicated that the de of this mixture was >90%.

^{1}H NMR (500 MHz, C_6D_6): δ 6.15–6.08 (m, 1H), 5.22–5.14 (m, 2H), 4.82 (s, 1H), 4.13 (s, 5H), 4.10 (d, $^3J_{HH}$=4.0 Hz, 1H), 3.74–3.69 (m, 1H), 3.63–3.58 (m, 1H), 3.19 (d, $^3J_{HH}$=4.0 Hz, 1H), 2.81–2.77 (m, 1H), 2.68–2.64 (m, 1H), 2.09–2.04 (m, 1H), 1.85–1.74 (m, 2H), 1.50–1.44 (m, 1H), 1.18 (s, 3H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, C_6D_6): δ 138.6, 116.6, 71.0, 70.9, 69.0, 63.8, 58.2 (br), 55.3, 54.9, 45.5, 38.7, 30.8, 29.0, 25.3.

^{11}B NMR (160 MHz, C_6D_6): δ 14.3.

FTIR (thin film) 3071, 2960, 2868, 1636, 1431, 1382, 1361, 1210, 1152, 1128, 1106, 1081 cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{31}BN_2Fe$ (M^+) 366.1924, found 366.1933.

$[\alpha]_D$ −510 (*c* 0.10, CH_2Cl_2; >90% de).

Table 1, entry 2. In a glove box, a vial was charged with a solution of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline adduct (40.0 mg, 0.0670 mmol) in CH_2Cl_2 (1.6 mL). This solution was cooled to −35 °C, and allylmagnesium bromide (1.0 M solution in Et_2O; 79 μL, 0.079 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 3 h, and then it was concentrated under vacuum. The resulting residue was purified by silica gel chromatography

(pentane/Et_2O/Et_3N). Repurification of this material by flash chromatography (pentane/Et_2O) furnished the desired product as an orange foam (27.1 mg, 83%). ^{1}H NMR analysis indicated that the de of this mixture was 87%.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 6.68 (s, 1H), 6.59 (s, 1H), 5.99–5.90 (m, 1H), 5.23 (s, 1H), 5.01–4.94 (m, 2H), 4.24 (d, $^3J_{HH}$=5.0 Hz, 1H), 4.20 (s, 5H), 4.13–4.03 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.17 (d, $^3J_{HH}$=5.0 Hz, 1H), 3.11–3.07 (m, 1H), 2.94–2.88 (m, 1H), 2.73–2.69 (m, 2H), 1.29 (app. s, 12H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.4, 146.8, 138.6, 136.9, 128.5, 116.0, 112.0, 111.4, 70.8, 70.1, 69.1, 58.5 (br), 58.5, 56.5, 56.1, 55.4, 48.9, 47.0, 30.8, 30.6, 29.8.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 16.8.

FTIR (thin film) 3070, 2973, 2932, 2908, 2831, 1635, 1610, 1514, 1464, 1362, 1251, 1209, 1189, 1157, 1105 cm^{-1}.

HRMS (EI) calcd for $C_{27}H_{37}BN_2O_2Fe$ (M^+) 488.2292, found 488.2283.

$[\alpha]_D$ −340 (*c* 0.10, CH_2Cl_2; 87% de).

Table 1, entry 3. In a glove box, a vial was charged with a solution of the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline adduct (18.4 mg, 0.0310 mmol) in CH_2Cl_2 (0.75 mL). This solution was cooled to −35 °C, and lithium triethylborohydride (1.0 M solution in THF; 37 μL, 0.037 mmol) was added dropwise. The reaction mixture was allowed to stand at −35 °C, with occasional shaking, for 2 h, and then it was concentrated under vacuum. The resulting residue was purified by flash chromatography (pentane/Et_2O/Et_3N), which furnished the desired product as an orange oil (9.6 mg, 69%). ^{1}H NMR analysis indicated that the de of this mixture is 86%.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 6.63 (s, 1H), 6.60 (s, 1H), 5.19 (s, 1H), 4.33 (q, $^3J_{HH}$=6.0 Hz, 1H), 4.18 (s, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56–3.50 (m, 1H), 3.52–3.31 (m, 1H), 3.11–3.05 (m, 1H), 2.84 (d, $^3J_{HH}$=4.5 Hz, 1H), 2.63–2.58 (m, 1H), 1.49 (d, $^3J_{HH}$=6.5 Hz, 3H), 1.28 (s, 9H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.2, 147.1, 134.8, 127.9, 112.3, 110.4, 70.2, 69.5, 68.6, 56.4 (br), 56.2, 56.0, 55.9, 54.6, 44.9, 30.2, 29.4, 22.9.

^{11}B NMR (160 MHz, CD_2Cl_2): δ 16.7.

FTIR (thin film) 3052, 2963, 2928, 2830, 1610, 1515, 1464, 1393, 1360, 1330, 1246, 1230, 1209, 1118, 1105 cm^{-1}.

HRMS (EI) calcd for $C_{24}H_{33}BN_2O_2Fe$ (M^+) 448.1979, found 448.1996.

$[\alpha]_D$ −480 (*c* 0.10, CH_2Cl_2; 86% de).

General procedure for B–N cleavage (Table 1). In a glove box, TBAF (1.0 M solution in THF; 4 equiv) was added to a solution of compound **7** in THF (0.6 mL). The course of the reaction was followed by ^{11}B NMR. After the starting material had been consumed, the reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2/Et_3N).

Table 1, entry 1: B–N cleavage and assay of ee. The general procedure was followed. The 2-allyl-2-methylpyrrolidine was derivatized with trifluoromethanesulfonyl anhydride according to a procedure in lit. 16.

The enantiomeric excess of the sulfonamide was determined to be 94% by GC analysis (Chiraldex β-PH; 20 m×0.25 mm, 105 °C oven temperature, helium as carrier gas; (*S*) isomer (minor) 41.9 min, (*R*) isomer (major) 43.2 min). The configurational assignment (*R*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ +28 (*c* 0.36, CH_2Cl_2); lit.[16] (*R*) enantiomer, $[\alpha]_D$ +29 (*c* 2.0, CH_2Cl_2; 100% ee).

Table 1, entry 2: B–N cleavage and assay of ee. The general procedure was followed.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 6.65 (s, 1H), 6.53 (s, 1H), 5.71–5.63 (m, 1H), 5.10–5.03 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.08–2.97 (m, 2H), 2.66–2.60 (m, 3H), 2.36–2.31 (m, 1H), 1.34 (s, 3H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ 147.5, 147.4, 135.4, 135.2, 127.7, 118.0, 112.0, 109.7, 56.2, 55.8, 55.0, 47.1, 39.1, 30.4, 29.3.

FTIR (thin film) 3312, 3072, 2931, 2832, 1637, 1610, 1514, 1465, 1401, 1366, 1354, 1325, 1259, 1225, 1153 cm^{-1}.

HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ (M^++H) 248.1645, found 248.1652.

$[\alpha]_D$ −53 (*c* 0.63, THF; 86% ee).

The enantiomeric excess was determined to be 86% by HPLC analysis (Daicel Chiralpak OD; hexane:*i*-PrOH= 97:3, 1.0 mL/min; (*R*) isomer (minor) 13.8 min, (*S*) isomer (major) 15.5 min). The configurational assignment (*S*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ −53 (*c* 0.63, THF); lit.[17] (*R*) enantiomer, $[\alpha]_D$ +48 (*c* 2.1, THF; 76% ee).

Table 1, entry 3: B–N cleavage and assay of ee: (*R*)-salsolidine. The general procedure was followed.

^{1}H NMR (500 MHz, C_6D_6): δ 6.49 (s, 1H), 6.38 (s, 1H), 3.97 (q, $^3J_{HH}$=7.0 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.07–3.03 (m, 1H), 2.84–2.79 (m, 1H), 2.71–2.65 (m, 1H), 2.50–2.45 (m, 1H), 1.39 (d, $^3J_{HH}$=6.5 Hz, 3H).

The enantiomeric excess was determined to be 87% by HPLC analysis (Daicel Chiralpak OD; hexane:*i*-PrOH= 80:20, 0.5 mL/min; (*S*) isomer (minor) 18.2 min, (*R*) isomer (major) 21.4 min). The configurational assignment (*R*) was made by comparison with the optical rotation reported in the literature: $[\alpha]_D$ +39 (*c* 0.070, EtOH); lit.[18] (*R*) enantiomer, $[\alpha]_D$ +59 (*c* 2, EtOH; 100% ee).

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5. For leading references to pioneering studies of 1,2-azaborolyl chemistry, see: (a) Schmid, G. *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, Chapter 3.17; (b) Schmid, G. *Comments Inorg. Chem.* **1985**, *4*, 17–32.
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8. Selectivity factor (s)=(rate of fast-reacting enantiomer/rate of slow-reacting enantiomer). For a classic review of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.
9. By reacting **6** with TBAF, enantiopure DMAP derivative (+)-**5** can be recovered in 94% yield (along with the B-fluorinated (η^5-1,2-azaborolyl)iron complex: 78% yield and >95% ee).
10. For a review of *peri* interactions in naphthalene derivatives, see: Balasubramaniyan, V. *Chem. Rev.* **1966**, *66*, 567–641.
11. For leading references to asymmetric additions to imines, see: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
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Nickel-catalyzed coupling of terminal allenes, aldehydes, and silanes

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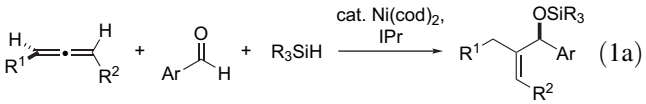
Abstract—The development of a nickel-catalyzed coupling of terminal allenes, aldehydes, and silanes is described. This transformation selectively provides 1,1-disubstituted allylic alcohols, protected as a silyl ether. The choice of the reducing agent is essential for achieving selectivity in this coupling process. A trialkylphosphine (Cyp_3P) and an *N*-heterocyclic carbene (IPr) are complementary in this reaction.

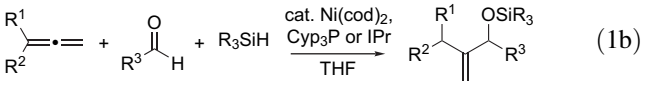
1. Introduction

Nickel is a versatile metal that catalyzes several important transformations, such as, Ziegler–Natta polymerization, hydrogenation, cross coupling, hydrometallation, and multicomponent coupling reactions.[1] We and others have developed several nickel-catalyzed coupling reactions that provided synthetically useful alcohol and amine derivatives.[2] The most effort has been directed toward coupling reactions of aldehydes with either an alkyne or a 1,3-diene, and an organophosphine has often served as a supporting ligand. Also, in these reactions a third coupling partner provides either a hydrogen atom (reductive coupling) or an organic substituent (alkylative coupling), and organozinc and organoboron are the most common such reagents. More recently, organosilanes and *N*-heterocyclic carbene (NHC) ligands have also been reported to be useful alternatives in nickel-catalyzed alkyne–aldehyde (Montgomery)[2g] and 1,3-diene–aldehyde (Mori)[2w–bb] reductive coupling reactions.

We have found the silane/NHC combination to be useful in related allene–aldehyde coupling reactions as well. When employed in nickel-catalyzed coupling of chiral 1,3-disubstituted allenes and aldehydes, *Z*-trisubstituted allylic alcohols are afforded with high selectivity and with complete chirality transfer (Eq. 1a).[2r,s] Herein, we summarize our work on nickel-catalyzed coupling reactions of terminal allenes, aldehydes, and silanes, a process that affords allylic alcohols that differ from those obtained in the allene coupling reactions that were described previously in high regioselectivity and site selectivity (Eq. 1b).



(1a)



(1b)

Allylic alcohols are often prepared by reactions that involve the addition of an alkenyl metal reagent to an aldehyde or a ketone. Two examples are the Nozaki–Hiyama–Kishi reaction[3] and the addition of alkenyl zinc species to aldehydes.[4] The use of transition metals in these two methods allows coordination of chiral ligands to induce asymmetric addition to the carbonyl, providing enantiomerically enriched allylic alcohols.[3g–j,4] The nickel-catalyzed reductive coupling of allenes and aldehydes described in this work is distinct from these strategies since the preparation of a vinyl halide or a vinyl metal species is not required.

Most intramolecular and intermolecular coupling reactions of allenes and aldehydes afford homoallylic alcohols, in which one of the sp^2-hybridized carbons of the allene is the site of C–C bond formation.[5] Catalyzed by several transition metals, cyclization of allenylaldehydes provided homoallylic alcohols in high diastereoselectivity.[5a–j] Transition metal-catalyzed intermolecular couplings of allenes and aldehydes also provided homoallylic alcohols in most cases.[5k–w,2r–t] Other methods of intermolecular and intramolecular coupling of allenes and aldehydes include the single electron transfer process from Pattenden and Crandall,[6a–c] as well as the recently developed SmI_2 mediated reductive coupling from Gillmann, Reissig, and Molander.[6d–f] The

keywords: Allene; Allylic alcohol; *N*-Heterocyclic carbene; Nickel; Silane.
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SmI_2 mediated process gave either allylic or homoallylic alcohols, depending on the nature of the substrates.

The three-component couplings of allenes, aldehydes, and silanes described herein are differentiated from the others in that an *allylic* alcohol derivative is the major product, where C–C bond formation occurs at the sp-hybridized carbon of the allene.[2r,s]

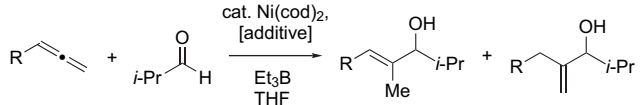
2. Results

Triethylborane (Et_3B) has emerged as an efficient and functional group-tolerant reducing agent in several nickel-catalyzed reactions developed by our group and by others, such as reductive coupling reactions of a diene, an alkyne, or an enyne with an aldehyde, ketone, epoxide, or imine.[7] Thus the starting point for our investigations of the reductive coupling reactions between allenes and aldehydes commenced with a $Ni(cod)_2/Et_3B$ system. A mixture of allene **1a**, isobutyraldehyde, $Ni(cod)_2$, an additive, and Et_3B provided two major coupling products, **2a** and **3a′** (Table 1). Certain additives improved the yield significantly. Phosphines Cyp_3P and $(o\text{-anis})_3P$ provided slightly better yields (entries 3 and 5) than tributylphosphine and NMDPP (entries 2 and 4). Dropwise addition of the allene further increased the yield, possibly due to a minimization of oligomerization of the allene (entries 8 and 9). Without this mode of addition, a substantial amount of **1b** oligomerized under the reaction conditions, affording **2k** in <5% yield (entries 6 and 7). Allylic alcohol **2** predominated over **3′** in all cases regardless of the presence of additives (entries 1–9).

In contrast to these cases using Et_3B, those in which triethylsilane (Et_3SiH) was employed afforded geminally disubstituted allylic alcohol as the exclusive three-component coupling product, along with a product corresponding to hydrosilylation of the allene (Table 2, entry 1). Remarkably, trisubstituted allylic alcohol **2a** was not observed in an NMR spectrum of any of the crude reaction mixtures. Several commercially available silanes were examined next. With Cyp_3P as the supporting ligand, Et_3SiH and *tert*-butyldimethylsilane ($t\text{-BuMe}_2SiH$) provided moderate yields of **3a** (Table 2, entries 1 and 2). Triisopropylsilane afforded **3a** only upon heating (entry 3). Under similar conditions other silanes did not provide **3a** in significant yields (entries 4–7). Diethylzinc in ether did not provide the desired reductive coupling (entry 8).

Solvent and ligand effects were briefly examined (Tables 3 and 4). Although toluene, ethyl acetate, and methanol could also be used, tetrahydrofuran (THF) was found to be the best

Table 1. Additive effects in the $Ni(cod)_2/Et_3B$ system[a]



1a : R = Cy
1b : R = Ph

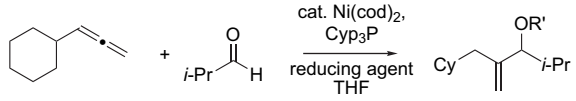
2a : R = Cy
2k : R = Ph

3a' : R = Cy
3k' : R = Ph

Entry	Allene	Additive	Yield (%)[b] **2**+**3′**	**2**:**3′**
1	**1a**	None	9	n.d.
2	**1a**	Bu_3P	10	n.d.
3	**1a**	Cyp_3P[c]	25	6:1
4	**1a**	NMDPP[c]	15	n.d.
5	**1a**	$(o\text{-Anis})_3P$	26	2:1
6	**1b**	$(o\text{-Anis})_3P$	<5	n.d.
7	**1b**	Cyp_3P	<5	n.d.
8[d]	**1b**	Cyp_3P	24	n.d.
9[d]	**1a**	Cyp_3P	50	8:1

[a] General procedure: to a mixture of $Ni(cod)_2$ (20 mol %) and an additive (40 mol %) in THF were added the aldehyde, Et_3B, and the allene at room temperature under argon. The reaction was stirred for 18 h at room temperature.
[b] Isolated yield of **2** and **3′**.
[c] Cyp=cyclopentyl. NMDPP=neomenthyldiphenylphosphine.
[d] The allene was dissolved in THF and added to the reaction mixture via a syringe pump over 1–3 h.

Table 2. Examination of reducing agents[a]

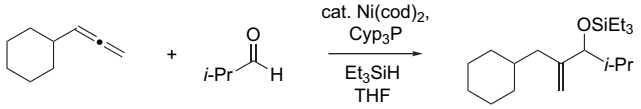


1a **3a**

Entry	Reducing agent	Yield (%)[b]	**3a**:**2a**
1	Et_3SiH	51[h]	>95:5
2[c]	$t\text{-BuMe}_2SiH$	53	>95:5
3[d,e]	$i\text{-Pr}_3SiH$[f]	24	>95:5
4[d]	Ph_2MeSiH[f]	<5	n.d.
5[d]	Me_2PhSiH[f]	<5	n.d.
6	$(EtO)_3SiH$	<5	n.d.
7	Ph_2SiH2	<5	n.d.
8[g]	Et_2Zn[f]	<5	n.d.

[a] General procedure: to a solution of $Ni(cod)_2$ (10 mol %) and Cyp_3P (10 mol %) were added the reducing agents (200 mol %) and the aldehyde (200 mol %). Allene **1a** (100 mol %) in THF was added to the reaction mixture over 8–12 h. The reaction mixture was stirred for 18 h at room temperature.
[b] Isolated yield.
[c] Cyp_3P (20 mol %) was used instead of 10 mol %.
[d] Cyclohexanecarboxaldehyde (300 mol %) was used instead of isobutyraldehyde.
[e] The reaction was heated to 50 °C in toluene.
[f] Reducing agent (300 mol %) was used.
[g] Diethylether was used as the solvent.
[h] Average of two runs.

Table 3. Ligand ratio and solvent effects[a]

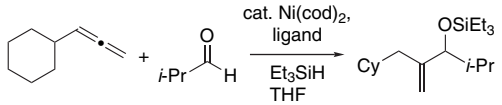


1a **3a**

Entry	Ligand (mol %)	Solvent	Yield (%)[b]
1	None	THF	<5
2	10	THF	51[c]
3	20	THF	50
4	10	EtOAc	40
5	20	EtOAc	21
6	10	MeOH	36
7	20	MeOH	27
8	10	Toluene	46

[a] General procedure: to a solution of $Ni(cod)_2$ (10 mol %) and Cyp_3P were added Et_3SiH (200 mol %) and the aldehyde (200 mol %). Allene **1a** (100 mol %) in THF was added to the reaction mixture over 4 h. The reaction mixture was stirred for 18 h at room temperature.
[b] Isolated yield.
[c] Average of two runs.

Table 4. Ligand screen[a]

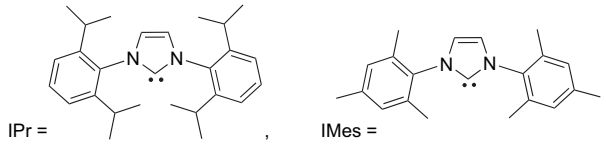


1a **3a**

Entry	Ligand	Yield (%)[b]
1	Cyp_3P	51[c]
2	Cy_3P	41
3	Bu_3P	<10
4	$(o\text{-Anis})_3P$	<10
5	Ph_3P	<10
6	NMDPP	<10
7	BINAP	<10

[a] General procedure: to a solution of $Ni(cod)_2$ (10 mol %) and ligand (10 mol %) were added Et_3SiH (200 mol %) and the aldehyde (200 mol %). Allene **1a** (100 mol %) in THF was added to the reaction mixture over 4 h. The reaction mixture was stirred for 18 h at room temperature.
[b] Isolated yield.
[c] Average of two runs.

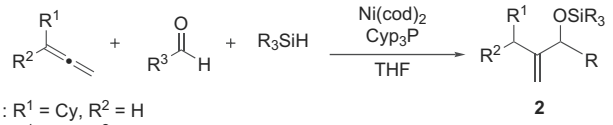
solvent for this coupling reaction (Table 3, entry 2). The nickel/ligand ratio was also found to be an important variable. A 1:1 ratio of $Ni(cod)_2$ and Cyp_3P was optimal, regardless of the choice of solvent (Table 3, entries 2–7). Most strikingly, among phosphines examined, only large and electron donating ones such as Cy_3P and Cyp_3P were compatible with the Ni/Et_3SiH system (Table 4, entries 1 and 2). The *N*-heterocyclic carbene IPr, which is also large and is also a strong electron donor, was also an excellent ligand for this coupling reaction (vide infra). Smaller phosphines such as Bu_3P and Ph_3P and bidentate ligand BINAP only afforded a trace amount of coupling product **3a** (Table 4, entries 3–7). Finally, increasing the amount of aldehyde and silane to 300 mol % further increased the yield (Table 5).



The catalyst system derived from $Ni(cod)_2$ and Cyp_3P was found to promote the coupling of **1a**, **1b**, and **1c** with various aliphatic and aromatic aldehydes in good yield and excellent regioselectivity when a silane was employed as a reducing agent (Table 5). In all cases, carbon–carbon bond formation occurred at the sp-hybridized carbon (rather than the sp^2-hybridized carbons) of the allenes (regioselectivity). No trace of homoallylic alcohol product was observed in any case. Also noteworthy was the fact that the more hindered double bond reacted with the aldehyde, rather than the less substituted double bond. This site selectivity was not affected by the steric bulk around the allene. Allene **1c**, possessing two geminal alkyl substituents, also underwent coupling with aliphatic aldehydes with the same sense of site selectivity as **1a** and **1b** (Table 5, entries 7–9).

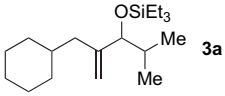
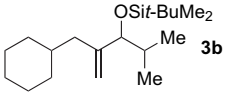
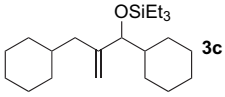
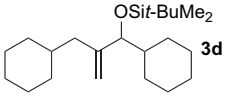
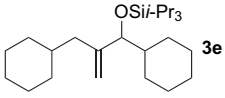
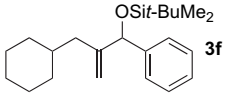
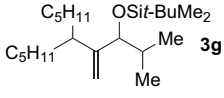
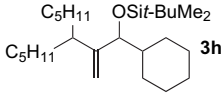
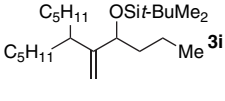
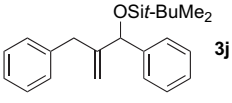
The size of the silane, in contrast, did affect the yield of the coupling product significantly. Switching from *t*-$BuMe_2SiH$ to Et_3SiH lowered the yield substantially (Table 5, entries 1–4) due to competing hydrosilylation of the allene and more hydrosilylation of allene was observed in the latter

Table 5. Reaction scope[a]



1a : R^1 = Cy, R^2 = H
1b : R^1 = Ph, R^2 = H
1c : R^1 = R^2 = n-C_5H_{11}

2

Entry	Allene	Aldehyde	Silane	Product	Yield (%)[b]
1	**1a**	*i*-Pr	Et_3SiH	 **3a**	52
2	**1a**	*i*-Pr	*t*-$BuMe_2SiH$	 **3b**	71
3	**1a**	Cy	Et_3SiH	 **3c**	46
4	**1a**	Cy	*t*-$BuMe_2SiH$	 **3d**	73
5	**1a**	Cy	*i*-Pr_3SiH	 **3e**	24
6	**1a**	Ph	*t*-$BuMe_2SiH$	 **3f**	86[c]
7	**1c**	*i*-Pr	*t*-$BuMe_2SiH$	 **3g**	75
8	**1c**	Cy	*t*-$BuMe_2SiH$	 **3h**	68
9	**1c**	*n*-Bu	*t*-$BuMe_2SiH$	 **3i**	35
10[d]	**1b**	Ph	*t*-$BuMe_2SiH$	 **3j**	56 (5)[e]

[a] General procedure: to a solution of $Ni(cod)_2$ (10 mol %) and Cyp_3P (10 mol %) were added Et_3SiH (300 mol %) and the aldehyde (300 mol %). Allene **1a** (100 mol %) in THF was added to the reaction mixture over 5–9 h. The reaction mixture was stirred for 18 h at room temperature.
[b] Isolated yield.
[c] Cyp_3P was replaced by IPr, and the reaction mixture was cooled to −78 °C before the addition of allene **1a** in one portion. The reaction was warmed to room temperature over 8 h.
[d] The general procedure was followed except that Cyp_3P was replaced by IPr.
[e] Cyp_3P was employed as the ligand. Yield was determined by NMR of the crude mixture versus DMF as an external standard.

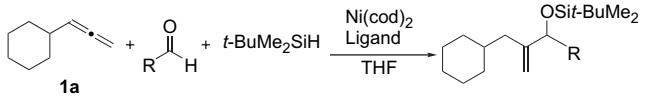
case. This phenomenon might be related to the relative size of those two organosilanes. Triisopropylsilane (*i*-Pr_3SiH), however, appeared to be too bulky for either the coupling or hydrosilylation to occur efficiently (entry 5).

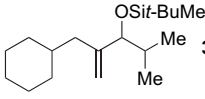
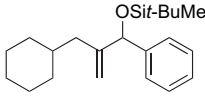
With Cyp_3P as the supporting ligand, oligomerization of **1b** was pronounced, and **3j** was obtained in only 5% yield (entry 10). Nevertheless, this problem was alleviated when Cyp_3P was replaced by IPr (entry 10), and the same regioselectivity and site selectivity were observed as with Cyp_3P.

We have recently reported the nickel-catalyzed coupling of chiral 1,3-disubstituted allenes and aromatic aldehydes using the $Ni(cod)_2/Et_3SiH$ system.[2r,s] While *N*-heterocyclic carbene IPr provided similar site selectivity and regioselectivity as Cyp_3P, only IPr provided complete chirality transfer from an enantiomerically enriched allene to the product. Moreover, it was also found that slow addition of these 1,3-disubstituted allenes was not necessary as long as the allene was added to the reaction mixture at −78 °C. Accordingly, a set of experiments were conducted to determine whether Cyp_3P or IPr was the better ligand for the coupling of terminal allenes and aldehydes and whether the mode of addition affected the yield of the reaction (Table 6).

Cyp_3P was the more efficient ligand for the coupling of terminal allenes and aliphatic aldehydes (Table 6, entries 1–4). The *N*-heterocyclic carbene IPr, however, was the ligand of choice for the coupling with aromatic aldehydes (entries 5–8). Slow addition of cyclohexylallene **1a** to the reaction mixture allowed coupling with isobutyraldehyde to proceed smoothly to afford **3b** in good yield when Cyp_3P was the ligand (entry 1). Under the same condition IPr afforded **3b** only in 12% yield (entry 3). Starting the reaction at −78 °C did not improve the yield of the coupling with aliphatic aldehydes, regardless of whether Cyp_3P or IPr was used (entries 2 and 4). On the other hand, IPr was an excellent ligand for the coupling of allenes and aromatic aldehydes. Slow addition of **1a** to the reaction mixture resulted in smooth coupling with benzaldehyde, giving **3b** in 65% yield (entry 7). Furthermore, in contrast to the results obtained with aliphatic aldehydes, slow addition of **1a** was unnecessary. When **1a** was added to the reaction system in one portion at −78 °C, an increase in yield was observed (entry 8). In fact, in this case the reaction could also be conducted at 0 °C without the use of dropwise addition, but a slight decrease in yield was observed (entry 9).

Table 6. Comparison of Cyp_3P and IPr as ligands



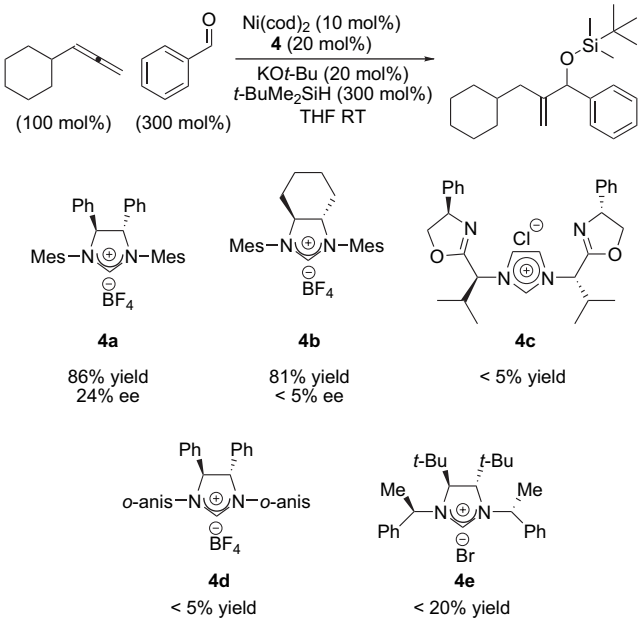
Entry	R (aldehyde)	Ligand	Condition[a]	Product	Yield (%)[b]
1	*i*-Pr	Cyp_3P[c]	A	 **3b**	70
2	*i*-Pr		B		<5
3	*i*-Pr	IPr[d]	A		12
4	*i*-Pr		B		8
5	Ph	Cyp_3P[c]	A	 **3f**	23
6	Ph		B		<5
7	Ph	IPr[d]	A		65
8	Ph		B		86
9	Ph		C		71

[a] Condition A: allene was diluted in THF and added to the reaction over 4 h at room temperature and the reaction mixture continued to stir for 12 h. Condition B: silane, aldehyde, and allene were each added consecutively in one portion to the catalyst mixture at −78 °C. The reaction was slowly warmed to room temperature over 15 h. Condition C: same as condition B except that the allene was added to the reaction mixture at 0 °C instead of −78 °C.

[b] Yield was determined by NMR of the crude mixture versus DMF as an external standard.

[c] $Ni(cod)_2$: $PCyp_3$ ratio was 1:1.

[d] $Ni(cod)_2$: IPr ratio was 1:2.



Scheme 1. Evaluation of chiral *N*-heterocyclic carbene ligands.

3. Discussion

Since the first stable *N*-heterocyclic carbene (NHC) was isolated by Arduengo,[8] derivatives of NHCs were developed and applied extensively as ligands on transition metals and as organocatalysts.[9,10] As ligands on metal catalysts, NHCs are electron rich σ donors, enabling processes such as the oxidative addition of aryl chlorides[9d,e] and providing more reactive and stable olefin metathesis catalysts.[9d] The Ni/NHC system catalyzed several transformations such as reduction of aryl halides and imines,[12a,b] polymerization,[12c,d] Heck reaction,[12e] and cycloaddition[12f] and annulation.[12g]

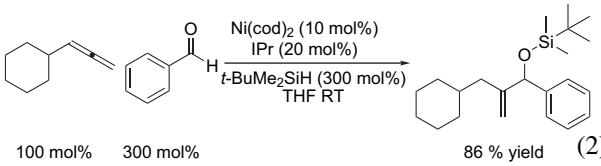
N-Heterocyclic carbene ligands have also been used in other Ni-catalyzed reactions. In the nickel-catalyzed reductive coupling of 1,3-diene and aldehydes, Mori and Sato showed that regioselectivity can be tuned by using either a phosphine ligand or an *N*-heterocyclic carbene.[2w–bb] Montgomery demonstrated that the *N*-heterocyclic carbene IMes had a broad substrate scope of alkynes in the nickel-catalyzed coupling

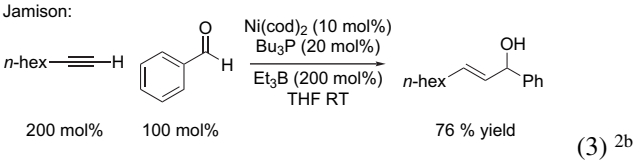
of alkynes, aldehydes, and silanes.[2g] However, the same reaction was sluggish when IMes was replaced by Bu_3P. A crossover experiment indicated that different mechanisms were operating in these two cases and also explained the difference in reactivity.

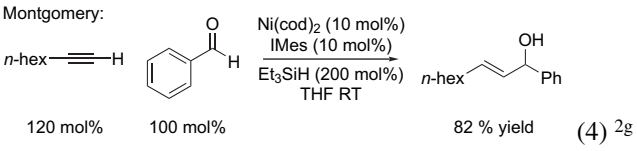
The nickel-catalyzed coupling of allenes and aldehydes described herein demonstrated that phosphines and *N*-heterocyclic carbenes are complementary as supporting ligands for nickel, depending on the nature of the aldehyde coupling partner (aliphatic vs aromatic). In the nickel-catalyzed coupling of allenes and aldehydes, *N*-heterocyclic carbene IPr had a larger substrate scope with respect to the allene, enabling the coupling of alkyl allenes **1a** and **1c** and aryl allene **1b**. Although Cyp_3P did not tolerate aryl allene **1b**, it did promote coupling reactions with aliphatic aldehydes with allenes bearing one aliphatic substituent (**1a** and **1c**). The reduced yield that was observed with aliphatic aldehydes when IPr was employed may have its origins in the basicity of this supporting ligand. Being more basic than Cyp_3P, it is possible that IPr was inactivated by deprotonation of the α-protons of aliphatic aldehydes.[11] More experiments are necessary to confirm this hypothesis, however, since there are examples of aliphatic aldehydes being tolerated in reactions using NHC ligands.[13]

The nickel-catalyzed allene–aldehyde coupling described herein is complementary also to the nickel-catalyzed coupling reactions of alkynes and aldehydes (Scheme 2). The allene–aldehyde coupling provides a different type of disubstituted allylic alcohol product (geminal, Eq. 2) from the alkyne–aldehyde couplings (vicinal, Eqs. 3 and 4). For example, the reductive coupling of the terminal alkyne 1-octyne with benzaldehyde affords a *trans*-1,2-disubstituted allylic alcohol with high selectivity using either the $Ni(cod)_2/Bu_3P$–Et_3B system developed in our group (Eq. 3) or the $Ni(cod)_2$/NHC–Et_3SiH system developed by Montgomery (Eq. 4). In contrast, the allene–aldehyde coupling described here provided 1,1-disubstituted allylic alcohol (Eq. 2). The same substitution pattern is obtained in a related nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates that we recently reported.[2u]

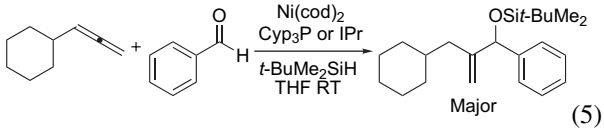
A further distinguishing characteristic is that the regioselectivity and site selectivity of the nickel-catalyzed coupling of allenes and aldehydes are distinctly different among the R_3SiH, Et_3B, and R_2Zn systems (Scheme 3). C–C bond formation occurred between the sp-hybridized carbon of the allene and the aldehyde in the R_3SiH and Et_3B systems (Scheme 3, Eqs. 5 and 6). These two systems, however, have the opposite site selectivity. Whereas in the R_3SiH system addition occurs across the internal double bond, the less substituted double bond reacts in the Et_3B system. The organozinc system developed by Montgomery also affords C–C bond formation between the less substituted sp^2-hybridized carbon of the allene and the aldehyde, but homoallylic alcohols are obtained (Scheme 3, Eq. 7). A related process, the nickel-catalyzed dicarboxylation of an allene by Mori and Sato C–C bond formation occurs between the sp-hybridized carbon of the allene and CO_2 (Scheme 3, Eq. 8). Given these observations, it appears that R_3SiH, Et_3B, and R_2Zn each direct the allene–aldehyde coupling through different mechanisms. The formation of a nickellacycle has been proposed as the first step in the catalytic cycle in all of these examples, and thus R_3SiH, Et_3B, and R_2Zn may play a large role in directing the formation and subsequent reactions of such a nickellacycle species. One possibility is that Et_3B and R_2Zn, being more Lewis acidic than R_3SiH, interact with the aldehyde, giving a larger species that may be accommodated in the nickellacycle in a very different arrangement than the aldehyde itself. More studies are required to further understand the mechanism of these nickel-catalyzed coupling reactions of allenes and aldehydes.[14]

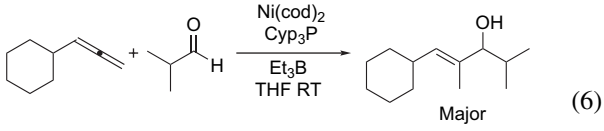


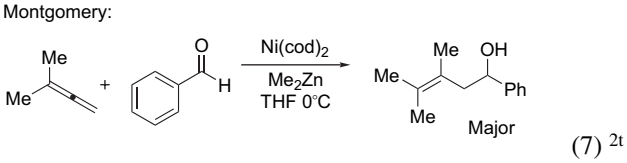


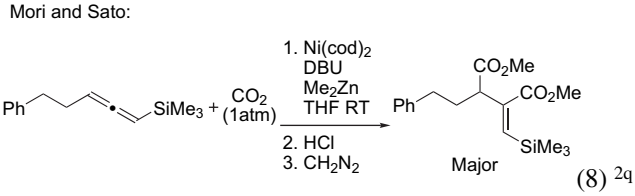


Scheme 2. Comparison between allene–aldehyde coupling and alkyne–aldehyde coupling.









Scheme 3. Nickel-catalyzed allene couplings.

4. Conclusion

In summary, the nickel-catalyzed coupling of allenes, aldehydes, and silanes provides 1,1-disubstituted allylic alcohols with high regioselectivity and high site selectivity. The optimal ligand, however, is different for aliphatic (Cyp_3P) and aromatic (IPr) aldehydes. These transformations are complementary to other allene–aldehyde coupling reactions. Carbon–carbon bond formation occurs between the sp-hybridized carbon of allene and aldehyde, regardless of ligand type, as long as a silane is used as the reducing agent. The use of chiral NHCs resulted in low enantiomeric excess to the coupling product, but nevertheless represents the first example of an enantioselective, nickel-catalyzed coupling of allene and aldehyde.[14] Applications to natural product synthesis and further investigations to develop a highly enantioselective version of this reaction are ongoing.

5. Experimental

5.1. General

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran was distilled from a blue solution of sodium benzophenone ketyl. Triethylsilane, triisopropylsilane, and *tert*-butyldimethylsilane were purchased from Aldrich Chemical Co. and were saturated with nitrogen before use. Benzaldehyde was purchased from Aldrich Chemical Co. and was distilled before use. All aliphatic aldehydes were distilled over magnesium sulfate under argon before use. Bis(*cyclo*-octadienyl)nickel(0) ($Ni(cod)_2$) and tricyclopentylphosphine were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere, and used without further purification. 1,3-Bis-(2,6-di-isopropylphenyl)imidazol-2-ylidene (NHC-IPr) was prepared according to literature procedure.[15]

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometer in $CDCl_3$, unless otherwise noted. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in parts per million from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin–Elmer 2000 FTIR. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns. Specific rotations ($[\alpha]_D$) were measured on a Perkin–Elmer 241 polarimeter at 589 nm.

5.2. Preparation of allenes

5.2.1. Propa-1,2-dienyl-cyclohexane (1a). Prepared by the method of Brandsma.[16] Cyclohexyl-magnesium chloride (50 mL, 100 mmol, 2 M in ether) was dissolved in anhydrous THF (80 mL) and cooled to −78 °C under argon. After 10 min of cooling, a THF (8 mL) solution of anhydrous lithium bromide (2 g) and anhydrous copper(I) bromide (1 g) was added to the Grignard solution in one portion. The reaction mixture was stirred for 20 min at −78 °C. Propargyl bromide (13.4 mL, 120 mmol) was dissolved in anhydrous THF (10 mL) in an oven-dried round bottom flask and was cooled at −78 °C for 15 min. The propargyl bromide solution was taken up by a 50 mL syringe and added to the reaction mixture over 30 min. During this time the reaction mixture was kept below −50 °C with rigorous stirring. After the addition was complete the reaction mixture was stirred for 30 min at −78 °C. The dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was poured into an aqueous NH_4Cl solution (10 g NH_4Cl, 100 mL). The mixture was extracted with 200 mL pentane. The aqueous layer was extracted again with 100 mL pentane. The combined pentane solution was washed repeatedly with water and finally with brine. The solution was dried with $MgSO_4$ and pentane was removed in rotovap. Purification via flash chromatography on silica followed by distillation afforded **1a** as a colorless oil (7.9 g, 65% yield). ^1H NMR (500 MHz, $CDCl_3$, δ): 5.10 (q, J=6.4 Hz, 1H), 4.69 (dd, J=6.7, 3.4 Hz, 2H), 1.99 (m, 1H), 1.80–1.02 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 207.6, 96.3, 75.6, 36.8, 33.2, 26.4, 26.2. IR (NaCl, thin film): 2925, 2852, 2662, 1955, 1445, 839.

5.2.2. Propa-1,2-dienyl-benzene (1b). Prepared according to the method of Myers.[17] Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH/ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred for 10 min below −10 °C. 1-Phenyl-2-propyn-1-ol (1.22 mL, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred for 10 min, and *o*-nitrobenzenesulfonylhydrazine[17b] (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 °C for 2 h and was allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with pentane (300 mL) and washed five times with ice cold water to remove THF. The mixture was dried with $MgSO_4$. Column chromatography in pentane afforded **1b** as a colorless oil (250 mg, 21% yield). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.40–7.28 (m, 4H), 7.25–7.16 (m, 1H), 6.18 (t, J=6.8 Hz, 1H), 5.16 (d, J=6.8 Hz, 2H).

5.2.3. 6-Vinylidene-undecane (1c). 2-Octyn-1-ol (4.3 mL, 30 mmol) and triethylamine (17 mL, 120 mmol) were

dissolved in anhydrous dichloromethane (35 mL) in a 100 mL round bottom flask. The reaction mixture was stirred for 10 min at −78 °C. Methanesulfonyl chloride (7 mL, 90 mmol) was added dropwise. After the addition was complete the reaction was stirred for 2 h at −78 °C. The dry ice/acetone bath was replaced by a sodium chloride/ice slush bath. The reaction mixture was stirred for 90 min at −10 °C. The reaction mixture was poured into water (50 mL). The organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined dichloromethane solution was washed with water and dried with $MgSO_4$. Purification via flash chromatography on silica afforded methanesulfonic acid oct-2-ynyl ester. In an oven-dried 50 mL round bottom flask magnesium turning (0.56 g) was stirred in anhydrous THF (4 mL). A few drops of 1,2-dibromoethane were added. Gentle heating was applied to initiate the reaction. *n*-Pentylbromide (2.84 mL, 23 mmol) was added slowly at a rate that caused and maintained a gentle reflux. When most of the magnesium vanished more *n*-pentylbromide (1 mL) was added. The solution was cooled down to slightly warm (pentylmagnesium bromide was not soluble in cold THF). Meanwhile anhydrous CuBr (3.44 g, 24 mmol) and anhydrous LiBr (2.08 g, 24 mmol) were dissolved in anhydrous THF (40 mL) in an ice bath and stirred vigorously. Once the mixture became homogeneous, the warm pentylmagnesium bromide solution was added via a syringe with a thick needle. The reaction mixture was stirred rigorously for 20 min at 0 °C. The reaction mixture was cooled to −78 °C. Methanesulfonic acid oct-2-ynyl ester in anhydrous THF (30 mL) was added to the reaction mixture dropwise via a syringe pump over 30 min. Once the addition was complete, the dry ice/acetone bath was allowed to warm back to room temperature and stirred for 12 h. The reaction mixture was quenched with ice cold saturated NH_4Cl (80 mL) and extracted with 250 mL hexane. The aqueous layer was extracted again with hexane until the aqueous layer became blue. The combined hexane solution was then washed two times with saturated NH_4Cl, once with water (50 mL), and finally with brine (50 mL). Purification via flash column chromatography on silica afforded 6-vinylidene-undecane **1c** (2.54 g, 47% from 2-octyn-1-ol). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.64 (p, J=3.0 Hz, 2H), 1.96–1.90 (m, 4H), 1.46–1.39 (m, 4H), 1.35–1.26 (m, 8H), 0.94–0.87 (t, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 205.9, 103.6, 75.4, 32.3, 31.8, 27.5, 22.8, 14.3. IR (thin film NaCl): 2957, 2929, 2873, 2859, 1958, 843.

5.3. Nickel-catalyzed couplings of allenes and aldehydes

5.3.1. Standard procedure A. A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (28 mg, 0.1 mmol, 10 mol %) and tricyclopentylphosphine (28 μL, 0.1 mmol, 10 mol %) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (2 mL) at room temperature under argon and stirred for 10 min at room temperature. Silane (3 mmol, 300 mol %) was added in one portion. Aldehyde (3 mmol, 300 mol %) was added in one portion. Finally allene (1 mmol, 100 mol %) in THF (8 mL) was added into the reaction mixture at room temperature via a syringe pump over 8 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic alcohol coupling product.

5.3.2. Standard procedure B. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (7 mg, 0.025 mmol, 10 mol %) and tricyclopentylphosphine (7 μL, 0.025 mmol, 10 mol %) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF or toluene (0.5 mL) at room temperature under argon and stirred for 10 min at room temperature. Silane (0.75 mmol, 300 mol %) was added in one portion. Aldehyde (0.75 mmol, 300 mol %) was added in one portion. Finally allene (0.25 mmol, 100 mol %) in THF or toluene (2 mL) was added into the reaction mixture at room temperature via a syringe pump over 3.5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic alcohol coupling product.

5.3.3. Standard procedure C. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (10 mg, 0.036 mmol, 15 mol %) and tricyclopentylphosphine (10 μL, 0.036 mmol, 15 mol %) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (0.5 mL) at room temperature under argon and stirred for 10 min at room temperature. Silane (0.75 mmol, 300 mol %) was added in one portion. Aldehyde (0.75 mmol, 300 mol %) was added in one portion. Finally allene (0.25 mmol, 100 mol %) in THF or toluene (3 mL) was added into the reaction mixture at room temperature via a syringe pump over 5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic alcohol coupling product.

5.3.4. (1-Cyclohexylmethyl-1-isopropyl-allyloxy)-triethylsilane (3a). The reaction of propa-1,2-dienyl-cyclohexane (**1a**) (148 μL, 1 mmol) and isobutyraldehyde (272 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and triethylsilane (480 μL, 3 mmol) in THF following the standard procedure A described above afforded **3a** in 52% yield as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.72 (d, J=6.1 Hz, 1H), 2.00–1.00 (m, 14H), 0.96 (t, J=8.0 Hz, 9H), 0.85 (t, J=6.32 Hz, 6H), 0.59 (q, J=7.98 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 149.0, 111.0, 82.0, 39.4, 35.9, 34.1, 33.7, 31.8, 26.9, 26.7, 26.6, 20.1, 17.6, 7.3, 5.2; IR (NaCl, thin film): 3077, 2955, 2923, 2877, 2853, 1811, 1646, 1459, 1449, 1414, 1063, 1007, 904, 834, 740, 725; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{38}OSi$, 333.2584; found, 333.2593.

5.3.5. *tert*-Butyl-(2-cyclohexylmethyl-1-isopropyl-allyloxy)-dimethylsilane (3b). The reaction of propa-1,2-dienyl-cyclohexane (**1a**) (148 μL, 1 mmol) and isobutyraldehyde

(272 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A described above afforded **3b** in 71% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.70 (d, J=5.8 Hz, 1H), 1.98–1.60 (m, 9H), 1.58–1.40 (m, 1H), 1.38–1.10 (m, 4H), 0.92 (s, 9H), 0.843 (dd, J=6.9, 6.6 Hz, 6H), 0.04 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.8, 111.1, 81.5, 39.7, 35.7, 34.2, 33.6, 31.7, 26.9, 26.7, 26.6, 26.2, 20.3, 18.5, 17.3, −4.1, −4.8; IR (NaCl, thin film): 3077, 2957, 2927, 2855, 1647, 1463, 1251, 1057, 863, 838, 774; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{38}OSi$, 333.2584; found, 333.2590.

5.3.6. (1-Cyclohexyl-2-cyclohexylmethyl-allyloxy)-triethylsilane (3c). The reaction of propa-1,2-dienyl-cyclohexane (**1a**) (148 μL, 1 mmol) and cyclohexanecarboxaldehyde (361 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and triethylsilane (480 μL, 3 mmol) in THF following the standard procedure A described above afforded **3c** in 46% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.93 (m, 1H), 4.79 (m, 1H), 3.72 (d, J=6.7 Hz, 1H), 2.00–0.80 (m, 24H), 0.96 (t, J=7.6 Hz, 9H), 0.59 (q, 7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.6, 111.1, 81.8, 41.5, 39.0, 35.6, 34.1, 33.7, 30.4, 28.4, 26.9, 26.9, 26.7, 26.7, 26.6, 26.5, 7.3, 5.2; IR (NaCl, thin film): 3076, 2923, 2876, 2852, 1809, 1644, 1449, 1239, 1063, 1008, 898, 827, 740; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{42}OSi$, 373.2897; found, 373.2892.

5.3.7. *tert*-Butyl-(1-cyclohexyl-2-cyclohexylmethyl-allyloxy)-dimethylsilane (3d). The reaction of propa-1,2-dienyl-cyclohexane (**1a**) (148 μL, 1 mmol) and cyclohexanecarboxaldehyde (361 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A described above afforded **3d** in 73% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.94 (m, 1H), 4.80 (m, 1H), 3.70 (d, J=6.1 Hz, 1H), 2.00–0.80 (m, 24H), 0.91 (s, 9H), 0.03 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.4, 111.2, 81.4, 41.5, 39.3, 35.6, 34.2, 33.7, 30.7, 28.1, 26.9, 26.9, 26.7, 26.7, 26.6, 26.6, 26.2, 18.5, −4.1, −4.7; IR (NaCl, thin film): 3076, 2926, 1645, 1450, 1251, 1061, 900, 837, 774; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{42}OSi$, 373.2897; found, 373.2893.

5.3.8. (1-Cyclohexyl-2-cyclohexylmethyl-allyloxy)-triisopropylsilane (3e). The reaction of propa-1,2-dienyl-cyclohexane (**1a**) (37 μL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and triisopropylsilane (154 μL, 0.75 mmol) in toluene following the standard procedure B described above (except that 1 mL toluene was used to dissolve $Ni(cod)_2$ and tricyclopentylphosphine) afforded **3e** in 24% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.96 (m, 1H), 4.82 (m, 1H), 3.95 (d, J=5.8 Hz, 1H), 2.00–0.80 (m, 25H), 1.10 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.6, 110.9, 81.9, 42.8, 39.5, 35.6, 34.2, 33.8, 30.2, 28.6, 26.9, 26.8, 26.8, 26.7, 26.6, 18.5, 13.1; IR (NaCl, thin film): 3079, 2924, 2865, 2852, 1645.71, 1449, 1086, 1062, 883; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{48}OSi$, 415.3367; found, 415.3366.

5.3.9. *tert*-Butyl-(2-cyclohexylmethyl-1-phenyl-allyloxy)-dimethylsilane (3f). A 7 mL vial and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (7 mg, 0.025 mmol, 10 mol %) and IPr (19 mg, 0.05 mmol, 20 mol %) were added to the flask. The vial was sealed with a septum and electrical tape. The sealed vial was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (3 mL) at room temperature under argon and stirred for 10 min at room temperature. The mixture was cooled to −78 °C. *t*-$BuMe_2SiH$ (125 μL, 0.75 mmol, 300 mol %) was added in one portion. Benzaldehyde (76 μL, 0.75 mmol, 300 mol %) was added in one portion. Finally allene (37 μL, 0.25 mmol, 100 mol %) was added. The reaction was stirred for 2 h at −78 °C. The dry ice/acetone bath was then covered with aluminum foil and the temperature was slowly raised to room temperature. The reaction was stirred for a total of 15 h. THF and other volatiles were removed under reduced pressure. Purification via flash chromatography on silica afforded **3f** in 86% yield as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.35–7.20 (m, 5H), 5.24 (s, 1H), 5.10 (s, 1H), 4.83 (s, 1H), 1.80 (m, 1H), 1.70 (m, 6H), 1.45 (m, 1H), 1.15 (m, 3H), 0.92 (s, 9H), 0.75 (m, 2H), 0.07 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.0, 143.7, 128.1, 127.1, 126.7, 110.9, 78.4, 39.5, 35.8, 33.7, 33.480, 26.8, 26.6, 26.5, 26.1, 18.5, −4.7, −4.7; IR (NaCl, thin film): 2926, 2854, 1472, 1449, 1252, 1090, 1065, 867, 835, 776, 699. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{38}OSi$, 367.2428; found, 367.2431.

5.3.10. *tert*-Butyl-(1-isopropyl-2-methylene-3-pentyl-octyloxy)-dimethylsilane (3g). The reaction of 6-vinylidene-undecane (**1c**) (57 μL, 0.25 mmol) and isobutyraldehyde (68 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure C described above afforded **3g** in 75% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 5.10 (m, 1H), 4.83 (m, 1H), 3.79 (br s, 1H), 1.80–1.68 (m, 2H), 1.46–1.18 (m, 22H), 0.97 (d, J=6.7 Hz, 3H), 0.94 (s, 9H), 0.93–0.85 (m, 6H), 0.76 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.7, 108.3, 79.7, 41.4, 36.2, 34.0, 32.5, 32.5, 30.9, 27.5, 26.7, 26.2, 22.9, 22.9, 21.4, 18.5, 14.9, 14.4, 14.3, −3.9, −4.8; IR (NaCl, thin film): 2958, 2929, 2858, 1647, 1463, 1250, 1056, 902, 865, 839, 774. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{48}OSi$, 391.3367; found, 391.3365.

5.3.11. *tert*-Butyl-(1-cyclohexyl-2-methylene-3-pentyl-octyloxy)-dimethylsilane (3h). The reaction of 6-vinylidene-undecane (**1c**) (57 μL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure B described above afforded **3h** in 68% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 5.06 (m, 1H), 4.83 (m, 1H), 3.76 (br s, 1H), 1.90–1.00 (m, 28H), 0.94 (s, 9H), 0.90 (m, 6H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.2, 108.4, 79.8, 41.2, 41.1, 36.2, 34.2, 32.5, 32.5, 32.1, 27.4, 27.1, 27.0, 26.8, 26.6, 26.3, 25.5, 22.9, 22.925, 18.5, 14.4, 14.3, −3.9, −4.7; IR (NaCl, thin film): 2929, 2856, 1647, 1463, 1251, 1103, 902, 835, 774. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{52}OSi$, 431.3680; found, 431.3700.

5.3.12. *tert*-Butyl-dimethyl-(2-methylene-3-pentyl-1-propyl-octyloxy)-silane (3i). The reaction of 6-vinylideneundecane (**1c**) (57 μL, 0.25 mmol) and *n*-butyraldehyde (68 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine, and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure C described above afforded **3i** in 35% yield as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.09 (br s, 1H), 4.76 (br s, 1H), 3.97 (t, J=4.9 Hz, 1H), 1.90–1.82 (m, 1H), 1.55–1.20 (m, 23H), 0.92 (s, 9H), 0.88 (m, 6H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 156.0, 107.6, 75.8, 40.7, 39.1, 35.9, 34.7, 32.5, 27.4, 26.9, 26.2, 22.9, 18.8, 18.5, 14.4, 14.3, −4.2, −4.7. IR (NaCl, thin film): 2958, 2930, 2858, 1646, 1463, 1255, 1085, 902, 836, 774. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{48}OSi$, 391.3367; found, 391.3350.

5.3.13. (2-Benzyl-1-phenyl-allyloxy)-*tert*-butyldimethylsilane (3j). The reaction of phenylallene (**1b**) (121 μL, 1 mmol) and benzaldehyde (305 μL, 3 mmol) with $Ni(cod)_2$, IPr (78 mg, 0.2 mmol), and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A (described above except that tricyclopentylphosphine was replaced by IPr) afforded **3j** in 56% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43–7.33 (m, 4H), 7.30 (t, J=7.4 Hz, 3H), 7.22 (t, J=7.3 Hz, 1H), 7.10 (d, J=7.0 Hz, 2H), 5.35 (s, 1H), 5.19 (s, 1H), 4.71 (d, J=1.4 Hz, 1H), 3.39 (d, J=16.1 Hz, 1H), 3.05 (d, J=16.1 Hz, 1H), 0.97 (s, 9H), 0.09 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 151.8, 143.3, 139.7, 129.6, 128.4, 128.2, 127.3, 126.6, 126.1, 112.1, 77.8, 37.6, 26.1, 18.5, −4.7, −4.8; IR (NaCl, thin film): 3028, 2956, 2929, 2857, 1648, 1602, 1494, 1251, 1091, 1067, 868, 835, 776, 699. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{30}OSi$, 361.1958; found, 361.1959.

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Use of a highly effective intramolecular Pauson–Khand cyclisation for the formal total synthesis of (±)-α- and β-cedrene by preparation of cedrone

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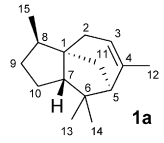
Dedicated with warmth and the utmost respect to our fellow countryman, Professor David W. MacMillan, in recognition of his broad and outstanding contributions to organic synthesis and on the occasion of being honoured with the first Tetrahedron Young Investigator Award

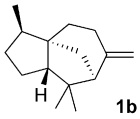
Abstract—The cedrene carbon skeleton was directly and efficiently assembled from a simple monocyclic precursor by the strategic use of a high yielding intramolecular Pauson–Khand cyclisation reaction. A small number of further synthetic manipulations provided a concise formal total synthesis of α- and β-cedrene. The cyclisation precursor was readily prepared, with a stereoselective ketone alkenylation selectively providing the olefin required for efficient access to the natural target.

1. Introduction

The tricyclic sesquiterpenes α-cedrene **1a** and β-cedrene **1b** can be isolated from *Juniperus cedrus* and *Juniperus thurifera*, alongside a variety of closely related oxygenated terpenoid analogues.[1] Driven by the intriguing and preparatively challenging [5.3.1.0^{1,5}] tricyclic structure, the cedrene family of natural products has been the focus of considerable synthetic endeavours[2] over the years since initial characterisation in 1953. As part of our continuing series of studies to further develop the overall effectiveness and applicability of the Pauson–Khand† annulation reaction,[3] we sought to utilise this cyclisation process as the central synthetic transformation within routes towards α-cedrene **1a** and, in so doing, establish a direct and efficient pathway for the synthesis of this structurally demanding tricyclic skeleton. Following the preliminary communication of our initial endeavours towards these goals,[4] we have subsequently made key improvements to the overall selectivity and effectiveness of our preparative pathway. Full details of our revised synthetic approaches to this class of tricyclic sesquiterpene natural product are now presented.



1a



1b

2. Results and discussion

2.1. Initial synthetic approaches to the Pauson–Khand cyclisation precursor

Our synthetic approach is initiated with the introduction of α,β-unsaturation into the commercially available cyclohexanedione monoethylene acetal **2** (Scheme 1). Following straightforward preparation of the enol ether **3**, Saegusa oxidation[5] afforded the enone **4**. More specifically, use of stoichiometric quantities of palladium(II) acetate, provided the enone **4** in 92% yield. On the other hand, the considerably more economical catalytic modification[6] of this useful transformation was investigated and delivered **4** in a respectable 82% yield, whilst requiring the use of only 5 mol % of palladium(II) acetate. With the desired enone in hand, ytterbium(III) triflate trihydrate-catalysed[7] 1,4-addition of the trimethylsilyl enol ether of ethyl isobutyrate directly

Keywords: Pauson–Khand reaction; Cedrene; Tricyclic sesquiterpene; Stereoselective Wittig reaction; Cobalt.
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† Hitherto one of us has preferred to use the initially designated name of 'Khand' reaction for this synthetic process; in light of what has now become common usage and following comments from the referees, we have subsequently employed the more widely accepted term 'Pauson–Khand' throughout this paper.

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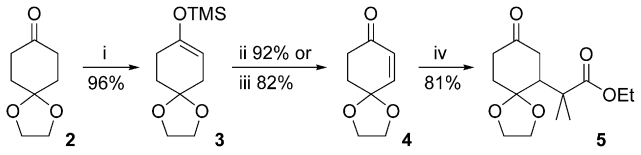
afforded the ester **5** in a yield of 81%. Use of the anhydrous form of ytterbium(III) triflate led to the isolation of the trimethylsilyl enol ether of ketone **5**, from the direct silylation of the enolate resulting from conjugate addition, as a by-product (cf. compound **13** vide infra). It should also be noted that employment of the more commonly used titanium tetrachloride as a stoichiometric mediator of this type of Michael addition resulted in unwanted removal of the ketone protection, even at −78 °C.

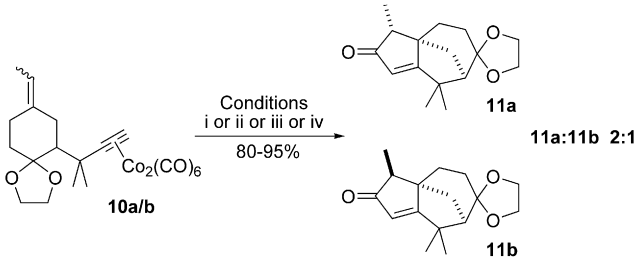


Scheme 1. Reagents and conditions: (i) TMSOTf, Et_3N, DCM, −5 °C, 15 min; (ii) 1.05 equiv $Pd(OAc)_2$, CH_3CN, rt, 24 h; (iii) 5 mol % $Pd(OAc)_2$, DPPE, 1.4 equiv diallyl carbonate, CH_3CN, 81 °C, 40 h; (iv) 10 mol % $Yb(OTf)_3\cdot 3H_2O$, $Me_2CC(OEt)OTMS$, DCM, rt, 24 h.

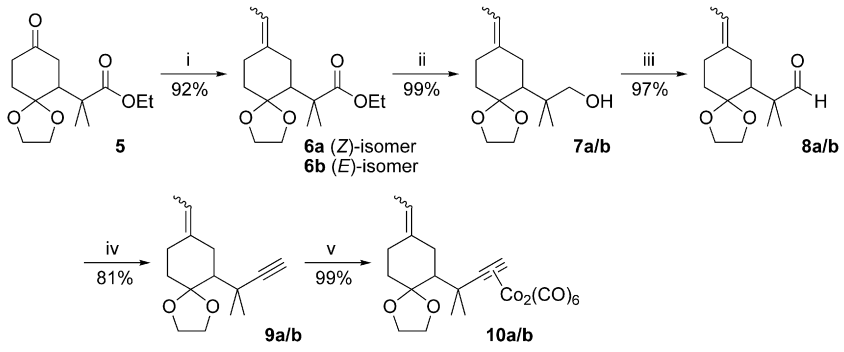
Ethylidenation of the ketone carbonyl of **5** was now considered as the next step in our synthetic sequence. Indeed, this was viewed as a key transformation in a stereochemical sense, with the (*E*)-isomer **6b** being required to provide the requisite orientation of the C-15 methyl group of α-cedrene **1a**. Using the ethyltriphenylphosphonium bromide salt and *n*-butyllithium with ketone **5** in a standard Wittig process at 0 °C, a 92% yield of olefins **6a/6b** was obtained, as a 2:1 mixture of geometric isomers (Scheme 2). Since the products **6a** and **6b** were inseparable, they were employed in combination to allow the planned synthetic route to be established and with a view to identification of individual isomers at a later stage. In this respect and as shown in Scheme 2, total reduction of the ester functionality of **6a/6b** with lithium aluminium hydride delivered alcohols **7a/7b** in 99% yield. This was followed by oxidation to aldehydes **8a/8b** in a yield of 97% using the Dess–Martin periodinane.[8] For the conversion of aldehydes into alkynes, previous studies in our laboratory had shown the Ohira–Bestmann technique (with the reagent dimethyl acetyldiazomethylphosphonate)[9] to be practically accessible and effective. In this instance, this mild protocol delivered alkynes **9a/9b** in 81% yield. In turn, these were routinely complexed with octacarbonyldicobalt to furnish the stable cyclisation precursors **10a/10b** in almost quantitative yield. At this stage and with the requisite complexes in hand, the proposed Pauson–Khand annulation for the assembly of the desired tricyclic carbon α-cedrene skeleton could now be investigated.

2.2. Pauson–Khand cyclisations to the tricyclic cedrene skeleton

A series of techniques for promoting the key intramolecular Pauson–Khand cyclisation of **10a/10b** were probed. As shown in Scheme 3, two different amine *N*-oxides were employed at room temperature,[10] a soluble alkyl methyl sulfide was used under more forcing conditions,[11] and our more recently developed solid-supported alkyl methyl sulfide was also applied.[3i] To our delight, in every instance, the Pauson–Khand cyclisation took place smoothly to provide the enones **11a/11b** in high yield. This clearly demonstrates the novel applicability of this annulation process to the direct construction of such complex tricyclic systems from simple monocyclic substrates. The optimum Pauson–Khand annulation yield of 95% was achieved using Sugihara's technique with the soluble *n*-butyl methyl sulfide in 1,2-DCE at reflux.[11] The alternative polymer-supported sulfide provided a somewhat reduced yield of 80% for the same cyclisation. Having stated this, it is worth noting that the work-up procedure with this solid-phase reagent was greatly facilitated by the ability of the resin-based species to sequester the unwanted cobalt residues, enabling removal of these by-products by simple filtration. It is important to point out that our key Pauson–Khand cyclisation could also be achieved very effectively at room temperature. In this respect, the commercially available dihydrate of trimethylamine *N*-oxide ($TMANO\cdot 2H_2O$) and the monohydrate of *N*-methylmorpholine *N*-oxide ($NMO\cdot H_2O$) afforded cyclopentenones **11a/11b** in high yields of 91% and 84%, respectively.



Scheme 3. Reagents and conditions: (i) 9 equiv $TMANO\cdot 2H_2O$, acetone, rt, 16 h, 91%; (ii) 8 equiv $NMO\cdot H_2O$, DCM, rt, 16 h, 84%; (iii) 4.3 equiv *n*-BuSMe, 1,2-DCE, 83 °C, 30 min, 95%; (iv) 3.6 equiv polymer-supported sulfide, 1,2-DCE, 83 °C, 30 min, 80%.



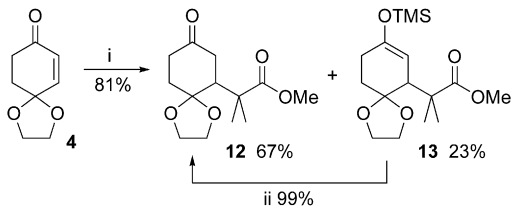
Scheme 2. Reagents and conditions: (i) $Ph_3P^+CH_2CH_3\ Br^-$, *n*-BuLi, THF, 0 °C, 2 h; (ii) $LiAlH_4$, Et_2O, 0 °C, 1 h; (iii) Dess–Martin periodinane, 10% CH_3CN in DCM, rt, 1 h; (iv) $AcC(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, rt, 5 d; (v) $Co_2(CO)_8$, petrol, rt, 2 h.

As shown in Scheme 3, the product cyclopentenones **11a/11b** were obtained as a mixture of stereoisomers in a ratio of 2:1. This indicated that the relative stereochemistry present in the initial olefins **6a/6b** had been carried through to cyclisation precursors **10a/10b** and onto the Pauson–Khand products without change. At this stage, the diastereomers **11a/11b** were now separable by silica column chromatography and the individual cyclopentenones were independently characterised by X-ray crystallographic analyses.[12] Disappointingly, the major isomer **11a** featured the (C-15) methyl group, adjacent to the carbonyl, with the undesired (α) stereochemistry, whilst the minor isomer **11b** possessed the required methyl group (β) orientation. Therefore, despite the excellent levels of efficiency realised for the Pauson–Khand cyclisation process, this stereochemical elucidation and outcome identified a clearly limiting feature of our synthetic route to this stage.

2.3. Probing the stereoselectivity of the key Wittig olefination process

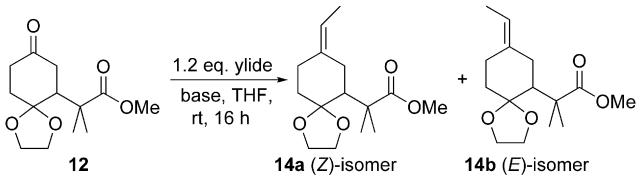
Having made the assignments of relative stereochemistry within **11a** and **11b**, it was now apparent that the specific ratio of olefin geometric isomers achieved through ethylidenation of **5** (as shown in Scheme 2) was 2:1 (*Z*)-**6a**:(*E*)-**6b**. Accordingly, endeavours to access enhanced proportions of the requisite *E*-isomer (**6b**) and a generally more useful isomer ratio, in relation to the synthesis of α-cedrene, were required. In this regard and as part of preliminary investigations, simply utilising a lower olefination reaction temperature of −78 °C, with *n*-butyllithium again being used as base, did not affect the alkene stereoisomeric ratio obtained. Furthermore, use of weaker bases (e.g., K_2CO_3, KOH, NaOEt) in protic solvents (e.g., EtOH) at higher temperatures proved ineffective.

At this stage it was clear that a more detailed exploration of the Wittig olefination process was required. Having stated this and prior to any investigation into the stereoselectivity of olefin formation, it was recognised that use of the ethyl ester **5** did not readily allow use of ^{1}H NMR techniques for the determination of the product alkene ratios. Indeed, to this stage in the programme, analysis of isomeric olefin ratios had been performed by ^{13}C NMR integration. Whilst this had proved reliable, in the sense that the olefin mixtures had been carried through the synthetic scheme and the ratios confirmed as detailed above, a clearly more readily utilisable ^{1}H NMR spectroscopic method for alkene composition determination was desired. To this end, the equivalent methyl ester **12** was routinely prepared as shown in Scheme 4; in this process, once again using hydrated ytterbium(III) triflate as catalyst with enone **4**, the desired keto ester **12** was prepared in 67% yield, along with a 23% yield of the silyl enol ether **13**. This latter species was readily converted to the ester **12** in 99% yield under mild conditions with 2% aqueous oxalic acid, leaving the acetal protecting group intact.



Scheme 4. Reagents and conditions: (i) 10 mol % $Yb(OTf)_3 \cdot 3H_2O$, $Me_2CC(OMe)OTMS$, DCM, rt, 24 h; (ii) 2% aq oxalic acid, Et_2O, rt, 12 h.

First of all, in order to obtain a direct comparison with the ethyl ester **5**, the methyl ester **12** was subjected to olefination conditions, which were almost identical to those previously employed as part of the initial synthetic route towards the Pauson–Khand cyclisation precursor. More specifically, use of the ethyltriphenylphosphonium bromide salt and *n*-butyllithium with **12** at room temperature (Scheme 5, Table 1, Entry 1) delivered the alkenes **14a** and **14b** in similar yield and selectivity (89% and 1.6:1; **14a**:**14b**) to that obtained with the equivalent ethyl ester precursor **5** (with olefin ratios being determined by ^{1}H NMR spectroscopy; see Section 4).



Scheme 5. Wittig olefination of keto methyl ester **12**; see Table 1.

Table 1. Wittig olefination of keto methyl ester **12**

Entry	Ylide	Base	Yield (%)	Ratio **14a**:**14b**
1	$Ph_3P^+Et\ Br^-$	*n*-BuLi	89	1.6:1
2	$Ph_3P^+Et\ Br^-$	NaHMDS	77	1:2.4
3	$Ph_3P^+Et\ Br^-$	KHMDS	85	1:2.3
4	$Ph_3P^+Et\ Cl^-$	KHMDS	79	1:2.3
5	$Ph_3P^+Et\ I^-$	KHMDS	90	1:2.3
6	$Ph_3P^+Et\ Cl^-$	NaHMDS	75	1:2.5
7	$Et_4P^+\ Br^-$	NaHMDS	75	1:1.1
8	$Et_4P^+\ Br^-$	KHMDS	75	1:1.1

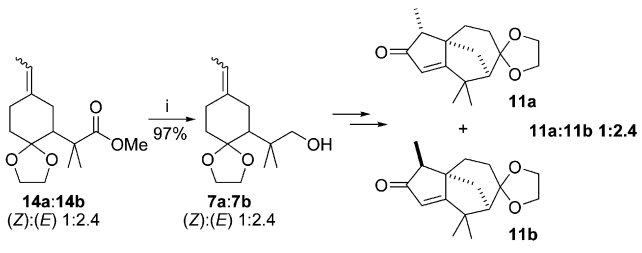
In a very general sense, the efficiency and stereoselectivity of Wittig olefination reactions are known to be affected by the type of ylide used, the base employed, the carbonyl compound, the reaction solvent, and the base/ylide metal counter ion.[13] Whilst olefin stereoselectivity studies have focused on the use of aldehyde substrates within the Wittig process, the parameters and reaction components listed were considered for investigation with the requisite starting cyclic ketone as part of this programme. In this respect, with aldehydes, the use of 'salt-free' conditions (traditionally defined as the absence of lithium salts) is known to enhance the *Z*-selectivity of Wittig olefinations.[13,14] In contrast, the presence of lithium salts, as in the Wittig processes described to this stage, is known to deplete this stereoselectivity. Based on this, we moved to simply amend the counter ion associated with the bases used. Remarkably, when NaHMDS and KHMDS were employed with the same Wittig salt and keto ester **12**, the selectivity of our olefination process was completely reversed, with the desired alkene **14b** now being formed predominantly over **14a** (Table 1, Entries 2 and 3) in ratios of 1:2.4 and 1:2.3, respectively. Considering the minimal local differences on either side of the ketonic carbonyl group, these

observed selectivities are even more notable. Amendment of the halide counter ion associated with the Wittig salt moderately affected yields (Table 1, Entries 4–6) but did deliver the maximum **14a**:**14b** ratio of 1:2.5 (Entry 6). Overall, these were exceedingly pleasing outcomes from such a simple change in reagents and, more importantly, overturned the only significant inefficiency in the synthetic approach to α-cedrene as previously described.[4]

Finally in this area, Schlosser has shown how the replacement of triarylphosphonium ylides with trialkylphosphonium species can, again, considerably affect the stereoselectivity of such olefination processes.[15] When the tetraethylphosphonium bromide salt was utilised with both NaHMDS and KHMDS, the ratios of alkenes produced (1:1.1; **14a**:**14b**; Table 1, Entries 7 and 8) provided no further preparative advantages in this synthetic programme. Additionally, the application of a number of alternative solvents (e.g., DME, glyme) and additives (e.g., 18-c-6) did nothing to further enhance the proportion of **14b** formed over that described above.

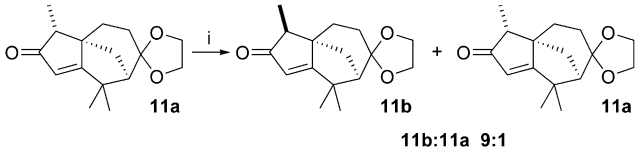
2.4. Selective access to the desired cyclopentenone epimer 11b

From that described above, the desired olefin for use in the α-cedrene synthesis could now be formed predominately and in ratios of up to 1:2.5 (**14a**:**14b**). With this more favourable and selective olefination procedure in place and with a view to complete confirmation of our olefin stereochemical assignments, an isomerically-enriched alkene mixture (1:2.4; **14a**:**14b**) was taken on in the synthetic pathway, as described previously. In this respect, $LiAlH_4$ reduction of **14a/14b** proceeded in excellent yield to deliver **7a/7b**, with the same olefinic ratio of 1:2.4 being observed (Scheme 6). From this point the remainder of the synthetic pathway (as described in Scheme 2) proceeded without complication. Gratifyingly, on Pauson–Khand cyclisation and stereoisomer separation, a 1:2.4 ratio of the undesired cyclopentone **11a** to the required epimer **11b** was obtained.



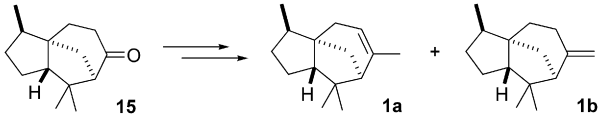
Scheme 6. Reagents and conditions: (i) $LiAlH_4$, Et_2O, rt, 1 h.

As described to this stage, the desired cyclopentenone **11b** could now be accessed in excellent yield and in appreciable excess. Despite this, since isomeric mixtures from olefins **14a/14b** were carried through the synthesis, quantities of the undesired cyclisation product **11a** were also produced. In order to further enhance the overall effectiveness of our route towards the cedrene natural products, a simple α-methyl epimerisation process was attempted. Following a very short exploratory programme, it was found that optimal efficiency was provided by utilising LiOH in a refluxing mixture of THF and H_2O. This almost completely transformed the unwanted stereoisomer **11a** into the desired cyclopentenone **11b** and generated a separable 1:9 mixture of undesired to desired stereoisomers in quantitative yield (Scheme 7). Consequently, this provided further amplification of the efficiency of the overall synthetic pathway described here. Moreover, separation of these isomers and further epimerisation was facilitated allowing, in theory, near complete transformation to the desired isomer over several runs.

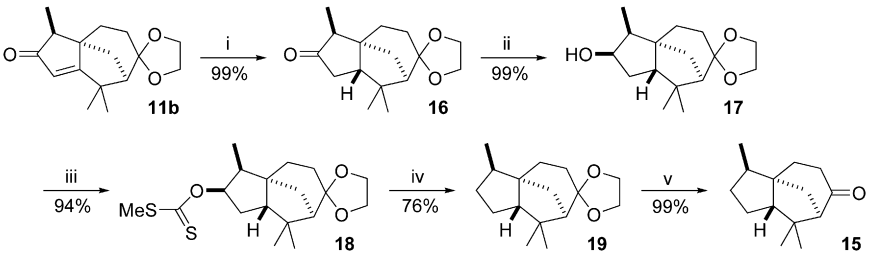


Scheme 7. Reagents and conditions: (i) LiOH, THF/H_2O (5:1), reflux, 3 d.

2.5. Formal total synthesis of α-cedrene 1a and β-cedrene 1b



In a number of instances α-cedrene **1a** (and β-cedrene **1b**) have been readily accessed in two steps from cedrone **15**[2a,e,h] and, consequently, preparation of this latter compound from the key Pauson–Khand cyclisation product would complete our formal total synthesis of the natural sesquiterpenes. With an efficient and selective route to **11b** now having been established, this cyclopentenone was subjected to palladium-catalysed hydrogenation to give **16** in 99% yield (Scheme 8). This reduction process proved to be completely stereoselective, with the relative stereochemistry present in this saturated tricyclic skeleton, again, being confirmed by X-ray analysis.[12] As shown, the newly introduced bridgehead H-atom (at C-7) has the requisite stereochemistry. In due course, lithium aluminium hydride reduction of the carbonyl functionality of **16** was achieved in an excellent 99% yield; at the 0 °C reaction temperature this protocol was totally selective and afforded only one detectable alcohol isomer, tentatively assigned as compound **17**. In turn, the secondary alcohol **17** was reduced following the well-established Barton–McCombie method.[16] In this respect, the xanthate ester intermediate **18** was formed very readily, and the required deoxygenated product **19** was obtained when **18** was treated with tributyltin hydride in the presence of a catalytic amount of AIBN initiator, using degassed benzene as solvent, and in a yield of 71% over the two steps. Finally, the ketone protection was removed using mild conditions, as discovered in our own laboratories, which involved the use of sub-stoichiometric quantities of carbon tetrabromide and triphenylphosphine in acetone.[17] This delivered the desired cedrone target **15** in 99% yield, to complete our concise formal total synthesis of α- and β-cedrene, **1a** and **1b**.



Scheme 8. Reagents and conditions: (i) 10% Pd/C, H_2 (45 psi), toluene, rt, 3 h; (ii) $LiAlH_4$, Et_2O, 0 °C, 2 h; (iii) *n*-BuLi, CS_2, MeI, 0 °C–rt, 110 min; (iv) Bu_3SnH, AIBN, degassed C_6H_6, 80 °C, 48 h; (v) 8 mol % Ph_3P/CBr_4, acetone, rt, 1 h.

3. Conclusions

We have now shown that strategic use of an intramolecular Pauson–Khand reaction, with a simple monocyclic precursor, can allow the direct and highly efficient construction of the challenging tricyclic [5.3.1.$0^{1,5}$] carbon skeleton of α-cedrene **1a** (and β-cedrene **1b**). Furthermore, the overall efficiency of this approach has been considerably enhanced by the ability to reverse the originally observed selectivity of the central Wittig olefination procedure on the requisite cyclic ketone intermediate. In the key Pauson–Khand annulation process, the olefinic precursors react with retention of stereochemistry to deliver the desired cyclopentenone epimer, for synthesis of the targeted natural products, in excess. To further amplify the efficiency of this overall synthetic programme, the residual and undesired cyclopentenone product was also shuttled through to the required isomer by a simple base-mediated epimerisation process. In turn, the desired cyclopentenone intermediate so obtained was further elaborated to cedrone **15**, thus constituting a formal total synthesis of α- and β-cedrene. Finally, it is also worth noting that compound **11a** was subjected to a sequence of reactions similar to those performed on **11b** to deliver a synthesis of *epi*-cedrone.

4. Experimental

4.1. General

Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by distilling commercial solvents from sodium benzophenone ketyl and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Light petroleum refers to the fraction of bp 30–40 °C and was distilled prior to use. All organometallic complexes were stored under nitrogen at, or below, −20 °C and all reactions were performed under a nitrogen atmosphere unless otherwise stated. ^1H and ^{13}C NMR were run on a Bruker WM 250 and a Bruker WM 400 in $CDCl_3$ solutions. Chemical shifts are reported in parts per million downfield relative to tetramethylsilane (δ 0.00); coupling constants are reported in hertz. Infrared spectra were obtained on a Mattson 1000 or Nicolet Impact 400D FTIR spectrometer in CH_2Cl_2 solutions or as films. High resolution mass spectrometry was performed on a JEOL Instruments JMS-AX505HA mass spectrometer system or a Finnigan MAT 900XLT high resolution double focussing mass spectrometer. Mass spectral data are reported as *m/z*.

4.1.1. 8-((Trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene 3. A solution of trimethylsilyl trifluoromethanesulfonate (1.86 g, 1.52 ml, 8.39 mmol) in dichloromethane (20 ml) was added over a 10 min period to a stirred solution of 1,4-dioxaspiro[4.5]decan-8-one **2** (1.19 g, 7.63 mmol) and triethylamine (2.30 g, 3.30 ml, 22.9 mmol) in dichloromethane (70 ml) at −5 °C. The mixture was stirred for 15 min before the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution (5 ml) and then water (35 ml). The organic phase was separated, dried, and evaporated under reduced pressure to leave a crude residue, which was extracted with light petroleum (3×20 ml). The light petroleum extracts were combined and filtered through a pad of silica using light petroleum as the eluent. The filtrate was evaporated under reduced pressure to give *8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene* **3** (1.67 g, 96%) as a colourless oil. IR ν_{max} (film)/cm^{-1} 1664 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (9H, s, $(CH_3)_3Si$), 1.81 (2H, t, *J* 6.6, C^{10}-H), 2.20 (2H, m, C^9-H), 2.26 (2H, m, C^6-H), 3.97 (4H, m, $C^{2,3}$-H) and 4.73 (1H, m, C^7-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.5 ($(CH_3)_3Si$), 28.7, 31.3, 34.1, 64.6 ($C^{2,3}$), 100.8 (C^7), 107.9 (C^5) and 150.0 (C^8); HRMS (EI) *m/z* Calcd for $C_{11}H_{20}O_3Si$ (M^+): 228.1182. Found: 228.1181.

4.1.2. 1,4-Dioxaspiro[4.5]dec-6-en-8-one 4. Palladium(II) acetate (1.03 g, 4.60 mmol) was added to a solution of 8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene **3** (1.00 g, 4.39 mmol) in acetonitrile (70 ml) and the mixture was stirred for 24 h at 25 °C. The solvent was then evaporated under reduced pressure and the black residue was filtered through a pad of silica using dichloromethane as the eluent. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (50 ml) to remove traces of acetic acid. The organic phase was dried and evaporated under reduced pressure to give *1,4-dioxaspiro[4.5]dec-6-en-8-one* **4** (0.62 g, 92%) as a pale yellow oil. Found: C, 62.31; H, 6.35. $C_8H_{10}O_3$ requires C, 62.30; H, 6.50%; IR ν_{max} (film)/cm^{-1} 1683 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (2H, t, *J* 6.5, C^{10}-H), 2.63 (2H, t, *J* 6.5, C^9-H), 4.05 (4H, m, $C^{2,3}$-H), 6.00 (1H, d, *J* 10.2, C^7-H) and 6.61 (1H, d, *J* 10.2, C^6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 35.4, 65.2 ($C^{2,3}$), 104.1 (C^5), 130.6 (C^7), 146.6 (C^6) and 198.8 (C^8); HRMS (EI) *m/z* Calcd for $C_8H_{11}O_3$ (M^++1): 155.0708. Found: 155.0710.

Compound **4** was also prepared by the following method: a solution of palladium(II) acetate (36.0 mg, 0.16 mmol) and 1,2-bis-(diphenylphosphino)ethane (58.0 mg, 0.14 mmol) in acetonitrile (50 ml) was heated to reflux before diallyl carbonate (0.64 g, 4.51 mmol) and 8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene **3** (0.74 g, 3.24 mmol) were added. The mixture was heated under reflux for a further 40 h.

The solvent was then evaporated under reduced pressure to leave a crude residue, which was purified by filtration through a pad of silica using 50% diethyl ether in light petroleum as the eluent. The filtrate was then evaporated under reduced pressure to give *1,4-dioxaspiro[4.5]dec-6-en-8-one* **4** (0.41 g, 82%) as a pale yellow oil. Analytical data were as given above.

4.1.3. Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate 5. Ytterbium(III) trifluoromethanesulfonate trihydrate (0.06 g, 0.09 mmol) was added to a stirred solution of 1,4-dioxaspiro[4.5]dec-6-en-8-one **4** (0.14 g, 0.91 mmol) and 1-ethoxy-1-((trimethylsilyl)oxy)-2-methylpropene (0.23 g, 1.43 mmol) in dichloromethane (20 ml) at 25 °C. The mixture was stirred for 24 h before it was filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 10–50% diethyl ether in light petroleum gradient as the eluent to give *ethyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate* **5** (0.20 g, 81%) as a pale yellow oil. IR ν_{max} (film)/cm^{-1} 1721 (C=O) and 1689 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, s, CH_3C), 1.13 (3H, s, CH_3C), 1.24 (3H, t, J 7.1, CH_3CH_2), 1.74 (1H, app dt, J 13.5 and 5.5), 1.99 (1H, m), 2.36 (1H, m), 2.48 (1H, m), 2.58 (2H, t, J 13.5), 2.71 (1H, dd, J 13.5 and 3.9) and 3.91–4.14 (6H, overlapping m, CH_3CH_2, OCH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 19.5, 27.1, 33.5, 38.3, 39.9, 42.6, 48.8, 60.4 (CH_3CH_2), 63.6 (OCH_2), 64.8 (OCH_2), 109.6 (OCO), 177.6 (OC=O) and 210.2 (C=O); HRMS (EI) m/z Calcd for $C_{14}H_{22}O_5$ (M^+): 270.14672. Found: 270.14603.

4.1.4. Ethyl 2-((*Z*)/(*E*)-8-ethylidene-1,4-dioxaspiro[4.5]-decan-6-yl)-2-methylpropanoate 6a/6b. A solution of *n*-butyllithium in hexanes (2.5 M, 4.90 ml, 12.2 mmol) was added over a 5 min period to a stirred solution of ethyltriphenylphosphonium bromide (4.40 g, 11.8 mmol) in tetrahydrofuran (170 ml) at 0 °C. The resultant orange solution was stirred for 5 min then a solution of ethyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate **5** (2.60 g, 9.63 mmol) in tetrahydrofuran (30 ml) was added. The mixture was stirred for a further 2 h before the solvent was evaporated under reduced pressure and replaced by hexanes, causing precipitation of triphenylphosphine oxide. This precipitate was removed by filtration through a pad of silica using 10% diethyl ether in light petroleum as the eluent. The filtrate was evaporated under reduced pressure to leave a residue, which was purified by filtration through a second pad of silica using 10% diethyl ether in light petroleum as the eluent to give *ethyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]-decan-6-yl)-2-methylpropanoate* **6** (2.50 g, 92%) as a pale yellow oil containing both (*Z*)- and (*E*)-isomers in a ratio of 2:1. IR ν_{max} (film)/cm^{-1} 1736 (C=O) and 1450 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–1.36 (12H, overlapping m), 1.60 (2H, m), 1.79 (1H, m), 1.96 (1H, m), 2.08–2.28 (2H, overlapping m), 2.51+2.65 (total of 1H, both m), 3.79–4.14 (6H, overlapping m, CH_3CH_2, OCH_2CH_2O) and 5.21 (1H, m, $=CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 13.5, 14.6, 20.3, 25.1, 25.8, 27.8, 27.9, 33.9, 34.8, 35.8, 36.9, 42.9, 43.1, 51.2, 51.8, 60.4 (CH_3CH_2), 60.5 (CH_3CH_2), 63.6 (OCH_2CH_2O), 64.6 (OCH_2CH_2O), 111.6 (OCO), 111.7 (OCO), 117.2 ($=CHCH_3$), 117.6 ($=CHCH_3$), 137.8 (C=CH), 137.9 (C=CH), 178.8 (OC=O) and 178.9 (OC=O); HRMS (EI) m/z Calcd for $C_{16}H_{26}O_4$ (M^+): 282.18311. Found: 282.18408.

4.1.5. (*Z*)/(*E*)-8-Ethylidene-6-(2-methylpropan-1-ol-2-yl)-1,4-dioxaspiro[4.5]decane 7a/7b. Lithium aluminium hydride (0.30 g, 7.81 mmol) was added to a stirred solution of ethyl 2-((*Z*)/(*E*)-8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate **6a/6b** (2.20 g, 7.80 mmol) in diethyl ether (100 ml) at 0 °C and the mixture was stirred for a further 1 h. The reaction was quenched by the addition of water (0.3 ml) then 10% aqueous sodium hydroxide solution (0.3 ml) and lastly another portion of water (0.9 ml). This resulted in a white granular precipitate, which was removed by filtration through a pad of kieselguhr that was washed thoroughly with diethyl ether. The filtrate was evaporated under reduced pressure to give *8-ethylidene-6-(2-methylpropan-1-ol-2-yl)-1,4-dioxaspiro[4.5]decane* **7** (1.86 g, 99%) as a colourless oil containing both (*Z*)- and (*E*)-isomers in a ratio of 2:1. IR ν_{max} (film)/cm^{-1} 3489 (O–H) and 1440 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83+0.87 (3H, 2×s, 2×CH_3C), 1.01+1.05 (3H, 2×s, 2×CH_3C), 1.31 (1H, dt, J 13.4 and 4.8), 1.57 (3H, m), 1.69 (1H, dd, J 13.4 and 4.8), 1.83–2.24 (4H, overlapping m), 2.44+2.66 (1H, both m), 3.08 (1H, m), 3.38 (1H, m), 3.55 (1H, m), 3.88–4.22 (4H, overlapping m, OCH_2CH_2O) and 5.16 (1H, m, $=CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 13.1, 22.0, 22.1, 24.6, 27.3, 27.5, 33.3, 35.3, 36.1, 36.4, 38.4, 38.6, 47.8, 48.4, 63.0 (OCH_2CH_2O), 63.4 (OCH_2CH_2O), 71.8 (CH_2OH), 112.9 (OCO), 116.2 ($=CHCH_3$), 116.5 ($=CHCH_3$), 137.8 (C=CH) and 138.0 (C=CH); HRMS (EI) m/z Calcd for $C_{14}H_{24}O_3$ (M^+): 240.17254. Found: 240.17255.

4.1.6. (*Z*)/(*E*)-8-Ethylidene-6-(2-methylpropanal-2-yl)-1,4-dioxaspiro[4.5]decane 8a/8b. The Dess–Martin periodinane (3.26 g, 7.69 mmol) was added to a stirred solution of (*Z*)/(*E*)-8-ethylidene-6-(2-methylpropan-1-ol-2-yl)-1,4-dioxaspiro[4.5]decane (1.50 g, 6.25 mmol) in 10% acetonitrile in dichloromethane (70 ml) at 25 °C. The mixture was stirred for 1 h before the reaction was quenched by the addition of aqueous sodium thiosulfate solution (8.5 g in 20 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). This two phase mixture was stirred vigorously for 30 min before the organic phase was separated, dried, and evaporated under reduced pressure to leave a crude residue, which was purified by filtration through a pad of silica using 20% diethyl ether in light petroleum as the eluent. Evaporation of the solvent under reduced pressure gave *8-ethylidene-6-(2-methylpropanal-2-yl)-1,4-dioxaspiro[4.5]decane* **8** (1.44 g, 97%) as a pale yellow oil containing both (*Z*)- and (*E*)-isomers in a ratio of 2:1. IR ν_{max} (film)/cm^{-1} 2819 (aldehyde C–H), 2710 (aldehyde C–H) and 1727 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99+1.03 (6H, 2×(2×s), 2×(2×CH_3C)), 1.31 (1H, m, $(CH_3)_2CCH$), 1.59 (3H, m, ($=CHCH_3$)), 1.81 (1H, m), 1.91 (1H, m), 2.08 (1H, m), 2.22 (2H, m), 2.54+2.67 (1H, 2×m), 3.62 (1H, q, J 7.1, OCH_2CH_2O), 3.86 (3H, m, OCH_2CH_2O), 5.24 (1H, m, $=CHCH_3$) and 9.31+9.32 (1H, 2×s, O=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 13.2, 16.2, 23.4, 23.5, 24.6, 25.2, 33.4, 34.2, 35.4, 36.4, 46.9, 47.0, 50.5, 51.1, 63.1 (OCH_2CH_2O), 63.7 (OCH_2CH_2O), 111.0 (OCO), 111.1 (OCO), 117.2 ($=CHCH_3$), 117.6 ($=CHCH_3$), 136.9 (C=CH), 137.1 (C=CH), 202.4 (O=CH) and 202.6

(O=CH); HRMS (EI) *m/z* Calcd for $C_{14}H_{22}O_3$ (M^+): 238.15689. Found: 238.15734.

4.1.7. (*Z*)/(*E*)-8-Ethylidene-6-(3-methylbut-1-yn-3-yl)-1,4-dioxaspiro[4.5]decane 9a/9b. Potassium carbonate (1.30 g, 9.42 mmol) was added to a stirred solution of (*Z*)/(*E*)-8-ethylidene-6-(2-methylpropanal-2-yl)-1,4-dioxaspiro[4.5]decane **8a/8b** (1.50 g, 6.30 mmol) and dimethyl (1-diazo-2-oxopropyl)phosphonate (1.82 g, 9.48 mmol) in methanol (40 ml) at 25 °C. The mixture was stirred for 5 d and further portions (5×0.5 equiv) of both potassium carbonate (5×0.43 g) and dimethyl (1-diazo-2-oxopropyl)phosphonate (5×0.60 g) were added to the reaction mixture at regular intervals over this time period. The solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether (50 ml) and water (50 ml). The organic phase was separated and the aqueous phase was extracted with another portion of diethyl ether (50 ml). The combined organic phase was dried, filtered, and evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using 10% diethyl ether in light petroleum as the eluent to give *8-ethylidene-6-(3-methylbut-1-yn-3-yl)-1,4-dioxaspiro[4.5]decane* **9** (1.19 g, 81%) as a pale yellow oil containing both (*Z*)- and (*E*)-isomers in a ratio of 2:1. IR ν_{max} (film)/cm^{-1} 2110 (C≡C) and 1427 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33–1.41 (7H, 1×m+4×s, $(CH_3)_2CCH$), 1.59 (3H, m, (=CHCH_3)), 1.71 (1H, m), 1.84 (1H, m), 1.90–2.28 (3H, overlapping m), 2.45 (1H, m), 2.90 (1H, m), 3.95–4.06 (4H, overlapping m, OCH_2CH_2O) and 5.21 (1H, m, =C*H*CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 13.1, 24.7, 28.3, 28.4, 28.9, 30.2, 30.4, 33.4, 33.5, 34.1, 35.9, 36.9, 37.1, 51.4, 52.0, 63.5 (OCH_2CH_2O), 63.8 (OCH_2CH_2O), 63.9 (OCH_2CH_2O), 68.0 (≡CH), 68.1 (≡CH), 92.8 (C≡), 93.0 (C≡), 112.2 (OCO), 112.3 (OCO), 116.7 (=*C*HCH$_3$), 117.0 (=*C*HCH$_3$), 137.4 (*C*=CH) and 137.7 (*C*=CH); HRMS (EI) *m/z* Calcd for $C_{15}H_{22}O_2$ (M^+): 234.16198. Found: 234.16165. Also isolated from this reaction was the starting aldehyde **8a/8b** (0.14 g).

4.1.8. Hexacarbonyl((*Z*)/(*E*)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro[4.5]decane)-dicobalt-(Co–Co) 10a/10b. A solution of (*Z*)/(*E*)-8-ethylidene-6-(3-methylbut-1-yn-3-yl)-1,4-dioxaspiro[4.5]decane **9a/9b** (1.18 g, 5.04 mmol) in light petroleum (10 ml) was added to a stirred solution of octacarbonyldicobalt (1.78 g, 5.20 mmol) in light petroleum (40 ml) over a 5 min period at 25 °C. The mixture was stirred for 2 h before it was filtered through a pad of silica using 10% diethyl ether in light petroleum as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–10% diethyl ether in light petroleum gradient as the eluent to give *hexacarbonyl((Z)/(E)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro[4.5]decane)dicobalt-(Co–Co)* **10** (2.60 g, 99%) as a red oil containing both (*Z*)- and (*E*)-isomers in a ratio of 2:1. IR ν_{max} (film)/cm^{-1} 2089 (C=O), 2013 (C=O), 1465 (C=C) and 1442 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88–1.44 (7H, m), 1.57–1.76 (4H, m), 1.85–1.99 (1H, m), 2.01–2.23 (2H, m), 2.39–2.53 (1H, m), 2.97 (1H, d, *J* 13.1), 4.02 (4H, m, OCH_2CH_2O), 5.20 (1H, m, =C*H*CH$_3$) and 6.17+6.22 (1H, 2×s, ≡CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 13.7, 14.5, 22.8, 24.8, 28.3, 30.1, 30.2, 32.0, 32.2, 33.5, 34.6, 36.1, 37.0, 37.2, 42.1, 42.3, 52.2, 53.0, 63.3 (OCH_2CH_2O), 63.8 (OCH_2CH_2O), 75.5, 75.9, 113.2 (OCO), 113.4 (OCO), 116.8 (=*C*HCH$_3$), 117.4 (=*C*HCH$_3$), 137.4 (*C*=CH), 137.7 (*C*=CH) and 200.8 (CO); HRMS (EI) *m/z* Calcd for $C_{20}H_{22}Co_2O_7$ (M^+−CO): 492.00295. Found: 492.00162.

4.1.9. Cyclopentenones 11a and 11b. A solution of hexacarbonyl((*Z*)/(*E*)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro[4.5]decane)dicobalt-(Co–Co) **10a/10b** (2:1) (188.0 mg, 0.36 mmol) and *n*-butyl methyl sulfide (0.16 g, 1.54 mmol) in 1,2-dichloroethane (5 ml) was heated under reflux for 30 min. The black mixture was then filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–50% diethyl ether in light petroleum gradient as the eluent to give *cyclopentenones* **11a** and **11b** (90.0 mg, 95% combined) as a 2:1 mixture (by proton-NMR). Compounds **11a** and **11b** were subsequently separated by column chromatography on silica using a 0–30% diethyl ether in light petroleum gradient as the eluent. This afforded **11a** (59.0 mg) and **11b** (31.0 mg) as colourless crystalline solids.

Analytical data for **11a** are as follows: mp 90–91 °C; IR ν_{max} (film)/cm^{-1} 3042 (vinyl C–H), 2978, 2927, 2876, 1702 (C=O) and 1625 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, d, *J* 7.5, CHCH_3), 1.17 (3H, s, $(CH_3)_2$C), 1.28 (1H, m), 1.47 (3H, s, $(CH_3)_2$C), 1.70–2.03 (6H, overlapping m), 2.18 (1H, q, *J* 7.5, C*H*CH$_3$), 3.82 (1H, m, OCH_2CH_2O), 3.91 (2H, m, OCH_2CH_2O), 3.98 (1H, m, OCH_2CH_2O) and 5.70 (1H, s, C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9 (CH*C*H$_3$), 22.8 ((*C*H$_3$)$_2$C), 31.8, 32.7, 32.9 ((*C*H$_3$)$_2$C), 39.3, 42.5 ((CH$_3$)$_2$*C*), 52.7 (*C*HCH$_3$), 55.8 (C*C*HCH$_2$), 57.2 (CH$_2$*C*CHCH$_3$), 63.7 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 110.2 (OCO), 119.8 (*C*H=C), 201.3 (CH=*C*) and 213.8 (C=O); HRMS (EI) *m/z* Calcd for $C_{16}H_{22}O_3$ (M^+): 262.15689. Found: 262.15650. Single crystals of cyclopentenone **11a** were obtained from diethyl ether/light petroleum, mounted in an inert oil, and transferred to the cold gas stream of the diffractometer. *Crystal data*. $C_{16}H_{22}O_3$, *M*=262.16, monoclinic, *a*=6.0402(13), *b*=31.423(4), *c*=7.7111(13) Å, β=107.469(15)°, *U*=1396.1(4) Å^3, *T*=295 K, space group $P2_1/n$ (no. 14), *Z*=4, μ(Mo Kα)=0.085 mm^{-1}, 2977 reflections measured, 2721 unique (R_{int}=0.0609), which were used in all calculations. Final *R*1=0.0481. The final *wR*(F^2) was 0.1418 (all data). See Ref. 12 for full crystal data.

Analytical data for **11b** are as follows: mp 87–88 °C; IR ν_{max} (film)/cm^{-1} 3039 (vinyl C–H), 2966, 2940, 2883, 1702 (C=O), 1625 (C=C), 1453, 1370, 1108 and 1095; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* 7.2, CHCH_3), 1.15 (1H, m), 1.19 (3H, s, $(CH_3)_2$C), 1.47 (3H, s, $(CH_3)_2$C), 1.71–1.86 (4H, overlapping m), 1.97 (1H, d, *J* 5.0, CC*H*CH$_2$), 2.22 (1H, d, *J* 11.8), 2.27 (1H, q, *J* 7.2, C*H*CH$_3$), 3.83 (1H, m, OCH_2CH_2O), 3.91 (2H, m, OCH_2CH_2O), 4.00 (1H, m, OCH_2CH_2O) and 5.80 (1H, s, C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.0 (CH*C*H$_3$), 22.8 ((*C*H$_3$)$_2$C), 31.2, 33.0 ((*C*H$_3$)$_2$C), 33.9 (C*C*H$_2$CH$_2$), 38.0, 42.5 ((CH$_3$)$_2$*C*), 55.2 (*C*HCH$_3$), 56.5 (C*C*HCH$_2$), 56.7 (CH$_2$*C*CHCH$_3$), 63.7 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 110.2 (OCO), 121.1 (*C*H=C), 200.5 (CH=*C*) and 211.6 (C=O); HRMS (EI)

m/z Calcd for $C_{16}H_{22}O_3$ (M^+): 262.15689. Found: 262.15698. Single crystals of cyclopentenone **11b** were obtained from diethyl ether/light petroleum, mounted in an inert oil, and transferred to the cold gas stream of the diffractometer. *Crystal data*. $C_{16}H_{22}O_3$, M=262.16, monoclinic, a=6.069(3), b=16.253(5), c=14.087(3) Å, β=93.40(3)°, U=1387.1(7) Å^3, T=123 K, space group $P2_1/n$ (no. 14), Z=4, μ(Mo Kα)=0.085 mm^{-1}, 3105 reflections measured, 2835 unique (R_{int}=0.032), which were used in all calculations. Final $R1$=0.067. The final $wR(F^2)$ was 0.084 (all data). See Ref. 12 for full crystal data.

4.1.10. Alternative preparations of cyclopentenones 11a and 11b.

4.1.10.1. Use of trimethylamine *N*-oxide. Trimethylamine *N*-oxide dihydrate (0.18 g, 1.62 mmol) was added to a stirred solution of hexacarbonyl((*Z*)/(*E*)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro-[4.5]decane)dicobalt-(Co–Co) **10a/10b** (2:1) (95.0 mg, 0.18 mmol) in acetone (3 ml) at 25 °C. The mixture was stirred for 16 h before it was filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–50% diethyl ether in light petroleum gradient as the eluent to give *cyclopentenones* **11a** and **11b** (43.0 mg, 91% combined) as a 2:1 mixture (by proton-NMR). Analytical data were as given above.

4.1.10.2. Use of *N*-methylmorpholine *N*-oxide. *N*-Methylmorpholine *N*-oxide monohydrate (0.20 g, 1.48 mmol) was added to a stirred solution of hexacarbonyl((*Z*)/(*E*)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro[4.5]decane)dicobalt-(Co–Co) **10a/10b** (2:1) (99.0 mg, 0.19 mmol) in dichloromethane (3 ml) at 25 °C. The mixture was stirred for 16 h before it was filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–50% diethyl ether in light petroleum gradient as the eluent to give *cyclopentenones* **11a** and **11b** (42.0 mg, 84% combined) as a 2:1 mixture (by proton-NMR). Analytical data were as given above.

4.1.10.3. Use of polymer-supported sulfide.[3i] A mixture of hexacarbonyl((*Z*)/(*E*)-8-ethylidene-6-[μ-[(1,2-η:1,2-η)-3-methylbut-1-yn-3-yl]]-1,4-dioxaspiro[4.5]decane)-dicobalt-(Co–Co) **10a/10b** (2:1) (54.0 mg, 0.10 mmol) and polymer-supported sulfide (1 mmol g^{-1}, 0.36 g, 0.36 mmol) in 1,2-dichloroethane (3 ml) was heated under reflux for 30 min. The mixture was then filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–50% diethyl ether in light petroleum gradient as the eluent to give *cyclopentenones* **11a** and **11b** (21.0 mg, 80% combined) as a 2:1 mixture (by proton-NMR). Analytical data were as given above.

4.1.11. Methyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate 12 and methyl 2-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene-6-yl)-2-methylpropanoate 13.

Ytterbium(III) trifluromethanesulfonate trihydrate (20 mg, 0.03 mmol) was added to a stirred solution of 1,4-dioxaspiro[4.5]dec-6-en-8-one **4** (50 mg, 0.32 mmol) and 1-methoxy-1-((trimethylsilyl)oxy)-2-methylpropene (87 mg, 0.50 mmol) in dichloromethane (5 ml) at 25 °C. Stirring was continued for a further 24 h before filtration through a pad of silica using diethyl ether as the eluent to give a crude residue. Separation was achieved using column chromatography eluting with diethyl ether/light petroleum (10–50% mixtures) yielding *methyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate* **12** (55 mg, 67%) and *methyl 2-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro-[4.5]dec-7-ene-6-yl)-2-methylpropanoate* **13** (24 mg, 23%).

Analytical data for **12** are as follows: Found: C, 61.06; H, 7.83. $C_{13}H_{20}O_5$ requires C, 60.96; H, 7.87%; mp 60.6–60.8 °C; IR ν_{max} (film)/cm^{-1} 1698 (C=O) and 1724 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, s, CH_3C), 1.15 (3H, s, CH_3C), 1.71–1.79 (1H, m), 1.98–2.04 (1H, m), 2.37–2.41 (1H, m), 2.47–2.52 (1H, m), 2.53–2.71 (3H, overlapping m), 3.65 (3H, s, CH_3O) and 3.92–4.05 (4H, m, OCH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3C), 27.3 (CH_3C), 33.6 (CH_2), 38.5 (CH_2), 40.0 (CH_2), 42.9 (($CH_3)_2C$), 49.2 (CH), 52.0 (CH_3O), 63.9 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 109.7 (OCO), 178.3 (OC=O) and 210.3 (C=O); HRMS (ES^+) *m/z* Calcd for $C_{13}H_{21}O_5$ (M^++1): 257.1389. Found: 257.1386.

Analytical data for **13** are as follows: Found: C, 58.85; H, 8.56. $C_{16}H_{28}O_5Si$ requires C, 58.56; H, 8.60%; IR ν_{max} (film)/cm^{-1} 1668 (C=C) and 1724 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (9H, s, $(CH_3)_3Si$), 1.14 (3H, s, CH_3C), 1.17 (3H, s, CH_3C), 1.58–1.64 (1H, m), 1.89–1.97 (1H, m), 2.03–2.08 (1H, m), 2.27–2.37 (1H, m), 2.93–2.94 (1H, m), 3.65 (3H, s, CH_3O), 3.72–3.78 (2H, m, OCH_2CH_2O), 3.89–3.96 (2H, m, OCH_2CH_2O) and 4.76–4.78 (1H, m, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.6 ($(CH_3)_3Si$), 20.0, 27.2, 28.4, 31.1, 44.3, 49.8, 51.8, 65.2, 101.8 (C=*C*H), 109.4 (OCO), 152.2 (*C*=CH) and 179.0 (OC=O); HRMS (ES^+) *m/z* Calcd for $C_{16}H_{29}O_5Si$ (M^++1): 329.1784. Found: 329.1789.

4.1.12. Methyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate 12 by hydrolysis of methyl 2-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene-6-yl)-2-methylpropanoate 13.

To a stirred solution of methyl 2-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene-6-yl)-2-methylpropanoate **13** (0.44 g, 1.35 mmol) in diethyl ether (5 ml) aqueous oxalic acid (2% w/w, 5 ml) was added. Stirring was continued for 12 h before saturated aqueous sodium bicarbonate solution (5 ml) was added. Separation and evaporation under reduced pressure gave *methyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate* **12** (0.34 g, 99%). Analytical data were as given above.

4.1.13. Methyl 2-((*Z*)/(*E*)-8-ethylidene-1,4-dioxaspiro-[4.5]decan-6-yl)-2-methylpropanoate 14a/14b.

To a stirred suspension of ethyltriphenylphosphonium bromide (87 mg, 0.234 mmol) in THF (4 ml) at room temperature, a standardised solution of *n*-butyllithium (1.94 M, 0.13 ml, 0.252 mmol) in hexane was added dropwise. Stirring of the resulting orange slurry was continued for 1 h before a solution of methyl 2-(1,4-dioxaspiro[4.5]decan-8-on-6-yl)-2-methylpropanoate **12** (50 mg, 0.195 mmol) in THF (1 ml)

was added. Stirring was continued for a further 16 h before evaporation of the solvent under reduced pressure. Diethyl ether (10 ml) was added before the slurry was sonicated in a cleaning bath for 2 min. Filtration through a pad of silica using diethyl ether as the eluent gave a crude residue, which was purified using column chromatography eluting with diethyl ether/light petroleum (0–40% mixtures). This gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (46 mg, 89%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1.6:1. This ratio was determined by the ^{1}H NMR integration of the signals at δ 2.57–2.59 and 2.60–2.61 ppm; from correlation and full assignment of both the ^{1}H and ^{13}C NMR spectra, these signals were identified as those relating to an allylic cyclohexyl H positioned *syn*- to the olefinic methyl group within the (*E*)- and (*Z*)-isomers, respectively. Found: C, 67.02; H, 9.06. $C_{15}H_{24}O_4$ requires C, 67.14; H, 9.01%; IR ν_{max} (film)/cm^{-1} 1443 (C=C) and 1730 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07–1.18 (m, 6H), 1.20–1.30 (m, 1H), 1.51 (t, 3H, *J* 6.5, C*H*$_3$CH=C), 1.70–1.88 (m, 1H), 1.89–1.91 (m, 1H), 2.08–2.11 (m, 0.61H), 2.12–2.22 (m, 2.39H), 2.57–2.59 (m, 0.39H), 2.60–2.61 (m, 0.61H), 3.75 (s, 3H, CH_3O), 3.76–3.91 (m, 4H, OCH_2CH_2O) and 5.12–5.20 (m, 1H, CH_3CH=C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 20.1, 25.0, 25.7, 27.7, 32.2, 33.2, 33.8, 34.7, 35.6, 36.6, 36.7, 42.9, 51.3, 51.8, 63.5, 64.6, 111.5, 117.1, 137.5 and 179.2; HRMS (ES$^+$) *m/z* Calcd for $C_{15}H_{25}O_4$ (M^++1): 269.1753. Found: 269.1752.

4.1.14. Alternative preparations of alkenes 14a and 14b.

4.1.14.1. Use of NaHMDS and ethyltriphenylphosphonium bromide. Using a similar procedure to that described in Section 4.1.13, with a standardised solution of sodium hexamethyldisilazide (0.273 M, 0.86 ml, 0.234 mmol) in THF, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (40 mg, 77%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.4.

4.1.14.2. Use of KHMDS and ethyltriphenylphosphonium bromide. Using a similar procedure to that described in Section 4.1.13, with a standardised solution of potassium hexamethyldisilazide (0.357 M, 0.67 ml, 0.239 mmol) in THF, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (44 mg, 85%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.3.

4.1.14.3. Use of KHMDS and ethyltriphenylphosphonium chloride. Using a similar procedure to that described in Section 4.1.13, with ethyltriphenylphosphonium chloride (76 mg, 0.234 mmol) and a standardised solution of potassium hexamethyldisilazide (0.357 M, 0.67 ml, 0.239 mmol) in THF, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (41 mg, 79%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.3.

4.1.14.4. Use of KHMDS and ethyltriphenylphosphonium iodide. Using a similar procedure to that described in Section 4.1.13, with ethyltriphenylphosphonium iodide (98 mg, 0.234 mmol) and a standardised solution of potassium hexamethyldisilazide (0.357 M, 0.67 ml, 0.239 mmol) in THF, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (47 mg, 90%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.3.

4.1.14.5. Use of NaHMDS and ethyltriphenylphosphonium chloride. Using a similar procedure to that described in Section 4.1.13, with ethyltriphenylphosphonium chloride (76 mg, 0.234 mmol) and a standardised solution of sodium hexamethyldisilazide (0.273 M, 0.86 ml, 0.234 mmol) in THF, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (39 mg, 75%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.5.

4.1.14.6. Use of NaHMDS and tetraethylphosphonium bromide. Using a similar procedure to that described in Section 4.1.13, with tetraethylphosphonium bromide (53 mg, 0.234 mmol), a standardised solution of sodium hexamethyldisilazide (0.273 M, 0.86 ml, 0.234 mmol) in THF, and sonication for 5 min on reaction work-up, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (39 mg, 75%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:1.1.

4.1.14.7. Use of KHMDS and tetraethylphosphonium bromide. Using a similar procedure to that described in Section 4.1.13, with tetraethylphosphonium bromide (53 mg, 0.234 mmol), a standardised solution of potassium hexamethyldisilazide (0.357 M, 0.67 ml, 0.239 mmol) in THF, and sonication for 5 min on reaction work-up, gave *methyl 2-(8-ethylidene-1,4-dioxaspiro[4.5]decan-6-yl)-2-methylpropanoate* **14** (39 mg, 75%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:1.1.

4.1.15. (*Z*)/(*E*)-8-Ethylidene-6-(2-methylpropan-1-ol-2-yl)-1,4-dioxaspiro[4.5]decane 7a/7b from reduction of methyl 2-((*Z*)/(*E*)-8-ethylidene-1,4-dioxaspiro[4.5]-decan-6-yl)-2-methylpropanoate 14a/14b.

To a stirred solution of methyl 2-((*Z*)/(*E*)-8-ethylidene-1,4-dioxaspiro-[4.5]decan-6-yl)-2-methylpropanoate **14a/14b** (1:2.4) (35 mg, 0.137 mmol) in diethyl ether (5 ml) at room temperature, lithium aluminium hydride (6 mg, 0.15 mmol) was added as a powder. Stirring of the grey emulsion was continued for 1 h at room temperature before water (0.1 ml) was added. Stirring was continued for a further 5 min before addition of aqueous sodium hydroxide solution (10% w/w, 0.1 ml). Finally, water (0.3 ml) was added and the resulting granular precipitate removed by filtration through Celite using diethyl ether as the eluent. Water (30 ml) was added to the filtrate and the organic phase was separated and dried over sodium sulfate to give *8-ethylidene-6-(2-methylpropan-1-ol-2-yl)-1,4-dioxaspiro[4.5]decane* **7a/7b** (32 mg, 97%) as a mixture containing both (*Z*)- and (*E*)-isomers in a ratio of 1:2.4. This ratio was determined by ^{1}H NMR integration as shown below. IR ν_{max} (film)/cm^{-1} 3489 (O–H) and 1440 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (2.13H, s, CH_3), 0.87 (0.87H, s, CH_3), 1.01 (2.13H, s, CH_3), 1.05 (0.87H, s, CH_3), 1.27–1.35 (1H, m), 1.58–1.64 (3H, m), 1.70–1.78 (1H, m), 1.86–1.95 (2H, m), 2.08–2.09 (0.29H, m), 2.15–2.24 (1.71H, overlapping m), 2.47–2.48 (0.29H, m), 2.71–2.74 (0.71H, m), 3.08–3.14 (1H, m), 3.34–3.40 (1H, m), 3.53–3.59 (1H, m), 3.88–4.02 (4H, m) and 5.19–5.24 (1H, m, =C*H*CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 13.1, 22.0, 22.1, 24.6, 27.3, 27.5, 27.6, 33.3, 35.3, 36.1, 36.4, 38.4, 38.6, 47.8, 48.4, 63.0 (OCH_2CH_2O), 63.4 (OCH_2CH_2O), 71.8 (CH_2OH), 112.9 (OCO), 116.2 (=*C*HCH_3), 116.5 (=*C*HCH_3), 137.8 (*C*=CH) and 138.0 (*C*=CH).

4.1.16. Cyclopentenone 11b by epimerisation of cyclopentenone 11a. Cyclopentenone **11a** (25 mg, 0.095 mmol) was treated with lithium hydroxide (11.5 mg, 0.48 mmol) in THF (5 ml) and water (1 ml) at reflux for 3 d. This mixture was then extracted with diethyl ether and the organic phase washed with water before drying over sodium sulfate. This gave a mixture of cyclopentenones **11a** and **11b** in a ratio of 1:9 by ^{1}H NMR integration of the signals at δ 5.70 and 5.80 ppm. Separation of **11a** and **11b** was then achieved as described in Section 4.1.9.

4.1.17. Cyclopentanone 16. Palladium on charcoal (10%, 30 mg) was added to a solution of cyclopentenone **11b** (365.0 mg, 1.39 mmol) in toluene (20 ml). The mixture was placed under 45 psi of hydrogen gas and agitated using a Cook apparatus for 3 h. The mixture was then filtered through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to give *cyclopentanone* **16** (365.0 mg, 99%) as a colourless crystalline solid, mp 44–45 °C; IR ν_{max} (film)/cm^{-1} 2959, 2921, 2876, 1704 (C=O), 1459 and 1363; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, d, J 7.6, CHCH_3), 0.96 (3H, s, (CH_3)$_2$C), 1.22 (3H, s, (CH_3)$_2$C), 1.52 (2H, overlapping m), 1.62–1.69 (2H, overlapping m), 1.75 (1H, m), 1.83–1.94 (2H, m), 2.03 (1H, dt, J 8.6 and 1.2), 2.14 (1H, q, J 7.6, CHCH$_3$), 2.24 (1H, ddd, J 18.2, 6.9 and 1.5, O=CCH_2CH), 2.34 (1H, dd, J 18.1 and 10.8, O=CCH_2CH), 3.76–3.89 (3H, overlapping m, OCH$_2$CH$_2$O) and 3.96 (1H, m, OCH$_2$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8 (CHCH$_3$), 26.7 ((CH_3)$_2$C), 29.2 ((CH_3)$_2$C), 30.5, 31.3, 38.3 (O=CCH$_2$CH), 41.9 ((CH$_3$)$_2$$C$), 42.2 (C$CH_2$CH), 49.4 (CH$_2$$C$CHCH$_3$), 49.5 (O=CCH$_2$$C$H), 50.9 ($CHCH_3$), 56.2 (C$CHCH_2$), 63.4 (O$CH_2CH_2$O), 64.8 (OCH$_2$$CH_2$O), 111.0 (OCO) and 221.4 (C=O); HRMS (EI) m/z Calcd for $C_{16}H_{24}O_3$ (M$^+$): 264.17254. Found: 264.17280. Single crystals of ketone **16** were obtained from diethyl ether/light petroleum, mounted in an inert oil, and transferred to the cold gas stream of the diffractometer. *Crystal data*. $C_{16}H_{24}O_3$, M=264.17, monoclinic, a=8.3280(3), b=8.3930(3), c=10.2120(4) Å, β=106.696(2)°, U=683.70(4) Å^3, T=150 K, space group $P2_1/n$ (no. 14), Z=2, μ(Mo Kα)=0.087 mm^{-1}, 5455 reflections measured, 3107 unique (R_{int}=0.0273), which were used in all calculations. Final $R1$=0.0340. The final $wR(F^2)$ was 0.0825 (all data). See Ref. 12 for full crystal data.

4.1.18. Cyclopentanol 17. Lithium aluminium hydride (37.0 mg, 0.97 mmol) was added to a stirred solution of cyclopentanone **16** (260.0 mg, 0.985 mmol) in diethyl ether (20 ml) at 0 °C. The mixture was stirred for 2 h before it was allowed to warm to 25 °C and the reaction was quenched by the addition of water (0.04 ml) then 10% aqueous sodium hydroxide solution (0.04 ml) and, lastly, another portion of water (0.12 ml). This resulted in a white granular precipitate, which was removed by filtration through a pad of silica using diethyl ether as the eluent. The filtrate was evaporated under reduced pressure to give *cyclopentanol* **17** (259 mg, 99%) as a colourless crystalline solid, mp 75–85 °C; IR ν_{max} (film)/cm^{-1} 3317 (O–H), 2959, 2889, 1459, 1376, 1114 and 1051; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, d, J 7.0, CHCH_3), 0.98 (3H, s, (CH_3)$_2$C), 1.18 (3H, s, (CH_3)$_2$C), 1.28–1.52 (4H, overlapping m), 1.63–1.93 (8H, overlapping m), 3.57 (1H, m, CHOH), 3.75–3.87 (3H, overlapping m, OCH$_2$CH$_2$O) and 3.95 (1H, m, OCH$_2$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (CHCH$_3$), 26.5 ((CH_3)$_2$C), 28.7 ((CH_3)$_2$C), 30.6, 31.9, 35.6 (HOCHCH$_2$CH), 40.7 ((CH$_3$)$_2$$C$), 42.8, 50.2 (CH$_2$$C$CHCH$_3$), 50.4 ($CHCH_3$), 52.6 (HOCHCH$_2$$C$H), 57.9 (C$CHCH_2$), 63.3 (O$CH_2CH_2$O), 64.7 (OCH$_2$$CH_2$O), 81.5 (HOCH) and 111.8 (OCO); HRMS (EI) m/z Calcd for $C_{16}H_{26}O_3$ (M$^+$): 266.18819. Found: 266.18727.

4.1.19. Xanthate ester 18. A solution of *n*-butyllithium in hexanes (2.5 M, 0.30 ml, 0.75 mmol) was added over a 5 min period to a stirred solution of cyclopentanol **17** (187.0 mg, 0.703 mmol) in tetrahydrofuran (5 ml) at 0 °C. The mixture was stirred for 5 min before carbon disulfide (85.0 mg, 0.067 ml, 1.12 mmol) was added and the mixture was allowed to warm to 25 °C. The mixture was stirred for 80 min before the reaction was quenched by the addition of methyl iodide (0.12 g, 0.052 ml, 0.84 mmol) and then stirred for a further 30 min. The mixture was then partitioned between diethyl ether (30 ml) and water (30 ml), the organic phase separated, and the aqueous phase extracted with another portion of diethyl ether (30 ml). The combined organic phase was dried, filtered, and evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–30% diethyl ether in light petroleum gradient as the eluent. This gave *xanthate ester* **18** (235.0 mg, 94%) as a pale yellow oil, which was characterised by infrared and NMR spectroscopy and was then used immediately in the next synthetic step. IR ν_{max} (film)/cm^{-1} 2966, 1485, 1376, 1223 and 1057; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, d, J 7.2, CHCH_3), 1.01 (3H, s, (CH_3)$_2$C), 1.20 (3H, s, (CH_3)$_2$C), 1.47–1.57 (3H, m), 1.68–1.92 (6H, overlapping m), 2.06 (1H, m), 2.23 (1H, m), 2.55 (3H, s, CH_3S), 3.79–3.90 (3H, overlapping m, OCH$_2$CH$_2$O), 3.97 (1H, m, OCH$_2$CH$_2$O) and 5.37 (1H, m, CHOC=S); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 19.0, 26.6, 28.7, 31.9, 32.0, 32.8, 41.3, 42.5, 46.9, 50.0, 52.8, 58.0, 63.8 (OCH$_2$CH$_2$O), 65.2 (OCH$_2$$CH_2$O), 92.1 ($C$HOC=S), 111.5 (OCO) and 216.2 (OC=S).

4.1.20. Acetal 19. A solution of xanthate ester **18** (45.0 mg, 0.126 mmol), tri-*n*-butyltin hydride (0.50 g, 1.71 mmol) and AIBN (13.0 mg, 0.08 mmol) in deoxygenated benzene (20 ml) was heated under reflux for 48 h. The solvent was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 0–20% diethyl ether in light petroleum gradient as the eluent to give *acetal* **19** (24.0 mg, 76%) as a colourless oil. IR ν_{max} (film)/cm^{-1} 2959, 2876, 1472, 1363 and 1102; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, d, J 7.1, CHCH_3), 0.97 (3H, s, (CH_3)$_2$C), 1.17 (3H, s, (CH_3)$_2$C), 1.24–1.90 (13H, overlapping m), 3.78–3.90 (3H, overlapping m, OCH$_2$CH$_2$O) and 3.97 (1H, m, OCH$_2$CH$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (CHCH$_3$), 25.8, 26.9 ((CH_3)$_2$C), 28.2 ((CH_3)$_2$C), 31.4, 31.6, 37.3 (CH_2CHCH$_3$), 41.6 ((CH$_3$)$_2$$C$), 41.7, 41.8 ($CHCH_3$), 53.6 (CH$_2$$C$CHCH$_3$), 56.7 (CH$_2CH_2$CHC), 58.1 (C$CHCH_2$), 63.4 (O$CH_2CH_2$O), 64.8 (OCH$_2$$CH_2$O) and 112.2 (OCO); HRMS (EI) m/z Calcd for $C_{16}H_{26}O_2$ (M$^+$): 250.19328. Found: 250.19432.

4.1.21. Cedrone 15.[2a,e] Triphenylphosphine (2.6 mg, 0.01 mmol) and carbon tetrabromide (3.3 mg, 0.01 mmol) were added to a stirred solution of acetal **19** (32.0 mg,

0.13 mmol) in acetone (5 ml) at 25 °C. The mixture was stirred for 1 h before the solvent was evaporated under reduced pressure to leave a crude residue, which was purified by column chromatography on silica using a 5–20% diethyl ether in light petroleum gradient as the eluent to give *cedrone* **15** (26.1 mg, 99%) as a colourless oil. IR ν_{max} (film)/cm^{-1} 2960, 2877, 1715 and 1460; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, J 7.1, CHCH_3), 1.00 (3H, s, (CH_3)$_2$C), 1.01 (3H, s, (CH_3)$_2$C), 1.42 (1H, m), 1.51 (1H, m), 1.56–1.76 (4H, overlapping m), 1.80–2.00 (4H, overlapping m), 2.27–2.36 (2H, overlapping m, O=CCHCH$_2$+CH$_2$CH_2C=O) and 2.48 (1H, dd, J 18.3 and 7.8, CH$_2$CH_2C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (CHCH$_3$), 25.7, 26.0 ((CH$_3$)$_2$C), 26.4 ((CH$_3$)$_2$C), 32.1, 36.8, 37.0, 41.5, 41.8, 43.0 ((CH$_3$)$_2C$), 54.6 (CH$_2C$CHCH$_3$), 57.1 (CH$_2$CH$_2C$HC), 67.3 (O=CCHCH$_2$) and 214.4 (C=O); HRMS (EI) *m/z* Calcd for $C_{14}H_{22}O$ (M^+): 206.16707. Found: 206.16753.

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Brønsted acid-promoted cyclizations of siloxy alkynes with unactivated arenes, alkenes, and alkynes

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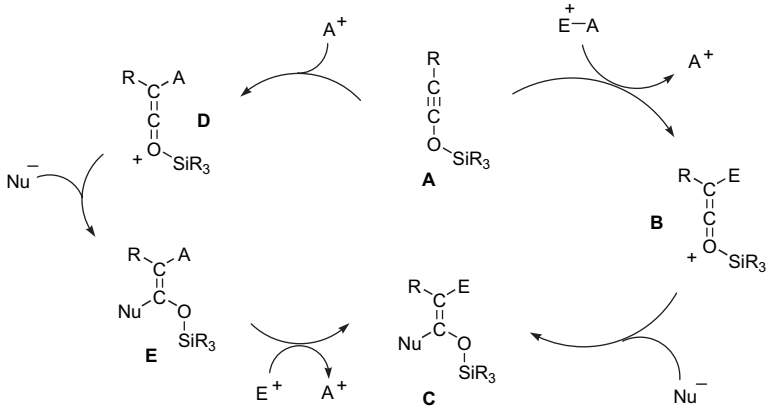
Abstract—In this article, we describe the development of a general concept for the development of new carbon–carbon bond-forming processes, which is based on Brønsted acid-mediated activation of a siloxy alkyne, followed by efficient interception of the resulting highly reactive ketenium ion by unactivated arenes, alkenes or alkynes. We found that trifluoromethane sulfonimide ($HNTf_2$) proved to be a superior promoter of these reactions compared to a range of other Brønsted acids. This finding could be attributed to a high acidity of $HNTf_2$ in aprotic organic solvents combined with a low nucleophilicity of the NTf_2^- anion. Depending on the nature of the nucleophile, the carbocyclizations proceeded either via *6-endo-dig* or *5-endo-dig* manifolds. In the case of 1-siloxy-1,5-diynes, the cyclizations occurred with a concomitant halide abstraction or arylation.

1. Introduction

Invention of efficient reactions that enable formation of new carbon–carbon bonds is of central significance in organic synthesis. Our laboratory has been engaged in a comprehensive investigation of fundamental reactivity of siloxy alkynes as a prelude to the development of a series of new carbon–carbon bond-forming processes.[1] While enol silanes have been extensively employed in organic synthesis,[2] siloxy alkynes have only been utilized in a very few transformations prior to our work,[3] including Arens olefination[4] and Danheiser benzannulation.[5] We felt that siloxy alkynes had a significantly greater potential for the development of an arsenal of new reactions of broad applicability. We anticipated that such processes could be enabled by two alternative modes of activation depicted in Scheme 1. The first pathway is based on the LUMO-lowering activation of an electrophile, which is expected to react with electron-rich alkyne **A**; subsequent trapping of the ketenium intermediate **B** would give the expected product **C**. Alternatively, direct activation of the alkyne **A** by either a soft or hard π-acid would generate a highly reactive intermediate **D**, which would be expected to react with appropriate nucleophiles and electrophiles to give **C**. It is important to note that siloxy



Scheme 1. General strategy for siloxy alkyne activation.

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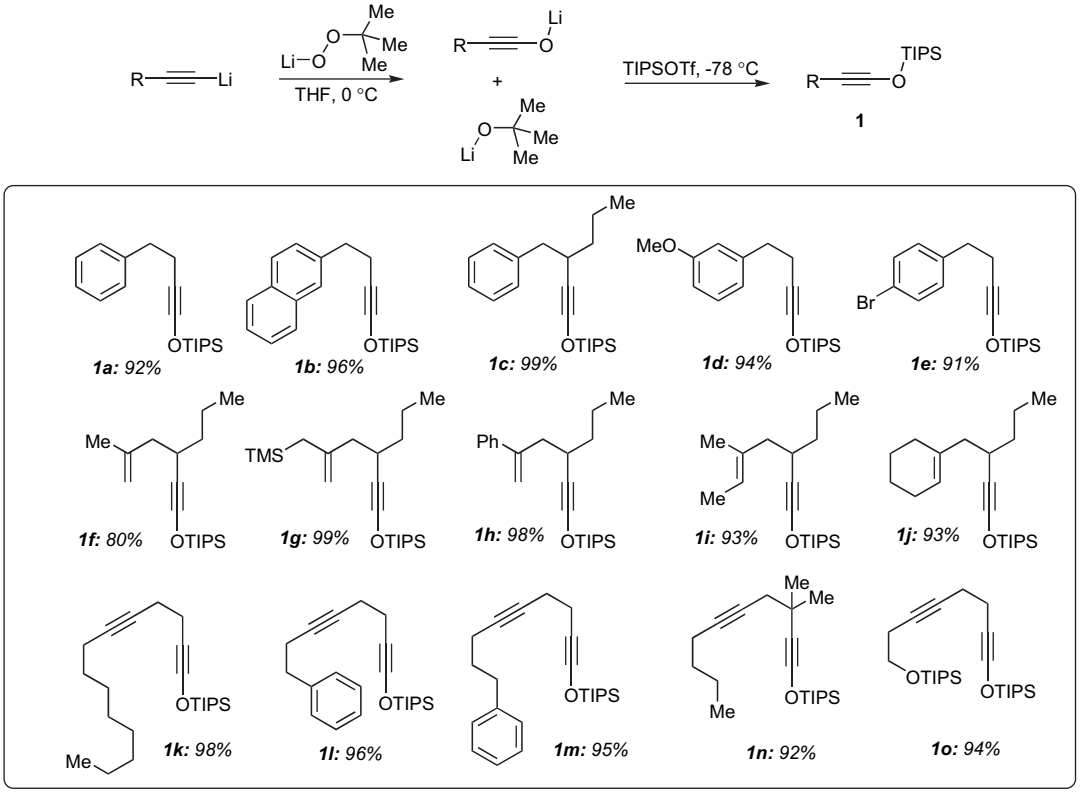
alkynes would offer a unique platform for the generation of highly reactive ketenium ions **B** an **D**, which cannot be obtained from the corresponding ketenes.[6] Due to the high reactivity of ketenium ions, we anticipated that a broad range of nucleophiles and electrophiles could be potentially employed. The challenge was to ensure that these highly reactive intermediates would undergo productive bond-forming transformations. In this account, we describe the full details of our investigation that resulted in the successful development of a series of new Brønsted acid-promoted carbocyclizations of siloxy alkynes with unactivated arenes, alkenes, and alkynes.

2. Siloxy alkynes: preparation

The general approach for the preparation of siloxy alkynes relies on O-silylation of the corresponding ynolate anion. Bulky silyl groups, i.e., TBS or TIPS, must be employed to ensure sufficient hydrolytic stability of the resulting ynol silanes. Several methods for the generation of ynolate anions have been developed.[7] During our studies, we found that the protocol reported by Julia in 1993[8] represents a simple, versatile, and highly efficient approach to a range of structurally diverse siloxy alkynes. The Julia method entails the generation of the acetylide anion from the corresponding terminal alkyne, followed by the addition of lithium *tert*-butyl hydroperoxide,[9] at 0 °C which promotes facile oxidation of the lithium acetylide to give lithium ynolate and lithium *tert*-butoxide (Scheme 2). While silyl chloride was employed in the original Julia's report to furnish the corresponding siloxy alkyne in 60% yield, we found that the use of triisopropylsilyl trifluoromethanesulfonate (TISPOTf) resulted in formation of the desired siloxy alkynes in excellent isolated yields. This modification also enables the use of only 1 equiv of the silylating agent to enable selective silylation of the ynolate anion in the presence of a bulkier lithium *tert*-butoxide. The Julia protocol was employed for the preparation of a series of 1-siloxy-1-alkynes **1**, which were required for this study (Scheme 2). We found that the Kowalski protocol[7d] was better suited for the preparation of siloxy alkynes **1n**. While siloxy alkynes are stable toward bulb-to-bulb distillation, in many instances, the products were obtained in a sufficiently pure form for the use in the next transformation directly.

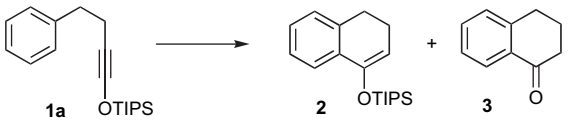
3. Development of arene–siloxyalkyne carbocyclizations

Our investigation of the cyclization of 4-phenyl-1-siloxy-1-butyne (**1a**, Scheme 3) began with an examination of a range of metal salts known to promote alkyne carbocyclizations, including $PtCl_2$, $GaCl_3$, $HfCl_4$, and $Hg(OTf)_2$.[10] Unfortunately, formation of the desired cyclization product **2** was not observed under a range of reaction conditions examined. Prompted by our recently developed [2+2] cycloadditions of siloxy alkynes, we decided to examine several silver-based catalysts. Indeed, we found that treatment of alkyne **1a** with $AgNTf_2$ (20 mol %) resulted in the formation of silyl enol ether **2** in 65% isolated yield (Scheme 3). Interestingly, the use of AgOTf gave rise to the isolation of tetralone **3** as a sole reaction product, albeit in a low yield. This dramatic difference in the outcome of these two experiments indicated that the nature of silver counterion played a dominant role in controlling the efficiency and the outcome of the reaction. In order to probe the role of silver in the process, we subjected



Scheme 2. Preparation of siloxy alkynes.

alkyne **1a** to $HNTf_2$ (10 mol %), which resulted in a facile cyclization to give the same product **2** that was observed using $AgNTf_2$. A series of additional studies indicated that $HNTf_2$, which is produced following the rearomatization event, was most likely the active catalyst when $AgNTf_2$ was employed initially for cyclization of **1a**. Interestingly, the efficiency of the reaction diminished significantly when TfOH was employed favoring the formation of tetralone **3**. Thus, the optimized conditions for the cyclizations of **1a** entailed the use of 10 mol % of $HNTf_2$ at ambient temperature to give silyl enol ether **2** in 86% isolated yield.[11]

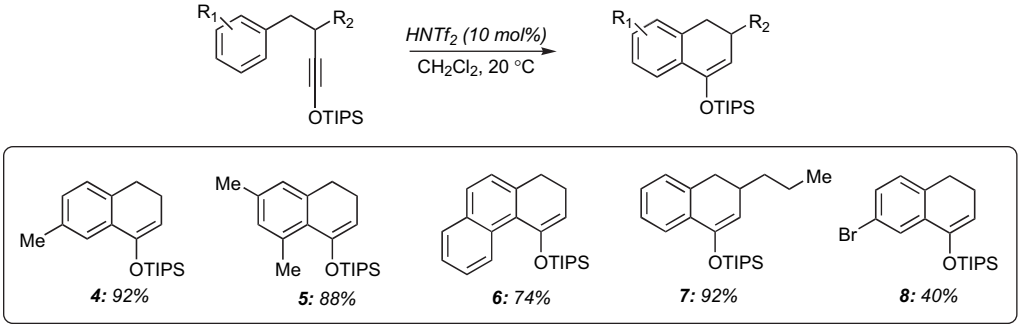


$AgNTf_2$ (20 mol%)	65%	none
AgOTf (20 mol%)	none	15%
$HNTf_2$ (10 mol%)	86%	none
HOTf (20 mol%)	none	25%

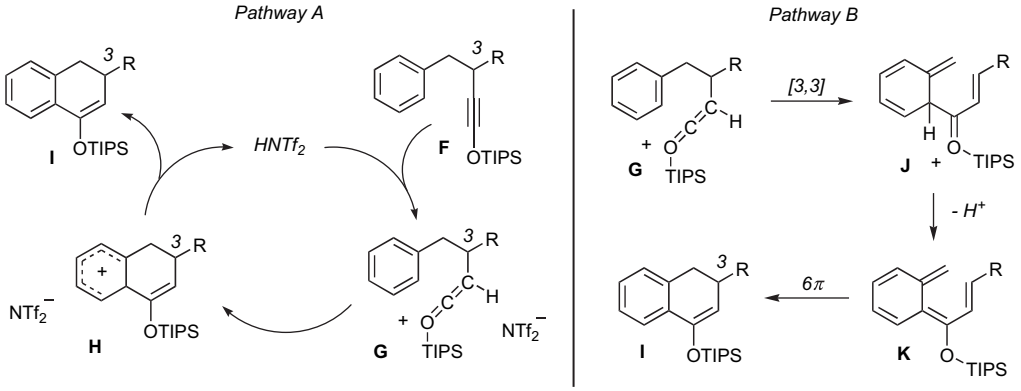
Scheme 3. Effect of silver salts and Brønsted acids on carbocyclization of alkyne **1a**.

Having established an effective reaction protocol, we examined the scope of arene substitution in this process. We found that di- and tri-alkyl substituted benzenes efficiently participated in the cyclization to give the expected silyl enol ethers **4** and **5**, respectively (Scheme 4). Furthermore, 2-naphthyl-1-siloxy-1-butyne afforded tricyclic enol silane **6** in 74% yield. Alkyl substitution at the 3-position of the alkyne was well tolerated as demonstrated by efficient assembly of silyl enol ether **7**. Importantly, the chirality of this product was fully preserved when the starting silyl enol ether was prepared in highly enantiomerically enriched form via semi-preparative HPLC using a chiral stationary phase. In addition to expanding the scope of the process, this experiment provided an important mechanistic probe (vide infra). It is highly noteworthy that successful participation of a range of unactivated arenes in the carbocyclization with siloxy alkynes distinguishes this process uniquely from the metal-mediated carbocyclizations of alkynes that generally require electron-rich arenes or alkenes.[10] Indeed, as expected, introduction of electron-donating substitution into the arene moiety resulted in a facile cyclization to give silyl enol ether as a 72:25 mixture of *para/ortho* cyclized products in combined yield of 84% (not shown). Bromine substitution was also tolerated. However, the product **8** was obtained in lower yield, presumably due to the electron-withdrawing effect of the halogen atom.

Based on the results obtained in the studies described above, we propose that the cyclization reaction proceeds via a mechanism depicted in Scheme 5A. The catalytic process begins with the protonation of siloxy alkyne **F** by $HNTf_2$ to give highly reactive ketenium ion **G**, which is poised for intramolecular interception by the arene to give σ-complex **H**. Elimination of the proton regenerates the Brønsted acid catalysts and affords the observed enol silane **I**. We believe that the low nucleophilicity of the NTf_2^- anion is crucial for enabling the formation and effective interception of highly reactive ketenium ion **G**. An alternative mechanism shown in Scheme 5B involving a [3,3]-sigmatropic rearrangement of ketenium ion **G**, followed by 6π-electron cyclization of intermediate **K** would result in racemization of stereogenic



Scheme 4. Scope of arene–siloxyalkyne carbocyclizations catalyzed by $HNTf_2$.

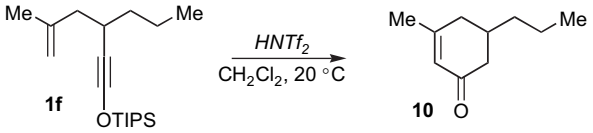


Scheme 5. Mechanism of the arene–siloxyalkyne carbocyclization.

center at the C(3) position of **I** (see Scheme 4), which was not observed.

4. Development of 1-siloxy-1,5-enyne carbocyclizations

We next examined the possibility of achieving the 6-*endo-dig* carbocyclization of the 1-siloxy-1,5-enyne **1f** to give cyclohexenone **10** (Scheme 6) or the corresponding silyl enol ether (not shown). Since $HNTf_2$ proved effective in catalyzing the corresponding arene alkyne cyclizations, our study began by treatment of enyne **1f** with 10 mol % of this Brønsted acid (Scheme 6). Indeed, the desired enone **10** was produced, albeit in low isolated yield. Further studies depicted in Scheme 6 demonstrated that $HNTf_2$ could indeed promote the efficient conversion of enyne **1f** to enone **10**. However, the stoichiometric amount of acid was required to accomplish this transformation; enone **10** was obtained in 74% isolated yield employing 120 mol % of $HNTf_2$.



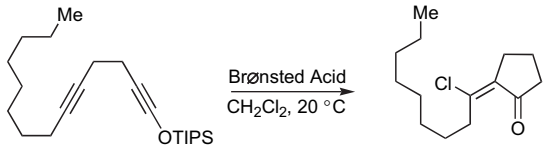
$HNTf_2$	Yield, %
10 mol%	20
50 mol%	50
120 mol%	74

Scheme 6. Development of $HNTf_2$-promoted 1-siloxy-5,1-enyne cyclization.

Investigation of the scope of $HNTf_2$-promoted siloxy enyne cyclization is summarized in Scheme 7. Cyclization of phenyl-substituted enyne proceeded efficiently to give phenyl cyclohexanone **11** in 80% yield. Similarly, treatment of enyne containing an allyl silane functionality (R_1=CH_2TMS) resulted in facile formation of enone **10** with a concomitant loss of trimethyl silyl group. During these studies, we found that an alternative protocol, which entailed the use of 1–4 equiv of MsOH in CH_2Cl_2 proved more effective for a series of other enones shown in Scheme 7, which corresponded to the cyclizations of either trisubstituted or monosubstituted alkenes. Indeed, under these conditions, enones **12** and **13** were obtained in good to excellent yields, further expanding the scope of this process. Our efforts to identify a catalytic protocol to effect these siloxy enyne cyclizations have been thus far unsuccessful. The challenge entails the ability to regenerate the active Brønsted acid catalyst upon loss of the proton following the initial carbon–carbon bond-forming event.

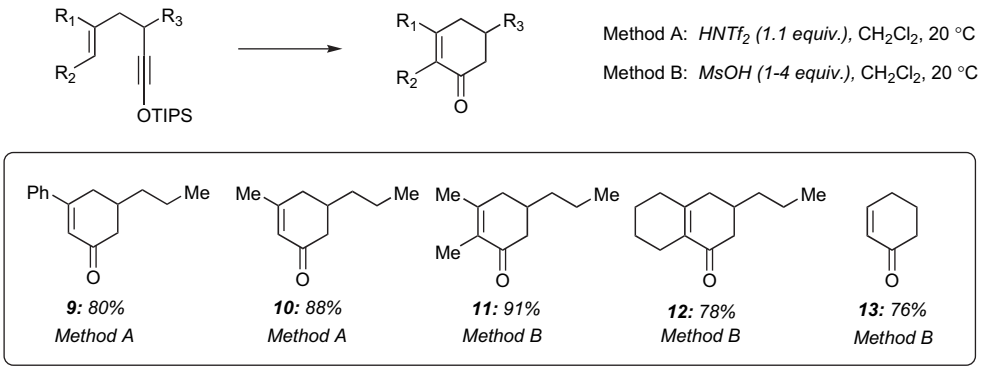
5. Development of 1-siloxy-1,5-diyne carbocyclizations

Having established that $HNTf_2$ was capable of efficient activation of siloxy alkynes toward intramolecular trapping by unactivated arenes and alkenes, we next examined the application of this concept to the carbocyclization of 1-siloxy-1,5-diynes. It was our expectation that Brønsted acid would promote chemoselective activation of the more electron-rich siloxy alkyne, which should enable the carbocyclization via an intramolecular attack by the other alkyne fragment. 1-Siloxy-1,5-diyne **1k** (Scheme 8) was prepared according to the Julia protocol described above. Treatment of 1-siloxy-1,5-diyne **1k** with $HNTf_2$ (110 mol %) in CH_2Cl_2 resulted in an efficient transformation of **1k** to a new product, which was isolated in 70% yield. Analysis of the reaction by GC–MS indicated incorporation of the chlorine atom into the reaction product. Based on the combination of COSY, NOESY, and HMBC experiments, the structure of the reaction product was assigned as enone **14**, which was generated as a single alkene isomer. This assignment was further confirmed by the synthesis of **14** using an independent method.[12] Interestingly, the outcome of the carbocyclization of 1-siloxy-1,5-diyne **1k** was significantly different from that observed in our prior studies of cyclizations of siloxy alkynes with arenes and alkenes. Not only the diyne carbocyclization favored the 5-*endo-dig* pathway, but also the



$HNTf_2$ (1.1 equiv)	70%
HBF_4 (1.1 equiv)	32%
TfOH (1.1 equiv)	22%
TFA (1.1 equiv)	20%
TsOH (1.1 equiv)	<5%

Scheme 8. Development of $HNTf_2$-promoted 1-siloxy-1,5-diyne cyclization.



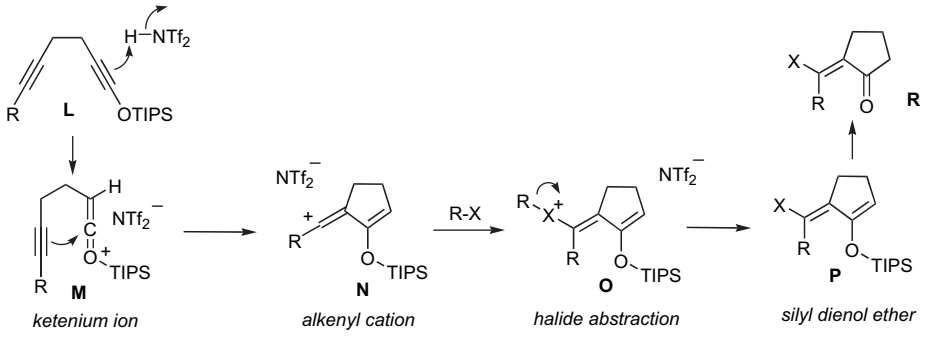
Scheme 7. Scope of $HNTf_2$-promoted 1-siloxy-5,1-enyne cyclization.

process proceeded with a concomitant incorporation of the chloride originating exclusively from CH_2Cl_2. Subsequent studies revealed that $HNTf_2$ proved superior to any of the other Brønsted acids examined (Scheme 8). While HBF_4, TfOH, and TFA were able to promote the reaction, the efficiency of the process deteriorated significantly (32%, 22%, and 20% yields, respectively). Interestingly, the use of either CSA or anhydrous HCl resulted in the formation of uncyclized products resulting from the hydrolysis of siloxyalkyne to the corresponding silyl ester and acid chloride, respectively.

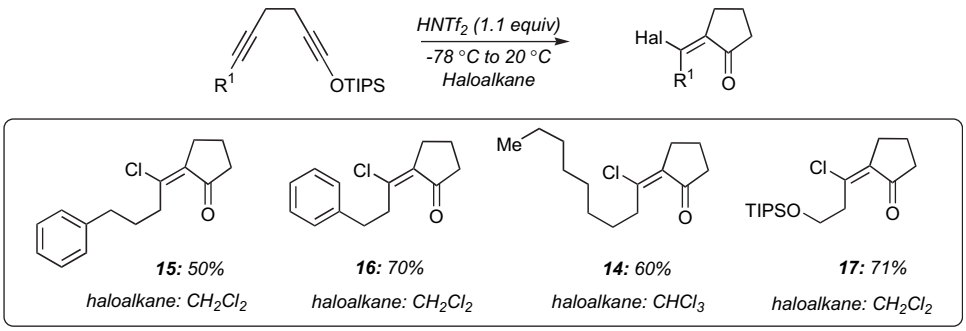
We propose that carbocyclization of 1-siloxy-1,5-diynes proceeds according to the reaction mechanism depicted in Scheme 9. Initial protonation occurs chemoselectively at the more electron-rich siloxy alkyne to give an intermediate ketenium ion **M**. This highly reactive cation is poised for *5-endo-dig* intramolecular interception by the proximate alkyne to give alkenyl cation **N**, which in turn abstracts a chloride ion from CH_2Cl_2 presumably via the intermediacy of halonium ion **O**. The final step entails the protodesilylation of enol silane **P** to give enone **R**. The silyl enol ether can be detected and isolated as the major product by conducting the reaction in the presence of substoichiometric amount (20–30 mol %) of $HNTf_2$ or by subjecting a diyne **L** to 110 mol % of $HNTf_2$, followed by treatment of the crude reaction mixture with Et_3N. Importantly, halide abstraction by structurally different alkenyl cations finds two precedents in the literature,[13] which provides further support for our mechanistic analysis. Furthermore, subsequent GC–MS analysis of the cyclization, which was performed in the presence of MeOH, revealed the formation of XCH_2OMe providing another evidence of the generation of XCH_2^+ cations in the reaction mixture.

Our initial investigation of the scope of this process is depicted in Scheme 10. We found that a range of diyne substitution was well tolerated in the reaction. Subjection of phenyl-substituted diynes to the general reaction protocol (1.1 equiv $HNTf_2$, CH_2Cl_2, 20 °C) efficiently afforded the expected enones **15** and **16**. Interestingly, the chloride abstraction was favored over the possible intra- or intermolecular arylation of the intermediate alkenyl cation. We found that the replacement of CH_2Cl_2 with $CHCl_3$ as a reaction medium was also effective in producing enone **14**. Furthermore, TIPS-protected primary alcohol in enone **17** was retained under the standard cyclization conditions, demonstrating that the reaction protocol was fully compatible with the use of silyl protecting group despite the presence of a strong Brønsted acid.

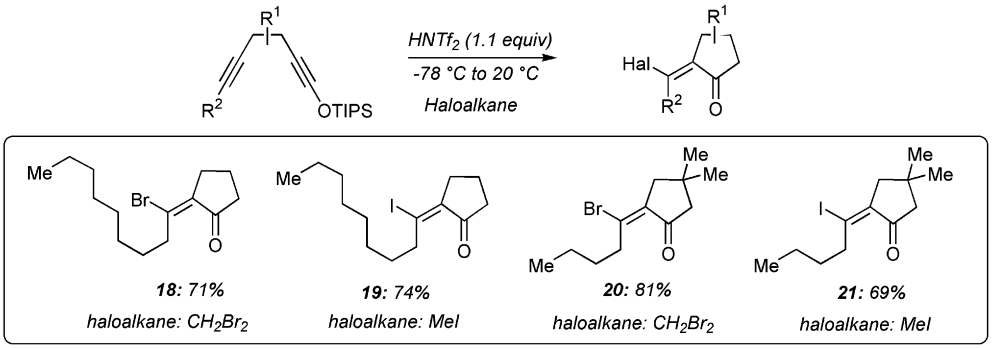
Having observed efficient chloride abstraction in the cyclizations described above, we decided to examine next the possibility of incorporation of other halides into the enone products. Subjection of diyne **1k** to $HNTf_2$ (1.1 equiv) in CH_2Br_2 afforded β-bromo enone **18** in 71% yield (Scheme 11) as a single alkene isomer. The use of MeI as a reaction solvent resulted in efficient formation of the expected iodoenone **19**. Subjection of 3,3-dimethyl siloxy diyne to $HNTf_2$ in either CH_2Br_2 or MeI afforded the corresponding enones **20** and **21**, indicating that the increased steric congestion proximate to the siloxy alkyne moiety did not lower the reaction efficiency. It is noteworthy that excellent diastereoselectivity of the present method combined with the ability to access a range of β-halo enones compares this approach favorably to other known methods for the preparation of this class of compounds. At present, however, this concept could not be extended to cyclizations of homologous 1-siloxy-1,6-enynes.



Scheme 9. Mechanism of the siloxy diyne carbocyclization.

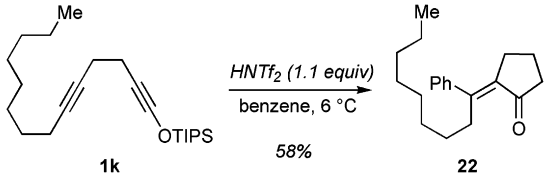


Scheme 10. Scope of siloxy diyne cyclization using CH_2Cl_2 and $CHCl_3$.



Scheme 11. Scope of siloxy diyne cyclization using CH_2Br_2 and MeI.

During these studies, we also discovered that generation of alkenyl cations could enable carbon–carbon bond-forming event via an intermolecular arylation. Indeed, treatment of diyne **1k** with $HNTf_2$ in benzene afforded tetrasubstituted enone **22** (Scheme 12), which was generated as a single detectable alkene isomer. The alkene geometry is controlled, presumably, via a less sterically hindered approach of the nucleophile *syn* to the methylene moiety of the alkenyl cation (Scheme 9).



Scheme 12. $HNTf_2$-promoted 1-siloxy-1,5-diyne cyclization–arylation.

6. Concluding remarks

We have presented a broadly useful concept for Brønsted acid-based activation of siloxy alkynes that enabled the development of a series of new carbocyclization reactions via the intermediacy of highly reactive ketenium ions. We found that trifluoromethane sulfonimide $HNTf_2$ proved to be superior reaction promoter compared to a range of other Brønsted acids.[14] This finding could be attributed to a high acidity of $HNTf_2$ in aprotic organic solvents combined with a low nucleophilicity of the NTf_2^- anion. Depending on the nature of the nucleophile, the carbocyclizations proceeded either via *6-endo-dig* or *5-endo-dig* manifolds. In the case of 1-siloxy-1,5-diynes, the cyclizations occurred with a concomitant halide abstraction or arylation.

7. Experimental

7.1. General

Ethyl acetate (ACS grade), hexanes (ACS grade), and diethyl ether (ACS grade) were purchased from Fisher Scientific and used without further purification. Anhydrous dichloromethane (HPLC grade) was purified by distillation over calcium hydride. Anhydrous tetrahydrofuran was freshly distilled from sodium–benzophenone. Triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) was distilled under reduced pressure over calcium hydride. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Whatman precoated silica gel plates. Flash column chromatography was performed over silacycle silica gel (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-400 or DMX-500 spectrometers using residue solvent peaks as internal standards. Infrared spectra were recorded with a Nicolet FTIR spectrometer and are reported in reciprocal centimeter (cm^{-1}). Mass spectra were recorded with a Varian Saturn 2000 GC–MS using EI method or an Agilent 1100 LCMS using APCI or ES methods. Preparation of terminal alkynes was described in detail in our previous reports.[1d,f]

7.2. Procedure for the preparation of siloxy alkynes

Anhydrous *tert*-butyl hydroperoxide (TBHP) was prepared following a detailed literature procedure.[9] *Caution: solutions of oxidants and oxidizable substrates are potentially hazardous and possibly subject to violent decomposition by adventitious catalysts*. Safety considerations related to handling solutions of TBHP have been previously discussed. See Ref. 9 and further references cited therein. A solution of alkyne (2 mmol) in THF (10 mL) was treated at −78 °C with freshly prepared 1.0 M solution of LiHMDS in THF (2.4 mL). At the same time, a solution of lithium *tert*-butyl peroxide was generated by treating a solution of anhydrous *tert*-butyl hydrogen peroxide (3.7 M in toluene, 2.4 mmol, 0.65 mL) in THF (10 mL) with 1.0 M LiHMDS (2.6 mL) at −78 °C. Lithium *tert*-butyl peroxide solution was transferred to the alkynyl lithium solution via cannula and the resulting mixture was allowed to warm to 0 °C over 0.5 h, stirred at the same temperature for 2 h and cooled to −78 °C before triisopropylsilyl trifluoromethanesulfonate (2.6 mmol, 0.7 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C, stirred for 0.5 h and diluted with hexanes (50 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (40 mL), H_2O (40 mL), and brine (30 mL), then dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to purification via bulb-to-bulb distillation.

7.2.1. Siloxy alkyne 1a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, 2H, J=7.1, 8.1 Hz), 7.21 (d, 2H, J=8.1 Hz), 7.18 (t, 1H, J=7.1 Hz), 2.75 (t, 2H, J=7.5 Hz), 2.39 (t, 2H, J=7.5 Hz), 1.21 (h, 3H, J=7.3 Hz), 1.09 (d, 18H, J=7.3 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 128.4, 128.2, 125.9, 87.2, 36.4, 29.9, 19.3, 17.3, 11.8; IR (neat, cm^{-1}) 3296, 2945, 2868, 2279, 1603, 1454; MS (APCI) calculated for $[C_{19}H_{31}OSi]^+$: 303.21; found: 303.1.

7.2.2. Siloxy alkyne 1b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.72 (m, 3H), 7.66 (s, 1H), 7.47–7.41 (m, 2H), 7.37 (d, 1H, J=8.5 Hz), 2.93 (t, 2H, J=7.5 Hz), 2.51 (t, 2H, J=7.5 Hz), 1.15 (h, 3H, J=7.5 Hz), 1.04 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 133.5, 132.1, 127.7, 127.5, 127.4, 127.2, 126.6, 125.1, 87.4, 36.4, 29.8, 19.2, 18.0, 17.3, 11.7; IR (neat, cm^{-1}) 2945, 2867, 2278, 1463; MS (APCI) calculated for $[C_{23}H_{33}OSi]^+$: 353.23; found: 353.2.

7.2.3. Siloxy alkyne 1c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 2.69 (d, 2H, J=7.0 Hz), 2.56 (m, 1H), 1.57 (m, 1H), 1.44–1.30 (m, 3H), 1.20 (h, 3H, J=7.5 Hz), 1.09 (d, 18H, J=7.5 Hz), 0.89 (t, 3H, J= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 129.2, 127.9, 125.7, 88.5, 42.8, 37.8, 33.5, 32.2, 20.5, 17.3, 13.9, 11.7; IR (neat, cm^{-1}) 3063, 3027, 2946, 2868, 2273, 2077, 1604, 1464; MS (APCI) calculated for $[C_{22}H_{37}OSi]^+$: 345.26; found: 345.2.

7.2.4. Siloxy alkyne 1d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, 1H, J=8.0 Hz), 6.80 (d, 1H, J=8.0 Hz), 6.76 (s, 1H), 6.74 (d, 1H, J=8.0 Hz), 3.80 (s, 3H), 2.74 (t, 2H, J=7.5 Hz), 2.39 (t, 2H, J=7.5 Hz), 1.19 (h, 3H, J=7.5 Hz), 1.09 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 143.1, 129.1, 120.8, 114.2, 111.2, 87.2, 55.1, 36.5, 29.9, 19.2, 17.3, 11.7; IR (neat, cm^{-1}) 2946, 2868, 2279, 1602, 1585, 1490; MS (APCI) calculated for $[C_{20}H_{33}O_2Si]^+$: 333.22; found: 333.2.

7.2.5. Siloxy alkyne 1e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, 2H, J=8.5 Hz), 7.08 (d, 2H, J=8.5 Hz), 2.69 (t, 2H, J=7.5 Hz), 2.37 (t, 2H, J= 7.5 Hz), 1.17 (h, 3H, J=7.0 Hz), 1.06 (d, 18H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 131.2, 130.3, 119.7, 87.5, 35.6, 29.4, 19.1, 17.3, 11.7; IR (neat, cm^{-1}) 2945, 2867, 2279, 1592, 1488, 1463; MS (APCI) calculated for $[C_{19}H_{30}BrOSi]^+$: 381.12; found: 381.1.

7.2.6. Siloxy alkyne 1f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.71 (s, 1H), 2.43 (m, 1H), 2.13–2.05 (m, 2H), 1.71 (s, 3H), 1.54 (m, 1H), 1.42–1.31 (m, 3H), 1.25 (h, 3H, J=7.5 Hz), 1.11 (d, 18H, J=7.5 Hz), 0.89 (t, 3H, J= 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 111.6, 88.0, 44.9, 38.0, 33.6, 28.5, 22.2, 20.5, 17.4, 13.9, 11.8; IR (neat, cm^{-1}) 2947, 2869, 2274, 2078, 1649, 1464; MS (APCI) calculated for $[C_{19}H_{37}OSi]^+$: 309.26; found: 309.2.

7.2.7. Siloxy alkyne 1g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (s, 1H), 4.56 (s, 1H), 2.42 (m, 1H), 2.08 (dd, 1H, J=8.5, 14.5 Hz), 1.58–1.48 (m, 2H), 1.42–1.32 (m, 2H), 1.24 (h, 3H, J=7.5 Hz), 1.12 (d, 18H, J=7.5 Hz), 1.07 (m, 2H), 0.87 (t, 3H, J=7.0 Hz), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 108.8, 88.0, 45.3, 38.0, 33.9, 28.7, 26.5, 20.5, 17.4, 14.0, 11.8, −1.3; IR (neat, cm^{-1}) 3073, 2955, 2869, 2274, 2078, 1632, 1464; MS (APCI) calculated for $[C_{22}H_{45}OSi_2]^+$: 381.30; found: 381.2.

7.2.8. Siloxy alkyne 1h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, 2H, J=7.5 Hz), 7.31 (dd, 2H, J=6.0, 7.5 Hz), 7.25 (t, 1H, J=6.0 Hz), 5.29 (d, 1H, J=1.5 Hz), 5.12 (d, 1H, J=1.5 Hz), 2.63 (dd, 1H, J=7.0, 9.0 Hz), 2.57 (dd, 1H, J=6.5, 9.0 Hz), 2.35 (m, 1H), 1.53 (m, 1H), 1.43–1.23 (m, 6H), 1.12 (d, 18H, J=7.5 Hz), 0.85 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 141.2, 128.2, 127.2, 126.3, 114.0, 88.2, 42.6, 37.9, 33.6, 28.8, 20.4, 17.4, 14.0, 11.8; IR (neat, cm^{-1}) 3082, 2947, 2868, 2273, 2076, 1628, 1464, 1385; MS (APCI) calculated for $[C_{24}H_{39}OSi]^+$: 371.28; found: 371.2.

7.2.9. Siloxy alkyne 1i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (q, 1H, J=5.5 Hz), 2.40 (m, 1H), 2.04 (m, 2H), 1.58–1.51 (m, 7H), 1.36–1.32 (m, 3H), 1.28–1.21 (m, 3H), 1.11 (d, 18H, J=7.5 Hz), 0.88 (t, 3H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 120.0, 88.0, 46.8, 38.0, 33.9, 28.6, 20.5, 17.3, 15.4, 14.0, 13.3, 11.8; IR (neat, cm^{-1}) 2947, 2869, 2273, 2077, 1602, 1464; MS (APCI) calculated for $[C_{20}H_{39}OSi]^+$: 323.28; found: 323.2.

7.2.10. Siloxy alkyne 1j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (s, 1H), 2.38 (m, 1H), 2.05–1.83 (m, 6H), 1.60–1.50 (m, 5H), 1.41–1.37 (m, 2H), 1.23 (h, 3H, J=7.5 Hz), 1.11 (d, 18H, J=7.5 Hz), 0.88 (t, 3H, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 122.5, 87.8, 45.3, 38.1, 33.9, 28.3, 28.1, 25.3, 23.0, 22.5, 20.5, 17.4, 14.0, 11.7; IR (neat, cm^{-1}) 2929, 2868, 2273, 1607, 1464; MS (APCI) calculated for $[C_{22}H_{40}OSi]^+$: 349.29; found: 349.5.

7.2.11. Siloxy alkyne 1k. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30–2.24 (m, 4H), 2.14–2.11 (m, 2H), 1.51–1.44 (m, 2H), 1.34–1.22 (m, 13H), 1.13–1.12 (d, 18H, J=7.5 Hz), 0.88 (t, 3H, J=6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.3, 80.7, 79.2, 31.9, 29.5, 29.2, 29.1, 29.1, 28.9, 22.7, 20.4, 18.7, 18.2, 17.3, 14.1, 11.8; IR (neat, cm^{-1}) 2928, 2868, 2361, 2281; MS (APCI) calculated for $[C_{23}H_{43}OSi]^+$: 363.31; found: 363.3.

7.2.12. Siloxy alkyne 1l. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.24–7.21 (m, 3H), 2.82 (t, 2H, J=7.5 Hz), 2.46–2.42 (m, 2H), 2.31–2.26 (m, 4H), 1.32–1.24 (m, 3H), 1.15 (d, 18H, J=4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 128.4, 128.3, 126.1, 87.4, 80.1, 80.0, 35.5, 29.4, 21.0, 20.3, 18.1, 17.3, 11.8; IR (neat, cm^{-1}) 3028, 2945, 2868, 2280, 1604; MS (APCI) calculated for $[C_{23}H_{35}OSi]^+$: 355.25; found: 355.2.

7.2.13. Siloxy alkyne 1m. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.23–7.19 (m, 3H), 2.74 (t, 2H, J=7.8 Hz), 2.35–2.29 (m, 4H), 2.20–2.17 (m, 2H), 1.85–1.79 (m, 2H), 1.34–1.25 (m, 3H), 1.15 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 128.5, 128.2, 125.7, 87.4, 80.2, 79.9, 34.8, 30.6, 29.4, 20.4, 18.2, 18.0, 17.3, 11.8; IR (neat, cm^{-1}) 2945, 2868, 2280, 1604, 1463; MS (APCI) calculated for $[C_{24}H_{37}OSi]^+$: 369.26; found: 369.2.

7.2.14. Siloxy alkyne 1n. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (t, 2H, J=2.4 Hz), 2.18–2.13 (m, 2H), 1.51–1.36 (m, 4H), 1.30–1.22 (m, 3H), 1.20 (s, 6H), 1.12 (d, 18H, J=7.1 Hz), 0.90 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.2, 81.9, 77.6, 37.8, 34.5, 31.2, 30.1, 29.2, 21.9, 18.5, 17.3, 13.6, 11.8; IR (neat, cm^{-1}) 2961, 2869,

2361, 2277; MS (APCI) calculated for $[C_{21}H_{39}OSi]^+$: 335.28; found: 335.2.

7.2.15. Siloxy alkyne 1o. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (t, 2H, J=7.5 Hz), 2.41–2.37 (m, 2H), 2.29–2.23 (m, 4H), 1.30–1.22 (m, 3H), 1.13 (d, 18H, J=7.5 Hz), 1.10–1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.4, 80.5, 77.4, 62.6, 29.4, 23.2, 20.4, 18.0, 17.9, 17.3, 12.0, 11.8; IR (neat, cm^{-1}) 2867, 2728, 2281, 1623, 1464; MS (APCI) calculated for $[C_{26}H_{51}O_2Si_2]^+$: 451.34; found: 451.2.

7.3. Procedure for aryl siloxy alkyne cyclizations catalyzed by $HNTf_2$

Under N_2 atmosphere, a flame-dried Airfree® flask was charged with CH_2Cl_2 (25 mL) and siloxy alkyne (0.31 mmol). The solution was treated with $HNTf_2$ in CH_2Cl_2 (0.153 M, 0.2 mL, 0.1 equiv) dropwise as an orange color developed. After stirring at room temperature for 1 h, the reaction mixture was treated with diisopropylethylamine (0.1 mL) and stirred further for 0.5 h. The resulting solution was then diluted with hexanes (20 mL), washed with HCl (1 M, 10 mL), saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel flash chromatography to afford the silyl enol ether.

7.3.1. Silyl enol ether 2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, J=7.5 Hz), 7.20 (t, 1H, J=7.5 Hz), 7.15 (t, 1H, J=7.5 Hz), 7.10 (d, 1H, J=7.5 Hz), 5.17 (t, 1H, J=5.0 Hz), 2.75 (t, 2H, J=8.0 Hz), 2.30 (dt, 2H, J=5.0, 8.0 Hz), 1.29 (h, 3H, J=6.5 Hz), 1.13 (d, 18H, J=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 137.1, 133.7, 127.1, 126.9, 126.1, 122.0, 103.8, 28.2, 22.2, 18.1, 12.8; IR (neat, cm^{-1}) 2943, 2890, 2866, 1638, 1464; MS (APCI) calculated for $[C_{19}H_{31}OSi]^+$: 303.21; found: 303.2.

7.3.2. Silyl enol ether 4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.01 (d, 1H, J=7.5 Hz), 6.97 (d, 1H, J=7.5 Hz), 5.16 (t, 1H, J=5.0 Hz), 2.71 (t, 2H, J=7.5 Hz), 2.33 (s, 3H), 2.28 (dt, 2H, J=5.0, 7.5 Hz), 1.30 (h, 3H, J=7.5 Hz), 1.24 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 135.4, 134.1, 133.5, 127.6, 126.7, 122.7, 103.7, 27.7, 22.3, 21.3, 18.1, 12.8; IR (neat, cm^{-1}) 3043, 2944, 2866, 1638, 1609, 1463; MS (APCI) calculated for $[C_{20}H_{33}OSi]^+$: 317.23; found: 317.2.

7.3.3. Silyl enol ether 5. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2H), 5.18 (t, 1H, J=5.0 Hz), 2.61 (t, 2H, J=7.5 Hz), 2.51 (3, 3H), 2.26 (s, 3H), 2.12 (dt, 2H, J=5.0, 7.5 Hz), 1.28 (h, 3H, J=7.5 Hz), 1.11 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 139.2, 136.2, 134.0, 131.0, 129.7, 125.6, 104.7, 30.3, 22.7, 22.4, 20.9, 18.1, 13.0; IR (neat, cm^{-1}) 2944, 2867, 1629, 1463; MS (APCI) calculated for $[C_{21}H_{35}OSi]^+$: 331.25; found: 331.2

7.3.4. Silyl enol ether 6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, 1H, J=8.0 Hz), 7.82–7.67 (m, 2H), 7.67 (d, 1H, J=8.2 Hz), 7.50–7.35 (m, 2H), 7.31 (d, 1H, J=8.2 Hz), 5.46 (t, 1H, J=5.0 Hz), 2.82 (t, 1H, J=7.0 Hz), 2.32 (dt, 1H, J=5.0, 7.0 Hz), 1.30 (h, 3H, J=7.5 Hz), 1.10 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 136.9, 133.5, 129.62, 129.59, 128.0, 127.62, 127.59, 126.0, 125.0, 1254.5, 106.5, 30.5, 21.9, 18.0, 12.8; IR (neat, cm^{-1}) 3051, 2944, 2866, 1630, 1463; MS (APCI) calculated for $[C_{23}H_{33}OSi]^+$: 353.23; found: 353.2.

7.3.5. Silyl enol ether 7. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, 1H, J=7.5 Hz), 7.20 (t, 1H, J=7.5 Hz), 7.15 (t, 1H, J=7.5 Hz), 7.10 (d, 1H, J=7.5 Hz), 5.10 (d, 1H, J=4.0 Hz), 2.83 (dd, 1H, J=6.0, 10.0 Hz), 2.55 (dd, 1H, J=5.0, 10.0 Hz), 2.47 (m, 1H), 1.38–1.35 (m, 4H), 1.29 (h, 3H, J=7.5 Hz), 1.13 (d, 18H, J=7.5 Hz), 0.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 136.4, 133.5, 127.2, 127.1, 126.0, 121.8, 109.1, 37.4, 34.4, 33.0, 20.1, 18.1, 14.2, 12.8; IR (neat, cm^{-1}) 3062, 2945, 2867, 2077, 1635, 1464; MS (APCI) calculated for $[C_{22}H_{37}OSi]^+$: 345.26; found: 345.2.

7.3.6. Silyl enol ether 8. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 1H, J=2.0 Hz), 7.26 (dd, 1H, J=2.0, 7.5 Hz), 6.97 (d, 1H, J=7.5 Hz), 5.21 (t, 1H, J=4.5 Hz), 2.69 (t, 2H, J=8.0 Hz), 2.29 (dt, 2H, J=4.5, 8.0 Hz), 1.29 (h, 3H, J=7.5 Hz), 1.13 (d, 18H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 135.8, 135.7, 129.8, 128.5, 125.1, 120.0, 104.9, 27.6, 22.0, 18.1, 12.8; IR (neat, cm^{-1}) 3062, 2944, 2890, 2866, 1636, 1591, 1477; MS (APCI) calculated for $[C_{19}H_{30}BrOSi]^+$: 381.12; found: 381.2.

7.4. Procedure for $HNTf_2$-promoted 1-siloxy-5,1-enyne cyclization

Under N_2 atmosphere, a flame-dried Airfree® flask was charged with CH_2Cl_2 (2 mL) and $HNTf_2$ (0.16 M in CH_2Cl_2, 0.16 mmol, 1 mL). Siloxy enyne (0.13 mmol) was added dropwise to the solution and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with hexanes (3×10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography to afford the desired enone.

7.4.1. Enone 9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.42–7.39 (m, 3H), 6.40 (d, 1H, J=2.5 Hz), 2.87 (dd, 1H, J=4.0, 18.0 Hz), 2.59 (d, 1H, J=4.0 Hz), 2.45 (dd, 1H, J=5.0, 18.0 Hz), 2.20 (m, 1H), 2.16 (dd, 1H, J=12.5, 14.0 Hz), 1.49–1.39 (m, 4H), 0.94 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 159.1, 138.8, 129.9, 128.7, 126.1, 125.2, 43.6, 38.0, 34.9, 34.8, 19.7, 14.1; IR (neat, cm^{-1}) 2957, 2927, 2871, 1663, 1606, 1447; MS (EI) calculated for $[C_{15}H_{18}]^+$: 214.14; found: 214.

7.4.2. Enone 10. ^{1}H and ^{13}C NMR spectra of compound **10** are in agreement with those described in the literature.

7.5. Procedure for MsOH-promoted 1-siloxy-5,1-enyne cyclization

Under N_2 atmosphere, a flame-dried Airfree® flask was charged with CH_2Cl_2 (2 mL) and MsOH (0.046 g, 0.48 mmol). Siloxy enyne (0.12 mmol) was added dropwise to the solution and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with hexanes (3×10 mL).

The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography to afford the desired enone.

7.5.1. Enone 11. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, 1H, J=10.0, 24.0 Hz), 2.31 (d, 1H, J=17.5 Hz), 2.08–1.94 (m, 3H), 1.89 (s, 3H), 1.73 (s, 3H), 1.35–1.26 (m, 4H), 0.87 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 154.4, 130.8, 43.9, 39.5, 38.1, 34.1, 21.5, 19.6, 14.1, 10.7; IR (neat, cm^{-1}) 2958, 2925, 2872, 1667, 1636, 1465, 1380; MS (EI) calculated for $C_{16}H_{18}O$: 166.14; found: 166.

7.5.2. Enone 12. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (m, 1H), 2.30–1.90 (m, 8H), 1.72–1.65 (m, 2H), 1.57–1.45 (m, 2H), 1.35–1.28 (m, 4H), 0.90 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 156.3, 132.0, 44.2, 38.1, 34.3, 31.8, 22.1, 22.0, 19.6, 17.7, 14.1, 12.2; IR (neat, cm^{-1}) 2928, 2869, 1665, 1636, 1457, 1436; MS (EI) calculated for $C_{13}H_{20}O$: 192.15; found: 192.

7.6. Procedure for $HNTf_2$-promoted cyclizations of 1-siloxy-1,5-diynes

An oven-dried Airfree® flask was filled with nitrogen, charged with a solution of $HNTf_2$ (77.3 mg, 0.28 mmol) in CH_2Cl_2 (or $CHCl_3$ 10 mL; or CH_2Br_2 10 mL; or MeI 5 mL; or PhH 10 mL), and cooled to −78 °C (−60 °C in $CHCl_3$; −50 °C in CH_2Br_2; −60 °C in MeI; 6 °C in PhH). This solution was slowly treated with siloxy diyne (0.25 mmol) dissolved in the same solvent (5 mL) causing a red color to develop immediately. After stirring at low temperature for 10 min, the reaction mixture was allowed to warm to room temperature and diluted with CH_2Cl_2 (30 mL; or hexanes for PhH case), washed with saturated aqueous $NaHCO_3$ (15 mL), H_2O (15 mL), and brine (15 mL), then dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography.

7.6.1. Enone 14. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (t, 2H, J=7.5 Hz), 2.78 (t, 2H, J=7.4 Hz), 2.43 (t, 2H, J=7.9 Hz), 1.93–1.87 (m, 2H), 1.60–1.54 (m, 2H), 1.34–1.26 (m, 10H), 0.88 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 150.7, 133.0, 41.4, 34.9, 31.8, 31.6, 29.3, 29.2, 28.8, 28.0, 22.6, 18.8, 14.1; IR (neat, cm^{-1}) 2927, 2855, 1718, 1621; MS (APCI) calculated for $[C_{14}H_{24}ClO]^+$: 243.15; found: 243.1.

7.6.2. Enone 15. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2H), 7.12–7.08 (m, 3H), 3.02 (t, 2H, J=7.3 Hz), 2.69 (t, 2H, J=7.5 Hz), 2.57 (t, 2H, J=7.8 Hz), 2.34 (t, 2H, J=7.8 Hz), 1.86–1.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 149.8, 141.8, 133.4, 128.3, 128.2, 125.8, 41.3, 35.0, 34.6, 31.5, 29.6, 18.7; IR (neat, cm^{-1}) 3026, 2938, 1717, 1617; MS (APCI) calculated for $[C_{15}H_{18}ClO]^+$: 249.11; found: 249.1.

7.6.3. Enone 16. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.16 (m, 4H), 7.12–7.10 (m, 1H), 3.25 (t, 2H, J=8.0 Hz), 2.80 (t, 2H, J=8.0 Hz), 2.68 (t, 2H, J=7.3 Hz), 2.29 (t, 2H, J=7.8 Hz), 1.81–1.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 148.6, 140.3, 133.7, 128.6, 128.2, 126.1, 41.1, 36.8, 34.2, 31.5, 18.7; IR (neat, cm^{-1}) 3028, 2929, 1716, 1621; MS (APCI) calculated for $[C_{14}H_{16}ClO]^+$: 235.09; found: 235.1.

7.6.4. Enone 17. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (t, 2H, J=6.5 Hz), 3.30 (t, 2H, J=6.5 Hz), 2.78 (t, 2H, J=7.3 Hz), 2.42 (t, 2H, J=8.0 Hz), 1.93–1.87 (m, 2H), 1.16–1.00 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 146.6, 134.7, 61.2, 41.2, 38.4, 31.6, 18.7, 17.9, 11.9; IR (neat, cm^{-1}) 2943, 2866, 1719, 1627, 1464, 1383; MS (APCI) calculated for $[C_{17}H_{32}ClO_2Si]^+$: 331.19; found: 331.1.

7.6.5. Enone 18. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 (t, 2H, J=7.5 Hz), 2.76 (t, 2H, J=7.4 Hz), 2.47 (t, 2H, J=7.9 Hz), 1.93–1.87 (m, 2H), 1.60–1.54 (m, 2H), 1.31–1.28 (m, 10H), 0.88 (t, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 145.9, 135.9, 41.8, 37.2, 34.7, 31.8, 29.3, 29.2, 28.9, 28.7, 22.6, 18.7, 14.1; IR (neat, cm^{-1}) 2927, 2855, 1718, 1616; MS (APCI) calculated for $[C_{14}H_{24}BrO]^+$: 287.10; found: 287.0.

7.6.6. Enone 19. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (t, 2H, J=7.5 Hz), 2.71 (t, 2H, J=7.4 Hz), 2.52 (t, 2H, J=7.9 Hz), 1.92–1.86 (m, 2H), 1.56–1.50 (m, 2H), 1.31–1.28 (m, 10H), 0.88 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 141.7, 129.5, 42.5, 41.0, 40.3, 31.8, 30.3, 29.4, 29.2, 28.4, 22.6, 18.8, 14.1; IR (neat, cm^{-1}) 2925, 2854, 1716, 1603; MS (APCI) calculated for $[C_{14}H_{24}IO]^+$: 335.09; found: 335.0.

7.6.7. Enone 20. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (t, 2H, J=7.5 Hz), 2.56 (s, 2H), 2.30 (s, 2H), 1.59–1.53 (m, 2H), 1.38–1.30 (m, 2H), 1.10 (s, 6H), 0.92 (t, 3H, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3, 145.9, 136.7, 56.3, 49.2, 37.0, 32.6, 31.0, 28.5, 21.7, 13.9; IR (neat, cm^{-1}) 2956, 2930, 2869, 1720, 1619, 1464; MS (APCI) calculated for $[C_{12}H_{20}BrO]^+$: 259.07; found: 259.0.

7.6.8. Enone 21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 (t, 2H, J=7.3 Hz), 2.52 (s, 2H), 2.38 (s, 2H), 1.55–1.49 (m, 2H), 1.38–1.31 (m, 2H), 1.10 (s, 6H), 0.92 (t, 3H, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 142.6, 129.6, 57.0, 54.8, 40.9, 32.7, 32.4, 28.4, 21.5, 13.9; IR (neat, cm^{-1}) 2955, 2928, 2869, 1718, 1606, 1464; MS (APCI) calculated for $[C_{12}H_{20}IO]^+$: 307.06; found: 307.0.

7.6.9. Enone 22. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 7.32–7.31 (m, 1H), 7.20–7.19 (m, 2H), 3.02 (t, 2H, J=7.0 Hz), 2.50 (t, 2H, J=7.0 Hz), 2.36 (t, 2H, J=7.8 Hz), 1.81–1.75 (m, 2H), 1.30–1.21 (m, 12H), 0.85 (t, 3H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 153.1, 142.4, 132.2, 128.1, 127.6, 127.4, 40.6, 32.5, 31.8, 31.6, 28.6, 29.4, 29.2, 28.7, 22.6, 20.3, 14.1; IR (neat, cm^{-1}) 3057, 3020, 2956, 2926, 2855, 1732, 1706, 1616; MS (APCI) calculated for $[C_{20}H_{29}O]^+$: 285.22; found: 285.2.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.037.

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14. The acidity of $HNTf_2$ was found to be higher than that of HOTf in gas phase (Ref. 14a), while the trend in H_2O or AcOH is reversed (Ref. 14b). The acidity of the two acids in ionic liquid is comparable (Ref. 14c). (a) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.; Hu, L.; Sung, K.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P. *J. Am. Chem. Soc.* **1994**, *116*, 3047; (b) Foropoulus, J.; DesMarteau, D. D. *Inorg. Chem.* **1984**, *23*, 3720; (c) Thomazeau, C.; Bourbigou, H. O.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264.

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Preparation of 2-arylindole-4-carboxylic amide derivatives

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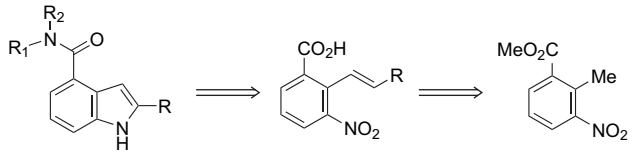
Abstract—A practical, highly efficient protocol has been developed for the synthesis of functionalized 2-arylindole-4-carboxylic amide derivatives. Commercially available methyl 2-methyl-3-nitrobenzoate gave substituted nitrostyrene benzoic acids by reaction with aromatic aldehydes in the presence of DBU in DMSO. Conversion of these products to the desired amides was followed by Pd-catalyzed reductive cyclization employing carbon monoxide as the terminal reductant to provide the 2-arylindole-4-carboxylic amide derivatives in excellent overall yield for the simple three-step sequence.

1. Introduction

The synthesis and functionalization of indoles continues to be a major area of focus for both academic and industrial researchers.[1,2] The prevalence of this important heterocycle as the central pharmacophore in a wide range of medicinal agents is a testament to the powerful biological activity that this key subunit provides as it is recognized as one of the most important 'privileged structures'.[3] Recently, we have outlined highly efficient methodologies for the synthesis of variously functionalized indoles[4] and tetrahydrobenzofurans[5] by taking advantage of the underlying versatility of nitrobenzenes. In a continuing program to exploit these methodologies which rapidly enhance molecular complexity with excellent atom economy and synthetic practicality, we have identified that commercially available methyl 2-methyl-3-nitrobenzoate **3** is an extremely attractive raw material for the preparation of indoles of type **1**.

Indoles of general type **1** have been shown to possess a wide range of biological activity including CC chemokine receptor 5 (CCR5) antagonists,[6] serotonin (5-HT) subtype 2A receptor antagonist,[7] muscarinic M_2 receptor antagonists,[8] bradycardic agents,[9] histone deacetylase inhibitors,[10] p38α mitogen activated protein kinases (MAPK) inhibitors,[11] matrix metalloproteinases (MMPs) inhibitors,[12] and poly(ADP-ribose) polymerase-1-inhibitors.[13] Typically indoles of this subclass have been prepared from commercially available indole 4-carboxylic acid or 4-bromoindole,[14] both of which are expensive reagents and require extensive manipulation if a more substituted pharmacophore is needed. A concise route to indoles **1** from **3** would feature reaction with a substituted aldehyde followed by reductive cyclization (Scheme 1). In this paper, we document the implementation of this strategy.



1 2 3

Scheme 1.

2. Results and discussion

The widespread use of *ortho*-nitrostyrenes as synthetically useful intermediates has been limited by available methods for their preparation. Traditional approaches have relied on Wittig reactions of either 2-nitrobenzaldehydes or 2-nitrophosphonium and phosphonate salts.[15] Alternatively, cross-coupling approaches involving 2-halonitrobenzenes or 2-nitrophenylstannanes have received considerable attention as an attractive method for the preparation of a range of *ortho*-nitrostyrenes.[16] While each of these approaches offers certain advantages, they often require multiple steps for the construction of the appropriate starting materials and generally require purification by chromatography. In addition, these strategies have a high environmental burden since they suffer from poor atom economy and generate a significant amount of phosphorous or tin by-products. We have recently demonstrated that reactions of 2-nitrotoluenes or 2-trimethylsilylmethylnitrobenzenes with aromatic aldehydes via an addition/elimination protocol is an effective, high yielding method for the construction of *ortho*-nitrostyrenes.[4] In order to access indoles of class **1**, an efficient synthesis of nitrostyrenes of type **2** was imperative and we

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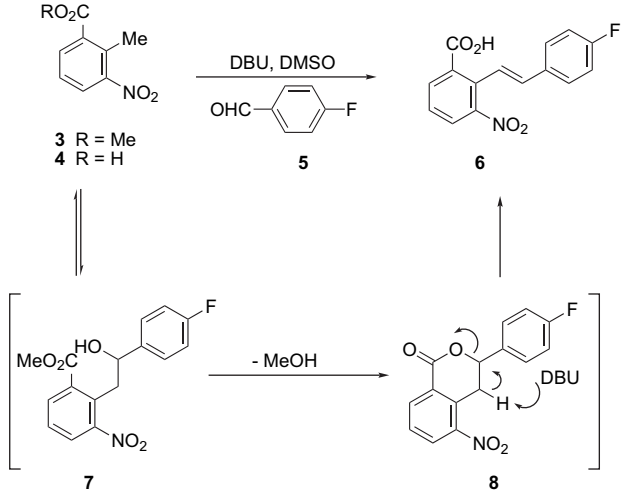
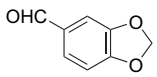
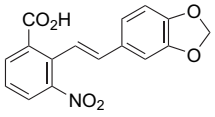
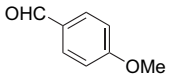
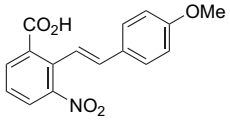
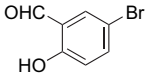
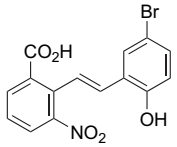
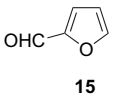
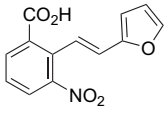
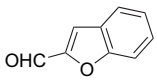
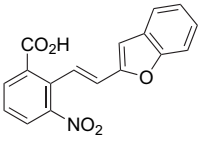
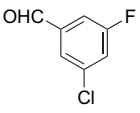
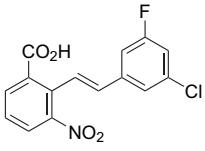
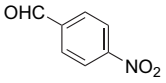
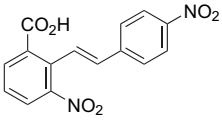
envisioned that reaction of commercially available nitrotoluene **3** with simple aldehydes would allow for a remarkably straightforward synthesis of these high value targets.

Our investigations began with the reaction of methyl 2-methyl-3-nitrobenzoate **3** with 4-fluorobenzaldehyde (Scheme 2). It has previously been demonstrated that the reaction of *ortho*-nitrotoluenes with aromatic aldehydes in the presence of DBU in DMSO is a reversible process[5] and only modest to good yields of the corresponding nitro alcohols are obtained.[17] Based on the juxtaposition of the methyl ester with the reacting center and its capacity to serve as an intramolecular electrophilic trap of the intermediate nitro alcohol, reaction of **3** with aldehydes was anticipated to lead to formation of a lactone intermediate. Treatment of **3** with 1.0 equiv of 4-fluorobenzaldehyde **5** with 1.0 equiv of DBU in DMSO for 6 h at rt gave nitrostyrene benzoic acid **6** in 57% yield. Analysis of the crude reaction mixture by HPLC and NMR revealed the presence of unreacted starting material **3** (36%), 4-fluorobenzaldehyde **5**, and carboxylic acid **4** (7%). The presence of acid **4** suggested that competitive hydrolysis of the starting material was occurring under the reaction conditions. The overall sequence involved deprotonation of the nitrotoluene **3** by DBU followed by the addition to **5** to give nitro alcohol intermediate **7**, which undergoes intramolecular cyclization to lactone **8**. Deprotonation of **8** by DBU was followed by elimination of the carboxylate anion to furnish the observed nitrostyrene benzoic acid product **6** upon workup. Optimization of the reaction parameters revealed that upon treatment of **3** with 1.5 equiv of **5** with 2.0 equiv of DBU in dry DMSO for 12 h followed by heating to 50 °C for 30 min afforded **6** in 90% HPLC assay yield.[18] Under these conditions, <5% of the corresponding hydrolyzed starting material **4** was observed. Furthermore, none of the intermediate lactone **8** was observed in the crude reaction mixture. After an extractive workup to remove excess **5**, the product **6** was obtained in 84% isolated yield by crystallization from MeOH/water. The reaction sequence was general and allowed for the preparation of an array of structurally diverse nitrostyrene benzoic acids in good to excellent yield (Table 1). Substrates containing electron donating (entries 1–5) or electron withdrawing groups (entries 6 and 7) participated equally as well. In all cases, the *trans*-nitrostyrene benzoic acids were the exclusive products.



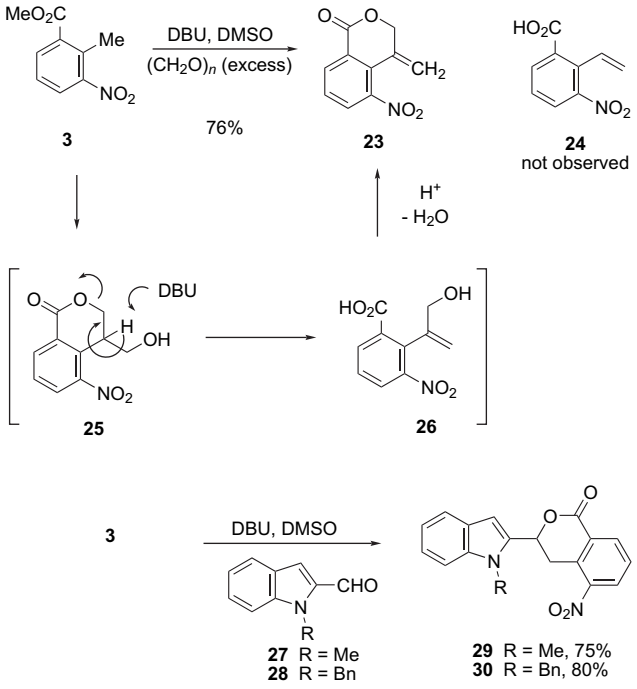
Scheme 2.

Table 1

Entry	Aldehyde	Nitrostyrene
1	 **9**	 **10** 68%
2	 **11**	 **12** 61%
3	 **13**	 **14** 79%
4	 **15**	 **16** 90%
5	 **17**	 **18** 82%
6	 **19**	 **20** 88%
7	 **21**	 **22** 82%

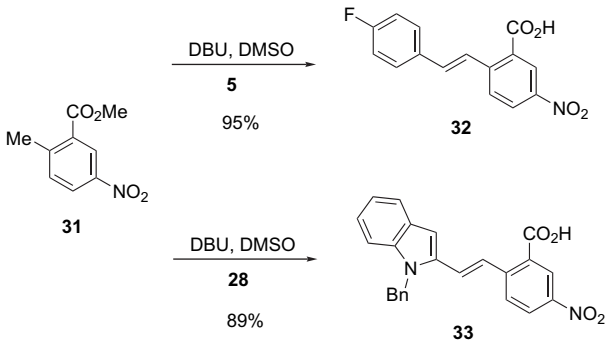
Interesting reactivity was noted when nitrobenzoate **3** was allowed to react with excess paraformaldehyde and indole-2-carboxaldehydes **27** and **28** (Scheme 3). For example, treatment of **3** with an excess of paraformaldehyde in the presence of 2 equiv of DBU in DMSO at 50 °C for 12 h followed by an extractive workup and acidification with aqueous HCl did not give the expected vinyl nitrobenzoic acid **24**. Isochromanone **23** was isolated as the sole product in 76% yield.[19] Presumably, reaction of **3** with paraformaldehyde was followed by deprotonation and reaction with a second equivalent of paraformaldehyde leading to intermediate

25. Although the exact order of transformations leading to **25** was not explicitly clear, elimination of the carboxylate anion affords intermediate **26**, which upon acidification and intramolecular cyclization gave **23**. Reaction of **3** with **27** or **28** only led to trace amounts of the corresponding nitrostyrene benzoic acids (<8%), and isochromanones **29** and **30** were isolated in 75% and 80% yields, respectively. A satisfactory rationale to account for the interruption of the pathway leading to the expected nitrostyrene carboxylic acid products in the presence of *N*-methyl- or *N*-benzyl substituents is currently unavailable. However, we speculate that steric influences of the indole substituents and the close proximity of the nitro group prevent the approach of the base and elimination of the carboxylate anion.



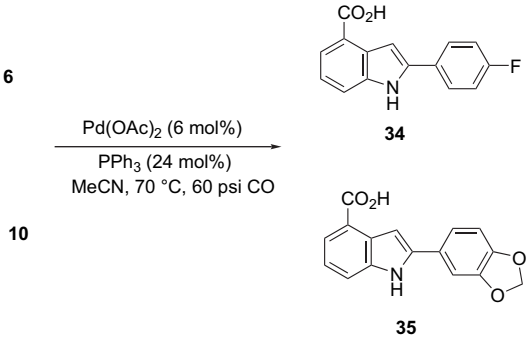
Scheme 3.

We have also examined the reaction of the regio-isomeric methyl 2-methyl-5-nitrobenzoate **31** with aldehydes **5** and **28** (Scheme 4).[20] Reaction of **31** with **5** under the optimized reaction conditions described above led to the formation of nitrostyrene benzoic acid **32** in 95% isolated yield. In this case, the product could be obtained by direct crystallization from the crude reaction mixture. In similar fashion, nitrostyrene benzoic acid **33** was obtained in 89% yield when reacted with aldehyde **28**.



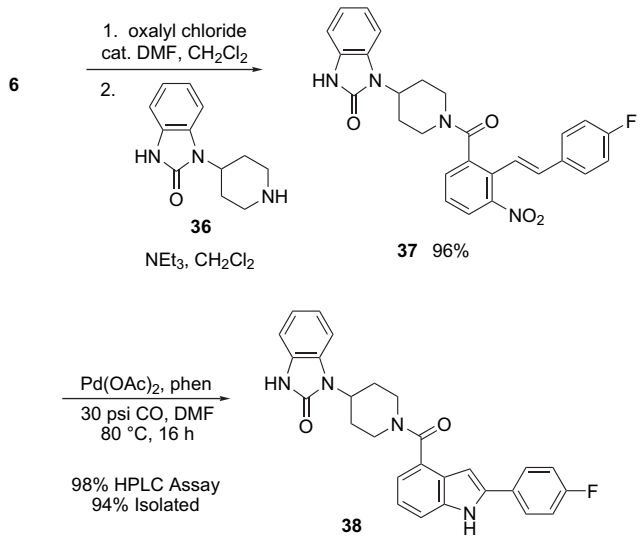
Scheme 4.

Reductive cyclization of aromatic nitrocompounds is an extremely powerful method for the preparation of the indole nucleus.[21] Transition metal catalyzed reductive cyclizations employing carbon monoxide as the stoichiometric reductant has recently emerged as a highly versatile method for the construction of indoles due to superior yields, diminished amounts of reaction by-products, and favorable environmental impact.[16,17,21] For the preparation of indoles of subclass **1** bearing an amido-substituent in the four position of the indole ring, a two-step sequence involving either reductive cyclization of the *ortho*-nitrostyrenes followed by amide formation or amide formation followed by reductive cyclization was required. With nitrostyrene benzoic acids in hand, initial efforts were focused on reductive cyclization of these substrates (Scheme 5). For example, reductive cyclization of nitrostyrenes **6** and **10** was accomplished under the conditions discovered by Söderberg.[16] Reaction of **6** and **10** with 6 mol % $Pd(OAc)_2$, 24 mol % PPh_3 in acetonitrile at 70 °C under an atmosphere of 60 psi CO for 16 h afforded indole carboxylic acids **34** and **35** in 89% and 92% HPLC assay yields,[18] respectively. The isolation of **34** and **35** in pure form was plagued by both solubility issues of the corresponding products and the difficulty in removing the excess triphenylphosphine and triphenylphosphine oxide. Consequently, the isolated yields of **34** and **35** were <50% after crystallization. Due to this difficulty, our attention turned to conversion of the benzoic acid moiety to the required amide functionality prior to reductive cyclization.



Scheme 5.

Treatment of nitrostyrene benzoic acid **6** with oxalyl chloride in the presence of a catalytic amount of DMF in CH_2Cl_2 afforded the intermediate acid chloride, which was not isolated (Scheme 6). Reaction with 4-(2-keto-1-benzimidazolinyl)piperadine **36** in the presence of NEt_3 gave, after workup, amido nitrostyrene **37**, which was isolated as a highly crystalline solid in 96% yield. The reductive cyclization of **37** was conducted under the optimized reaction conditions previously disclosed from these laboratories.[17,22] Thus, reaction of **37** with 1 mol % $Pd(OAc)_2$, 7 mol % 1,10-phenanthroline (phen), in DMF at 80 °C under an atmosphere of 30 psi CO for 16 h afforded indole **38** in 98% HPLC assay yield.[18] In this case, isolation of **38** was simply a matter of filtering the reaction mixture through Celite, followed by the addition of 1 M H_3PO_4, which precipitated the



Scheme 6.

product in analytically pure form and in 94% isolated yield. The sequence whereby the appropriately substituted nitrostyrene carboxylic acid was converted to the required amide followed by reductive cyclization provided an excellent, high yielding means of preparing the highly functionalized derivatives shown in Table 2. The use of 1 M H_3PO_4 for the isolation of the product aided in the removal of trace amounts of 1,10-phenanthroline from the product and was mild enough that sensitive functionalities such as a Boc-protecting group were preserved (see Table 2, entry 3).

In conclusion, a concise three-step method for the preparation of many highly functionalized 'drug-like' 2-aryl-indole-4-carboxylic amide derivatives has been developed. This efficient protocol involved reaction of nitrotoluene **3** with substituted aldehydes in the presence of DBU in DMSO to provide the nitrostyrene benzoic acids, which were subsequently converted to their amide derivatives. Catalytic reductive cyclization provided the desired 2-aryl-indole-4-carboxylic amide derivatives in excellent overall

Table 2

Entry, acid	Amine	Amide	Indole[a]
1, **16**	$NHMe_2$	**39** 99%	**40** 98%, (91%)
2, **6**	**41**	**42** 99%	**43** 97% (93%)
3, **10**	**44**	**45** 98%	**46** 99% (95%)
4, **20**	**47**[23]	**48** 98%	**49** 98% (94%)
5, **10**	**50**	**51** 97%	**52** 98% (92%)

[a] Yield in parenthesis reflects isolated yield after crystallization from the crude reaction mixture.

yield. The overall sequence does not require the use of chromatography and offers an extremely attractive strategy for direct entry into this uniquely substituted pharmacophore. The biological activity of these substrates is currently under active investigation and will be reported in due course.

3. Experimental

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate/hexanes mixture as the eluent unless specified otherwise.

3.1. General procedure for the preparation of 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzoic acid (2)

To a stirred containing 1.50 g (7.69 mmol) of methyl 2-methyl-3-nitrobenzoate **3** and 11.5 mmol of the appropriately substituted aldehyde in 10 mL of dry DMSO was added 2.34 g (15.38 mmol) of DBU. The resulting mixture was stirred at rt for 12 h, heated to 50 °C for 30 min, and then cooled to rt. To the crude reaction mixture was added 20 mL of 1 N NaOH solution and the mixture was washed with EtOAc (2×25 mL) to remove the excess aldehyde. The aqueous layer was then made acidic with concd HCl, extracted with EtOAc, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue recrystallized from MeOH/water to give the 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzoic acid (**2**) in analytically pure form.

3.1.1. Preparation of 2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrobenzoic acid (6). According to the general procedure, treatment of a mixture of 2.32 g (11.90 mmol) of **3** and 2.21 g (17.83 mmol) of 4-fluorobenzaldehyde **5** with 3.61 g (23.77 mmol) of DBU afforded 2.87 g (84%) of **6** as a bright yellow solid: mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.50 (d, 1H, J=16.5 Hz), 7.03 (m, 2H), 7.46 (m, 4H), 7.95 (dd, 1H, J=8.0 and 1.0 Hz), 8.17 (dd, 1H, J=8.0 and 1.0 Hz), 12.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 115.7 (d, J=22 Hz), 122.4, 127.7, 128.0, 128.6 (d, J=8 Hz), 131.3, 132.6, 133.2, 134.2, 134.4, 151.0, 162.3 (d, J=247 Hz), 171.4; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.43; H, 3.22; N, 4.79.

3.1.2. Preparation of 2-(*trans*-2-benzo[1,3]dioxol-5-yl-vinyl)-3-nitrobenzoic acid (10). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.73 g (11.50 mmol) of piperonal **9** with 2.34 g (15.38 mmol) of DBU afforded 1.64 g (68%) of **10** as a bright yellow solid: mp 134–135 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.01 (s, 2H), 6.43 (d, 1H, J=16.5 Hz), 6.88 (m, 2H), 7.16 (s, 1H), 7.32 (d, 1H, J=16.5 Hz), 7.57 (t, 1H, J=7.9 Hz), 8.01 (d, 1H, J=7.9 Hz), 8.02 (d, 1H, J=7.9 Hz), 12.0 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 101.7, 106.2, 108.9, 121.6, 122.5, 126.6, 128.8, 131.3, 132.0, 133.4, 133.5, 134.7, 148.0, 148.4, 150.5, 168.2. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 61.35; H, 3.54; N, 4.47. Found: C, 60.99; H, 3.49; N, 4.43.

3.1.3. Preparation of 2-[*trans*-2-(4-methoxyphenyl)-vinyl]-3-nitrobenzoic acid (12). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.57 g (11.50 mmol) of 4-methoxybenzaldehyde **11** with 2.34 g (15.38 mmol) of DBU afforded 1.40 g (61%) of **12** as a yellow solid: mp 158–159 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.74 (s, 3H), 6.47 (d, 1H, J=16.6 Hz), 6.91 (d, 2H, J=8.7 Hz), 7.32 (d, 1H, J=16.6 Hz), 7.41 (d, 2H, J=8.7 Hz), 7.57 (t, 1H, J=8.1 Hz), 8.01 (d, 1H, J=8.1 Hz), 8.02 (d, 1H, J=8.1 Hz), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.7, 114.7, 120.9, 126.6, 128.6, 128.7, 129.4, 132.1, 133.3, 133.6, 134.7, 150.5, 160.1, 168.2. Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 63.92; H, 4.22; N, 4.21.

3.1.4. Preparation of 2-[*trans*-2-(5-bromo-2-hydroxy-phenyl)-vinyl]-3-nitrobenzoic acid (14). According to the general procedure, treatment of a mixture of 1.20 g (6.15 mmol) of **3** and 1.85 g (9.22 mmol) of 5-bromosalicylaldehyde **13** with 1.87 g (12.30 mmol) of DBU afforded 1.77 g (79%) of **14** as a tan solid: mp 154 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.70 (d, 1H, J=16.7 Hz), 6.82 (d, 1H, J=8.5 Hz), 7.28 (d, 1H, J=8.5 Hz), 7.65 (m, 3H), 8.05 (m, 2H), 10.15 (br s, 1H), 12.10 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.1, 118.4, 124.2, 125.9, 126.5, 127.6, 128.9, 129.4, 131.9, 132.1, 133.3, 134.7, 150.4, 154.8, 168.1. Anal. Calcd for $C_{15}H_{10}BrNO_5$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.11; H, 2.76; N, 3.89.

3.1.5. Preparation of 2-(*trans*-2-furan-2-yl-vinyl)-3-nitrobenzoic acid (16). According to the general procedure, treatment of a mixture of 2.50 g (12.81 mmol) of **3** and 1.85 g (19.21 mmol) of 2-furaldehyde **15** with 3.90 g (25.62 mmol) of DBU afforded 2.99 g (90%) of **16** as a yellow solid: mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (m, 3H), 7.47 (m, 3H), 7.90 (dd, 1H, J=7.9 and 1.2 Hz), 8.15 (dd, 1H, J=7.9 and 1.2 Hz), 12.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.5, 111.6, 120.1, 122.7, 127.5, 127.7, 131.2, 133.6, 134.0, 143.1, 150.8, 151.9, 171.4. Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 59.99; H, 3.51; N, 5.43.

3.1.6. Preparation of 2-(*trans*-2-benzofuran-2-yl-vinyl)-3-nitrobenzoic acid (18). According to the general procedure, treatment of a mixture of 630 mg (3.23 mmol) of **3** and 708 mg (4.85 mmol) of 2-benzofurancarboxaldehyde **17** with 983 mg (6.46 mmol) of DBU afforded 820 mg (82%) of **18** as a yellow solid: mp 154–155 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.63 (m, 1H), 7.01 (s, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.65 (m, 4H), 8.12 (m, 2H), 12.03 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 107.5, 111.5, 121.9, 122.0, 123.8, 124.6, 125.9, 126.9, 128.8, 129.4, 131.0, 133.6, 134.5, 150.3, 153.9, 154.7, 167.9. Anal. Calcd for $C_{17}H_{11}NO_5$: C, 66.02; H, 3.58; N, 4.53. Found: C, 66.10; H, 3.66; N, 4.54.

3.1.7. Preparation of 2-[*trans*-2-(3-chloro-5-fluoro-phenyl)-vinyl]-3-nitrobenzoic acid (20). According to the general procedure, treatment of a mixture of 1.58 g (8.10 mmol) of **3** and 1.92 g (12.14 mmol) of 3-chloro-5-fluorobenzaldehyde **19** with 2.47 g (15.38 mmol) of DBU afforded 2.29 (88%) of **20** as a yellow solid: mp

142–143 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.41 (d, 1H, J=16.4 Hz), 7.05 (m, 2H), 7.21 (s, 1H), 7.55 (m, 2H), 7.99 (d, 1H, J=7.4 Hz), 8.23 (d, 1H, J=7.4 Hz), 11.49 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.9 (d, J=20 Hz), 115.9 (d, J=20 Hz), 123.0, 125.8, 126.6, 127.8, 128.4, 131.2, 131.3, 133.7, 134.3, 135.4 (d, J=10 Hz), 139.5 (d, J=10 Hz), 150.8, 162.4 (d, J=250 Hz), 170.9; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −111.2. Anal. Calcd for $C_{15}H_9ClFNO_4$: C, 56.00; H, 2.82; N, 4.35. Found: C, 55.83; H, 2.73; N, 4.33.

3.1.8. Preparation of 3-nitro-2-[*trans*-(4-nitrophenyl)-vinyl]-benzoic acid (22). According to the general procedure, treatment of a mixture of 1.50 g (7.69 mmol) of **3** and 1.74 g (11.50 mmol) of 4-nitrobenzaldehyde **21** with 2.34 g (15.38 mmol) of DBU afforded 1.98 (82%) of **22** as a yellow solid: mp 172–173 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.64 (d, 1H, J=16.6 Hz), 7.65 (t, 1H, J=8.0 Hz), 7.77 (m, 3H), 8.10 (m, 2H), 8.20 (d, 2H, J=8.8 Hz), 12.12 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 124.6, 127.1, 128.1, 129.0, 129.7, 130.9, 131.9, 133.9, 134.5, 143.3, 147.3, 150.3, 167.8. Anal. Calcd for $C_{15}H_{10}N_2O_6$: C, 57.33; H, 3.21; N, 8.91. Found: C, 57.32; H, 3.19; N, 8.88.

3.1.9. Preparation of 4-methylene-5-nitro-isochroman-1-one (23). According to the general procedure, treatment of a mixture of 1.00 g (5.12 mmol) of **3** and 2.00 g of solid paraformaldehyde with 1.56 g (10.25 mmol) of DBU afforded 799 mg (76%) of **23** as a white solid: mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.00 (s, 2H), 5.55 (s, 1H), 5.72 (s, 1H), 7.61 (t, 1H, J=8.0 Hz), 7.86 (d, 1H, J=8.0 Hz), 8.33 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.2, 121.8, 126.7, 128.5, 129.6, 129.8, 130.1, 134.0, 147.3, 162.3. Anal. Calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.79; H, 3.78; N, 6.69.

3.1.10. Preparation of 3-(1-methyl-1*H*-indol-2-yl)-5-nitro-isochroman-1-one (29). According to the general procedure, treatment of a mixture of 2.00 g (10.25 mmol) of **3** and 2.45 g (15.4 mmol) of 1-methylindole-2-carboxaldehyde **27** with 3.12 g (20.50 mmol) of DBU afforded 2.48 g (75%) of **29** as a yellow solid: mp 166–167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.47 (dd, 1H, J=15.7 and 5.7 Hz), 3.73 (s, 3H), 3.78 (dd, 1H, J=15.7 and 3.3 Hz), 6.05 (s, 1H), 6.36 (m, 1H), 7.03 (dt, 1H, J=7.9 and 0.8 Hz), 7.15 (dt, 1H, J=7.9 and 0.8 Hz), 7.23 (d, 1H, J=8.3 Hz), 7.41 (d, 1H, J=7.9 Hz), 7.70 (t, 1H, J=7.9 Hz), 8.06 (d, 1H, J=7.9 Hz), 8.50 (d, 1H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8, 81.5, 102.4, 109.4, 119.6, 120.2, 121.5, 127.4, 129.3, 130.0, 131.2, 132.0, 133.2, 137.6, 143.2, 167.1. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.89; H, 4.22; N, 8.66.

3.1.11. Preparation of 3-(1-benzyl-1*H*-indol-2-yl)-5-nitro-isochroman-1-one (30). According to the general procedure, treatment of a mixture of 1.56 g (7.99 mmol) of **3** and 2.82 g (12.00 mmol) of 1-benzylindole-2-carboxaldehyde **28** with 2.43 g (15.99 mmol) of DBU afforded 2.55 g (80%) of **30** as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (dd, 1H, J=15.8 and 6.6 Hz), 3.71 (dd, 1H, J=15.8 and 3.1 Hz), 5.45 (d, 1H, J=17.5 Hz), 5.54 (d, 1H, J=17.5 Hz), 6.26 (m, 1H), 6.28 (s, 1H), 6.90 (m, 2H), 7.09 (m, 2H), 7.22 (m, 4H), 7.51 (d, 1H, J=7.8 Hz), 7.67 (t, 1H, J=7.8 Hz), 8.09 (d, 1H, J=7.8 Hz), 8.45 (dd, 1H, J=8.0 and 0.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.4, 46.5, 81.3, 103.4, 109.9, 119.9, 120.4, 121.8, 125.8, 127.4, 127.8, 128.9, 129.5, 129.9, 131.3, 132.0, 133.6, 137.4, 137.7, 143.3, 143.5, 167.3. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.43; H, 4.66; N, 7.00.

3.1.12. Preparation of 2-[*trans*-2-(4-fluorophenyl)-vinyl]-5-nitrobenzoic acid (32). According to the general procedure, treatment of a mixture of 2.00 g (10.25 mmol) of **31** and 1.91 g (15.37 mmol) of 4-fluorobenzaldehyde **5** with 3.12 g (20.50 mmol) of DBU afforded 2.80 g (95%) of **32** as a bright yellow solid: mp 216–217 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.21 (m, 2H), 7.37 (d, 1H, J=16.4 Hz), 7.61 (m, 2H), 7.89 (d, 1H, J=16.4 Hz), 8.03 (d, 1H, J=8.8 Hz), 8.29 (m, 1H), 8.53 (s, 1H), 12.61 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 116.3 (d, J=20.0 Hz), 125.6, 126.0, 126.6, 128.5, 129.6 (d, J=8.0 Hz), 130.7, 133.5, 134.1, 144.7, 146.2, 163.1 (d, J=245.0 Hz), 167.3. Anal. Calcd for $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88. Found: C, 62.77; H, 3.55; N, 4.93.

3.1.13. Preparation of 2-[*trans*-2-(1-benzyl-1*H*-indol-2-yl)-vinyl]-5-nitrobenzoic acid (33). According to the general procedure, treatment of a mixture of 2.30 g (11.78 mmol) of **31** and 4.16 g (17.68 mmol) of 1-benzylindole-2-carboxaldehyde **28** with 3.59 g (23.57 mmol) of DBU afforded 4.18 g (89%) of **33** as a red solid: mp 168–169 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.67 (s, 2H), 6.97 (s, 1H), 7.14 (m, 7H), 7.43 (d, 1H, J=8.3 Hz), 7.56 (d, 1H, J=7.8 Hz), 7.64 (d, 1H, J=16.1 Hz), 8.13 (m, 2H), 8.26 (dd, 1H, J=8.8 and 2.3 Hz), 8.54 (s, 1H), 13.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 46.2, 110.9, 120.7, 121.1, 123.1, 124.0, 126.0, 126.4, 126.8, 126.9, 127.7, 128.1, 128.2, 129.1, 130.9, 137.9, 138.4, 139.0, 144.2, 146.0, 167.5. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.66; N, 7.05.

3.1.14. Preparation of 2-(4-fluorophenyl)-1*H*-indole-4-carboxylic acid (34). In a 10 mL pressure tube was added sequentially 115 mg (0.400 mmol) of **6**, 5.4 mg (0.024 mmol) of $Pd(OAc)_2$, 25.2 mg of PPh_3 (0.096 mmol), and 3 mL of MeCN. The resulting mixture was heated at 70 °C under an atmosphere of 60 psi CO for 16 h and then cooled to rt. HPLC assay of the crude reaction mixture revealed 91 mg (89%) of **34**. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was recrystallized (2×) from an EtOAc/hexane mixture followed by recrystallization from MeOH/water to afford 50 mg (49%) of **34** as a light tan solid: mp 170 °C (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (m, 2H), 7.27 (m, 1H), 7.53 (s, 1H), 7.64 (d, 1H, J=8.0 Hz), 7.29 (m, 2H), 8.04 (d, 1H, J=7.5 Hz), 8.58 (br s, 1H), 12.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.5, 116.2 (d, J=20 Hz), 116.5, 120.4, 121.5, 124.8, 127.3, 128.1, 129.4, 137.7, 139.4, 163.2 (d, J=250.0 Hz), 173.0; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95; N, 5.49. Found: C, 70.66; H, 3.98; N, 5.53.

3.1.15. Preparation of 2-benzo[1,3]dioxol-5-yl-1*H*-indole-4-carboxylic acid (35). In a 10 mL pressure tube

was added sequentially 198 mg (0.632 mmol) of **10**, 8.51 mg (0.038 mmol) of $Pd(OAc)_2$, 39.8 mg (0.152 mmol) of PPh_3, and 4 mL of MeCN. The resulting mixture was heated at 70 °C under an atmosphere of 60 psi CO for 16 h and then cooled to rt. HPLC assay of the crude reaction mixture revealed 163 mg (92%) of **35**. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was recrystallized (2×) from an EtOAc/hexane mixture followed by recrystallization from MeOH/water to afford 76 mg (43%) of **35** as a tan solid: mp 275–276 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.05 (s, 2H), 6.99 (d, 1H, J=8.0 Hz), 7.13 (t, 1H, J=7.8 Hz), 7.25 (s, 1H), 7.38 (d, 1H, J=8.0 Hz), 7.44 (s, 1H), 7.58 (d, 1H, J=8.0 Hz), 7.67 (d, 1H, J=7.8 Hz), 11.69 (br s, 1H), 12.61 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 99.7, 101.8, 106.3, 109.3, 116.2, 119.9, 120.9, 121.5, 123.2, 126.5, 128.9, 138.3, 140.2, 147.7, 148.5, 169.0. Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.49; H, 4.01; N, 4.99.

3.2. General procedure for the preparation of 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzamides

To a stirred solution of 10 mmol of the appropriate nitrostyrene benzoic acid in 30 mL of CH_2Cl_2 was added 1.65 g (13.00 mmol) of oxalyl chloride followed by one drop of DMF. The resulting mixture was stirred for 1.5 h at rt and concentrated under reduced pressure and then re-dissolved in 15 mL of CH_2Cl_2. The resulting solution of the acid chloride was then added dropwise to a mixture of 13.0 mmol of the appropriately substituted amine and 1.52 g (15.00 mmol) of NEt_3. The mixture was stirred at rt for 30 min, diluted with 15 mL of 1 N HCl, and the layers separated. The organic layer was washed with 15 mL of 2 N NaOH, washed with 15 mL of brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude amide, which was recrystallized from MeOH/water.

3.3. General procedure for the preparation of 2-aryl-indole-4-carboxylic amides

In a 20 mL pressure tube was sequentially added 1.0 mmol of the appropriately substituted 2-[*trans*-2-(aryl)-vinyl]-3-nitrobenzamide, 0.01 mmol of $Pd(OA)_2$, 0.07 mmol of 1,10-phenanthroline, and 4 mL of DMF. The resulting mixture was then heated at 80 °C under an atmosphere of 30 psi CO for 16 h, and cooled to rt, and was filtered through a pad of Celite eluting with 2 mL of DMF. Quantitative HPLC analysis of the crude reaction mixture was conducted at this point. The solution was then added dropwise to a solution of 10 mL of 1 M H_3PO_4. The resulting slurry of the product was stirred at rt for 30 min and filtered. The solid was dried under vacuum/N_2 sweep for 6–12 h to give the desired indole.

3.3.1. Preparation of 1-(1-{2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrobenzoyl}-piperidin-4-yl)-1,3-dihydro-benzimidazol-2-one (37). According to the general procedure, treatment of a mixture of 600 mg (2.09 mmol) of **6** with 345 mg (2.72 mmol) of oxalyl chloride followed by reaction with 590 mg (2.72 mmol) of **36** in the presence of 317 mg (3.13 mmol) of NEt_3 afforded 980 mg (96%) of **37** as a yellow solid: mp 242–243 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (m, 1H), 1.92 (m, 1H), 2.07 (m, 1H), 2.25 (m, 1H), 2.47 and 2.48 (m, due to rotamers, 1H), 2.92 and 3.12 (m, due to rotamers, 1H), 3.52 (m, 1H), 4.41 and 4.52 (m, due to rotamers, 1H), 5.01 (m, 1H), 6.15 and 6.55 (m, due to rotamers, 1H), 6.86–7.70 (m, 11H), 7.95 (m, 1H), 10.30 and 10.41 (m, due to rotamers, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7 and 29.2 (due to rotamers), 29.3 and 30.1 (due to rotamers), 41.5, 46.1, and 46.9 (due to rotamers), 50.6 and 50.7 (due to rotamers), 108.8, 109.9, and 110.1 (due to rotamers), 116.1 and 116.3 (d, due to rotamers J=22 Hz), 120.4 and 120.5 (due to rotamers), 121.1 and 121.2 (due to rotamers), 121.5 and 121.6 (due to rotamers), 125.1 and 125.2 (due to rotamers), 128.0 and 128.2 (due to rotamers), 128.5 and 128.6 (due to rotamers), 128.7 (d, J=10 Hz), 128.9 and 129.0 (due to rotamers), 129.5 and 129.9 (due to rotamers), 131.6 and 131.7 (due to rotamers), 132.5 and 132.6 (due to rotamers), 135.5 and 135.8 (due to rotamers), 137.8, 148.8, and 148.9 (due to rotamers), 155.0 and 155.1 (due to rotamers), 163.1 (d, J=250 Hz), 167.9 and 168.1 (due to rotamers); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{27}H_{23}FN_4O_4$: C, 66.66; H, 4.77; N, 11.52. Found: C, 66.43; H, 4.63; N, 11.51.

3.3.2. Preparation of 1-{1-[2-(4-fluorophenyl)-1*H*-indole-4-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one (38). According to the general procedure, reductive cyclization of 98 mg (0.201 mmol) of **37** in the presence of 0.500 mg (2.02 μmol) of $Pd(OAc)_2$ and 2.54 mg (0.014 mmol) of 1,10-phenanthroline afforded 90 mg (98%) of **38** by HPLC assay of the crude reaction mixture. Workup afforded 86 mg (94%) of **38** as a colorless solid: mp 215–216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.90 (br m, 2H), 2.54 (br m, 2H), 3.24 (br m, 2H), 3.80 (br m, 1H), 4.56 (m, 1H), 4.96 (br m, 1H), 6.96 (m, 4H), 7.11 (m, 4H), 7.29 (m, 1H), 7.41 (m, 1H), 7.91 (m, 2H), 10.10 (s, 1H), 11.05 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 29.1, 30.2, 41.5, 46.5, 50.7, 98.3, 108.6, 109.0, 112.2, 115.7 (d, J=10 Hz), 118.2, 120.7, 121.6, 125.8, 126.6, 127.2, 127.4, 128.7, 129.1, 137.6, 138.2, 155.5, 163.3 (d, J=250 Hz), 168.0; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −113.3. Anal. Calcd for $C_{27}H_{23}FN_4O_2$: C, 71.35; H, 5.10; N, 12.33. Found: C, 70.99; H, 5.05; N, 12.29.

3.3.3. Preparation of 2-(*trans*-2-furan-2-yl-vinyl)-*N*,*N*-dimethyl-3-nitrobenzamide (39). According to the general procedure, treatment of a mixture of 650 mg (2.51 mmol) of **16** with 414 mg (3.26 mmol) of oxalyl chloride followed by reaction with 170 mg (3.13 mL of a 2 M solution in THF, 3.77 mmol) of *N*,*N*-dimethylamine afforded 710 mg (99%) of **39** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.74 (s, 3H), 3.03 (s, 3H), 6.40 (m, 2H), 6.71 (d, 1H, J=16.4 Hz), 7.19 (d, 1H, J=16.4 Hz), 7.44 (m, 2H), 7.53 (d, 1H, J=7.6 Hz), 7.88 (dd, 1H, J=8.1 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0, 38.1, 111.2, 111.9, 118.2, 124.0, 124.8, 128.2, 129.1, 131.5, 137.9, 143.3, 148.9, 152.0, 169.4. Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.01; H, 4.95; N, 9.80.

3.3.4. Preparation of 2-furan-2-yl-1*H*-indol-4-carboxylic acid kemethylamide (40). According to the general procedure, reductive cyclization of 150 mg (0.524 mmol) of **39** in the presence of 1.18 mg (5.24 μmol) of $Pd(OAc)_2$ and

6.61 mg (0.037 mmol) of 1,10-phenanthroline afforded 131 mg (98%) of **40** by HPLC assay of the crude reaction mixture. Workup afforded 121 mg (91%) of **40** as a white solid: mp 233 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.84 (br s, 3H), 3.02 (br s, 3H), 6.59 (m, 2H), 6.90 (d, 1H, J=3.2 Hz), 6.96 (d, 1H, J=7.5 Hz), 7.11 (t, 1H, J=7.5 Hz), 7.40 (d, 1H, J=7.5 Hz), 7.74 (s, 1H), 11.73 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 35.0, 38.9, 97.3, 107.0, 112.5, 112.7, 118.7, 121.9, 126.0, 128.7, 130.8, 137.1, 143.4, 147.8, 170.5. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.55; H, 5.32; N, 10.89.

3.3.5. Preparation of {2-[*trans*-2-(4-fluorophenyl)-vinyl]-3-nitrophenyl}-pyrrolidin-1-yl-methanone (42). According to the general procedure, treatment of a mixture of 300 mg (1.04 mmol) of **6** with 172 mg (1.36 mmol) of oxalyl chloride followed by reaction with 111 mg (1.36 mmol) of pyrrolidine **41** in the presence of 158 mg (1.57 mmol) of NEt_3 afforded 352 mg (99%) of **42** as a yellow solid: mp 94–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (m, 4H), 3.05 (t, 2H, J=6.2 Hz), 3.52 (t, 2H, J=6.2 Hz), 6.90 (d, 1H, J=16.4 Hz), 7.02 (m, 2H), 7.23 (d, 1H, J=16.4 Hz), 7.42 (m, 3H), 7.58 (d, 1H, J=8.0 Hz), 7.92 (dd, 1H, J=8.0 and 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 25.8, 45.9, 47.8, 115.8 (d, J=20.0 Hz), 120.2, 124.9, 128.4 (d, J=10.0 Hz), 128.6, 129.2, 131.5, 132.6, 135.3, 139.2, 148.7, 163.0 (d, J=250.0 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −113.2. Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.82; H, 4.99; N, 8.15.

3.3.6. Preparation of [2-(4-fluorophenyl)-1*H*-indol-4-yl]-pyrrolidin-1-yl-methanone (43). According to the general procedure, reductive cyclization of 140 mg (0.411 mmol) of **42** in the presence of 0.923 mg (4.11 μmol) of $Pd(OAc)_2$ and 5.19 mg (0.029 mmol) of 1,10-phenanthroline afforded 123 mg (97%) of **43** by HPLC assay of the crude reaction mixture. Workup afforded 118 mg (93%) of **43** as a white solid: mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (m, 2H), 1.95 (m, 2H), 3.37 (t, 2H, J=6.7 Hz), 3.75 (t, 2H, J=6.7 Hz), 6.71 (s, 1H), 6.94 (m, 2H), 7.05 (t, 1H, J=7.5 Hz), 7.12 (d, 1H, J=7.5 Hz), 7.35 (d, 1H, J=7.5 Hz), 7.60 (m, 2H), 10.4 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.2, 45.9, 49.0, 98.3, 112.8, 115.5 (d, J=30.0 Hz), 118.3, 121.1, 126.2, 127.2, 128.5 (d, J=10.0 Hz), 128.6, 137.6, 138.5, 162.3 (d, J=250.0 Hz), 170.3; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −111.1. Anal. Calcd for $C_{19}H_{17}FN_2O$: C, 74.01; H, 5.56; N, 9.08. Found: C, 74.36; H, 5.73; N, 8.89.

3.3.7. Preparation of 4-[2-*trans*-(2-benzo[1,3]-dioxol-5-yl-vinyl)-3-nitrobenzoyl]-piperazine-1-carboxylic acid *tert*-butyl ester (45). According to the general procedure, treatment of a mixture of 2.00 g (6.38 mmol) of **10** with 1.05 g (8.30 mmol) of oxalyl chloride followed by reaction with 1.55 g (8.30 mmol) of **44** in the presence of 1.00 g (9.60 mmol) of NEt_3 afforded 3.00 mg (98%) of **45** as a yellow solid: mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.08 (m, 2H), 3.29 (m, 3H), 3.41 (m, 1H), 3.61 (m, 1H), 3.70 (m, 1H), 5.98 (s, 2H), 6.88 (m, 3H), 6.99 (s, 1H), 7.10 (d, 1H, J=16.4 Hz), 7.46 (t, 1H, J=7.8 Hz), 7.55 (dd, 1H, J=7.8 and 1.2 Hz), 7.94 (dd, 1H, J=8.1 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 41.6, 43.4, 45.9, 46.4, 80.5, 101.5, 105.7, 108.6, 118.4, 122.5, 125.1, 128.2, 130.0, 130.5, 131.7, 136.8, 137.5, 148.5, 148.6, 148.8, 154.3, 168.1. Anal. Calcd for $C_{25}H_{27}N_3O_7$: C, 62.36; H, 5.65; N, 8.73. Found: C, 62.33; H, 5.66; N, 8.71.

3.3.8. Preparation of (2-benzo[1,3]dioxol-5-yl-1*H*-indol-4-yl)-piperazin-1-yl methanone hydrochloride (46). According to the general procedure, reductive cyclization of 160 mg (0.332 mmol) of **45** in the presence of 0.75 mg (3.32 μmol) of $Pd(OAc)_2$ and 4.19 mg (0.023 mmol) of 1,10-phenanthroline afforded 147 mg (99%) of **46** by HPLC assay of the crude reaction mixture. Workup afforded 142 mg (95%) of **46** as a colorless solid: mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 3.30–4.10 (br m, 8H), 6.01 (s, 2H), 6.64 (s, 1H), 6.83 (d, 1H), 7.11 (m, 4H), 7.35 (m, 1H), 9.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 25.9, 27.3, 43.1, 62.6, 80.3, 97.7, 101.3, 106.2, 108.8, 112.5, 118.9, 119.2, 121.5, 126.3, 126.6, 126.7, 137.0, 139.4, 147.6, 148.3, 154.6, 170.6. Anal. Calcd for $C_{25}H_{27}ClN_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.79; H, 6.01; N, 9.32.

3.3.9. Preparation of {2-[*trans*-2-(3-chloro-5-fluorophenyl)-vinyl]-3-nitrophenyl}-(4-methanesulfonyl-piperazin-1-yl)-methanone (48). According to the general procedure, treatment of a mixture of 890 mg (2.77 mmol) of **20** with 457 mg (3.60 mmol) of oxalyl chloride followed by reaction with 591 mg (3.60 mmol) of **47**[23] in the presence of 420 mg (4.15 mmol) of NEt_3 afforded 1.27 g (98%) of **48** as a yellow solid: mp 179–180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 2.79 (m, 2H), 3.24 (m, 4H), 3.69 (m, 1H), 3.95 (m, 1H), 6.78 (d, 1H, J=16.4 Hz), 7.07 (m, 2H), 7.25 (m, 1H), 7.33 (d, 1H, J=16.4 Hz), 7.59 (m, 2H), 8.06 (dd, 1H, J=7.6 and 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 41.3, 45.5, 45.6, 46.3, 1120 (d, J=22 Hz), 116.6 (d, J=25 Hz), 122.8, 123.9, 125.6, 129.0, 129.3, 131.9, 134.1, 136.0 (d, J=11 Hz), 137.4, 139.2 (d, J=8.0 Hz), 148.5, 163.4 (d, J=250 Hz), 167.5; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −111.1. Anal. Calcd for $C_{20}H_{19}ClFN_3O_5S$: C, 51.34; H, 4.09; N, 8.98. Found: C, 51.22; H, 4.02; N, 8.96.

3.3.10. Preparation of [2-(3-chloro-5-fluorophenyl)-1*H*-indol-4-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (49). According to the general procedure, reductive cyclization of 145 mg (0.310 mmol) of **48** in the presence of 0.70 mg (3.10 μmol) of $Pd(OAc)_2$ and 3.91 mg (0.022 mmol) of 1,10-phenanthroline afforded 132 mg (98%) of **49** by HPLC assay of the crude reaction mixture. Workup afforded 127 mg (94%) of **49** as a colorless solid: mp 143–144 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6, 400 MHz) δ 2.77 (s, 3H), 3.17 (br m, 4H), 3.70 (br m, 4H), 6.78 (s, 1H), 6.95 (d, 1H, J=8.0 Hz), 7.00 (d, 1H, J=7.9 Hz), 7.11 (t, 1H, J=7.9 Hz), 7.41 (d, 1H, J=7.9 Hz), 7.45 (d, 1H, J=7.9 Hz), 7.61 (d, 1H, J=7.9 Hz), 11.5 (br s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 100 MHz) δ 27.0, 34.9, 46.0, 99.3, 110.8 (d, J=30.0 Hz), 113.4, 114.8 (d, J=20.0 Hz), 118.8, 121.4, 122.1, 126.0, 126.8, 135.2 (d, J=10.0 Hz), 135.6 (d, J=10.0 Hz), 136.9, 137.8, 162.3 (d, J=250.0 Hz), 170.0; ^{19}F NMR ($CDCl_3$/DMSO-d_6, 75 MHz) δ −110.9. Anal. Calcd for $C_{20}H_{19}ClFN_3O_3S$: C, 55.11; H, 4.39; N, 9.64. Found: C, 55.23; H, 4.38; N, 9.66.

3.3.11. Preparation of [2-*trans*-2-benzo[1,3]dioxol-5-yl-vinyl]-morpholin-4-yl methanone (51). According to the general procedure, treatment of a mixture of 2.50 g (7.98 mmol) of **10** with 1.32 g (10.4 mmol) of oxalyl chloride followed by reaction with 900 mg (10.4 mmol) of morpholine **50** in the presence of 1.21 g (12.0 mmol) of NEt_3 afforded 2.96 g (97%) of **51** as a yellow solid: mp 134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (m, 2H), 3.50 (m, 3H), 3.67 (m, 3H), 5.99 (s, 2H), 6.77–6.91 (m, 3H), 7.01 (s, 1H), 7.10 (d, 1H, J=16.4 Hz), 7.45 (t, 1H, J=7.9 Hz), 7.55 (dd, 1H, J=7.6 and 1.3 Hz), 7.93 (dd, 1H, J=7.9 and 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.8, 46.7, 66.2, 66.4, 101.3, 105.5, 108.4, 118.2, 122.4, 124.9, 128.0, 129.8, 129.9, 130.3, 131.7, 136.6, 137.2, 148.3, 148.5, 167.8. Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.49; H, 4.55; N, 7.29.

3.3.12. Preparation of (2-benzo[1,3]dioxol-5-yl-1*H*-indol-4-yl)-morphorlin-4-yl methanone (52). According to the general procedure, reductive cyclization of 180 mg (0.471 mmol) of **51** in the presence of 1.06 mg (4.71 μmol) of $Pd(OAc)_2$ and 5.94 mg (0.033 mmol) of 1,10-phenanthroline afforded 162 mg (98%) of **52** by HPLC assay of the crude reaction mixture. Workup afforded 152 mg (92%) of **52** as a colorless solid: mp 181–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (br m, 8H), 5.90 (s, 2H), 6.61 (s, 1H), 6.73 (d, 1H, J=8.0 Hz), 7.03 (m, 2H), 7.14 (dd, 1H, J=8.0 and 1.1 Hz), 7.18 (s, 1H), 7.29 (dd, 1H, J=7.3 and 1.1 Hz), 10.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.6, 46.0, 63.8, 67.2, 97.2, 101.2, 106.2, 108.6, 112.8, 118.7, 119.4, 121.1, 126.2, 126.5, 126.6, 137.3, 139.7, 147.4, 148.2, 170.8. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.66; H, 5.20; N, 7.99.

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A highly enantio- and diastereoselective 1,3-dimethylallylation of aldehydes

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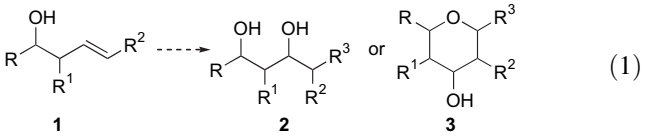
Abstract—A highly enantio- and diastereoselective pentenylation of aldehydes is described. The homoallylic alcohol derived from 1,3-dimethylallylation of (–)-menthone undergoes an efficient allyl-transfer reaction with a wide range of aliphatic aldehydes in the presence of an acid catalyst to give rise to the corresponding 4-methyl-2(*E*)-penten-4-yl-5-ol products in good yields with high enantio- and 4,5-*syn*-selectivities.

1. Introduction

The stereocontrolled synthesis of homoallylic alcohols remains an important subject in organic synthesis due to the wide occurrence of these structural motifs in a number of polyketide natural products. Moreover, homoallylic alcohols can serve as aldol surrogates upon elaboration on the alkene moiety,[1] and as substrates for the Prins reaction that provides tetrahydropyrans (Eq. 1).[2] Accordingly, many methods have been developed for the synthesis of homoallylic alcohols, largely making use of the asymmetric allylation of aldehydes.[3] However, rarely do these protocols allow for access to a disubstituted homoallylic alcohol system (**1**, R_1 and $R_2 \neq H$),[4,5] the precursor for a decorated bispropionate **2** or tetrahydropyran **3**. Thus, the development of an efficient method for the preparation of substituted homoallylic alcohols with reliable control of stereochemistry would be of significant synthetic value.



(1)

In our investigations aimed at the chemical synthesis of kendomycin,[6] we envisioned that the *C*-aryl glycoside core could be assembled by a Prins reaction with homoallylic alcohol **6** and aromatic aldehyde **7** (Scheme 1).[7] It was anticipated that the requisite intermediate **6** would arise from the asymmetric pentenylation of aldehyde **4**[6] with a reagent such as Hoffmann's boronic ester **5**.[4] While this plan could indeed be practiced, the high cost for the large-scale preparation and reaction of **5** led us to explore an alternative approach.[8] Noting the allyl-transfer reactions developed by Nokami[9] and Loh,[10] we sought to examine the prospect of extending these methods to the synthesis of **6**. Herein, we report the design, synthesis, and application of a (–)-menthone-derived homoallylic alcohol that accomplishes an allyl-transfer reaction with a range of aldehydes to provide 4-methyl-2-penten-4-yl-5-ol systems with high stereoselectivities.

2. Results and discussion

The design of an allyl-transfer reagent was based on a 2-oxonia-[3,3]-sigmatropic rearrangement mechanism as depicted in Scheme 2. In order to procure **12** (cf. **1**, $R_1 = R_2 = CH_3$) with *E*- and *syn*-selectivities, the condensation of the *Z*-configured **9** with an aldehyde would seem required to achieve transfer of the pentenyl unit through a chair-like transition state adopting the sterically demanding R_L group at an equatorial position. An additional consideration was the utilization of a tertiary alcohol as the pentenyl donor, which should establish a favorable equilibrium for the product formation due to the stability of oxocarbenium ion intermediate **11** vis-à-vis that of **10**. While the feasibility of an allyl-transfer process had never been demonstrated for the preparation of a disubstituted homoallylic alcohol such as **12**,[11] the high levels of enantioselectivities, observed in monosubstituted systems,[9c,9d,10] held promise for an analogous approach to stereospecific pentenyl-transfer processes.

The preparation of an appropriate pentenyl donor of general type **9** was initiated by evaluating 1,3-dimethylallylation of

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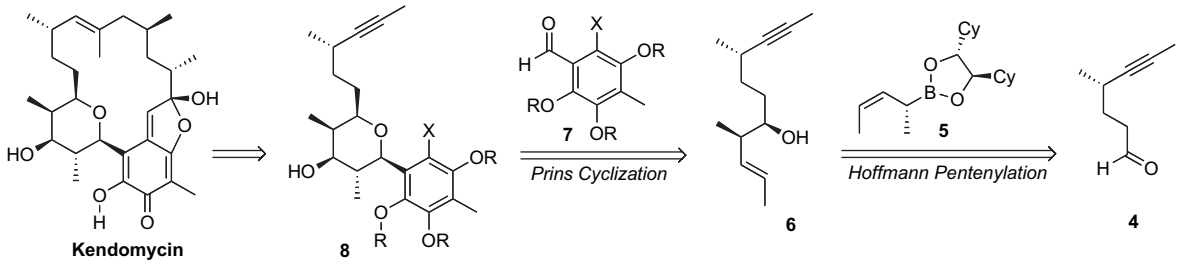
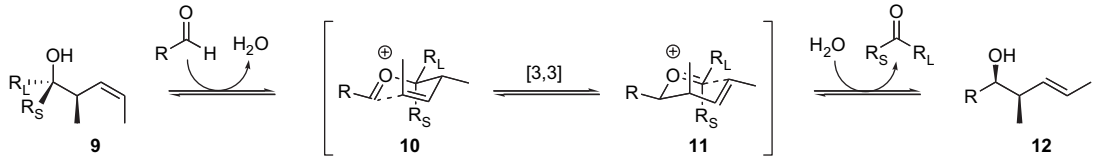


Scheme 1. The Prins approach to the total synthesis of kendomycin.

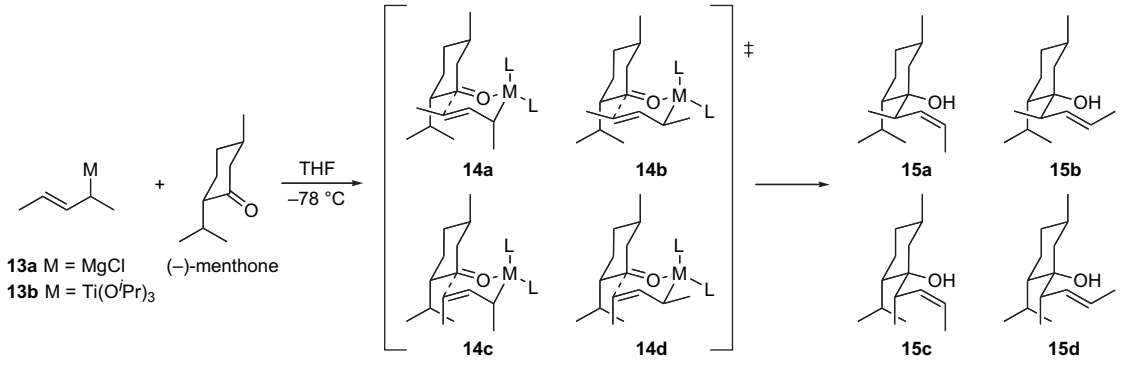


Scheme 2. Strategy for stereospecific pentenylation of aldehydes.

several chiral ketones, among which we focused on menthone due to its ready availability and the well established stereochemical outcome in carbonyl addition processes.[12] In practice, the addition of 1,3-dimethylallyl Grignard reagent **13a** to (–)-menthone gave the desired alcohol **15a** as the major product along with minor diastereomers **15b–d** in a 10:2:1:2 ratio (Scheme 3). With titanium reagent **13b**,[9c,13] the diastereoselectivity was significantly increased to a ratio of 30:4:1:2. Using these two protocols, **15a** could be obtained as a single isomer (>99%) in 30–40% yield after simple chromatographic purification.[14] The major isomer **15a** appears to be derived from transition state **14a**, in which the 1,3-dimethylallyl unit adds to the carbonyl group via the *syn*,*anti* conformation to minimize the *gauche* interactions of the methyl group with the ligands that are more unfavorable than its $A^{1,3}$ interaction with the hydrogen,[13] thus forming the *Z* geometry in **15a**. It should also be noted that the configuration of the carbinol center of **15a–d** results from the exclusive β-face attack of **13**, as predicted on the basis of the strong facial preference of (–)-menthone.[12]

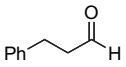
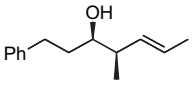
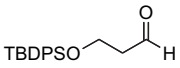
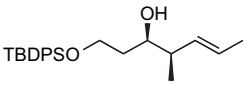
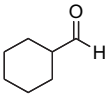
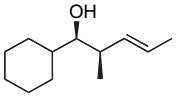
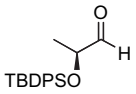
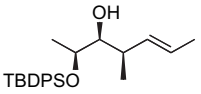
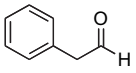
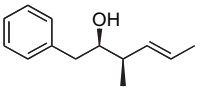
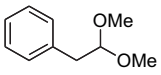
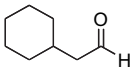
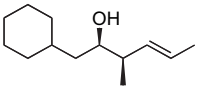
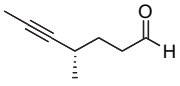
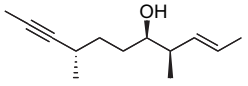
With homoallylic alcohol **15a** in hand, we then tested its capability to stereospecifically transfer the pentenyl group to aldehydes. As illustrated in Table 1, a range of aldehydes underwent the desired pentenylation process to give rise to the corresponding adducts in good yields with high stereoselectivities. The major diastereomers were uniformly found to be of *E*-geometry and 4,5-*syn*-stereochemistry, and enantiomerically pure as determined by chiral HPLC or chiral SFC analysis (>99% ee). Typically, the reactions were performed with 2.0 equiv of **15a** and 10 mol % *p*-toluenesulfonic acid monohydrate in CH_2Cl_2 at ambient temperature for 12 h. Lowering the amount of the pentenyl donor **15a** to 1.0 equiv resulted in diminished yields mainly due to the competing Prins process of the product with the starting aldehyde. Both linear and α-branched aldehydes worked well, with the latter requiring longer reaction times (24–48 h, entries 3 and 4). Notably, in addition to aldehyde **16e**, its dimethyl acetal **16f** also proved to be a viable substrate for the reaction without deprotection, thus highlighting an advantage unavailable from the pentenylboronate addition method (entries 5 vs 6).[4] Finally, aldehyde **4**, the intermediate used in our Prins approach to kendomycin, participated well in the reaction providing the desired homoallylic alcohol **6** in 80% yield with 10:1 diastereoselectivity (entry 8).

Although the present reaction could be applied to a range of substrates, it did not fare well with sterically hindered (**16h**), α,β-unsaturated (**16i**), and aromatic (**16j**) aldehydes (Fig. 1). In these cases, no or very low conversion (<15%) occurred over a prolonged reaction time (>48 h).



Scheme 3. Double stereodifferentiating 1,3-dimethylallyl addition to (–)-menthone.

Table 1. Stereospecific pentenyl-transfer reactions of **15a** with aldehydes **16**

Entry	Aldehyde	Product	Yield (%)[a]	dr[b]	er[c]
1	 **16a**	 **17a**	71	17:1	>99:1
2	 **16b**	 **17b**	57	9:1	>99:1
3	 **16c**	 **17c**	64	5:1	>99:1[f]
4	 **16d**	 **17d**	67 (81)[d]	>20:1[g]	—
5	 **16e**	 **17e**	79[e]	10:1	>99:1
6	 **16f**		66[e]	10:1	>99:1
7	 **16g**	 **17g**	69	11:1	>99:1[f]
8	 **4**	 **6**	80	10:1[g]	—

[a] Isolated yield.
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Enantiomeric ratio determined by chiral HPLC or chiral SFC.
[d] Yield based on the recovered aldehyde.
[e] Combined yield of the mixture of two inseparable diastereomers.
[f] Enantiomeric ratio determined as the corresponding benzoate ester.
[g] Only two diastereomers were detected.

The proposed mechanism of the reaction is shown in Scheme 4, in which the stereospecific 1,3-dimethylallyl-transfer from homoallylic alcohol **15a** to an aldehyde is achieved through a 2-oxonia-[3,3]-sigmatropic rearrangement.[9,10] Under acid catalysis, alcohol **15a** is condensed with the aldehyde to form oxocarbenium ion **18**, which exists in fast equilibrium with **19** via an oxonia-Cope process that involves a chair-like transition state employing the R group at an equatorial position. The more populated cation **19** is then hydrolyzed to afford the homoallylic alcohol **12** and (–)-menthone.[15] This mechanism explains the *E*-olefin geometry and *syn*-stereochemistry observed in the major

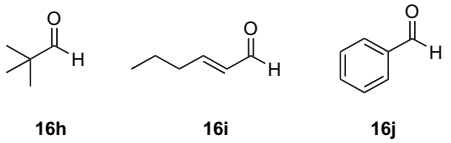
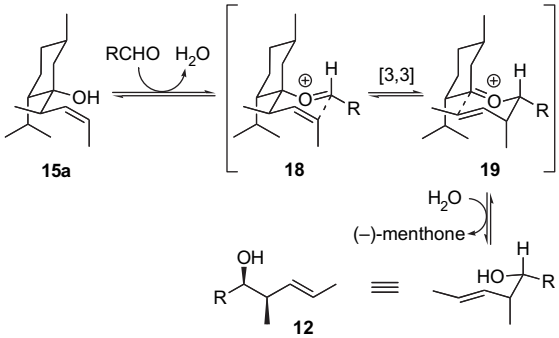


Figure 1. Unreactive aldehydes.



Scheme 4. Proposed mechanism of pentenylation.

diastereomer, and the attenuated reactivity of **15a** toward the aldehydes (cf. Fig. 1) that would have to generate a sterically congested (R=*t*-Bu) or too stable (R=alkenyl, aromatic) oxocarbenium ion **18**.

3. Conclusion

In summary, an efficient and highly stereospecific pentenylation reagent for aldehydes has been developed. The *Z*-homoallylic alcohol **15a** readily prepared from (–)-menthone reacts smoothly with a range of aliphatic aldehydes under operationally simple and mild acid-catalyzed conditions to provide the corresponding 4-methyl-2-penten-4-yl-5-ol product with high 2*E*- and 4,5-*syn*-selectivities.

4. Experimental

4.1. General method

Unless otherwise noted, commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using Silicycle silica gel 60 F_{254} plates and visualized using UV light, anisaldehyde, ceric sulfate or potassium permanganate. Flash chromatography was performed on Silicycle silica gel 60 (40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 MHz, 500 MHz or 600 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant in hertz (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift in parts per million from the central peak of $CDCl_3$ (77.23 ppm). Infrared (IR) spectra were recorded on a Nicolet 730 FT-IR spectrometer and reported in frequency of the absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Princeton University Mass Spectrometry Facility. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at 589 nm.

4.2. Synthesis of 15a

4.2.1. Method A: synthesis of 15a by addition of Grignard reagent 13a to (–)-menthone. To a THF suspension of magnesium powder (480 mg, 19.8 mmol) were added a few drops of dibromoethane followed by slow addition of dimethylallyl chloride[16] (1.04 g, 10.0 mmol) at room temperature. Upon completion of the addition, the suspension was cooled to 0 °C, and a THF solution of (–)-menthone (1.54 g, 10 mmol) was added dropwise. After 3 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The ^{1}H NMR analysis of the crude product indicated 70% conversion of (–)-menthone and the diastereomeric ratio to be 10:2:1:2. Separation of the major isomer by flash column chromatography (silica gel, hexanes/toluene=15/1 to 10/1 to 4/1) afforded pure **15a** (790 mg, 35% after a single separation; the mixed fractions could be collected and further purified) as a colorless liquid: $[\alpha]_D^{23}$ +6.2 (*c* 2.3, $CHCl_3$); IR (film) 3010, 2953, 2869, 1456, 1378, 1178 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (dq, *J*=10.9, 6.9 Hz, 1H), 5.38 (ddq, *J*=10.9, 10.2, 1.8 Hz, 1H), 3.07 (dq, *J*=10.2, 6.9 Hz, 1H), 2.18 (m, 1H), 1.76 (m, 2H), 1.71 (dd, *J*=6.8, 1.8 Hz, 3H), 1.53 (m, 2H), 1.40 (m, 1H), 1.31 (s, 1H), 1.29 (m, 1H), 1.01 (m, 1H), 0.96 (d, *J*=6.9 Hz, 3H), 0.93 (d, *J*=6.9 Hz, 3H), 0.91 (d, *J*=7.0 Hz, 3H), 0.86 (d, *J*=6.5 Hz, 3H), 0.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 127.1, 77.25, 46.2, 41.7, 37.6, 35.6, 27.7, 25.5, 23.6, 22.9, 20.7, 18.1, 15.8, 13.6; HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{15}H_{28}O$ 224.2140, found 224.2141.

4.2.2. Method B: synthesis of 15a by addition of titanium reagent 13b to (–)-menthone. To a THF suspension of magnesium powder (480 mg, 19.8 mmol) were added a few drops of dibromoethane followed by slow addition of dimethylallyl chloride[12] (1.04 g, 10.0 mmol) at room temperature. Upon completion of the addition, the suspension was stirred for 1 h and filtered through a sintered glass funnel under argon. The filtrate was slowly cannulated to a THF solution of $ClTi(O^iPr)_3$ (1.0 M in THF, 10.0 mL, 10.0 mmol) at −78 °C. The resulting solution was stirred at −78 °C for additional 1 h, and a THF solution of (–)-menthone (1.54 g, 10.0 mmol) was added dropwise. The reaction mixture was stirred for an additional 4 h at −78 °C and quenched by aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The ^{1}H NMR analysis of the crude product indicated 55% conversion and the diastereomeric ratio to be 30:4:1:2. Purification of the major isomer by flash column chromatography (silica gel, hexanes/toluene=15/1 to 10/1 to 4/1) afforded analytically pure **15a** (838 mg, 37% after a single separation; the mixed fractions could be collected and further purified) as a colorless liquid.

4.3. General procedure for homoallylic alcohol 17 synthesis (Table 1)

To a 1.0 mL CH_2Cl_2 solution of **15a** (112 mg, 0.50 mmol) and aldehyde **16** (0.25 mmol) was added $TsOH\cdot H_2O$ (4.8 mg, 0.025 mmol) at 25 °C. This solution was stirred for 12–24 h while the progress of the reaction was being monitored by TLC. After complete consumption of aldehyde **16**, the reaction mixture was concentrated, and the crude product was analyzed by ^{1}H NMR for the determination of the diasteromeric ratio (dr). Purification of the crude product by flash column chromatography afforded alcohol **17** in a diastereomerically pure form. The enatiomeric ratio (er) of the major diastereomer was determined by chiral HPLC or chiral SFC.

4.3.1. (*E*)-(3*R*,4*R*)-4-Methyl-1-phenyl-hept-5-en-3-ol (17a). Following the general procedure, the reaction of aldehyde **16a** (34 mg, 0.25 mmol) with **15a** gave alcohol **17a** (36 mg, 71%) as a colorless oil: dr=17:1 by ^{1}H NMR (600 MHz); er>99:1 by chiral HPLC (Chiralpak AD, 10% water in methanol, 1.0 mL/min, 4.40 min (+) isomer, 4.85 min for (−) isomer); $[\alpha]_D^{23}$ +35 (*c* 0.95, $CHCl_3$); IR

(film) 3396, 3026, 2933, 2879, 1496, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.23 (m, 3H), 5.53 (dqd, J=15.2, 6.6, 0.9 Hz, 1H), 5.37 (ddq, J=15.2, 7.6, 1.5 Hz, 1H), 3.49 (m, 1H), 2.88 (ddd, J=13.8, 10.5, 5.2 Hz, 1H), 2.65 (ddd, J=13.5, 9.8, 5.2 Hz, 1H), 2.27 (m, 1H), 1.83 (m, 1H), 1.70 (dd, J=6.4, 0.6 Hz, 3H), 1.65 (m, 1H), 1.49 (s, 1H), 1.02 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 133.4, 128.7, 128.6, 126.5, 126.0, 74.6, 42.9, 35.9, 32.7, 18.3, 15.3; HRMS-EI (*m/z*): $[M-H_2O]^+$ calcd for $C_{14}H_{18}$ 186.1409, found 186.1410.

4.3.2. (*E*)-(3*R*,4*R*)-1-(*tert*-Butyldiphenylsilanyloxy)-4-methyl-hept-5-en-3-ol (17b). Following the general procedure, the reaction of aldehyde **16b**[17] (78 mg, 0.25 mmol) with **15a** afforded alcohol **17b** (54 mg, 57%) as a colorless oil: dr=9:1 by ^1H NMR (500 MHz); er>99:1 by chiral SFC ((*R*,*R*) Whelk-01 (25×0.46 cm), 10% isopropanol (0.1% DEA) in CO_2 (100 bar), 3.0 mL/min, 3.26 min (−) isomer, 3.57 min for (+) isomer); $[\alpha]_D^{23}$ +6.6 (*c* 0.70, $CHCl_3$); IR (film) 3510, 2860, 1470, 1430, 1110, 1080 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.42 (m, 6H), 5.46 (dqd, J=15.3, 6.4, 0.7 Hz, 1H), 5.35 (ddq, J=15.3, 7.9, 1.6 Hz, 1H), 3.85 (m, 2H), 3.68 (m, 1H), 3.10 (d, J=3.1 Hz, 1H), 2.21 (m, 1H), 1.71 (m, 1H), 1.66 (d, J=6.2 Hz, 3H), 1.62 (m, 1H), 1.05 (s, 9H), 1.03 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 133.8, 133.2, 129.9, 127.9, 125.6, 75.4, 63.8, 43.2, 35.8, 26.9, 19.2, 18.2, 16.0; HRMS-EI (*m/z*): $[M-{}^tBu]^+$ calcd for $C_{20}H_{25}O_2Si$ 325.1624, found 325.1606.

4.3.3. (*E*)-(1*R*,2*R*)-1-Cyclohexyl-2-methyl-pent-3-en-1-ol (17c). Following the general procedure, the reaction of aldehyde **16c** (28 mg, 0.25 mmol) with **15a** afforded alcohol **17c** (29 mg, 64%) as a colorless oil: dr=5:1 by ^1H NMR (500 MHz); er>99:1 by chiral HPLC (Chiralpak AD, 5% water in methanol, 1.0 mL/min, 5.12 min (−) isomer, 5.71 min for (+) isomer); $[\alpha]_D^{23}$ +26 (*c* 0.35, $CHCl_3$); IR (film) 3390, 2930, 2850, 1450, 980, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$); δ 5.48 (dqd, J=15.3, 6.1, 1.0 Hz, 1H), 5.40 (ddq, J=15.4, 6.7, 1.5 Hz, 1H), 3.14 (t, J=5.8 Hz, 1H), 2.34 (m, 1H), 1.90 (m, 1H), 1.74 (m, 2H), 1.68 (dd, J=6.1, 1.3 Hz, 3H), 1.64 (m, 1H), 1.58 (m, 1H), 1.46 (s, 1H), 1.40 (m, 1H), 1.29–0.94 (m, 5H), 0.97 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 125.3, 79.2, 40.4, 38.9, 29.9, 28.2, 26.7, 26.5, 26.2, 18.3, 13.8; HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{12}H_{22}O$ 182.1671, found 182.1674.

4.3.4. (*E*)-(2*S*,3*S*,4*R*)-2-(*tert*-Butyldiphenylsilanyloxy)-4-methyl-hept-5-en-3-ol (17d). Following the general procedure, the reaction of aldehyde **16d**[18] (78 mg, 0.25 mmol) with **15a** afforded alcohol **17d** (64 mg, 67%) as a colorless oil: dr>20:1 by ^1H NMR (600 MHz); $[\alpha]_D^{23}$ +5.42 (*c* 1.53, $CHCl_3$); IR (film) 3561, 2961, 2931, 2858, 1427, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.27 (dq, J=15.3, 6.1 Hz, 1H), 5.19 (ddq, J=15.3, 7.6, 1.5 Hz, 1H), 3.93 (qd, J=6.4, 3.3 Hz, 1H), 3.05 (td, J=7.6, 3.3 Hz, 1H), 2.44 (d, J=7.6 Hz, 1H), 2.28 (m, 1H), 1.56 (d, J=6.1 Hz, 3H), 1.08 (s, 9H), 1.05 (d, J=6.4 Hz, 3H), 1.02 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 136.1, 134.5, 134.3, 133.4, 130.0, 129.8, 127.9, 127.6, 125.4, 79.7, 70.4, 40.3, 27.3, 21.2, 19.6, 18.2, 16.5; HRMS-EI (*m/z*): $[M-{}^tBu]^+$ calcd for $C_{20}H_{25}O_2Si$ 325.1624, found 325.1626.

4.3.5. (*E*)-(2*R*,3*R*)-3-Methyl-1-phenyl-hex-4-en-2-ol (17e). Following the general procedure, the reaction of aldehyde **16e** (31 mg, 0.25 mmol) with **15a** afforded a mixture of alcohols **17e** and its diastereomer of undetermined stereochemistry (38 mg, 79%) as a colorless oil. The same alcohol **17e** (48 mg, 66%) was obtained from the reaction of dimethyl acetal **16f** (42 mg, 0.25 mmol) with **15a** according to the general procedure: dr=10:1 by ^1H NMR (500 MHz); er of the major alcohol **17e**>99:1 by chiral HPLC (Chiralpak AD, 10% water in methanol, 1.0 mL/min, 4.75 min (+) isomer, 6.13 min for (−) isomer); $[\alpha]_D^{23}$ +6.6 (*c* 0.70, $CHCl_3$); $[\alpha]_D^{23}$ +43 (*c* 0.83, $CHCl_3$); IR (film) 3441, 3027, 2963, 2917, 2880, 1495, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.23 (m, 3H), 5.55 (dq, J=15.2, 6.1 Hz, 1H), 5.45 (ddq, J=15.2, 7.3, 1.2 Hz, 1H), 3.67 (m, 1H), 2.89 (dd, J=13.8, 3.7 Hz, 1H), 2.58 (dd, J=13.8, 9.5 Hz, 1H), 2.29 (m, 1H), 1.71 (d, J=6.1 Hz, 3H), 1.52 (d, J=4.0 Hz, 1H), 1.09 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 133.7, 129.5, 128.7, 126.5, 126.3, 76.3, 42.4, 41.0, 18.4, 15.6; HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{13}H_{18}O$ 190.1358, found 190.1365.

4.3.6. (*E*)-(2*R*,3*R*)-1-Cyclohexyl-3-methyl-hex-4-en-2-ol (17g). Following the general procedure, the reaction of aldehyde **16g**[19] (26 mg, 0.21 mmol) with **15a** afforded alcohol **17g** (28 mg, 69%) as a colorless oil: dr=11:1 by ^1H NMR (500 MHz); er>99:1 (determined as a benzoate ester) by chiral HPLC (Chiralpak AD, 5% water in methanol, 1.0 mL/min, 5.34 min (+) isomer, 6.02 min for (−) isomer); $[\alpha]_D^{23}$ +44 (*c* 0.42, $CHCl_3$); IR (film) 3370, 2920, 2850, 1450, 990, 970; ^1H NMR (500 MHz, $CDCl_3$): δ 5.50 (ddq, J=15.3, 6.4, 0.9 Hz, 1H), 5.37 (ddq, J=15.3, 7.6, 1.5 Hz, 1H), 3.57 (m, 1H), 2.19 (m, 1H), 1.81 (app. d, J=12.8 Hz, 1H), 1.69 (d, J=6.1 Hz, 3H), 1.69–1.63 (m, 4H), 1.45 (m, 1H), 1.33–1.10 (m, 6H), 0.91 (m, 1H), 0.97 (d, J=7.0 Hz, 3H), 0.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 133.5, 126.1, 72.3, 42.9, 41.6, 34.6, 34.2, 32.7, 26.7, 26.5, 26.2, 18.2, 14.8; HRMS-EI (*m/z*): $[M-H_2O]^+$ calcd for $C_{13}H_{22}$ 178.1721, found 178.1712.

4.3.7. (*E*)-(4*R*,5*R*,8*S*)-4,8-Dimethyl-undec-2-en-9-yn-5-ol (6). Following the general procedure, the reaction of aldehyde **4**[6] (99 mg, 0.80 mmol) with **15a** afforded alcohol **6** (125 mg, 80%) as a colorless oil: dr=10:1 by ^1H NMR (500 MHz); $[\alpha]_D^{23}$ +51 (*c* 0.45, $CHCl_3$); IR (film) 3392, 2964, 2931, 2858, 1451, 1429, 1376 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (dqd, J=15.3, 6.1, 0.9 Hz, 1H), 5.39 (ddq, J=15.3, 6.6, 1.5 Hz, 1H), 3.46 (m, 1H), 2.42 (m, 1H), 2.25 (m, 1H), 1.79 (d, J=2.4 Hz, 3H), 1.70 (dd, J=6.1, 1.5 Hz, 3H), 1.38–1.64 (m, 5H), 1.15 (d, J=7.0 Hz, 3H), 1.01 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 126.3, 83.8, 76.1, 75.0, 42.8, 33.7, 31.7, 26.0, 21.7, 18.3, 15.1, 3.7; HRMS-EI (*m/z*): (the corresponding TBS ether) $[M-Me]^+$ calcd for $C_{18}H_{33}OSi$ 293.2301, found 293.2290.

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Strained silacycle-catalyzed asymmetric Diels–Alder cycloadditions: the first highly enantioselective silicon Lewis acid catalyst

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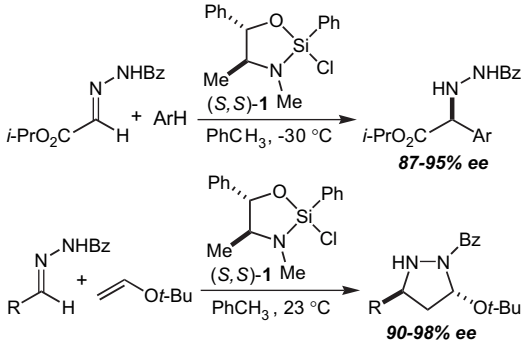
Abstract—The first highly enantioselective silicon Lewis acid catalyst for an asymmetric organic transformation has been developed. The catalyst derives its activity from the strain induced in the silicon center by virtue of being constrained in a five-membered ring. A simple tridentate ligand has been developed and the derived chlorosilane complex catalyzes the Diels–Alder cycloaddition of methacrolein and cyclopentadiene with 94% ee.

1. Introduction

The possibility that silicon—with all of its inherent practical advantages—might serve as a useful Lewis acid for asymmetric synthesis, has long captured the imagination of organic chemists. Three strategies have emerged for rendering otherwise unreactive silanes Lewis acidic for the promotion/catalysis of organic reactions: (1) attachment of strongly electron-withdrawing groups to the silicon center (e.g., TMSOTf),[1] (2) Lewis base activation of otherwise only weakly Lewis acidic silanes such as $RSiCl_3$ and $SiCl_4$,[2] and (3) constraining the silicon in a small ring (strained silacycles).[3] Despite some creative ideas,[4] the first approach has yielded no highly enantioselective chiral catalysts for asymmetric synthesis. In contrast, the second approach has led to the development of several highly enantioselective reactions.[5] It is typically the Lewis base that serves as the catalyst, however, while the silane component is employed as a stoichiometric reagent. We have recently reported the first examples of highly enantioselective chiral silicon Lewis acid-mediated carbon–carbon bond forming reactions based on the third approach (Scheme 1),[6] and it was natural to wonder whether the same concept might be applied for the discovery of the first highly enantioselective silicon Lewis acid catalyst. Because of its prominent role in the development of chiral Lewis acid catalysis,[7] the Diels–Alder reaction of enals with cyclopentadiene was chosen as the proving ground for this idea.



Scheme 1. Two reactions mediated by silane **1**.

Silane Lewis acid **1** (prepared and employed as a 2:1 mixture of diastereomers) has proven effective both for Friedel–Crafts alkylations of acylhydrazones and [3+2] enol ether–acylhydrazone cycloadditions (Scheme 1).[8] Mechanistic investigations have revealed that these reactions proceed by way of covalent attachment of the hydrazone to the silane Lewis acid with chloride displacement and protonation of the amino group of the pseudoephedrine. Such reactions are therefore mechanistically distinct from the proposed simple Lewis acid activation of methacrolein for a Diels–Alder cycloaddition with cyclopentadiene, and there was no reason a priori to believe that silane **1** would prove effective for this reaction. Indeed, **1** is wholly ineffective as a catalyst for this process, and replacement of the phenyl group

Keywords: Silicon; Lewis acid; Catalyst; Diels–Alder; Enantioselective.
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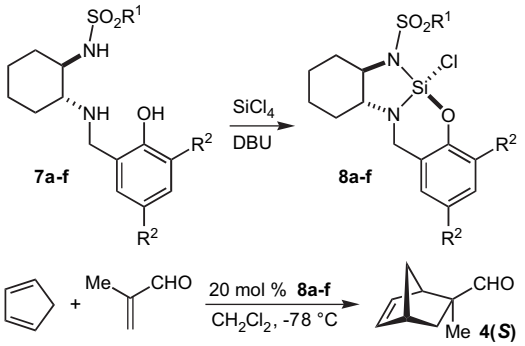
on the silane with various other alkyl, aryl, and heteroatom substituents proved fruitless as well.

2. Results and discussion

A breakthrough was achieved when we examined chiral ligands that carry three functional groups for attachment to the silane. Ephedrine-derived aminophenol **2** was treated with $SiCl_4$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give silane **3** as a single (unassigned) diastereomer (Scheme 2). We were then delighted to discover that **3** is indeed a competent (albeit non-selective) catalyst for the Diels–Alder reaction between cyclopentadiene and methacrolein, producing aldehyde **4**(*R*) in 58% yield and 6% ee. In this and in every case, the *exo* diastereomer was produced highly selectively (>95:5). The diphenylethylenediamine-derived aminophenol **5** was next examined, and the derived silane **6** was also found to be a competent catalyst providing aldehdye **4**(*S*) as the major product in 46% yield and 37% ee. The commonly employed cyclohexanediamine ligand motif was examined in the form of **7a**, which was employed to generate silane **8a** (the illustrated and observed NOE interaction allowed the assignment of relative configuration at the silicon center in **8a**). Gratifyingly, **8a** proved to be a significantly improved catalyst, giving **4**(*S*) in 75% yield and 56% ee, and providing our first true lead catalyst for optimization. Finally, we note that silane **9** is completely inactive under otherwise identical conditions, clearly supporting the hypothesis that the strain induced by the five-membered rings in **3**, **6**, and **8a** is an essential component of their Lewis acidity and catalytic activity.

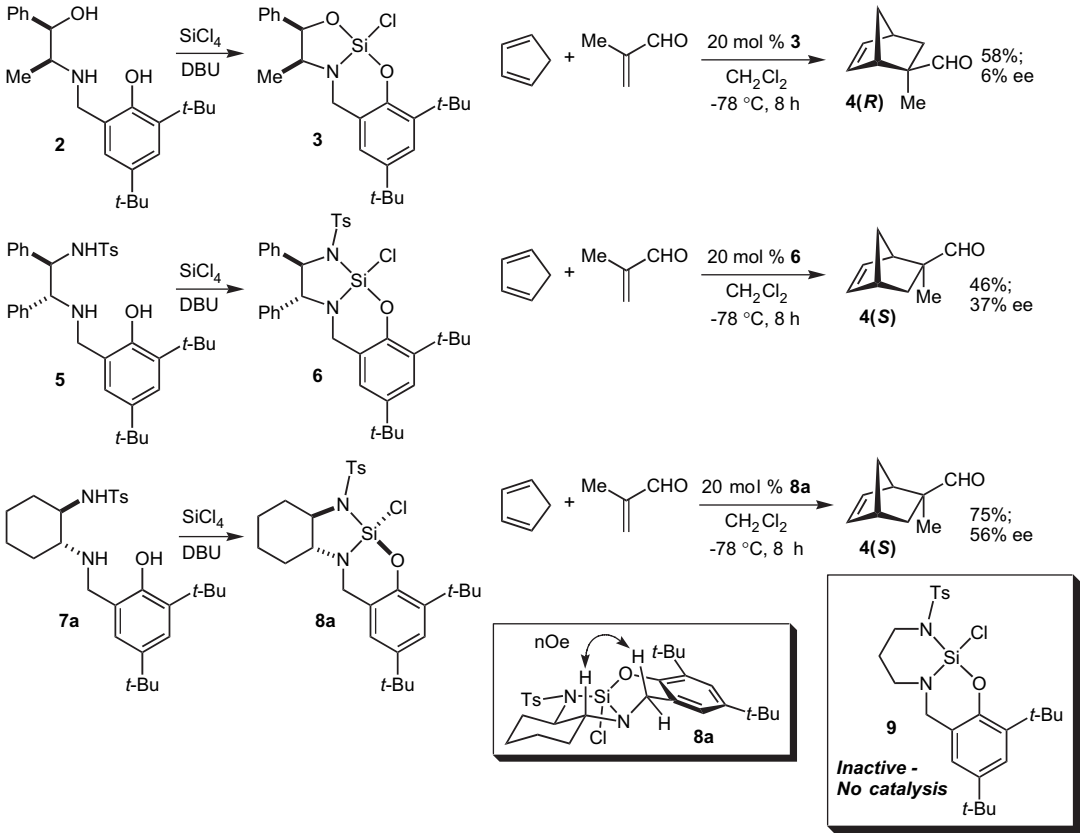
Having recorded a proof of concept with silane **8a**, we turned to a survey of the sulfonamide substituent (R^1) as well as the substituents on the phenol ring (R^2) in an effort to optimize both for efficiency and enantioselectivity (Table 1). Although in some cases the silanes could be isolated in reasonable purity, it was more convenient to employ them in situ. Thus, the precursor sulfonamidoaminophenols **7a–f** were treated with $SiCl_4$ and DBU and the resulting solutions of silanes **8a–f** were simply treated with cyclopentadiene and

Table 1. Optimization of catalyst structure



Entry (cat.)	R^1	R^2	Yield (%)	ee (%)
1 (**8a**)	*p*-Tolyl	*t*-Bu	72	−56[a]
2 (**8b**)	Me	*t*-Bu	75	−75[a]
3 (**8c**)	Mesityl	*t*-Bu	58	−33[a]
4 (**8d**)	*p*-Tolyl	Br	69	57
5 (**8e**)	*p*-F–C_6H_4	H	56	88
6 (**8f**)	*p*-Tolyl	H	78	94

[a] Major enantiomer was **4**(*R*).



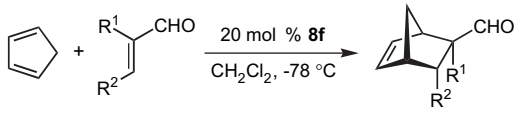
Scheme 2. Initial discovery of competent silane Lewis acid catalysts.

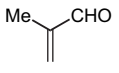
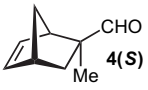
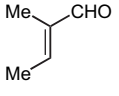
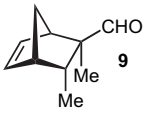
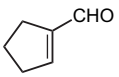
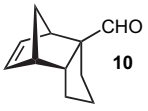
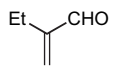
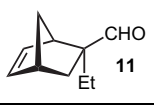
methacrolein. As shown, simple changes to the sulfonamide group and the substituents on the phenol ring produced dramatic changes in the enantioselectivity. Indeed, it was possible to obtain either moderately good enantioselectivity for the *R* enantiomer (entry 2) or excellent enantioselectivity for the *S* enantiomer (entry 6) using the same enantiomer of the cyclohexanediamine core. As shown, the optimal catalyst was the simple tosylamide-unsubstituted phenol **8f**. Using 20 mol % of this catalyst and the in situ procedure, **4**(*S*) was produced in 78% yield and 94% ee. *Silane* **8f** *thus represents the first highly enantioselective silicon Lewis acid catalyst developed for asymmetric synthesis*.

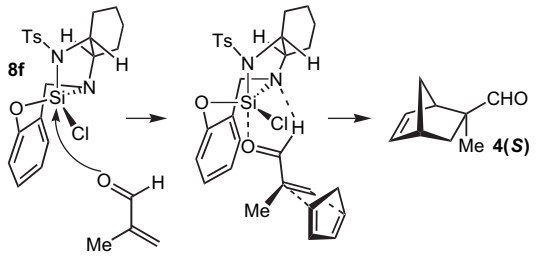
A brief survey of the scope with respect to the enal structure in Diels–Alder reactions with cyclopentadiene catalyzed by **8f** was carried out (Table 2). Whereas β-substitution necessitated extended reaction times, such substrates were nevertheless well tolerated from the standpoint of enantioselectivity (entries 2 and 3). In contrast, and surprisingly, α-substitution beyond a simple methyl group caused a dramatic drop in enantioselectivity (entry 4).

In an attempt to construct a mechanistic model for stereochemical induction, we began with two assumptions: (1) in order for the five-membered diazasilacyclopentane ring to be accommodated in the presumed trigonal bipyramidal (tbp) silane–aldehyde complex, one of the two nitrogens must occupy an apical position, and this will likely be the more electron-poor tosylamide nitrogen, and (2) the aldehyde oxygen will bind to the silane opposite this tosylamide nitrogen so as to occupy the other apical position in the complex (Scheme 3). If a hydrogen bond between the amine and the formyl hydrogen—a type of interaction proposed by Corey to be an essential element in the success of numerous enantioselective chiral Lewis acid catalyzed reactions[9]—is further invoked as depicted, an intriguingly simple model for asymmetric induction emerges as the phenyl ring clearly provides highly effective shielding of the back face of the dienophile. This model can also explain the surprisingly dramatic drop-off in enantioselectivity observed with ethacrolein (Table 2, entry 4). The added methyl group (relative to methacrolein) in this dienophile must swing away from the approaching cyclopentadiene in the transition state, but cannot do so without being forced into a costly steric interaction with the phenyl ring. The likely result is a shift to a greater population of the *s*-cis form of the enal, and in turn eroded levels of enantioselectivity.

Table 2. Survey of enal scope



Entry	Enal	Product	*t* (h)	Yield (%)	ee (%)
1		 **4(*S*)**	8	78	94
2		 **9**	48	87	90
3		 **10**	24	79	86
4		 **11**	16	88	54



Scheme 3. A model for asymmetric induction.

3. Conclusion

We have developed the first highly enantioselective silicon Lewis acid catalyst for asymmetric synthesis. The catalyst is easily and inexpensively prepared and may be employed in situ. Lewis acid catalysts for the Diels–Alder reaction are legion,[7] however, and a powerful new strategy for enal *and* enone activation in Diels–Alder reactions has recently emerged.[10] The significance of this work is therefore not specifically tied to the Diels–Alder reaction, but rather lies in the potential for the development of improved silicon Lewis acid catalyst designs for a broader range of transformations. The present work establishes the validity of this notion and delineates a strategy for achieving such catalysts.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. Flash chromatography was performed on EM silica gel 60 (230–240 mesh). Degassed solvents were obtained from the solvent purification system by passage through a column of activated alumina. ^{1}H NMR spectra were recorded on a Bruker DRX-300 (300 MHz), Bruker DRX-400 (400 MHz), or DMX-500 (500 MHz) spectrometer, and are reported in parts per million from $CDCl_3$ (7.26 ppm), C_6D_6 (7.15 ppm), or DMSO-d_6 (2.50 ppm) as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad; integration; coupling constant(s) in Hertz; assignment. ^{29}Si NMR spectra were recorded on a Bruker DRX-300 (60 MHz) spectrometer and are reported in parts per million from tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded on a Bruker DRX-300 (338.6 MHz) spectrometer and are reported in parts per million from $CFCl_3$ as internal standard. Proton decoupled ^{13}C NMR spectra were recorded on a Bruker

DRX-300 or Bruker DRX-400 (100 MHz) spectrometer using $CDCl_3$ (77.0 ppm), C_6D_6 (128.0 ppm), or DMSO-d_6 (40.5 ppm) as internal standard. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer. Low-resolution mass spectra were obtained on a JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory. Optical rotations were obtained on a JASCO DIP-1000 polarimeter using a 10 cm path length cell.

4.1.1. Synthesis of ligand 7f. The Schiff base formed by condensation of cyclohexanediamine monotosylamide and salicylaldehyde has been prepared and characterized previously.[11] We prepared the (*R*,*R*)-cyclohexanediamine-derived Schiff base according to this procedure. To a cooled (0 °C) solution of this Schiff base (3.0 mmol) in CH_2Cl_2 (4.0 mL) and MeOH (12.0 mL) was added $NaBH_4$ (337 mg, 9.0 mmol). The reaction mixture was warmed to room temperature after 15 min and stirred for an additional 3 h. The reaction was then quenched by the addition of 1 M NaOH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with brine (1×5 mL), dried over $MgSO_4$, filtered, and concentrated. The solid residue was then purified by recrystallization (Et_2O/CH_2Cl_2) to afford 1.01 g (90%) of ligand **7f** as a white solid. $[\alpha]_D^{21}$ +9.77 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 2H, *J*=5.0 Hz, 1.6 Hz, $SO_2C_6(o\text{-}H_2)(m\text{-}H_2)CH_3$), 7.24 (d, 2H, *J*=7.9 Hz, $SO_2C_6(o\text{-}H_2)(m\text{-}H_2)CH_3$), 7.15 (dt, 1H, *J*=1.5 Hz, 7.7 Hz, one of $NCH_2C_6H_4$), 6.91 (dd, 1H, *J*=1.3 Hz, 6.1 Hz, one of $NCH_2C_6H_4$), 6.81–6.73 (m, 2H, two of $NCH_2C_6H_4$), 4.67 (br s, 1H, $NHSO_2Ar$), 3.93 (d, 1H, *J*=13.9 Hz, one of NCH_2Ar), 3.84 (d, 1H, *J*=13.9 Hz, one of NCH_2Ar), 3.02–2.95 (br m, 1H, $CHNHSO_2Ar$), 2.37 (s, 3H, $SO_2C_6H_4CH_3$), 2.31–2.26 (m, 1H, $CHNHCH_2Ar$), 2.14–2.08 (br m, 1H, Cy–*H*), 1.70–1.58 (br m, 3H, Cy–H_3), 1.23–1.12 (m, 4H, Cy–H_4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.7, 137.6, 129.8, 129.8, 128.5, 128.0, 126.9, 126.9, 123.1, 119.0, 116.4, 60.9, 57.1, 50.0, 33.4, 31.1, 24.8, 24.0, 21.5; IR (KBr) 3319, 3237, 3043, 2932, 2857, 1613, 1590, 1478, 1449, 1411, 1322, 1262, 1150, 1091, 934, 912, 748, 666, 547 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{27}N_2O_3S$ $[M+H]^+$ 375.1742, found 375.1733.

4.2. General procedure for the Diels–Alder reactions in Table 2

To a cooled (−78 °C) solution of $SiCl_4$ (149 μL, 1.30 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (612 μL, 4.09 mmol) in CH_2Cl_2 (13.0 mL) is added a solution of **7f** (500 mg, 1.33 mmol) in CH_2Cl_2 (13.0 mL). The reaction mixture is slowly warmed to room temperature over the course of 4 h, and after an additional 4 h at room temperature, the resulting solution of the catalyst **8f** in CH_2Cl_2 (0.0500 M) is used directly for the Diels–Alder reactions.

To a cooled (−78 °C) solution of catalyst **8f** (0.05 M in CH_2Cl_2, 4.0 mL, 0.20 mmol) and cyclopentadiene (250 μL, 3.8 mmol) is added the unsaturated aldehyde (1.0 mmol) dropwise. After the indicated reaction time (see Table 2), the mixture is diluted with CH_2Cl_2 (1.0 mL) and quenched with a solution of 4:1 MeOH/H_2O (250 μL). The organic layer is washed with brine (1×1 mL), dried over Na_2SO_4, and concentrated. The residue is purified by flash chromatography (100% pentane → 20% Et_2O/pentane) to afford the pure bicyclic aldehyde products in the yields and enantioselectivities indicated in Table 2.

4.2.1. Diels–Alder reaction products—characterization and determination of enantioselectivity.

4.2.1.1. Table 2, entry 1. The physical and spectral data for this compound matched previously reported data.[12] The diastereoselectivity (*exo*:*endo* ratio = 96:4) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.69 (s, 1H, C*H*O, *exo*), 9.39 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 94%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.31 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.25 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.22 (d, 1H, one of CH_2O-(*R*)-MTPA, major).

4.2.1.2. Table 2, entry 2. The physical and spectral data for this compound matched previously reported data.[13] The diastereoselectivity (*exo*:*endo* ratio>98:2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.62 (s, 1H, C*H*O, *exo*), 9.37 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 90%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.25 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.20 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.14 (d, 1H, one of CH_2O-(*R*)-MTPA, major). The absolute configuration was assigned by analogy to the methacrolein reaction.

4.2.1.3. Table 2, entry 3. The physical and spectral data for this compound matched previously reported data.[14] The diastereoselectivity (*exo*:*endo* ratio>96:4) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.73 (s, 1H, C*H*O, *exo*), 9.45 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 86%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (br s, 1H, =CH–C*H*, major), 2.63 (br s, 1H, =CH–C*H*, minor).

4.2.1.4. Table 2, entry 4. The physical and spectral data for this compound matched previously reported data.[13] The diastereoselectivity (*exo*:*endo* ratio>95:5) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.70 (s, 1H, C*H*O, *exo*), 9.42 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 54%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.37 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.33 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.29 (d, 1H, one of CH_2O-(*R*)-MTPA, minor). The absolute configuration was assigned by analogy to the methacrolein reaction.

Acknowledgements

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Enantioselective homoallyl-cyclopropanation of dibenzylideneacetone by modified allylindium halide reagents—rapid access to enantioenriched 1-styryl-norcarene

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Abstract—Dibenzylideneacetone (**8**) reacts with in situ-generated allylindium halide reagents to yield the product of a homoallyl-cyclopropanation reaction: 2-(3″-butenyl)-1,1-bis[(*E*)-2′-phenylethenyl]cyclopropane (**9**), which proceeds via step-wise cleavage of the C=O bond and delivery of two allyl fragments from the reagent. A range of enantiomerically enriched ligands have been tested as stoichiometric asymmetric modifiers for this process. Enantiopure compounds such as cinchona alkaloids, ephedra, aminoalcohols and tartaric acid derivatives, which have proven of utility as asymmetric modifiers for the indium-mediated allylation of aldehydes and ketones, were very inefficient in the process **8**→**9**. However, mandelic acid derivatives, in particular mandelates, were found to be of significant potential. The absolute stereochemistry of the cyclopropane **9** has been determined by degradation to 1,1-dicarboxymethyl-2-butylcyclopropane, converging with an independent enantioselective synthesis starting from hexene. Under optimised conditions, viz. using allylindium iodide reagents and working-up with aqueous Na_2SO_3 to avoid iodine-mediated polymerisation, (*S*)-**9** can be generated in 86% yield and with (*S*)-methyl mandelate as modifier useful enantiopurity (94/6 er) was observed. The cyclopropane product ((*S*)-**9**) undergoes RCM using standard conditions to afford a norcarene unit ((1*S*,6*S*)-1-(*E*)-2′-(phenylethenyl)-bicyclo[4.1.0]hept-2-ene) without loss of enantiopurity.

1. Introduction

The use of an organoindium compound[1] as a reagent to facilitate C–C bond formation was first described by Gilman and Jones in 1940.[2] Ph_3In, generated by oxidative transfer of phenyl from Ph_2Hg to indium metal, was reacted with a range of carbonyl compounds, including benzylideneacetone with which it underwent clean 1,4-addition. The direct generation of organoindium halide reagents from simple organohalides and indium metal, thereby avoiding the use of R_2Hg,[3,4] is extremely slow. The procedure is generally only practical with MeI and EtI,[5] which function as both reactant and solvent. An exception to this is the highly reactive 'Riecke' form of indium, which facilitates the preparation of indium-based Reformatsky reagents.[6] However, it was the pioneering work of Araki et al.[7] on the facile reaction of allylic bromides and iodides with commercially available indium powder that marked the onset of a period of extremely rapid development in the field. The manifold applications that have emerged since then have predominantly involved the use of indium metal or indium(I) iodide, in combination with an allyl halide,[8] to effect allylation,[9] most often in water (Barbier type conditions) or in an aprotic organic solvent such as THF or DMF. The mildness of the conditions lend themselves to the synthesis of complex natural products, particularly carbohydrates, without the need for extensive use of protecting groups.[10] Unsurprisingly, the growing range of substrates, reagents and conditions that have been developed to harness the power of indium in organic synthesis has been the subject of numerous reviews.[11] Although the major focus in terms of substrate has been carbonyl compounds,[11] other electrophiles including imines,[12] alkenes and alkynes,[13] acetals,[14] epoxides,[15] allylic sulfonium salts[16] and pyridinium salts[17] have proven of utility. There has also been progress towards the development of more 'green' conditions for organoindium-mediated processes, which include solvent free reactions,[18] use of *sc*-CO_2[19] and ionic liquids as solvent,[20] and the development of catalytic indium methodology.[21]

The indium-mediated allylation of aldehydes and asymmetric ketones (**1**), leads, via alkoxide **2**, to homoallylic alcohols (**3**) in which a new stereogenic centre is generated at the hydroxyl-bearing carbon. The stereoselectivity of this reaction,

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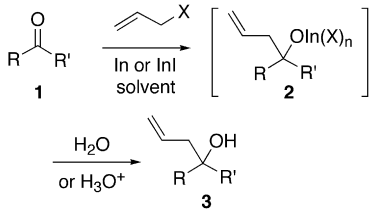
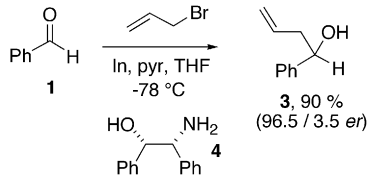
Scheme 1, has been of much interest, with many investigations into the use of proximal functionality to 'direct' the stereochemical course of reaction and thus engender diastereoselectivity.[11] The diastereoselective indium-mediated allylation of other functionality, such as imines and aldimines,[22] hydrazones,[23] azetidinones[24] and cyclopropenes[25] has also been achieved.



Scheme 1. A generic scheme for indium-mediated allylation of an aldehyde (R′=H) or asymmetric ketone (R≠R′) leading to a new stereogenic centre.

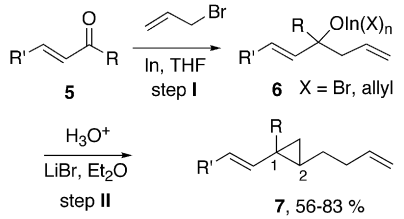
The asymmetric allylation of ketones and aldehydes by way of stoichiometrically-modified allyl–metal reagents (e.g., based on Zn, Sn, B) is a reaction of considerable current interest, particularly in relation to the enantioselective construction of quaternary carbon centres.[26] It is perhaps surprising that despite the extensive investigations into diastereoselective indium-mediated allylation, the corresponding developments in enantioselective allylation have been much less marked. The first examples were from Araki et al., who reported on the asymmetric modification of indium-mediated Reformatsky reactions with cinchona alkaloids.[27] The same modifiers were subsequently used by Loh et al. for the indium-mediated enantioselective allylation (and propargylation) of aldehydes.[28] For example, allylation of PhCHO by allyl bromide/indium in THF/hexane in the presence of (+)-cinchonine (2 equiv) proceeds in up to 86/14 er at −78 °C. The use of cinchonine as asymmetric modifier in the indium-mediated allylation of imines has also been reported (up to 72/28 er).[29] More recently, Singaram et al. reported on the application of simple aminoalcohols, e.g., **4**, as modifiers, for aldehyde allylation Scheme 2.[30] Under optimised conditions, the best modifier (**4**, 2.0 equiv) facilitates selective generation of one enantiomer (up to 96.5/3.5 er) in the allylation of a range of aldehydes at −78 °C. At higher temperatures, the selectivity drops markedly.



Scheme 2. Asymmetric indium-mediated allylation of benzaldehyde employing 1,2-diphenyl-2-aminoethanol (1*S*,2*R*-**4**) as super-stoichiometric enantiopure modifier (indium/**4**/allyl bromide/pyr/PhCHO=2/2/2/2/1).

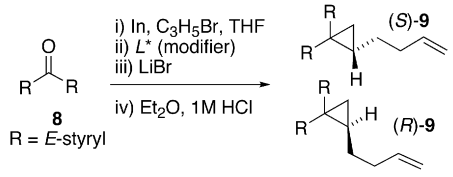
A key issue of such reactions is the requirement of stoichiometric or super-stoichiometric quantities of enantiomerically enriched, ideally enantiomerically pure, chiral modifier. In practice, this limits the choice of modifiers that will be genuinely applicable in synthesis to those derived from the chiral pool or products of commercial resolution. Recent reports from Cook et al., on the use of catalytic (10 mol %) quantities of 2,2′-dihydroxy-1,1′-binaphthalene, and derivatives, to engender asymmetric allyl transfer (allyl iodide, indium, THF, 4 Å MS) to aryl hydrazones (up to 96/4 er),[31] as well as the use of indium catalysts for asymmetric allyl transfer from Sn,[32] bode well for the developments in this area.[33]

In 1998 we reported that α,β-unsaturated ketones and aldehydes (**5**) react with in situ-generated allylindium halide reagents[34] in THF to yield, on acidic aqueous work-up of the indate (**6**+LiBr), homoallyl-vinylcyclopropanes **7**, Scheme 3.[35]



Scheme 3. The homoallyl-cyclopropanation of α,β-unsaturated ketones (R=alkyl, aryl) and aldehydes (R=H) mediated by allylindium halide reagents in THF at ambient temperature. When R=CH=CHR′, C(1) in **7** is nonstereogenic and the configuration of C(2) is determined in step **II**.

The addition of allylindium halide reagents to α,β-unsaturated ketones and aldehydes (**5**) followed by acidic hydrolysis gives homoallyl alcohol-type products arising from [1,2]-addition to the carbonyl (Step **I**, Scheme 3) rather than [1,4]-addition to the enone.[36] We thus proposed that the generation of **7** involves an acid-catalysed C–O bond cleavage[37] of an indium alkoxide (**6**) concomitant with a second allyl unit being delivered to the homoallylic terminus from indium (Step **II**, Scheme 3).[38] In the case of the reaction of a symmetrically substituted bis-α,β-unsaturated ketone, the intermediate **6**, in which R=CH=CHR′, is formally achiral (ignoring issues of indium-based stereocentres) and the homoallylic alkene terminus is pro-chiral. Consequently, the cyclopropane stereogenic centre[39] (C(2) in **7**, Scheme 3) is generated not on the initial allylation (step **I**), but on the C–O cleavage/ring-closure/allylation (step **II**). In parallel with the efforts towards the discovery and development of enantioselective indium-mediated allylations, vide supra, we have been testing whether the C–C bond-forming event in the homoallyl-cyclopropanation reaction can be rendered asymmetric by virtue of a simple stoichiometric chiral modifier. The homoallyl-cyclopropanation process is mechanistically distinct[38] from the conventional asymmetric indium-mediated allylation of carbonyls, Scheme 2, and it is thus also of interest to determine whether the same types of asymmetric modifier are effective. Herein we report our preliminary studies in this area using the bis-α,β-unsaturated ketone, dibenzylideneacetone ('dba', **8**), as a prototype substrate for the asymmetric homoallyl-cyclopropanation to generate **9** (Scheme 4; cf. **5** and **7**, in



Scheme 4. Reaction of dibenzylideneacetone (**8**) used to test potential asymmetric modifiers (*L**) in the homoallyl-cyclopropanation reaction (→**9**); see also Table 1.

Scheme 3, where R=PhCH=CH, R′=Ph). We present a low-cost, commercially available and enantiomerically pure modifier, which yields **9** under technically simple and scaleable conditions, in up to 94/6 er[40] and in good yield (86%).

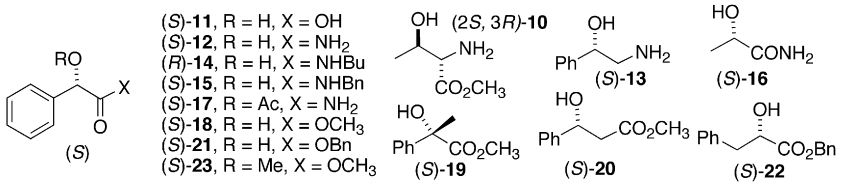
2. Results and discussion

Using the conditions described in our original report for the homoallyl-cyclopropanation of α,β-unsaturated ketones and aldehydes[35] (see Scheme 3), we began by testing a range of commercially available enantiomerically pure aminoalcohols and diols as modifiers for the reaction (**8**→**9**). An extensive screening of chiral HPLC columns and conditions facilitated the near base-line resolution of the chiral racemic hydrocarbon (±)-**9** by use of a rigorously alcohol-free hexane eluent in combination with an OD-H column, thus allowing rapid assay of the enantioselectivity. Based on the work of Araki et al.,[27] and Loh et al.,[28] an obvious starting point for modifier screening was the cinchona alkaloids. Whilst there was some selectivity in the reaction (**8**→**9**) it was low (maximum 44/56 er) and the yields were moderate (42–51%).

A key point that emerged was that *racemic* cyclopropane (±)-**9** was obtained if the alkaloid was added after the ketone **8**. Whether the modifier was added before or with the ketone made no difference to the selectivity. Testing a range of ephedra, tartaric acid derivatives and aminoalcohols led to improved selectivities but with lower yields. The most promising selectivity (79/21 er; 21% yield) was obtained with threonine methyl ester (**10**, Table 1, entry 1), and on the basis that valinol and phenylglycinol gave no selectivity, we concluded that the hydroxyl-bearing, rather than amine-bearing, stereocentre was crucial. To further explore this issue, (*S*)-mandelic acid ((*S*)-**11**), was converted to (*S*)-mandelamine ((*S*)-**13**), via (*S*)-mandelamide ((*S*)-**12**). However, like valinol and phenylglycinol, using the aminoalcohol (*S*)-**13** as modifier gave *racemic* **9** (Table 1, entry 2). Somewhat unexpectedly, (*S*)-mandelamide ((*S*)-**12**) (1.0 equiv) gave the most encouraging combination of selectivity and yield: 25/75 er (*S*)-(+)-**9**, 27% yield, (Table 1, entry 3). However, although this modifier was also efficient in a semi-catalytic stoichiometry (Table 1, entry 4), use of super-stoichiometric quantities to increase the enantioselectivity led to plummeting yields (entries 5 and 6).

In order to address the issue of low yields in the asymmetric modification of the homoallyl-cyclopropanation reaction (**8**→**9**), we employed factorial based experimental design,[41] to analyse the reaction both in the presence and absence of 1.0 equiv (*S*)-mandelamide modifier ((*S*)-**12**). Whilst some minor interactions were discovered, a key factor that emerged was a strong dependence of the yield, and an inverse dependence of the enantioselectivity, on the allylindium halide reagent[34] concentration at the point when the ketone **8** is added: high concentrations gave higher ultimate yields of **9** and lower concentrations gave higher enantioselectivity. However, the efficient generation of the allylindium halide reagent requires high concentration of allyl halide. We thus compromised by generating the reagent at 2.0 M (in indium) and then diluting to 0.11 M before adding the ketone **8**, resulting in an improved yield of **9** (73%)

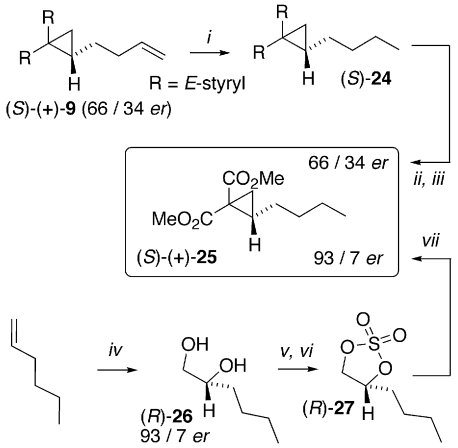
Table 1. The effect of a range of enantiomerically pure alcohols, especially α-hydroxy carbonyl derivatives, as modifiers (*L** in Scheme 4) for the asymmetric homoallyl-cyclopropanation of dibenzylideneacetone (**8**, 0.11 M in THF, rt) to give cyclopropane **9**



Entry	Modifier	Stoichiometry *L**/**8**	Yield **9**/%[a]	er **9** (*R*/*S*)[b]
1	(2*S*,3*R*)-**10**	1.0	21[c]	79/21[c]
2	(*S*)-**13**	1.0	68[c]	50/50[c]
3	(*S*)-**12**	1.0	27[c]	25/75[c]
4	(*S*)-**12**	0.5	47[c]	32/68[c]
5	(*S*)-**12**	2.0	8[c]	15/85[c]
6	(*S*)-**12**	4.0	0[c,d]	—[c]
7	(*S*)-**12**	1.0	73	34/66
8	(*R*)-**14**	1.0	22	73/27
9	(*S*)-**15**	1.0	0	—
10	(*S*)-**16**	1.0	70	50/50
11	(*S*)-**17**	1.0	70	50/50
12	(*S*)-**11**	1.0	67	42/58
13	(*S*)-**18**	**1.0**	**71**	**20/80**
14	(*S*)-**18**	2.0	39	11/89
15	(*S*)-**19**	1.0	38	34/66
16	(*S*)-**20**	1.0	38	50/50
17	(*S*)-**21**	1.0	70	24/76
18	(*S*)-**22**	1.0	66	25/75
19	(*S*)-**23**	1.0	70	48/52

[a] Isolated yield after silica-gel chromatography.
[b] Determined by chiral HPLC (OD-H, see Section 4 for details).
[c] Reaction conducted at 1.0 M **8**.
[d] 1*E*-1-Phenyl-3-*E*-styryl-hexa-1,3,5-triene was isolated in 49% yield.

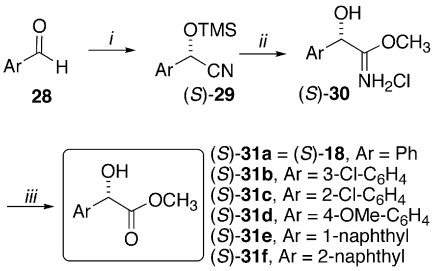
with moderate selectivity (34/66 er) Table 1, entry 7. With sufficient material in hand, we then established the absolute configuration of (*S*)-(+)-**9** (34/66 er) by degradation (**9**→**24**→**25**) to converge with an asymmetric synthesis of (*S*)-**25** starting from hexene (→**26**→**27**→**25**), a key feature being the double S_N2-inversion (C(1) then C(2)) in **27** with dimethyl malonate anion, Scheme 5.



Scheme 5. The converging degradation of **9** (34/66 er) and asymmetric synthesis of (*S*)-**25** employed to deduce the absolute configuration of (*S*)-(+)-**9**. Conditions: (i) $Cp_2Zr(Cl)H$, CH_2Cl_2, then H_2O; (ii) cat. $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O; (iii) $TMSCHN_2$, MeOH, toluene; (iv) cat. [$(DHQD)_2PYR$], cat. $KOsO_4\cdot H_2O$, $K_3Fe(CN)_6$, *tert*-BuOH, H_2O; (v) $SOCl_2$, CCl_4; (vi) cat. $RuCl_3\cdot 3H_2O$, $NaIO_4$, H_2O; (vii) $CH_2(CO_2CH_3)_2$, DME, NaH (2.5 equiv).

Chiral GC analysis of the two samples of **25** (one from each route), demonstrated conclusively that (*S*)-(+)-**25** (34/66 er) was derived from (+)-**9**, which establishes the *S* configuration for the latter. Returning back to the asymmetric homoallyl-cyclopropanation, we screened a range of α-hydroxy carbonyl derivatives and analogues of mandelamide (*S*)-**12**, for their potential as modifiers, Table 1, entries 8–19. Using *N*-alkylated analogues of the mandelamide (*N*-Bu and *N*-Bn derivatives (*R*)-**14** and (*S*)-**15**, respectively) resulted in low or no yield, respectively (entries 8 and 9). The phenyl and hydroxyl groups in mandelamide (*S*)-**12** proved crucial for selectivity ((*S*)-lactic acid amide ((*S*)-**16**) and (*S*)-*O*-acetylmandelamide ((*S*)-**17**) both giving racemic **9** in 70% yield, entries 10 and 11), however, the amide group was not: the parent mandelic acid ((*S*)-**11**) gave **9** in 67% yield with some, albeit lower, selectivity, entry 12. Somewhat surprisingly, the methyl ester ((*S*)-methyl mandelate, (*S*)-**18**), a relatively inexpensive item of commerce,[42] proved far superior, giving (*S*)-**9** in good yield and high selectivity, entry 13. Moreover, doubling the stoichiometry of (*S*)-**18**, led to an improved selectivity without a dramatic reduction in yield as was observed with the mandelamide ((*S*)-**12**, entry 14, compared to entry 5). The hydrogen at the stereogenic centre in (*S*)-**18** appears to be important: methyl atrolactate ((*S*)-**19**) gave reduced selectivity (entry 15) whilst the homologated ester (β-hydroxy carbonyl, (*S*)-**20**) was completely ineffective, entry 16. Ester variants of mandelate (*S*)-**18** were also screened, without improvement, for example, the benzyl ester (*S*)-**21** gave slightly lower selectivity, entry 17. Interestingly, the homologue of this ester, maintaining the α-hydroxy carbonyl relationship, but placing a methylene spacer between the aromatic ring and the stereogenic centre ((*S*)-**22**) was of similar efficacy (entry 18, compare entry 17). As with mandelamide, the hydroxy group in the mandelate is crucial: the *O*-methylated methyl mandelate ((*S*)-**23**) gave essentially racemic product, entry 19.

Choosing then to explore a range of methyl mandelate analogues in which the aryl ring is varied, we sought a high yielding synthesis for such modifiers in high enantiomeric purity. The vanadium-catalysed asymmetric addition of trimethylsilylcyanide (TMSCN) to aldehydes (**28**→**29**) developed by Belokon' and North et al., Scheme 6,[43] proved efficient.



Scheme 6. The one-pot procedure employed to make methyl mandelate derivatives (89/11→99/1 er) for use as modifiers, *L** in asymmetric homoallyl-cyclopropanation, Scheme 4. Conditions: (i) TMSCN, vanadyl (1*R*,2*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidenato)-1,2-cyclohexane diamine (0.6 mol %), CH_2Cl_2; (ii) Et_2O, MeOH, HCl; (iii) H_2O, $NaHCO_3$.

Testing the methodology with benzaldehyde (**28a**), we found that we could smoothly convert the resulting silylated mandelonitrile ((*S*)-**29a**) in situ (MeOH/HCl; then H_2O) to (*S*)-methyl mandelate ((*S*)-**18**, 91/9 er) via the imidate ((*S*)-**30a**). To address the issue of screening nonenantiopure mandelate modifiers ((*S*)-**31**) arising from the imperfect enantioselectivity in the initial TMS-cyanohydrin generation (**28**→**29**), we tested the relationship between the enantiopurity of the simple mandelate modifier (50, 60, 75, 90 and 100% (*S*)-**18**) and that of the product (*S*)-**9** from the asymmetric homoallyl-cyclopropanation reaction, which was found to be linear, Figure 1.

We were also concerned about the effect of any vanadium or salen ligand contaminants in the potential modifiers, Scheme 6, but we found that the crude sample of (*S*)-**18** (91/9 er) as obtained after imidate hydrolysis gave (*S*)-**9** in 75/25 er, fully consistent with that predicted by the linear correlation, Figure 1. On this basis, we then screened a range of aryl-variants of **18** as modifiers, Table 2.

Despite some small improvements in selectivity, e.g., the 4-methoxy- and 1-naphthyl-derivatives (*S*)-**31d** and (*S*)-**31e**, Table 2, entries 4 and 5, the major effect of aryl substitution was a decrease in the yield of **9**, and in balance the simple methyl mandelate modifier ((*S*)-**18**) appeared best. Since both enantiomers of mandelic acid and methyl mandelate are commercially available,[42] we focussed on optimising the conditions to use this modifier. In our earlier work on the homoallyl-cyclopropanation process, we reported that yields were made more reproducible and substantially improved by addition of LiBr to the reaction mixture after the initial reaction of the ketone with the allylindium reagent and before the aqueous acidic work-up.[35] We proposed that the formation of an indate type intermediate could stabilise allylindium moieties towards acidic hydrolysis. Given the pronounced

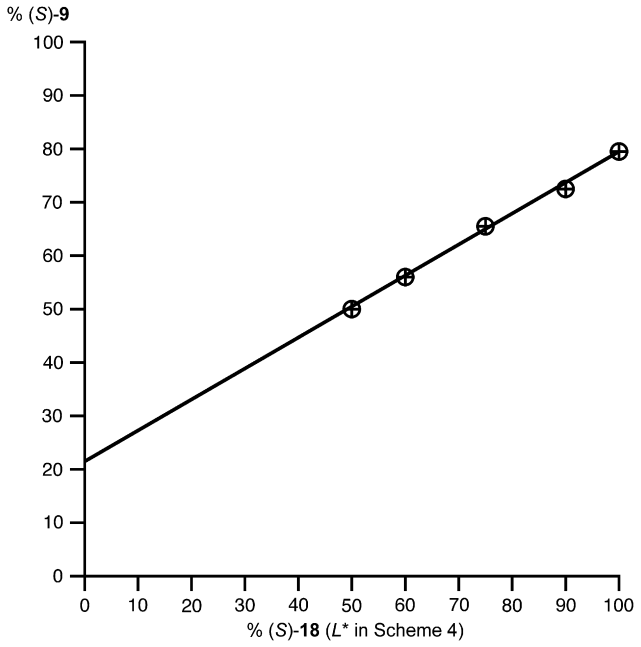


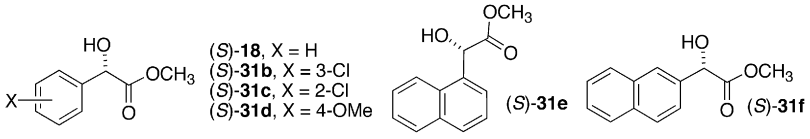
Figure 1. The linear relationship observed between the enantiopurity of (*S*)-methyl mandelate ((*S*)-**18**, *x*-axis) used as modifier (1.0 equiv) in the reaction of homoallyl-cyclopropanation reaction of dibenzylideneacetone (**8**) by an allylindium bromide reagent system generated in situ, and the enantiopurity of product ((*S*)-**9**, *y*-axis). Correlation by linear regression: ((*S*)-**9** (%)=0.58(±0.018), (*S*)-**18** (%)=+21.2(±1.3)).

effect that added halide has on the reaction it was interesting to determine the effect of switching from a bromide-based reagent system to the one based on iodide. However, reaction of ketone **8** with the analogous allylindium iodide reagent, in the presence or absence of modifier (*S*)-**18**, followed by addition of LiBr, or LiI, resulted in the isolation of a dark, intractable, tar-like product, Table 2, entry 7. The ^{1}H NMR spectra of these products suggested them to be polymeric, however, TLC analysis prior to the aqueous acidic work-up revealed the presence of some cyclopropane product **9**.[44] Given the ready reaction of cyclopropanes with electrophiles,[45] such as halonium ions or heavy metal halides, we suspected that polymerisation, perhaps initiated by I_2 or I_3^-, was causing destruction of **9**—certainly the reaction mixture became yellow in colour on addition of the aqueous acid. Consistent with this interpretation, termination of the work-up by washing with saturated aqueous Na_2SO_3, gave a colourless organic phase from which the cyclopropane **9** was isolated in good yield (81%) and also in higher selectivity (11/89 er, Table 2, entry 8) than when bromide-based reagent was employed. Moreover, when 2 equiv of modifier (*S*)-**18** is employed, the yield and selectivity increased, giving **9** in 86% yield and 6/94 er, Table 2, entry 9.[38c] The most selective modifier from the indium allyl bromide-based conditions (the 1-naphthyl derivative, (*S*)-**31e**, entry 5) gave lower selectivity using iodide (entry 10).

3. Conclusion

In summary, we have developed a simple asymmetric modification of the indium-mediated homoallyl-cyclopropanation of dibenzylideneacetone **8** by using enantiomerically pure, commercially available and relatively inexpensive, methyl mandelate ((*S*)-**18**). The asymmetric modifiers that have been successfully employed in the mechanistically distinct allylation of aldehydes, ketones and imines (cinchona alkaloids, aminoalcohols, binols)[27–29] are rather poor modifiers for the homoallyl-cyclopropanation process. The key to

Table 2. The effect of a range of enantiomerically enriched (*S*)-methyl mandelates (1.0 equiv) as modifiers for the asymmetric homoallyl-cyclopropanation of dibenzylideneacetone (**8**, 0.11 M in THF) by allylindium reagents derived from indium metal and allyl bromide or allyl iodide at rt

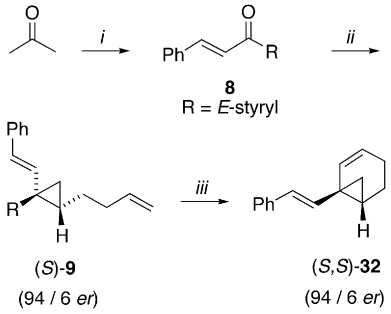


Entry	Modifier (Ar=)	Allyl reagent (halide=)	Yield **9**/%[a]	er **9** (*R*/*S*)[b]
1	(*S*)-**18**	Br	71	20/80[c]
2	(*R*)-**31b**[d]	Br	62	68/32
3	(*R*)-**31c**[e]	Br	68	70/30
4	(*S*)-**31d**[f]	Br	41	17/83
5	(*S*)-**31e**[g]	Br	50	14/86
6	(*S*)-**31f**[h]	Br	53	26/74
7	(*S*)-**18**	I	0[i]	—
8	(*S*)-**18**	I	81[j]	11/89
9	(*S*)-**18**[k]	**I**	**86**[j,k]	**6/94**
10	(*S*)-**31e**[l]	I	45[j,k]	11/89

[a] Isolated yield after purification by silica-gel chromatography.
[b] Determined by chiral HPLC (OD-H, see Section 4 for details), then extrapolated to er expected for 100% enantiopurity in the modifier.
[c] Data from Table 1, entry 13.
[d] >99/1 er.
[e] >99/1 er.
[f] 89/11 er.
[g] 92/8 er.
[h] 90/10 er.
[i] Product mixture consisted of an intractable dark brown tar. Analogous results obtained in absence of modifier or on replacement of LiI with LiBr.
[j] Ether phase washed with saturated aqueous Na_2SO_3 after 1 M HCl.
[k] Modifier (2.0 equiv).
[l] 98/2 er.

attaining good yield in combination with high selectivity is using the indium/allyl iodide reagent combination, with aqueous Na_2SO_3 included in the work-up procedure to avoid indium salt/iodine-mediated polymerisation of the cyclopropane product **9**.

We have previously reported that homoallyl-vinylcyclopropanes undergo Ru-catalysed ring closing metathesis (RCM) to generate norcarenes.[46] The potential utility of the enantioselective homoallyl-cyclopropanation reaction is outlined in Scheme 7: using standard conditions (*S*)-**9** (94/6 er) undergoes RCM to yield (1*S*,6*S*)-**32** in 52% isolated yield, chiral HPLC analysis confirmed that there was no racemisation.



Scheme 7. Synthesis of enantioenriched 1-styryl-norcarene (*S*,*S*)-**32** in three steps from acetone/benzaldehyde. Conditions: (i) PhCHO (2.0 equiv), NaOH, EtOH, H_2O; (ii) In, allyl iodide, THF, then (*S*)-**18** (2.0 equiv), then Et_2O, 1 M HCl, then Na_2SO_3; (iii) 5 mol % $RuCl_2(PCy_3)_2$=CHPh, CH_2Cl_2.

The route thus provides rapid access to an enantiomerically enriched norcarene (bicyclo[4.1.0]hept-2-ene) building block of potential synthetic utility and in only three steps from very simple reactants: acetone, benzaldehyde and allyl iodide.

We are currently investigating the mechanism of the asymmetric homoallyl-cyclopropanation process[36–38] as well as exploring the range of ketones, aldehydes and other modifiers that can be employed. These studies will be reported in full in due course.

4. Experimental

4.1. General

Reactions were conducted under an inert atmosphere of dry nitrogen using standard Schlenk/vacuum line techniques. *Solvents* were HPLC quality and dried by passage through an Anhydrous Technologies drying train (activated alumina) followed by freeze-thaw degas cycles under vacuum/nitrogen as appropriate. *Chiral HPLC Analysis* was performed on Agilent 1100 or 1050 series instruments under two sets of conditions. Conditions **A**: *Chiralcel* OD-H; 4.6×250 mm; 0.5 mL min^{-1} hexane; detecting at 254 nm; ambient temperature; analyte loaded as solution in eluent; Conditions **B**: *Chiralcel* OJ-H; 4.6×250 mm; 1.0 mL min^{-1} hexane/*iso*-propyl alcohol (9:1); detecting at 210 nm; ambient temperature; analyte loaded as solution in eluent. *Chiral GC Analysis* was performed on a Shimadzu GC17A instrument equipped with an FID detector and a *Supelco* γ-*TA* column 0.25 mm×30 m; carrier gas He; flow rate 1.0 mL min^{-1}; oven temperature 120 °C. *NMR spectra* were acquired on JEOL instruments (operating at 270, 300 and 400 MHz (^{1}H frequency)) and recorded in $CDCl_3$. ^{1}H and $^{13}C\{^1H\}$ NMR spectra were referenced internally to $CHCl_3$ (^{1}H, 7.27 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) or to TMS (0.00 ppm). Assignments are based on HH COSY, HMQC ($^1J_{C,H}$) and DEPT. Mass spectra were obtained using the EI source on a Fisons *Micromass Autospec* mass spectrometer. Flash column chromatography: *Merck* silica gel 60. TLC: 0.25 mm, *Merck* silica gel 60 F_{254} visualising at 254 nm or with acidic (H_2SO_4) aqueous $KMnO_4$ solution (ca. 2%).

4.1.1. (*S*)-2-(3″-Butenyl)-1,1-bis[(*E*)-2′-phenylethenyl]-cyclopropane[35] (*S*)-(9). Under a nitrogen atmosphere, indium metal power (100 mesh, Mg-free) (459 mg, 4.0 mmol) was added to 2.0 mL of dry THF with stirring, to give a grey suspension. Addition of allyl iodide (0.55 mL, 6.0 mmol) resulted in an immediate exothermic reaction affording a clear solution, which was stirred for a further 10 min before adding (*S*)-methyl mandelate ((*S*)-**18**, 332 mg, 2.0 mmol). After stirring for a further 10 min, dibenzylideneacetone (**8**) (235 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature (approximately 40–60 min). LiI (133 mg, 1.0 mmol) was then added and the reaction mixture was heated to 60 °C for 1 h before cooling to ambient temperature. After addition of 15 mL of Et_2O/15 mL of 1 M HCl (aqueous), the aqueous layer was separated and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with saturated Na_2SO_3 solution, saturated brine, dried ($MgSO_4$), filtered and then concentrated in vacuo. Purification by silica gel column chromatography (hexane/ethyl acetate 50/1, 20×5 cm) collecting fractions with R_f value 0.67, gave (*S*)-(**9**) as yellow oil, 256.5 mg (86%). Eluting with 9/1 hexane/EtOAc gave (*S*)-**18**, 131.4 mg (39%). Chiral HPLC method **A**: t_R (*R*)-(**9**) 91 min (6%), (*S*)-(**9**) 96 min (94%); $[\alpha]_D^{23}$ +68(±4) (*c* 2.48 in $CHCl_3$); The ^{1}H and ^{13}C NMR spectra were identical to those previously reported,[35b] however, it should be noted that the subsequent preparation of ^{13}C-labelled samples of **9** (unpublished) has revealed (HMQC/NOE data) a pair of cross-assignments in the ^{1}H NMR and ^{13}C NMR. The previously reported ^{1}H NMR data (400 MHz, $CDCl_3$) is 6.18 (1H, d, ^3J=15.62 Hz, 2′-H_{anti}), 6.35 (1H, d, ^3J=16.11 Hz, 1′-H_{anti}), 6.39 (1H, d, ^3J=16.11 Hz, 1′-H_{syn}), 6.47 (1H, d, ^3J=15.62 Hz, 2′-H_{syn}). New assignment: 6.18 (1H, d, ^3J=15.62 Hz, 1′-H_{anti}), 6.35 (1H, d, ^3J=16.11 Hz, 2′-H_{anti}), 6.39 (1H, d, ^3J=16.11 Hz, 1′-H_{syn}), 6.47 (1H, d, ^3J=15.62 Hz, 2′-H_{syn}). Previously reported ^{13}C NMR data (68 MHz, $CDCl_3$) is 127.4 (1′-C_{syn}), 130.0 (1′-C_{anti}), 131.7 (2′-C_{syn}), 136.2 (2′-C_{anti}). New assignment: 127.4 (2′-C_{anti}), 130.0 (1′-C_{syn}), 131.7 (2′-C_{syn}), 136.2 (1′-C_{anti}).

4.1.2. (1*S*,6*S*)-1-(*E*)-2′-(Phenylethenyl)-bicyclo[4.1.0]-hept-2-ene[46] (1*S*,6*S*)-(32). Following the published procedure for preparation of (±)-**32**[46] the homoallyl-cyclopropanation product (*S*)-(**9**) (6/94 er), (330 mg, 1.1 mmol) underwent RCM catalysed by a solution of $RuCl_2(PCy_3)_2$=CHPh (27 mg, 3 mol %) in 20 mL of CH_2Cl_2 to afford, after work-up and chromatography, a clear, colourless oil, 111.5 mg (52%). NMR data (^{1}H, ^{13}C) were identical to that reported.[46] Analysis by chiral HPLC method **B**: t_R

(1*R*,6*R*)-(**32**) 39 min (6%), (1*S*,6*S*)-(**32**) 47 min (94%); $[\alpha]_D^{23}$ −64(±5) (*c* 2.58 in $CHCl_3$).

4.1.3. (*S*)-2-Butyl-1,1-bis[(*E*)-2′-phenylethenyl]cyclopropane (*S*)-(24). Under nitrogen, at 0 °C, cyclopropane (*S*)-(**9**) (34/66 er, 862.9 mg, 2.87 mmol) was dissolved in 10 mL dry CH_2Cl_2 and added via cannula to $Cp_2Zr(H)Cl$[47] (1.04 g, 4.03 mmol) with stirring. After 16 h, 10 mL distilled water was added and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organics were dried ($MgSO_4$), filtered through a plug of silica gel and concentrated in vacuo. Purification by silica gel column chromatography (ethyl acetate/hexane 1/50) gave a colourless oil, 670.5 mg (77%). $[\alpha]_D^{26}$ +38 (*c* 1.07 in $CHCl_3$); Anal. Calcd for $C_{23}H_{26}$ (302.45): C 91.3, H 8.7; found: C 90.6, H 8.7; ν_{max} (film)/cm^{-1}: 3025, 2960, 2925, 1595, 1495, 1450, 1075, 1030, 960, 790, 745, 690; δ_H (400 MHz, $CDCl_3$): 1.06–1.14 (4H, m), 1.29–1.43 (2H, m), 1.44–1.66 (6H, m), 6.36 (1H, d, ^3J=15.9 Hz, 1′-H_{anti}), 6.54 (1H, d, ^3J=15.9 Hz, 2′-H_{anti}), 6.58 (1H, d, ^3J=15.9 Hz, 1′-H_{syn}), 6.65 (1H, d, ^3J=15.9 Hz, 2′-H_{syn}), 7.30–7.59 (10H, m, 10×CH_{arom}); δ_C (75 MHz, $CDCl_3$): 14.2 (4″-*C*), 20.0 (*C*H_2), 22.5 (*C*H_2), 29.0 (*C*H_2), 29.3 (2-*C*), 29.8 (1-*C*), 32.0 (*C*H_2), 125.8 (*o*-C_{arom}), 126.0 (*o*-C_{arom}), 126.7 (*p*-C_{arom}), 127.0 (*p*-C_{arom}), 127.2 (2′-C_{anti}), 128.5 and 128.6 (2×*m*-C_{arom}), 130.2 (1′-C_{syn}), 131.5 (2′-C_{syn}), 136.3 (1′-C_{anti}), 137.6 and 137.7 (2×*i*-C_{arom}); HRMS (EI) obsd: 302.2039 [M$^+$]; calcd: 302.2035; MS (EI, %): 302 (75), 259 (6), 245 (90), 231 (30), 215 (53), 202 (35), 191 (12), 178 (13), 167 (57), 153 (56), 141 (56), 141 (65), 128 (59), 115 (56), 103 (25), 91 (100), 86 (14), 77 (23), 65 (14), 55 (10).

4.1.4. (*S*)-1,1-Dicarboxymethyl-2-butylcyclopropane (*S*)-(25). Ruthenium trichloride trihydrate (5.06 mg, 19.4 μmol) was added to a stirred, biphasic mixture of (*S*)-(**24**) (317.4 mg, 1.05 mmol) and $NaIO_4$ (1.85 mg, 8.65 mmol) in 4 mL CCl_4, 4 mL MeCN and 6 mL distilled water.[48] The brown mixture was stirred for 24 h and then 20 mL CH_2Cl_2 and 20 mL distilled water were added. The aqueous phase was extracted with 3×20 mL CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo and redissolved in 20 mL Et_2O, filtered through Celite and concentrated in vacuo to yield off-white crystals (304.4 mg) comprising a 2/1 mixture of benzoic acid and (*S*)-2-butylcyclopropane-1,1-dicarboxylic acid, which was used without further purification; selected NMR data for (*S*)-2-butylcyclopropane-1,1-dicarboxylic acid as confirmed by hydrolysis (KOH/aqueous MeOH, reflux, 4 h) of a sample of pure (±)-**25**: δ_H (400 MHz, $CDCl_3$): 0.90 (3H, t, *J*=7.1 Hz, 4″-H_3), 1.25–1.49 (4H, m, 3″-H_2), 1.62–1.79 (2H, m, 2″-H_2), 1.89 (1H, dd, ^3J=8.8 Hz, ^2J=4.1 Hz, 3-*H*), 2.06 (1H, dd, ^3J=9.3 Hz, ^2J=4.1 Hz, 3-*H*), 2.23 (1H, dddd, ^3J=7.3, 7.3, 8.8, 9.3 Hz, 2-*H*), 9.4–10.6 (2H, br m, 2×1′-*H*); δ_C (75 MHz, $CDCl_3$): 13.9 (4″-*C*), 22.2 (*C*H_2), 26.0 (3-*C*), 26.9 (1″-*C*), 30.5 (1-*C*), 31.1 (*C*H_2), 39.5 (2-*C*), 173.9 (1′-*C*), 176.7 (1′-C). The crude product was dissolved in a mixture of 2.0 mL dry MeOH/7 mL toluene and then a hexane solution of $TMSCHN_2$[49] (2 M, 3.84 mmol) was added to the stirred solution. After 16 h, 0.5 mL AcOH (8 mmol) was added, and then the volatiles were removed in vacuo to yield 341.27 mg of a mixture comprising 2/1 methylbenzoate and (*S*)-(**25**). Chiral GC analysis: t_R (*R*)-(**25**) 10 min (34%), (*S*)-(**25**) 11 min (66%). In a separate procedure, (*S*)-(**25**) was prepared as follows: under nitrogen 0.21 mL dimethyl malonate (1.83 mmol) was added to a stirred suspension of 60% NaH in oil (183.5 mg, 4.59 mmol) and 5 mL DME. After 30 min, (*R*)-(+)-4-butyl-[1,3,2]-dioxathiolane-2,2-dioxide (*R*)-(**27**) (346.4 mg, 1.92 mmol) was dissolved in 4 mL DME and added via cannula. After 4 h, 2 mL aqueous NH_4Cl solution (2.8 M) was added and the aqueous phase was extracted with 3×10 mL ethyl acetate, dried ($MgSO_4$) and filtered. Purification by silica gel column chromatography (ethyl acetate/hexane 1/25) and Kugelrohr distillation (oven temperature 170 °C, 22 Torr) gave a colourless oil, 198.4 mg (51%). $[\alpha]_D^{26}$ +44.5 (*c* 2.49 in $CHCl_3$); Anal. Calcd for $C_{11}H_{18}O_4$ (214.26): C 61.7, H 8.5; found: C 61.8, H 8.5; ν_{max} (film)/cm^{-1}: 2955 m, 2930 m, 2960 m, 1725 s, 1440 s, 1330 s, 1280 s, 1250 m, 1210 s, 1130 s, 1080 m, 880 m, 705 m; δ_H (300 MHz, $CDCl_3$): 0.89 (3H, t, ^3J=7.1 Hz, 4″-H_3), 1.13–1.50 (8H, m, 3″-H_2, 2″-H_2, 1″-H_2, 3-H_2), 1.90 (1H, dddd, ^3J=8.3, 8.3, 8.3, 6.0 Hz, 2-*H*), 3.72 (3H, s, 2′-H_3), 3.76 (3H, s, 2′-H_3); δ_C (75 MHz, $CDCl_3$): 13.9 (4″-*C*), 21.3 (*C*H_2), 22.2 (*C*H_2), 28.3 (*C*H_2), 28.7 (3-*C*), 30.9 (*C*H_2), 33.8 (1-*C*), 52.4, 52.5; Chiral GC analysis: t_R (*R*)-(**25**) 10 min (7%), (*S*)-(**25**) 11 min (93%).

4.1.5. (*R*)-1,2-Hexandiol (*R*)-(26).[50] Hydroquinidine 2,5-diphenylpyrimidine-4,6-diyldiether [$(DHQD)_2PYR$] (250.0 mg, 0.280 mmol), potassium carbonate (12.8 g, 92.7 mmol), potassium ferricyanide (29.5 g, 92.9 mmol) and potassium osmate dihydrate (89.5 mg, 0.244 mmol) were stirred in 310 mL of 1/1 *tert*-BuOH/distilled water, at room temperature. The mixture was cooled to 0 °C and then 3.9 mL 1-hexene (31.3 mmol) was immediately added. The resulting slurry was stirred for 2 days and then stored in a freezer for 2 weeks. Sodium sulfite (45.0 g, 479 mmol) was added and the slurry was warmed to room temperature with stirring. After 3 h, the slurry was extracted with 3×150 mL ethyl acetate. The combined organic extracts were washed with 300 mL distilled water, 200 mL saturated aqueous brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography by eluting with Et_2O and then distilled (160 °C, 22 Torr) to yield a colourless liquid, 2.23 g (60%). $[\alpha]_D^{23}$ +3.54 (neat), (lit.[51] for (*S*)-(**26**) $[\alpha]_D^{28}$ −4.0 (neat)); ν_{max} (film)/cm^{-1}: 3340 br, 2960 s, 2930 s, 2860 s, 1470 m, 1340 w, 1030 s, 1060 s; δ_H (400 MHz, $CDCl_3$): 0.92 (3H, t, ^3J=6.4 Hz, 6-H_3), 1.29–1.49 (6H, m, 5-H_2, 4-H_2, 3-H_2), 2.10 (2H, br s, 2×O*H*), 3.44 (1H, dd, ^3J=7.8 Hz, ^2J=10.7 Hz, 1-*H*), 3.66 (1H, dd, ^3J=2.9 Hz, ^2J=10.7 Hz, 1-*H*), 3.71 (1H, m, 2-*H*); δ_C (75 MHz, $CDCl_3$): 14.0 (6-*C*), 22.7 (*C*H_2), 27.7 (*C*H_2), 32.9 (*C*H_2), 66.8 (1-*C*), 72.3 (2-*C*).

4.1.6. (*R*)-4-Butyl-[1,3,2]-dioxathiolane-2,2-dioxide (*R*)-(27).[52] Thionyl chloride (0.18 mL, 2.47 mmol) was added to a stirred solution of (*R*)-(**26**) (448 mg, 4.08 mmol) in 4 mL CCl_4. The mixture was heated to reflux for 2 h, cooled to 0 °C and 4 mL MeCN, $RuCl_3 \cdot 3H_2O$ (4.30 mg, 0.0164 mmol), $NaIO_4$ (1.78 g, 8.32 mmol) and 6 mL distilled water were added.[53] After 2 h, the reaction mixture was diluted with 30 mL Et_2O and the organic phase was washed with 1 mL distilled water, 3×2 mL saturated aqueous $NaHCO_3$, 1 mL saturated aqueous brine, dried ($MgSO_4$) and filtered through silica. After concentration in vacuo, the residue was distilled (Kugelrohr, oven temp 200 °C, 22 Torr) to yield a colourless liquid, 692.0 mg

(94%). $[\alpha]_D^{26}$ +9.4 (*c* 2.59 in $CHCl_3$), (lit.[52] $[\alpha]_D^{22}$ +6.0 (*c* 5.11 in $CHCl_3$)); ν_{max} (film)/cm^{-1}: 2960 m, 2875 m, 2930 m, 1470 m, 1380 s, 1025 s, 970 s, 825 s; δ_H (300 MHz, $CDCl_3$): 0.94 (3H, t, ^3J=7.1 Hz, 6-*H*$_3$), 1.35–1.49 (4H, m, 5-*H*$_2$, 4-*H*$_2$), 1.77–1.82 (1H, m, 1-*H*), 4.74 (1H, dd, ^3J=5.9 Hz, ^2J=8.8 Hz, 1-*H*), 5.00 (1H, dddd, ^3J=8.1, 8.1, 5.9, 4.9 Hz, 2-*H*); δ_C (75 MHz, $CDCl_3$, ppm): 13.7 (6-*C*), 22.2 (*C*H$_2$), 26.6 (*C*H$_2$), 31.9 (3-*C*), 73.2 (1-*C*), 83.5 (2-*C*).

4.1.7. Vanadyl (1*R*,2*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidenato)-1,2-cyclohexane diamine.[43] A solution of (1*R*,2*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diamine (1.0 g, 18 mmol) in 20 mL THF and vanadyl sulfate hydrate (0.6 g, 2.2 mmol) in 32 mL hot ethanol, were mixed and the resulting solution was refluxed for 3 h. The solvent was then removed in vacuo and the residue was extracted with CH_2Cl_2, filtered, concentrated in vacuo and then absorbed onto silica. Elution with CH_2Cl_2 followed by ethyl acetate/methanol (2/1) gave, after concentration, a green crystalline solid, 0.48 g (44%); mp>320 °C; $[\alpha]_D^{23}$ −1200 (*c* 0.01 in $CHCl_3$), (lit.[43] $[\alpha]_D^{23}$ −950 (*c* 0.01 in $CHCl_3$)); ν_{max} (film)/cm^{-1}: 2955 m, 1615 m, 1560 m, 1435 m, 1395 m, 1365 m, 1270 s, 1250 s, 1180 s, 1065 m, 1020 s, 955 s, 925 s, 870 s, 845 s, 815 m, 760 s, 660 m; δ_H (400 MHz, $CDCl_3$): 1.36 (9H, s, C(C*H*$_3$)$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$), 1.53 (9H, s, C(C*H*$_3$)$_3$), 1.54 (9H, s, C(C*H*$_3$)$_3$), 1.98 (4H, m, 2×CH$_2$), 1.92 (2H, m, C*H*$_2$), 2.50–2.79 (2H, m, C*H*$_2$), 3.80 (1H, m, *H*CN), 4.25 (1H, br m, *H*CN), 7.51 (1H, d, ^4J=2.5 Hz, ArC*H*), 7.56 (1H, d, ^4J=2.5 Hz, ArC*H*), 7.71 (1H, d, ^4J=2.5 Hz, ArC*H*), 7.76 (1H, d, ^4J=2.5 Hz, ArC*H*), 8.52 (1H, br s, *H*C═N), 8.76 (1H, br s, *H*C═N); δ_C (75 MHz, $CDCl_3$): 24.12 (*C*H$_2$), 24.52 (*C*H$_2$), 29.18 (C(*C*H$_3$)$_3$), 29.95 (C(*C*H$_3$)$_3$), 30.79 (*C*H$_2$), 31.40 (C(*C*H$_3$)$_3$), 31.42 (C(*C*H$_3$)$_3$), 34.48 (*C*(CH$_3$)$_3$), 34.52 (*C*(CH$_3$)$_3$), 35.57 (*C*(CH$_3$)$_3$), 35.74 (*C*(CH$_3$)$_3$), 69.88 (*C*(H)N), 70.69 (*C*(H)N), 120.92 (Ar*C*), 121.88 (Ar*C*), 128.38 (Ar*C*H), 129.15 (Ar*C*H), 131.64 (Ar*C*H), 131.91 (Ar*C*H), 135.00 (Ar*C*), 135.95 (Ar*C*), 143.94 (Ar*C*), 160.97 (Ar*C*O), 161.14 (Ar*C*O), 161.15 (H*C*═N), 164.91 (H*C*═N).

4.1.8. (*S*)-Methyl 1-naphthylglycolate (*S*)-(31e).[54] The following procedure[43] is typical for the range of methyl arylglycolates prepared by V-catalysed asymmetric addition of TMSCN. To a solution of vanadyl (1*R*,2*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidenato)-1,2-cyclohexane diamine[43] (36.2 mg, 0.06 mmol, 0.6 mol %) in CH_2Cl_2 (12 mL) was added 1-naphthaldehyde (1.56 g, 10.0 mmol) followed by trimethylsilylcyanide (1.7 g, 17.25 mmol) and the solution was stirred for 24 h at room temperature to afford 1-napthyltrimethylsilyloxyacetonitrile. After filtration through silica gel (ethyl acetate/hexane 1/5) and concentration in vacuo, the crude silyloxyacetonitrile was dissolved in Et_2O (120 mL) and the solution was cooled to 0 °C. Then HCl-saturated MeOH (30 mL) was added dropwise and the solution was left to stand at <5 °C for 24 h. The precipitated solid was separated by decantation, washed with cold Et_2O (3×50 mL), dissolved in distilled water (100 mL) and extracted with Et_2O (3×50 mL). After washing with saturated aqueous $NaHCO_3$ (100 mL), distilled water (2×50 mL) and saturated brine (100 mL), the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a viscous, colourless oil, 824 mg (38%). $[\alpha]_D^{23}$ +130 (*c* 1.2 acetone), (lit.[54] $[\alpha]_D^{23}$ +106.2 (*c* 1.0 in acetone)); chiral HPLC conditions **B**: t_R (*R*)-(**31e**) 72 min (4%), (*S*)-(**31e**) 75 min (96%); ν_{max} (film)/cm^{-1}: 3446 br, 3050 w, 2955 w, 1950 w, 1730 s, 1600 w, 1510 m, 1435 m, 1395 s, 1355 w, 1215 s, 1165 s, 1095 s, 1065 s, 1010 m, 970 m, 920 w, 900 w, 885 w, 865 w, 800 s, 785 s, 775 s, 655 m, 730 m; δ_H (400 MHz, $CDCl_3$): 3.71 (3H, s, 3′-*H*$_3$), 5.81 (1H, s, 2′-*H*), 7.40–7.58 (4H, m, 6-*H*, 7-*H*, 8-*H*, 9-*H*), 7.84–7.91 (2H, m, 2-*H*, 3-*H*), 8.16 (1H, d, ^3J=8.6 Hz, 4-*H*); δ_C (100 MHz, $CDCl_3$): 53.0 (3′-*C*), 71.4 (1′-*C*), 123.6 (*C*H$_{arom}$), 125.2 (*C*H$_{arom}$), 125.9 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 129.5 (*C*H$_{arom}$), 133.0 (*C*$_{arom}$), 134.0 (*C*$_{arom}$), 174.6 (2′-*C*); MS (EI, %) *m*/*z* 216 [M$^+$] (45), 157 (100), 139 (7), 129 (90), 102 (8), 84 (12), 75 (8), 69 (14), 63 (10).

4.1.9. (*S*)-Methyl 2-naphthylglycolate (*S*)-(31f).[55] Compound (*S*)-(**31f**) was prepared by an identical procedure to (*S*)-(**31e**), but starting from 2-napthylaldehyde (408.5 mg, 2.6 mmol) to yield a colourless, viscous liquid, 172.1 mg (31%). $[\alpha]_D^{24}$ +149 (*c* 1.14 $CHCl_3$), (lit.[55] for (*R*)-(**31f**) $[\alpha]_D^{23}$ −164.0 (*c* 1.00 in $CHCl_3$)); chiral HPLC conditions **B**: t_R (*R*)-(**31f**) 40 min (10%), (*S*)-(**31f**) 41 min (90%); ν_{max} (film)/cm^{-1}: 3470 m, 3055 w, 2965 w, 1725 s, 1510 w, 1440 w, 1390 w, 1365 w, 1305 m, 1270 w, 1255 w, 1220 s, 1170 w, 1145 w, 1085 s, 985 m, 945 w, 925 w, 905 w, 870 wm, 860 w, 830 m, 775 w, 750 s, 735 m, 665 w; δ_H (400 MHz, $CDCl_3$) 3.67 (1H, br, O*H*), 3.76 (3H, s, 3′-*H*$_3$), 5.36 (1H, d, ^3J=5.4 Hz, 2′-*H*), 7.46–7.55 (3H, m, C*H*$_{arom}$), 7.81–7.88 (3H, m, C*H*$_{arom}$), 7.91 (1H, br, C*H*$_{arom}$); δ_C (100 MHz, $CDCl_3$) 53.0 (3′-*C*), 73.0 (1′-*C*), 124.1 (*C*H$_{arom}$), 125.9 (*C*H$_{arom}$), 126.3 (2×*C*H$_{arom}$), 127.7 (*C*H$_{arom}$), 128.5 (*C*H$_{arom}$), 133.1 (*C*$_{arom}$), 133.3 (*C*$_{arom}$), 135.5 (*C*$_{arom}$), 174.1 (2′-*C*); MS (EI, %) *m*/*z* 216 [M$^+$] (46), 157 (100), 139 (7), 29 (90), 102 (8), 83 (11), 75 (8), 69 (13), 63 (10).

4.1.10. (*S*)-Methyl ρ-methoxymandelate (*S*)-(31d).[56] Compound (*S*)-(**31d**) was prepared by an identical procedure to (*S*)-(**31f**), but starting from *p*-anisaldehyde (446.5 mg, 3.28 mmol) to yield a crystalline solid, 221.1 mg (34%); mp 51–52 °C (lit.[56] 63–64 °C); $[\alpha]_D^{23}$ +93 (*c* 1.08 in acetone), (lit.[56] $[\alpha]_D^{20}$ +119.7 (*c* 3.3 in acetone)); chiral HPLC conditions **B**: t_R (*R*)-(**31d**) 73 min (11%), (*S*)-(**31d**) 76 min (89%); ν_{max} (film)/cm^{-1}: 3435 br, 3010 w, 2970 w, 2940 w, 2840 w, 2050 w, 1900 w, 1725 s, 1610 m, 1585 w, 1510 m, 1440 m, 1450 m, 1385 m, 1330 m, 1300 m, 1250 s, 1215 s, 1185 s, 1170 s, 1115 m, 1075 s, 1025 s, 975 m, 940 w, 910 m, 865 w, 835 s, 820 m, 795 s, 750 s, 710 m; δ_H (400 MHz, $CDCl_3$): 3.44 (1H, d, ^3J=5.6 Hz, OH), 3.74 (3H, s, 3′-*H*$_3$), 3.80 (3H, s, 1″-*H*$_3$), 5.12 (1H, d, ^3J=5.6 Hz, 1′-*H*), 6.89 (2H, d, ^3J=9.0 Hz, *o*-C*H*$_{arom}$), 7.32 (2H, d, ^3J=9.0 Hz, *m*-C*H*$_{arom}$); δ_C (100 MHz, $CDCl_3$): 52.9 (3′-*C*), 55.2 (1″-*C*), 72.4 (1′-*C*), 114.0 (*m*-*C*H$_{arom}$), 127.9 (*o*-*C*H$_{arom}$), 130.4 (1-*C*H$_{arom}$), 174.3 (2′-*C*); MS (EI, %) *m*/*z* 196 [M$^+$] (16), 137 (100), 131 (8), 119 (7), 109 (35), 94 (28), 83 (21), 77 (31), 69 (28).

4.1.11. (*R*)-Methyl-2-chloromandelate[57] (*R*)-(31c). The following procedure is typical for the range of methyl mandelates prepared by esterification of the parent acid. (*R*)-2-Chloromandelic acid (1.07 g, 5.72 mmol) was dissolved in methanol (35 mL). After addition of concentrated sulfuric acid (0.05 mL) the solution was refluxed until all the (*R*)-2-chloromandelic acid had been consumed (monitored by

TLC). After concentrating in vacuo, the residue was dissolved in *tert*-BuOMe (75 mL) and washed with saturated aqueous Na_2CO_3 (2×35 mL) and saturated brine (2× 35 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield a colourless liquid, 859.9 mg (75%; ca. 96% pure according to ^{1}H NMR analysis with benzylbenzoate internal standard) (*R*)-(**31c**); $[\alpha]_D^{24}$ −179 (*c* 2.17 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3500 br, 2990 w, 2955 w, 1725 s, 1600 w, 1495 m, 1445 m, 1375 m, 1250 s, 1210 m, 1140 s, 1095 s, 1070 s, 1030 m, 975 m, 940 w, 915 w, 870 w, 785 m, 730 m, 695 s, 655 s; δ_H (270 MHz, $CDCl_3$, ppm): 3.77 (3H, s, 3′-*H*$_3$), 5.58 (1H, s, 1′-*H*), 7.24–7.32 (2H, m, C*H*$_{arom}$), 7.35–7.44 (2H, m, C*H*$_{arom}$); δ_C (68 MHz, $CDCl_3$, ppm): 53.2 (3′-*C*), 70.5 (1′-*C*), 127.2 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 129.8 (*C*H$_{arom}$), 130.0 (*C*H$_{arom}$), 133.6 (*C*$_{arom}$), 136.1 (*C*$_{arom}$), 173.7 (2′-*C*).

4.1.12. (*R*)-Methyl-3-chloromandelate[58] (*R*)-(31b). Compound (*R*)-(**31b**) was prepared by an identical procedure to (*R*)-(**31c**), but starting from (*R*)-(−)-3-chloromandelic acid (502 mg, 2.69 mmol) to yield a colourless liquid, 242.5 mg (45%; ca. 90% pure according to ^{1}H NMR analysis with benzylbenzoate internal standard); $[\alpha]_D^{24}$ −121 (*c* 4.19 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3500 br, 2955 w, 1740 s, 1600 m, 1580 m, 1475 m, 1435 s, 1360 m, 1215 s, 1190 s, 1105 s, 1075 s, 1000 m, 980 m, 885 m, 770 s, 705 s, 685 s; δ_H (270 MHz, $CDCl_3$): 3.77 (3H, s, 3′-*H*$_3$), 5.15 (1H, s, 1′-*H*), 7.25–7.56 (4H, m, C*H*$_{arom}$); δ_C (68 MHz, $CDCl_3$): 54.4 (3′-*C*), 73.4 (1′-*C*), 125.9 (*C*H$_{arom}$), 126.1 (*C*H$_{arom}$), 127.9 (*C*H$_{arom}$), 129.8 (*C*H$_{arom}$), 131.0 (*C*$_{arom}$), 141.3 (*C*$_{arom}$), 174.7 (2′-*C*).

4.1.13. (*S*)-Methyl atrolactate (*S*)-(19).[59] Compound (*S*)-(**19**) was prepared by an identical procedure to (*R*)-(**31c**), but starting from (*S*)-atrolactic acid (268 mg, 1.61 mmol) to yield a colourless oil, 156.7 mg (54%; ca. 88% pure according to ^{1}H NMR analysis with benzylbenzoate internal standard); $[\alpha]_D^{24}$ +55 (*c* 0.51 in $CHCl_3$), (lit.[59] $[\alpha]_D^{26}$ +54.50 (*c* 2.84 in $CHCl_3$)); ν_{max} (film)/cm^{-1}: 3450 br, 2955 w, 1730 s, 1595 w, 1575 w, 1475 m, 1440 s, 1220 s, 1190 s, 1130 m, 1085 s, 1050 s, 1035 s, 980 m, 950 m, 910 w, 865 w, 785 m, 755 s, 705 s; δ_H (270 MHz, $CDCl_3$): 1.79 (3H, s, 1′-C*H*$_3$), 3.75 (3H, s, 3′-*H*$_3$), 7.23–7.40 (3H, m, C*H*$_{arom}$), 7.50–7.58 (2H, m, C*H*$_{arom}$); δ_C (68 MHz, $CDCl_3$): 26.8 (1′-*C*H$_3$), 53.2 (3′-*C*), 76.0 (1′-*C*), 125.2 (*C*H$_{arom}$), 127.8 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 142.8 (*C*$_{arom}$), 176.1 (2′-*C*).

4.1.14. (*S*)-Methyl-α,α-methoxyphenylacetate (*S*)-(18).[60] Compound (*S*)-(**18**) was prepared by an identical procedure to (*R*)-(**31c**), but starting from *O*-methyl (*S*)-mandelic acid (516 mg, 3.11 mmol) to yield a colourless liquid, 345.3 mg (62%; ca. 84% pure according to ^{1}H NMR analysis with benzylbenzoate internal standard); $[\alpha]_D^{24}$ +107 (*c* 1.01 in $CHCl_3$) (lit.[60] $[\alpha]_D^{23}$ +125 (*c* 0.97 in $CHCl_3$)); ν_{max} (film)/cm^{-1}: 2955 w, 2830 w, 2960 m, 1750 s, 1495 w, 1455 m, 1435 m, 1350 w, 1260 m, 1195 s, 1175 s, 1105 s, 1075 m, 1010 s, 930 w, 905 w, 850 w, 785 w, 730 s, 695 s; δ_H (270 MHz, $CDCl_3$): 3.39 (3H, s, 1″-*H*$_3$), 3.70 (3H, s, 3′-*H*$_3$), 4.78 (1H, s, 1′-*H*), 7.25–7.49 (5H, m, C*H*$_{arom}$); δ_C (68 MHz, $CDCl_3$): 53.4 (1″-*C*), 58.4 (3′-*C*), 83.7 (1′-*C*), 128.4 (*C*H$_{arom}$), 129.8 (*C*H$_{arom}$), 129.9 (*C*H$_{arom}$), 137.6 (*C*H$_{arom}$), 172.3 (2′-*C*).

4.1.15. (*S*)-Mandelamide (*S*)-(12).[61] (*S*)-Mandelic acid (8.8 g, 57.8 mmol) was dissolved in 230 mL MeOH and cooled to 0 °C. Acetyl chloride (4.2 mL, 59.1 mmol) was added and the solution was allowed to warm to room temperature and stirred for 24 h. Concentration in vacuo gave a colourless liquid, which was dissolved in 35 mL MeOH. Aqueous 105 mL NH_3 (35% w/v) was added and the solution was stored at <5 °C for a further 24 h. Concentration in vacuo gave a white solid, which was recrystallised from hot EtOH to yield white plates, 3.88 g (45%); mp 112–114 °C, (lit.[62] 118–120 °C); $[\alpha]_D^{25}$ +57 (*c* 1.05 in EtOH); ν_{max} (film)/cm^{-1}: 3345 br, 3180 br, 2930 w, 1955 w, 1680 m, 1655 m, 1610 m, 1495 m, 1450 m, 1420 m, 1340 m, 1290 m, 1250 m, 1190 m, 1100 m, 1080 m, 1055 s, 1025 m, 1000 m, 930 m, 895 m, 860 m, 760 m, 705 s, 690 s; δ_H (300 MHz, CD_3OD): 4.98 (1H, s, 1′-*H*), 7.24–7.37 (3H, m, C*H*$_{arom}$), 7.46 (2H, ddd, ^3J=8.1 Hz, ^4J=1.7 Hz, ^5J= 0.5 Hz, *o*-C*H*$_{arom}$); δ_C (75 MHz, CD_3OD): 75.4 (1′-*C*), 127.9 (*o*-*C*H$_{arom}$), 129.1 (*p*-*C*H$_{arom}$), 129.3 (*m*-*C*H$_{arom}$), 141.7 (*i*-*C*$_{arom}$), 178.6 (2′-*C*).

4.1.16. (*S*)-Acetoxy mandelamide (*S*)-(17).[63] Under a nitrogen atmosphere, (*S*)-(**12**) (606.4 mg, 4.01 mmol) was dissolved in 24 mL pyridine. Acetic anhydride (1.2 mL, 12.7 mmol) was added and the solution was stirred for 18 h. Concentration in vacuo gave an off-white solid, which was recrystallised from hot EtOH to yield white crystals, 397.5 mg (51%); mp 133–134 °C, (lit. 112–113 °C, for non-enantiomerically pure (*R*)-(**17**); $[\alpha]_D^{25}$ +139 (*c* 1.01 in EtOH), (lit.[63] for nonenantiomerically pure (*R*)-(**17**) $[\alpha]_D^{25}$ −145 (*c* 1.0 in $CHCl_3$)); ν_{max} (film)/cm^{-1}: 3380 m, 3160 m, 2160 w, 1980 w, 1740 s, 1665 s, 1630 m, 1590 w, 1495 w, 1455 w, 1420 m, 1380 m, 1320 w, 1295 w, 1265 m, 1220 s, 1190 s, 1105 m, 1080 m, 1030 s, 1005 m, 990 m, 950 s, 910 m, 855 w, 800 m, 755 s, 715 s, 695 s; δ_H (270 MHz, CD_3OD): 2.20 (3H, s, Ac-*H*$_3$), 5.95 (1H, s, 1′-*H*), 7.30–7.41 (3H, m, C*H*$_{arom}$), 7.42–7.55 (2H, m, *o*-C*H*$_{arom}$); δ_C (100 MHz, CD_3OD): 20.7 (Ac-*C*H$_3$), 76.8 (1′-*C*), 128.6 (*C*H$_{arom}$), 129.6 (*C*H$_{arom}$), 130.0 (*C*H$_{arom}$), 137.0 (*i*-*C*$_{arom}$), 171.6 (Ac-*C*═O), 174.1 (2′-*C*).

4.1.17. (*R*)-*N*-Butyl mandelamide (*R*)-(14).[64] Following a similar procedure to (*S*)-(**12**), but using butylamine, (*R*)-mandelic acid (1.042 g, 6.86 mmol) gave, after column chromatography, (MeCN), a clear colourless oil, 925 mg (65%); $[\alpha]_D^{25}$ +23 (*c* 1.2 in EtOH); δ_H (270 MHz, $CDCl_3$): 0.87 (1H, t, ^3J=7.15 Hz, 4′-*H*$_3$), 1.24–1.26 (2H, m, 3′-*H*$_2$), 1.40–1.43 (2H, m, 2′-*H*$_2$), 3.18–3.20 (1H, m, 1′-*H*$_2$), 4.13–4.16 (1H, m, 2-O*H*), 4.90–4.93 (0.5H, m, 2-*H rot. A*), 4.95–4.98 (0.5H, m, 2-*H rot. B*), 6.33–6.45 (1H, br s, N*H*), 7.26–7.40 (5H, m, C*H*$_{arom}$); δ_C (75 MHz, $CDCl_3$): 13.6 (4′-*C*), 19.7 (3′-*C*), 31.4 (2′-*C*), 39.1 (1′-*C*), 73.95 (2-*C rot. A*/*B*), 74.01 (2-*C rot. A*/*B*), 126.7, 128.4, 128.7 (*C*H$_{arom}$), 139.6 (C$_{arom}$), 172.2 (*C*═O); MS (EI, %) *m*/*z* 207 (M^+, 8) 191 (3), 179 (33), 136 (25), 107 (100), 84 (40), 79 (77), 73 (25), 57 (56).

4.1.18. (*S*)-*N*-Benzyl mandelamide (*S*)-(15).[65] Following a similar procedure to (*S*)-(**12**), but using benzylamine, (*S*)-mandelic acid (1.25 g, 7.89 mmol) gave a yellow oil, which was crystallised from boiling MeOH to yield white needles, 1.00 g (51%); mp 128–130 °C (from MeOH) (lit.[65] 136 °C); $[\alpha]_D^{24}$ +98 (*c* 1.06 in $CHCl_3$) (lit.[65] $[\alpha]_D^{24}$

+82.2 (*c* 1.09 in $CHCl_3$)); ν_{max}(film)/cm^{-1}: 3405 m, 3185 br, 2940 w, 2895 w, 1900 w, 1645 s, 1600 w, 1585 w, 1535 s, 1495 m, 1450 m, 1440 m, 1340 w, 1310 w, 1290 m, 1260 w, 1240 m, 1210 w, 1195 w, 1180 w, 1095 m, 1080 m, 1065 s, 1030 m, 925 m, 850 w, 815 w, 780 w, 755 s, 735 s, 705 s; δ_H (400 MHz, CD_3OD): 4.41 (2H, s, CH_2Ph), 5.06 (1H, s, C*H*OH), 7.19–7.36 (8H, m, CH_{arom}), 7.46 (2H, dd, J=8.1 Hz, $^4J_{HH}$=1.7 Hz, *o*-CH_{arom}CHOH); δ_C (100 MHz, CD_3OD): 43.6 (*C*H_2Ph), 75.4 (*C*HOH), 127.9, 128.2, 128.4, 129.1, 129.4, 129.5 (*C*H_{arom}), 139.9 (*i*-*C*$_{arom}$), 141.8 (*i*-*C*$_{arom}$), 175.5 (*C*ONHBn).

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42. Both enantiomers of methyl mandelate are available from Aldrich, UK price £48.70/5g. Mandelic acid is substantially cheaper ((R)- £30.40/25g; (S)- £124.40/100 g) and is conveniently converted to the methyl ester (MeOH, H_2SO_4) without racemisation, see Section 4 for details.
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Enantioselective organocatalytic epoxidation using hypervalent iodine reagents

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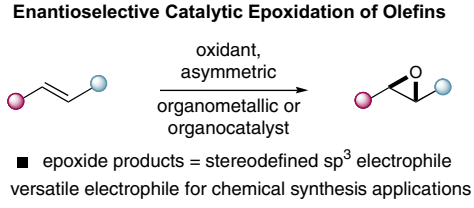
Abstract—A rare example of a hypervalent iodine reagent participating in a 1,4-heteroconjugate addition reaction is reported for the organocatalytic, asymmetric epoxidation of α,β-unsaturated aldehydes using imidazolidinone catalyst **1**. Development of an 'internal syringe pump' effect via the slow release of iodosobenzene from an iminoiodinane source provides high levels of reaction efficiency and enantiomeric control in the asymmetric epoxidation of electron-deficient olefins. ^{15}N NMR studies were conducted to elucidate the reaction pathways that lead to catalyst depletion in the presence of prototypical oxidants. These NMR studies also provided the mechanistic foundation for the application of iminoiodinanes as an internal slow release oxidant to circumvent these catalyst depletion pathways.

1. Introduction

The enantioselective catalytic oxidation of olefins is arguably one of the most powerful transformations known to practitioners of chemical synthesis.[1] Indeed, since the invention of the Sharpless asymmetric epoxidation,[2] there has been an ever-increasing demand for catalyst-controlled processes that allow efficient and predictable access to enantioenriched oxiranes. Significant efforts to expand the scope of such catalytic epoxidations have been made via the seminal contributions of Jacobsen[3] and Katsuki[4] using metal-ligated systems for the electrophilic delivery of oxygen. Complementary to these established organometallic strategies, Shi,[5] Denmark,[6] Yang,[7] and Armstrong[8] have developed an elegant organocatalytic approach that relies upon a ketone-derived dioxirane catalyst for the asymmetric epoxidation of trisubstituted and 1,2-*trans*-disubstituted alkenes. These epoxidation methods are applicable to several olefin classes; however, they do not encompass the enantioselective epoxidation of electron-deficient olefins.



Existing technologies for the enantioselective epoxidation of olefins[9] via LUMO-lowering activation have been founded upon the Weitz–Scheffer reaction,[10] wherein a nucleophilic chiral peroxide adds to an enone or enal (Fig. 1). This strategy of hydroperoxide delivery via a homogeneous chiral metal complex has been adopted and developed by Enders[11] in a stoichiometric manner and in a catalytic approach by Jackson[12] and Shibasaki.[13] Alternatively, asymmetric phase transfer agents have been utilized to transport a reactive oxo-species to olefin substrates as epitomized in the work of Roberts[14] using polyamino acids and in the cinchona alkaloid-derived salts of Lygo[15] and Corey.[16]

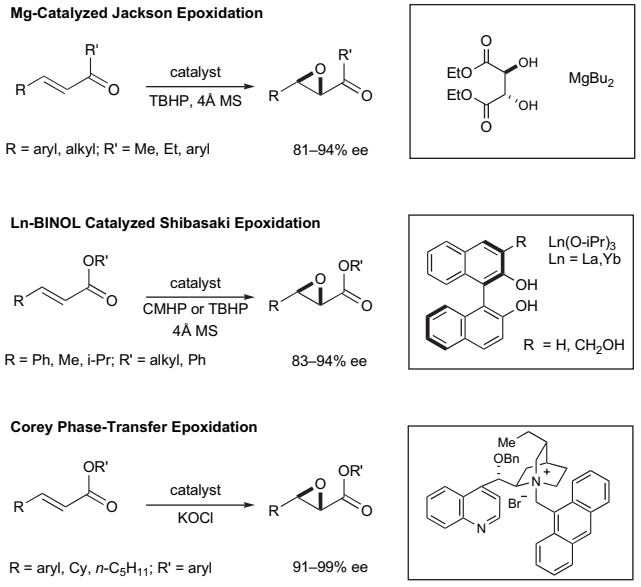


Figure 1. General methods for catalytic nucleophilic epoxidations.

Keywords: Epoxidation; Organocatalysis; Enantioselective; Iodosobenzene.
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Most recently, Jørgensen and co-workers[17] have demonstrated the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes using iminium catalysis. In these elegant studies, a variety of enals rapidly underwent asymmetric epoxidation using hydrogen peroxide as the stoichiometric oxidant in the presence of a proline-derived catalyst. In this publication, we further demonstrate the use of our chiral imidazolidinone salts as iminium activation catalysts for the asymmetric epoxidation of α,β-unsaturated aldehydes. This transformation provides rapid access to enantio-enriched 1,2-*trans*-formyl epoxides, an ambiphilic class of electrophile of known value in chemical synthesis.[18]

In 2002, we initiated studies to develop a novel organocatalytic strategy for the asymmetric epoxidation of electron-deficient olefins based upon the activation principle of iminium catalysis. Having demonstrated the capacity of chiral amines to function as asymmetric catalysts and building on previous successes in cycloadditions and 1,4-conjugate additions,[19] it was anticipated that a nucleophilic oxygen that incorporated a suitable leaving group could add with enantiofacial selectivity to an iminium-activated α,β-unsaturated aldehyde (Fig. 2). Subsequent enamine formation followed by intramolecular trapping of the pendent electrophilic oxygen with concomitant expulsion of the oxygen-tethered leaving group should then produce an oxirane (Fig. 3). At the outset of these studies, we felt that the proposed cyclization step had good precedent given related

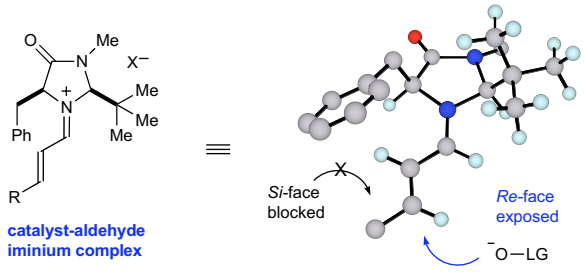


Figure 2. Rationale of catalyst-controlled enantioselectivity utilizing an MM3-2 model of the catalyst.

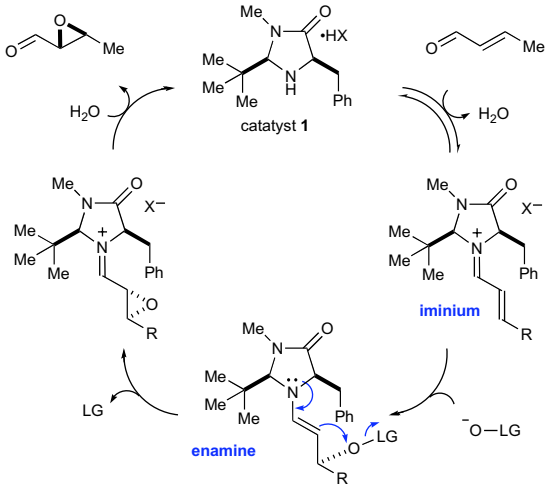


Figure 3. Proposed organocatalytic cycle for oxirane formation and the generation of an α,β-epoxy aldehyde.

cyclopropanation studies that were ongoing in our laboratory.[19a] In that methodology, a pendent thionium moiety functions as a suitable leaving group for intramolecular enamine cyclization to yield three-membered carbocycles. With this in mind, we recognized that an analogous epoxidation mechanism would rely on the judicious selection of an ambiphilic oxygen source that could function as a viable nucleophile for the conjugate addition step, yet would be suitably electrophilic (via incorporation of an electronegative leaving group (LG)) to enable intramolecular enamine oxidation and oxirane formation.

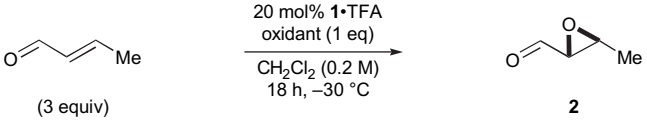
2. Results and discussion

2.1. Preliminary investigations

Our studies began with an investigation to define potential oxygen sources that would participate in the requisite 1,4-heteroconjugate addition/enamine cyclization. Initial experiments were performed with crotonaldehyde and a variety of commercially available oxidants in the presence of catalyst **1**·trifluoroacetic acid (TFA) salt. To our delight, the desired 2,3-epoxyaldehyde product (**2**) was readily accessed using a variety of oxygen sources (Table 1). Implementation of *m*-CPBA provided the epoxide product **2** with encouraging selectivity levels (Table 1, entry 3, 73% ee); however, studies to define the utility of this reagent (solvent, temperature) resulted in little improvement in overall enantiocontrol. The use of peroxides, such as *tert*-butyl hydrogen peroxide and hydrogen peroxide[20] also provided the desired oxirane with notable enantioselectivities (Table 1, entries 4 and 5). However, attempts to employ such oxidants with less reactive substrates (such as cinnamaldehyde) resulted mainly in the production of the catalyst *N*-oxide derivative, a catalyst depletion pathway that significantly reduces reaction efficiency. Unfortunately, bleach and pyridine *N*-oxide were not found to be viable reagents for this process (Table 1, entry 6).

We next examined the use of hypervalent λ^3-iodanes as potential oxidants for this organocatalytic Weitz–Scheffer reaction. While iodosobenzene is routinely employed as an oxygen transfer agent in metal-oxo mediated epoxidations,[21]

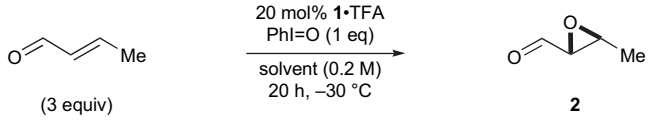
Table 1. Initial survey of oxygen sources for epoxidation



Entry	Oxidant	% Conversion[a]	% ee[b]
1	Pyridine *N*-oxide	NR	—
2	OXONE®	NR	—
3	*m*-CPBA	34	73
4	*t*-BuOOH[c]	35	69
5	H_2O_2[d]	9	59
6	NaOCl[e]	9	0
7	PhI=O	43	72

[a] Conversion determined by GC relative to methyl benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] Used as 5 M solution in decane.
[d] Used as a 50% solution in water.
[e] Used as a 5.25% solution in water.

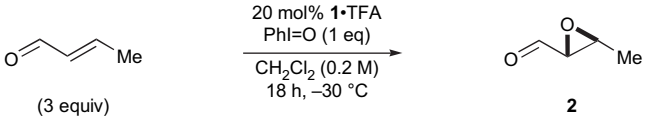
Table 2. Effect of solvent on the epoxidation reaction



Entry	Solvent	ε[a]	% Conversion[b]	% ee[c]
1	DMF (10% H_2O)	—	87	25
2	MeCN	36.6	55	33
3	Acetone	21.0	41	42
4	CH_2Cl_2	8.9	50	80
5	THF	7.5	14	76
6	THF (10% H_2O)	—	12	75
7	$CHCl_3$	4.8	45	82
8	Ether	4.3	29	63
9	Toluene	2.4	63	64

[a] See Ref. 38.
[b] Conversion determined by GC relative to tridecane.
[c] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

Table 3. Effect of acid co-catalyst on the epoxidation reaction



Entry	HX	pK_a	% Conversion[a]	% ee[b]
1	TfOH	−14	74	87
2	$HClO_4$	−10	68	88
3	*p*-TSA[c]	−2.6	50	76
4	TFA	−0.3	42	72
5	DCA[d]	1.3	27	72
6	CNA[e]	2.5	27	69

[a] Conversion determined by GC relative to benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] *p*-Toluenesulfonic acid.
[d] Dichloroacetic acid.
[e] Cyanoacetic acid.

its oxidative properties generally derive from the electrophilic character of the hypervalent iodine. However, there are a few reported cases in which iodosobenzene has been found to possess sufficient ylide character to participate in nucleophilic addition via the oxygen center.[22] Given the remarkable lability of the phenyliodonio moiety (~10^6 times better leaving group than triflate),[21] we postulated that the use of hypervalent λ^3-iodanes might enable a rapid ring closure from the electrophilic character of the hypervalent iodine and thereby minimize the intervention of a reversible oxo-conjugate addition (an equilibrium process that would diminish kinetic enantiocontrol). Moreover, we presumed that the oxidation byproduct, iodobenzene, would have no deleterious impact on the organocatalytic cycle (Fig. 3).

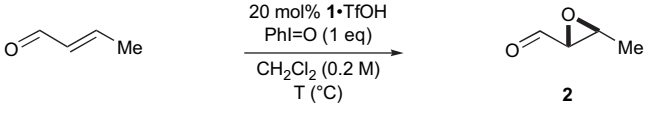
Indeed, exposure of crotonaldehyde to iodosobenzene in the presence of catalyst **1**·TFA provided epoxide **2** with encouraging levels of enantiocontrol (Table 1, entry 7, 72% ee). A survey of reaction media (Table 2) revealed that high dielectric solvents typically enabled superior efficiencies while lower dielectric systems provided higher asymmetric induction. Balancing this apparent dichotomy, CH_2Cl_2 and $CHCl_3$ demonstrated useful efficiencies while maintaining optimal enantioselectivity (Table 2, entries 4 and 7, 80–82% ee). On this basis, we selected halogenated media for further exploratory studies.

The impact of the Brønsted acid co-catalyst component on this organocatalytic epoxidation was next examined. As revealed in Table 3, an apparent correlation was observed between reaction conversion/enantiocontrol and the pK_a of the acid co-catalyst. More specifically, stronger acids, such as TfOH and $HClO_4$, provided the epoxide adduct with useful selectivities and yields (entries 1 and 2, pK_a −10 to −14, 87–88% ee), while acids with higher pK_a rendered poor conversions (entries 5 and 6, pK_a 1.3–2.5, 27% conversion). This trend can be rationalized on the basis that the stronger acid co-catalyst enables a higher equilibrium content of the catalyst–substrate iminium adduct thereby increasing the rate of addition–cyclization sequence.[23] Moreover, the observed enantioselectivity is likely to track reaction efficiency given the traditional requirements for the catalyst-controlled pathway to kinetically out-compete the non-catalyzed (racemic) process.

The influence of temperature on this epoxidation protocol was next investigated (Table 4). As expected on the basis of Boltzman distributions, a significant improvement in enantioselectivity was realized by lowering the reaction temperature. More surprising, however, was the accompanying increase in reaction efficiency with the same temperature trend. Subsequent studies (vide infra) have revealed that lower temperatures are essential to avoid detrimental reaction pathways such as catalyst oxidation and substrate decomposition.

Having established what we believed to be the optimal oxidation conditions, we next examined the scope of the olefin component in this organocatalytic oxirane formation. As revealed in Table 5, α,β-unsaturated aldehydes that incorporate alkyl group substituents are susceptible to iodosobenzene epoxidation with good efficiency and enantioselectivities (entries 1–3, 80–93% ee). To our disappointment, however, substrates that form more stabilized iminium species with catalyst **1** (such as cinnamaldehyde, entry 4) demonstrated diminished conversion and lower levels of asymmetric induction. At this juncture we hypothesized that a catalytic cycle wherein the 1,4-oxygen addition step is rate determining would be consistent with these findings. Moreover, we rationalized that implementation of a more nucleophilic iodosobenzene source should therefore provide an increase

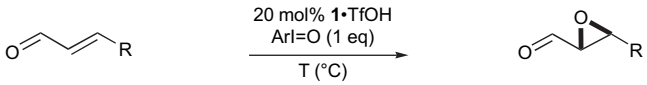
Table 4. Effect of temperature on reaction efficiency and selectivities



Entry	T (°C)	Time (h)	% Conversion[a]	% ee[b]
1	−20	18	49	83
2	−30	20	74	87
3	−40	15	98	89
4	−50	15	100	93

[a] Conversion determined by GC relative to benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

Table 5. Organocatalytic epoxidations with iodosobenzene: initial studies



Entry	R	ArI=O	T (°C)	Time (h)	% Yield	% ee[a]
1	Me[b]	PhI=O	−50	10	100[d]	93
2	*n*-Pr[b]	PhI=O	−50	15	93[e]	88
3	*i*-Pr[c]	PhI=O	−40	15	86[e]	80
4	Ph[c]	PhI=O	−40	15	78[f]	73
5	CO_2Me	PhI=O	−50	15	45	85
6	*n*-Pr[b]	*p*-MePhI=O	−40	15	21	85

[a] Enantiomeric excesses were determined by chiral GC analysis (Chiraldex Γ-TA).
[b] Three equivalents of starting aldehyde in CH_2Cl_2 (0.075 M).
[c] One equivalent of aldehyde in $CHCl_3$ (0.25 M).
[d] Yield based on NMR analysis using benzyl ether as a standard.
[e] Yield based on isolation of corresponding epoxy alcohol.
[f] Stereochemical determination via correlation to literature, see Section 3.

in both reaction rate and enantioselectivity. To this end, *p*-Me iodosobenzene[24] was prepared and employed in an analogous epoxidation protocol (Table 5). Surprisingly, this more nucleophilic oxidant provided lower levels of reaction efficiency (Table 5, entry 5, 21% yield) in comparison to the less nucleophilic iodosobenzene (Table 5, entry 2, 93% yield). A subsequent ^{1}H NMR investigation has revealed that *p*-Me iodosobenzene rapidly participates in imidazolidinone oxidation, a catalyst depletion pathway that has a dramatic impact on overall catalyst efficiency and conversion (Fig. 4, Ar=*p*-MePh).[25] Intriguingly, ^{1}H NMR studies have also revealed that a slower variant of the same catalyst decomposition pathway is observed using iodosobenzene as the reaction oxidant (Fig. 4, Ar=Ph). At this stage, we presumed that the diminished enantioselectivities observed in the cinnamaldehyde epoxidation case (Table 5, entry 4) could be attributed to the intervention of a catalyst oxidation pathway that is competitive with the iminium-catalyzed addition–cyclization step. With respect to the relative capacities of iodosobenzene and *p*-Me iodosobenzene to function as catalyst oxidants, we have determined that the tolyl-derived system is more soluble in halogenated solvents than its polymeric phenyl iodide counterpart. As a result, the relative concentration of *p*-Me iodosobenzene in solution was found to be much higher, a scenario that dramatically increases the rate of catalyst oxidation and leads to greatly diminished conversions with this iodane. On this basis, we began to focus upon identifying alternative sources of hypervalent iodane, which could be employed to slowly generate reactive iodosobenzene monomer in situ, and in doing so function as a type of 'internal syringe pump'. In this manner, we hoped the imidazolidinone would partition exclusively towards iminium formation with the aldehyde substrate, thereby avoiding catalyst oxidation and depletion.

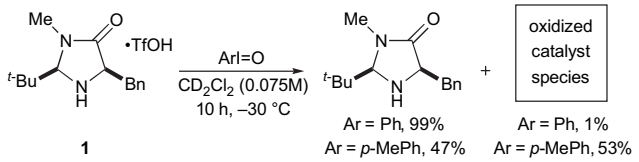


Figure 4. Mode of catalyst degradation when utilizing PhI=O and *p*-MePhI=O as the reagent in the epoxidation reaction.

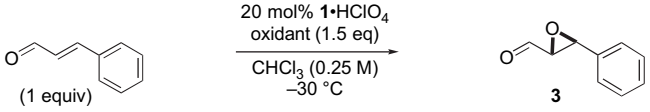
2.2. Secondary investigation: alternative iodosobenzene sources and the internal syringe pump effect

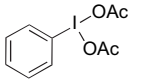
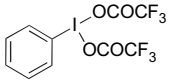
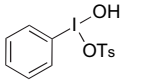
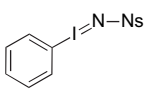
We next examined a range of hypervalent λ^3-iodane sources that we expected would slowly release iodosobenzene monomer when subjected to water or mild acid (Table 6). These studies were specifically performed with cinnamaldehyde with the anticipation that we might see an improvement in enantioselectivity with this substrate in comparison to analogous experiment with PhI=O (Table 5, entry 4, 73% ee). As revealed in Table 6, the use of commercially available diacetoxy iodosobenzene in the presence of water did indeed provide the desired epoxide with enhanced levels of enantiocontrol (entry 1, 84% ee); however, bis(trifluoroacetoxy) iodosobenzene and Koser's salt provided the oxirane **3** with poor efficiency (entries 2 and 3, 7–10% yield). Given that hypervalent I–N systems have been established to be less stable than the corresponding I–O class, we next examined the use of iminoiodanes as potential iodosobenzene surrogates in the presence of water or acid. To our great delight, exposure of cinnamaldehyde to [(nosylimino)iodo]benzene (NsNIPh) in the presence of catalyst **1** and 1 M acetic acid did indeed furnish epoxide **3** with excellent levels of conversion and enantiocontrol (entry 4, 100% conversion, 92% ee). It is noteworthy that arylsulfonylimino(aryl)iodanes are stable, easily storable compounds[21] that we have determined will function as controlled release iodosobenzene oxidants in the presence of acid or water (vide infra).

2.3. Epoxidation substrate scope

Having established the optimal oxidation conditions for epoxide formation, we next examined the scope of the α,β-unsaturated aldehyde component in this organocatalytic transformation. As revealed in Table 7, a variety of enal olefins can be successfully utilized with both high stereoselectivity and efficiency in the presence of NsNIPh. For example,

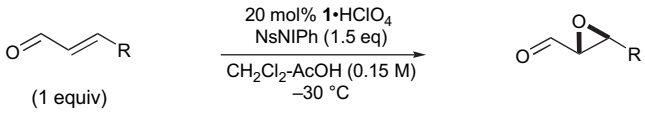
Table 6. Alternative iodosobenzene sources

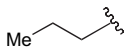
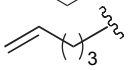
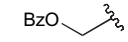
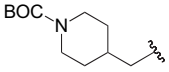
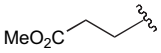
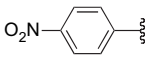
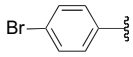


Entry	Oxidant	Additive	% Conversion[a]	% ee[b]
1		Water	68	84
2		Water	10	71
3[c]		Water	7	76
4		Water	71	80
		1 M AcOH	100	92

[a] Conversion determined by ^{1}H NMR analysis using MeOBn as a standard.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] Koser's salt = [(hydroxy)(tosyloxy)iodo]benzene.

Table 7. Enantioselective organocatalytic epoxidation: scope[a]



Entry	R	Time (h)	% Yield	% ee[b]
1	Me	10	88[c]	93
2		15	72	88
3		13	77	92
4		16	95[d]	92
5		15	89[e]	85
6		11	86	87
7		12	86	90
8		12	92[d]	92
9		6	89[d]	97
10		8	93[d]	93

[a] Products are single diastereomers, except in entry 1 (dr=1:7).
[b] Enantiomeric excess determined by chiral GC and SFC analysis.
[c] Yield determined by NMR analysis.
[d] $CHCl_3$ was used as solvent.
[e] Iodosobenzene was used as the oxidant at −40 °C.

the use of the previously problematic cinnamaldehyde system now provides the corresponding epoxide in 92% yield and 92% ee (entry 8). Moreover, electronic variation of the aryl ring substituents of this cinnamate system is well tolerated (entries 9 and 10, 89–92% yield, 92–97% ee). A variety of olefin components that incorporate alkyl substituents of varying steric demand can also be implemented (entries 1–3, 72–88% yield, 88–93% ee). It is important to note that functionalities that are often susceptible to oxidation (e.g., electron-deficient amines, electron-rich olefins) are compatible with NsNIPh, demonstrating its utility as a mild ambiphilic oxygen source (entries 4 and 6, 86–95% yield, 87–92% ee). It should also be noted that enals that incorporate electron-withdrawing groups (e.g., R=CO_2Me) do not provide the desired epoxide under these conditions. This issue was resolved by utilizing iodosobenzene as the oxidant as demonstrated in Table 5, entry 5.

2.4. Mechanistic studies

In an attempt to gain further insight into the inherent advantages of using NsNIPh in comparison to iodosobenzene in this organocatalytic epoxidation, various NMR studies were undertaken to examine (a) the controlled release of monomeric iodosobenzene from NsNIPh and (b) the subsequent effect of the monomeric iodosobenzene concentration on the rate of imidazolidinone catalyst oxidation.

2.4.1. ^{1}H NMR studies on the controlled release of monomeric iodosobenzene from NsNIPh. A low temperature ^{1}H NMR study (−30 °C) was performed to investigate the conversion of NsNIPh to monomeric iodosobenzene in the presence of deuterated chloroform and 1 M acetic acid (AcOD). As revealed in Figure 5, the sulfonamide (NsNIPh) does indeed undergo slow hydrolysis to provide a steady increase in the concentration of monomeric iodosobenzene over the course of 6 h. It is important to note that diacetoxy iodosobenzene (5%) and hemi-hydrolyzed nosyliodosobenzene (1%) were also present in the reaction solution.[26] In contrast, when the analogous ^{1}H NMR experiment was performed with oligomeric iodosobenzene, we observed the immediate formation of a relatively high concentration of iodosobenzene monomer (38%) that remained constant over the course of this 6-h study. Again, diacetoxy iodosobenzene (2%) was detected in this experiment. These NMR studies clearly demonstrate that the proposed slow release of monomeric iodosobenzene from NsNIPh ('internal syringe pump' effect) is not only feasible, but likely operational.

2.4.2. ^{15}N NMR studies on catalyst depletion as a function of oxidant concentration. To investigate the role of monomeric iodosobenzene concentration on catalyst depletion (via a variety of presumed amine oxidation pathways), we next turned to ^{15}N NMR studies. In this context, we first investigated the use of ^{15}N isotopically labeled imidazolidinone **4** as a catalyst for the epoxidation of cinnamaldehyde using (a) oligomeric iodosobenzene and (b) NsNIPh as the respective reaction oxidants. It should be noted that in both cases, reaction efficiencies and enantioselectivities were observed that were within experimental error of the corresponding results observed with catalyst having natural abundance nitrogen. With respect to catalyst depletion, we observed striking differences in both the rate and nature of imidazolidinone decomposition as a function of these two oxidants and presumably, therefore, the corresponding iodosobenzene monomer concentration. As illustrated in

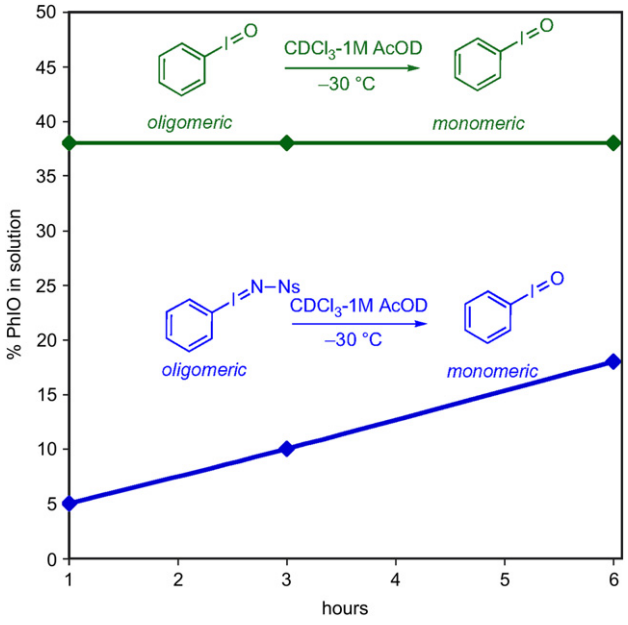


Figure 5. The solution content of monomeric iodosobenzene (PhIO) versus time as a function of iodane source.

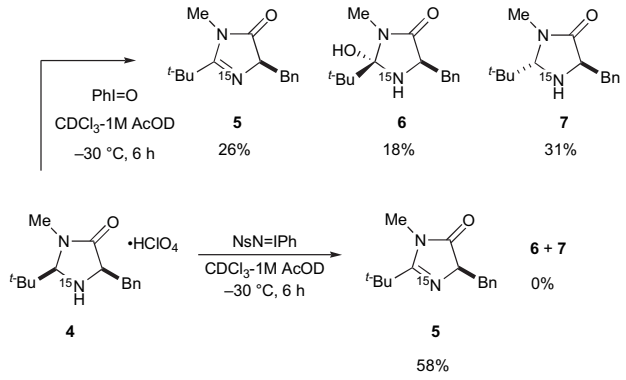


Figure 6. Mode of catalyst degradation when utilizing iodosobenzene or NsNIPh in the epoxidation of cinnamaldehyde as observed by ^{15}N NMR.

Figure 6, the use of oligomeric iodosobenzene leads to the formation of three catalyst-derived amines over the course of the reaction, namely imine **5**, aminol **6**, and the corresponding trans catalyst isomer **7**. In contrast, the analogous reaction that employs NsNIPh leads only to the formation of the corresponding imine **5** (Fig. 7). It should be noted that isolation and separate resubjection of catalyst derivatives **5**, **6**, and **7** to the outlined epoxidation conditions have confirmed that each of these amine species is catalytically inactive. More important, however, is that the rate of catalyst consumption appears to be a function of the source of monomeric iodosobenzene. As revealed in Figure 7, real time ^{15}N NMR studies performed on a low temperature epoxidation reaction with oligomeric iodosobenzene clearly demonstrates that the formation of imine **5** occurs within the first 20 min of the reaction protocol (Fig. 7a). Moreover, after 6 h there is almost complete conversion of the catalyst to amine derivatives **5**, **6**, and **7** (Fig. 7b). In contrast, the use of the slow release oxidant NsNIPh results in almost no formation of catalyst oxidation products after 20 min (Fig. 7c), and only imine adduct **5** is formed in observable quantities after 6 h (Fig. 7d). Notably, significant quantities of the active catalyst **4** remain after 6 h when NsNIPh is employed, highlighting that the 'internal syringe pump' concept is critical to achieving useful levels of catalyst efficiency within this epoxidation protocol.

In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of an enantioselective enal epoxidation protocol. This new organocatalytic reaction allows for the enantioselective formation of oxiranes from a wide array of electronically and sterically diverse α,β-unsaturated aldehydes. Fundamental to these studies has been the recognition that hypervalent iodine reagents are suitable oxidants for organocatalytic Weitz–Scheffer epoxidations using imidazolidinone catalyst **1**. Optimal levels of reaction efficiency and enantiocontrol have been accomplished using an 'internal syringe pump' protocol wherein the controlled release of monomeric iodosobenzene from an in situ iminoiodinane source is accomplished using a mild acid. NMR studies (^{15}N) have revealed that this slow, in situ production of monomeric iodosobenzene from NsNIPh is central to alleviating losses in catalytic efficiency arising from a variety of imidazolidinone oxidation pathways.

3. Experimental

3.1. General

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[27] Iodosobenzene reagents were synthesized and iodometrically titrated for purity prior to use.[28] All non-aqueous solvents were purified according to the method of Grubbs[29] and were transferred

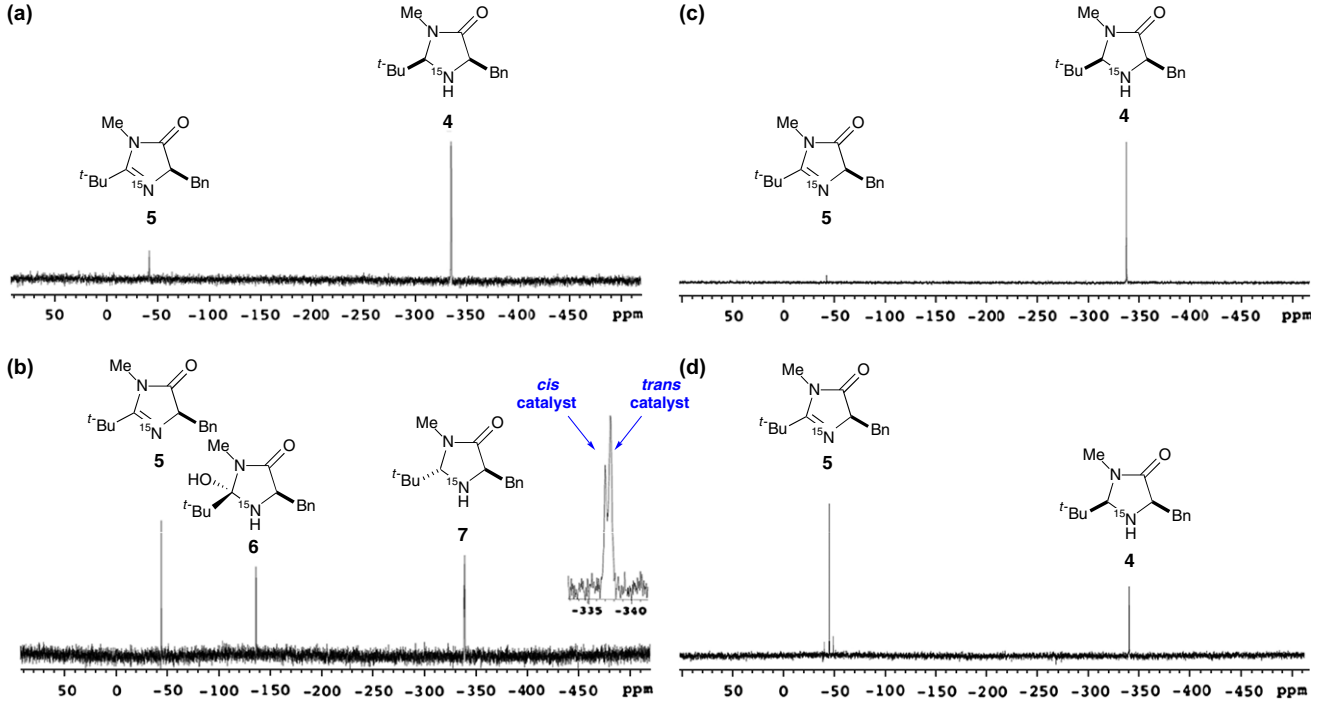


Figure 7. Catalyst degradation products during epoxidations mediated by iodosobenzene (a, c) and NsNIPh (b, d), as observed by ^{15}N NMR.

under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Chromatographic purification of products was accomplished using force-flow chromatography on ICN 60 32–64 mesh silica gel 63 according to the method of Still[30] and where noted, Iatrobeads 6RS-8060 was used in place of silica gel. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, anisaldehyde, $KMnO_4$ or ninhydrin stain. ^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz or 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (hertz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. ^{15}N NMR spectra were externally referenced to 7 M nitromethane in deuterated chloroform and are reported in terms of chemical shift. IR spectra were recorded on a Perkin–Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett–Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex Γ-TA and Varian Chirasil-Dex-CB (30 m×0.25 mm) columns. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralpak AD-H column (25 cm) and AD guard (5 cm).

3.2. General epoxidation procedures

3.2.1. General epoxidation procedure A (using PhIO). A solution of the trifluoromethanesulfonic acid salt of (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 equiv) in dichloromethane (0.075 M) was prepared in a scintillation vial equipped with a magnetic stir bar at −50 or −40 °C (as noted) and stirred for 10 min. The aldehyde (3.0 equiv) and iodosobenzene (1.0 equiv) were then added to form a light yellow suspension and the reaction mixture was stirred at constant temperature for 10–15 h until no further conversion was observed as determined by TLC analysis. The cold solution was then filtered through Celite, washed with ether, and concentrated in vacuo. The resulting residue was purified by column chromatography (solvents noted) to provide the title compounds.

3.2.2. General epoxidation procedure B (using NsNIPh). A scintillation vial equipped with a magnetic stir bar was charged with perchloric acid (70 wt %, 0.2 equiv), dichloromethane, and 20 vol % of 1 M AcOH (0.15 M), and (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 equiv) and allowed to stir for 10 min at −30 °C. The aldehyde (1.0 equiv) and [(nosylimino)iodo]benzene (1.5 equiv) were then added to form a light yellow suspension in an icy solution, which was stirred at constant temperature for 6–16 h until complete consumption of the starting material was observed. The resulting solution was then treated with pH 7 buffer, filtered through Celite, and extracted with Et_2O (2×4 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo and the resulting residue was purified by column chromatography (solvents noted) to provide the title compounds.

3.3. Synthesis and characterization

3.3.1. ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (4). To a three-necked 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer were added L-phenylalanine (98% ^{15}N-labeled, 3.0 g, 18.05 mmol) and methanol (36 mL) under an Ar atmosphere. Thionyl chloride (3.3 mL, 45.1 mmol) was then added dropwise at which time the reaction mixture became homogenous with exotherm and evolution of gas. The resulting solution was then refluxed for 12 h and then cooled to room temperature and partitioned with aqueous $NaHCO_3$ (30 mL) and EtOAc (2×30 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified on a short plug of silica gel and washed with EtOAc (20 mL) to yield ^{15}N-labeled (*R*)-methyl 2-amino-3-phenylpropanoate as a clear oil (3.22 g, quantitative yield).

To the resulting methyl ester (3.22 g, 18.05 mmol) was added methylamine (8 M in EtOH, 10 mL) and the resulting solution was stirred at room temperature for 12 h under an Ar atmosphere. The reaction was then diluted with 0.5 M aqueous HCl (20 mL) and partitioned by EtOAc (2× 20 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give ^{15}N-labeled (*R*)-2-amino-*N*-methyl-3-phenylpropanamide as a clear oil (3.22 g, quantitative yield).

To a dry, three-necked 100 mL round-bottom flask equipped with a reflux condenser, Dean–Stark trap, and magnetic stir bar was added $FeCl_3$ (586 mg, 3.61 mmol) under an N_2 atmosphere. A solution of the amide (3.22 g, 18.05 mmol) and pivaldehyde (2.10 mL, 18.05 mmol) in toluene (36 mL) was added by cannula addition to the flask containing $FeCl_3$. The reaction was refluxed for 12 h under an Ar atmosphere and cooled to room temperature before diluting with brine (50 mL) and partitioning with EtOAc (2×30 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil. ^1H NMR shows a cis:trans ratio of 1.2:1.0. The desired *cis*-isomer was purified from the *trans*-isomer by flash chromatography (silica gel, 50% EtOAc in hexanes) to yield the title compound as a yellow crystalline solid (2.13 g, 48% yield). IR (film) 3338, 2958, 1700, 1395, 1101, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H, aryl *H*), 4.07 (s, 1H, *N*,*N*-acetal *H*), 3.72–3.71 (br m, 1H, α-amino *H*), 3.17 (dt, 1H, *J*=3.8, 13.5 Hz, benzyl *H*), 2.95 (ddd, 1H, *J*=2.5, 8.0, 13.5 Hz, benzyl *H*), 2.30 (s, 3H, *N*-CH_3), 1.76 (br s, 1H, N*H*), 0.85 (s, 3H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.46, 142.90, 138.06, 129.78, 128.76, 126.82, 82.65 (d, $J_{^{15}N-C}$=3.02 Hz), 59.58 (d, $J_{^{15}N-C}$=3.64 Hz), 38.43 (d, $J_{^{15}N-C}$=2.39 Hz), 35.19 (d, $J_{^{15}N-C}$=1.76 Hz), 25.51 (d, $J_{^{15}N-C}$=1.13 Hz); ^{15}N NMR (50 MHz, $CDCl_3$) δ −337.08; ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOH) for the $HClO_4$ salt of the title compound, δ −336.35; HRMS (FAB$^+$) exact mass calculated for [M]$^+$ ($C_{15}H_{22}N^{15}NO$) requires *m*/*z*

247.1703, found *m/z* 247.1726; $[\alpha]_D$ −46.4 (*c* 1.10, $CHCl_3$).

3.3.2. ^{15}N-labeled (2*S*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one (8). The title compound was prepared and isolated from the procedure for ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one as a yellow crystalline solid (1.57 g, 35% yield). IR (film) 3306, 2953, 1684, 1394, 1096, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H, aryl *H*), 3.85–3.83 (br m, 1H, α-amino *H*), 3.81 (t, 1H, *J*=1.5 Hz, *N*,*N*-acetal *H*), 3.11 (dt, 1H, *J*=3.6, 14.1 Hz, benzyl *H*), 2.89 (ddd, 1H, *J*=2.7, 6.9, 14.1 Hz, benzyl *H*), 2.89 (s, 3H, *N*-CH_3), 1.86 (br s, 1H, N*H*), 0.90 (s, 3H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.53, 137.68, 129.70, 128.74, 126.89, 83.62 (d, $J_{^{15}N-C}$=3.02 Hz), 59.71 (d, $J_{^{15}N-C}$=4.08 Hz), 38.77, 37.93, 31.54, 25.57; ^{15}N NMR (50 MHz, $CDCl_3$) δ −337.68; HRMS (FAB$^+$) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N^{15}NO$) requires *m/z* 248.1781, found *m/z* 247.1790; $[\alpha]_D$ −60.0 (*c* 1.13, $CHCl_3$).

3.3.3. (*R*)-2-*tert*-Butyl-4-benzyl-1-methyl-1*H*-imidazol-5(4*H*)-one (6). A scintillation vial equipped with a stir bar was charged with dichloromethane (5 mL), iodobenzene diacetate (403 mg, 1.25 mmol), and activated 3 Å molecular sieves (500 mg). After stirring for 10 min, (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (61.6 mg, 0.25 mmol) was added to the vial and the reaction was stirred for 3 h at room temperature. The reaction was filtered through Celite, concentrated in vacuo, and purified by flash chromatography (Iatrobeads, 50% Et_2O in pentanes) to yield the title compound as a clear oil (51.9 mg, 85% yield). It should be noted that the crude reaction (as observed by NMR) initially produces the acetate addition product of the imine, which upon work-up and purification causes elimination of the acetate to yield the imine product. IR (film) 2961, 1706, 1636, 1495, 1425, 1395, 1366, 1232, 701, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H, aryl *H*), 4.73 (br s, 1H, α-imino *H*), 3.96 (dd, 1H, *J*=1.5, 14.4 Hz, benzyl *H*), 3.90 (d, 1H, *J*=14.7 Hz, benzyl *H*), 3.07 (s, 1H, *N*-CH_3), 0.97 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.12, 165.44, 135.72, 130.99, 129.58, 128.72, 126.98, 91.85, 36.76, 31.26, 26.34; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{15}H_{20}N_2O$) requires *m/z* 244.1576, found *m/z* 244.1586; $[\alpha]_D$ −76.3 (*c* 1.22, $CHCl_3$).

The title compound was also synthesized using ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one using the above procedure. ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOD) δ −42.2.

3.3.4. (5*R*)-2-*tert*-Butyl-5-benzyl-2-hydroxy-3-methyl-imidazolidin-4-one HCl salt (7). A scintillation vial equipped with a stir bar was charged with dichloromethane (5 mL) and 1 M AcOH (1 mL), iodosobenzene (161 mg, 0.5 mmol), and (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one (61.6 mg, 0.25 mmol). The reaction was stirred for 2 h at room temperature before filtration and concentration in vacuo. Purification was by flash chromatography (silica gel, 40% EtOAc in hexanes) and the isolated residue was dissolved in HCl (2 M in diethyl ether, 125 mL) and dichloromethane (12.5 mL) and cooled to −70 °C to facilitate precipitation. The precipitate was filtered and washed with cold ether and dried under reduced pressure to yield the title compound as a white solid (18 mg, 24% yield). IR (KBr) 2961, 1780, 1657, 1495, 1253, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H, aryl *H*), 4.79 (dd, 1H, *J*=3.0, 5.4 Hz, α-amino *H*), 4.00 (dd, 1H, *J*=5.4, 13.8 Hz, benzyl *H*), 3.35 (dd, 1H, *J*=3.0, 13.5 Hz, benzyl *H*), 3.09 (s, 3H, *N*-CH_3), 1.29 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.98, 175.16, 132.28, 130.27, 129.19, 128.59, 128.17, 61.05, 35.91, 35.86, 29.10, 28.54, 26.62; HRMS (FAB$^+$) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2O_2$) requires *m/z* 261.1603, found *m/z* 261.1605; $[\alpha]_D$ +4.2 (*c* 1.24, $CHCl_3$).

The title compound was also synthesized using ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one using the above procedure. ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOD) δ −134.06.

3.3.5. (2*R*,3*S*)-3-Methyloxirane-2-carbaldehyde (2). Prepared according to general epoxidation procedure A using crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 at −50 °C with benzyl ether as an internal standard to establish NMR yield. After filtration through silica gel, the title compound was obtained in a 100% NMR yield and 93% ee.

Also prepared according to general epoxidation procedure B with crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 and mesitylene as an internal standard to establish NMR yield. After filtration through silica gel, the title compound was obtained in an 88% NMR yield and 93% ee. Material for characterization was obtained by flash chromatography (Iatrobeads, 20% Et_2O in pentanes). IR (film) 3416, 2965, 2929, 1443, 1380, 1124, 871 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, 1H, *J*=6.0 Hz, C*H*O), 3.30 (qd, 1H, *J*=2.1, 5.1 Hz, C*H* oxirane), 3.08 (dd, 1H, *J*=2.1, 6.3 Hz, C*H* oxirane), 1.42 (d, 3H, *J*=5.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.59, 60.23, 53.06, 17.06; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_4H_6O_2$) requires *m/z* 86.03678, found *m/z* 86.03649; $[\alpha]_D$ +47.9 (*c* 2.7, $CHCl_3$). The enantiomeric purity was determined on the alcohol product, which was prepared by an $NaBH_4$ reduction, and analyzed by GLC analysis using a Bodman Γ-TA column (40 °C isotherm, 12 psi); (2*R*,3*S*) isomer t_R=57.1 min, (2*R*,3*S*) isomer t_R=58.7 min.

3.3.6. (2*R*,3*S*)-3-Propyloxirane-2-carbaldehyde (Table 5, entry 2 and Table 7, entry 2). Prepared according to general epoxidation procedure A using (*E*)-hex-2-enal (591 μL, 5.09 mmol) at −50 °C. After stirring for 15 h, this reaction was filtered through silica, washed with dichloromethane (30 mL), and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3×30 mL) and concentrated in vacuo at 0 °C, before purifying by flash chromatography (silica gel, 50% Et_2O in pentanes) to afford the title compound as a clear, colorless oil in 93% yield (182 mg, 1.57 mmol), 88% ee.

Also prepared according to general epoxidation procedure B using (*E*)-hex-2-enal (234 mL, 2.0 mmol) to afford the title

compound as a clear, colorless oil (162 mg, 72% yield, 88% ee) after silica gel chromatography (silica gel, 30–70% Et_2O in pentanes, linear gradient). IR (film) 2962, 2935, 2875, 1731, 1671, 1534, 1458, 1378, 1350, 1125, 1092, 1044, 915.1, 737.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, 1H, J=6.3 Hz, C*H*O), 3.23 (td, 1H, J=2.1, 5.1, 7.8 Hz, C*H* oxirane), 3.13 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 1.69–1.50 (m, 4H, CH_2CH_2), 0.98 (t, 3H, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 59.34, 56.83, 33.39, 19.39, 13.98; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_6H_9O_2$) requires m/z 113.0603, found m/z 113.0602; $[\alpha]_D$ +11.4 (c 2.38, $CHCl_3$). The enantiomeric purity was determined by GLC using a Bodman Γ-TA column (70 °C isotherm, 15 psi, flow=1.3 mL/min); (2*R*,3*S*) isomer t_R=8.87 min, (2*S*,3*R*) isomer t_R=9.79 min.

These data correlated with literature ^1H and ^{13}C NMR spectroscopic values for (2*S*, 3*R*)-3-propyloxirane-2-carbaldehyde.[31]

3.3.7. ((2*R*,3*S*)-3-Isopropyloxiran-2-yl)methanol (Table 5, entry 3). Prepared according to general epoxidation procedure A using (*E*)-4-methylpent-2-enal (592 μL, 5.09 mmol) and iodosobenzene (1.52 g, 6.92 mmol) in dichloromethane (18.3 mL) at −40 °C. After stirring for 15 h, this reaction was filtered through silica gel, washed with dichloromethane (50 mL), and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3×30 mL) and concentrated in vacuo at 0 °C, before purifying by flash chromatography (silica gel, 30–50% Et_2O in pentanes, linear gradient) to afford the title compound as a clear, colorless oil in 86% yield (505 mg, 4.35 mmol), 80% ee. IR (film) 2963, 2930, 1459, 1067, 895.1, 669.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (ddd, 1H, J=2.4, 5.7, 12.3 Hz, C*H*OH), 3.70 (ddd, 1H, J=4.20, 7.20, 12.3 Hz, C*H*OH), 3.02 (dt, 1H, J=3.00, 3.90 Hz, C*H* oxirane), 2.81 (dd, 1H, J=2.40, 6.90 Hz, C*H* oxirane), 1.70–1.59 (m, 1H, C*H*Me_2), 1.08 (d, 3H, J=6.60 Hz, CH_3), 1.02 (d, 3H, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.86, 61.14, 57.36, 30.07, 19.02, 18.37; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_6H_{11}O_2$) requires m/z 115.0759, found m/z 115.0702; $[\alpha]_D$ −14.0 (c 0.74, $CHCl_3$). The enantiomeric purity was determined by GLC analysis of the crude aldehyde product (60 °C isotherm, 12 psi); (2*R*,3*S*) isomer t_R=12.8, (2*S*, 3*R*) isomer t_R=16.2 min.

3.3.8. (2*R*,3*R*)-Methyl 3-formyloxirane-2-carboxylate (Table 5, entry 5). Prepared according to general epoxidation procedure A using 1 equiv of (*E*)-methyl 3-formylacrylate (250 mg, 2.19 mol) in dichloromethane (0.25 M) at −50 °C. The title compound was isolated as a clear, colorless oil (128 mg, 45% yield, 85% ee) after flash chromatography (silica gel, 30% ether in pentanes). IR (film) 3447, 1744, 1441, 1212 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, 1H, J=6.3 Hz, C*H*O), 3.62 (dd, 1H, J=1.5, 6.3 Hz, oxirane C*H*), 3.76 (d, 1H, J=1.8 Hz, oxirane C*H*), 3.83 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.03, 57.68, 53.37, 50.92; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_4H_5O_3$) requires m/z 101.0239, found m/z 101.0240; $[\alpha]_D$ +4.1 (c 0.75, $CHCl_3$). The enantiomeric purity was determined by SFC using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 80 °C oven, flow=4.0 mL/min); (2*S*,3*S*) isomer t_R=23.9 min, (2*R*,3*R*) isomer t_R=27.0 min.

3.3.9. (2*R*,3*S*)-3-Cyclohexyloxirane-2-carbaldehyde (Table 7, entry 3). Prepared according to general epoxidation procedure B using 3-cyclohexylacrylaldehyde[32] (147 mg, 1.06 mmol) to afford the title compound as a clear, colorless oil (124 mg, 77% yield, 92% ee) after flash chromatography (silica gel, 20% Et_2O in pentanes with 1% Et_3N). IR (film) 2928, 2853, 1730, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, 1H, J=6.0 Hz, C*H*O), 3.17 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 3.02 (dd, 1H, J=2.1, 6.6 Hz, C*H* oxirane), 1.85–1.66 (m, 5H), 1.41–1.30 (m, 1H), 1.26–1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_9H_{13}O_2$) requires m/z 153.0916, found m/z 153.0910; $[\alpha]_D$ +75.6 (c 1.02, $CHCl_3$). The enantiomeric purity was determined by GLC using a Varian Chirasil-Dex-CB column (80 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=42.07 min, (2*R*,3*S*) isomer t_R=46.87 min.

This data correlated with literature ^1H and ^{13}C NMR spectroscopic values.[31]

3.3.10. (2*R*,3*S*)-3-(Pent-4-enyl)oxirane-2-carbaldehyde (Table 7, entry 4). Prepared according to general epoxidation procedure B using 3-(*E*)-octa-2,7-dienal[33] (270 mg, 2.18 mol) to afford the title compound as a clear, colorless oil (292 mg, 95% yield, 92% ee) after flash chromatography (silica gel, 20% Et_2O in pentanes). IR (film) 1729, 1440, 1148, 993.1, 914.4, 849.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, 1H, J=6.3 Hz, C*H*O), 5.82–5.69 (m, 1H, C*H*=CH_2), 5.04–4.94 (m, 2H, CH=CH_2), 3.11 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 3.23–3.19 (m, 1H, C*H* oxirane), 2.10 (q, 2H, J=6.9 Hz, CH_2), 1.71–1.52 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_8H_{11}O_2$) requires m/z 139.0760, found m/z 139.0759; $[\alpha]_D$ +48.8 (c 1.10, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (80 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=21.75 min, (2*R*,3*S*) isomer t_R=22.27 min.

3.3.11. ((2*R*,3*S*)-3-Formyloxiran-2-yl)methyl benzoate (Table 7, entry 5). Prepared according to general epoxidation procedure A using (*E*)-3-formylallyl benzoate[34] (104 mg, 0.55 mol) to afford the title compound as a clear, colorless oil (101 mg, 89% yield, 85% ee) after flash chromatography (silica gel, 20% EtOAc in hexanes). IR (film) 3447, 1723, 1273, 1111, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, 1H, J=6.3 Hz, C*H*O), 8.08–8.04 (m, 2H, aryl *H*), 7.63–7.57 (m, 1H, aryl *H*), 7.49–7.44 (m, 2H, aryl *H*), 4.75 (dd, 1H, J=3.0, 12.6 Hz, CH_2), 4.34 (dd, 1H, J=5.4, 12.6 Hz, CH_2), 3.68 (m, 1H, C*H* oxirane), 3.44 (dd, 1H, J=2.1, 6.3 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.01, 166.15, 133.72, 129.97, 129.35, 128.73, 63.13, 56.73, 54.0; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{11}H_{10}O_4$) requires m/z 206.0579, found m/z

206.0581; $[\alpha]_D$ +16.0 (*c* 1.12, $CHCl_3$). The enantiomeric purity was determined by SFC using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 35 °C oven, flow=4.0 mL/min); (2*S*,3*R*) isomer t_R=4.19 min, (2*R*,3*S*) isomer t_R=4.96 min.

3.3.12. *tert*-Butyl 4-(((2*R*,3*S*)-3-formyloxiran-2-yl)-methyl)piperidine-1-carboxylate (Table 7, entry 6). A solution of *tert*-butyl 4-((*E*)-3-(methoxycarbonyl)allyl)piperidine-1-carboxylate[35] (1.8 g, 6.68 mmol) in ether (60 mL) in a 100 mL round-bottom flask was equipped with a magnetic stir bar and was cooled to −78 °C. DIBAL (1 M in hexanes, 13.4 mL) was added dropwise to the flask and the reaction was stirred at constant temperature for 15 min before warming to 0 °C. After 3 h, the reaction was quenched by the addition of a saturated solution of Rochelle's salt (30 mL) and was stirred at room temperature until the biphasic solution no longer effervesces and both layers became clear. The organic layer was extracted, dried, and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to yield *tert*-butyl 4-((*E*)-3-hydroxybut-2-enyl)piperidine-1-carboxylate as a clear oil (1.1 g, 61% yield). IR (film) 3436, 2915, 1669, 1429, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.62 (m, 2H, C*H*=C*H*), 4.08 (t, 2H, α-hydroxy CH_2), 4.03 (br s, 1H, O*H*), 3.20 (br t, 2H, *J*=12.0 Hz, piperidine CH_2), 1.98 (t, 2H, *J*=6.0 Hz, CH=CH–CH_2), 1.65 (br s, 1H, piperidine CH_2), 1.60 (br s, 1H, piperidine CH_2), 1.40 (s, 9H, C(CH_3)$_3$), 1.27 (m, 1H, piperidine CH_2), 1.07 (ddd, 2H, *J*=4.2, 12.0, 24.6 Hz, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.10, 130.99, 130.69, 79.45, 63.80, 39.42, 36.31, 32.09, 43.92, 39.42, 36.31, 32.09, 31.14, 28.67; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{25}NO_3$) requires *m*/*z* 255.1834, found *m*/*z* 255.1837.

In a scintillation vial equipped with a magnetic stir bar was a solution of *tert*-butyl 4-((*E*)-3-hydroxybut-2-enyl)piperidine-1-carboxylate (198 mg, 0.78 mmol), *N*-methylmorpholine *N*-oxide (96 mg, 0.82 mmol), and activated 3 Å molecular sieves (150 mg) in dichloromethane (4 mL) at room temperature. After 5 min, tetrapropylammonium perruthenate (14 mg, 0.04 mmol) was added in one portion. The reaction was complete after 30 min and was filtered through a pad of Celite and concentrated in vacuo and purified by flash chromatography (silica gel, 20% acetone in pentanes) to yield *tert*-butyl 4-((*E*)-3-formylallyl)piperidine-1-carboxylate as a light yellow oil (160 mg, 80% yield). IR (film) 2929, 1691, 1417, 1365, 1240, 1163, 976, 866, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, 1H, *J*=8.1 Hz, C*H*O), 6.78 (dt, 1H, *J*=7.2, 15.9 Hz, CH=C*H*), 6.01 (ddd, 1H, *J*=1.2, 2.7, 9.0 Hz, CHO–C*H*=CH), 3.20 (br d, 2H, *J*=11.1 Hz, piperidine CH_2), 2.66 (br t, 2H, *J*=12.0 Hz, piperidine CH_2), 2.24 (t, 2H, *J*=7.5 Hz, piperidine CH_2), 1.67 (br s, 1H, piperidine CH_2), 1.64 (br s, 1H, piperidine CH_2), 1.39 (s, 9H, C(CH_3)$_3$), 1.07 (ddd, 2H, *J*=3.0, 13.8, 25.8 Hz, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.90, 156.20, 154.95, 134.64, 79.62, 43.92, 39.76, 35.73, 32.08, 28.62; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_3$) requires *m*/*z* 253.1678, found *m*/*z* 253.1671.

The title compound was prepared according to general epoxidation procedure B using *tert*-butyl 4-((*E*)-3-formylallyl)-piperidine-1-carboxylate (156 mg, 0.62 mmol) to afford the title compound as a clear, yellow oil (134 mg, 86% yield, 87% ee) after flash chromatography (silica gel, 25% EtOAc in hexanes). IR (film) 3436, 2915, 2361, 1678, 1413, 1164, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, 1H, *J*=18.0 Hz, C*H*O), 4.08 (br d, 2H, *J*=10.5 Hz, piperidine CH_2), 3.26–3.21 (m, 1H, C*H* oxirane), 3.09 (dd, 1H, *J*=1.8, 6.3 Hz, C*H* oxirane), 3.72–3.63 (m, 2H, piperidine CH_2), 1.72–1.61 (m, 3H, piperidine CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 1.21–1.15 (m, 2H, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.36, 151.03, 79.63, 59.29, 55.27, 43.92, 38.31, 34.44, 32.38, 32.03, 28.64; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_4$) requires *m*/*z* 269.1627, found *m*/*z* 269.1628; $[\alpha]_D$ +30.9 (*c* 0.95, $CHCl_3$). The enantiomeric purity was determined by SFC analysis using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 35 °C oven, flow=4.0 mL/min); (2*S*, 3*R*) isomer t_R=6.97 min, (2*R*, 3*S*) isomer t_R=7.74 min.

3.3.13. Methyl 3-((2*R*,3*S*)-3-formyloxiran-2-yl)propanoate (Table 7, entry 7). Prepared according to general epoxidation procedure B using (*E*)-methyl 5-formylpent-4-enoate[36] (142 mg, 1.0 mol) to afford the title compound as a clear, colorless oil (137 mg, 86% yield, 90% ee) after flash chromatography (silica gel, 40% Et_2O in pentanes). IR (film) 1731, 1438, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, 1H, *J*=6.3 Hz, C*H*O), 3.72 (s, 3H, CO_2CH_3), 3.38–3.34 (m, 1H, C*H* oxirane), 3.20 (dd, 1H, *J*=2.0, 6.0 Hz, C*H* oxirane), 2.52 (t, 2H, *J*=6.9 Hz, CH_2CO_2Me), 2.15–1.88 (m, 2H, C$H_2CH_2CO_2$Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.06, 151.08, 59.29, 55.81, 52.16, 30.11, 26.66; HRMS (EI$^+$) exact mass calculated for $[M-H]^+$ ($C_7H_9O_4$) requires *m*/*z* 157.0501, found *m*/*z* 157.0501; $[\alpha]_D$ +27.3 (*c* 1.25, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (90 °C isotherm, 15 psi, flow=1.0 mL/min); (2*R*,3*S*) isomer t_R=60.62 min, (2*S*,3*R*) isomer t_R=62.23 min.

3.3.14. (2*R*, 3*S*)-3-Phenyloxirane-2-carbaldehyde (3) (Table 7, entry 8). Prepared using general epoxidation procedure A using cinnamaldehyde (159 μL, 1.26 mmol) and iodosobenzene (378 mg, 1.72 mmol) in dichloromethane (5.04 mL) at −40 °C. Flash chromatography (silica gel, 30% Et_2O in pentanes) afforded the title compound as a clear, light yellow oil in a 71% yield (133 mg, 0.90 mmol), 78% ee.

Prepared according to general epoxidation procedure B using cinnamaldehyde (94.4 μL, 0.75 mmol), 1 M AcOH (0.75 mL), and chloroform (3.0 mL). Flash chromatography (silica gel, 30% Et_2O in pentanes) afforded the title compound as a clear, light yellow oil (101 mg, 92% yield, 92% ee). IR (film) 1726, 1460, 1137, 990.8, 754.3, 697.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, 1H, *J*=6.0 Hz, C*H*O), 7.39–7.28 (m, 5H, aryl *H*), 4.17 (d, 1H, *J*=2.1 Hz, C*H* oxirane), 3.45 (dd, 1H, *J*=2.1, 6.0 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 129.4, 129.0, 125.9, 63.2, 56.9; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_9H_8O_2$) requires *m*/*z* 148.0524, found *m*/*z* 148.0522; $[\alpha]_D$ +35.8 (*c* 0.76, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Bodman Γ-TA column (90 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=29.9 min, (2*R*,3*S*) isomer t_R=33.1 min.

Absolute sense of rotation and spectroscopic data was in agreement with reported literature values.[37]

3.3.15. (2*R*,3*S*)-3-(4-Nitrophenyl)oxirane-2-carbaldehyde (Table 7, entry 9). Prepared according to general epoxidation procedure B using 4-nitrocinnamaldehyde (138 mg, 0.75 mmol) using 1 M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 40% Et_2O in hexanes with 2% NEt_3) afforded the title compound as a light yellow solid (154 mg, 89% yield, 97% ee). IR (film) 1727, 1605, 1520, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, 1H, J=6.0 Hz, C*H*O), 8.21 (dd, 2H, J=2.4, 9.1 Hz, aryl *H*), 7.46 (dd, 2H, J=2.4, 9.1 Hz, aryl *H*), 4.26 (d, 1H, J=1.8 Hz, C*H* oxirane), 3.41 (dd, 1H, J=1.8, 5.7 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 141.2, 126.3, 123.8, 62.5, 55.3; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_9H_7NO_4$) requires m/z 193.0375, found m/z 193.0374; $[\alpha]_D$ −13.0 (c 1.18, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Chirasil-DEX CB column (120 °C ramp 5 °C/min to 145 °C, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R= 74.8 min, (2*R*,3*S*) isomer t_R=75.9 min.

3.3.16. (2*R*,3*S*)-3-(4-Bromophenyl)oxirane-2-carbaldehyde (Table 7, entry 10). Prepared according to general epoxidation procedure B using 4-bromocinnamaldehyde (158 mg, 0.75 mmol) using 1 M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 30% Et_2O in pentanes with 2% NEt_3) afforded the title compound as a clear oil (158 mg, 93% yield, 93% ee). IR (film) 1727, 1490, 1070, 1011, 824.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, 1H, J=6.0 Hz, C*H*O), 7.48 (d, 2H, J=9.0 Hz, aryl *H*), 7.14 (d, 2H, J=9.0 Hz, aryl *H*), 4.11 (d, 1H, J=1.8 Hz, C*H* oxirane), 3.37 (dd, 1H, J=1.7, 6.2 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 132.2, 127.5, 62.92, 56.28; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_9H_7O_2Br$) requires m/z 225.9629, found m/z 225.9626; $[\alpha]_D$ −10.5 (c 0.945, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the alcohol using a Chiralpak AD column (5% EtOH/hexanes, flow= 1.0 mL/min); (2*R*,3*S*) isomer t_R=33.7 min, (2*S*,3*R*) isomer t_R=36.9 min.

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Asymmetric phase-transfer catalysis of homo- and heterochiral quaternary ammonium salts: development and application of conformationally flexible chiral phase-transfer catalysts

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Abstract—Inspired by the considerable difference of catalytic activity and stereocontrolling ability between the conformationally rigid, homo- and heterochiral quaternary ammonium bromides **1**, conformationally flexible, *N*-spiro chiral quaternary ammonium bromides of type **4** have been designed and synthesized. Reliable procedures for the preparation of the appropriately substituted biphenyl subunits have been established by the repeated use of *ortho* magnesiation–halogenation as a key synthetic tool. The relationship between the structure of achiral biphenyl moiety and the reactivity and selectivity of **4** has been evaluated in the asymmetric alkylation of glycinate Schiff base **2** under typical phase-transfer conditions, leading to the identification of **4l** as an optimal catalyst structure to exhibit an excellent enantiocontrol in the reactions with various alkyl halides. The molecular structure of **4l** was determined by X-ray crystallographic analysis and its unique behavior in solution was examined by a variable-temperature ^{1}H NMR study. These investigations uncovered that the observed high chiral efficiency originated from the efficient asymmetric phase-transfer catalysis of homochiral-**4l**, which rapidly equilibrated with heterochiral-**4l** of low catalytic activity and stereoselectivity.

1. Introduction

The use of chiral quaternary ammonium salts readily prepared from naturally occurring *cinchona* alkaloids, cinchonine and cinchonidine as chiral phase-transfer catalysts has provided a unique yet reliable tool for catalytic asymmetric synthesis, and its utility has been well documented in the number of valuable chemical transformations including stereoselective functionalization of protected glycine derivative **2**.[1] Recent attractive emergence of a series of appropriately modified *cinchona* alkaloid-based catalysts as well as the elaboration of purely synthetic chiral quaternary ammonium salts strongly suggest the significant importance and usefulness of rational molecular design of chiral catalysts.[1,2] Our own contribution to this rapidly growing area was the design of chiral C_2-symmetric quaternary ammonium bromides of type **1**, which efficiently catalyze the phase-transfer alkylation of **2** with excellent enantioselectivities, providing a practical method for the asymmetric synthesis of both natural and unnatural α-amino acids.[3] For example, the reaction of **2** with benzyl bromide (1.2 equiv) in the presence of 1 mol % of (*S*,*S*)-**1** in 50% aqueous KOH/toluene (volume ratio=1:3) at 0 °C for 3 h under argon atmosphere gave rise to the corresponding benzylation product **3a**, protected phenylalanine, in 91% yield with 94% ee (*R*). The characteristic feature of (*S*,*S*)-**1** is the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl units. Since this structure seemed essential for attaining sufficient reactivity and enantioselectivity, we were intrigued by which binaphthyl moiety would be more critically associated with its chiral efficiency. This initial concern led us to prepare the diastereomeric, heterochiral quaternary ammonium bromide (*R*,*S*)-**1** and to evaluate its reactivity and selectivity as a chiral phase-transfer catalyst. Interestingly, the benzylation of **2** under similar conditions proceeded slowly, and, after 60 h, furnished **3a** in 47% yield with low enantiomeric excess (11% ee, *R*). We also observed that the enantiomeric (*S*,*R*)-**1** exerted comparable catalytic activity in the benzylation with the opposite sense of asymmetric induction (51%, 11% ee, *S*). The significant rate retardation apparently indicates that the parent homochiral ammonium bromide (*S*,*S*)- or (*R*,*R*)-**1** has substantially higher catalytic activity than the heterochiral (*R*,*S*)- or (*S*,*R*)-**1**.[4] Indeed, the benzylation of **2** with each 0.5 mol % of (*S*,*S*)-**1** and (*R*,*S*)-**1** under otherwise similar phase-transfer conditions at 0 °C for 13 h afforded **3a** in 88% yield with 94% ee, and the use of each 0.5 mol % of (*S*,*S*)-**1** and (*S*,*R*)-**1** as catalyst, though a mismatched combination in terms of the enantioselectivity, resulted in formation of **3a** in 92% yield with 93% ee after 8.5 h at 0 °C as shown in Scheme 1.

Keywords: Asymmetric phase-transfer alkylation; Atropinversion; Biphenyl unit; Conformational flexibility; Molecular design.
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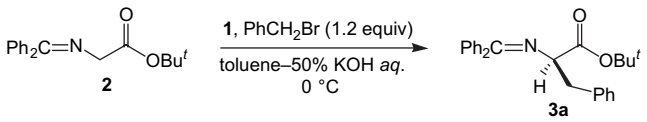
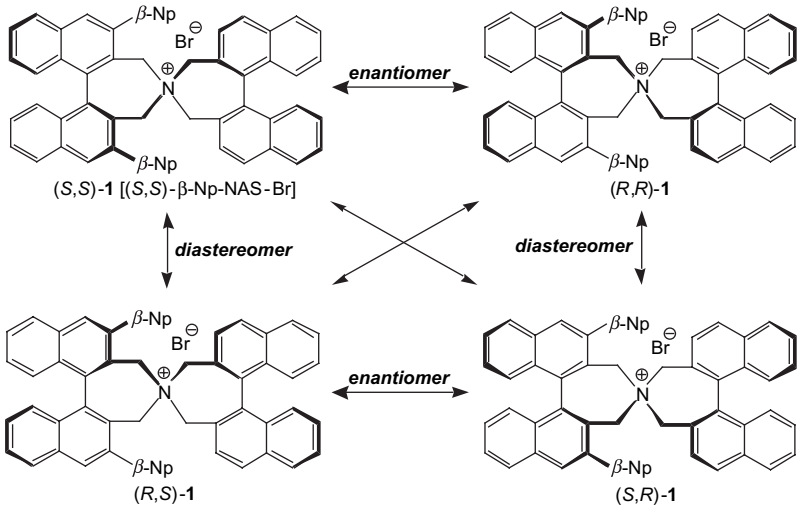
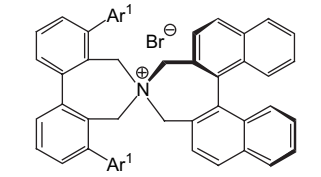


(*S*,*S*)-**1** (1 mol%), 3 h : 91%, 94% ee (*R*)
(*R*,*S*)-**1** (1 mol%), 60 h : 47%, 11% ee (*R*)
(*S*,*R*)-**1** (1 mol%), 60 h : 51%, 11% ee (*S*)
(*S*,*S*)-**1** (0.5 mol%), (*R*,*S*)-**1** (0,5 mol%), 13 h : 88%, 94% ee (*R*)
(*S*,*S*)-**1** (0.5 mol%), (*S*,*R*)-**1** (0,5 mol%), 8.5 h : 92%, 93% ee (*R*)

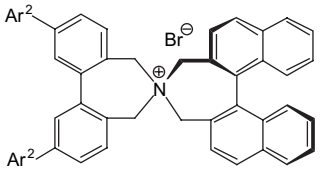


Scheme 1.

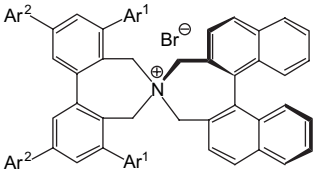
These results suggested that high levels of catalytic activity and stereoselectivity could be retained even if *one of the two chiral binaphthyl subunits of **1** was racemic*. On the basis of the interesting findings, we sought to develop a new *N*-spiro chiral C_2-symmetric quaternary ammonium bromide **4** by incorporating an achiral biphenyl structure. Our assumption was that the conformationally flexible biphenyl subunits could be atropisomerically biased by the simple chiral binaphthyl unit through the central nitrogen atom so that **4** could exert chiral efficiency as high as the conformationally rigid homochiral catalyst (*S*,*S*)-**1**. This approach, if successful, should lead to simplification of the molecular design and hence allows fruitful modification of the chiral catalysts. In this article, we wish to describe the detailed procedure for the facile synthesis of conformationally flexible **4**, and its reactivity and selectivity as chiral phase-transfer catalyst is explored in relation to the unique behavior in solution, revealing that **4** exhibits high chiral efficiency in the asymmetric alkylation of **2** by taking advantage of the considerable difference of activity between the two possible diastereomeric conformers through rapid interconversion.[5,6]



4a : Ar^1 = H
4b : Ar^1 = Ph
4c : Ar^1 = 3,5-Me_2-C_6H_3
4d : Ar^1 = 3,5-(*t*-Bu)$_2$-C_6H_3
4e : Ar^1 = 3,4,5-F_3-C_6H_2
4f : Ar^1 = 3,5-$(CF_3)_2$-C_6H_3
4g : Ar^1 = β-Np
4h : Ar^1= 3,5-Ph_2-C_6H_3



4i : Ar^2 = Ph
4j : Ar^2 = β-Np
4k : Ar^2 = 3,4,5-F_3-C_6H_2

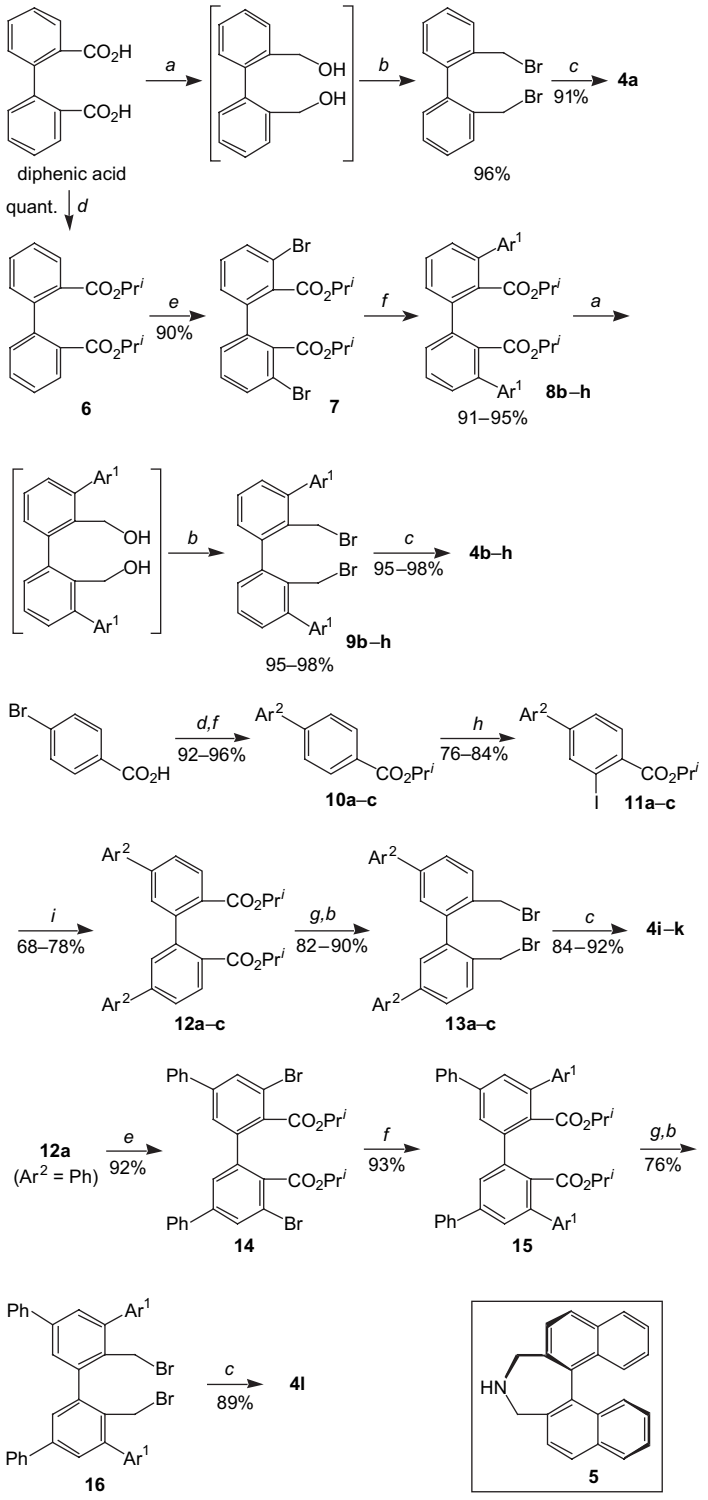


4l : Ar^1 = 3,5-Ph_2-C_6H_3, Ar^2 = Ph

2. Results and discussion

2.1. Synthesis of conformationally flexible C_2-symmetric chiral quaternary ammonium bromide 4

Because the simple chiral element of the new catalyst **4** can be served by previously known optically active *secondary* amine **5**,[3c,7] we focused on the synthesis of appropriately substituted achiral biphenyl moiety, which has been accomplished concisely in a five-step sequence starting from commercially available diphenic acid as illustrated in Scheme 2. Diphenic acid was first converted to the corresponding isopropyl ester **6** quantitatively. For the subsequent selective bromination of the 3,3′-position of **6**, we fortunately found that *ortho* magnesiation–bromination technique using magnesium 2,2,6,6-tetramethylpiperamide and bromine was quite effective, furnishing **7** in 90% yield.[8] This success allowed the preparation of **8** having a variety of 3,3′-aromatic substituents by Suzuki–Miyaura cross coupling reaction. Then, simple reduction of **8** by $LiAlH_4$ and, without any purification, subsequent treatment with PBr_3 afforded the requisite bis-bromide **9**. Finally, reaction of **9** with **5** under basic conditions as previously reported[3c] afforded conformationally flexible quaternary ammonium bromides **4b**–**h**.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) PBr_3, THF, 0 °C to rt; (c) **5**, K_2CO_3, CH_3CN, reflux; (d) $SOCl_2$, 0 °C to reflux, then *i*-PrOH, pyridine; (e) $(TMP)_2Mg$, THF, 0 °C to rt, then Br_2, −78 °C to rt; (f) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 90 °C; (g) $LiAlH_4$, THF, 0 °C to rt; (h) $(TMP)_2Mg$, THF, 0 °C to rt, then I_2, −78 °C to rt; (i) activated Cu, DMF, reflux.

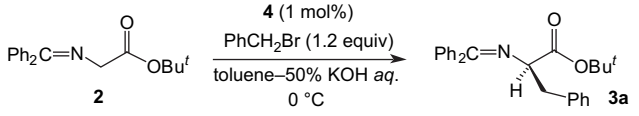
In addition, the synthesis of the catalyst **4** having an aromatic group at 5,5′-positions of the biphenyl subunit has also been executed by means of the *ortho* magnesiation–halogenation procedure[8] as included in Scheme 2. Commercially available 4-bromobenzoic acid was first transformed into its isopropyl ester and then coupled with an appropriate boronic acid using the palladium catalyst to prepare **10**. Treatment of the ester **10** with $(TMP)_2Mg$ in THF followed by the reaction with iodine resulted in the production of **11**, a requisite candidate for the next Ullmann coupling. Refluxing a mixture of **11** with activated copper in DMF facilitated the biphenyl formation to give **12**, which was further derivatized to **13** through the reduction and bromination sequences. The subsequent use of **13** for the quaternization of **5** led to the

formation of catalysts **4i**–**k**. In a meantime, installment of 3,3′-(3,5-diphenylphenyl) groups on **12** and the generation of bromomethyl functionality at 2,2′-position could be conducted in a manner as described. The final assembly of **16** thus obtained with **5** afforded **4l**.

2.2. Evaluation of the reactivity and selectivity of 4 in the asymmetric alkylation of glycinate Schiff base 2

We then pursued the systematic evaluation of the reactivity and selectivity of **4** in the phase-transfer-catalyzed benzylation of **2** starting from the use of **4a** consisted of (*S*)-binaphthyl and simple biphenyl subunits. Thus, treatment of **2** with benzyl bromide (1.2 equiv) in 50% aqueous KOH/toluene (volume ratio=1:3) in the presence of 1 mol % of **4a** at 0 °C for 36 h under argon atmosphere resulted in the formation of **3a** in 62% isolated yield. Its enantiomeric excess was revealed to be appreciable (64% ee) and the absolute configuration was assigned to be *R*, the same with that of the major enantiomer in the reaction with (*S*,*S*)-**1** (Table 1, entry 1). This observation could be rationalized by the preferred nature of homochiral conformer (*S*,*S*)-**4a** in solution on the basis of the elegant study of Lacour on the conformational preference of the simple spirobi[dibenzazepinium] cation.[9] It was of interest that introduction of phenyl substituent to 3,3′-position of the biphenyl subunit (**4b**) brought a substantial decrease of the enantioselectivity (53% ee, entry 2), while similar modification at 5,5′-position (**4i**) led to the enhancement of the selectivity (72% ee, entry 3). At this stage, we assumed that the erosion of enantiocontrol might stem from the intervention of heterochiral conformer (*R*,*S*)-**4b**. Meanwhile, the installment of aromatic substituents at 5,5′-position of the biphenyl moiety (Ar^2) would not deliver major influence on the stereodynamic of the chiral ammonium cation, and thus only the beneficial effect of the extended aromatic surface could be extracted. This interpretation prompted us to further examine the impact of steric and electronic properties of Ar^2 particularly on the stereoselectivity, which consequently turned out to be marginal as included in Table 1 (entries 4 and 5). In sharp contrast, however, manipulation of 3,3′-aromatic substituents dramatically altered both the reactivity and selectivity of the catalyst **4**. On one hand, the phase-transfer-catalyzed benzylation of **2** in the presence of 3,5-dimethylphenyl-substituted **4c** under otherwise similar conditions afforded **3a** in 90% yield with 80% ee (entry 6), though use of sterically more demanding **4d** as catalyst cancelled the improvement (entry 7). On the other, significant loss of the catalytic activity was observed when electron-withdrawing substituent such as 3,4,5-trifluorophenyl group was introduced and, to our surprise, no production of **3a** was detected under the influence of **4f** having 3,5-bis(trifluoromethyl)phenyl unit (entries 8 and 9). Eventually, highest level of enantioselectivity was obtained with **4g** possessing β-naphthyl group (entry 10), and more conjugated *meta*-terphenyl group was identified as an ideal 3,3′-substituent of this type of catalyst for attaining sufficient reactivity and selectivity (entry 11). These results clearly demonstrate that appropriate choice of the 3,3′-substituents allows the

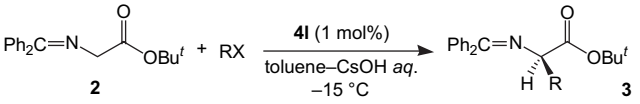
Table 1. Evaluation of the reactivity and selectivity of **4** in the phase-transfer-catalyzed asymmetric benzylation of **2**[a]

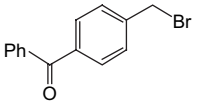
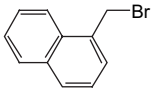
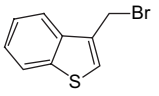


Entry	4	React. time (h)	% Yield[b]	% ee[c] (config)[d]
1	**4a** [Ar^1=H]	36	62	64 (*R*)
2	**4b** [Ar^1=Ph]	18	87	53 (*R*)
3	**4i** [Ar^2=Ph]	4	96	72 (*R*)
4	**4j** [Ar^2=β-Np]	32	73	67 (*R*)
5	**4k** [Ar^2=3,4,5-F_3-C_6H_2]	48	90	60 (*R*)
6	**4c** [Ar^1=3,5-Me_2-C_6H_3]	14	90	80 (*R*)
7	**4d** [Ar^1=3,5-(*t*-Bu)$_2$-C_6H_3]	2	70	60 (*R*)
8	**4e** [Ar^1=3,4,5-F_3-C_6H_2]	22	25	84 (*R*)
9	**4f** [Ar^1=3,5-$(CF_3)_2$-C_6H_3]	29	n.r.	n.d.
10	**4g** [Ar^1=β-Np]	18	85	87 (*R*)
11	**4h** [Ar^1=3,5-Ph_2-C_6H_3]	27	95	92 (*R*)
12	**4l** [Ar^1=3,5-Ph_2-C_6H_3, Ar^2=Ph]	48	81	95 (*R*)
13[e]	**4l** [Ar^1=3,5-Ph_2-C_6H_3, Ar^2=Ph]	16	87	94 (*R*)

[a] Unless otherwise noted, the reaction was carried out with **2** (0.5 mmol) and 1.2 equiv of benzyl bromide in the presence of 1 mol % of **4** in 50% aqueous KOH/toluene (volume ratio=1:3) at 0 °C for the given reaction time under argon atmosphere.
[b] Isolated yield.
[c] Enantiopurity of **3a** was determined by HPLC analysis using a chiral column with hexane/2-propanol as solvent.
[d] Absolute configuration of **3a** was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[10]
[e] Use of $CsOH\cdot H_2O$ (3 equiv) in water (29.2 μL) as a base and the reaction was performed at −15 °C.

Table 2. Catalytic enantioselective phase-transfer alkylation of **2** with conformationally flexible catalyst **4l**[a]



Entry	RX	React. time (h)	% Yield[b]	% ee[c] (config)[d]
1	4-F-$C_6H_4CH_2Br$	36	83	95 (*R*)
2	4-Me-$C_6H_4CH_2Br$	29	83	96 (*R*)
3	2,6-Me_2-$C_6H_3CH_2Br$	64	90	90 (*R*)
4		18	91	94 (*R*)
5		18	92	92 (*R*)
6		19	91	93 (*R*)
7	CH_2=$CHCH_2Br$	16	85	93 (*R*)
8	CH_2=C(Me)CH_2Br	21	85	96 (*R*)
9[e]	EtI	15	61	93 (*R*)

[a] Unless otherwise specified, the reaction was conducted with **2** (0.5 mmol) and 1.2 equiv of RX in the presence of 1 mol % of **4l** in aqueous CsOH/toluene at −15 °C for the given reaction time under argon atmosphere.
[b] Isolated yield.
[c] Enantiopurity of **3** was determined by HPLC analysis using a chiral column with hexane/2-propanol as solvent.
[d] Absolute configuration of **3** was determined by comparison of the HPLC retention time with the literature value or the authentic sample independently synthesized by the reported procedure.[3c,10]
[e] With 5 equiv of alkyl halide.

homochiral (*S*,*S*)-**4** to exert high catalytic and chiral efficiency despite its conformational flexibility; this creates a solid basis for further fine-tuning of **4** by making use of the ample structural modularity of achiral biphenyl subunit. For instance, the catalyst **4l** having 3,3′-bis(3,5-diphenylphenyl)-5,5′-diphenyl-1,1′-biphenyl substructure can be readily assembled and was found to provide even more rigorous stereocontrol in the benzylation of **2** (entry 12). Although the reactivity was sacrificed to certain extent, it was recovered by the use of aqueous CsOH as a basic phase at a lower reaction temperature without detrimental effect on the enantioselectivity (entry 13).

As summarized in Table 2, the asymmetric phase-transfer catalysis of **4l** accommodates a variety of alkyl halides, and the corresponding alkylation products **3** were obtained in good to high chemical yields with excellent enantioselectivities using 1 mol % of the catalyst with stirring for 15–64 h at −15 °C. In detail, a series of benzylic bromides with substituents of different steric and electronic properties were employable, allowing the preparation of structurally diverse phenylalanine analogues (entries 1–4). The effectiveness of **4l** was further demonstrated by using 1-bromomethylnaphthalene and 3-bromomethylbenzothiophene as an electrophilic partner, respectively (entries 5 and 6). Enantiomerically enriched allylglycine derivatives are also accessible (entries 7 and 8), and the reaction with simple alkyl halide such as ethyl iodide appeared feasible (entry 9).

2.3. Elucidation of structure of 4 and its behavior in solution

To analyze the dynamic structural behavior of **4h** and **4l** in solution, a variable-temperature ^{1}H NMR study was conducted in dichloromethane-d_2. The temperature dependence of the ^{1}H NMR signals of benzylic protons of **4h** at low temperature range is shown in Figure 1. The peak broadening at 283–263 K and sharpening to two sets of four benzylic

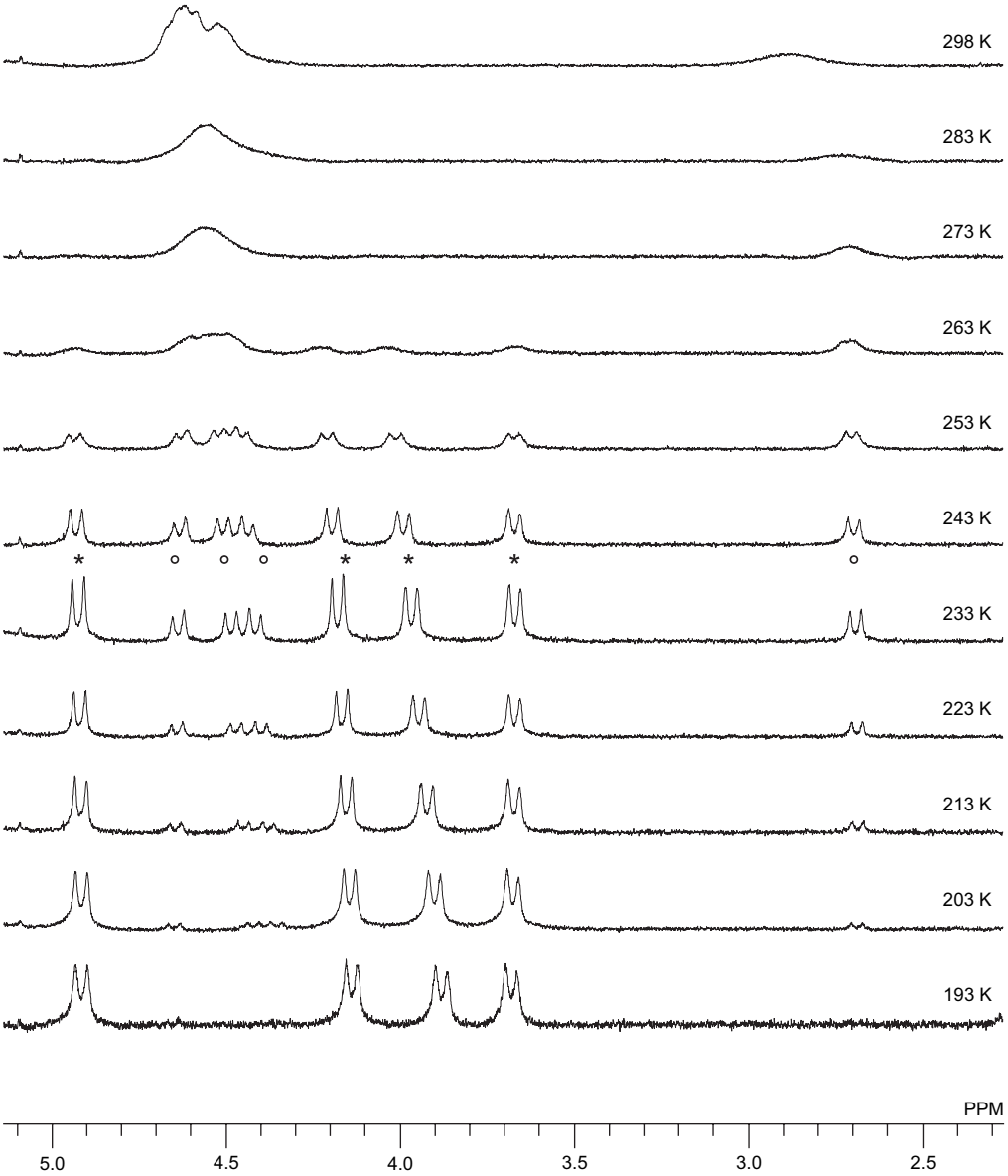


Figure 1. The temperature dependence of the ^{1}H NMR signals of the benzylic protons of homo- (★) and heterochiral (○) conformers of **4h**.[11]

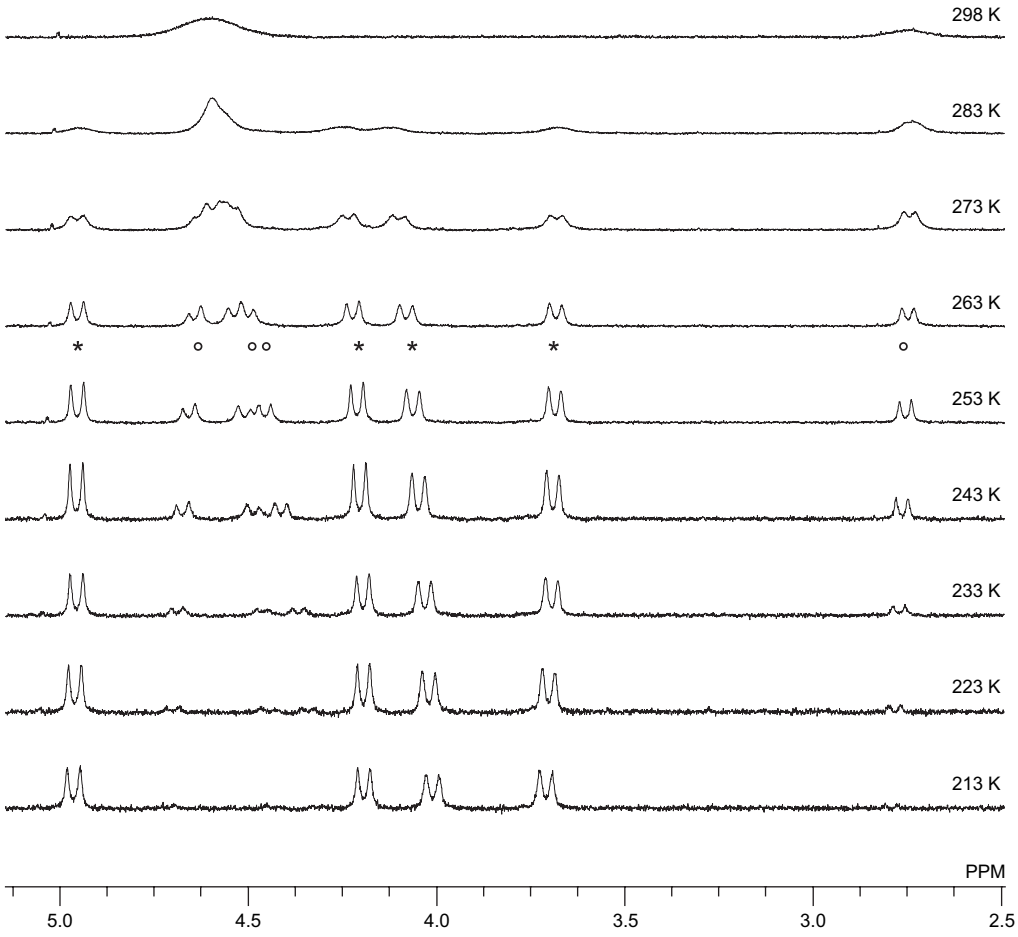
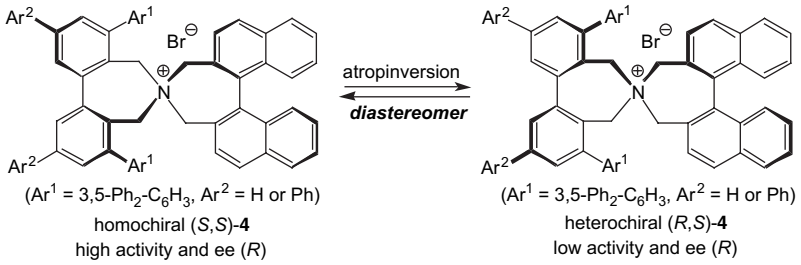


Figure 2. The temperature dependence of the ^{1}H NMR signals of the benzylic protons of homo- (★) and heterochiral (○) conformers of **4l**.[11]

signals (nearly 1:1 ratio) at 243 K clearly indicates that there is a rapid equilibrium between two diastereomeric, homochiral (*S*,*S*)-**4h** and heterochiral (*R*,*S*)-**4h**, and the composition of conformational structures depends on temperature. On the basis of the initial studies with conformationally rigid catalyst of type **1**, the homochiral isomer is assumed to be catalytically more active and, interestingly, the existence ratio of (*S*,*S*)-**4h** was found to decrease as the temperature was increased, being approximately 1:2.8 of (*S*,*S*)-**4h**/(*R*,*S*)-**4h** at 0 °C.[12] Similar tendency was observed in the case of **4l** (Fig. 2), and the stereochemical preference toward the heterochiral isomer at higher temperature (above 25 °C) was also supported by the single crystal X-ray diffraction analysis of **4l** after recrystallization from CH_2Cl_2/hexane at room temperature, uncovering its heterochiral molecular structure (Fig. 3).[13] However, the ratio of (*S*,*S*)-**4l**/(*R*,*S*)-**4l** was revealed to be 1:1.2 at 0 °C and 1:0.68 at −15 °C.[12] The increased existence ratio of homochiral (*S*,*S*)-**4l** around the reaction temperature suggested that the introduction of 5,5′-diphenyl substituents not only extended the attractive aromatic surface but also affected the stereodynamic of **4l**, consequently imparting it with higher enantiocontrolling ability than **4h**.



3. Summary

We have designed and prepared conformationally flexible, *N*-spiro chiral quaternary ammonium bromides **4** incorporating a modular achiral biphenyl structure as a conceptually new chiral phase-transfer catalyst. The concise synthetic route to the appropriately substituted biphenyl subunit has

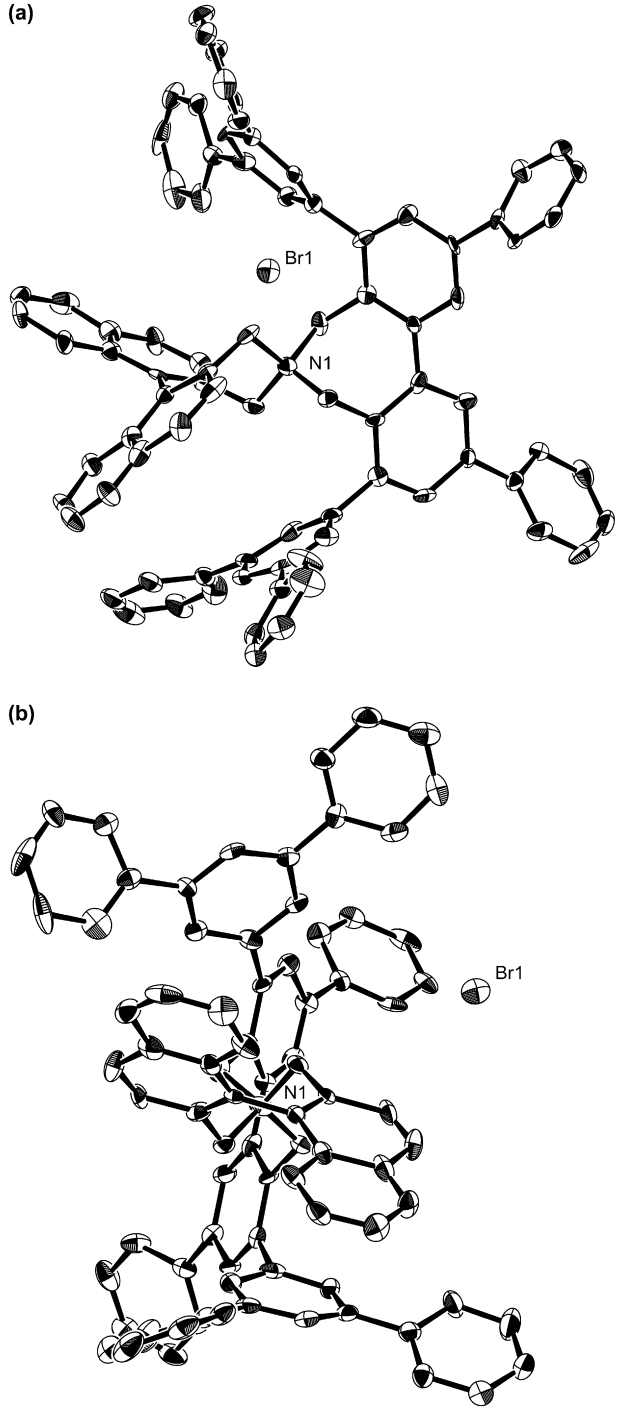


Figure 3. ORTEP diagram of (*S*)-**4l** [(a) top view; (b) side view].

been established by employing the selective *ortho* magnesiation–halogenation as an essential technique. Systematic evaluation of the structure–activity relationship of **4** in the phase-transfer-catalyzed asymmetric benzylation of glycinate Schiff base **2** revealed that **4l** possessing 3,3′-bis(3,5-diphenylphenyl)-5,5′-diphenyl-1,1′-biphenyl substructure displayed a prominent enantiocontrolling ability. Further, the general applicability of the **4l**-catalyzed enantioselective alkylation was demonstrated with representative alkyl halides. The three-dimensional molecular structure of **4l** was unequivocally determined by X-ray crystallographic analysis, and its behavior in solution was investigated by a variable-temperature ^{1}H NMR study, together with the similar stereodynamic of structurally more simple **4h**. This provided a compelling evidence to support that the origin of the high chiral efficiency laid on the considerable difference of catalytic activity between the rapidly equilibrated homo- and heterochiral isomers, and homochiral-**4l** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce the corresponding alkylation product **3** with high enantiomeric excess, while heterochiral-**4l** showed low reactivity and stereoselectivity. Our approach parallels the successful utilization of flexible ligand to magnify the effect of other chiral ligand through coordinative interaction with metal center,[6] and should offer a new yet simple strategy for the molecular design of chiral phase-transfer catalysts.

4. Experimental

4.1. General information

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million from tetramethylsilane as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, hept=heptet, sept=septet, m=multiplet, br=broad), coupling constants (hertz), and assignment. ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using 4.6 mm×25 cm Daicel Chiralcel OD or OD-H. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF workstation, Bruker microTOF, and JMS-HX100. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were determined on a BÜCHI Melting Point B-545 and are uncorrected. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). In experiments requiring dry solvents, ether, and tetrahydrofuran (THF) were purchased from Kanto Chemical Co. Inc. as 'dehydrated'. Toluene was dried over sodium metal. Other simple chemicals were purchased and used as such.

4.2. Representative procedure for catalytic asymmetric alkylation of glycine *tert*-butyl ester benzophenone Shiff base (2) under phase-transfer conditions (Table 1, entry 13)

To a 10 mL two-neck flask containing a Teflon-coated magnetic stirring bar and $CsOH\cdot H_2O$ (265 mg, 1.5 mmol) was introduced water (29.2 μL) with stirring under argon atmosphere. Then, (*S*)-**4l** (5.0 mg, 0.005 mmol) and a solution of glycine *tert*-butyl ester benzophenone Schiff base (**2**; 148 mg, 0.5 mmol) in toluene (3 mL) were added and the mixture was cooled to −15 °C. After 10 min of gentle

stirring, benzyl bromide (73.6 μL, 0.6 mmol) was added dropwise and the reaction mixture was stirred vigorously for 16 h. The resulting mixture was poured into brine and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residual oil was purified by column chromatography on silica gel (EtOAc/hexane=1:12 to 1:6 as eluent) to give **3a**[10] (168 mg, 0.436 mmol; 87% yield, 94% ee) as a colorless oil. The catalyst (*S*)-**4l** can be recovered by further eluting with MeOH/CH_2Cl_2.[14] The enantiomeric excess of **3a** was determined by chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol=100:1, flow rate=0.5 mL min^{-1}, retention time=13.7 min (*R*) and 24.6 min (*S*)).

4.3. Characterization of chiral quaternary ammonium salt (*R*,*S*)-1 (Ar^1=2-naphthyl)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (2H, s, ArH), 8.09 (2H, d, *J*=8.3 Hz, ArH), 7.85 (2H, br, ArH), 7.79–7.75 (4H, m, ArH), 7.70–7.64 (6H, m, ArH), 7.59 (2H, d, *J*=8.7 Hz, ArH), 7.47–7.44 (6H, m, ArH), 7.36–7.30 (6H, m, ArH), 7.26–7.21 (4H, m, ArH), 7.06–7.02 (2H, m, ArH), 6.90 (2H, d, *J*=8.7 Hz, ArH), 4.66 (4H, s, $ArCH_2$), 4.40 (2H, d, *J*=12.7 Hz, $ArCH_2$), 2.60 (2H, d, *J*=12.3 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.4, 136.0, 135.8, 134.2, 133.7, 131.9, 131.1, 130.2, 129.5, 129.1, 128.8, 128.2, 128.0, 127.7, 127.6, 127.5, 127.2, 127.2, 126.9, 126.8, 126.6, 126.5, 126.4, 126.2, 125.9, 124.4, 63.6, 59.5 ppm; IR (KBr) 3647, 3400, 3047, 3008, 2989, 1624, 1589, 1506, 1456, 1351, 1028, 895, 877, 821, 777, 746 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{64}H_{44}N$ (M^+): 826.3476, found: 826.3474; $[\alpha]_D^{28}$ 146.6 (*c* 0.25, $CHCl_3$).

4.4. Representative procedure for the preparation of (*S*)-4a–h and their characterizations

4.4.1. 2,2′-Bis(isopropoxycarbonyl)-1,1′-biphenyl (6). Diphenic acid (1.26 g, 5.0 mmol) was placed in a dry two-neck flask with a stirring bar under argon atmosphere and $SOCl_2$ (5 mL) was introduced at 0 °C. The mixture was refluxed for 4 h and excess $SOCl_2$ was removed under reduced pressure. Then, *i*-PrOH (5 mL) and pyridine (1 mL) were added and the mixture was heated to reflux for 1 h. The resulting solution was washed with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (short-pass, EtOAc/hexane=1:4 as eluent) to give **6** (1.63 g, quant.) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, dd, *J*=1.2, 7.5 Hz, ArH), 7.49 (2H, dt, *J*=1.2, 7.5 Hz, ArH), 7.42 (2H, dt, *J*=1.2, 7.5 Hz, ArH), 7.18 (2H, dd, *J*=1.2, 7.5 Hz, ArH), 4.92 (2H, sept, *J*=6.3 Hz, $CH(CH_3)_2$), 0.99 (6H, d, *J*=6.3 Hz, CH_3), 0.89 (6H, d, *J*=6.3 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 143.1, 130.7, 130.1, 129.9, 129.6, 126.7, 67.8, 21.3, 21.2 ppm; IR (KBr) 2974, 1699, 1599, 1439, 1373, 1350, 1288, 1105, 1049, 916, 770, 710 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{22}O_4Na$ ([M+Na]$^+$): 349.1411, found: 349.1410.

4.4.2. 3,3′-Dibromo-2,2′-bis(isopropoxycarbonyl)-1,1′-biphenyl (7). To a THF solution of $(TMP)_2Mg$ (0.31 M, 2.25 mmol)[8] was added **6** (126 mg, 0.5 mmol) in THF (2 mL) dropwise at 0 °C under argon atmosphere and the mixture was stirred for 3 h at room temperature. After being cooled to −78 °C, Br_2 (264 μL, 5.0 mmol) was added and stirring was continued for 1 h at room temperature. This mixture was then poured into cooled 1 N HCl, washed with saturated Na_2SO_3, and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane=1:20 to 1:10 as eluent) furnished **7** (218 mg, 0.450 mmol, 90%) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, dd, *J*=2.4, 6.7 Hz, ArH), 7.26–7.21 (4H, m, ArH), 4.97 (2H, sept, *J*=6.3 Hz, $CH(CH_3)_2$), 1.18 (6H, s, CH_3), 0.89 (6H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.1, 135.9, 132.1, 129.4, 128.7, 119.1, 69.2, 21.5, 20.9 ppm; IR (KBr) 2980, 1724, 1583, 1551, 1439, 1375, 1286, 1101, 1059, 912, 858, 795, 766 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{20}Br_2O_4Na$ ([M+Na]$^+$): 504.9623, found: 504.9621.

4.4.3. 2,2′-Bis(isopropoxycarbonyl)-3,3′-bis(3,5-diphenylphenyl)-1,1′-biphenyl (8h). A mixture of **7** (484 mg, 1.0 mmol), 3,5-diphenylphenylboronic acid (658 mg, 2.4 mmol), $Pd(OAc)_2$ (11.6 mg, 0.05 mmol), PPh_3 (40.1 mg, 0.15 mmol), and K_2CO_3 (419 mg, 3.0 mmol) in DMF (5 mL) was degassed and backfilled with argon. This mixture was heated at 90 °C for 8 h. After cooling to room temperature, the resulting mixture was poured into 1 N HCl and extracted with Et_2O. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane=1:20 to 1:10 as eluent) afforded **8h** (744 mg, 0.95 mmol, 95%) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, t, *J*=2.0 Hz, ArH), 7.68–7.64 (12H, m, ArH), 7.51–7.34 (18H, m, ArH), 4.75 (2H, sept, *J*=6.3 Hz, $CH(CH_3)_2$), 0.86 (6H, d, *J*=5.9 Hz, CH_3), 0.67 (6H, d, *J*=5.9 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 141.7, 141.5, 140.7, 139.9, 138.3, 133.9, 129.1, 129.0, 128.9, 128.4, 127.4, 127.2, 126.3, 125.0, 68.4, 21.4, 21.0 ppm; IR (KBr) 2976, 1722, 1595, 1574, 1499, 1450, 1412, 1373, 1265, 1103, 1065, 883, 760, 700 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{56}H_{46}O_4Na$ ([M+Na]$^+$): 805.3273, found: 805.3288.

4.4.4. 2,2′-Bis(bromomethyl)-3,3′-bis(3,5-diphenylphenyl)-1,1′-biphenyl (9h). To a suspension of $LiAlH_4$ (142 mg, 3.0 mmol) in THF (3 mL) was added **8h** (783 mg, 1.0 mmol) portionwise at 0 °C and the reaction mixture was stirred for 4 h at room temperature. Then, ether (3 mL) was added and the reaction was quenched by the sequential treatment with H_2O (142 μL), 15% NaOH (142 μL), and H_2O (284 μL). After 1 h of additional stirring, this mixture was filtered through a pad of Celite and the filtrate was concentrated. This crude 3,3′-bis(3,5-diphenylphenyl)-2,2′-bis(hydroxymethyl)-1,1′-biphenyl was used for the subsequent bromination without further purification. A THF (ca. 3 mL) solution of 3,3′-bis(3,5-diphenylphenyl)-2,2′-bis(hydroxymethyl)-1,1′-biphenyl (1.0 mmol) was cooled to 0 °C and PBr_3 (52.8 μL, 0.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and poured into H_2O. Extractive workup was performed with EtOAc and the combined extracts were dried over Na_2SO_4. Removal of volatiles and purification of the residue by column chromatography on silica gel (CH_2Cl_2/hexane=1:10 as eluent) gave **9h** (605 mg, 0.76 mmol, 76%

in two steps) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, t, J=1.6 Hz, ArH), 7.75–7.73 (12H, m, ArH), 7.50–7.43 (14H, m, ArH), 7.40–7.36 (4H, m, ArH), 4.43 (2H, d, J=9.7 Hz, $ArCH_2$), 4.30 (2H, d, J=9.7 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.5, 141.3, 140.9, 140.6, 133.2, 130.4, 129.8, 128.8, 128.0, 127.5, 127.2, 126.8, 125.0, 31.3 ppm; IR (KBr) 3038, 1593, 1580, 1497, 1410, 1217, 1030, 885, 758, 700, 615, 538 cm^{-1}. Fragment peaks could be detected; MS (APCI) *m/z* 867.787 (M^+).

4.4.5. Chiral quaternary ammonium salt (*S*)-4h (Ar^1= 3,5-diphenylphenyl). A mixture of **9h** (398 mg, 0.5 mmol), chiral *secondary* amine **5** (147 mg, 0.5 mmol), K_2CO_3 (139 mg, 1.0 mmol) in CH_3CN (3 mL) was refluxed for 6 h. This mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2=1:30 to 1:10 as eluent) to give **4h** (440 mg, 0.435 mmol, 87%) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.08 (44H, br m, ArH), 4.83 (4H, d, J=13.1 Hz, $ArCH_2$), 4.57 (2H, d, J=13.5 Hz, $ArCH_2$), 2.78 (2H, br, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.6, 139.8, 139.6, 136.2, 133.7, 131.0, 130.7, 130.5, 130.0, 129.7, 129.2, 128.6, 128.4, 127.6, 127.0, 127.0, 126.9, 126.8, 126.6, 126.2, 124.8, 124.6, 63.3, 58.1 ppm; IR (KBr) 3399, 3055, 2959, 1593, 1574, 1499, 1454, 1414, 1358, 883, 825, 760, 696 cm^{-1}; HRMS (FAB) calcd for $C_{72}H_{62}N$ (M^+): 930.4103, found: 930.4101; $[\alpha]_D^{24}$ 55.0 (*c* 0.25, $CHCl_3$); mp 243–245 °C (dec).

4.4.6. Chiral quaternary ammonium salt (*S*)-4a (Ar^1=H). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (2H, d, J=8.3 Hz, ArH), 8.08–8.04 (4H, m, ArH), 7.88 (2H, br d, J=6.3 Hz, ArH), 7.74–7.68 (6H, m, ArH), 7.64–7.60 (2H, m, ArH), 7.44 (2H, d, J=8.7 Hz, ArH), 7.39–7.36 (2H, m, ArH), 4.75 (2H, d, J=13.1 Hz, $ArCH_2$), 4.32 (2H, d, J=13.1 Hz, $ArCH_2$), 3.99 (2H, d, J=13.5 Hz, $ArCH_2$), 3.93 (2H, d, J=13.1 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 136.7, 134.4, 132.0, 131.8, 131.3, 130.8, 129.7, 129.3, 128.6, 127.7, 127.6, 127.5, 127.3, 126.3, 125.5, 61.4, 60.9 ppm; IR (KBr) 3638, 3385, 3053, 2359, 1622, 1456, 1354, 1200, 1028, 878, 854, 818, 758 cm^{-1}; HRMS (FAB) calcd for $C_{36}H_{28}N$ (M^+): 474.2223, found: 474.2238; $[\alpha]_D^{28}$ −110.2 (*c* 0.25, $CHCl_3$).

4.4.7. Chiral quaternary ammonium salt (*S*)-4b (Ar^1= Ph). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.04 (28H, br, ArH), 4.61 (4H, br, $ArCH_2$), 4.41 (2H, d, J=13.3 Hz, $ArCH_2$), 2.71 (2H, br, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.5, 138.8, 136.2, 133.9, 130.9, 130.6, 129.5, 129.1, 128.3, 127.5, 127.1, 127.0, 126.7, 126.0, 124.1, 63.1, 57.7 ppm; IR (thin film) 3356, 3055, 2955, 2891, 2178, 1595, 1508, 1464, 1360, 1250, 1196, 1030, 922, 870, 839, 826, 797, 760, 727, 706 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{48}H_{36}N$ (M^+): 626.2842, found: 626.2842; $[\alpha]_D^{24}$ 213.9 (*c* 0.25, $CHCl_3$); mp 298–299 °C (dec).

4.4.8. Chiral quaternary ammonium salt (*S*)-4c (Ar^1= 3,5-dimethylphenyl). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–6.49 (24H, br, ArH), 4.56–4.45 (6H, m, $ArCH_2$), 2.82 (2H, br, $ArCH_2$), 2.04 (12H, br, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.6, 138.8, 138.3, 136.4, 134.1, 131.0, 130.8, 129.5, 129.2, 128.9, 128.4, 127.4, 127.3, 127.2, 126.9, 126.2, 124.1, 63.2, 57.8 ppm; IR (thin film) 3335, 3053, 3007, 2949, 2916, 2176, 1599, 1578, 1508, 1456, 1379, 1360, 1304, 1250, 1225, 1200, 1030, 922, 908, 854, 837, 822, 793, 748, 727 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{52}H_{44}N$ (M^+): 682.3464, found: 682.3468; $[\alpha]_D^{24}$ 190.0 (*c* 0.25, $CHCl_3$); mp 280–283 °C (dec).

4.4.9. Chiral quaternary ammonium salt (*S*)-4d (Ar^1= 3,5-di-*tert*-butylphenyl). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–6.79 (24H, m, ArH), 4.68 (2H, d, J=12.8 Hz, $ArCH_2$), 4.53 (2H, d, J=13.2 Hz, $ArCH_2$), 4.15 (2H, d, J=12.4 Hz, $ArCH_2$), 2.58 (2H, d, J=12.8 Hz, $ArCH_2$), 0.98 (18H, s, CH_3), 0.86 (18H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 144.3, 142.0, 137.8, 135.8, 133.6, 130.5, 130.3, 129.8, 128.3, 128.1, 127.0, 126.5, 126.3, 125.7, 124.6, 122.2, 120.6, 63.5, 58.5 ppm; IR (thin film) 3337, 3055, 2961, 2903, 2868, 2174, 1707, 1593, 1578, 1464, 1427, 1395, 1362, 1250, 1223, 1200, 1032, 924, 907, 880, 839, 826, 787, 750, 723 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{64}H_{68}N$ (M^+): 850.5345, found: 850.5346; $[\alpha]_D^{22}$ 101.5 (*c* 0.25, $CHCl_3$); mp 354–356 °C (dec).

4.4.10. Chiral quaternary ammonium salt (*S*)-4e (Ar^1= 3,4,5-trifluorophenyl). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.99 (6H, m, ArH), 7.74–7.73 (4H, m, ArH), 7.60 (2H, t, J=7.4 Hz, ArH), 7.41–7.29 (6H, m, ArH), 7.26 (2H, s, ArH), 7.01 (2H, br, ArH), 5.04 (2H, d, J=11.8 Hz, $ArCH_2$), 4.85 (2H, d, J=13.3 Hz, $ArCH_2$), 4.32 (2H, d, J=13.3 Hz, $ArCH_2$), 2.89 (2H, d, J=12.6 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (d, J_{C-F}=257 Hz), 142.4, 140.5, 137.9, 136.7, 134.8 (m), 134.2, 131.4, 131.1, 130.7, 130.2, 129.9, 128.7, 127.8, 127.4, 127.0, 126.1, 124.3, 114.0, 63.7, 58.3 ppm; IR (thin film) 3055, 3011, 2955, 2926, 2893, 1614, 1526, 1422, 1362, 1281, 1246, 1209, 1146, 1043, 922, 908, 891, 866, 837, 822, 795, 764, 748, 731 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{48}H_{30}NF_6$ (M^+): 734.2269, found: 734.2277; $[\alpha]_D^{24}$ 147.3 (*c* 0.25, $CHCl_3$); mp 293–295 °C (dec).

4.4.11. Chiral quaternary ammonium salt (*S*)-4f [Ar^1= 3,5-bis(trifluoromethyl)phenyl]. White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–7.23 (24H, m, ArH), 5.27 (2H, d, J=12.3 Hz, $ArCH_2$), 4.96 (2H, d, J=13.5 Hz, $ArCH_2$), 4.07 (2H, d, J=13.5 Hz, $ArCH_2$), 2.52 (2H, d, J=12.3 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.4, 140.3, 136.7, 134.1, 131.5, 131.0, 130.6, 130.6, 129.7, 128.4, 127.4, 127.0, 126.9, 126.7, 126.0, 124.5, 122.5 (q, $^1J_{C-F}$=273 Hz), 121.1 (m), 63.1, 58.0 ppm; IR (thin film) 3057, 3011, 2986, 2953, 2891, 1618, 1508, 1458, 1377, 1277, 1173, 1132, 1051, 1030, 922, 903, 870, 847, 835, 820, 791, 731, 714 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{52}H_{32}NF_{12}$ (M^+): 898.2303, found: 898.2338; $[\alpha]_D^{24}$ 116.4 (*c* 0.25, $CHCl_3$); mp 316–318 °C (dec).

4.4.12. Chiral quaternary ammonium salt (*S*)-4g (Ar^1= 2-naphthyl). White powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.20 (18H, br m, ArH), 7.79 (4H, t, J=7.9 Hz, ArH), 7.34 (4H, t, J=7.1 Hz, ArH), 7.05 (2H, t, J=7.5 Hz,

ArH), 6.90 (2H, d, J=8.7 Hz, ArH), 4.83 (2H, br, $ArCH_2$), 4.56–7.52 (4H, br, $ArCH_2$), 2.98 (2H, br, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.7, 136.2, 135.8, 133.5, 132.8, 132.2, 131.7, 130.9, 130.3, 129.3, 129.0, 128.8, 128.6, 127.9, 127.5, 127.2, 126.8, 126.8, 126.7, 126.5, 126.4, 126.3, 125.5, 124.0, 63.0, 57.6 ppm; IR (thin film) 3383, 3051, 1622, 1595, 1504, 1456, 1357, 1197, 864, 821, 797, 752 cm^{-1}; HRMS (FAB) calcd for $C_{56}H_{40}N$ (M^+): 726.3163, found: 726.3167; $[\alpha]_D^{22}$ 174.2 (c 0.25, $CHCl_3$); mp 202–203 °C (dec).

4.5. Typical procedure for the synthesis of (*S*)-4i–k and their characterizations

4.5.1. 4-Phenylbenzoic acid isopropyl ester (10a). The title compound was prepared from 4-phenylbenzoic acid, and the esterification was conducted as described for the synthesis of **6** [chromatography on silica gel (short-pass, EtOAc/hexane=1:4 as eluent), colorless oil, quant.]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J=8.3 Hz, ArH), 7.64 (2H, d, J=7.9 Hz, ArH), 7.60 (2H, d, J=7.5 Hz, ArH), 7.46–7.43 (2H, m, ArH), 7.39–7.35 (1H, m, ArH), 5.28 (1H, sept, J=6.3 Hz, CH(CH_3)$_2$), 1.38 (6H, d, J=6.3 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 145.2, 139.9, 129.9, 129.5, 128.7, 127.9, 127.1, 126.8, 68.3, 22.0 ppm; IR (neat) 2980, 1713, 1611, 1478, 1404, 1279, 1178, 1101, 1009, 920, 858, 748, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{16}O_2Na$ ([M+Na]$^+$): 263.1041, found: 263.1043.

4.5.2. 2-Iodo-4-phenylbenzoic acid isopropyl ester (11a). To a THF solution of $(TMP)_2Mg$ (0.31 M, 12.5 mmol)[8] was added **10a** (1.20 g, 5.0 mmol) in THF (20 mL) dropwise at 0 °C under argon atmosphere and the mixture was stirred for 3 h at room temperature. After being cooled to −78 °C, a THF (5 mL) solution of I_2 (7.63 g, 30.0 mmol) was added and stirring was continued for 1 h at room temperature. This mixture was then poured into cooled 1 N HCl, washed with saturated Na_2SO_3, and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane=1:20 to 1:10 as eluent) afforded **11a** (1.54 g, 4.20 mmol, 84%) as an yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, d, J=2.0 Hz, ArH), 7.85 (1H, d, J=7.9 Hz, ArH), 7.60 (1H, dd, J=2.0, 7.9 Hz, ArH), 7.58–7.55 (2H, m, ArH), 7.48–7.44 (2H, m, ArH), 7.42–7.38 (1H, m, ArH), 5.29 (1H, sept, J=6.3 Hz, CH(CH_3)$_2$), 1.42 (6H, d, J=6.3 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 145.1, 139.6, 138.2, 133.8, 130.9, 128.8, 128.3, 127.0, 126.3, 94.5, 69.4, 21.9 ppm; IR (neat) 2980, 1720, 1593, 1468, 1373, 1285, 1250, 1103, 1015, 756, 693 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}O_2INa$ ([M+Na]$^+$): 389.0006, found: 389.0009.

4.5.3. 2,2′-Bis(isopropoxycarbonyl)-5,5′-diphenyl-1,1′-biphenyl (12a). The solution of **11a** (1.46 g, 4.0 mmol) in dry DMF (4 mL) was added activated Cu (2.0 g) and the mixture was refluxed for 3 days. After cooling to room temperature, the resulting mixture was filtered through a pad of Celite to remove Cu. This filtrate was washed with 1 N HCl and brine, and concentrated. Purification of the crude product by column chromatography on silica gel (EtOAc/hexane=1:20 as eluent) furnished **12a** (746 mg, 1.56 mmol, 78%) as a white powder; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (2H, d, J=7.9 Hz, ArH), 7.67 (2H, dd, J=1.6, 7.9 Hz, ArH), 7.64–7.61 (4H, m, ArH), 7.48 (2H, d, J=1.6 Hz, ArH), 7.45–7.42 (4H, m, ArH), 7.38–7.34 (2H, m, ArH), 4.95 (2H, sept, J=6.3 Hz, CH(CH_3)$_2$), 1.00 (6H, d, J=2.4 Hz, CH_3), 0.89 (6H, d, J=2.4 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.9, 143.7, 139.7, 130.6, 129.0, 128.8, 128.7, 127.9, 127.1, 125.4, 68.0, 21.5, 21.4 ppm; IR (KBr) 2982, 1695, 1604, 1452, 1383, 1288, 1148, 1105, 916, 851, 760, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{32}H_{30}O_4Na$ ([M+Na]$^+$): 501.2037, found: 501.2036.

4.5.4. 2,2′-Bis(bromomethyl)-5,5′-diphenyl-1,1′-biphenyl (13a). The title compound was obtained as described for the synthesis of **9h**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (8H, m, ArH), 7.59 (2H, d, J=1.7 Hz, ArH), 7.44 (4H, t, J=7.5 Hz, ArH), 7.36 (2H, t, J=7.5 Hz, ArH), 4.46 (2H, d, J=10.2 Hz, CH_2), 4.30 (2H, d, J=9.9 Hz, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.9, 139.8, 131.2, 128.9, 128.8, 127.8, 127.3, 127.2, 31.9 ppm; IR (thin film) 3057, 3028, 2972, 2924, 2853, 1601, 1564, 1477, 1437, 1379, 1223, 1204, 903, 864, 837, 820, 756, 733 cm^{-1}. Fragment peaks could only be detected; MS (APCI) m/z 411.331 (M^+).

4.5.5. Chiral quaternary ammonium salt (*S*)-4i (Ar^2= phenyl). White powder; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (2H, d, J=8.5 Hz, ArH), 8.10 (2H, d, J=8.5 Hz, ArH), 8.09 (2H, d, J=8.2 Hz, ArH), 8.03–7.92 (4H, m, ArH), 7.94 (2H, s, ArH), 7.71–7.69 (4H, m, ArH), 7.65–7.61 (2H, m, ArH), 7.52–7.37 (10H, m, ArH), 4.77 (2H, d, J=13.3 Hz, $ArCH_2$), 4.43 (2H, d, J=13.3 Hz, $ArCH_2$), 4.04 (4H, t, d, J=13.9 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.4, 139.4, 136.9, 134.6, 132.8, 131.5, 131.0, 129.1, 128.8, 128.5, 128.4, 128.1, 127.9, 127.7, 127.5, 127.4, 125.7, 125.4, 61.4, 60.6 ppm; IR (thin film) 3055, 3030, 2955, 2924, 2853, 2158, 1730, 1597, 1558, 1508, 1485, 1454, 1356, 1261, 1157, 1028, 1016, 923, 889, 864, 824, 799, 760, 725 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{48}H_{36}N$ (M^+): 626.2855, found: 626.2842; $[\alpha]_D^{26}$ −208.0 (c 0.25, $CHCl_3$); mp 323–326 °C (dec).

4.5.6. Chiral quaternary ammonium salt (*S*)-4j (Ar^2= 2-naphthyl). White powder; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (2H, d, J=8.2 Hz, ArH), 8.19 (2H, s, ArH), 8.14–8.07 (10H, m, ArH), 7.98 (2H, d, J=8.7 Hz, ArH), 7.96–7.93 (2H, m, ArH), 7.91–7.88 (2H, m, ArH), 7.84 (2H, dd, J=1.7, 8.5 Hz, ArH), 7.64 (2H, t, J=7.0 Hz, ArH), 7.56–7.52 (4H, m, ArH), 7.48 (2H, d, J=8.5 Hz, ArH), 7.40 (2H, t, J=7.6 Hz, ArH), 4.83 (2H, d, J=13.1 Hz, $ArCH_2$), 4.47 (2H, d, J=13.5 Hz, $ArCH_2$), 4.16 (2H, d, J=13.1 Hz, $ArCH_2$), 4.05 (2H, d, J=12.1 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.6, 136.9, 136.7, 134.6, 133.6, 133.1, 132.9, 131.5, 131.0, 128.9, 128.8, 128.8, 128.4, 127.9, 127.7, 127.7, 127.5, 126.7, 126.6, 126.6, 125.7, 125.4, 125.3, 61.5, 60.6 ppm; IR (thin film) 3313, 3196, 3053, 2172, 1609, 1597, 1558, 1506, 1497, 1456, 1395, 1348, 1192, 1028, 1018, 924, 908, 872, 816, 750, 727 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{56}H_{40}N$ (M^+): 726.3155, found: 726.3155; $[\alpha]_D^{26}$ −127.9 (c 0.25, $CHCl_3$); mp 329–330 °C (dec).

4.5.7. Chiral quaternary ammonium salt (*S*)-4k (Ar^2= 3,4,5-trifluorophenyl). White powder; ^1H NMR (400 MHz,

$CDCl_3$) δ 8.29 (2H, d, J=8.0 Hz, ArH), 8.10–8.06 (4H, m, ArH), 8.00 (2H, br, ArH), 7.87–7.82 (4H, m, ArH), 7.64 (2H, t, J=7.3 Hz, ArH), 7.47–7.38 (4H, m, ArH), 7.33 (3H, t, J=7.1 Hz, ArH), 7.23 (1H, d, J=6.5 Hz, ArH), 4.92–4.85 (2H, m, $ArCH_2$), 4.42 (2H, br, $ArCH_2$), 4.32–4.16 (2H, m, $ArCH_2$), 4.00 (2H, br, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 152.8, 152.8, 152.7, 151.5 (ddd, J_{C-F}=4.1, 9.8, 51.6 Hz), 150.3, 150.3, 150.2, 150.2, 142.0, 141.4, 139.9 (dt, J_{C-F}=15.5, 15.5, 254 Hz), 136.9, 135.6 (dd, J_{C-F}=7.4, 12.3 Hz), 134.6, 133.2, 131.5, 131.0, 128.8, 128.6, 128.0, 127.9, 127.7, 127.7, 127.6, 126.6, 125.5, 111.7 (m), 61.4, 60.1 ppm; IR (thin film) 3352, 3049, 2986, 2932, 2178, 1618, 1595, 1568, 1499, 1443, 1393, 1360, 1296, 1242, 1119, 989, 908, 874, 822, 764, 752, 727 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{48}H_{30}NF_6$: 734.2274 (M^+), found: 734.2277 (M^+); $[\alpha]_D^{22}$ −210.3 (*c* 0.25, $CHCl_3$); mp 308–310 °C (dec).

4.6. Synthesis of (*S*)-4l

Chiral quaternary ammonium salt (*S*)-**4l** was prepared from **12a** in a manner similar to the preparation of (*S*)-**4b–h** from **6**. Characterizations of each intermediate and (*S*)-**4l** are as follows.

4.6.1. 3,3′-Dibromo-2,2′-bis(isopropoxycarbonyl)-5,5′-diphenyl-1,1′-biphenyl (14). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J=1.6 Hz, ArH), 7.58–7.54 (6H, m, ArH), 7.46–7.44 (4H, m, ArH), 7.41–7.37 (2H, m, ArH), 5.00 (2H, sept, J=6.3 Hz, $CH(CH_3)_2$), 1.12 (6H, d, J=1.6 Hz, CH_3), 0.89 (6H, d, J=1.6 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 142.7, 138.7, 138.0, 134.3, 130.4, 128.8, 128.3, 127.4, 126.9, 119.7, 69.3, 21.5, 21.0 ppm; IR (KBr) 2980, 1722, 1595, 1537, 1499, 1373, 1281, 1177, 1141, 1101, 1043, 916, 883, 758, 696 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{32}H_{28}O_4Br_2Na$ ($[M+Na]^+$): 657.0264, found: 657.0247.

4.6.2. 2,2′-Bis(isopropoxycarbonyl)-3,3′-bis(3,5-diphenylphenyl)-5,5′-diphenyl-1,1′-biphenyl (15). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, s, ArH), 7.75 (2H, s, ArH), 7.71–7.65 (18H, m, ArH), 7.48–7.33 (18H, m, ArH), 4.76 (2H, sept, J=6.3 Hz, $CH(CH_3)_2$), 0.82 (6H, d, J=6.3 Hz, CH_3), 0.68 (6H, d, J=6.3 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 141.6, 141.4, 141.3, 140.6, 140.6, 139.4, 138.9, 132.5, 128.7, 128.6, 127.7, 127.7, 127.6, 127.5, 127.3, 127.1, 127.0, 126.2, 125.1, 68.4, 21.2, 20.9 ppm; IR (KBr) 2983, 1720, 1593, 1497, 1450, 1387, 1277, 1101, 1078, 881, 760, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{68}H_{54}O_4Na$ ($[M+Na]^+$): 957.3948, found: 957.3914.

4.6.3. 2,2′-Bis(bromomethyl)-3,3′-bis(3,5-diphenylphenyl)-5,5′-diphenyl-1,1′-biphenyl (16). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, s, ArH), 7.83 (4H, s, ArH), 7.79–7.71 (16H, m, ArH), 7.50–7.34 (18H, m, ArH), 4.54 (2H, d, J=9.7 Hz, $ArCH_2$), 4.40 (2H, d, J=9.7 Hz, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 141.6, 141.4, 141.3, 140.6, 139.5, 132.1, 129.0, 128.8, 128.8, 128.4, 127.8, 127.5, 127.3, 127.1, 126.8, 125.2, 31.3 ppm; IR (KBr) 3058, 3032, 1592, 1496, 1448, 1411, 1389, 1217, 1075, 1028, 881, 759, 696 cm^{-1}. Fragment peaks could only be detected; MS (APCI) *m/z* 867.787 (M^+).

4.6.4. Chiral quaternary ammonium salt (*S*)-4l (Ar^1=3,5-diphenylphenyl, Ar^2=Ph). White powder; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.10 (52H, br m, ArH), 4.96 (2H, d, J=13.5 Hz, $ArCH_2$), 4.85 (2H, br, $ArCH_2$), 4.65 (2H, d, J=13.1 Hz, $ArCH_2$), 2.77 (2H, br, $ArCH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.6, 139.5, 136.1, 133.6, 130.4, 129.6, 128.8, 128.5, 128.2, 128.1, 127.8, 127.6, 127.4, 126.9, 126.7, 126.5, 63.3, 58.0 ppm; IR (KBr) 3370, 3057, 3033, 1593, 1497, 1456, 1383, 1354, 1028, 881, 819, 760, 698 cm^{-1}; HRMS (FAB) calcd for $C_{84}H_{60}N$: 1082.4729 (M^+), found: 1082.4713 (M^+); $[\alpha]_D^{25}$ 41.2 (*c* 0.25, $CHCl_3$); mp 303–306 °C (dec).

4.7. X-ray structure determination of chiral quaternary ammonium salt (*S*)-4l

The single crystal of (*S*)-**4l** (colorless needle) was obtained by recrystallization from CH_2Cl_2/hexane solvent system and was mounted on a CryoLoop (Hampton Research Co. Ltd). Data of X-ray diffraction were collected by a Rigaku RAXIS-RAPID Imaging Plate two-dimensional area detector using graphite-monochromated Mo Kα radiation (λ= 0.71069 Å) to a maximum 2θ value of 55°. All of the crystallographic calculations were performed using teXsan software package of the Molecular Structure Corp. The crystal structure was solved by the direct methods and refined by the full-matrix least squares using SIR-97. All non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. The crystallographic data were summarized in the following table.

Experimental details			
Empirical formula	$C_{87}H_{66}BrNCl_6$	T, °C	−150.0
Formula weight	1418.11	μ (Mo Kα), cm^{-1}	8.75
Crystal system	Monoclinic	No. of reflns measrd	30,354
Space group	$P2_1$ (#4)	No. of reflns obsd	8194
a, Å	12.8560 (6)	No. of variable	856
b, Å	18.0233 (8)	$R1$	0.048
c, Å	15.0569 (9)	wR	0.123
V, Å^3	3463.9 (3)	Goodness of fit	1.20
Z	2	Max shift/error in final cycle	0.002
D_{calcd}, g cm^{-3}	1.360		

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Domino intramolecular enyne metathesis/cross metathesis approach to the xanthanolides. Enantioselective synthesis of (+)-8-*epi*-xanthatin

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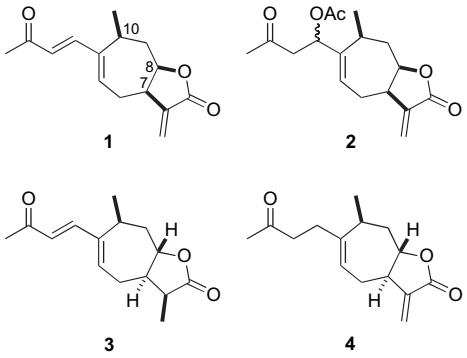
Abstract—The first total synthesis of (+)-8-*epi*-xanthatin (**1**) has been achieved in 14 steps starting from the commercially available ester **24**, which was converted into aldehyde **23** in six steps. An enantioselective aldol reaction of **23** gave **30**, which was transformed into triflate **22** in four steps, setting the stage for a palladium-catalyzed carbonylation reaction to form acrylate **34**. Compound **34** was then subjected to a deprotection/lactonization sequence to furnish enyne **21**, which underwent a domino enyne ring-closing metathesis/cross metathesis process to form a seven-membered carbocycle and (*E*)-conjugated dienone, thereby completing the synthesis of **1**. This domino ruthenium-catalyzed metathesis reaction thus serves as an efficient method to construct the core of xanthanolide and other sesquiterpene lactones.

1. Introduction

The xanthanolide sesquiterpene lactones are isolated primarily from the genus *Xanthium* (family Compositae). The phytochemical composition of this genus is quite homogeneous, and xanthanolides are isolated from every species.[1] The xanthanolides can be divided into two structural classes depending upon the stereochemistry at C(8), although both are characterized by a five-membered γ-butyrolactone that is fused to a seven-membered carbocycle. The xanthumin class is exemplified by (+)-8-*epi*-xanthatin (**1**) and xanthumin (**2**), which comprise a *cis*-fused γ-butyrolactone, whereas (−)-dihydroxanthatin (**3**) and 8-*epi*-tomentosin (**4**) are representative of the xanthinin class and incorporate a *trans*-fused lactone. 8-*epi*-Xanthatin has not only been isolated from various species in the genus *Xanthium*,[1c,2] but it has also been obtained by elimination of acetic acid from **2**.[3]

The structures of numerous xanthanolides are well documented, and many, including **1**, exhibit interesting biological profiles. For example, xanthanolides **1** and **2** have been shown to halt the larval growth of *Drosophila melanogaster* (fruit fly) at doses as small as 1.3 mg of **1** or **2** in 2 g of growth medium.[2b] Compounds **1** and **2** also display antimalarial activity against the chloroquine resistant *Plasmodium falciparum* strain K1 with IC_{50} values of 125 and 31 μg/mL, respectively.[4] More recently, **1** has been shown to inhibit the in vitro proliferation of several cultured human tumor cell lines, including A-549 (lung adenocarcinoma), SK-OV-3 (ovarian adenocarcinoma), SK-MEL-2 (malignant melanoma), XF-498 (central nervous system carcinoma), and HCT-15 (colon adenocarcinoma) with ED_{50} values ranging between 0.2 and 1.5 μg/mL (IC_{50} values ranging between 0.8 and 6.1 μM).[5] Because **4** was found to be inactive toward these tumor cell lines, it is apparent that the α-methylene-γ-butyrolactone and the conjugated enone functionalities contribute to cytotoxicity.[5a,6] In conjunction with these tumor inhibition studies, **1** was found to inhibit the in vitro farnesylation of human lamin-B by farnesyltransferase in a dose-dependent manner (IC_{50}=64 μM).[5b]



Keywords: Cross metathesis; Ring-closing metathesis; Enantioselective; Domino reactions.
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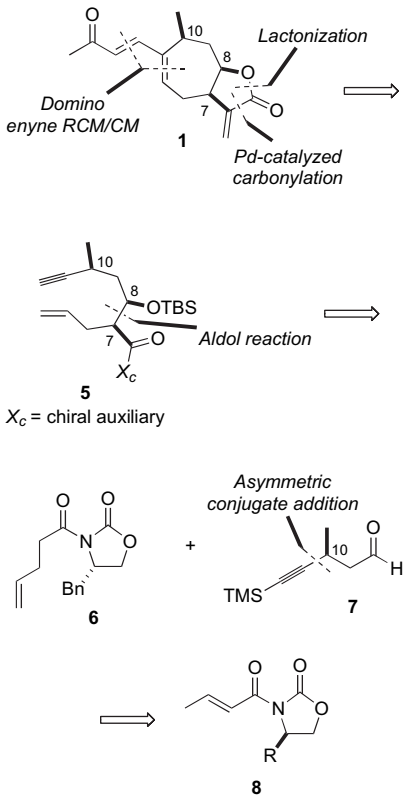
Despite their promising biological activities and interesting structures, there have been few accounts of synthetic efforts directed toward the xanthanolide core.[7] In the first reported total synthesis of a xanthanolide, Morken utilized a stereoselective Oshima–Utimoto reaction[8] and sequential ruthenium-catalyzed metathesis reactions to synthesize **3**.[9] Our contemporaneous interest in 8-*epi*-xanthatin arose as a result of our ongoing efforts to expand the scope of ruthenium-catalyzed ring-closing metathesis (RCM) reactions in the context of natural product total synthesis. We have recently applied RCM cyclizations to the syntheses of a number of complex targets including dihydrocorynantheol[10] as well as the anticancer alkaloids manzamine A,[11] FR900482,[12] and (−)-peduncularine[13] together with the potent nicotinic acetylcholine receptor (+)-anatoxin-a.[14] In the context of these studies, we envisioned that an attractive strategy for constructing the xanthanolide core and the (*E*)-conjugated dienone present in many of the members of this class of natural products might feature a domino enyne RCM/cross metathesis (CM) process. Despite the extensive use of enyne RCM reactions in organic synthesis,[15] there are few applications of this reaction coupled with a subsequent CM in a domino sequence.[16] Coupled with the biological activity profiles of the xanthanolides and a lack of synthetic approaches for their construction, we undertook the total synthesis of (+)-8-*epi*-xanthatin (**1**), the details of which we report in this account.[17]



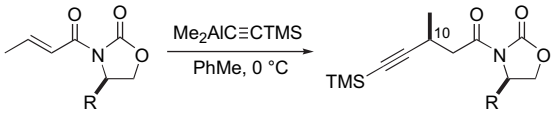
Scheme 1.

2. Results and discussion

2.1. First generation approach

In our first approach to **1**, we targeted enyne **5** as a versatile gateway because it contains the requisite absolute stereochemistry at C(7)–C(8) and C(10) as well as the appropriate functional handles for completing the synthesis (Scheme 1). This advanced intermediate would allow for the construction of the seven-membered cycloheptene ring and (*E*)-conjugated dienone moieties via a domino enyne RCM/CM sequence prior to installing the reactive α-methylene-γ-butyrolactone functionality. We envisaged the assembly of enyne **5** via an asymmetric aldol reaction[18] between the known oxazolidinone **6**[19] and the functionalized aldehyde **7**, which in turn would be assembled using an asymmetric conjugate addition of an appropriate metal acetylide to the chiral *N*-enoyloxazolidinone **8**. For example, Kunz has shown that dialkylaluminum chlorides as well as mixed organoaluminum reagents participate in diastereoselective conjugate additions to *N*-enoyloxazolidinones derived from amino acids and carbohydrates.[20,21]

In accordance with the above retrosynthetic analysis, we began to explore reaction conditions for constructing aldehyde **7** via a diastereoselective conjugate addition of an aluminum acetylide species to the chiral *N*-enoyloxazolidinones **8a–c** (Scheme 2). In a preliminary experiment, we found that reaction of **8a**[22] and the organoaluminum species derived from the transmetalation of lithium (trimethylsilyl)acetylene with Me_2AlCl at 0 °C delivered the desired 1,4-addition product **9a** in 93% yield (dr=1.9:1)[23] (Scheme 2).[24] Inspired by these results, we reasoned that increasing the steric bulk at the 4-position of the oxazolidinone might improve the diastereoselectivity of the pivotal conjugate addition. The known acyl oxazolidinone **8b**[25] and the new acyl oxazolidinone **8c** were therefore prepared (Scheme 3). The synthesis of **8c** commenced with the treatment of L-serine methyl ester hydrochloride (**10**) with phosgene to afford a known intermediate oxazolidinone,[26] which was allowed to react with excess 2-naphthyllithium to provide tertiary alcohol **11**. Alcohol **11** was deoxygenated according to the method of Gribble to afford **12**,[27] which was acylated with (*E*)-crotonyl chloride to provide **8c**. The conjugate addition reactions employing **8b** and **8c** provided the adducts **9b** and **9c** with roughly a twofold enhancement in the diastereomeric ratio obtained with **8a** (Scheme 2). Although the yield of **9b** was comparable to that of **9a**, the yield of **9c** was somewhat lower.



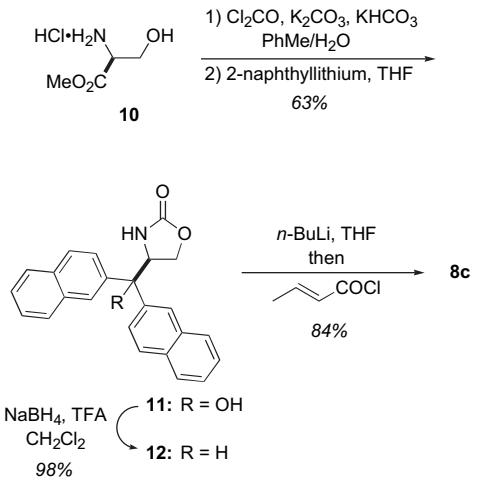
8a: R = Ph
b: R = $CH(Ph)_2$
c: R = $CH(2\text{-naphthyl})_2$

9a: *93%* (*dr* = 1.9:1)[a]
b: *92%* (3.4:1)
c: *78%* (3.2:1)

[a]The *dr* reflects the ratio of C(10*S*:10*R*) (see ref 24).

Scheme 2.

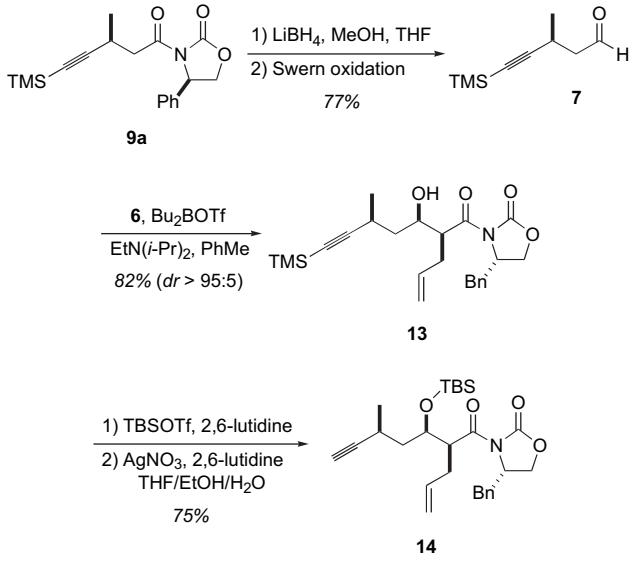
Although the stereoinduction provided by the chiral oxazolidinones in **8a–c** was modest, these auxiliaries did indeed afford the addition products with the appropriate stereochemistry at C(10).[24] In an effort to improve upon the diastereoselectivity obtained during these addition reactions, we turned our attention to the method of Schwartz, who



Scheme 3.

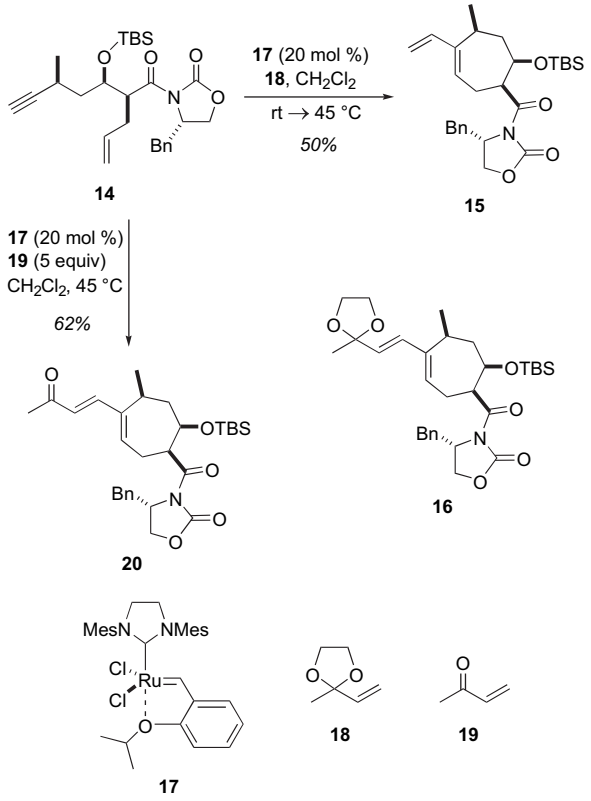
developed a procedure for the nickel(I)-catalyzed conjugate addition of aluminum acetylides to achiral enones.[28] We queried whether use of a nickel acetylide species might lead to improved diastereoselection. However, when we applied the Schwartz protocol without added chiral ligands to additions to **8a–c**, **9a–c** were formed in lower yields (<70%) with no diastereoselectivity.[29]

Although we had not been able to secure **9a** with high diastereoselectivity, it was possible to separate it from the minor C(10) epimer so we could examine the viability of the key domino enyne RCM/CM reaction.[24] Toward this end, imide **9a** was reduced, and the resulting alcohol was oxidized under Swern conditions to provide aldehyde **7** (Scheme 4).[30] The boron-mediated asymmetric aldol reaction between **7** and oxazolidinone **6** proceeded in 82% yield and excellent diastereoselectivity (dr>95:5)[23] to afford **13**. This aldol reaction proceeded in highest yield when toluene was used as the solvent and EtN(*i*-Pr)$_2$ as the base; employing CH_2Cl_2 as the solvent and Et_3N as the base consistently gave **13** in 10–20% lower yield. Protection of the secondary alcohol as a *tert*-butyldimethylsilyl ether followed by deprotection of the alkyne provided **14**.[31]



Scheme 4.

With **14** in hand, we explored conditions to effect the key enyne RCM/CM transformation. The phosphine-free ruthenium catalyst **17**[32] was employed owing to its reported superiority in tandem RCM/CM reactions.[16b] We first conducted the domino enyne RCM/CM sequence using dioxolane **18**,[33] which has been found to participate in CM reactions,[34] because its use would introduce the requisite enone moiety in a suitably protected form. In this way, subsequent transformation of the oxazolidinone moiety in **15** to the α-methylene-γ-butyrolactone could be performed without additional protection/deprotection steps (Scheme 5). However, the enyne RCM/CM reaction of **14** and **18** gave only the cyclic diene **15** (50%) with the remainder of the mass balance corresponding to the homodimer of **15**;[35] none of the desired **16** was isolated. When the metathesis reaction was conducted under an atmosphere of ethylene, **15** was produced in 59% yield, but **16** was still not detected in the reaction mixture. Interestingly, formation of the homodimer of **15** was completely suppressed under these conditions. Failing in these attempts to perform a domino RCM/CM, we examined the simple CM reaction of **15** with **18** as a route to **16**, but all such experiments were unavailing, even when large excesses of **18** were used; only **15** was recovered. These results led us to the inescapable conclusion that the protected enone **18** was not a suitable coupling partner for this particular CM reaction.



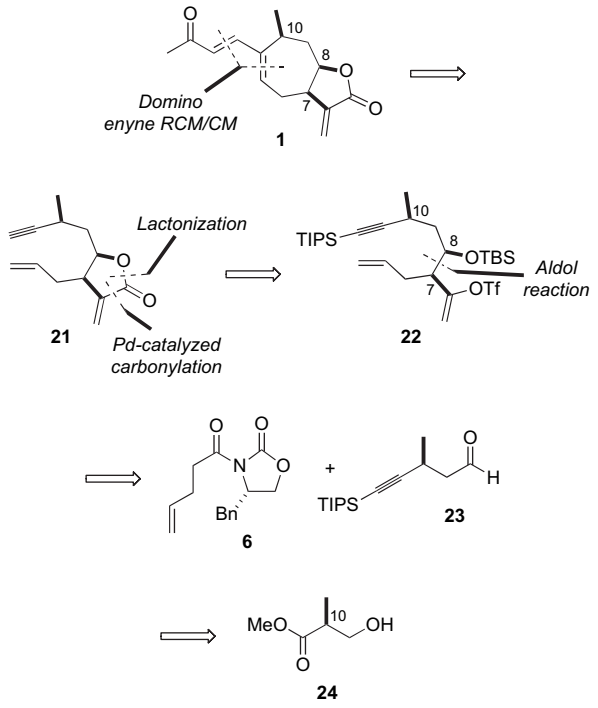
Scheme 5.

In the wake of these disappointments, we were pleased to discover that the domino RCM/CM reaction of enyne **14** and methyl vinyl ketone (**19**) proceeded cleanly to provide **20** in 62% yield.[36] This result was indeed promising as it nicely supported our original hypothesis that we could induce a domino enyne RCM/CM reaction to assemble the

seven-membered ring and pendant enone found in the xanthanolides.

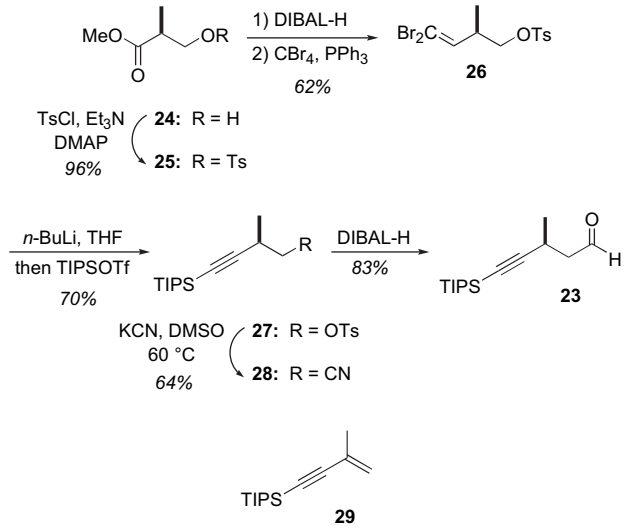
2.2. Second-generation approach

Inasmuch as the conjugate additions of aluminum acetylides to *N*-enoyloxazolidinones proceeded with modest diastereoselectivity, we queried whether an alternative route to the synthesis of **1** would prove viable. Moreover, it occurred to us that incorporating the α-methylene-γ-butyrolactone prior to the key domino RCM/CM sequence would enable us to minimize unproductive functional group manipulations. Indeed, Paquette had shown that the α-methylene-γ-butyrolactone functionality is stable to the conditions of ruthenium-catalyzed RCM reactions.[37] A second-generation strategy was thus designed in which the lactone moiety in **21** would be elaborated via a palladium-catalyzed carbonylation of the enol triflate **22** followed by a lactonization (Scheme 6). The stereocenters at C(7)–C(8) in **22** would be assembled by an asymmetric aldol reaction of oxazolidinone **6** and aldehyde **23**, whereas the remaining stereocenter at C(10) would be obtained from enantiomerically pure **24**, which is commercially available.



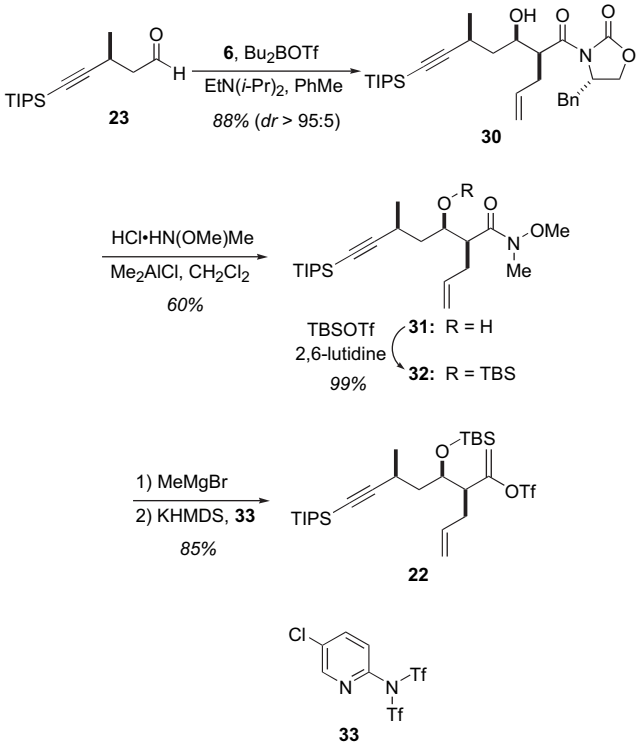
Scheme 6.

The first step in reducing the strategy in Scheme 6 to practice involved converting the ester **24** into the tosylate **25** (Scheme 7). Reduction of the ester moiety and application of the Corey–Fuchs homologation[38] protocol to the resulting aldehyde delivered vinyl dibromide **26**, which upon treatment with *n*-BuLi and trapping the lithium acetylide generated in situ with TIPSOTf afforded alkyne **27**. Displacement of the primary tosylate in **27** with potassium cyanide afforded the corresponding nitrile **28** in modest yield (64%) owing to competitive β-elimination to form enyne **29** (20%). Reduction of nitrile **28** with DIBAL-H afforded aldehyde **23**.[39]



Scheme 7.

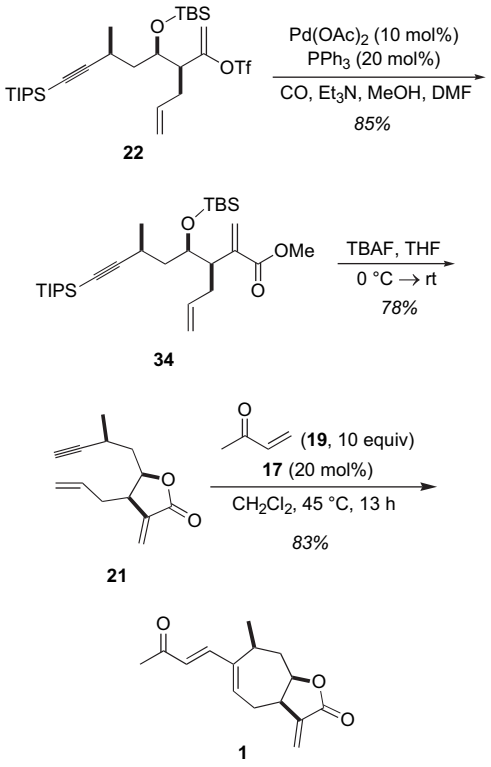
The aldol coupling reaction between **23** and **6** proceeded in good yield to afford **30** with excellent diastereoselectivity (dr>95:5)[23] (Scheme 8). The secondary alcohol group of the *N*,*O*-dimethyl amide **31**, which was prepared from **30** using the method of Weinreb,[40] was protected as its *tert*-butyldimethylsilyl ether to deliver **32**. Subsequent treatment of amide **32** with MeMgBr provided the corresponding ketone, which was readily transformed into the requisite enol triflate **22** in 85% overall yield by kinetic deprotonation using KHMDS and trapping of the resultant enolate with *N*-(5-chloro-2-pyridyl)triflimide (**33**).[41]



Scheme 8.

The final phase of the synthesis was initiated with the palladium-catalyzed carbonylation of **22** in the presence of

MeOH to deliver acrylate **34** in 85% yield (Scheme 9).[42] Simultaneous removal of the two silyl protecting groups and intramolecular lactonization was effected with TBAF to afford **21** in 78% yield,[43] thereby setting the stage for the pivotal domino enyne RCM/CM sequence. In the event, reaction of enyne **21** and enone **19** in the presence of catalyst **17** provided **1** in 83% yield. The ^{1}H and ^{13}C NMR spectral data of the synthetic **1** thus obtained were consistent with those previously reported.[2b,5a,b,44,45] Moreover, it exhibited an optical rotation $\{[\alpha]_D^{24}$ +23.4 (*c* 0.333, $CHCl_3$)} in close accord with the previously reported value $\{[\alpha]_D^{20}$ +25 (*c* 0.5, $CHCl_3$)}.[5b]



Scheme 9.

3. Conclusions

The first total synthesis of the sesquiterpene lactone (+)-8-*epi*-xanthatin has been completed by a route that required only 14 steps in the longest linear sequence and proceeded in an overall yield of 5.5%. The essential elements of the approach comprise a sequence for palladium-catalyzed carbonylation and lactonization to construct the α-methylene-γ-butyrolactone functionality and a domino enyne RCM/CM process to elaborate the seven-membered carbocycle with its pendant enone array. Indeed, the synthesis underscores the significant utility of domino ruthenium-catalyzed metathesis reactions for the rapid construction of functionalized, polycyclic ring systems that are found in natural products. During the course of these studies, we also investigated aluminum-mediated conjugate addition reactions to chiral α,β-unsaturated imides. Other applications of olefin metathesis to solve challenging problems in total synthesis are under active investigation in our laboratories, and the results of these studies will be disclosed in due course.

4. Experimental

4.1. General

Unless otherwise indicated, all starting materials and solvents were obtained from commercial suppliers and used without further purification. All solvents contained less than 50 ppm H_2O by Karl Fisher coulometric moisture analysis. Tetrahydrofuran (THF) was dried by passage through two columns of activated neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves and stored under argon. Toluene (PhMe) was first passed through a column of neutral alumina, then through a column of Q5 reactant and stored under argon. Methylene chloride (CH_2Cl_2), triethylamine (Et_3N), 2,6-lutidine, Hünig's base ($EtN(i\text{-}Pr)_2$), trimethylsilyl chloride (TMSCl), triisopropyl silyltrifluoromethanesulfonate (TIPSOTf), and dimethylsulfoxide (DMSO) were distilled from calcium hydride and used immediately. Reactions involving air or moisture-sensitive reagents or intermediates were performed in flame-dried glassware under an atmosphere of dry nitrogen or argon. All reaction temperatures are reported as the temperature of the surrounding bath. Flash chromatography was performed following the Still[46] protocol with ICN Silitech 32-63 D 60A silica gel with the indicated solvents. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica plates. The plates were visualized with ultraviolet light, potassium permanganate, or ceric ammonium molybdate. Proton (^{1}H) and carbon (^{13}C) NMR spectra were obtained using a Varian Unity Plus (400 MHz) or Varian Unity Plus (500 MHz) spectrometer as solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported as parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet; comp, complex multiplet; app, apparent. Low-resolution chemical ionization mass spectra (CI) were obtained on a Finnigan TSQ-70 instrument in positive ionization mode. High-resolution mass spectra (HRMS) were obtained on a VG Analytical ZAB-2E instrument in positive ionization mode. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR either neat or as solutions in $CDCl_3$ on sodium chloride plates or as a KBr pellet and are reported in wavenumbers (cm^{-1}). Melting points are uncorrected. Percent yields are given for compounds that were ≥95% pure as judged by ^{1}H NMR spectroscopy.

4.1.1. (3*S*)-(3-Methyl-5-trimethylsilanylpent-4-ynoyl)-(4*R*)-phenyloxazolidin-2-one (9a). A solution of *n*-BuLi (2.46 M in hexane, 4.4 mL, 11.0 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (1.5 mL, 11.0 mmol) in PhMe (80 mL) at 0 °C. The mixture was stirred at this temperature for 0.5 h, whereupon the cooling bath was removed and stirring continued at room temperature for an additional 0.5 h. The solution was then cooled to 0 °C, whereupon Me_2AlCl (1.0 M in hexane, 11.0 mL, 11.0 mmol) was added dropwise and stirring continued for 0.5 h. To this mixture was added a solution of **8a** (998 mg, 4.32 mmol) in PhMe (30 mL), and stirring was continued at 0 °C for 0.5 h. The reaction was then slowly quenched by the sequential addition of saturated aqueous Rochelle's

salt (40 mL), H_2O (40 mL), and EtOAc (50 mL). The resulting mixture was stirred at room temperature overnight and then extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (2:1) to afford 873 mg (61%) of the desired major diastereomer **9a** as a colorless solid and 458 mg (32%) of the undesired adduct (10*R*)-**9a** as a colorless solid.

Major diastereomer (**9a**): mp=24–25 °C; ^{1}H NMR (500 MHz) δ 7.38–7.26 (comp, 5H), 5.44–5.38 (m, 1H), 4.69–4.65 (m, 1H), 4.27–4.24 (m, 1H), 3.22 (app d, *J*=6.1 Hz, 1H), 3.06–2.94 (comp, 2H), 1.17 (d, *J*=6.8 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz) δ 170.3, 153.6, 138.9, 129.2, 128.7, 125.9, 109.8, 84.5, 70.0, 57.7, 42.4, 22.7, 20.8, 0.1; IR ($CDCl_3$) 2958, 2173, 1784, 1713, 1384, 1197, 843 cm^{-1}; mass spectrum (CI) *m*/*z* 330.1542 [$C_{18}H_{24}NO_3Si$ (M+1) requires 330.1526], 330 (base), 314.

Minor diastereomer (10*R*)-**9a**: mp=25–26 °C; ^{1}H NMR (500 MHz) δ 7.38–7.26 (comp, 5H), 5.42 (dd, *J*=8.8, 3.8 Hz, 1H), 4.67 (t, *J*=8.8 Hz, 1H), 4.26 (dd, *J*=8.8, 3.8 Hz, 1H), 3.21–3.14 (m, 1H), 3.04–2.95 (comp, 2H), 1.14 (d, *J*=6.8 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz) δ 170.3, 153.7, 139.0, 129.2, 128.7, 125.9, 109.7, 84.7, 70.0, 57.6, 42.2, 23.0, 20.8, 0.1; IR (neat) 2959, 2171, 1786, 1708, 1386, 1198, 843 cm^{-1}; mass spectrum (CI) *m*/*z* 330.1537 [$C_{18}H_{24}NO_3Si$ (M+1) requires 330.1526], 330 (base), 314.

4.1.2. (4*R*)-Benzhydryl-3-[(3*S*)-methyl-5-trimethylsilanylpent-4-ynoyl]oxazolidin-2-one (9b). Prepared as a white foam in 71% yield along with 21% yield of the undesired adduct (10*R*)-**9b** as a white foam according to the procedure described above for **9a**.

Major diastereomer (**9b**): mp=24–25 °C; ^{1}H NMR (500 MHz) δ 7.34–7.27 (comp, 5H), 7.26–7.24 (m, 1H), 7.12–7.10 (comp, 2H), 7.08–7.06 (comp, 2H), 5.32–5.29 (m, 1H), 4.75 (d, *J*=5.0 Hz, 1H), 4.46–4.39 (comp, 2H), 3.11–2.94 (comp, 3H), 1.19 (app dd, *J*=6.9, 1.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) δ 170.6, 153.3, 139.5, 137.9, 129.4, 128.9, 128.7, 128.3, 127.9, 127.1, 110.2, 84.5, 64.7, 56.2, 50.2, 42.5, 22.6, 20.8, 0.2; IR (neat) 2962, 2165, 1784, 1704, 1389, 1280, 1249, 1212, 838, 756, 697 cm^{-1}; mass spectrum (CI) *m*/*z* 420.1986 [$C_{25}H_{30}NO_3Si$ (M+1) requires 420.1995], 420 (base), 404, 326, 254, 167.

Minor diastereomer (10*R*)-**9b**: mp=25–26 °C; ^{1}H NMR (500 MHz) δ 7.34–7.26 (comp, 5H), 7.24–7.20 (m, 1H), 7.17–7.14 (comp, 2H), 7.10–7.07 (comp, 2H), 5.34–5.30 (m, 1H), 4.67 (d, *J*=5.8 Hz, 1H), 4.43–4.36 (comp, 2H), 3.04 (dd, *J*=15.9, 6.8 Hz, 3H), 2.96 (app sext, *J*=6.7 Hz, 1H), 2.87 (dd, *J*=15.9, 6.4 Hz, 1H), 1.13 (app d, *J*=6.6 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz) δ 170.4, 153.3, 139.5, 138.0, 129.3, 128.9, 128.7, 128.4, 127.9, 127.1, 109.8, 84.9, 65.2, 56.3, 51.0, 42.3, 22.9, 20.9, 0.1; IR (neat) 2966, 2167, 1784, 1702, 1496, 1455, 1390, 1367, 1249, 1208, 1114, 844, 756, 703 cm^{-1}; mass spectrum (CI) *m*/*z* 420.1985 [$C_{25}H_{30}NO_3Si$ (M+1) requires 420.1995], 420 (base), 404, 326, 167.

4.1.3. (4*R*)-[(Dinaphthalen-2-yl)methyl]-3-[(3*S*)-methyl-5-trimethylsilanylpent-4-ynoyl]oxazoldin-2-one [(10*S*)-9c] and [(10*R*)-9c]. Prepared as a white foam in 78% yield according to the procedure described above for **9a** (dr= 3.2:1); mp (mixture)=24–25 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (mixture of diastereomers) δ 7.95–7.82 (comp, 6.5H), 7.76 (br s, 1H), 7.70 (br s, 1H), 7.56–7.48 (comp, 4H), 7.32 (dd, *J*=8.6, 1.8 Hz, 0.28H), 7.27 (dd, *J*=8.5, 1.7 Hz, 0.78H), 7.21 (overlapping pair of dd, *J*=8.3, 1.8 Hz for the minor set, and *J*=8.6, 1.8 Hz for the major set, total integral is 1H), 5.45–5.50 (m, 1H), 4.91 (d, *J*=4.1 Hz, 0.76H), 4.86 (d, *J*=5.1 Hz, 0.26H), 4.78–4.71 (m, 1H), 4.55 (dd, *J*=9.2, 2.3 Hz, 0.72H), 4.51 (dd, *J*=9.2, 2.3 Hz, 0.25H), 3.11 (dd, *J*=16.7, 6.6 Hz, 0.73H), 2.98–2.82 (comp, 2.23H), 1.11 (d, *J*=6.8 Hz, 2.33H), 0.98 (d, *J*=6.2 Hz, 0.75H), 0.13 (s, 6.3H), 0.11 (s, 2.1H); ^{13}C NMR (125 MHz, DMSO-d_6) (mixture of diastereomers) δ 170.4, 169.9, 153.6, 153.5, 137.6, 137.5, 136.4, 136.3, 133.2, 133.1, 133.0, 132.5, 132.1, 128.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.9, 127.7, 127.6, 126.8, 126.6, 126.5, 126.4, 126.2, 111.6, 110.8, 85.5, 84.2, 65.2, 64.8, 55.8, 50.7, 50.1, 42.3, 23.0, 22.5, 20.7, 20.5, 0.4, 0.3 δ; IR (neat) 2962, 2164, 1782, 1704, 1385, 1249, 1212, 842, 759 cm^{-1}; mass spectrum (CI) *m*/*z* 520.2306 [$C_{33}H_{34}NO_3Si$ (M+1) requires 520.2308], 520, 267 (base).

4.1.4. (4*R*)-[Hydroxy(dinaphthalen-2-yl)methyl]oxazolidin-2-one (11). A solution of *tert*-BuLi (1.7 M in pentane, 2.8 mL, 4.7 mmol) was added dropwise via syringe to a solution of 2-bromonaphthalene (0.49 g, 2.4 mmol) in THF (5 mL) at −78 °C. The resulting yellowish-green slurry was stirred at −78 °C for 10 min, whereupon the mixture was transferred to a 0 °C bath and stirring continued for 10 min. The mixture was cooled to −78 °C, whereupon a solution of the oxazolidinone derived from **10**[25] (0.11 g, 0.76 mmol) in THF (2 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h, whereupon a saturated aqueous solution of NH_4Cl (10 mL) was added and the cooling bath removed. The mixture was poured into brine (30 mL), and the biphasic mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was dissolved in a minimal volume of DMSO and purified by flash chromatography eluting with EtOAc/hexanes (4:1) to afford 188 mg (67%) of **11** as a white solid (63% from **10**); mp=197–199 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15–8.14 (m, 1H), 8.10–8.09 (m, 1H), 7.92 (br t, *J*=7.8 Hz, 2H), 7.83–7.81 (comp, 2H), 7.77 (dd, *J*=9.0, 3.8 Hz, 2H), 7.70 (br s, 1H), 7.52–7.45 (comp, 6H), 6.30 (s, 1H), 5.29–5.26 (m, 1H), 4.32 (t, *J*=8.8 Hz, 1H), 4.21 (dd, *J*=8.6, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 142.0, 141.9, 132.6, 132.5, 131.9, 131.8, 128.3, 128.2, 127.7, 127.4, 127.3, 127.2, 126.1, 126.0, 125.9, 125.8, 125.4, 125.1, 124.7, 124.3, 77.9, 65.0, 57.5; IR (KBr) 3402, 1732, 1416, 1236, 1033, 754 cm^{-1}; mass spectrum (CI) *m*/*z* 370. 1453 [$C_{24}H_{20}NO_3$ (M+1) requires 370.1443], 370 (base), 352, 283, 169.

4.1.5. (4*R*)-[(Dinaphthalen-2-yl)methyl]oxazolidin-2-one (12). TFA (3 mL) was added dropwise via syringe to a slurry of **11** (185 mg, 0.501 mmol) and $NaBH_4$ (95 mg, 2.5 mmol) in CH_2Cl_2 (7 mL) at room temperature, during which time a vigorous evolution of H_2 was observed. The reaction mixture was stirred at room temperature for 21 h, diluted with

H_2O (10 mL), and neutralized (pH=7) by the addition of solid KOH pellets. The resulting biphasic mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude yellow solid thus obtained was purified by recrystallization from MeOH–hexanes. The crystals were collected by vacuum filtration, rinsed with cold hexanes (2×5 mL), and dried under reduced pressure to afford 173 mg (98%) of **12** as an off-white crystalline solid; mp=120–122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (br d, J=3.6 Hz, 2H), 7.91–7.86 (comp, 3H), 7.84–7.80 (comp, 4H), 7.53–7.42 (comp, 6H), 5.06–5.01 (m, 1H), 4.40–4.36 (comp, 2H), 4.04–3.98 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.7, 139.0, 138.6, 133.1, 133.0, 132.0, 131.9, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 126.8, 126.7, 126.6, 126.4, 126.3, 126.1, 125.9, 125.7, 67.9, 56.3, 54.2; IR (neat) 3274, 3053, 1756, 1404, 1239, 1026, 756 cm^{-1}; mass spectrum (CI) m/z 354.1492 [$C_{24}H_{20}NO_2$ (M+1) requires 354.1494], 355 (base), 267, 129.

4.1.6. 3-But-2-enoyl-(4*R*)-(dinaphthalen-2-ylmethyl)oxazolidin-2-one (8c). A solution of *n*-BuLi (2.36 M in hexanes, 63 μL, 0.15 mmol) was added to a solution of **12** (44 mg, 0.13 mmol) in THF (0.5 mL) at −78 °C, whereupon the mixture was stirred for an additional 0.5 h. To this mixture was added freshly distilled *trans*-crotonyl chloride (18 μL, 0.19 mmol). The solution was allowed to warm to room temperature over a 2 h period and then quenched by adding a solution of saturated aqueous NH_4Cl (2 mL). The resulting layers were separated, and the aqueous phase was extracted with EtOAc (3×2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (2:3) to afford 44 mg (84%) of **8c** as a white solid; mp=48–51 °C; ^{1}H NMR (400 MHz) δ 7.88–7.74 (comp, 6H), 7.66–7.57 (comp, 2H), 7.54–7.45 (comp, 4H), 7.35–7.24 (comp, 3H), 7.20–7.08 (m, 1H), 5.62–5.58 (m, 1H), 5.14 (d, J=5.1 Hz, 1H), 4.57–4.48 (comp, 2H), 1.93 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 164.7, 153.2, 146.9, 137.1, 135.4, 133.2, 133.0, 132.6, 132.2, 128.5, 128.3, 127.7, 127.6, 127.5, 127.4, 127.1, 126.3, 126.2, 126.1, 126.0, 121.5, 64.7, 56.1, 50.8, 18.4; IR (neat) 3054, 2957, 2932, 2870, 1779, 1682, 1634, 1340, 1208, 749, 668 cm^{-1}; mass spectrum (CI) m/z 422.1752 [$C_{28}H_{24}NO_3$ (M+1) requires 422.1756], 422 (base), 354, 267.

4.1.7. (3*S*)-Methyl-5-trimethylsilanylpent-4-yn-1-ol. Solid $LiBH_4$ (49 mg, 2.1 mmol) and dry MeOH (78 μL, 1.9 mmol) were sequentially added to a solution of **9a** (637 mg, 1.93 mmol) in THF (19 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, whereupon the cooling bath was removed and stirring continued at room temperature for 8 h. The reaction was poured into a mixture of 25% aqueous NaOH (40 mL) and Et_2O (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (4:1) to afford 270 mg (82%) of the product as a yellow oil; ^{1}H NMR (400 MHz) δ 3.83–3.70 (comp, 2H), 2.66–2.55 (m, 1H), 1.93 (br s, 1H), 1.73–1.58 (comp, 2H), 1.17 (d, J=6.8 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz) δ 111.2, 85.2, 61.2, 39.3, 23.9, 21.1, 0.1; IR (neat) 3350, 2961, 2167, 1250, 841, 760 cm^{-1}; mass spectrum (CI) m/z 171.1207 [$C_9H_{19}OSi$ (M+1) requires 171.1205], 171 (base), 155, 139.

4.1.8. (3*S*)-Methyl-5-trimethylsilanylpent-4-ynal (7). To a solution of oxalyl chloride (410 μL, 4.66 mmol) in CH_2Cl_2 (58 mL) at −78 °C DMSO (0.67 mL, 9.4 mmol) was added via syringe. The mixture was stirred at −78 °C for 15 min, whereupon a solution of the above alcohol (264 mg, 1.55 mmol) in CH_2Cl_2 (4 mL) was added via cannula and stirring continued for 1 h. Et_3N (2.6 mL, 19 mmol) was added via syringe, and the reaction mixture was transferred to a 0 °C bath and stirring continued for 0.5 h. The reaction was quenched by adding H_2O (15 mL) and poured into 1 N HCl (70 mL). The biphasic mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were dried ($MgSO_4$), filtered through a 0.5-in. plug of neutral Al_2O_3 rinsing with CH_2Cl_2 (300 mL) and Et_2O (200 mL), and concentrated at atmospheric pressure. The resulting crude residue was triturated with pentane (5 mL) and filtered. Concentration of the filtrate at atmospheric pressure afforded 246 mg (94%) of **7** as a yellow oil; ^{1}H NMR (400 MHz) δ 9.76 (t, J=2.1 Hz, 1H), 2.97 (app sext, J=6.8 Hz, 1H), 2.63–2.41 (comp, 2H), 1.21 (d, J=6.8 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz) δ 201.1, 109.1, 85.7, 49.8, 21.5, 20.9, 0.1; IR (neat) 2962, 2169, 1714, 1410, 1250, 842, 760 cm^{-1}; mass spectrum (CI) m/z 169.1050 [$C_9H_{17}OSi$ (M+1) requires 169.1049], 169 (base).

4.1.9. 3-[(2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-trimethylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (13). To a solution of oxazolidinone **6** (594 mg, 2.29 mmol) and EtN(*i*-Pr)$_2$ (400 μL, 2.29 mmol) in anhydrous PhMe (12 mL) at −78 °C was added Bu_2BOTf (570 μL, 2.30 mmol).[47] The mixture was stirred at −78 °C for 1 h, whereupon aldehyde **7** (285 mg, 1.69 mmol) in anhydrous PhMe (2 mL) was added dropwise via cannula. The mixture was stirred at −78 °C for 30 min and then at room temperature for 6 h. The mixture was cooled to 0 °C, whereupon pH 7.0 phosphate buffer (2 mL), MeOH (1 mL), and 30% H_2O_2 (500 μL) were added successively, and stirring was continued for 1 h. The mixture was poured into H_2O (30 mL), and the resulting biphasic mixture extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 615 mg (82%) of **13** as a colorless oil (dr>95:5 by ^{1}H NMR); ^{1}H NMR (500 MHz) δ 7.33–7.29 (comp, 2H), 7.27–7.23 (m, 1H), 7.21–7.18 (comp, 2H), 5.89–5.80 (m, 1H), 5.13–5.09 (m, 1H), 5.05–5.02 (m, 1H), 4.72–4.67 (m, 1H), 4.25–4.19 (comp, 2H), 4.17–4.09 (comp, 2H), 3.28 (dd, J=13.5, 3.4 Hz, 1H), 2.75–2.69 (m, 1H), 2.68–2.55 (comp, 3H), 2.44–2.38 (m, 1H), 1.63–1.50 (comp, 2H), 1.18 (d, J=7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz) δ 174.8, 153.7, 135.3, 135.2, 129.4, 129.0, 127.4, 117.3, 110.9, 85.2, 70.4, 66.0, 55.6, 47.3, 40.5, 38.0, 32.1, 23.8, 21.4, 0.1; IR (neat) 3524, 2963, 2165, 1782, 1698, 1386, 1249, 1208, 1102, 842, 760, 701 cm^{-1}; mass spectrum (CI) m/z 428.2254 [$C_{24}H_{34}NO_4Si$ (M+1) requires 428.2257], 428 (base), 412, 356, 250.

4.1.10. 3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-7-trimethylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one. To a solution of alcohol **13** (463 mg,

1.08 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added 2,6-lutidine (1.2 mL, 10.0 mmol) and TBDMSOTf (720 μL, 3.1 mmol). The resulting solution was stirred at 0 °C for 2 h, whereupon MeOH (3 mL) was added and the cooling bath removed. After warming to room temperature, the mixture was poured into H_2O (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 536 mg (92%) of the product as a yellow oil; ^{1}H NMR (500 MHz) δ 7.32–7.28 (comp, 2H), 7.26–7.22 (m, 1H), 7.22–7.19 (comp, 2H), 5.90–5.81 (m, 1H), 5.14–5.09 (m, 1H), 5.04–5.01 (m, 1H), 4.64–4.59 (m, 1H), 4.25–4.21 (m, 1H), 4.17–4.14 (m, 1H), 4.12–4.03 (m, 1H), 3.28 (dd, J=13.3, 3.1 Hz, 1H), 2.67 (dd, J=13.3, 10.0 Hz, 1H), 2.58–2.48 (comp, 2H), 2.34–2.26 (m, 1H), 1.81–1.75 (m, 1H), 1.68–1.63 (m, 1H), 1.18 (d, J=6.9 Hz, 3H), 0.84 (s, 9H), 0. 13 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz) δ 174.0, 153.1, 135.5, 135.3, 129.5, 128.9, 127.3, 117.1, 111.4, 85.5, 71.9, 65.7, 56.0, 48.1, 41.5, 37.7, 33.1, 25.7, 24.0, 21.6, 18.0, 0.2, −4.4, −4.7; IR (neat) 2955, 2167, 1784, 1696, 1384, 1248, 1207, 1095, 837, 778 cm^{-1}; mass spectrum (CI) m/z 542.3120 [$C_{30}H_{48}NO_4Si_2$ (M+1) requires 542.3122], 542 (base), 526, 484, 410.

4.1.11. 3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanoxyl)-(5*S*)-methylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (14). Solid $AgNO_3$ (3.30 g, 19.0 mmol) was added in one portion to a solution of the preceding alkyne (695 mg, 1.28 mmol) in THF/EtOH/H_2O/2,6-lutidine (1:1:1:0.1) (65 mL) at room temperature. The resulting solution was stirred for 30 min and filtered through a pad of Celite (3 cm) rinsing with Et_2O (300 mL). The combined filtrate and washings were washed with brine (200 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×75 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure The residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to afford 493 mg (82%) of **14** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.32–7.28 (comp, 2H), 7.26–7.23 (m, 1H), 7.22–7.19 (comp, 2H), 5.89–5.80 (m, 1H), 5.12–5.08 (m, 1H), 5.04–5.00 (m, 1H), 4.65–4.60 (m, 1H), 4.28–4.24 (m, 1H), 4.15–4.04 (comp, 3H), 3.28 (dd, J=13.4, 3.2 Hz, 1H), 2.64 (dd, J=13.5, 10.2 Hz, 1H), 2.55–2.47 (comp, 2H), 2.39–2.33 (m, 1H), 2.05 (d, J=2.2 Hz, 1H), 1.78–1.67 (comp, 2H), 1.21 (d, J=7.0 Hz, 3H), 0.83 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 174.0, 153.1, 135.5, 135.2, 129.5, 128.9, 127.3, 117.1, 88.6, 71.9, 69.3, 65.7, 56.0, 48.0, 41.7, 37.8, 33.4, 25.8, 22.8, 21.8, 18.0, −4.4, −4.6; IR (neat) 3307, 2931, 1784, 1696, 1384, 1249, 1208, 1096, 837, 779 cm^{-1}; mass spectrum (CI) m/z 470.2720 [$C_{27}H_{40}NO_4Si$ (M+1) requires 470.2727], 470 (base), 454, 412, 338.

4.1.12. (4*S*)-Benzyl-(3*S*)-[(7*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-4-vinylcyclohept-3-enecarbonyl]oxazolidin-2-one (15). A solution of **14** (20 mg, 0.0426 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was degassed by bubbling with a stream of argon for 10 min, whereupon dioxolane **18** (15 mg, 0.128 mmol) and catalyst **17** (5 mg, 0.009 mmol) were added. The mixture was stirred at 45 °C for 22 h and then cooled to room temperature, whereupon DMSO (50 μL) was added and stirring continued for 12 h. The mixture was concentrated under reduced pressure and purified by flash chromatography eluting with pentane/Et_2O (2:1) to give 10 mg (50%) of **15** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.33–7.29 (comp, 2H), 7.27–7.25 (m, 1H), 7.21–7.19 (comp, 2H), 6.21 (dd, J=17.4, 10.9 Hz, 1H), 5.74–5.71 (m, 1H), 5.09 (d, J=17.4 Hz, 1H), 4.91 (d, J=10.9 Hz, 1H), 4.61–4.56 (m, 1H), 4.24–4.21 (m, 1H), 4.19–4.16 (m, 1H), 4.14–4.07 (comp, 2H), 3.27 (dd, J=13.3, 3.2 Hz, 1H), 3.03–2.96 (m, 1H), 2.83–2.76 (m, 1H), 2.72 (dd, J=13.3, 9.8 Hz, 1H), 2.25–2.14 (comp, 2H), 1.78 (ddd, J=14.7, 6.1, 2.0 Hz, 1H), 1.21 (d, J=7.4 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (125 MHz) δ 173.9, 153.3, 145.5, 140.2, 135.5, 129.5, 128.9, 128.4, 127.3, 110.4, 71.9, 65.8, 55.8, 45.8, 38.3, 37.9, 31.2, 25.8, 24.0, 20.5, 17.9, −4.4, −5.5; IR (neat) 2929, 1784, 1698, 1388, 1350, 1242, 1210, 1099, 1072, 835, 776 cm^{-1}; mass spectrum (CI) m/z 470.2728 [$C_{27}H_{40}NO_4Si$ (M+1) requires 470.2727], 470 (base), 338.

4.1.13. (4*S*)-Benzyl-(3*S*)-[7(*R*)-(*tert*-butyldimethylsilanyloxy)-5(*S*)-methyl-4-(3-oxobut-1-enyl)cyclohept-3-enecarbonyl]oxazolidin-2-one (20). A solution of **14** (364 mg, 0.775 mmol) in anhydrous CH_2Cl_2 (155 mL) was degassed with argon for 10 min, whereupon freshly distilled methyl vinyl ketone (320 μL, 3.88 mmol) and catalyst **17** (97 mg, 0.160 mmol) were added. The mixture was stirred at 45 °C for 20 h and cooled to room temperature, whereupon DMSO (600 μL) was added and stirring continued for 6 h. The mixture was concentrated under reduced pressure and purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 245 mg (62%) of **20** as a white solid; mp=24–26 °C; ^{1}H NMR (500 MHz) δ 7.34–7.30 (comp, 2H), 7.28–7.24 (m, 1H), 7.20–7.18 (comp, 2H), 7.02 (d, J=16.1 Hz, 1H), 6.20 (m, 1H), 6.08 (d, J=16.1 Hz, 1H), 4.61–4.56 (m, 1H), 4.27–4.25 (m, 1H), 4.16–4.07 (comp, 3H), 3.27 (dd, J=13.4, 3.3 Hz, 1H), 3.13–3.06 (m, 1H), 2.82–2.75 (m, 1H), 2.73 (d, J=13.3, 9.7 Hz, 1H), 2.32–2.27 (comp, 4H), 2.23–2.17 (m, 1H), 1.80 (ddd, J=14.7, 5.6, 1.8 Hz, 1H), 1.23 (d, J=7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (125 MHz) δ 198.9, 173.3, 153.3, 147.6, 144.7, 138.8, 135.3, 129.4, 129.0, 127.4, 124.8, 71.7, 65.9, 55.8, 45.7, 38.0, 37.8, 31.8, 27.3, 25.8, 24.4, 20.4, 17.8, −4.3, −5.6; IR (neat) 2928, 2856, 1778, 1702, 1667, 1590, 1386, 1354, 1256, 1195, 985, 837, 774 cm^{-1}; mass spectrum (CI) m/z 512.2833 [$C_{29}H_{42}NO_5Si$ (M+1) requires 512.2832], 512 (base), 494, 454, 380, 362, 205, 163.

4.1.14. (2*S*)-Methyl-3-(toluene-4-sulfonyloxy)propionic acid methyl ester (25). To a solution of alcohol **24** (5.36 g, 45.4 mmol) in anhydrous CH_2Cl_2 (65 mL) at 0 °C was added Et_3N (7.60 mL, 54.4 mmol), DMAP (1.10 g, 9.07 mmol), and TsCl (10.4 g, 54.4 mmol) successively. The cooling bath was removed after 1 h, and the mixture was stirred at room temperature for 20 h. The mixture was poured into water (50 mL), and the resulting biphasic solution was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a volume of approximately 15 mL. This solution was filtered through a pad of

silica (2 cm) rinsing with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure to afford 11.8 g (96%) of **25** as a light yellow oil with spectral characteristics identical to those previously reported.[48]

4.1.15. 4,4-Dibromo-(2*R*)-methyl-1-(toluene-4-sulfonyloxy)but-3-ene (26). To a solution of ester **25** (2.0 g, 7.34 mmol) in anhydrous PhMe (36.5 mL) at −78 °C was added DIBAL-H (1 M in PhMe, 8.1 mL, 8.08 mmol) dropwise via syringe. The mixture was stirred for 1.5 h at −78 °C, whereupon EtOAc (30 mL) was added and the cooling bath removed. Once the mixture had warmed to room temperature, saturated aqueous Rochelle's salt (100 mL) was added, and the biphasic mixture was stirred vigorously for 3 h. The layers were separated, and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organics were washed with water (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure (20 mmHg) to afford the crude aldehyde (ca. 2.0 g) as a yellow oil that was used in the next step without further purification.

Solid CBr_4 (4.88 g, 14.7 mmol) was added in one portion to a solution of PPh_3 (7.70 g, 29.4 mmol) in anhydrous CH_2Cl_2 (37 mL) at 0 °C. After stirring for 10 min, a solution of the preceding aldehyde (ca. 2.0 g) and 2,6-lutidine (1.7 mL, 14.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. Stirring was continued at 0 °C for 1 h, whereupon saturated aqueous NH_4Cl (6 mL) was added and the cooling bath removed. The reaction mixture was poured into saturated aqueous NH_4Cl (40 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/pentane (2:1) to give 1.82 g (62% from **25**) of **26** as a white solid; mp 74–76 °C; ^{1}H NMR (400 MHz) δ 7.79–7.77 (m, 2H), 7.37–7.35 (m, 2H), 6.13 (d, J=9.2 Hz, 1H), 3.92–3.90 (comp, 2H), 2.83–2.73 (m, 1H), 2.45 (s, 3H), 1.02 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 145.3, 138.5, 132.9, 130.2, 128.2, 91.3, 72.2, 38.1, 21.9, 15.7; IR ($CDCl_3$) 2973, 1598, 1458, 1360, 1176, 1097, 973, 813, 784, 666 cm^{-1}; mass spectrum (CI) m/z 396.9119 [$C_{12}H_{15}O_3SBr_2$ (M+1) requires 396.9109], 401, 399 (base), 397.

4.1.16. Toluene-4-sulfonic acid-(2*R*)-methyl-4-triisopropylsilanylbut-3-ynyl ester (27). *n*-BuLi (2.47 M in hexane, 4.10 mL, 10.1 mmol) was added dropwise via syringe to a solution of the preceding dibromide (1.61 g, 4.04 mmol) in anhydrous THF (13.3 mL) at −78 °C. After 1 h at −78 °C, the reaction mixture was allowed to warm to −20 °C, and stirring was continued at this temperature for 1 h. The reaction mixture was cooled to −78 °C, whereupon TIPSOTf (3.30 mL, 12.1 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h, whereupon MeOH (4 mL) was added and stirring continued for 10 min. The reaction mixture was poured into saturated aqueous NH_4Cl (30 mL), and the resulting biphasic mixture was extracted with Et_2O (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 1.11 g (70%) of **27** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.79–7.77 (comp, 2H), 7.35–7.33 (comp, 2H), 4.06 (dd, J=9.2, 5.8 Hz, 1H), 3.87 (dd, J=9.2, 7.8 Hz, 1H), 2.87–2.78 (m, 1H), 2.45 (s, 3H), 1.19 (d, J=6.8 Hz, 3H), 1.04–0.96 (comp, 21H); ^{13}C NMR (125 MHz) δ 144.8, 133.1, 129.8, 127.9, 107.4, 82.9, 72.6, 27.2, 21.6, 18.5, 17.7, 11.1; IR (neat) 2942, 2865, 2170, 1599, 1463, 1365, 1190, 1178, 1098, 980, 667, 554 cm^{-1}; mass spectrum (CI) m/z 395.2075 [$C_{21}H_{35}O_3SiS$ (M+1) requires 395.2076], 395, 351, 329, 285 (base).

4.1.17. (3*S*)-Methyl-5-triisopropylsilanylpent-4-ynenitrile (28). To a solution of tosylate **27** (1.11 g, 2.81 mmol) in anhydrous DMSO (11.2 mL) was added anhydrous KCN (385 mg, 5.91 mmol). The mixture was stirred at 60 °C for 3 h and then allowed to cool to room temperature, whereupon it was slowly poured into a 15% brine (40 mL). The resulting mixture was extracted with Et_2O (3×10 mL), and the combined organics were dried (Na_2SO_4), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (4:1) to give 451 mg (64%) of the nitrile **28** and 125 mg (20%) of enyne **29** as colorless oils; ^{1}H NMR (400 MHz) δ 2.91–2.83 (m, 1H), 2.58–2.47 (comp, 2H), 1.35 (d, J=6.8 Hz, 3H), 1.08–1.02 (comp, 21H); ^{13}C NMR (125 MHz) δ 117.4, 108.5, 83.2, 25.4, 24.4, 20.6, 18.5, 11.1; IR (neat) 2943, 2866, 2173, 1463, 1382, 1331, 1120, 996, 883, 667 cm^{-1}; mass spectrum (CI) m/z 250.1991 [$C_{15}H_{28}NSi$ (M+1) requires 250.1991], 250 (base), 206, 157.

Enyne **29**: ^{1}H NMR (500 MHz) δ 5.34–5.33 (m, 1H), 5.24–5.22 (m, 1H), 1.91–1.90 (comp, 3H), 1.08–1.07 (comp, 21H); ^{13}C NMR (125 MHz) δ 127.2, 122.2, 108.5, 89.3, 23.5, 18.6, 11.3; IR (neat) 2944, 2865, 2253, 1465, 1383, 1096 cm^{-1}; mass spectrum (CI) m/z 223.1875 [$C_{14}H_{27}Si$ (M+1) requires 223.1882], 223 (base), 181, 157.

4.1.18. (3*S*)-Methyl-5-triisopropylsilanylpent-4-ynal (23). DIBAL-H (1 M in CH_2Cl_2, 5.4 mL, 5.35 mmol) was added dropwise via syringe to a solution of nitrile **28** (445 mg, 1.78 mmol) in anhydrous CH_2Cl_2 (18 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, whereupon 1 N HCl (5 mL) was added and the cooling bath was removed. The mixture was poured into 1 N HCl (25 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated at atmospheric pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 371 mg (83%) of **23** as a yellow oil; ^{1}H NMR (500 MHz) δ 9.81 (t, J=2.1 Hz, 1H), 2.99 (app sext., J=6.9 Hz, 1H), 2.54 (ddd, J=16.5, 7.4, 2.1 Hz, 1H), 2.48 (ddd, J=16.5, 6.9, 2.1 Hz, 1H), 1.24 (d, J=6.9 Hz, 3H), 1.05–0.98 (comp, 21H); ^{13}C NMR (125 MHz) δ 201.2, 111.0, 81.7, 50.0, 21.8, 21.2, 18.6, 11.2; IR (neat) 2943, 2866, 2167, 1730, 1463, 996, 883, 676 cm^{-1}; mass spectrum (CI) m/z 253.1990 [$C_{15}H_{29}OSi$ (M+1) requires 253.1988], 253 (base), 209, 157.

4.1.19. 3-[(2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (30). Bu_2BOTf (470 μL, 1.88 mmol)[47] was added via syringe to a solution of oxazolidinone **6** (407 mg, 1.57 mmol) and EtN(*i*-Pr)$_2$ (330 μL, 1.88 mmol) in anhydrous PhMe

(11 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, whereupon aldehyde **23** (475 mg, 1.88 mmol) in anhydrous PhMe (2 mL) was added dropwise via syringe. The mixture was stirred at −78 °C for 30 min and then at room temperature for 6 h. The mixture was cooled to 0 °C, whereupon pH 7.0 phosphate buffer (2 mL), MeOH (1 mL), and 30% H_2O_2 (500 μL) were added successively; stirring was continued for 1 h. The mixture was poured into H_2O (30 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to give 705 mg (88%) of **30** as a colorless oil (dr>95:5 by ^1H NMR); ^1H NMR (500 MHz) δ 7.33–7.30 (comp, 2H), 7.27–7.24 (m, 1H), 7.21–7.19 (comp, 2H), 5.88–5.80 (m, 1H), 5.12–5.08 (m, 1H), 5.03–5.01 (m, 1H), 4.68 (ddt, *J*=10.2, 7.0, 3.6 Hz, 1H), 4.28–4.25 (comp, 2H), 4.15–4.09 (comp, 2H), 3.27 (dd, *J*=13.3, 3.2 Hz, 1H), 2.80–2.72 (m, 1H), 2.65–2.56 (comp, 2H), 2.42–2.37 (m, 1H), 1.65–1.60 (m, 1H), 1.54–1.50 (m, 1H), 1.20 (d, *J*=6.8 Hz, 3H), 1.06–0.97 (comp, 21H); ^{13}C NMR (125 MHz) δ 174.8, 153.6, 135.3, 135.2, 129.4, 128.9, 127.3, 117.2, 112.8, 80.8, 70.6, 65.9, 55.6, 47.4, 40.8, 38.0, 32.1, 23.9, 21.7, 18.6, 11.2; IR (neat) 3523, 2942, 2162, 1782, 1698, 1462, 1386, 1350, 1237, 1208, 1102, 997, 918, 883, 702 cm^{-1}; mass spectrum (CI) *m/z* 512.3195 [$C_{30}H_{45}NO_4Si$ (M+1) requires 512.3196], 512 (base), 468, 318.

4.1.20. (2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoic acid methoxymethylamide (31). Me_2AlCl (1 M in hexane, 5.25 mL, 5.25 mmol) was added dropwise via syringe to a solution of HCl·HN(OMe)Me (512 mg, 5.25 mmol) in anhydrous CH_2Cl_2 (8.0 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min, the cooling bath was removed, and stirring was continued at room temperature for 30 min. The mixture was cooled to 0 °C, whereupon alcohol **30** (671 mg, 1.31 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise via syringe. The mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The reaction was quenched at 0 °C with 1 N HCl (5 mL). The mixture was poured into 1 N HCl (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:2) to give 311 mg (60%) of **31** as a colorless oil; ^1H NMR (500 MHz) δ 5.75 (ddt, *J*=17.1, 10.0, 7.0 Hz, 1H), 5.06 (dd, *J*=17.1, 1.6 Hz, 1H), 4.97 (dd, *J*=10.0, 0.8 Hz, 1H), 4.16–4.13 (m, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 3.08–3.00 (br s, 1H), 2.76 (dtd, *J*=10.9, 7.0, 4.1, 1H), 2.55–2.48 (m, 1H), 2.38–2.33 (m, 1H), 1.69 (ddd, *J*=13.4, 10.0, 4.1 Hz, 1H), 1.42 (ddd, *J*=13.4, 10.9, 2.4 Hz, 1H), 1.20 (d, *J*=7.0 Hz, 3H), 1.05–0.96 (comp, 21H); ^{13}C NMR (125 MHz) δ 176.2, 136.1, 116.7, 113.2, 80.5, 70.3, 61.5, 45.3, 42.0, 31.9, 30.9, 24.0, 21.8, 18.6, 11.2; IR (neat) 3449, 2941, 2865, 2161, 1640, 1463, 1384, 994, 817, 883, 676 cm^{-1}; mass spectrum (CI) *m/z* 396.2934 [$C_{22}H_{42}NO_3Si$ (M+1) requires 396.2934], 397 (base), 352.

4.1.21. (2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-7-triisopropylsilanylhept-6-ynoic acid methoxymethylamide (32). To a solution of the preceding amide (262 mg, 0.662 mmol) in anhydrous CH_2Cl_2 (9.5 mL) at 0 °C was added 2,6-lutidine (460 μL, 3.97 mmol) and TBDMSOTf (300 μL, 1.32 mmol). The resulting solution was stirred at 0 °C for 1 h, whereupon MeOH (3 mL) was added and the cooling bath removed. After warming to room temperature, the mixture was poured into H_2O (20 mL), and the resulting biphasic mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexane/EtOAc (3:1) to give 334 mg (99%) of **32** as a yellow oil; ^1H NMR (500 MHz) δ 5.74 (ddt, *J*=17.1, 10.0, 7.1 Hz, 1H), 5.07–5.02 (m, 1H), 4.97–4.94 (m, 1H), 4.11–4.07 (m, 1H), 3.62 (s, 3H), 3.15 (s, 3H), 3.08–3.00 (br s, 1H), 2.55–2.49 (m, 1H), 2.45–2.40 (m, 1H), 2.26–2.21 (m, 1H), 1.67–1.62 (comp, 2H), 1.18 (d, *J*=7.0 Hz, 3H), 1.06–0.96 (comp, 21H), 0.86 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 174.4, 136.5, 116.4, 113.5, 80.6, 72.2, 61.1, 47.5, 42.7, 33.3, 32.0, 26.0, 24.1, 22.2, 18.6, 18.1, 11.3, −4.2; IR (neat) 2941, 2864, 2163, 1668, 1463, 1382, 1253, 1096, 996, 883, 838, 776, 676 cm^{-1}; mass spectrum (CI) *m/z* 510.3798 [$C_{28}H_{56}NO_3Si_2$ (M+1) requires 510.3799], 510 (base), 466, 452.

4.1.22. (3*S*)-Allyl-(4*R*)-(*tert*-butyldimethylsilanyloxy)-(6*S*)-methyl-8-triisopropylsilanyloct-7-yn-2-one. MeMgBr (3 M in Et_2O, 1.10 mL, 3.27 mmol) was added dropwise via syringe to a solution of the preceding amide (333 mg, 0.653 mmol) in anhydrous THF (6.6 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 1.5 h, whereupon saturated aqueous NH_4Cl (5 mL) was added. The mixture was poured into a 15% brine solution (20 mL), and the resulting biphasic mixture was extracted with EtOAc (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to give 292 mg (96%) of the ketone as a yellow oil; ^1H NMR (500 MHz) δ 5.72 (ddt, *J*=17.1, 10.3, 7.2 Hz, 1H), 5.05–4.96 (comp, 2H), 4.12–4.08 (m, 1H), 2.83–2.79 (m, 1H), 2.59–2.50 (m, 1H), 2.45–2.38 (m, 1H), 2.22 (s, 3H), 2.04–1.97 (m, 1H), 1.51–1.44 (m, 1H), 1.29–1.22 (m, 1H), 1.18 (d, *J*=6.8 Hz, 3H), 1.08–1.01 (comp, 21H), 0.92 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz) δ 210.1, 136.2, 116.5, 113.0, 81.0, 72.1, 58.9, 41.2, 32.8, 32.3, 25.9, 24.2, 22.2, 18.6, 18.1, 11.5, −4.0, −4.6; IR (neat) 2942, 2865, 2162, 1714, 1642, 1463, 1253, 1171, 1085, 837, 776, 677 cm^{-1}; mass spectrum (CI) *m/z* 465.3582 [$C_{27}H_{53}O_2Si_2$ (M+1) requires 465.3584], 465, 449, 421 (base), 407, 367, 199.

4.1.23. Trifluoromethanesulfonic acid (2*S*)-allyl-(3*R*)-(*tert*-butyldimethylsilanyloxy)-(5*S*)-methyl-1-methylene-7-triisopropylsilanylhept-6-ynyl ester (22). A solution of the preceding ketone (48 mg, 0.103 mmol) in anhydrous THF (200 μL) was added dropwise via cannula to a solution of KHMDS (0.5 M in PhMe, 410 μL, 0.207 mmol) in THF (200 μL) at −78 °C. The solution was stirred at −78 °C for 20 min, whereupon triflimide **33** (100 mg, 0.258 mmol) in anhydrous THF (300 μL) was added via cannula. The resulting mixture was stirred at −78 °C for 1 h, 0 °C for 1 h, then at room temperature for 1 h. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (2 mL). The mixture was poured into a 15% brine solution (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL).

The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (20:1) to give 55 mg (89%) of **22** as a yellow oil; ^1H NMR (500 MHz) δ 5.75 (ddt, J=17.1, 10.2, 6.8 Hz, 1H), 5.24 (d, J=4.0 Hz, 1H), 5.11–5.04 (comp, 2H), 4.91 (d, J=4.0 Hz, 1H), 4.08–4.05 (m, 1H), 2.60–2.52 (m, 1H), 2.51–2.48 (m, 1H), 2.29–2.19 (comp, 2H), 1.54–1.45 (comp, 2H), 1.19 (d, J=7.0 Hz, 3H), 1.06–0.99 (comp, 21H), 0.87 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{19}F NMR (470 MHz) δ −74.59 (s, 3F); ^{13}C NMR (125 MHz) δ 155.9, 134.9, 118.4 (J_{CF}=320.3 Hz), 117.4, 112.8, 105.7, 81.1, 71.7, 51.1, 41.5, 32.5, 25.9, 24.1, 22.2, 18.6, 18.1, 11.2, −4.1, −4.4; IR (neat) 2942, 2865, 2162, 1660, 1422, 1251, 1213, 1143, 936, 838, 776, 677 cm^{-1}; mass spectrum (CI) m/z 597.3078 [$C_{28}H_{52}O_4Si_2F_3$ requires 597.3077], 597, 441, 367 (base).

4.1.24. (3*R*)-Allyl-(4*R*)-(*tert*-butyl-dimethyl-silanyloxy)-(6*S*)-methyl-2-methylene-8-triisopropylsilanyl-oct-7-ynoic acid methyl ester (34). A solution of **22** (54 mg, 0.091 mmol) in anhydrous DMF (400 μL) was degassed by bubbling with a stream of CO for 5 min and then added to a solution of similarly degassed anhydrous MeOH (150 μL, 3.62 mmol), Et_3N (25 μL, 0.181 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and PPh_3 (4 mg, 0.0181 mmol). The mixture was stirred under an atmosphere of CO (balloon) at room temperature for 3.5 h. The reaction mixture was poured into H_2O (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (20:1) to give 39 mg (85%) of **34** as a yellow oil; ^1H NMR (500 MHz) δ 6.27–6.26 (m, 1H), 5.47–5.46 (m, 1H), 5.72–5.64 (m, 1H), 4.99–4.92 (comp, 2H), 3.95 (ddd, J=9.2, 5.0, 2.7 Hz, 1H), 3.71 (s, 3H), 2.95–2.91 (m, 1H), 2.58–2.50 (m, 1H), 2.42–2.37 (m, 1H), 2.22–2.16 (m, 1H), 1.56–1.51 (m, 1H), 1.40–1.35 (m, 1H), 1.16 (d, J=6.8 Hz, 3H), 1.06–1.00 (comp, 21H), 0.85 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz) δ 168.1, 140.5, 136.7, 126.0, 116.1, 113.5, 80.5, 72.7, 51.8, 46.0, 42.3, 34.2, 26.0, 23.9, 22.1, 18.6, 18.2, 11.3, −4.0, −4.1; IR (neat) 2943, 2864, 2163, 1724, 1463, 1253, 1155, 1090, 1058, 996, 883, 837, 775, 660 cm^{-1}; mass spectrum (CI) m/z 507.3688 [$C_{29}H_{55}O_3Si_2$ (M+1) requires 507.3690], 507 (base), 449, 375.

4.1.25. (4*R*)-Allyl-(5*R*)-[(2*S*)-methylbut-3-ynyl]-3-methylenedihydrofuran-2-one (21). A solution of TBAF·$3H_2O$ (74 mg, 0.233 mmol) in THF (500 μL) was added via syringe to a solution of acrylate **34** (38 mg, 0.075 mmol) in anhydrous THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The mixture was poured into saturated aqueous NH_4Cl (10 mL), and the resulting biphasic mixture was extracted with Et_2O (3×5 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography eluting with pentane/Et_2O (3:1) to give 12 mg (78%) of **21** as a yellow oil; ^1H NMR (400 MHz) δ 6.23 (d, J=2.2 Hz, 1H), 5.77 (ddt, J=17.1, 10.3, 6.8 Hz, 1H), 5.57 (d, J=2.2 Hz, 1H), 5.17–5.09 (comp, 2H), 4.89 (ddd, J=10.9, 7.2, 2.4 Hz, 1H), 3.20–3.13 (m, 1H), 2.82–2.73 (m, 1H), 2.37–2.22 (comp, 2H), 2.09 (d, J=2.4 Hz, 1H), 1.69–1.62 (m, 1H), 1.59–1.52 (m, 1H), 1.23 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 170.4, 138.6, 134.4, 122.3, 118.3, 87.3, 79.1, 69.9, 42.3, 38.1, 32.6, 23.0, 21.7; IR (neat) cm^{-1}; mass spectrum (CI) m/z 205.1229 [$C_{13}H_{17}O_2$ (M+1) requires 205.1229], 409 (dimer), 205 (base).

4.1.26. 8-*epi*-Xanthatin (1). A solution of lactone **21** (7 mg, 0.034 mmol) in anhydrous CH_2Cl_2 (6.9 mL) was degassed by bubbling through a stream of argon for 10 min, whereupon freshly distilled methyl vinyl ketone (29 μL, 0.34 mmol) and catalyst **17** (4.3 mg, 0.007 mmol) was added. The mixture was stirred at 45 °C for 12 h and then cooled to room temperature, whereupon DMSO (50 μL) was added and stirring continued for 6 h. The mixture was concentrated and then purified by flash chromatography eluting with Et_2O to give 7 mg (83%) of **1** as a colorless oil; $[\alpha]_D^{24}$ +23.4 (c 0.333, $CHCl_3$); ^1H NMR (400 MHz) δ 6.97 (d, J=16.1 Hz, 1H), 6.32 (d, J=3.4 Hz, 1H), 6.20 (dd, J=9.0, 6.3 Hz, 1H), 6.13 (d, J=16.1 Hz, 1H), 5.57 (d, J=2.9 Hz, 1H), 4.68–4.62 (m, 1H), 3.45–3.37 (m, 1H), 2.87–2.78 (m, 1H), 2.65–2.56 (m, 1H), 2.53–2.46 (m, 1H), 2.29 (s, 3H), 2.17 (ddd, J=14.2, 7.1, 2.2 Hz, 1H), 1.95–1.86 (m, 1H), 1.17 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 198.7, 170.0, 146.7, 143.1, 138.3, 135.9, 126.1, 122.8, 78.4, 41.4, 36.5, 31.9, 27.9, 27.2, 21.7; IR (neat) 2957, 2360, 1761, 1664, 1619, 1592, 1274, 1256, 980 cm^{-1}; mass spectrum (CI) m/z 247.1333 [$C_{15}H_{19}O_3$ (M+1) requires 247.1334], 247 (base), 249.

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6, 2.5 Hz), 1.91 (ddd, J=14, 12, 12 Hz), 1.18 (d, J=7 Hz).[44] ^{13}C NMR ($CDCl_3$) δ 198.3, 169.6, 146.4, 142.7, 138.0, 135.6, 125.8, 122.4, 78.1, 41.1, 36.2, 31.6, 27.6, 26.9, 21.4.[2b]

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Amino acid-peptide-catalyzed enantioselective Morita–Baylis–Hillman reactions

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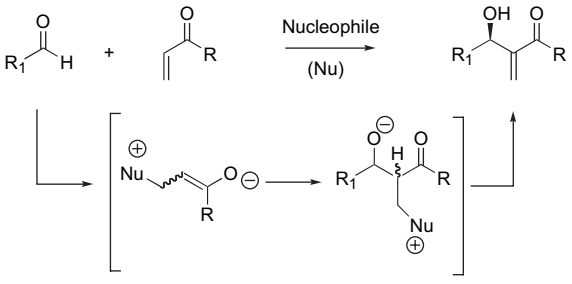
This article is dedicated to Professor David W. C. MacMillan on the occasion of his receiving the Tetrahedron Young Investigator Award

Abstract—Peptide-based catalysts in the presence of proline as co-catalyst have been found to catalyze the enantioselective ketone-based Morita–Baylis–Hillman reaction. The co-catalyst combination has afforded catalysis where enantioselectivities of up to 81% have been obtained.

1. Introduction

Our laboratory has been investigating peptide-based nucleophiles and bases that enable a number of new enantioselective processes, including catalytic asymmetric group transfers (acylation,[1] phosphorylation,[2] sulfinylation[3]), azidation,[4] and carbon–carbon bond-forming reactions.[5] Due to the diversity of function and structure that peptides provide,[6] we sought to extend the scope of these catalysts to the enantioselective Morita–Baylis–Hillman reaction.[5d] The Morita–Baylis–Hillman (MBH) reaction is a powerful carbon–carbon bond-forming reaction whose multi-step mechanism allows numerous possibilities for catalyst intervention (Eq. 1).[7] There have been many recent contributions to the enantioselective MBH reaction.[8] Hatakeyama and co-workers have developed cinchona alkaloid-based chiral nucleophiles for the acrylate ester-based MBH reaction in excellent enantioselectivities.[9] In addition, Shi and Jiang have reported the Hatakeyama's cinchona alkaloid catalyst, in the presence of proline as a co-catalyst, affords up to 31% ee for the methyl vinyl ketone (MVK)-based MBH reaction.[10] In an important control study, Shi and co-workers had shown that the co-catalyst system of proline and imidazole was effective for the production of MBH products, albeit with minimal ee.[11]



(1)

2. Results and discussion

We embarked upon studying the ketone-based Morita–Baylis–Hillman reaction by first screening a variety of substrates, including aldehydes and activated alkenes using *N*-methyl imidazole (NMI) as catalyst. In analogy to Shi and co-workers, we likewise were interested in determining whether NMI would serve as a catalyst in the MVK-Morita–Baylis–Hillman reaction. We reasoned if imidazole could catalyze the MBH reaction in the presence of L-proline, then NMI should also serve as a catalyst. Indeed, initial experiments demonstrated that NMI could catalyze the Morita–Baylis–Hillman reaction of MVK and 4-nitrobenzaldehyde (Fig. 1a), although only affording 40% conversion after 24 h. Using only proline as a catalyst afforded no reaction in the same time frame.[12] However, the combination of proline and NMI (10 mol % each) led to a near doubling of rate, yielding 75% conversion to the desired Morita–Baylis–Hillman product within 24 h (Fig. 1c). Interestingly, MBH product **1** was generated with <10% ee, implying that the chirality of L-proline did not lead to substantial ee in this case.

Abbreviations: Chg, α-cyclohexylglycine; Cha, 3-cyclohexylalanine; Phe, phenylalanine; Ala, alanine; Leu, leucine; Pro, proline; Trp(Boc), Boc protected tryptophan; HPhe, homophenylalanine; $Arg(Boc)_2$, di-Boc protected arginine; Gln(Trt), trityl protected glutamine; Pip, pipecolinic acid.

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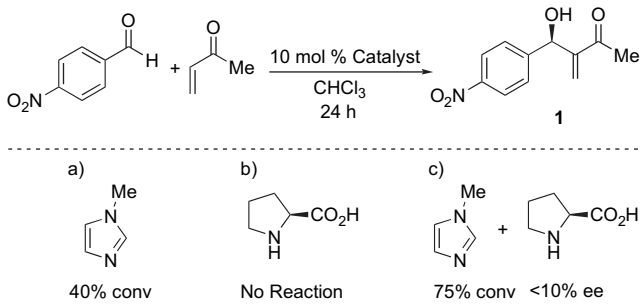


Figure 1. MBH reaction of 4-nitrobenzaldehyde and MVK in the presence of (a) NMI as catalyst, (b) Proline (Pro) as catalyst, and (c) co-catalyst combination of NMI and Pro.

Optimistic that replacing NMI with π-(methyl)histidine (Pmh)-containing peptides could afford an enantioselective reaction, we set out to screen peptide catalysts in the MVK-MBH reaction. We began screening libraries of peptides, which were available in our laboratory. These libraries consisted of tetrapeptides and octapeptides, which were biased toward β-hairpin scaffolds,[13] as well as pentapeptides, which were unbiased. The pentapeptides consisted of sequences, which contained Pmh at the *i*-position and at the *i*+4-position either an alanine or phenylalanine. Positions *i*+1 through *i*+3 were random sequences of 16 different amino acids.[14]

A selectivity profile from this initial catalyst screen of 105 peptides revealed a number of interesting trends.[15] Of the peptide catalysts screened, peptides, which provided up to 21% ee for the reaction of 4-nitrobenzaldehyde and MVK in the presence of proline were identified (Fig. 2).

Examining peptide catalysts which afforded 17–21% ee in the initial peptide screen offered useful comparisons. Three of the most active peptides screened showed homology within the peptide framework. Peptides **2**–**4** contained

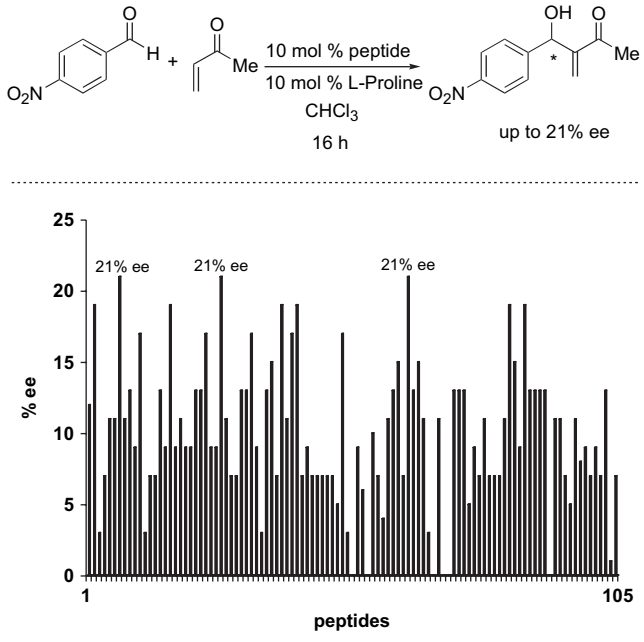


Figure 2. Initial screen of peptide catalysts in the MVK-MBH reaction.

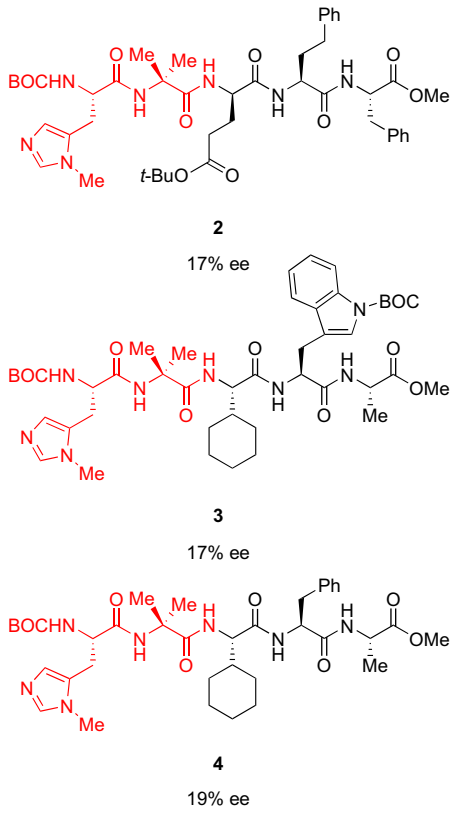


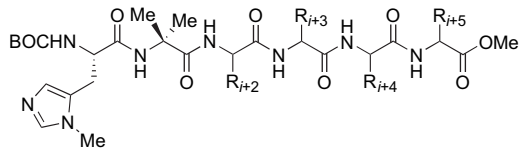
Figure 3. Selective pentapeptides which contain similar sequences.

Boc-Pmh at the *i*-position and Aib (α-aminoisobutyric acid) at the *i*+1-position, followed by the rest of the peptide sequence (Fig. 3).[16]

Based on the trends apparent within the peptide sequences of catalysts **2**–**4**, we speculated that the information embedded within the residues of these peptides would lead to an improved peptide catalyst. Thus, we began exploring the structure–activity relationship (SAR) of each position of peptides **3** and **4**.[17] Capitalizing on the Boc-Pmh-Aib sequence specificity at the N-terminus of the peptide, we made single point mutations on the peptide. We immediately discovered upon synthesizing modified catalysts that different peptide sequences could lead to higher ee, including 57% ee in the reaction of 2-nitrobenzaldehyde with MVK in the presence of proline (Fig. 4).[18] (At this stage, we began a parallel screen of both the 2- and 4-substituted nitrobenzaldehyde substrates.) Peptide **6**, with Cha at the *i*+2-position, yields 57% ee in the MBH product; peptide **5** resulted in 45% ee. Stereochemical modifications within the peptide sequence also proved to have a significant effect on the enantioselectivity. For example, peptide **7**, with D-Ala at the *i*+2-position, delivers reduced selectivity (23% ee).

We were also curious whether increasing the peptide chain length would perturb selectivity. To this end, we synthesized peptides of variable chain length. Hexamers **8** and **9** led to increased enantioselectivity (Fig. 4, peptide **8**, 47% ee and peptide **9**, 49% ee; cf. peptide **5**, 45% ee).

At this stage, we had observed that both residue identity and chain length were determinants of reaction enantioselectivity.



Peptide	R_{i+2}	R_{i+3}	R_{i+4}	R_{i+5}	%ee
5	Chg	Phe	D-Phe	-	45
6	Cha	Phe	D-Phe	-	57
7	D-Ala	Phe	D-Phe	-	23
8	Chg	Phe	D-Phe	D-Phe	47
9	Chg	Phe	D-Phe	Phe	49

Figure 4. Preliminary SAR based on hit pentapeptide sequences.

Therefore, we sought a method to rapidly screen the catalysts. A more combinatorial approach to the synthesis of new peptides was desired.[19] A 42-membered directed library[20] of hexapeptides was synthesized based on peptides **8** and **9**. The focused library incorporated 20 unique amino acids into the *i*+1 through *i*+4 positions of the hexamer sequence.[21] The amino acids that were used are listed in the abbreviations on the first page of the article.

The 42 peptides, which were synthesized in the library were then screened in the MBH reaction. The peptide selectivities ranged from 25 to 61% ee in the reaction of 2-nitrobenzaldehyde and MVK in the presence of L-proline and peptide catalyst (10 mol % each) at room temperature. Peptides **10** and **11** indeed provided a boost in enantioselectivity, with catalyst **10** affording 60% ee and peptide **11** yielding MBH product in 61% ee (Fig. 5).

At this stage, we wondered whether further extension of the peptide chain would continue to afford more selective catalysts. Because peptide **11** had afforded the highest level of selectivity in the MBH reaction, we took this sequence and continued to optimize in an iterative manner.[22] Representative amino acids were evaluated at the *i*+5, *i*+6, and *i*+7 positions. While aliphatic, aromatic, branched aliphatic, and other amino acids were inserted at each position, it is important to note that at no position was a comprehensive set of residues explored. Thus, we remain uncertain as to whether the optimum sequence has been discovered. Nevertheless, our observations indicated that heptameric and octameric sequences appeared to increase the enantioselectivity of the reaction. However, upon reaching the decapeptide stage, the enantioselectivity appeared to plateau (Table 1).[23] It is important to underscore further that at no sequence length was a comprehensive exploration of residues explored. Thus, although peptide **18** emerged as that exhibiting maximum enantioselectivity (78% ee), it may be that superior sequences may be found at shorter chain lengths, or longer sequences. Efficient methodology for a comprehensive survey of residues at a given chain length is, at this time, elusive.[24]

With a co-catalyst combination of octapeptide **18**-proline available that afforded MBH product **1** in 78% ee, we wished

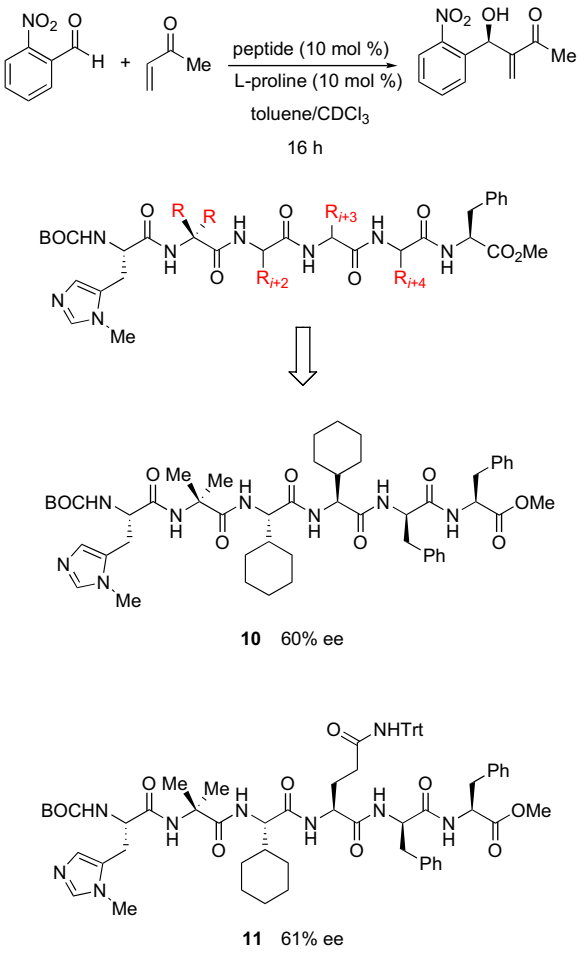
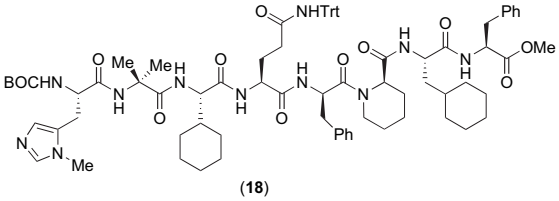


Figure 5. Directed library design for the synthesis of 42 new hexapeptides.

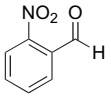
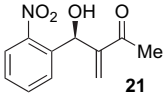
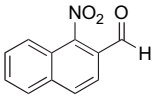
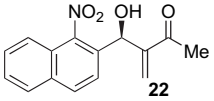
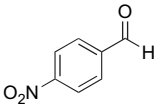
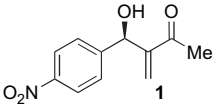
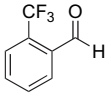
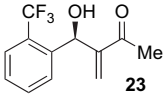
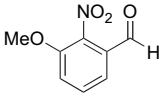
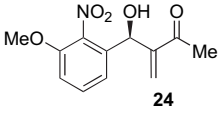
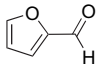
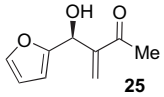
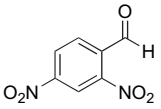
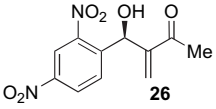
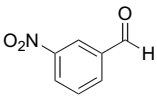
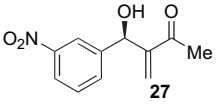
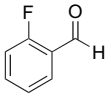
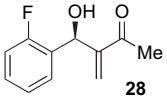
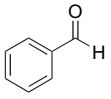
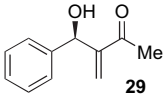
Table 1. Catalyst screen for the MVK-MBH reaction with 2-nitrobenzaldehyde[a]

Entry	Catalyst	% ee[b]
1	Boc-Pmh-OMe (**12**)	19
2	Boc-Pmh-Aib-OMe (**13**)	33
3	Boc-Pmh-Aib-Phe-OMe (**14**)	33
4	Boc-Pmh-Aib-Phe-D-Phe-OMe (**15**)	40
5	Boc-Pmh-Aib-Cha-hPhe-D-Phe-OMe (**16**)	47
6	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-Phe-OMe (**11**)	61
7	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-(Boc)Trp-Phe-OMe (**17**)	73
8	 (**18**)	78
9	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Phe-Phe-OMe (**19**)	75
10	Boc-Pmh-Aib-Chg-Gln(Trt)-D-Phe-D-Pip-Cha-Val-(Boc)Trp-Phe-OMe (**20**)	74

[a] All reactions were conducted at 25 °C and proceeded to >75% conversion within 16 h as determined by ^{1}H NMR.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

to determine whether alteration of other reaction parameters could lead to improved selectivity and overall efficiency.[25] We also set out to determine whether the optimized reaction conditions were specific for 2-nitrobenzaldehyde. A variety of aromatic aldehydes were found to provide acceptable levels of reactivity in the MVK-based MBH reaction. As Table 2 illustrates, we observed 81% ee and 88% yield when 3-methoxy-2-nitrobenzaldehyde was used as a substrate (entry 5). Nitronaphthaldehyde participated in the MBH reaction affording **22** in up to 73% ee and in 92% yield (entry 2). *p*-Nitrobenzaldehyde and dinitrobenzaldehyde undergo the MBH reaction with MVK in 69 and 63% ee, respectively (81% yield, entry 3; 89% yield, entry 7). Another aldehyde examined was *o*-trifluoromethylbenzaldehyde, which afforded MBH product **23** in 71% ee and 52% yield (entry 4). Furaldehyde participates in the reaction generating MBH product **25** in 63% ee (entry 6).[26] In addition, 2-fluorobenzaldehyde undergoes the MBH reaction under the optimized reaction conditions in 65% ee with 55% yield (entry 9). Finally, two aldehydes which provided lower selectivities under the reaction conditions were 3-nitrobenzaldehyde and benzaldehyde, affording selectivities of 45 and 41% ee, respectively (entries 8 and 10).

Table 2. Substrate screen for the MVK-MBH reaction with co-catalyst **18**/Pro[a]

Entry	Substrate	BH product	% Yield	% ee[b]
1		 **21**	81	78
2		 **22**	92	73
3		 **1**	81	69
4		 **23**	52	71
5		 **24**	88	81
6[c]		 **25**	95	63
7		 **26**	89	63
8		 **27**	74	45
9		 **28**	55	65
10		 **29**	55	41

[a] All reactions were conducted at 25 °C and proceeded to >75% conversion within 16 h as established by ^{1}H NMR. Isolated yields are after silica gel chromatography.

[b] Enantioselectivities were determined by chiral HPLC. Reported ee values are the average of at least two runs.

[c] Reaction with furaldehyde, yield refers to conversion by ^{1}H NMR; isolated yields after catalytic hydrogenation of the olefin are comparable.

Other aldehydes in addition to those listed in Table 2 were examined as possible substrates for this reaction. These included a variety of aliphatic, 'nonactivated' aromatic aldehydes, and unsaturated aldehydes. Unfortunately, no reaction was observed with the following aldehydes: propionaldehyde, isobutyraldehyde, *trans*-cinnamaldehyde, cyclohexanecarboxaldehyde, 1-naphthaldehyde, hydrocinnamaldehyde, and *o*-tolualdehyde. The scope of the ketone partner was also investigated. Under the optimized reaction conditions, ethyl vinyl ketone (EVK) participates in the reaction with 2-nitrobenzaldehyde to deliver the product with a reduced selectivity of 69% ee. Other substituted ketones we examined afforded no reaction under the optimized conditions. For example, phenyl vinyl ketone, cyclohexyl vinyl ketone, and *tert*-butyl vinyl ketone were all screened in this reaction and exhibited no reactivity. Furthermore, non-ketone-based α,β-unsaturated compounds such as various acrylates and acrylonitriles were also unreactive under the reaction conditions. Clearly, further studies of these systems are necessary if expansion of substrate scope and reaction generality is to be achieved.

To probe the nature of proline–peptide catalyst interaction, we set out to identify the importance of the proline component in these reactions. In the absence of proline, catalyst **18** affords <10% ee, with low conversion. As noted earlier, the NMI-proline co-catalyst system provided MBH product in <10% ee. Thus, we felt the specific interactions of the peptide–proline co-catalyst system could be important. To probe these effects, we performed parallel co-catalytic reactions with octapeptide **18** and both enantiomers of proline. Indeed, double stereodifferentiating effects were observed. Whereas the combination of L-proline and octapeptide **18** affords (*R*)-Morita–Baylis–Hillman product **21** in 78% ee, the catalyst pair of D-proline and octapeptide **18** yields (*S*)-**21** in a reduced 39% ee (Fig. 6). Intriguingly, the opposite enantiomer is formed when using D-proline in the reaction. The enantiodivergence occurring in this reaction is of interest because it suggests that the stereochemistry of proline dictates which enantiomer of MBH product is formed.[27,28]

In order to further investigate the role of the amino acid component, we screened a number of other amino acids and derivatives as the co-catalyst. As illustrated in Table 3, other amino acids such as valine, alanine, phenylalanine, histidine, and tyrosine (entry 1) do not afford appreciable levels of enantioselectivity in the reaction of 2-nitrobenzaldehyde and MVK with peptide **18**. Protected versions of the amino acids are also not selective (entry 2). Of interest is sarcosine (entry 4), in stark contrast to glycine (entry 3), indeed affords

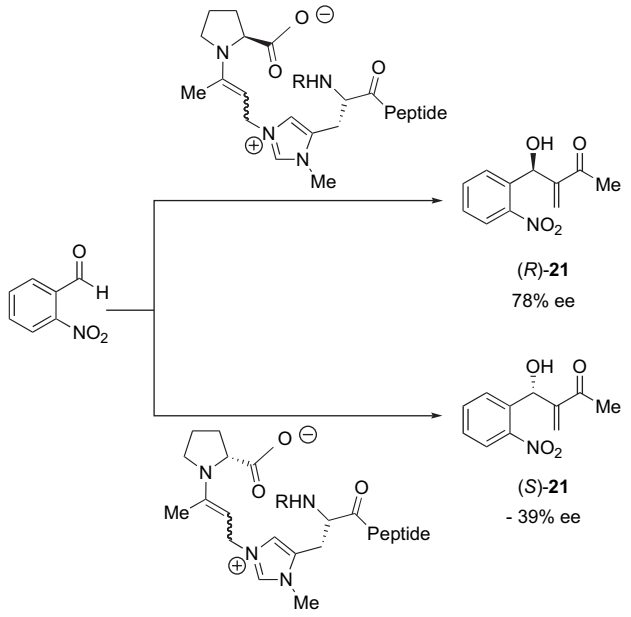
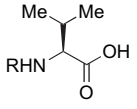
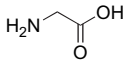
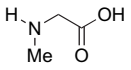
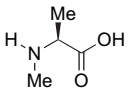
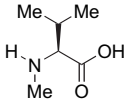
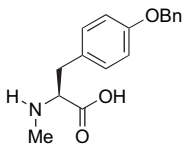


Figure 6. Matched and mismatched pairs of co-catalysts with proline and peptide **18**.

modest levels of enantioselectivity in the MBH reaction with peptide **18**. Because sarcosine provided appreciable levels of selectivity (44% ee in the MBH reaction with peptide **18**), we felt that screening a variety of *N*-methyl amino acids could provide useful information. Thus, a number of *N*-methyl amino acids were synthesized and screened; most of these amino acid derivatives afforded <11% ee for the MBH reaction (entries 6 and 7).[29] However, as shown in Table 3, *N*-methyl alanine (entry 5) afforded up to 31% ee in the reaction. From the data, one could conclude that more sterically hindered *N*-methyl amino acids begin to erode selectivity; however, sarcosine and *N*-methyl alanine allow for modest levels of enantiodiscrimination.

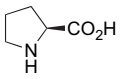
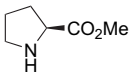
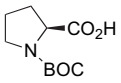
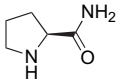
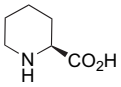
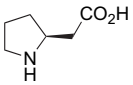
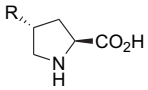
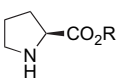
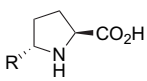
In addition to screening amino acid and amino acid derivatives as co-catalysts for the MBH reaction, we also examined other proline derivatives to explore the unique role of proline as a co-catalyst with peptide **18**. Simple modifications to the proline bifunctional nature (i.e., the amine and carboxylic acid termini, as in entries 2–4, 8, and 9; Table 4[30]) yield nonselective reactions with enantioselectivities of <10% ee. Furthermore, subtle alterations to the proline framework such as pipecolinic acid and homo-proline (entries 5 and 6)

Table 3. Amino acid co-catalysts in the MBH reaction with peptide **18**[a]

Entry	Co-catalyst	% ee[b]
1	(L)-Val, (L)-Ala, (L)-Phe, (L)-His, (L)-Tyr, (D)-Phe	<10
2	 R = BOC, FMOC	<10
3		<10
4		44
5		31
6		11
7		<10

[a] All reactions were conducted at 25 °C.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

Table 4. Proline derivatives as catalysts in the MBH reaction with **18**[a]

Entry	Compound	% ee[b]
1		78
2		<10
3		<10
4		<10
5		21
6		35
7	 R = O*t*Bu R = OH	39 <10
8		<10
9	 R = Li or Na	<10
10	 R = Me, Ph, vinyl	33–40

[a] All reactions were conducted at 25 °C.
[b] Determined by chiral HPLC. Reported ee values are the average of at least two runs.

afforded significantly reduced selectivities (21 and 35% ee, respectively). The reduced selectivity of pipecolinic acid is particularly noteworthy in light of our recent observation that NMI-pipecolinic acid is a particularly effective co-catalyst system for the intramolecular version of the MBH reaction.[5a] Hydroxy-proline derivatives also yield reduced selectivities (entry 7, 39 and <10% ee, depending on the protection of the hydroxyl group). In addition, 5-substituted proline derivatives were also synthesized and examined. 5-Substituted methyl, phenyl, and vinyl prolinates[31] (entry 10) were tested as co-catalysts in the MBH reaction with peptide **18**. These derivatives also provided lower selectivity than proline (entry 1) affording 33–40% ee in the MBH reaction.[32]

3. Conclusions

The data collected thus far indicate that a specific peptide–proline co-catalyst interaction may operate to afford an enantioselective reaction. A cohesive transition state assembly such as **30** could be operative (Fig. 7a). Enamines derived from proline have been shown to be effective asymmetric scaffolds for enantioselective reactions.[33] Perhaps the Pmh nucleophilic amine of the peptide catalyst adds to the proline iminium ion formed between MVK and proline. The addition product **30** could be stabilized by hydrogen bonding of the peptide backbone with the carboxylic acid of proline. However, the possibility of a two-catalyst transition state involving the peptide and proline-MVK conjugate addition product **31** is also a possible transition state (Fig. 7b). Not surprisingly, control experiments involving MVK and proline alone show efficient conjugate addition of the amine to the enone.

Exactly, which intermediates and transition states operate, **30** or **31**, a combination of both, or even another alternative transition state, is a matter of current investigation in our laboratory.[34] The possibility to fine-tune these peptide–proline interactions also presents a possible strategy for asymmetric catalyst development. Uncovering the identity of the non-covalent interactions responsible for the high levels of enantioselectivity observed for this reaction remains a challenge. In addition, understanding the precise role of the helix-inducing residue Aib, which proved to be important in obtaining selective peptide catalysts, represents another important task in our ongoing studies.[13]

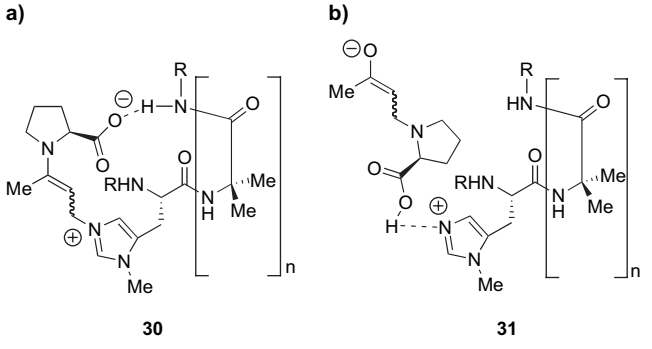


Figure 7. Possible transition state assemblies involving (a) proline–enamine intermediates and (b) peptide–proline-MVK conjugate addition product intermediates.

In summary, we have demonstrated success in the catalytic, asymmetric ketone-based Morita–Baylis–Hillman reaction using methyl vinyl ketone and a variety of aromatic aldehydes. Our catalyst system involves a peptide-based catalyst in the presence of proline as a co-catalyst. This co-catalyst system has enabled state-of-the-art enantioselectivities in the intermolecular MVK-MBH reaction with aldehydes, affording enantioselectivities in up to 81% ee. We have uncovered a unique peptide–proline co-catalyst interaction. Understanding such interactions could enable the discovery of other selective peptide catalysts and co-catalyst interactions, which could serve as catalysts for other carbon–carbon bond-forming reactions and group transfers. These explorations are currently underway in our laboratory.

4. Experimental

4.1. General

4.1.1. General procedures. Proton NMR spectra were recorded on a Varian 400 spectrometer. Proton chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ, 0.0 ppm), or with the solvent reference relative to TMS employed as an internal standard ($CDCl_3$, δ, 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constants [hertz], integration). Carbon NMR spectra were recorded on a Varian 400 (100 MHz) or 500 (125 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ, 77.0 ppm). All NMR spectra were acquired at ambient temperature. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 Å F_{254} precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, cerium ammonium molybdenate (CAM), or ninhydrin solutions. Flash column chromatography was performed using silica gel 60 Å (32–63 μm). Optical rotations were recorded on a Rudolph Research Analytical Autopol IV Automatic polarimeter at the sodium D line (path length 50 mm). High resolution mass spectra were acquired in the Mass Spectrometry facility at Boston College (Chestnut Hill, MA) or at the University of Illinois (Urbana-Champaign, IL). The method of ionization is indicated in parenthesis.

Analytical and preparative reverse phase HPLC were performed on a Rainin SD-200 chromatograph equipped with a single wavelength UV detector (214 or 254 nm). Analytical normal phase HPLC was performed on a Hewlett–Packard 1100 Series chromatograph equipped with a diode array detector (214 and 254 nm). All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Benzaldehyde and 2-furaldehyde were freshly distilled while all other aldehydes were used as received. Methyl vinyl ketone was used as received (Aldrich

Chemical Company, 99%). HPLC grade chloroform was purified by the method of Perrin.[35] $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc., and used as received in the catalytic reactions.[36] Stereochemical proofs were conducted as previously reported.[37]

4.1.2. Peptide synthesis. Peptides **11–20** were synthesized on commercially available Fmoc-Phe-Wang polystyrene solid support. Couplings were performed with 4 equiv of amino acid, 4 equiv of HBTU, and 8 equiv Hünig's base in DMF, for 3 h. Deprotections were performed in the presence of 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation; dipeptides were deprotected with 50% piperidine in DMF for 5 min). Peptides were cleaved from solid support by using a mixture of MeOH/DMF/Et_3N (9:1:1) for 3 days. The peptides were characterized by electrospray mass spectrometry (ESI^+) and used in reaction screens without further purification.

4.1.3. Data for peptides 11–20.

4.1.3.1. Boc-Pmh-OMe (12). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.78 (s, 1H), 5.22 (br d, J=7.6 Hz, 1H), 4.54 (m, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.09 (m, 2H), 1.43 (s, 9H); TLC R_f 0.51 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{13}H_{21}N_3O_4+H]^+$ requires m/z 284.1610. Found 284.1609 (FAB^+). HPLC retention time 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

4.1.3.2. Boc-Pmh-Aib-OMe (13). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 5.17 (s, 1H), 4.27 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.03 (d, J=6.4 Hz, 2H), 1.50 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H); TLC R_f 0.40 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{17}H_{28}N_4O_5+H]^+$ requires m/z 369.2138. Found 369.2138 (FAB^+). HPLC retention time 1.4 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.3 mL/min.

4.1.3.3. Boc-Pmh-Aib-Phe-OMe (14). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.30–7.11 (m, 5H), 6.81 (s, 1H), 6.78 (d, J=7.6 Hz, 1H), 6.73 (s, 1H), 5.25 (d, J=6.4 Hz, 1H), 4.82 (dd, J=13.6 Hz, 6.4 Hz, 1H), 4.19 (m, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.06 (m, 4H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 9H); TLC R_f 0.43 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{26}H_{37}N_5O_6+H]^+$ requires m/z 516.2822. Found 516.2823 (FAB^+). HPLC retention time 2.0 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.4. Boc-Pmh-Aib-Phe-D-Phe-OMe (15). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.33–7.15 (m, 10H), 6.86 (s, 1H), 6.76 (d, J=7.6 Hz, 1H), 6.58 (s, 1H), 5.10 (d, J=6.0 Hz, 1H), 4.80–4.69 (m, 2H), 4.25–4.20 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.39 (m, 2H), 3.16–3.04 (m, 3H), 2.98–2.88 (m, 2H), 1.44–1.40 (m, 15H); TLC R_f 0.44 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{35}H_{46}N_6O_7+Na]^+$ requires m/z 685.3326. Found 685.3322 (ESI^+). HPLC retention time 2.5 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.5. Boc-Pmh-Aib-Cha-hPhe-D-Phe-OMe (16). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J=8.8 Hz, 1H), 7.37 (s, 1H), 7.30–7.13 (m, 7H), 6.87 (s, 1H), 6.79 (s, 1H), 5.45 (d, J=5.3 Hz, 1H), 4.64 (m, 1H), 4.41 (m, 1H), 4.33 (m, 1H), 4.01 (m, 1H), 3.61 (s, 3H), 3.27 (s, 3H), 3.17–3.07 (m, 2H), 3.05 (d, J=4.4 Hz, 1H), 3.01 (d, J=4.0 Hz, 1H), 2.81 (dd, J=16.0 Hz, 9.6 Hz, 2H), 2.68 (m, 2H), 2.40–2.30 (m, 2H), 2.13–1.90 (m, 4H), 1.80–1.64 (m, 8H), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 9H), 1.25–0.94 (m, 4H); TLC R_f 0.53 (10% MeOH/CH_2Cl_2); exact mass calcd for $[C_{45}H_{63}N_7O_8+H]^+$ requires m/z 830.4816. Found 830.4817 (FAB^+). HPLC retention time 2.6 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.6. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-Phe-OMe (11). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=8.0 Hz, 2H), 7.31–7.07 (m, 27H), 7.03–6.91 (m, 2H), 6.84 (s, 1H), 5.47 (s, 1H), 4.74–4.67 (m, 1H), 4.51–4.45 (m, 1H), 4.41–4.25 (m, 1H), 4.20–4.16 (m, 1H), 4.07–4.05 (m, 1H), 3.50 (s, 3H), 3.26–3.21 (m, 1H), 3.18 (s, 3H), 2.99–2.94 (m, 2H), 2.72–2.66 (m, 2H), 2.36–2.06 (m, 5H), 1.80–1.09 (m, 27H); TLC R_f 0.43 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{67}H_{81}N_9O_{10}+Na]^+$ requires m/z 1194.6004. Found 1194.6016 (ESI^+). HPLC retention time 9.7 min on a RP-18 X Terra (Waters) column eluting with 75% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.7. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-(Boc)Trp-Phe-OMe (17). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (br d, J=7.8 Hz, 1H), 7.58–7.48 (m, 4H), 7.27–7.11 (m, 30H), 7.00 (s, 1H), 6.83 (s, 1H), 6.69 (br d, J=8.0 Hz, 1H) 5.54 (s, 1H), 4.67–4.55 (m, 2H), 4.10–3.97 (m, 3H), 3.42 (s, 3H), 3.30–3.20 (m, 2H), 3.18 (s, 3H), 3.13–2.97 (m, 2H), 2.92–2.86 (m, 3H), 2.76–2.70 (m, 2H), 2.39–2.29 (m, 3H), 2.18–2.10 (m, 5H), 1.85–1.50 (m, 14H), 1.49–1.36 (m, 6H), 1.30–1.00 (m, 12H); TLC R_f 0.48 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{83}H_{99}N_{11}O_{13}+H]^+$ requires m/z 1458.7502. Found 1458.7506 (FAB^+). HPLC retention time 5.1 min on a RP-18 X Terra (Waters) column eluting with 90% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.8. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Phe-OMe (18). ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J=7.6 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.60 (d, J=4.0 Hz, 1H), 7.38–7.06 (m, 24H), 6.90, (s, 1H), 6.78–6.77 (m, 2H), 5.99, (d, J=4.8 Hz, 1H), 4.60–4.52 (m, 2H), 4.35–4.32 (m, 2H), 4.15–4.10 (m, 3H), 3.54 (s, 3H), 3.27–3.12 (m, 3H), 2.97–2.94 (m, 4H), 2.85–2.78 (m, 2H), 2.62–2.57 (m, 2H), 2.48–2.41 (m, 2H), 2.25–2.19 (m, 5H), 2.11–2.04 (m, 2H), 1.75–1.12 (m, 44H); TLC R_f 0.47 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{82}H_{105}N_{11}O_{12}+H]^+$ requires m/z 1436.8022. Found 1436.8035 (ESI^+). HPLC retention time 3.4 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.9. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-L-Phe-Phe-OMe (19). ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.85 (br s, 1H), 7.59 (br s, 1H), 7.47 (br s, 1H), 7.26–7.08 (m, 27H), 6.99 (br s, 1H), 6.86 (m, 2H), 6.76 (s, 1H), 6.41 (s, 1H), 5.88 (s, 1H), 4.62–4.54 (m, 2H), 4.36–4.26 (m, 4H), 4.13 (m, 2H), 3.59 (s, 3H), 3.17 (s, 3H), 2.98–2.90 (m, 2H), 2.84–2.79 (m, 2H), 2.62–2.54 (m, 2H), 2.48–2.40 (m, 2H), 2.25–2.20 (m, 2H), 2.09–2.03 (m, 2H),

1.74–0.87 (m, 51H); TLC R_f 0.40 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{91}H_{114}N_{12}O_{13}+H]^+$ requires *m/z* 1583.8706. Found 1583.8703 (ESI^+). HPLC retention time 6.2 min on a RP-18 X Terra (Waters) column eluting with 85% MeOH/water at a flow rate of 0.2 mL/min.

4.1.3.10. Boc-Pmh-Aib-Chg-(trt)Gln-D-Phe-D-Pip-Cha-Val-(Boc)Trp-Phe-OMe (20). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.74 (br s, 1H), 8.17 (br s, 1H), 7.87 (d, *J*=7.2 Hz, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.40–6.91 (m, 30H), 6.75 (s, 2H), 6.71–6.89 (m, 1H), 5.98 (s, 1H), 4.74–4.70 (m, 5H), 4.48–4.08 (m, 6H), 3.64 (s, 3H), 3.23–2.84 (m, 15H), 2.25–2.09 (m, 4H), 1.69–0.76 (60H); TLC R_f 0.33 (8% MeOH/CH_2Cl_2); exact mass calcd for $[C_{103}H_{132}N_{14}O_{16}+Na]^+$ requires *m/z* 1843.9843. Found 1843.9840 (ESI^+). HPLC retention time 45.4 min on a RP-18 X Terra (Waters) column eluting with 55% MeOH/water at a flow rate of 0.2 mL/min.

4.1.4. General procedure for the Morita–Baylis–Hillman reaction.

4.1.4.1. Enantioselective Morita–Baylis–Hillman reaction employing catalyst 18 with product isolation. To a 10 mL round bottom flask, flame-dried and equipped with a stir bar, were added peptide **18** (0.0015 mmol), dissolved in $CHCl_3$/THF (1:2, 0.5 M), L-proline (0.0015 mmol), 2-nitrobenzaldehyde (0.015 mmol), and methyl vinyl ketone (0.029 mmol). The resulting mixture was stirred until complete loss of starting material was observed by TLC (2:1 hexane/ethyl acetate). The reaction mixture was diluted with chloroform and purification via silica gel chromatography (SiO_2, $CHCl_3$) afforded 2.7 mg (81%) of **21** as a pale yellow oil.

Compound **21**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=7.2 Hz, 1H), 6.22 (s, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 3.49 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5, 149.0, 147.8, 136.7, 133.5, 128.8, 128.5, 126.6, 124.5, 67.1, 26.2; IR (film, cm^{-1}) 3414, 1675, 1525, 1351; TLC R_f 0.52 (40% ethyl acetate/hexane); $[\alpha]_D$ −114 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}NO_4+Na]^+$ requires *m/z* 244.0586. Found 244.0585 (ESI^+). Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 95:5; flow rate 0.75 mL/min; 29.8 min (minor ent), 32.5 min (major ent).

Compound **22**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J*=8.8 Hz, 1H), 7.91 (d, *J*=7.3 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.66–7.58 (m, 3H), 6.29 (s, 1H), 6.00 (s, 1H), 5.89 (d, *J*=4.4 Hz, 1H), 3.51 (d, *J*=4.7 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 147.5, 146.2, 132.9, 130.8, 130.6, 128.5, 127.8, 127.7, 127.3, 124.0, 123.9, 121.5, 67.9, 26.2; IR (film, cm^{-1}) 3414, 2363, 2332, 1675, 1527, 1361; TLC R_f 0.45 (40% ethyl acetate/hexane); $[\alpha]_D$ −196 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{15}H_{13}N_1O_4+Na]^+$ requires *m/z* 294.0742. Found 294.0741 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-propanol 93:7; flow rate 0.75 mL/min; 34.1 min (minor ent), 38.1 min (major ent).

Characterization of (*R*)-**1** has been previously reported.[8d]

4.1.4.2. Proof of absolute stereochemistry. The absolute stereochemistry of the major adduct **1** was determined by comparing the sign of the specific rotation with reported literature data. The kinetic resolution of the racemic compound **1** by Sharpless epoxidation using L-(+)-diethyl tartrate leads to preferentially recovered starting material of the (*S*)-configuration. Measurement of the optical rotation and comparison to the literature showed the sample to be of the (*R*)-configuration: $[\alpha]_D$ −3.8 (*c* 0.53, $CHCl_3$); literature for (*R*)-**1**: $[\alpha]_D$ −12.1 (*c* 0.53, $CHCl_3$).

Compound **23**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J*=7.7 Hz, 1H), 7.66 (d, *J*=7.7 Hz, 1H), 7.59 (m, 1H), 7.42 (t, *J*=7.7 Hz, 1H), 6.19 (s, 1H), 6.06 (br s, 1H), 5.54 (s, 1H), 3.42 (d, *J*=3.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.9, 149.7, 139.2, 131.9, 127.7, 127.6, 127.3, 125.7, 122.6, 119.9, 67.3, 26.4; IR (film, cm^{-1}) 3420, 1678, 1312, 771; TLC R_f 0.48 (30% ethyl acetate/hexane); $[\alpha]_D$ −31 (*c* 0.83, $CHCl_3$); exact mass calcd for $[C_{12}H_{11}O_2F_3+Na]^+$ requires *m/z* 267.0609. Found 267.0605 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 95:5; flow rate 0.75 mL/min; 13.2 min (minor ent), 15.5 min (major ent).

Compound **24**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (t, *J*=8.1 Hz, 1H), 7.14 (d, *J*=7.7 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 6.24 (s, 1H), 5.96 (s, 1H), 5.66 (d, *J*=5.5 Hz, 1H), 3.89 (s, 3H), 3.46 (d, *J*=5.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.7, 150.9, 147.8, 140.2, 134.7, 131.4, 128.1, 119.6, 112.4, 68.1, 56.8, 26.5; IR (film, cm^{-1}) 3414, 1674, 1531; TLC R_f 0.30 (30% ethyl acetate/hexane); $[\alpha]_D$ −112 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{12}H_{10}N_4O_4+Na]^+$ requires *m/z* 274.0691. Found 274.0699 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/2-proponal 90:10; flow rate 0.75 mL/min; 30.7 min (minor ent), 33.7 min (major ent).

Compound **25**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 (s, 1H), 6.34–6.32 (m, 1H), 6.25–6.24 (m, 2H), 6.1 (s, 1H), 5.63 (d, *J*=5.8 Hz, 1H), 3.26 (br s, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.2, 154.2, 147.2, 141.6, 126.4, 109.9, 106.6, 65.2, 25.7; IR (film, cm^{-1}) 3320, 2957, 2923, 2852, 1714, 1667, 1510, 1462, 1376; TLC R_f 0.56 (30% ethyl acetate/hexane); $[\alpha]_D$ −6.5 (*c* 0.31, $CHCl_3$); exact mass calcd for $[C_9H_{10}O_3+Na]^+$ requires *m/z* 189.0528. Found 189.0526 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 95:5; flow rate 0.75 mL/min; 29.0 min (major ent), 37.0 min (minor ent).

Compound **26**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.80 (d, *J*=2.2 Hz, 1H), 8.48 (dd, *J*=8.4, 2.2 Hz, 1H), 8.05 (d, *J*=8.8 Hz, 1H), 6.30 (s, 1H), 6.23 (s, 1H), 5.85 (s, 1H), 3.55 (br s, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5, 148.1, 147.9, 147.2, 143.2, 130.6, 127.3, 127.1, 120.1, 67.4, 25.9; IR (film, cm^{-1}) 3408, 3106,

2357, 1673, 1606, 1536, 1347; TLC R_f 0.43 (40% ethyl acetate/hexane); $[\alpha]_D$ −135 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{10}N_2O_6+Na]^+$ requires *m/z* 289.0437. Found 289.0430 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel OJ column (Diacel). Conditions: hexane/ethanol 90:10; flow rate 0.75 mL/min; 54.3 min (major ent), 63.1 min (minor ent).

Compound **27**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 8.13 (m, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.52 (t, *J*=7.7 Hz, 1H), 6.29 (s, 1H), 6.09 (s, 1H), 5.67 (s, 1H), 3.36 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.1, 149.1, 148.4, 144.1, 132.9, 129.5, 127.9, 122.8, 121.6, 72.4, 26.8; IR (film, cm^{-1}) 3439, 1671, 1529, 1349; TLC R_f 0.44 (30% ethyl acetate/hexane); $[\alpha]_D$ −14 (*c* 1.0, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}NO_4+Na]^+$ requires *m/z* 244.0586. Found 244.0589 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 90:10; flow rate 0.75 mL/min; 19.9 min (minor ent), 35.3 min (major ent).

Compound **28**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 (m, 1H), 7.28 (m, 1H), 7.17 (m, 1H), 7.03 (m, 1H), 6.19 (s, 1H), 5.89 (br d, 1H), 5.87 (s, 1H), 3.44 (br d, *J*=5.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.0, 160.6, 158.2, 148.4, 128.8, 127.7, 126.5, 123.7, 114.9, 65.9, 26.1; IR (film, cm^{-1}) 3416, 1675, 1490; TLC R_f 0.48 (30% ethyl acetate/hexane); $[\alpha]_D$ +20 (*c* 0.68, $CHCl_3$); exact mass calcd for $[C_{11}H_{11}O_2F+Na]^+$ requires *m/z* 217.0641. Found 217.0643 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 98:2; flow rate 0.75 mL/min; 34.2 min (minor ent), 39.8 min (major ent).

Compound **29**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.22 (m, 5H), 7.78 (d, *J*=7.7 Hz, 1H), 6.15 (s, 1H), 5.98 (s, 1H), 5.56 (s, 1H), 3.55 (br s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.0, 149.9, 141.5, 128.1, 127.4, 126.4, 126.2, 72.2, 26.2; IR (film, cm^{-1}) 3414, 1673, 1369; TLC R_f 0.47 (30% ethyl acetate/hexane); $[\alpha]_D$ −19 (*c* 0.23, $CHCl_3$); exact mass calcd for $[C_{11}H_{12}O_2+Na]^+$ requires *m/z* 199.0735. Found 199.0732 (ESI^+). Assay of enantiomeric purity: enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Diacel). Conditions: hexane/ethanol 97:3; flow rate 0.75 mL/min; 31.1 min (minor ent), 35.7 min (major ent).

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23. We also synthesized peptides of shorter length, catalysts **12**–**15**, to determine if the length-selectivity trend would be apparent with smaller peptides. Shorter peptide lengths such as dipeptide **13**, tripeptide **14**, and tetrapeptide **15** did appear to follow this trend with the limited number of cases examined.
24. A brief study of the peptide/proline ratio revealed that 1:1 stoichiometry is optimal in the cases we explored.
25. In addition to solvent screens, temperature was also examined. A variety of ranges ($-20\ ^\circ C \rightarrow 50\ ^\circ C$) were screened, all of which afforded either low conversions to MBH product or significantly reduced enantioselectivities. Solvent screens with 21 different solvent combinations were examined. Mixtures (2:1) of either THF/$CHCl_3$ or toluene/$CHCl_3$ yielded similar selectivities of 78% ee in the MBH reaction of 2-nitrobenzaldehyde with peptide **18**.
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A multicomponent approach to substituted benzenes involving sequential nickel-catalyzed reactions

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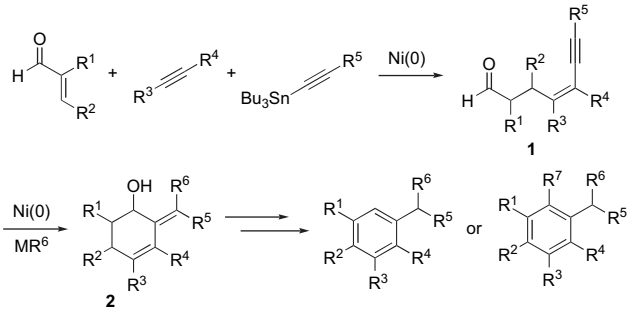
Abstract—Two sequential nickel-catalyzed reactions allow the preparation of highly functionalized alkylidene cyclohexenols. Dehydration of the resulting cycloadducts allows the preparation of densely functionalized aromatic ring systems, whereas a simple sequence involving oxidation followed by carbonyl addition or enolization allows additional diversity incorporation.

1. Introduction

Many approaches to substituted benzene derivatives have been developed, and most strategies involve functionalization of an existing benzene ring. For example, electrophilic and nucleophilic aromatic substitution,[1] directed metallation,[2] and metal-catalyzed cross-couplings of haloaromatics or aryl triflates[3] are very commonly employed. Strategies that involve preparation of the aromatic six-membered ring from non-aromatic precursors are often complementary to the types of substitution patterns that are most easily accessed by conventional approaches.[4] A recent report from our laboratory described the synthesis of substituted alkylidene cyclohexenol derivatives by two related nickel-catalyzed reactions performed in succession.[5] The first step of the sequence involves the three-component nickel-catalyzed coupling of enones, alkynes, and acetylenic stannanes to generate functionalized enynes **1** bearing an aldehyde functional group, and the second step involves a nickel-catalyzed reductive coupling to generate a product alkylidene cyclohexenol **2**. We envisioned that aromatization of the structures obtained by this sequence would provide an unusual and diverse entry to highly substituted benzene derivatives. The overall strategy has the potential to provide access to a very broad range of aromatics since up to five different widely available starting materials each introduce functionality into the aromatic products. Herein we describe the realization of this strategy (Scheme 1).



Scheme 1.

2. Results and discussion

Our previous report describing sequential nickel-catalyzed couplings for the preparation of alkylidene cyclohexenols provided easy access to the precursors of aromatic ring systems.[5] Whereas a broad range of substrates were reported in our original communication detailing the two-step entry to alkylidene cyclohexenols, eight examples of the three-component couplings of enals, alkynes, and acetylenic tin reagents were selected for the proposed aromatization sequence (Scheme 2). The typical coupling procedure involved coupling of an enal, alkyne, and acetylenic tin reagent in THF in the presence of TMSCl and a catalyst derived from in situ reduction of $Ni(acac)_2$ with DIBAL-H. This initial step of our entry to aromatic structures is based upon earlier studies from Ikeda that demonstrated related three-component couplings.[6] As these eight examples (**1a**–**h**) illustrate, variation of all three components is tolerated. The enal component can be as simple as acrolein, or substitution at the α- or β-carbon is allowed. Additionally, couplings of a cyclic enal (cyclohexene carboxaldehyde) also proceed in modest yield. In the alkyne component, internal and terminal alkynes participate with aromatic, aliphatic, or ether-containing groups. Finally, the acetylenic tin reagent may possess

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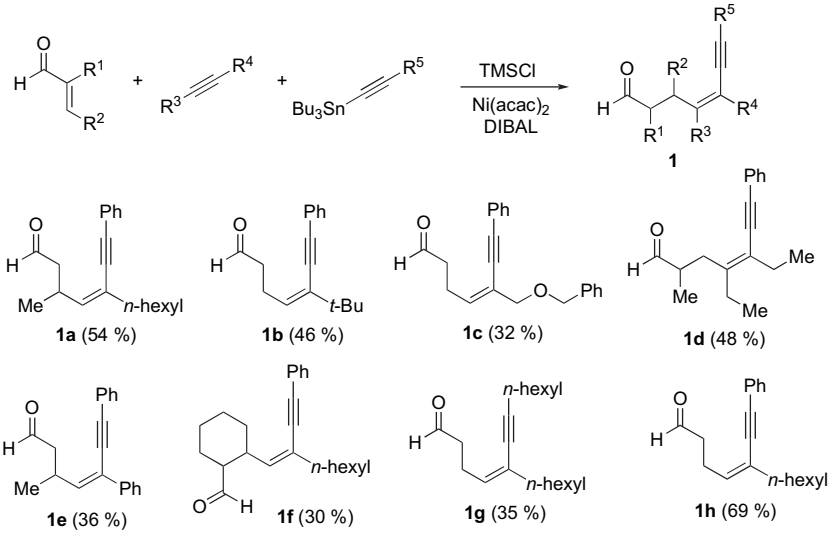


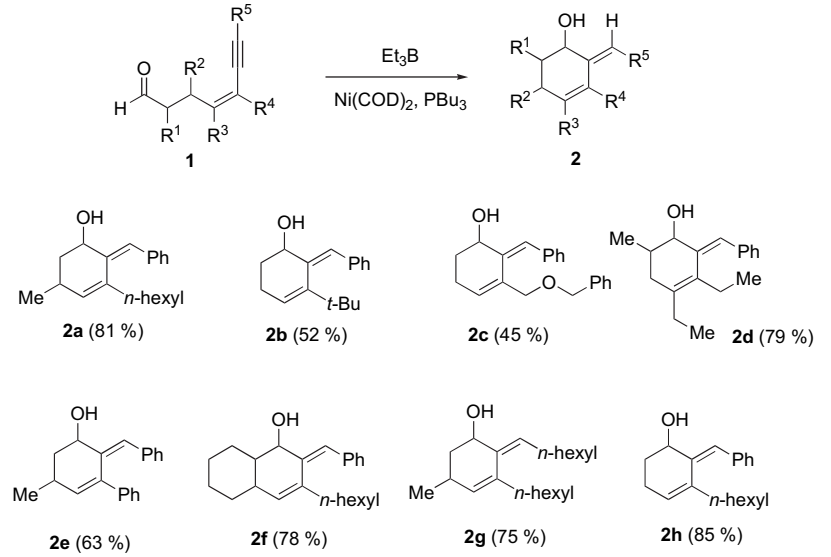
Scheme 2.

aromatic or aliphatic functional groups. While the chemical yields of this initial coupling step are disappointing, it should be noted that many side reactions are possible, including homo- or heterotrimerization of the two alkyne components or homodimerization of the alkynyl stannane.[4,7]

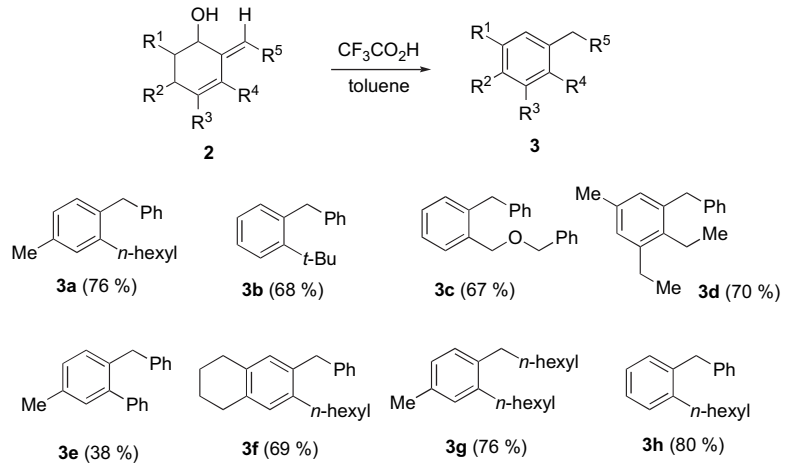
With these eight substrates in hand, nickel-catalyzed reductive cyclizations of enynals **1a–h** involving $Ni(COD)_2/PBu_3$ as catalyst and Et_3B as reducing agent provided access to the corresponding alkylidene cyclohexenols **2a–h** (Scheme 3). The corresponding alkylative cyclizations involving introduction of an alkyl group are also successful, but the products derived from Et_3B-mediated cyclizations were the focus of this study.[8] The reductive cyclization products that bear two or more stereocenters were typically generated as diastereomeric mixtures, which is inconsequential for the purpose of preparing aromatic structures.

Treatment of the alkylidene cyclohexenols **2a–h** with trifluoroacetic acid in toluene directly afforded the aromatic structures **3a–h** via dehydration (Scheme 4). This simple sequence affords access to a broad array of substitution patterns in aromatic ring systems, and should be amenable to many other substitution patterns not explicitly examined in this study.

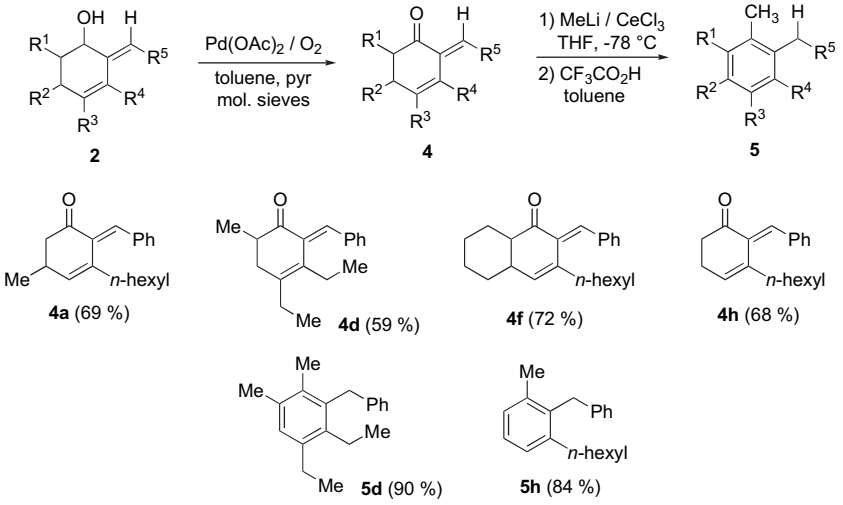
Alternatively, oxidation[9] of the alkylidene cyclohexenols with $Pd(OAc)_2/O_2$ provides alkylidene cyclohexenones **4** that resist aromatization via tautomerization (Scheme 5).[10] These substrates may be functionalized via organocerium reagent addition to the carbonyl, followed by acid-catalyzed dehydration to afford substituted benzenes **5** that now possess substituents derived from four different starting materials. The production of **4d** and **4h** and their conversion to aromatic structures **5d** and **5h** by $MeLi/CeCl_3$ addition[11] followed by trifluoroacetic acid-mediated dehydration illustrates the sequence (Scheme 5). As the various substrate combinations selected for this study illustrate, the following aromatic substitution patterns may be accessed: 1,2-disubstituted, 1,2,3-trisubstituted, 1,2,4-trisubstituted, 1,2,3,5-



Scheme 3.



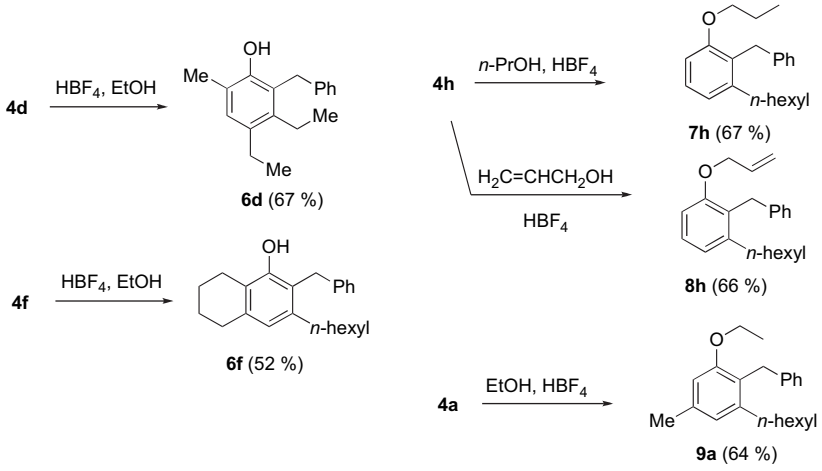
Scheme 4.



Scheme 5.

tetrasubstituted, and 1,2,3,4,5-pentasubstituted. Selection of alternative starting material combinations would allow many other regiochemical substitution patterns to be accessed.

We also considered the production of phenols and aryl ethers by a strategy that retains the oxygenation present in cyclohexenone **4**.[12,13] Direct aromatization of **4d** and **4f** to the corresponding phenol by tautomerization proceeded under forcing conditions to produce phenols **6d** and **6f** in modest yield (Scheme 6). Alkylidene cyclohexenone substrates **4a** and **4h** that possess a simple unsubstituted methylene α to the carbonyl resisted tautomerization, but were converted to



Scheme 6.

aryl ethers **7h**, **8h**, and **9a** in alcohol solvents with strong acids. Control experiments illustrated that the aryl ether products were not produced from O-alkylation of the corresponding phenol derivatives under the reaction conditions.

3. Conclusions

In summary, a variety of highly substituted aromatic structures may be obtained by two sequential nickel-catalyzed couplings, followed by aromatization. Depending on the aromatization sequence chosen, the products may be benzene derivatives, phenols, or aryl ethers. A wide array of substitution patterns are accessible by these procedures, which complement the patterns that are accessible by conventional procedures for the preparation of polysubstituted aromatic compounds.

4. Experimental

4.1. General

Unless otherwise noted, reagents were commercially available and were used without purification. Trimethylsilyl chloride and tributylphosphine were freshly distilled. Tetrahydrofuran (THF) was purified by alumina filtration under nitrogen using a solvent purification system (Innovative Technology, Inc., Model 3 SPS-400-3). All reactions were conducted in a flame-dried glassware under an atmosphere of nitrogen or argon. $Ni(COD)_2$ and $Ni(acac)_2$ were stored in a glove box under argon. ^1H and ^{13}C NMR spectra were obtained at room temperature on a Varian Mercury 400 or Varian Unity 500 MHz instruments. High-resolution mass spectra (HRMS) were obtained from the Central Instrument Facility at Wayne State University and at the University of Michigan.

4.2. General procedure for three-component couplings of α,β-unsaturated aldehydes, alkynes, and alkynyltins

A 0.02 M solution of $Ni(acac)_2$ (0.1 equiv) in THF was stirred at 0 °C, and a solution of DIBAL (0.1 equiv, 1.0 M in hexanes) was added dropwise, followed by the addition of the alkynyltin reagent (1.1 equiv). The alkyne (1.2 equiv), the α,β-unsaturated aldehyde (1.0 equiv), and TMSCl (1.2 equiv) were then added neat, and the reaction mixture was allowed to warm to room temperature and was stirred for 2.5 h (unless otherwise noted). The mixture was quenched by the addition of concd HCl (12 equiv, 2.0 M in acetone), stirred for 15 min, and was poured into concd NH_4F solution (four times the volume of the reaction mixture before quench). The two-phase mixture was vigorously stirred for 30 min and then filtered through Celite and washed with diethyl ether. The aqueous layer was extracted with diethyl ether; the combined organic layers were washed with satd $NaHCO_3$, brine, and dried over $MgSO_4$. The product was purified by flash chromatography on SiO_2 using hexane and CH_2Cl_2 as a solvent system.

4.2.1. (*Z*)-5-Hexyl-3-methyl-7-phenyl-hept-4-en-6-ynal (1a). Following the general procedure in Section 4.2, crotonaldehyde (0.66 mL, 8.0 mmol), 1-octyne (1.41 mL, 9.6 mmol), tributyl(phenylethynyl)tin (3.08 mL, 8.8 mmol), $Ni(acac)_2$ (206 mg, 0.80 mmol), DIBAL (0.80 mL, 0.80 mmol in 1.0 M solution), and TMSCl (1.22 mL, 9.60 mmol) were employed to produce, after flash chromatography (3:1 hexane/CH_2Cl_2), 1.22 g (54%) of product as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J=2.5 Hz, 1H), 7.43–7.45 (m, 2H), 7.28–7.34 (m, 3H), 5.56 (d, J=9.0 Hz, 1H), 3.35–3.44 (m, 1H), 2.42–2.44 (m, 2H), 2.18 (t, J=7.0 Hz, 2H), 1.54–1.60 (m, 2H), 1.28–1.35 (m, 6H), 1.13 (d, J=6.5 Hz, 3H), 0.88–0.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 140.8, 131.7, 128.5, 128.4, 123.8, 123.7, 94.7, 87.8, 50.9, 37.2, 31.9, 30.7, 28.8, 28.6, 22.8, 20.8, 14.3; IR (film, cm^{-1}) 2926, 2855, 1724, 1489, 1457, 755, 690; HRMS (EI) *m/e* calcd for $C_{20}H_{26}O$ 282.1984, found 282.1978 (M^+).

4.2.2. (*Z*)-5-*tert*-Butyl-7-phenyl-hept-4-en-6-ynal (1b). Following the general procedure in Section 4.2, acrolein (0.13 mL, 2.0 mmol), *tert*-butyl acetylene (0.30 mL, 2.4 mmol), tributyl(phenylethynyl)tin (0.77 mL, 2.2 mmol), $Ni(acac)_2$ (51 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol in 1 M solution), and TMSCl (0.3 mL, 2.4 mmol) were employed to produce, after flash chromatography (3:1 hexane/CH_2Cl_2), 220 mg (46%) of a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.44–7.46 (m, 2H), 7.29–7.33 (m, 3H), 5.77 (t, J=7.5 Hz, 1H), 2.7 (q, J=7.0 Hz, 2H), 2.58 (t, J=7.0 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 135.2, 131.6, 130.8, 128.6, 128.3, 123.9, 96.1, 87.1, 59.7, 43.7, 29.6, 23.8; IR (film, cm^{-1}) 2964, 2868, 1724, 1669, 1596, 1489, 1448, 1392, 1363, 1245, 908, 757, 691; HRMS (EI) *m/e* calcd for $C_{17}H_{20}O$ 240.1514, found 240.1513 (M^+).

4.2.3. (*Z*)-5-Benzyloxymethyl-7-phenyl-hept-4-ene-6-ynal (1c). Following the general procedure in Section 4.2, acrolein (0.17 mL, 2.5 mmol), benzyl propargyl ether (438 mg, 3.0 mmol), tributyl(phenylethynyl)tin (0.96 mL, 2.8 mmol), $Ni(acac)_2$ (64 mg, 0.25 mmol), DIBAL (0.25 mL, 0.25 mmol in 1.0 M solution), and TMSCl (0.38 mL, 3.0 mmol) were employed to produce, after flash chromatography (3:1 CH_2Cl_2/hexane), 240 mg (32%) of a dark brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (br s, 1H), 7.44–7.48 (m, 2H), 7.28–7.39 (m, 8H), 6.06 (t, J=7.5 Hz, 1H), 4.59 (s, 2H), 4.10 (s, 2H), 3.49 (q, J=7.5 Hz, 2H), 2.61–2.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 138.3, 137.1, 131.8, 128.64, 128.61, 128.6, 128.0, 127.9, 123.3, 122.3, 95.4, 85.9, 72.6, 72.4, 43.2, 23.3; IR (film, cm^{-1}) 2948, 2914, 2851, 2725, 1723, 1596, 1572, 1490, 1454, 1443, 913; HRMS (EI) *m/e* calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1468 (M^+).

4.2.4. (*Z*)-4,5-Diethyl-2-methyl-7-phenyl-hept-4-en-6-ynal (1d). Following the general procedure in Section 4.2, methacrolein (0.17 mL, 2.0 mmol), 3-hexyne (0.27 mL, 2.4 mmol), tributyl(phenylethynyl)tin (0.77 mL, 2.2 mmol), $Ni(acac)_2$ (51 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol in 1.0 M solution), and TMSCl (0.3 mL, 2.4 mmol) were employed to produce, after flash chromatography (3:1 hexane/CH_2Cl_2), 243 mg (48%) of a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, J=2.0 Hz, 1H), 7.39–7.41 (m, 2H), 7.28–7.32 (m, 3H), 2.79 (dd, J=13.0, 7.0 Hz, 1H), 2.59–2.66 (m, 1H), 2.5 (dd, J=13.5, 8.0 Hz, 1H), 2.27 (q, J=15.3, 2H), 2.18 (m, 2H), 1.14–1.17 (m, 6H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 145.6, 131.4, 128.5, 128.0, 124.1, 122.3, 93.2, 90.1, 46.1,

35.9, 25.3, 24.8, 14.0, 13.7, 13.4; IR (film, cm^{-1}) 3058, 2956, 2856, 1726, 1662, 1597, 1490, 1456, 756, 691; HRMS (EI) *m/e* calcd for $C_{18}H_{22}O$ 254.1671, found 254.1669 (M^+).

4.2.5. (*Z*)-3-Methyl-5,8-diphenyl-oct-4-en-7-ynal (1e). Following the general procedure in Section 4.2, crotonaldehyde (0.16 mL, 2.0 mmol), phenyl acetylene (0.26 mL, 2.4 mmol), tributyl(phenylethynyl)tin (0.77 mL, 2.2 mmol), $Ni(acac)_2$ (52 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol in 1.0 M solution), and TMSCl (0.3 mL, 2.4 mmol) were employed to produce, after flash chromatography (3:1 hexane/CH_2Cl_2), 197 mg (36%) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (t, J=2.4 Hz, 1H), 7.65–7.68 (m, 2H), 7.53–7.56 (m, 2H), 7.29–7.39 (m, 6H), 6.30 (d, J=6.0 Hz, 1H), 3.56–3.71 (m, 1H), 2.59 (dd, J=2.4, 6.0 Hz, 2H), 1.26 (d, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 141.4, 137.8, 131.8, 128.8, 128.7, 128.5, 128.2, 126.4, 123.8, 123.3, 96.5, 86.4, 50.8, 31.3, 20.6; IR (film, cm^{-1}) 3058, 2958, 2870, 2722, 1723, 1597, 1490, 1446, 1362, 1072, 1027, 908, 756, 691; HRMS (EI) *m/e* calcd for $C_{20}H_{18}O$ 274.1358, found 274.1357 (M^+).

4.2.6. (*Z*)-2-(2-Hexyl-4-phenyl-but-1-en-3-ynyl)cyclohexanecarbaldehyde (1f). Following the general procedure in Section 4.2, cyclohexanecarbaldehyde (0.11 mL, 1.0 mmol), 1-octyne (0.18 mL, 1.2 mmol), tributyl(phenylethynyl)tin (0.39 mL, 1.1 mmol), $Ni(COD)_2$ (28 mg, 0.1 mmol), and TMSCl (0.15 mL, 1.2 mmol) were employed to produce, after flash chromatography (3:1 hexane/CH_2Cl_2), 95 mg (30%) of a brown oil product of two inseparable diastereomers (2:1). ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 0.33H), 9.6 (d, J=3.5 Hz, 0.67H), 7.42–7.45 (m, 2H), 7.29–7.35 (m, 3H), 5.95 (d, J=9.5 Hz, 0.33H), 5.55 (d, J=9.5 Hz, 0.67H), 3.36–3.39 (m, 0.33H), 2.88 (qd, J=10.0, 3.8 Hz, 0.67H), 2.63 (dt, J=8.0, 4.0 Hz, 0.33H), 2.15–2.20 (m, 2H), 2.08 (tt, J=11.3, 3.5 Hz, 0.67H), 1.2–1.87 (m, 16H), 0.89–0.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) for two isomers δ 205.4, 205.1, 139.6, 137.1, 131.7, 128.5, 128.3, 124.7, 124.4, 123.7, 94.8, 94.4, 88.1, 88.0, 55.5, 53.3, 40.0, 37.6, 37.4, 37.2, 31.9, 31.8, 30.8, 28.8, 28.7, 28.6, 25.8, 25.3, 24.6, 24.2, 23.3, 23.2, 22.8, 14.3; IR (film, cm^{-1}) 2925, 2865, 2845, 2725, 1720, 1599, 1489, 1443, 755, 690; HRMS (EI) *m/e* calcd for $C_{23}H_{30}O$ 322.2297, found 322.2303 (M^+).

4.2.7. (*Z*)-5-Hexyl-3-methyl-tridec-4-en-6-ynal (1g). Following the general procedure in Section 4.2, crotonaldehyde (0.33 mL, 4.0 mmol), 1-octyne (0.65 mL, 4.8 mmol), tributyl(octynyl)tin (1.76 g, 4.4 mmol), $Ni(acac)_2$ (103 mg, 0.4 mmol), DIBAL (0.4 mL, 0.4 mmol in 1.0 M solution), and TMSCl (0.61 mL, 4.8 mmol) were employed to produce, after flash chromatography (4:1 hexane/CH_2Cl_2), 405 mg (35%) of a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (t, J=2.5 Hz, 1H), 5.38 (d, J=9.0 Hz, 1H), 3.21–3.30 (m, 1H), 2.30–2.36 (m, 4H), 2.03 (t, J=7.30 Hz, 2H), 1.52 (quintet, J=7.0 Hz, 2H), 1.35–1.48 (m, 4H), 1.23–1.33 (m, 10H), 1.05 (d, J=7.0 Hz, 3H), 0.85–0.89 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 138.9, 124.2, 95.7, 78.9, 50.9, 37.6, 31.9, 31.5, 30.5, 29.1, 28.8, 28.5, 22.8, 20.8, 19.7, 14.3, 14.25; IR (film, cm^{-1}) 2955, 2928, 2856, 1726, 1627, 1457, 1378, 1350, 1326, 1261, 1108, 1077, 907, 850, 729, 668, 650; HRMS (EI) *m/e* calcd for $C_{20}H_{34}O$ 290.2610, found 290.2607 (M^+).

4.2.8. (*Z*)-5-Hexyl-7-phenyl-hept-4-en-6-ynal (1h). Following the general procedure in Section 4.2, acrolein (0.13 mL, 2.0 mmol), 1-octyne (0.35 mL, 2.4 mmol), tributyl(phenylethynyl)tin (0.77 mL, 2.2 mmol), $Ni(acac)_2$ (51 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol of 1.0 M solution), and TMSCl (0.3 mL, 2.4 mmol) were employed to produce, after flash chromatography (2:1 hexanes/CH_2Cl_2), 370 mg (69%) of product as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J=1.2 Hz, 1H), 7.43 (m, 2H), 7.32 (m, 3H), 5.72 (t, J=7.5 Hz, 1H), 2.67 (q, J=7.0 Hz, 2H), 2.57 (m, 2H), 2.18 (t, J=7.7 Hz, 2H), 1.55 (m, 2H), 1.30 (m, 6H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 202.3, 134.7, 131.7, 128.5, 128.3, 125.3, 123.7, 94.7, 87.8, 43.6, 37.2, 31.9, 28.8, 28.6, 23.6, 22.8, 14.3; IR (film, cm^{-1}) 3029, 2854, 2722, 2253, 2200, 1724, 1596, 1489, 755, 732; HRMS (EI) *m/e* calcd for $C_{19}H_{24}O$ 268.1827, found 268.1822 (M^+).

4.3. General procedure for the reductive cyclizations of enynals

To a 0.01 M solution of $Ni(COD)_2$ (0.1 equiv) in toluene at room temperature was added Bu_3P (0.2 equiv) followed by Et_3B (2.0 equiv, 1.0 M solution in THF). A 0.2 M solution of the enynal (1.0 equiv) in toluene was then transferred to this mixture at room temperature, and the reaction mixture was stirred until starting material was consumed as judged by TLC analysis. The mixture was quenched with satd NH_4Cl solution followed by 1.0 M HCl solution. After being stirred for 5 min, the mixture was poured into water and extracted with Et_2O, washed with brine, and then dried over $MgSO_4$. The product was purified by flash chromatography on SiO_2.

4.3.1. (*E*)-2-Benzylidene-3-hexyl-5-methyl-cyclohex-3-enol (2a). Following the general procedure in Section 4.3, compound **1a** (181 mg, 0.64 mmol), $Ni(COD)_2$ (18.2 mg, 0.064 mmol) tributylphosphine (0.035 mL, 0.13 mmol), and triethylborane (1.28 mL, 1.28 mmol in 1.0 M solution) were employed to produce, after column chromatography (10:1 hexane/ethyl acetate), 129 mg (81%) of a yellow oil (two inseparable diastereomers, dr 1.2:1). ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.29 (m, 5H), 6.69 (s, 0.45H), 6.57 (s, 0.55H), 5.56 (br d, J=1.5 Hz, 0.55H), 5.47 (br d, J=1.5 Hz, 0.45H), 4.40 (br d, J=3.0 Hz, 0.55H), 4.29 (d, J=10.5 Hz, 0.45H), 2.61 (m, 0.55H), 2.54 (m, 0.45H), 2.26 (ddd, J=11.5, 6.0, 4.0 Hz, 0.45H), 2.12 (dt, J=14.0, 5.5 Hz, 0.55H), 1.87–1.97 (m, 1H), 1.73–1.83 (m, 2H), 1.59 (ddd, J=15.0, 8.3, 2.8 Hz, 0.55H), 1.41 (dt, J=11.0, 9.0 Hz, 0.45H), 1.26–1.31 (m, 1H), 0.82–1.17 (m, 10H), 0.79 (t, J=7.0 Hz, 1.35H), 0.78 (t, J=7.0 Hz, 1.65H); ^{13}C NMR (125 MHz, $CDCl_3$) for two isomers δ 141.3, 139.8, 139.3, 138.7, 135.9, 135.4, 134.5, 129.32, 129.26, 127.93, 127.91, 126.9, 126.6, 124.7, 120.6, 73.5, 72.0, 42.1, 39.6, 34.6, 34.3, 31.8, 31.73, 31.69, 31.6, 29.1, 29.05, 29.0, 28.96, 28.4, 22.9, 22.7, 22.6, 22.1, 14.4, 14.3; IR (film, cm^{-1}) 3328, 2955, 2925, 2856, 1491, 1454, 698; HRMS (EI) *m/e* calcd for $C_{20}H_{28}O$ 284.2140, found 284.2141 (M^+).

4.3.2. (*E*)-2-Benzylidene-3-*tert*-butyl-cyclohex-3-enol (2b). Following the general procedure in Section 4.3, compound **1b** (72 mg, 0.23 mmol), $Ni(COD)_2$ (8.3 mg 0.03 mmol) tributylphosphine (0.016 mL, 0.06 mmol), and triethylborane (0.6 mL, 0.6 mmol in 1.0 M solution) were employed to produce, after column chromatography (10:1 hexane/ethyl acetate), 38 mg (52%) of a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.28 (m, 4H), 7.16–7.19 (m, 1H), 6.51 (s, 1H), 5.97 (t, J=5.0 Hz, 1H), 4.42 (br s, 1H), 2.25–2.31 (m, 1H), 2.15–2.22 (m, 1H), 2.04–2.12 (m, 1H), 1.69 (br s, 1H), 1.53–1.61 (m, 1H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 142.5, 139.8, 129.2, 128.2, 127.1, 126.6, 122.6, 74.8, 35.9, 32.9, 31.7, 22.5; IR (film, cm^{-1}) 3364, 3024, 2958, 2866, 1297, 1492, 1476, 1446, 1392, 1364, 1249, 927, 738, 697; HRMS (EI) *m/e* calcd for $C_{17}H_{22}O$ 242.1671, found 242.1670 (M^+).

4.3.3. (*E*)-2-Benzylidene-3-benzyloxymethyl-cyclohex-3-enol (2c). Following the general procedure in Section 4.3, compound **1c** (105 mg, 0.345 mmol), $Ni(COD)_2$ (4.2 mg, 0.035 mmol) tributylphosphine (0.018 mL, 0.069 mmol), and triethylborane (0.69 mL, 0.69 mmol in 1 M solution) were employed to produce, after column chromatography (2:1 hexane/ethyl acetate), 48 mg (45%) of a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.29 (m, 8H), 7.15–7.16 (m, 2H), 6.66 (s, 1H), 6.05 (m, 1H), 4.41 (m, 1H), 4.08 (s, 2H), 3.66–3.72 (m, 2H), 2.46–2.50 (m, 1H), 2.34–2.4 (m, 1H), 2.07 (m, 1H), 1.93–2.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.7, 138.5, 132.3, 131.7, 129.2, 128.4, 128.1, 127.9, 127.6, 127.1, 124.4, 72.4, 71.3, 31.0, 23.4; IR (film, cm^{-1}) 3398, 3056, 3026, 2923, 2862, 1596, 1492, 1453, 1360, 1259, 1208, 1118, 1070, 1028, 920, 844, 803, 734, 697; HRMS (EI) *m/e* calcd for $C_{21}H_{22}O_2$ 306.1620, found 306.1619 (M^+).

4.3.4. (*E*)-2-Benzylidene-3,4-diethyl-6-methyl-cyclohex-3-enol (2d). Following the general procedure in Section 4.3, compound **1d** (412 mg, 1.62 mmol), $Ni(COD)_2$ (45 mg, 0.16 mmol) tributylphosphine (0.085 mL, 0.32 mmol), and triethylborane (3.24 mL, 3.24 mmol in 1 M solution) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 326 mg (79%) of two separable diastereomers (2:1) of a light yellow oil. Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 2H), 7.17–7.22 (m, 3H), 6.41 (s, 1H), 4.09 (d, J=4.5 Hz, 1H), 2.36 (dd, J=19.0, 6.8 Hz, 1H), 2.16–2.24 (m, 1H), 2.08–2.14 (m, 2H), 2.00–2.08 (m, 1H), 1.85–1.97 (m, 2H), 1.44 (d, J=6.5 Hz, 1H), 1.04–1.07 (m, 6H), 0.70 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 140.3, 138.9, 130.2, 129.3, 128.0, 126.7, 123.1, 77.9, 35.3, 34.9, 26.2, 22.1, 17.7, 14.5, 13.5; IR (film, cm^{-1}) 3336, 2960, 2929, 2872, 1598, 1490, 1456, 749, 698; HRMS (EI) *m/e* calcd for $C_{18}H_{24}O$ 256.1827, found 256.1829 (M^+). Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.31 (m, 5H), 6.48 (s, 1H), 3.94 (d, J=5.5 Hz, 1H), 2.55 (dd, J=18.5, 6.5 Hz, 1H), 1.90–2.21 (m, 6H), 1.72 (br s, 1H), 1.07 (t, J=14.5 Hz, 3H), 1.03 (d, J=7.0 Hz, 3H), 0.74 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 138.9, 138.6, 131.1, 129.3, 128.1, 126.6, 122.7, 78.7, 35.8, 35.7, 26.2, 22.4, 19.5, 14.6, 13.5; IR (film, cm^{-1}) 3409, 2961, 2928, 2871, 1597, 1491, 1456, 850, 758, 697; HRMS (EI) *m/e* calcd for $C_{18}H_{24}O$ 256.1827, found 256.1827 (M^+).

4.3.5. (*E*)-2-Benzylidene-5-methyl-3-phenyl-cyclohex-3-enol (2e). Following the general procedure in Section 4.3, compound **1e** (78 mg, 0.28 mmol), $Ni(COD)_2$ (8.0 mg, 0.028 mmol) tributylphosphine (0.015 mL, 0.05 mmol), and triethylborane (0.57 mL, 0.57 mmol in 1.0 M solution) were employed to produce, after column chromatography (8:1 hexane/ethyl acetate), two separable diastereomers (1.4:1) (49 mg, 63% yield). Major isomer (light yellow thick gum): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04–7.06 (m, 2H), 6.83–6.95 (m, 9H), 5.86 (d, J=3.5 Hz, 1H), 4.57 (dd, J=10.5, 2.5 Hz, 1H), 2.73–2.81 (m, 1H), 2.35–2.40 (ddd, J=11.0, 6.8, 4.5 Hz, 1H), 1.86 (br s, 1H), 1.58 (ddd, J=13.0, 11.0, 9.5 Hz, 1H), 1.23 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.3, 138.6, 137.4, 136.7, 129.5, 127.67, 127.65, 127.1, 126.4, 126.1, 123.0, 72.3, 41.8, 31.9, 22.4; IR (film, cm^{-1}) 3328, 3078, 3055, 3021, 2955, 2925, 2867, 1599, 1575, 1491, 1444, 1347, 1322, 1264, 1196, 1125, 1078, 1028, 758, 734, 696; HRMS (EI) *m/e* calcd for $C_{20}H_{20}O$ 276.1514, found 276.1516 (M^+). Minor isomer (light yellow oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04–7.06 (m, 2H), 6.87–6.95 (m, 8H), 6.72 (s, 1H), 5.93 (d, J=3.0 Hz, 1H), 4.62 (br d, J=4.0 Hz, 1H), 2.79–2.87 (m, 1H), 2.24 (dt, J=13.5, 6.5 Hz, 1H), 1.93 (br s, 1H), 1.74 (ddd, J=13.5, 8.5, 2.5 Hz, 1H), 1.24 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 139.3, 138.1, 137.0, 135.6, 129.5, 127.7, 127.65, 127.1, 126.5, 126.4, 126.3, 73.5, 39.6, 29.1, 21.8; IR (film, cm^{-1}) 3336, 3078, 3056, 3021, 2955, 2925, 2868, 1599, 1492, 1444, 1373, 126, 1203, 1128, 1076, 1030, 989, 958, 917, 863, 760, 740, 696; HRMS (EI) *m/e* calcd for $C_{20}H_{20}O$ 276.1514, found 276.1517 (M^+).

4.3.6. (*E*)-2-Benzylidene-3-hexyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-ol (2f). Following the general procedure in Section 4.3, compound **1f** (80 mg, 0.25 mmol), $Ni(COD)_2$ (14 mg, 0.0496 mmol) tributylphosphine (0.026 mL, 0.099 mmol), and triethylborane (0.50 mL, 0.50 mmol in 1.0 M solution) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 146 mg (75%) of partially separable diastereomers of light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) for mixture of all diastereomers δ 7.29–7.17 (m, 5H), 6.75, 6.67, 6.54 (s, 1H each isomer), 5.50, 5.40, 5.33 (s, 1H), 4.37, 4.08, 4.02 (s, s, d, J=9.5 Hz, 1H), 2.717 (s, 1H), 0.76–2.14 (m, 23H); ^{13}C NMR (125 MHz, $CDCl_3$) for mixture of all isomers δ 141.1, 139.5, 138.5, 136.1, 134.7, 133.4, 129.04, 129.0, 127.6, 126.4, 126.3, 121.8, 121.0, 75.4, 75.3, 49.8, 43.2, 42.4, 37.3, 34.4, 34.3, 32.5, 31.5, 31.47, 29.2, 29.0, 28.7, 28.5, 26.4, 26.1, 24.7, 22.6, 22.5, 21.1, 14.1; IR (film, cm^{-1}) 3354, 3019, 2923, 2853, 1491, 1446, 1377, 1018, 846, 698; HRMS (EI) *m/e* calcd for $C_{23}H_{32}O$ 324.2453, found 324.2455 (M^+).

4.3.7. (*E*)-2-Heptylidene-3-hexyl-5-methylcyclohex-3-enol (2g). Following the general procedure in Section 4.3, compound **1g** (194 mg, 0.669 mmol), $Ni(COD)_2$ (18 mg, 0.067 mmol) tributylphosphine (0.035 mL, 0.13 mmol), and triethylborane (1.34 mL, 1.34 mmol in 1.0 M solution) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 146 mg (75%) of two inseparable diastereomers (2.4:1) of light yellow oil. Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45–5.49 (m, 1H),

5.35–5.37 (m, 1H), 4.19 (br d, J=2.0 Hz, 1H), 2.51–2.53 (m, 1H), 2.35–2.43 (m, 1H), 2.14–2.23 (m, 3H), 1.99 (dt, J=13.5, 5.0 Hz, 1H), 1.55 (br s, 1H), 1.26–1.43 (m, 17H), 1.02 (d, 7.0 Hz, 3H), 0.86–0.89 (m, 6H), diagnostic chemical shifts for minor isomer: δ 4.12 (br d, J=9.5 Hz, 1H), 2.06–2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) for the two diastereomers: δ 137.6, 136.6, 135.7, 134.0, 133.1, 132.2, 129.2, 122.9, 75.2, 72.3, 41.5, 39.0, 36.4, 36.2, 32.1, 31.9, 31.0, 30.7, 30.6, 29.5, 29.4, 29.3, 29.2, 29.1, 27.3, 22.9, 22.8, 22.4, 21.7, 14.3; IR (film, cm^{-1}) 3330, 2953, 2922, 2854, 1606, 1456, 1377, 1092, 1035, 972, 840, 725; HRMS (EI) *m/e* calcd for $C_{20}H_{36}O$ 292.2766, found 292.2767 (M^+).

4.3.8. (*E*)-2-Benzylidene-3-hexylcyclohex-3-enol (2h). Following the general procedure in Section 4.3, compound **1h** (804 mg, 3.0 mmol), $Ni(COD)_2$ (83 mg, 0.3 mmol), tributylphosphine (0.15 mL, 0.6 mmol), and triethylborane (6.0 mL, 6.0 mmol of 1.0 M solution), were combined to produce, after flash chromatography (3:1 hexanes/Et_2O), 689 mg (85%) of product as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.59 (s, 1H), 5.64 (m, 1H), 4.36 (dd, J=7.0, 3.0 Hz, 1H), 2.27–2.44 (m, 2H), 2.02 (m, 1H), 1.94 (m, 1H), 1.85 (m, 2H), 1.71 (br s, 1H), 1.11 (m, 4H), 0.99 (m, 2H), 0.89 (m, 2H), 0.78 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 138.8, 136.1, 129.3, 128.7, 127.9, 126.8, 123.6, 73.0, 34.6, 31.7, 31.3, 29.05, 28.99, 23.4, 22.7, 14.2; IR (film, cm^{-1}) 3324, 3022, 1590, 1492, 1105, 698; HRMS (EI) *m/e* calcd for $C_{19}H_{26}O$ 270.1984, found 270.1985 (M^+).

4.4. General procedure for the aromatization of alkylidene cyclohexenols

To a 0.05 M solution of the alcohol in toluene, trifluoroacetic acid (2.0 equiv) was added, the reaction was heated to reflux until starting material was consumed as judged by TLC (typically 2–3 h, unless otherwise noted). The reaction mixture was then concentrated under vacuum and purified via column with pure hexanes (unless otherwise noted).

4.4.1. Benzyl-2-hexyl-4-methylbenzene (3a). Following the general procedure in Section 4.4, compound **2a** (51 mg, 0.18 mmol) and trifluoroacetic acid (TFA) (0.026 mL, 0.36 mmol) were employed to produce, after column chromatography (pure hexane), 36 mg (76%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.20 (t, J=7.3 Hz, 1H), 7.15 (d, J=7.5 Hz, 2H), 6.97–7.03 (m, 3H), 4.01 (s, 2H), 2.56 (m, 2H), 2.35 (s, 3H), 1.47–1.54 (m, 2H), 1.26–1.37 (m, 6H), 0.91 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 141.4, 136.1, 135.5, 130.6, 130.4, 129.0, 128.6, 126.8, 126.1, 38.7, 33.3, 32.0, 31.3, 29.7, 22.9, 21.3, 14.4; IR (film, cm^{-1}) 3026, 2999, 2954, 2925, 2856, 1602, 1494, 1453, 1377, 831, 724, 696; HRMS (EI) *m/e* calcd for $C_{20}H_{26}$ 266.2035, found 266.2033 (M^+).

4.4.2. 1-Benzyl-2-*tert*-butylbenzene (3b). Following the general procedure in Section 4.4, compound **2b** (59 mg, 0.24 mmol) and trifluoroacetic acid (TFA) (0.036 mL, 0.49 mmol) were employed to produce, after column chromatography (pure hexane), 40 mg (73%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J=8.0 Hz, 1H), 7.25–7.28 (m, 2H), 7.16–7.20 (m, 2H), 7.10–7.13 (t, J=7.5 Hz, 1H), 7.08 (d, J=7.5 Hz, 2H), 7.02 (d, J=7.5 Hz, 1H), 4.33 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 142.6, 139.0, 133.4, 129.3, 128.5, 126.3, 126.2, 126.0, 40.2, 36.0, 32.0; IR (film, cm^{-1}) 3060, 3025, 2957, 2872, 1601, 1492, 1452, 1395, 1364, 760, 728, 697; HRMS (EI) *m/e* calcd for $C_{17}H_{20}$ 224.1565, found 224.1567 (M^+).

4.4.3. 1-Benzyl-(benzyloxymethyl)benzene (3c). Following the general procedure in Section 4.4, compound **2c** (30 mg, 0.098 mmol) and trifluoroacetic acid (TFA) (0.015 mL, 0.20 mmol) were employed to produce, after column chromatography (6:1 hexane/CH_2Cl_2), 19 mg (67%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.42 (m, 1H), 7.32–7.37 (m, 4H), 7.23–7.31 (m, 5H), 7.13–7.19 (m, 2H), 7.08–7.10 (m, 2H), 4.52 (s, 2H), 4.51 (s, 2H), 4.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 139.5, 138.5, 136.5, 130.7, 129.5, 129.0, 128.6, 128.3, 128.1, 127.9, 126.7, 126.2, 72.6, 70.5, 38.6; IR (film, cm^{-1}) 2921, 2851, 1493, 1452, 1360, 732, 696; HRMS (ESI) *m/e* calcd for $C_{21}H_{20}ONa$ 311.1412, found 311.1411 $[M+Na]^+$.

4.4.4. 1-Benzyl-2,3-diethyl-5-methylbenzene (3d). Following the general procedure in Section 4.4, compound **2d** (17 mg, 0.066 mmol, mixture of isomers) and trifluoroacetic acid (TFA) (0.010 mL, 0.132 mmol) were employed to produce, after column chromatography (15:1 hexane/CH_2Cl_2), 11 mg (70%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J=7.0 Hz, 2H), 7.19 (t, J=7.5 Hz, 1H), 7.14 (d, J=7.0 Hz, 2H), 6.93 (s, 1H), 6.79 (s, 1H), 4.01 (s, 2H), 2.60–2.67 (m, 4H), 2.27 (s, 3H), 1.24 (t, J=7.8 Hz, 3H), 1.05 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 141.7, 138.5, 137.5, 135.3, 129.4, 129.0, 128.55, 128.0, 126.0, 39.3, 25.9, 21.7, 21.3, 16.0, 15.3; IR (film, cm^{-1}) 3062, 3025, 2964, 2927, 2872, 1603, 1578, 1494, 1451, 1375, 862, 733, 698; HRMS (EI) *m/e* calcd for $C_{18}H_{22}$ 238.1722, found 238.1725 (M^+).

4.4.5. 2-Benzyl-5-methylbiphenyl (3e). Following the general procedure in Section 4.4, compound **2e** (29 mg, 0.11 mmol) and trifluoroacetic acid (TFA) (0.016 mL, 0.21 mmol) were employed to produce, after column chromatography (pure hexane), 10 mg (38%) of a thick colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.37 (m, 3H), 7.24–7.26 (m, 1H), 7.17–7.22 (m, 3H), 7.11–7.15 (m, 3H), 7.09 (s, 1H), 6.98 (d, J=7.0 Hz, 2H), 3.93 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 142.0, 141.95, 135.9, 135.4, 131.1, 130.5, 129.5, 129.0, 128.4, 128.2, 127.0, 125.9, 38.8, 21.2; IR (film, cm^{-1}) 3026, 2917, 1600, 1488, 1452, 906, 835, 762, 728, 700; HRMS (EI) *m/e* calcd for $C_{20}H_{18}$ 258.1409, found 258.1409 (M^+).

4.4.6. 6-Benzyl-7-hexyl-1,2,3,4-tetrahydronaphthalene (3f). Following the general procedure in Section 4.4, compound **2f** (10.5 mg, 0.0324 mmol) and trifluoroacetic acid (TFA) (0.007 mL, 0.097 mmol) were employed to produce, after column chromatography (pure hexane), 6.8 mg (69%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 2H), 7.13–7.19 (m, 3H), 6.88 (s, 1H), 6.79 (s, 1H), 3.95 (s, 2H), 2.73 (m, 2H), 2.68 (m, 2H), 2.49 (m, 2H), 1.77 (quintet, J=3.3 Hz, 4H), 1.46 (m, 2H), 1.20–1.34

(m, 6H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 138.6, 135.7, 135.3, 134.7, 131.2, 130.2, 129.0, 128.5, 126.0, 38.7, 32.9, 32.0, 31.4, 29.7, 29.2, 29.16, 23.6, 22.8, 14.3; IR (film, cm^{-1}) 3025, 2924, 2855, 1602, 1494, 1452, 1436, 920, 870, 725, 696; HRMS (EI) *m/e* calcd for $C_{23}H_{30}$ 306.2348, found 306.2350 (M^+).

4.4.7. 1-Heptyl-2-hexyl-4-methylbenzene (3g). Following the general procedure in Section 4.4, compound **2g** (52 mg, 0.17 mmol, mixture of isomers) and trifluoroacetic acid (TFA) (0.060 mL, 0.34 mmol) were employed to produce, after column chromatography (pure hexane), 39 mg (80%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, J=7.5 Hz, 1H), 6.98 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 2.58 (t, J=8.3 Hz, 4H), 2.31 (s, 3H), 1.54–1.61 (m, 4H), 1.31–1.44 (m, 14H), 0.86–0.94 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 137.8, 135.3, 130.1, 129.3, 126.7, 33.0, 32.6, 32.1, 32.0, 31.8, 31.7, 30.0, 29.8, 29.5, 23.0, 22.9, 21.2, 14.4; IR (film, cm^{-1}) 2954, 2923, 2855, 1615, 1501, 1465, 1377, 817, 723; HRMS (EI) *m/e* calcd for $C_{20}H_{34}$ 274.2661, found 274.2660 (M^+).

4.4.8. 1-Benzyl-2-hexylbenzene (3h). Following the general procedure in Section 4.4, compound **2h** (58 mg, 0.19 mmol) and trifluoroacetic acid (TFA) (0.028 mL, 0.37 mmol) were employed to produce, after column chromatography (pure hexane), 43 mg (80%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3 (t, J=7.5 Hz, 2H), 7.12–7.23 (m, 7H), 4.06 (s, 2H), 2.61 (m, 2H), 1.53 (quintet, J=7.8 Hz, 2H), 1.27–1.38 (m, 6H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 141.3, 138.6, 130.6, 129.6, 129.0, 128.6, 126.7, 126.2, 126.1, 39.1, 33.2, 32.0, 31.1, 29.7, 22.9, 14.4; IR (film, cm^{-1}) 3062, 3025, 2955, 2924, 2851, 1601, 1494, 1452, 751, 729, 670; HRMS (EI) *m/e* calcd for $C_{19}H_{24}$ 252.1878, found 252.1882 (M^+).

4.5. General procedure for the palladium acetate oxidation of alkylidene cyclohexenols

To a toluene solution of palladium acetate (10 mol %) and MS 3 Å, pyridine was added (1.0 equiv) and the solution was heated to 80 °C for 10 min under a balloon of oxygen. After that, a toluene solution of the alcohol (1.0 equiv) (total concentration is 0.1 M with respect to the alcohol) was added dropwise and the reaction was stirred at 80 °C under oxygen until starting material was completely consumed as judged by TLC analysis. Then, the reaction mixture was filtered, the solvent was removed under vacuum, and the crude product was purified by column chromatography on SiO_2.

4.5.1. (*E*)-Benzylidene-3-hexyl-5-methylcyclohex-3-enone (4a). Following the general procedure in Section 4.5, compound **2a** (44 mg, 0.155 mmol), $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), pyridine (0.025 mL, 0.31 mmol), and MS 3 Å (78 mg) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 30 mg (69%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.26–7.34 (m, 5H), 5.98 (d, J=3.5 Hz, 1H), 2.65–2.76 (m, 1H), 2.58 (dd, J=16.5, 5.0 Hz, 1H), 2.16 (dd, J=16.5, 9.0 Hz, 1H), 1.95–2.07 (m, 2H), 1.17 (d, J=7.0 Hz, 3H), 1.08–1.14 (m, 4H), 0.87–1.04 (m, 4H), 0.78 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 138.3, 136.6, 136.1, 134.3, 133.1, 129.6, 128.5, 128.2, 44.8, 33.6, 31.6, 29.0, 28.8, 28.5, 22.6, 20.9, 14.2; IR (film, cm^{-1}) 3056, 3024, 2957, 2925, 2855, 1695, 1623, 1587, 1571, 1516, 1492, 1454, 1406, 1376, 1336, 1241, 1158, 1072, 1029, 830, 739, 698; HRMS (EI) *m/e* calcd for $C_{20}H_{26}O$ 282.1984, found 282.1982 (M^+).

4.5.2. (*E*)-2-Benzylidene-3,4-diethyl-6-methylcyclohex-3-enone (4d). Following the general procedure in Section 4.5, compound **2d** (42 mg, 0.16 mmol), $Pd(OAc)_2$ (7.3 mg, 0.033 mmol), pyridine (0.014 mL, 0.16 mmol), and MS 3 Å (82 mg) were employed to produce, after column chromatography (15:1 hexane/ethyl acetate), 24.5 mg (59%) of a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.35 (m, 6H), 2.41 (dd, J=14.5, 5.0 Hz, 1H), 2.19–2.36 (m, 5H), 2.05 (sextet, J=7.0 Hz, 1H), 1.20 (d, J=6.5 Hz, 3H), 1.10 (t, J=7.3 Hz, 3H), 0.72 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 141.1, 136.7, 135.9, 132.7, 131.2, 129.9, 128.4, 128.2, 39.8, 34.7, 26.9, 22.7, 16.3, 15.2, 12.8; IR (film, cm^{-1}) 2986, 2976, 2925, 2885, 1689, 1599, 1588, 1448, 1181, 1026, 929, 758, 697; HRMS (EI) *m/e* calcd for $C_{18}H_{22}O$ 254.1671, found 254.1671 (M^+).

4.5.3. (*E*)-2-Benzylidine-3-hexyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(2*H*)-one (4f). Following the general procedure in Section 4.5, compound **2f** (35 mg, 0.108 mmol), $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), pyridine (0.0093 mL, 0.108 mmol), and MS 3 Å (70 mg) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 25 mg (72%) of a light yellow oil (inseparable diastereomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 0.6H), 7.55 (s, 0.3H), 7.28–7.35 (m, 5H), 6.64 (s, 0.1H), 6.00 (d, J=5.5 Hz, 0.3H), 5.75 (s, 0.6H), 5.60 (s, 0.1H), 2.65 (m, 0.3H), 2.45–2.50 (m, 0.4H), 2.27–2.32 (m, 0.9H), 2.16 (m, 0.7H), 1.91–2.11 (m, 3H), 1.83–1.88 (m, 0.9H), 1.78–1.80 (m, 0.9H), 1.28–1.44 (m, 4.6H), 1.17–1.21 (m, 0.6H), 1.13 (m, 3.6H), 0.87–1.04 (m, 4.1H), 0.78 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) all isomers: δ 204.9, 203.7, 198.6, 137.6, 137.5, 136.7, 136.6, 135.1, 134.2, 133.9, 133.3, 133.1, 132.2, 130.1, 129.4, 129.34, 129.2, 128.2, 128.1, 127.9, 127.85, 127.7, 55.3, 50.1, 46.1, 43.1, 37.6, 33.5, 33.3, 32.8, 32.5, 31.7, 31.4, 30.2, 29.3, 28.84, 28.79, 28.64, 28.56, 28.2, 26.3, 25.9, 25.8, 25.7, 25.1, 24.5, 24.0, 23.5, 22.6, 22.4, 14.1, 14.0; IR (film, cm^{-1}) 2923, 2852, 1690, 1583, 149, 1455, 1383, 1152, 1067, 696; HRMS (EI) *m/e* calcd for $C_{23}H_{30}O$ 322.2297, found 322.2296 (M^+).

4.5.4. (*E*)-Benzylidene-3-hexylcyclohex-3-enone (4h). Following the general procedure in Section 4.5, compound **2h** (25 mg, 0.093 mmol), $Pd(OAc)_2$ (2.1 mg, 0.0093 mmol), pyridine (0.008 mL, 0.093 mmol), and MS 3 Å (46 mg) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 17 mg (68%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.26–7.34 (m, 5H), 6.06 (m, 1H), 2.42–2.49 (m, 4H), 2.03 (t, J=7.3 Hz, 2H), 1.09–1.15 (m, 4H), 0.92–1.04 (m, 4H), 0.77 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 139.5, 136.5, 134.8, 133.0, 129.6, 129.2, 128.5, 128.1, 36.2, 33.7, 31.6, 29.0, 28.8, 22.7, 22.2, 14.2; IR (film, cm^{-1}) 3060, 3027, 2955, 2854, 1694, 1625, 1586, 1492, 1446, 1339, 1252, 1171, 1015, 919, 758, 725, 697;

HRMS (EI) *m/e* calcd for $C_{19}H_{24}O$ 268.1827, found 268.1826 (M^+).

4.6. General procedure for the addition of alkyl lithium reagents to alkylidene cyclohexenones

A 0.05 M THF solution of anhydrous cerium chloride (5.0 equiv) was stirred for 3 h at room temperature. The slurry was cooled to −78 °C and the alkyl lithium (2.0 equiv) was added, the solution was stirred for an additional 1 h at −78 °C. Then, a THF solution of the ketone (1.0 equiv) was added dropwise, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to 0 °C, quenched with a 1 M HCl solution, stirred for 10 min at 0 °C, extracted with diethyl ether, and dried over $MgSO_4$, evaporated under vacuum and purified by column chromatography.

4.6.1. (*E*)-2-Benzylidene-3,4-diethyl-1,6-dimethylcyclohex-3-enol (alcohol precursor of 5d). Following the general procedure in Section 4.6, $CeCl_3$ (233 mg, 0.945 mmol), CH_3Li (0.24 mL, 0.38 mmol), and compound **4d** (48 mg, 0.19 mmol) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 44 mg (86% yield) of a light yellow oil (single diastereomer). ^1H NMR (500 MHz, $CDCl_3$) δ 7.22–7.28 (m, 4H), 7.16–7.19 (m, 1H), 6.57 (s, 1H), 2.45 (dd, J=18.0, 6.0 Hz, 1H), 2.10 (q, J=7.5 Hz, 2H), 1.87–2.04 (m, 4H), 1.69 (s, 1H), 1.40 (s, 3H), 1.05 (t, J=7.3 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H), 0.71 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 139.6, 137.5, 132.2, 129.2, 128.1, 126.4, 120.4, 74.7, 39.7, 37.2, 26.1, 25.3, 23.1, 16.2, 14.6, 13.3; IR (film, cm^{-1}) 3470, 3075, 3055, 3020, 2962, 2929, 2871, 2832, 1632, 1596, 1490, 1445, 1373, 1317, 1216, 1153, 1108, 1072, 920, 859, 748, 697, 650; HRMS (EI) *m/e* calcd for $C_{19}H_{26}O$ 270.1984, found 270.1984 (M^+).

4.6.2. 1-Benzyl-2,3-diethyl-5,6-dimethylbenzene (5d). Following the general procedure in Section 4.4, the alcohol precursor above (34 mg, 0.13 mmol) and trifluoroacetic acid (TFA) (0.019 mL, 0.25 mmol) were employed to produce, after column chromatography (pure hexane), 28.5 mg (90%), of a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 2H), 7.16–7.19 (m, J=7.5 Hz, 2H), 7.05 (d, J=7.0 Hz, 1H), 7.00 (s, 1H), 4.15 (s, 2H), 2.68 (q, J=7.8 Hz, 2H), 2.63 (q, J=7.8 Hz, 2H), 2.29 (s, 3H), 2.10 (s, 3H), 1.28 (t, J=7.5 Hz, 3H), 1.11 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 139.5, 138.7, 136.3, 134.6, 133.8, 129.1, 128.6, 128.2, 125.6, 35.4, 26.00, 22.6, 21.0, 16.2, 16.1, 15.7; IR (film, cm^{-1}) 3060, 3024, 2870, 1603, 1494, 1446, 1451, 1374, 1322, 1264, 1208, 1067, 1030, 1010, 946, 875, 843, 792, 728, 698; HRMS (EI) *m/e* calcd for $C_{19}H_{24}$ 252.1878, found 252.1876 (M^+).

4.6.3. (*E*)-2-Benzylidene-3-hexyl-1-methylcyclohex-3-enol (alcohol precursor of 5h). Following the general procedure in Section 4.6, $CeCl_3$ (138 mg, 0.56 mmol), CH_3Li (0.14 mL, 0.22 mmol), and compound **4h** (30 mg, 0.11 mmol) were employed to produce, after column chromatography (8:1 hexane/ethyl acetate), 25.7 mg (81% yield) of a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 2H), 7.17–7.22 (m, 3H), 6.78 (s, 1H), 5.58 (m, 1H), 2.36–2.40 (m, 1H), 2.22–2.29 (m, 1H), 1.80–1.91 (m, 3H), 1.71–1.77 (m, 1H), 1.68 (s, 1H), 1.39 (s, 3H), 0.82–1.17 (m, 8H), 0.78 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 139.5, 137.4, 129.2, 127.9, 127.74, 126.6, 120.8, 72.7, 38.4, 35.0, 31.7, 29.3, 29.1, 25.5, 24.9, 22.7, 14.3; IR (film, cm^{-1}) 3370, 3076, 3054, 3021, 2954, 2925, 2855, 1596, 1492, 1456, 1444, 1367, 1324, 1147, 1096, 1072, 982, 922, 831, 758, 698; HRMS (EI) *m/e* calcd for $C_{20}H_{28}O$ 284.2140, found 284.2139 (M^+).

4.6.4. 1-Benzyl-2-hexyl-6-methylbenzene (5h). Following the general procedure in Section 4.4, the alcohol precursor above (23 mg, 0.082 mmol) and trifluoroacetic acid (TFA) (0.012 mL, 0.16 mmol) were employed to produce, after column chromatography (pure hexane), 18 mg (84%) of a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.28 (m, 2H), 7.12–7.18 (m, 2H), 7.09 (d, J=6.5 Hz, 1H), 7.06 (d, J=7.0 Hz, 1H), 7.01 (d, J=7.5 Hz, 2H), 4.09 (s, 2H), 2.57 (m, 2H), 2.22 (s, 3H), 1.49 (quintet, J=7.6 Hz, 2H), 1.22–1.33 (m, 6H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 140.6, 137.7, 136.4, 128.6, 128.3, 128.2, 127.5, 126.6, 125.9, 34.8, 33.9, 31.9, 31.6, 29.6, 22.8, 20.6, 14.3; IR (film, cm^{-1}) 3063, 3025, 2955, 2927, 2857, 1603, 1587, 1494, 1467, 1452, 1378, 780, 755, 726; HRMS (EI) *m/e* calcd for $C_{20}H_{26}$ 266.2035, found 266.2035 (M^+).

4.7. General procedure for the synthesis of aryl alkyl ethers and phenols

To a 0.05 M solution of the cyclohexenone in the corresponding alcohol, tetrafluoroboric acid (HBF_4) (5.0 equiv, unless otherwise noted) was added at room temperature, the reaction was refluxed for 10–12 h (unless otherwise noted), quenched with ammonium chloride, extracted with diethyl ether, dried over $MgSO_4$, and purified by column chromatography (hexane/ethyl acetate) to yield the corresponding aryl alkyl ether and/or phenol.

4.7.1. 2-Benzyl-3,4-diethyl-6-methylphenol (6d). Following the general procedure in Section 4.7, compound **4f** (22 mg, 0.087 mmol), HBF_4 (0.11 mL, 0.87 mmol, 10.0 equiv, 48%, 7.87 M), and ethanol (1.7 mL) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 14.5 mg (67%) of a thick yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 2H), 7.15–7.20 (m, 3H), 6.91 (s, 1H), 4.44 (s, 1H), 4.11 (s, 2H), 2.63 (m, 4H), 2.22 (s, 3H), 1.23 (t, J=7.5 Hz, 3H), 1.09 (t, J=7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 140.5, 139.7, 134.2, 129.5, 128.8, 128.3, 126.4, 124.3, 121.2, 32.3, 25.6, 22.5, 16.3, 16.1, 15.6; IR (film, cm^{-1}) 3568, 3082, 3060, 3024, 2963, 2928, 2870, 1603, 1579, 1493, 1474, 1451, 1375, 1315, 1240, 1209, 947, 878, 730, 698; HRMS (EI) *m/e* calcd for $C_{18}H_{22}O$ 254.1671, found 254.1669 (M^+).

4.7.2. 2-Benzyl-3-hexyl-5,6,7,8-tetrahydronaphthalen-1-ol (6f). Following the general procedure in Section 4.7, compound **4f** (21 mg, 0.065 mmol), HBF_4 (0.17 mL, 1.3 mmol, 20.0 equiv, 48%, 7.87 M), and ethanol (1.3 mL) were employed to produce, after column chromatography (3:1 hexane/CH_2Cl_2), 11 mg (52%) of white solid. Mp 50–52 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.27 (m, 2H), 7.16–7.19 (m, 3H), 6.59 (s, 1H), 4.58 (s, 1H), 4.04 (s, 2H),

2.74 (t, J=6.3 Hz, 2H), 2.53–2.57 (m, 4H), 1.81–1.86 (m, 2H), 1.74–1.79 (m, 2H), 1.45–1.51 (m, 2H), 1.23–1.3 (m, 6H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 140.6, 139.9, 136.6, 128.8, 128.3, 126.3, 122.4, 122.2, 120.8, 33.6, 31.92, 31.88, 31.7, 29.67, 29.66, 23.1, 23.1, 22.8, 14.3; IR (film, cm^{-1}) 3558, 3024, 1620, 1602, 1572, 1493, 1452, 1423, 1339, 1238, 1180, 1075, 1030, 947, 908, 727, 696; HRMS (EI) *m/e* calcd for $C_{23}H_{30}O$ 322.2297, found 322.2293 (M^+).

4.7.3. 2-Benzyl-3-hexyl-phenyl-*n*-propyl ether (7h). Following the general procedure in Section 4.7, compound **4h** (21 mg, 0.078 mmol), HBF_4 (0.055 mL, 0.39 mmol, 48%, 7.87 M), and *n*-propanol (1.6 mL) were employed to produce, after column chromatography (20:1 hexane/ethyl acetate), 16.3 mg (67%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.23 (m, 2H), 7.11–7.16 (m, 4H), 6.80 (d, J=7.5 Hz, 1H), 6.74 (d, J=7.5 Hz, 1H), 4.09 (s, 2H), 3.88 (t, J=6.3 Hz, 2H), 2.58 (m, 2H), 1.71 (sextet, J=7.0 Hz, 2H), 1.46 (m, 2H), 1.20–1.33 (m, 6H), 0.92 (t, J=7.5 Hz, 3H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 143.2, 141.9, 128.4, 128.3, 127.4, 127.1, 125.6, 121.7, 109.1, 69.9, 33.5, 31.9, 31.6, 31.4, 29.7, 22.9, 22.8, 14.3, 10.9; IR (film, cm^{-1}) 3062, 3026, 2958, 2927, 2857, 1602, 1584, 1494, 1460, 1390, 1316, 1259, 775, 727, 696, 626, 613; HRMS (EI) *m/e* calcd for $C_{22}H_{30}O$ 310.2297, found 310.2301 (M^+).

4.7.4. 2-Benzyl-3-hexyl-phenyl-allyl ether (8h). Following the general procedure in Section 4.7, compound **4h** (25 mg, 0.093 mmol), HBF_4 (0.059 mL, 0.47 mmol, 48%, 7.87 M), and allyl alcohol (1.0 mL) were employed to produce, after column chromatography (20:1 hexane/CH_2Cl_2, then 10:1 hexane/CH_2Cl_2), 18.9 mg (66%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.23 (m, 2H), 7.11–7.16 (m, 4H), 6.82 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 5.95 (m, 1H), 5.30 (dq, J=17.8, 1.8 Hz, 1H), 5.18 (dq, J=10.5, 1.5 Hz, 1H), 4.49 (d, J=4.5 Hz, 2H), 4.11 (s, 2H), 2.58 (m, 2H), 1.46 (quintet, J=7.6 Hz, 2H), 1.22–1.33 (m, 6H), 0.86 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 143.4, 141.7, 133.9, 128.4, 128.3, 127.6, 127.1, 125.6, 122.2, 116.9, 109.7, 69.2, 33.5, 31.9, 31.6, 31.3, 29.6, 22.8, 14.3; IR (film, cm^{-1}) 3062, 3026, 2954, 2927, 2857, 1602, 1582, 1494, 1452, 1423, 1379, 1315, 1258, 778, 727, 696, 640; HRMS (EI) *m/e* calcd for $C_{22}H_{28}O$ 308.2140, found 308.2142 (M^+).

4.7.5. 2-Benzyl-3-hexyl-5-methyl-phenyl-ethyl ether (9a). Following the general procedure in Section 4.7, compound **4a** (27 mg, 0.096 mmol), HBF_4 (0.06 mL, 0.48 mmol, 10.0 equiv, 48%, 7.87 M), and ethanol (1.9 mL) were employed to produce, after column chromatography (25:1 hexane/ethyl acetate), 19.0 mg (64%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.22 (m, 3H), 7.10–7.13 (m, 2H), 6.63 (s, 1H), 6.57 (s, 1H), 4.03 (s, 2H), 3.97 (q, J=6.8 Hz, 2H), 2.53 (m, 2H), 2.32 (s, 3H), 1.44 (quintet, J=8.0 Hz, 2H), 1.22–1.33 (m, 9H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 142.9, 142.2, 136.8, 128.5, 128.2, 125.5, 124.5, 122.5, 110.4, 63.9, 33.5, 31.9, 31.5, 31.4, 29.7, 22.8, 21.8, 15.2, 14.3; IR (film, cm^{-1}) 3023, 2954, 2925, 2857, 1610, 1580, 1493, 1453, 1290, 1181, 725, 696; HRMS (EI) *m/e* calcd for $C_{22}H_{30}O$ 310.2297, found 310.2297 (M^+).

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StePHOX, a new family of optically active, tunable phosphine–oxazoline ligands: syntheses and applications

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Abstract—A new class of optically active phosphine–oxazoline ligands has been synthesized wherein backbone chirality of these new ligands is installed by a Sharpless asymmetric dihydroxylation. Different backbone protecting groups as well as different substitution patterns on the oxazoline ring were studied. These ligands were tested in allylic substitution (with ee's up to 97%) and asymmetric Tsuji allylation.

1. Introduction

The phosphine–oxazoline (PHOX, Fig. 1) ligands comprise a versatile class of heterobidentate structures, which have a remarkably broad range of applications in asymmetric catalysis.[1] Several features of the PHOX ligands originally introduced by Pfaltz,[2] Helmchen,[3] and Williams,[4] are important. From an electronic perspective, the coordinating heteroatoms are sufficiently distinct that they render the reactivity of neighboring coordination sites, in a transition metal complex, nonequivalent. By altering the substitution of the aromatic backbone,[5] the electronic properties of the ligand can be fine tuned thereby leading to enhanced reactivity and selectivity for a reaction of interest. Similarly, the steric environment imposed by the ligand may be modified by altering the substituents on the oxazoline ring and on the phosphorus atom. In addition to these perturbations to the parent structure, several groups have examined alternate linkages that connect the phosphine and oxazoline groups. When these connecting elements are rendered chiral, new opportunities arise for ligand tuning and representative examples are depicted in Figure 1.[6]

To expand the tunability of the phosphine–oxazoline ligands, we have designed a new ligand class, coined StePHOX, which is depicted in Figure 2. The added control element is a dioxolane backbone, which connects the phosphine and oxazoline motifs. It was anticipated that chirality associated with the dioxolane linkage would impose itself on the ligand conformation such that the chirality on the oxazoline may not be required for asymmetric induction. Furthermore, the dioxolane offers an additional tuning element to those which are already present in the PHOX ligands. In this report, we describe an efficient synthetic route that provides members of the StePHOX ligand family. Also described, are structural studies on StePHOX–metal complexes and preliminary observations on enantioselective catalysis.

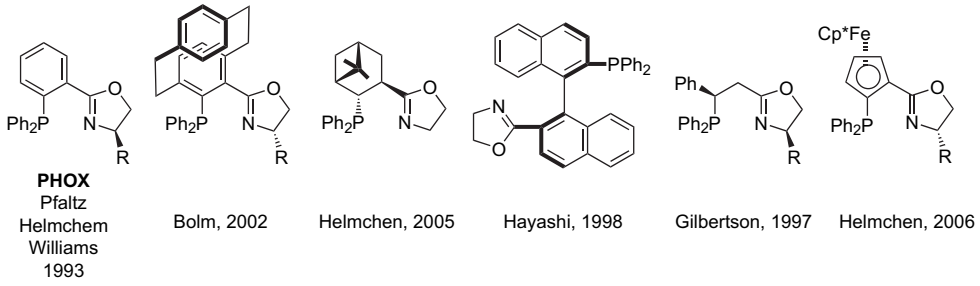

Figure 1.

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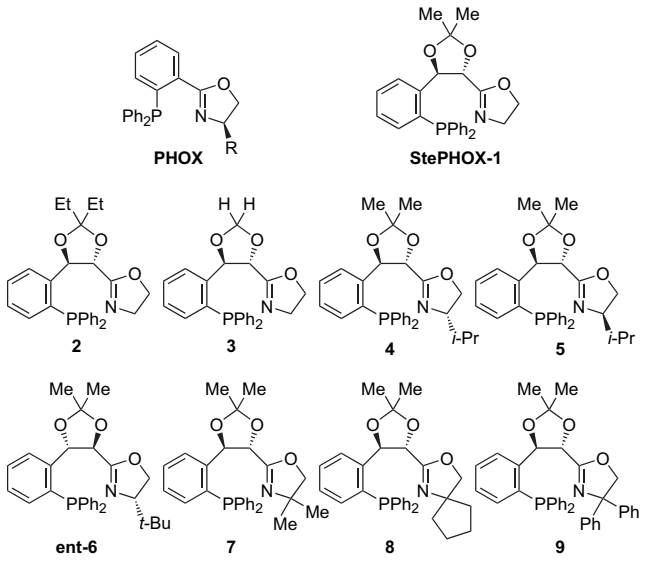
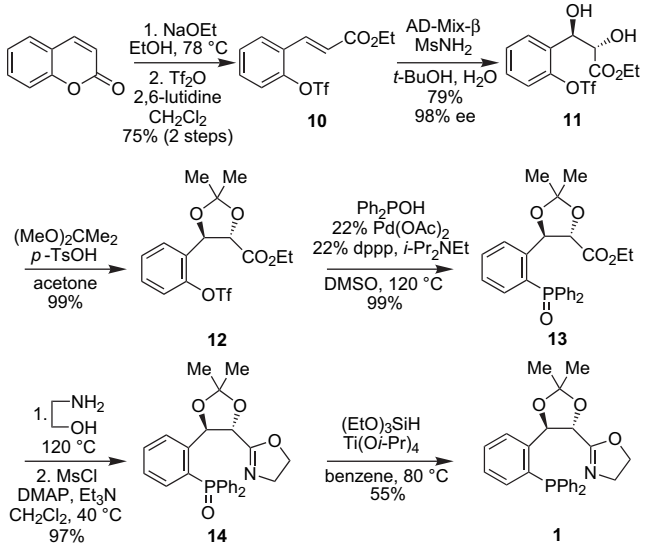


Figure 2.

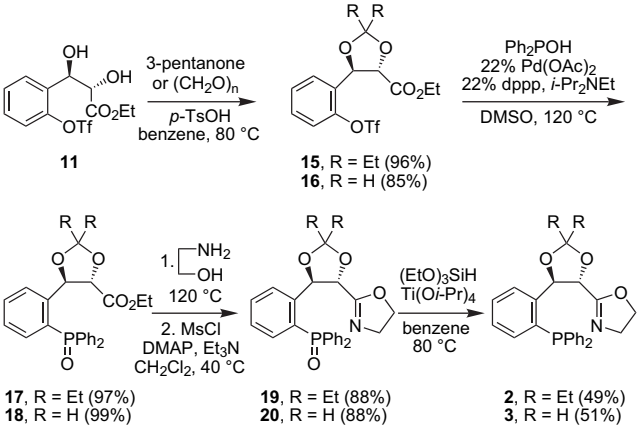
2. Results and discussion

A straightforward inexpensive route to the StePHOX family of ligands is described in Scheme 1. In this approach, inexpensive coumarin was treated with sodium ethoxide in refluxing ethanol[7] and the resulting *trans*-enoate was then converted to the derived triflate (**10**). Sharpless asymmetric dihydroxylation was then performed with AD-mix-β and methanesulfonamide to afford, in excellent enantiopurity, diol **11**.[8] After conversion of the diol to the corresponding ketal (**12**), catalytic phosphination yielded phosphine oxide **13**.[9] The ester was then condensed with ethanolamine at 120 °C in a sealed vial for 2 h to afford a hydroxyamide, which was immediately treated with MsCl, Et_3N, and catalytic DMAP to provide the oxazoline **14** in 97% yield. Finally, deoxygenation of phosphine oxide with triethoxysilane and titanium(IV) isopropoxide in refluxing benzene gave the parent ligand structure **1** in 55% yield.[10]



Scheme 1.

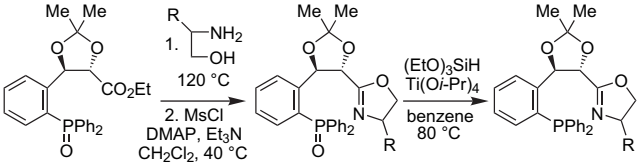
With this robust ligand synthesis in hand, several variants of the ligand structure were prepared. Using previously prepared diol **11**, two different protecting groups were introduced (Scheme 2). First, acetal **15** was prepared in 96% yield by heating diol **11** with 3-pentanone in benzene with catalytic TsOH. Alternatively, methylene acetal **16** was isolated in 85% yield after treating diol **11** with paraformaldehyde at 80 °C. Subsequently, compounds **15** and **16** were converted to **2** and **3** using a route, which is similar to that followed for the parent StePHOX ligand.



Scheme 2.

A second set of ligand structures was prepared, which possess substitution on the oxazoline ring. Accordingly, phosphine oxide **13** was condensed with an appropriate aminoalcohol at 120 °C for 2 h and the resulting hydroxyamide was then treated with MsCl, Et_3N, and catalytic DMAP to afford phosphine oxides **21**–**26** in good to excellent yields (Table 1). Deoxygenation was then performed as usual with

Table 1. Synthesis of ligands **4**–**9**

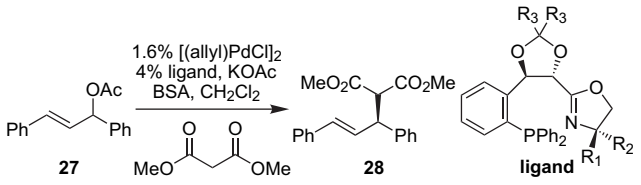


Aminoalcohol	Intermediate	Yield (%)	Ligand	Yield (%)
i-Pr, NH$_2$, OH	**21**	92	**4**	45
i-Pr, NH$_2$, OH	**22**	91	**5**	54
t-Bu, NH$_2$, OH	*ent*-**23**	84	*ent*-**6**	27
Me, Me, NH$_2$, OH	**24**	66	**7**	50
NH$_2$, OH	**25**	84	**8**	45
Ph, Ph, NH$_2$, OH	**26**	57	**9**	65

triethoxysilane and titanium(IV) isopropoxide in refluxing benzene to yield target ligands **4**–**9**. *tert*-Butyl substituted ligand *ent*-**6** was prepared starting from (*S*)-*tert*-leucinol, but employed *ent*-**13** as starting material.

The effectiveness of the StePHOX class of ligands was first assessed by employing them in an enantioselective Pd-catalyzed allylic alkylation reaction.[11,12] The parent StePHOX ligand **1** was examined first, using acetate **27** and dimethyl malonate (Table 2). This ligand, which possesses chirality solely on the backbone of the structure, provided the product **28** in 62% enantiomeric excess and favored the (*S*)-enantiomer. As can be seen in Table 1, replacement of the backbone dioxolane methyl groups, with either hydrogen atoms or ethyl groups (ligand **2** and **3**), leads to a slight decrease in enantioselection. In contrast to backbone modification, modification of the oxazoline group leads to much larger changes in selectivity. While attachment of an α-configured substituent (ligand **4**) leads to a only minor diminution in selectivity (62→48% ee), when the ligand bears a β-substituent (ligand **5**), a significant enhancement in enantioselection results (62→97% ee). This enhancement appears to be maximal with a β-isopropyl group, the corresponding ligand with a *tert*-butyl substituent exhibits diminished selectivity. Since ligand **5** exhibits significantly improved enantioselection, whereas epimeric ligand **4** exhibits only a moderate diminution in selectivity relative to **1**, it seemed reasonable to expect enhanced selectivity with geminally substituted ligands. Ligands **7**–**9** are all accessible from commercially available inexpensive aminoalcohols and the selectivity rivals were achieved with valinol derived **5**.

Table 2. StePHOX used in allylic substitution with compound **27**



Ligand	R_1	R_2	R_3	Yield (%)	ee **28** (%)
1	H	H	Me	64	62
2	H	H	Et	71	48
3	H	H	H	58	58
4	H	*i*-Pr	Me	61	46
5	*i*-Pr	H	Me	88	97
ent-**6**	*t*-Bu	H	Me	71	−79
7	Me	Me	Me	80	89
8	$CH_2CH_2CH_2CH_2$		Me	86	95
9	Ph	Ph	Me	79	75

To learn about the structure of the StePHOX ligands bound to a transition metal center, parent structure StePHOX **1** was treated with $(CH_3CN)_2PdCl_2$ and the resulting complex was crystallized from CH_2Cl_2. As can be observed in X-ray analysis depicted in Figure 3, the phosphine and oxazoline occupy cis coordination sites on the palladium center with the oxazoline ring oriented orthogonal to the palladium square plane and roughly parallel to a pseudo axial phenyl group on phosphorus.[13] Notably, the benzylic hydrogen on the ligand backbone resides 2.315 Å from the palladium atom. This example of preagostic bonding results in

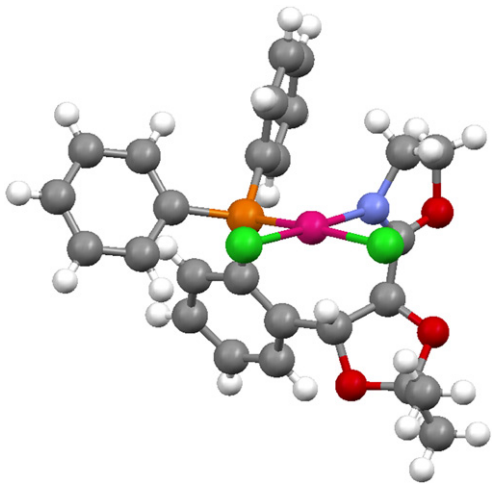


Figure 3. X-ray structure of **1**·$PdCl_2$.

significant downfield shifting of the hydrogen atom relative to the uncomplexed ligand structure in the ^{1}H NMR spectrum (6.03→9.42 ppm, vide infra).[14] The geminal methyl groups on the dioxolane ring are directed underneath the palladium square plane suggesting that, while tuning these elements did not substantially alter the selectivity in the allylic substitution reaction, they may have a significant impact on stereoselection in other catalytic transformations. In a similar fashion, elements attached to the oxazoline backbone and phosphorus atom, appear well positioned to impact reaction outcome.

On the basis of the X-ray analysis of **1**·$PdCl_2$ and the known requirements for selectivity in allylic substitution with PHOX complexes, it is not too surprising that ligand **1** does not provide high selectivity. Seminal studies by Helmchen[15] and Brown[16] suggest that electronic differentiation of the allylic termini in Pd–allyl complexes derived from P,N ligands, favors addition of nucleophiles to the carbon, which is *trans* to phosphorus.[17] Effective ligands are generally those that perturb the ratio of *endo*/*exo* π-allyl palladium complexes in favor of the *exo* isomer, and this ratio often determines the product enantioselection. In a symmetric allyl fragment, such as the one used here, the ratio of *exo*/*endo* isomer should dictate the ultimate ratio of product enantiomers.[18] Since the pseudo equatorial phenyl group on phosphorus in ligand **1** nearly bisects the palladium square plane, one would expect little bias in the conformer ratio and therefore, little selectivity. It is more surprising that ligand **4** does not lead to a selective reaction and clearly more detailed structural studies are required to understand these phenomena.

The significant enhancement in enantioselection that results from a β-configured substituent versus an α-substituent appears to arise from a difference in ligand conformation. As mentioned above, when StePHOX **1** is coordinated to $PdCl_2$, the benzylic hydrogen is shifted downfield as a result of an agostic interaction. This same agostic interaction is present in the Pd complex of ligand **4**, as determined by ^{1}H NMR analysis (Fig. 4). In contrast, when ligand **5** is treated with $PdCl_2$, a much smaller perturbation in the benzylic hydrogen resonance is observed (6.13→7.67 ppm) thereby

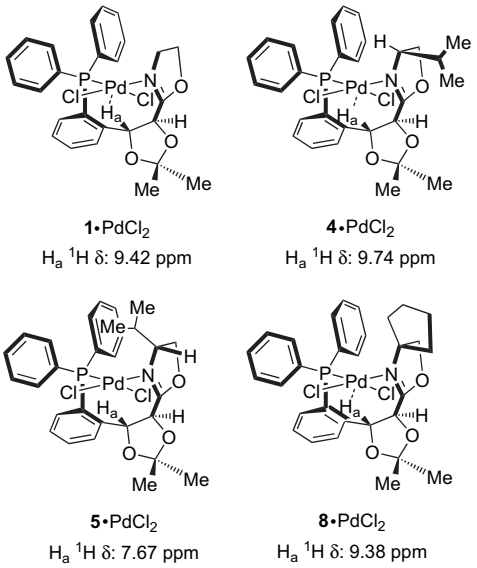
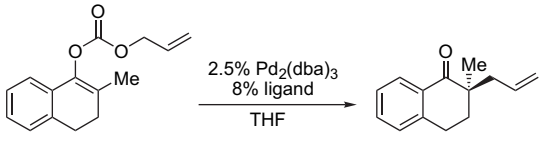


Figure 4.

suggesting that this hydrogen atom is in a different environment than in the corresponding complex of **1** and **4**. On the basis of the X-ray structure in Figure 3, one might expect that with a β-configured isopropyl group, steric interactions between the isopropyl group and the pseudo axial aryl ring are likely too severe (see **5**·$PdCl_2$ representation, Fig. 4) for the ligand to adopt the same conformation as StePHOX **1** or **4**. Contrary to our expectations, ligand **8** exhibits agostic bonding that is similar to **1** and **4** when coordinated to palladium, yet exhibits selectivity comparable to ligand **5**. It is tenable that conformational similarities between **5** and **8** arise in the context of a palladium allyl, but not in a palladium dichloride complex.

To further examine the usefulness of the StePHOX ligand class, the asymmetric Tsuji allylation was performed on compound **29** (Table 3).[19,20] The reactions were performed by premixing the appropriate ligand with tris(dibenzylideneacetone)dipalladium and then adding compound **29**. Compound **30** was isolated in good to excellent yield. Although the results with respect to enantioselectivity were less impressive than the previous example, the ligands showed encouraging levels of asymmetric induction. Again, it appears that substitution on the β-face of the ligand is important

Table 3. StePHOX used in Tsuji allylation with compound **29**



29 **30**

Entry	Ligand	Yield **30** (%)	ee **30** (%)
1	**1**	95	5
2	**4**	97	22
3	**5**	94	59
4	*ent*-**6**	86	−58
5	**7**	98	29
6	**8**	80	30

(entries 3 and 4) and it is relatively inconsequential on the α-face (entry 2). *gem*-Dialkyl substituted ligands **7** and **8** did not provide similarly high levels of selectivity as in the allylic substitution described above.

3. Conclusion

In summary, we have designed and synthesized a new highly tunable family of phosphine–oxazoline ligands that shows good to excellent enantioselectivities (ee's up to 97%) in the Pd-catalyzed allylic substitution and good enantioselectivities (ee's up to 59%) in the asymmetric Tsuji allylation. Current experiments are aiming to further improve the enantioselectivity and to develop new applications of this class of ligands.

4. Experimental

4.1. Synthesis of 10

Finely cut pieces of sodium (3.93 g, 0.17 mol) were added to a cooled (0 °C) solution of absolute EtOH (90 mL). The solution was stirred and allowed to warm to room temperature. A solution of coumarin (5.0 g in 47 mL, 34.2 mmol) was then added. The resulting yellow mixture was stirred at reflux for 16 h, cooled to room temperature, and the mixture was then concentrated under reduced pressure. A saturated aqueous solution of NH_4Cl (200 mL) was added to the crude reaction mixture and it was extracted with EtOAc (3×100 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was dissolved in 1/1 hexane/EtOAc (100 mL) and filtered through a pad of silica gel and the filtrate was then concentrated under reduced pressure to give the desired product (5.57 g) as an off-white solid. This material (4.15 g, 21.6 mmol) was dissolved in CH_2Cl_2 (70 mL) and 2,6-lutidine (3.8 mL, 32.4 mmol) was added. The solution was cooled to −78 °C and a solution of trifluoromethanesulfonic anhydride (4.5 mL, 27.0 mmol) in CH_2Cl_2 (38 mL) was added via canula. The reaction mixture was stirred for 0.5 h at −78 °C, 0.5 h at 0 °C, and 2 h at room temperature. Saturated aqueous NH_4Cl (100 mL) was then added and the mixture was extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (1/0 to 9/1 hexane/EtOAc) to give triflate **10** (8.28 g, 75% over two steps) as a yellow oil. IR (thin film, ν cm^{-1}): 2987, 1717, 1642, 1424, 1214, 1140. ^1H NMR: δ 7.85 (1H, d, J=16.0 Hz), 7.68 (1H, dd, J=7.8, 1.7 Hz), 7.47–7.33 (3H, m), 6.48 (1H, d, J=16.0 Hz), 4.26 (2H, q, J=7.1 Hz), 1.32 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 165.8, 147.6, 135.7, 131.5, 128.6, 128.2, 128.0, 122.6, 122.2, 117.0, 60.8, 14.1. MS (ESI) $(M+H)^+$: 325.1. HRMS (ESI) $(M+Na)^+$ calcd for $C_{12}H_{11}F_3O_5SNa$: 347.0171. Found: 347.0178.

4.2. Synthesis of 11

To a stirred solution of triflate **10** (8.11 g, 25.0 mmol) in *t*-BuOH (125 mL) and H_2O (125 mL) were added methanesulfonamide (2.38 g, 25.0 mmol) and AD-mix-β (35 g). The mixture was stirred at room temperature for 48 h and

then sodium sulfite (7.57 g, 60.0 mmol) was added. The resulting mixture was stirred for 0.5 h and then H_2O (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallized from hexane (100 mL) to give the first crop of white needles (2.51 g). The mother liquor was purified by flash chromatography (9/1 to 0/1 hexane/EtOAc) to give the desired product (5.8 g), which was recrystallized in hexane to give the second crop of white needles (2.42 g). Mother liquor was recrystallized a third time to give another crop of pure diol **11** (2.13 g, total=7.06 g, 79%). $[\alpha]_D^{25}$ −10.5 (*c* 1.25, $CHCl_3$). IR (thin film, ν cm^{-1}): 3398, 2989, 1740, 1424, 1214, 1140. ^1H NMR: δ 7.71–7.69 (1H, m), 7.44–7.37 (2H, m), 7.31–7.28 (1H, m), 5.37 (1H, dd, *J*=7.5, 2.4 Hz), 4.34 (1H, dd, *J*=5.6, 2.5 Hz), 4.29 (2H, q, *J*=7.2 Hz), 3.29 (1H, d, *J*=5.6 Hz), 2.92 (1H, d, *J*=7.5 Hz), 1.29 (3H, t, *J*=7.2 Hz). ^{13}C NMR: δ 172.2, 146.1, 133.0, 129.8, 129.3, 128.5, 121.1, 119.0, 73.1, 68.5, 62.6, 13.9. MS (ESI) $(M+H)^+$: 359.1; $(M+Na)^+$: 381.2. HRMS (ESI) $(M+Na)^+$ calcd for $C_{12}H_{13}F_3O_7SNa$: 381.0226. Found: 381.0232. Chiral HPLC analysis performed on Chiralcel OD-H, Daicel, 5% *i*-PrOH in hexane, 1.0 mL min^{-1}, wavelength: 220 nm.

4.3. Synthesis of 12

To a stirred solution of diol **11** (0.99 g, 2.76 mmol) in acetone (5.3 mL) were added 2,2-dimethoxypropane (2.1 mL) and *p*-toluenesulfonic acid (26 mg, 0.14 mmol). The solution was stirred at room temperature for 16 h and then Et_3N was added to neutralize the acid and the solvent was then removed. The crude product was extracted with Et_2O (3×10 mL) and saturated with aqueous $NaHCO_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (9/1 hexane/EtOAc) to give acetonide **12** (1.00 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ −4.7 (*c* 1.35, $CHCl_3$). IR (thin film, ν cm^{-1}): 2993, 2943, 1760, 1424, 1216, 1142. ^1H NMR: δ 7.68–7.65 (1H, m), 7.46–7.39 (2H, m), 7.32–7.30 (1H, m), 5.44 (1H, d, *J*=7.6 Hz), 4.30 (1H, d, *J*=7.6 Hz), 4.20 (2H, tt, *J*=14.3, 7.2 Hz), 1.60 (3H, s), 1.55 (3H, s), 1.22 (3H, t, *J*=7.2 Hz). ^{13}C NMR: δ 169.3, 147.5, 130.3, 128.9, 128.8, 121.2, 120.1, 117.0, 112.2, 81.0, 74.5, 61.8, 26.8, 25.6, 13.8. MS (ESI) $(M+H)^+$: 399.1. HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{17}F_3O_7SNa$: 421.0539. Found: 421.0548.

4.4. Synthesis of 13

To a stirred solution of acetonide **12** (1.32 g, 3.31 mmol) in DMSO (66 mL) were added diphenylphosphine oxide (1.43 g, 7.06 mmol), palladium(II) acetate (164 mg, 0.73 mmol), 1,3-bis(diphenylphosphino)propane (0.30 g, 0.73 mmol), and *N*,*N*-diisopropylethylamine (1.15 mL, 6.63 mmol). The orange solution was stirred at 120 °C for 3 h. The resulting dark red mixture was then cooled to room temperature and 5% aqueous HCl (400 mL) was added. The mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (1/1 hexane/EtOAc) to give phosphine oxide **13** (1.48 g, 99%) as a yellow foam. $[\alpha]_D^{25}$ +33.7 (*c* 0.76, $CHCl_3$). IR (thin film, ν cm^{-1}): 2989, 1756, 1437, 1194, 1104. ^1H NMR: δ 7.81 (1H, dd, *J*=7.6, 3.9 Hz), 7.68–7.57 (5H, m), 7.54–7.39 (6H, m), 7.28–7.24 (1H, m), 7.05 (1H, dd, *J*=13.9, 7.7 Hz), 6.06 (1H, d, *J*=7.3 Hz), 4.43 (1H, d, *J*=7.7 Hz), 4.26–4.12 (2H, m), 1.51 (3H, s), 1.26 (3H, s), 1.19 (3H, t, *J*=7.1 Hz). ^{13}C NMR: δ 169.0, 142.2 (d, J_{PC}=6.7 Hz), 133.3 (d, J_{PC}=102.9 Hz), 132.8 (d, J_{PC}=12.4 Hz), 132.4 (d, J_{PC}=104.5 Hz), 132.1 (d, J_{PC}=2.5 Hz), 131.9 (d, J_{PC}=9.6 Hz), 131.8 (d, J_{PC}=102.2 Hz), 131.5 (d, J_{PC}=2.7 Hz), 131.4 (d, J_{PC}=9.8 Hz), 131.3 (d, J_{PC}=4.7 Hz), 128.8 (d, J_{PC}=9.5 Hz), 128.1 (d, J_{PC}=12.2 Hz), 127.5 (d, J_{PC}=12.4 Hz), 111.0, 81.7, 76.6 (d, J_{PC}=5.4 Hz), 60.9, 26.7, 25.1, 13.6. ^{31}P NMR: δ 32.9. MS (ESI) $(M+H)^+$: 451.0. HRMS (ESI) $(M+H)^+$ calcd for $C_{26}H_{28}O_5P$: 451.1669. Found: 451.1672. $(M+Na)^+$ calcd for $C_{26}H_{27}O_5PNa$: 473.1488. Found: 473.1491.

4.5. Synthesis of 14

In a vial were added phosphine oxide **13** (1.95 g, 4.32 mmol) and ethanolamine (1.31 mL, 21.6 mmol). The vial was sealed with a screw cap and heated in an oil bath at 120 °C for 2 h. The resulting orange solution was diluted with brine and extracted with EtOAc (2×10 mL) and then with CH_2Cl_2 (2×10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude hydroxyamide (1.94 g, 97%) obtained was used in the next step without further purification. To the hydroxyamide (1.91 g, 4.10 mmol) were added CH_2Cl_2 (53 mL), Et_3N (1.14 mL, 8.21 mmol), and DMAP (5 mg, 0.04 mmol). The solution was cooled to 0 °C and methanesulfonyl chloride (0.64 mL, 8.21 mmol) was then added dropwise. The resulting solution was stirred for 1 h at 0 °C where TLC showed complete disappearance of the starting material. Another portion of Et_3N (5.15 mL, 36.9 mmol) was then added and the solution was stirred under reflux for 16 h. After cooling the solution, saturated aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (1/1 to 0/1 hexane/EtOAc) to give oxazoline **14** (1.78 g, 97%) as a white foam. $[\alpha]_D^{25}$ +31.6 (*c* 0.34, $CHCl_3$). IR (thin film, ν cm^{-1}): 3421, 3058, 2987, 2937, 1669, 1437, 1372, 1250, 1194. ^1H NMR: δ 7.79 (1H, dd, *J*=7.9, 4.0 Hz), 7.63–7.54 (5H, m), 7.52–7.46 (2H, m), 7.45–7.38 (4H, m), 7.25–7.20 (1H, m), 7.00 (1H, ddd, *J*=8.8, 8.2, 1.0 Hz), 6.07 (1H, d, *J*=8.2 Hz), 4.55 (1H, d, *J*=8.2 Hz), 4.24–4.17 (2H, m), 3.78–3.63 (2H, m), 1.49 (3H, s), 1.26 (3H, s). ^{13}C NMR: δ 164.1, 142.1 (d, J_{PC}=5.0 Hz), 133.0 (d, J_{PC}=94.3 Hz), 132.9 (d, J_{PC}=98.0 Hz), 132.4 (d, J_{PC}=4.9 Hz), 132.2 (d, J_{PC}=100.2 Hz), 132.2 (d, J_{PC}=9.6 Hz), 131.7 (d, J_{PC}=9.7 Hz), 131.6 (d, J_{PC}=3.2 Hz), 131.6 (d, J_{PC}=4.9 Hz), 129.3 (d, J_{PC}=9.6 Hz), 128.4 (d, J_{PC}=5.1 Hz), 128.3 (d, J_{PC}=5.0 Hz), 127.8 (d, J_{PC}=12.6 Hz), 110.9, 78.9, 76.7, 67.9, 54.4, 26.9, 25.6. ^{31}P NMR: δ 33.3. MS (ESI) $(M+H)^+$: 448.0. HRMS (ESI) $(M+H)^+$ calcd for $C_{26}H_{27}NO_4P$: 448.1672. Found: 448.1677. $(M+Na)^+$ calcd for $C_{26}H_{26}NO_4PNa$: 470.1492. Found: 470.1503.

4.6. Synthesis of 1

To a stirred solution of oxazoline **14** (0.56 g, 1.25 mmol) in benzene (63 mL) were added triethoxysilane (1.25 mL,

6.76 mmol) and titanium(IV) isopropoxide (0.20 mL, 0.69 mmol). The solution was stirred under reflux for 4 h. More triethoxysilane (0.23 mL, 1.25 mmol) and titanium(IV) isopropoxide (0.20 mL, 0.31 mmol) were added and the black solution was stirred under reflux for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (8/2 to 1/1 hexane/EtOAc) to give P,N-ligand **1** (0.26 g, 49%) as a white foam. The product was recrystallized in hexane/Et_2O to give white cubic crystals (0.18 g, 32%). $[\alpha]_D^{25}$ −39.0 (*c* 0.65, $CHCl_3$). IR (thin film, ν cm^{-1}): 3056, 2987, 1669, 1436, 1245, 1216, 1077. ^1H NMR: δ 7.68 (1H, dd, J=6.9, 3.1 Hz), 7.41 (1H, td, J=7.9, 1.2 Hz), 7.31–7.28 (6H, m), 7.26–7.15 (5H, m), 6.94 (1H, ddd, J=7.7, 4.1, 1.3 Hz), 6.15 (1H, t, J=7.9 Hz), 4.52 (1H, d, J=8.3 Hz), 4.07–4.00 (1H, m), 3.94–3.87 (1H, m), 3.64–3.55 (1H, m), 3.39–3.31 (1H, m), 1.59 (3H, s), 1.53 (3H, s). ^{13}C NMR: δ 164.0, 141.7 (d, J_{PC}=24.0 Hz), 137.2 (d, J_{PC}=11.3 Hz), 136.9 (d, J_{PC}=11.8 Hz), 136.0 (d, J_{PC}=17.1 Hz), 134.7 (d, J_{PC}=1.1 Hz), 133.6 (d, J_{PC}=17.6 Hz), 133.4 (d, J_{PC}=16.7 Hz), 129.9, 128.8, 128.7, 128.5 (d, J_{PC}=7.1 Hz), 128.4, 128.3, 127.1 (d, J_{PC}=6.0 Hz), 111.0, 77.9 (d, J_{PC}=148.1 Hz), 77.9 (d, J_{PC}=29.6 Hz), 67.9, 54.3, 27.1, 26.2. ^{31}P NMR: δ −17.7. MS (ESI) $(M+H)^+$: 432.1. HRMS (ESI) $(M+H)^+$ calcd for $C_{26}H_{27}NO_3P$: 432.1723. Found: 432.1726.

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Supplementary data

The supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.043.

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Enantioselective formation of quaternary stereocenters using the catalytic intramolecular Stetter reaction

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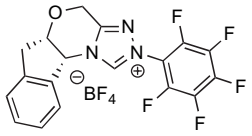
Abstract—Asymmetric formation of quaternary stereocenters has been accomplished using the catalytic intramolecular Stetter reaction. A variety of tethered aldehydes and Michael acceptors are cyclized in excellent yields and enantioselectivities.

1. Introduction

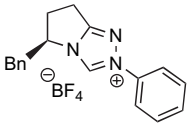
Catalytic carbon–carbon bond formation resulting in the creation of a quaternary stereocenter is a useful but challenging tool in organic chemistry.[1] In addition to established approaches using chiral auxiliaries,[2] significant progress has been made in recent years aimed at catalytic methods for the formation of quaternary stereocenters. These include the intramolecular Heck reaction,[3] rearrangement of enol carbonates,[4] transition metal-mediated π-allyl chemistry,[5] copper catalyzed S_N2' displacement of allylic leaving groups[6] and conjugate additions of β-keto esters to acrylates,[1b] phase-transfer alkylation of 1-indanones,[7] arylation of ketone enolates,[8] and enantioselective alkylation of tributyl tin enolates catalyzed by Cr(salen)Cl,[9] among others. Most recently, Stoltz and Trost have each reported the deracemization of quaternary stereocenters via Pd-catalyzed decarboxylative allylation of racemic β-keto esters.[10,11] Each of these approaches is useful but limited to a specific substrate scope.

Reactivity umpolung reverses the normal mode of aldehyde polarity, thus rendering an aldehyde nucleophilic.[12] Both benzoin and Stetter reactions exploit this reactivity and have been the subject of much recent research.[13] Both processes are catalyzed by azolium salts in the presence of base.[14] The benzoin reaction provides α-hydroxy ketones and has classically been limited to the homocoupling of two aldehydes.[15] Recently, creative approaches have been taken to expand its utility to provide cross-benzoin products.[16] The Stetter reaction, on the other hand, involves the addition of an aldehyde to a Michael acceptor and is an excellent way to access 1,4-dicarbonyl systems.[17]

Work in our laboratory has focused on the development of chiral triazolinylidene carbenes, derived from **1** and **2**.[18] These catalysts are capable of inducing addition of aromatic and aliphatic aldehydes to α,β-unsaturated esters, ketones, and nitriles.[18a,b] Recent work includes the extension of intramolecular Stetter reaction for the formation of contiguous stereocenters using α,β-disubstituted Michael acceptors[18d] and the desymmetrization of cyclohexadienones.[18f] We have previously communicated the formation of quaternary stereocenters using β,β-disubstituted Michael acceptors.[18c] Herein, we describe an expansion of the scope of this reaction to include a variety of heteroatoms tethering the aldehyde and Michael acceptor as well as the generation of five- and six-membered rings in the process of forming quaternary stereocenters in high enantioselectivity.



1c



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2. Results and discussion

Investigation of the formation of quaternary stereocenters began with substrates such as **3**. Substrates were prepared via phenol alkylation of the thioacetal of salicylaldehyde, followed by deprotection. A brief catalyst screen provided reaction conditions that afforded excellent yields and enantioselectivities of benzofuranone products (Eq. 1). Reaction of electron rich *para*-methoxy phenyl substituted aminoindanol-derived catalyst with **3** provides **5** in 45% yield and excellent enantiomeric excess. Catalyst **1b** provides an increase in yield and retains 99% ee. Pentafluorophenyl substituted catalyst **1c** proved to be the most efficient in terms of yield and enantioselectivity.

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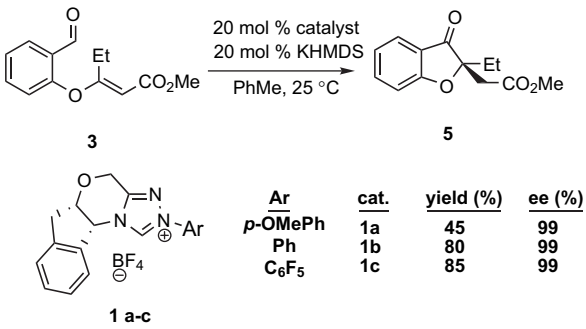
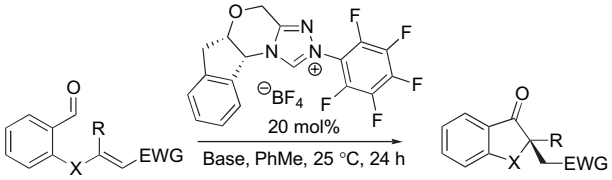


Using catalyst precursor **1c**, we further optimized the reaction conditions by using the very mild base triethylamine to generate the active catalyst. Having identified an efficient catalyst system providing desired reactivity with excellent enantioselectivity and yield, we examined the scope of this reaction beginning with substrates that contained aromatic backbones (Table 1). Benzofuranones **5** and **6** were obtained in high yields and enantiomeric excess. Thioethers are also competent substrates and react efficiently to provide benzothiophenone products in high yield and enantioselectivity (Entries 4 and 5). Reaction of thioether **7** provides benzothiophenone in 95% yield and 92% ee. A propyl group in the β-position is tolerated, providing 54% yield and 87% ee with triethylamine (Entry 4). Phenethyl substitution of the thioether substrate affords **12** in lower yield and 88% ee. A direct comparison between substrates **7** and **13** leads to the conclusion that an increase in steric bulk or electronic differences, i.e., ethyl versus phenyl, suppresses the reactivity while having little effect on enantioselectivity. An all carbon five-membered ring is formed in 95% yield and 99% ee (Entry 7). Overall, the intramolecular Stetter reaction tolerates aromatic aldehydes with varied β,β-substitution of the Michael acceptors and heteroatom tethers.

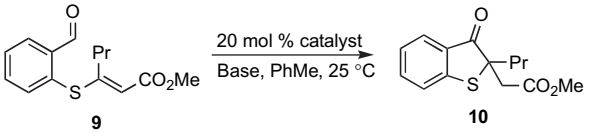
Table 1. Scope of aromatic substrates



Entry	Substrate	Product[a]	Base	Yield (%)	ee (%)[b]
1	X = H **3**	X = H **5**	NEt_3	96	97
2	= Br **4**	= Br **6**	NEt_3	92	89
3[c]	**7**	**8**	NEt_3 KO*t*-Bu	95 90	92 97
4	**9**	**10**	NEt_3 KO*t*-Bu	54 83	87 98
5	**11**	**12**	NEt_3 KO*t*-Bu	33 91	88 99
6	**13**	**14**	NEt_3 KO*t*-Bu	11 15	82 82
7	**15**	**16**	NEt_3	95	99

[a] Absolute configuration assigned analogy to **8**.
[b] Enantiomeric excess determined by HPLC analysis on chiral stationary phase.
[c] Absolute configuration established by single-crystal X-ray analysis.

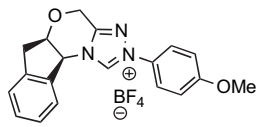
The observation that sulfur containing compounds generally provide cyclized products in lower yields and more moderate enantioselectivities prompted an additional screen of reaction conditions. This catalyst screen was performed using thioether **9**, which contains propyl substitution β to the ester. As expected, we found that aminoindanol catalyst **1c** and phenylalanine-derived catalyst **2** afford opposite enantiomers of the desired product in high selectivity (Eq. 2). Exposing **9** to catalyst **2** provides **10** in similar yield with an increase in enantioselectivity to 90%. Catalyst **1c** was then used with triethylamine but gave **10** in only moderate yield and selectivity. By changing the base to potassium *tert*-butoxide, an increase in yield and enantioselectivity was observed. The reaction conditions for thioether containing substrates were found to be 20 mol % catalyst loading, with 20 mol % potassium *tert*-butoxide, in toluene at 25 °C. Increased yields and enantioselectivities were obtained with potassium *tert*-butoxide in each sulfur containing substrate with the exception of **13**. A slight increase in reactivity was observed with **13** while the enantioselectivity remains 82%. We ascribe the reluctance of this substrate to participate in this reaction to steric crowding.



9 **10** (2)

cat.	base	yield (%)	ee (%)
2	KHMDS	80	90(S)
1c	NEt_3	54	87(R)
1c	KO*t*-Bu	83	98(R)

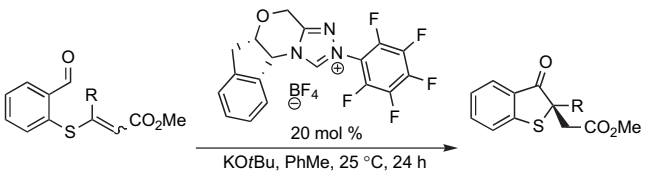
To further investigate the requirements of substrates that give high yield and enantioselectivity we synthesized both alkene isomers of the Michael acceptors. The use of either (*E*)- or (*Z*)-isomer results in good yields and enantioselectivities. Thioether *E*-**7** gives cyclized benzothiophenone in 90% yield and 97% ee. The corresponding *Z*-**7** gives **8** in 89% yield and 86% ee under the same reaction conditions. Highly electrophilic bis-ester **18** was obtained in the (*Z*)-geometry and provided cyclized product **19** in 85% yield and 90% ee when using catalyst **17**. Similar yields and lower enantioselectivities were also observed for the (*E*)-isomer of propyl- and phenethyl-substituted Michael acceptors. Use of (*E*)-isomers provided uniformly higher yields and enantioselectivities and provided the impetus for us to focus on (*E*)-isomers for the majority of the study (Table 2).



17

Although, the formation of five-membered rings and concomitant creation of quaternary stereocenters are very efficient, formation of the corresponding six-membered rings remains a challenge. Treatment of thioether **20** under the standard reaction conditions (20 mol % azolium salt and 20 mol % KHMDS in toluene) with achiral catalyst **22** affords cyclized product in 11% yield (Eq. 3). Exposure of

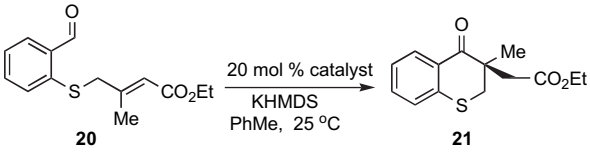
Table 2. Effect of substrate geometry



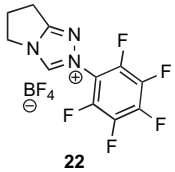
Entry	Substrate	Product	
1	*E*-**7**	**8**	(*E*) 90% yield, 97% ee
	Z-**7**		(*Z*) 89% yield, 86% ee
2	*E*-**9**	**10**	(*E*) 83% yield, 98% ee
	Z-**9**		(*Z*) 85% yield, 89% ee
3	*E*-**11**	**12**	(*E*) 91% yield, 99% ee
	Z-**11**		(*Z*) 92% yield, 84% ee
4	**18**	**19**	(*Z*) 85% yield, 90% ee[a]

[a] Results with catalyst **17** and KHMDS.

20 to the same reaction conditions with chiral catalyst **1c** provides no desired product and only the starting material was recovered. After investigating our most reactive catalysts, we found that catalyst **2** provides **21** in 11% yield and >99% ee. As we have noted a higher reactivity associated with ketones versus esters, we decided to investigate the six-membered ring formation utilizing a ketone Michael acceptor. In the event, exposure of methyl ketone **23** containing phenyl substitution to our reaction conditions provides the desired product in 55% yield and 99% ee (Eq. 4).

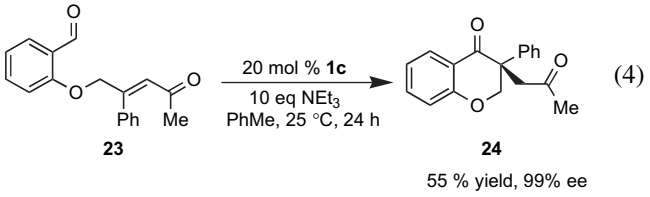


20 **21** (3)



22

cat.	yield (%)	ee (%)
22	11	-
1c	0	-
2	11	>99

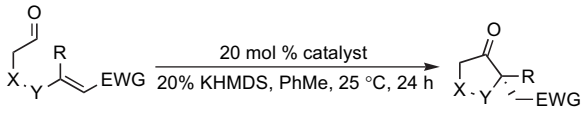


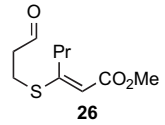
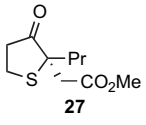
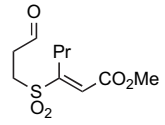
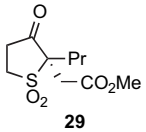
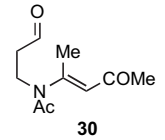
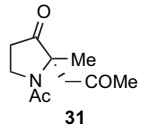
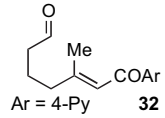
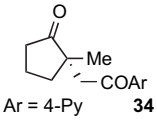
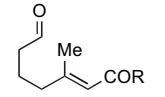
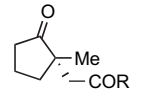
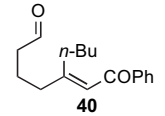
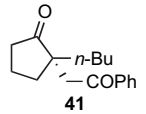
(4)

This method can be extended to substrates with aliphatic backbones, although the aliphatic substrates pose a particular challenge, as they may undergo aldol side reactions. Cyclization of aliphatic substrates to form tertiary stereocenters has been previously reported.[18a] Enantioselectivity when using substrates with aliphatic backbones is affected by the geometry of the alkene in the starting material, as is the case in earlier aromatic substrates. Optimized reaction conditions for aliphatic substrates were found to be 20 mol % catalyst and 20 mol % KHMDS in toluene. Subjecting *E*-**25** to the reaction conditions with catalyst **1c** gives cyclopentanone in 85% yield and 96% ee (Eq. 5). Cyclization proceeds in lower yield and enantioselectivity for *Z*-**25**.

(5)

Table 3. Substrate scope of aliphatic



Entry	Substrate	Product[a]	Catalyst	Yield (%)	ee (%)
1	 **26**	 **27**	**1c**, **2**	0	—
2	 **28**	 **29**	**2**	98	80[b]
3	 **30**	 **31**	**1**	65	95
4	 Ar = 4-Py **32**	 Ar = 4-Py **34**	**1**	85	96
5	=*p*-NO_2Ph **33**	=*p*-NO_2Ph **35**	**1**	90	84
6	 R = Me **36**	 R = Me **38**	**1**	81	95
7	= $(CH_2)_2$Ph **37**	= $(CH_2)_2$Ph **39**	**1**	63	99
8	 **40**	 **41**	**1**	71	98

[a] Absolute configuration assigned analogy to **37**.
[b] Enantioselectivity was determined by ^{1}H NMR using chiral shift reagent Eu(hfbc)$_3$.

Aliphatic substrates containing thioethers have also proven resistant to cyclization with catalyst **1** or **2** (Table 3). By changing the tether from a sulfide to a sulfone, cyclization was induced, providing the product in 98% yield and 80% ee. Thorpe–Ingold effect[19] may account for the success of this reaction. In addition, the electron withdrawing capability of the sulfone presumably contributes to the activation of the electron deficient alkene, thus promoting cyclization. The scope of aliphatic substrates includes nitrogen-containing substrates such as **30** that provides desired product in 65% yield and 95% ee. α,β-Unsaturated aromatic ketones **32** and **33** give the desired product in higher yields and enantioselectivities. Excellent selectivity was observed for the formation of quaternary stereocenters in **38** and **39** implementing aliphatic ketone Michael acceptors. Cyclization of α,β-unsaturated phenyl ketone **40** provided **41** in 98% ee. Aliphatic substrates with β-methyl substitution generally give high enantioselectivity.

We have expanded the scope of the intramolecular enantioselective Stetter reaction to afford quaternary stereocenters. The reaction is mild, general, and tolerates aromatic, aliphatic, sulfur, oxygen, and nitrogen tethering of aldehyde and Michael acceptor. The current substrate scope includes compounds with varying electronics and sterics. Ongoing efforts include elucidating the mechanism of this reaction and other factors contributing to the reactivity of these carbenes.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard (tetramethylsilane [TMS] or deuterated chloroform [$CDCl_3$]), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br s=broad singlet), integration, and coupling constant (Hz). Chemical shifts are reported in parts per million from ($CDCl_3$) taken as 77.0 ppm.

3.2. Synthesis and characterization

3.2.1. General procedure for the asymmetric intramolecular Stetter reaction of aromatic substrates. A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 equiv), evacuated for 5 min, and then covered with argon. Substrate (0.1 mmol, 1 equiv) in toluene (1 mL) was added via syringe, followed by the addition of KO*t*-Bu (0.2 mmol, 2 equiv to substrate), and the solution was stirred at ambient temperature under argon for 24 h.

The reaction mixture was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes to afford analytically pure product.

3.2.2. General procedure for the asymmetric intramolecular Stetter reaction of aliphatic substrates. A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 equiv) and toluene (1 mL) under argon. To this solution was added KHMDS (0.5 M in toluene) (0.02 mmol, 0.2 equiv) via syringe and the solution was stirred at ambient temperature for 5 min. Substrate (0.01 mmol, 1 equiv) in toluene was added (1 mL) via syringe and allowed to stir for 24 h at ambient temperature. The reaction mixture was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes to afford analytically pure product.

3.2.2.1. (*R*)-(3-Oxo-2-propyl-2,3-dihydro-benzo[*b*]thiophen-2-yl)-acetic acid methyl ester (10). R_f=0.43 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +21.2 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 6.0 min, major enantiomer: 7.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J=7.7 Hz), 7.53 (t, 1H, J=7.9 Hz), 7.37 (d, 1H, J=7.9 Hz), 7.2 (t, 1H, J=7.0 Hz), 3.56 (s, 3H), 3.07 (d, 1H, J=16.7), 2.96 (d, 1H, J=16.7 Hz), 1.86 (ddd, 2H, J=5.5, 6.8, 9.6 Hz), 1.54–1.35 (m, 1H), 1.26–1.03 (m, 1H), 0.84 (t, 3H, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 170.4, 152.1, 135.7, 131.3, 126.8, 124.9, 124.1, 62.7, 52.0, 42.8, 41.3, 17.9, 14.1; IR (NaCl, neat) 2958, 1741, 1699, 1591, 1449 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$: 265.0898. Found: 265.0885.

3.2.2.2. (*R*)-(3-Oxo-2-phenethyl-2,3-dihydro-benzo-[*b*]thiophen-2-yl)-acetic acid methyl ester (12). R_f=0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ −27.8 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 9.3 min, major enantiomer: 11.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1H, J=7.8 Hz), 7.57 (t, 1H, J=6.9 Hz), 7.43 (d, 1H, J=7.9 Hz), 7.26–7.10 (m, 6H), 3.59 (s, 3H), 3.12 (d, 1H, J=16.8 Hz), 3.00 (d, 1H, J=16.8 Hz), 2.79–2.67 (m, 1H), 2.47–2.37 (m, 1H), 2.27–2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 170.3, 152.0, 140.92, 136.0, 131.3, 128.6, 126.9, 126.3, 125.1, 124.3, 62.6, 52.2, 43.1, 41.2, 31.0; IR (NaCl, neat) 2950, 1741, 1699, 1591, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}O_3S$: 327.1055. Found: 327.1048.

3.2.2.3. (*R*)-(3-Oxo-2-phenyl-2,3-dihydro-benzo[*b*]-thiophen-2-yl)-acetic acid methyl ester (14). R_f=0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ −10.3 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 8.4 min, major enantiomer: 6.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J=7.9 Hz), 7.44 (t, 2H, J=8.1 Hz), 7.23–7.11 (m, 6H), 3.73 (s, 3H), 3.63 (d, 1H, J=14.0 Hz), 3.56 (d, 1H, J=14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 169.6, 151.6, 136.1, 134.2, 130.9, 130.1, 128.0, 127.4, 127.2, 125.3, 123.9, 64.6, 53.7, 39.9; IR (NaCl, neat) 2952, 1738, 1699, 1589, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}O_3S$: 299.0742. Found: 299.0739.

3.2.2.4. 2-Methoxycarbonylmethyl-3-oxo-2,3-dihydro-benzo[*b*]thiophene-2-carboxylic acid methyl ester (19). R_f=0.36 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +20.6 ($CHCl_3$); HPLC analysis—Chiracel AD-H column, 97:3 hexanes to isopropanol 1.0 mL/min. Minor enantiomer: 20.0 min, major enantiomer: 22.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, J=7.9 Hz), 7.58 (t, 1H, J=8.1 Hz), 7.40 (d, 1H, J=8.1 Hz), 7.25 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.53 (d, 1H, J=17.3 Hz), 3.11 (d, 1H, J=17.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 170.3, 168.5, 151.9, 136.3, 129.7, 127.7, 125.7, 124.1, 62.4, 53.9, 52.4, 39.7; IR (NaCl, neat) 2954, 1738, 1705, 1587 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{13}O_5S$: 281.0484. Found: 281.0480.

3.2.2.5. (*R*)-(3-Methyl-4-oxo-thiochroman-3-yl)-acetic acid methyl ester (21). R_f=0.38 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +41.6 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 8.8 min, major enantiomer: 7.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H, J=8.6 Hz), 7.36 (t, 1H, J=6.5 Hz), 7.25–7.14 (m, 2H), 4.13 (d, 1H, J=7.1 Hz), 4.11 (q, 2H, J=7.1 Hz), 3.74 (d, 1H, J=13.5 Hz), 3.01 (d, 1H, J=16.1 Hz), 2.98 (d, 1H, J=13.5 Hz), 2.56 (d, 1H, J=16.1 Hz), 1.40 (s, 3H), 1.23 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 171.2, 141.4, 133.2, 130.6, 130.0, 127.5, 125.2, 60.8, 43.6, 41.2, 36.6, 21.2, 14.4; IR (NaCl, neat) 2978, 1732, 1676, 1589, 1435 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$: 265.0898. Found: 265.0905.

3.2.2.6. (1,1,3,-Trioxo-2-propyl-tetrahydro-1,6-thiophene-yl)-acetic acid methyl ester (29). R_f=0.15 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +24.5 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.65 (ddd, 1H, J=12.5, 11.7, 8.5 Hz), 3.50 (ddd, 1H, J=12.5, 9.2, 2.4 Hz), 3.17 (d, 1H, J=17.9 Hz), 3.11 (ddd, 1H, J=17.9, 8.5, 2.2 Hz), 3.10 (d, 1H, J=17.9 Hz), 2.88 (ddd, 1H, J=17.9, 11.6, 9.1 Hz), 1.87 (ddd, 1H, J=14.1, 9.3, 7.1 Hz), 1.70 (dm, 1H, J=14.1 Hz), 1.48 (ddq, 2H, J=9.3, 7.1, 7.1 Hz), 0.93 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 171.4, 65.8, 52.8, 50.7, 39.4, 36.7, 36.3, 17.7, 14.4; IR (NaCl, neat) 2964, 1732, 1439, 1313 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_5S$: 248.0718. Found: 248.0705.

3.2.2.7. 1-Acetyl-2-methyl-(2-oxo-propyl)-pyrrolidin-3-one (31). R_f=0.21 (9:1 EtOAc/*i*-PrOH); $[\alpha]_D^{25}$ −57.1 ($CHCl_3$); GC analysis—chiraldex BPH column, 120 °C 1.5 mL/min. Minor enantiomer: 46.0 min, major enantiomer: 46.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (dd, 1H, J=18.6, 0 Hz), 3.82 (ddd, 1H, J=18.1, 8.9, 8.9 Hz), 3.75 (ddd, 1H, J=10.2, 10.2, 3.8 Hz), 2.96 (dd, 1H, J=18.8, 0 Hz), 2.90 (ddd, 1H, J=17.9, 9.0, 3.6 Hz), 2.66 (ddd, 1H, J=18.5, 9.4, 9.4 Hz), 2.03 (s, 3H), 2.01 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 207.3, 170.6, 64.1, 50.9, 43.9, 29.4, 23.2, 22.2; IR (NaCl, neat) 2915, 1745, 1706, 1634, 1414 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}NO_3$, 198.1130. Found 198.1135.

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Supplementary data

Synthesis and characterization for starting materials are provided in Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.042.

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Scope and selectivity in palladium-catalyzed directed C–H bond halogenation reactions

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Abstract—Palladium-catalyzed ligand directed C–H activation/halogenation reactions have been extensively explored. Both the nature of the directing group and the substitution pattern on the arene ring of the substrate lead to different reactivity profiles, and often different and complementary products, in the presence and absence of the catalyst.

1. Introduction

Halogenated organic compounds are important components of a variety of biologically active molecules and pharmaceutical agents.[1] Aryl, vinyl, and benzylic halides also serve as important precursors to organolithium[2] and Grignard reagents.[3] Aryl halides have been employed as substrates for nucleophilic aromatic substitution[4] and for benzyne generation.[5] Additionally, both aryl[6,7] and vinyl[8] halides have found widespread utility as substrates for a variety of cross-coupling reactions. As a result of the diverse potential applications of organic halides, the development of new regioselective, chemoselective, and functional group tolerant approaches to the synthesis of these molecules remains an important challenge.

Our group has recently developed several palladium-catalyzed methods for the chelate-directed oxidative functionalization of C–H bonds using hypervalent iodine(III) reagents as terminal oxidants. For example, the reaction of diverse organic substrates with $PhI(OAc)_2$[9a–d] or $[Ph_2I]BF_4$[9e,f] in conjunction with a Pd^{II} catalyst leads to the ligand-directed conversion of sp^2 and sp^3 C–H bonds to C–O and C–C bonds, respectively. These results suggested the possibility of an analogous Pd-catalyzed transformation for the direct conversion of C–H bonds to C–X (X=Cl, Br, I) bonds using electrophilic halogenating reagents such as $PhICl_2$. We envisioned that such a reaction would provide the desired products with complete regioselectivity and without the requirement for electron-rich substrates or strong acids/bases. These features would impart a significant advantage over many commonly used methods (e.g., electrophilic aromatic substitution (EAS),[10,11] directed *ortho*-lithiation (DoL),[12] and the addition of X_2 or HX to alkynes[13]) for the construction of certain classes of aryl and vinyl halides.

A key step in the proposed palladium-catalyzed directed C–H activation/halogenation reactions would require carbon–halogen bond-forming reductive elimination from a palladium center. This transformation is well known to be challenging from Pd^{II} (and most other metal complexes) because its microscopic reverse—the oxidative addition of aryl/vinyl/alkyl halides to Pd^0—is highly thermodynamically favored relative to the desired reductive elimination reaction. For example, Roy and Hartwig have shown that K_{eq} for direct reductive elimination of haloarenes from Pd^{II} ranges from $\sim 10^{-5}$ (for Ar–I) to $\sim 10^{-2}$ (for Ar–Cl).[14] As a result, the desired reaction is not amenable to catalysis via a traditional $Pd^{II/0}$ catalytic cycle. However, recent work from our group has shown that reductive elimination reactions from Pd^{IV} have very different electronic requirements than those from Pd^{II},[15] indicating that the desired carbon–halogen coupling could be facile from this oxidation state. A number of literature reports further supported the potential viability of this approach; for example, van Koten and Elsevier have both directly observed transient Pd^{IV} intermediates in the oxidation of Pd^{II} complexes with molecular halogen or $PhICl_2$.[16a,b,h] In addition, several groups have reported stoichiometric C–X coupling upon treatment of palladium(II)-aryl/alkyl complexes with oxidants such as X_2, $CuCl_2$, mixtures of peroxides and halide salts, or $PhICl_2$.[17] Furthermore, both oxypalladation and aminopalladation of alkenes at Pd^{II} have been terminated by C–X coupling under oxidizing reactions conditions.[16,17]

Based on this precedent, we felt that Pd-catalyzed C–H bond halogenation could potentially proceed by a catalytic cycle involving (i) ligand-directed C–H activation at a Pd^{II} center,[18] (ii) oxidation of the resulting palladacycle to

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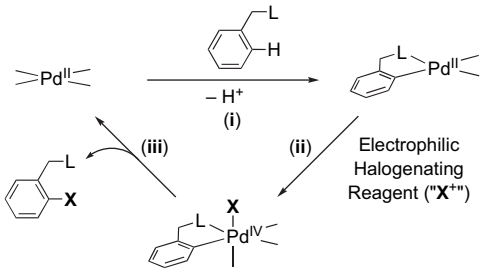
Pd^{IV}, and (iii) carbon–halogen bond-forming reductive elimination to form the desired product and regenerate the catalyst (Scheme 1). Importantly, a similar cycle was proposed in early work by Fahey, who demonstrated the palladium-catalyzed *ortho*-chlorination of azobenzene with Cl_2.[19] More recent preliminary communications from our group[9d,g,h] and later from Yu and co-workers[20a,b] have established that such Pd-catalyzed C–H activation/oxidative halogenation reactions can be general and practical methods for organic synthesis. Herein, we present a full account of our efforts in the development and exploration of these transformations. The scope and limitations of these reactions with respect to directing group and functional group tolerance are discussed in detail, and general trends that dictate the reactivity of diverse arene substrates in these transformations are identified.



Scheme 1. Proposed catalytic cycle for directed C–H bond halogenation.

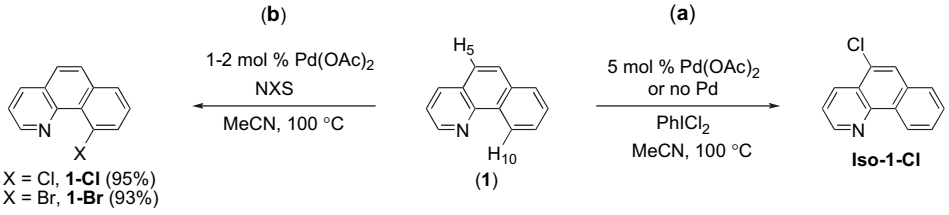
2. Results and discussion

Our initial studies focused on the palladium-catalyzed reaction of benzo[*h*]quinoline (**1**) with $PhICl_2$ (Eq. 1a). By analogy to reactions with the related iodine(III) oxidant $PhI(OAc)_2$,[9a–d] we expected to observe the selective conversion of C–H_{10} to a C–Cl bond. However, interestingly, the treatment of **1** with $PhICl_2$ in MeCN or AcOH afforded exclusive chlorination at the 5-position (~38% conversion by GC), both in the presence and the absence of Pd catalyst (Eq. 1a).

Palladium-catalyzed directed bromination of **1** was also possible using *N*-bromosuccinimide as a terminal oxidant.[9d] Analogous to NCS, reaction of **1** with NBS (1 mol % of $Pd(OAc)_2$, 1.1 equiv NBS, MeCN, 100 °C, 1.5 days) afforded a single product, where bromination occurred exclusively at the 10-position (**1-Br**) (Eq. 1b).[9d] In the absence of palladium, a mixture of isomeric mono-brominated products was obtained. Interestingly, $CuBr_2$ was also an effective oxidant for the Pd-catalyzed transformation, and afforded complete conversion to **1-Br** (as measured by ^1H NMR spectroscopy) in the presence of $Pd(OAc)_2$. In contrast, other brominating reagents (e.g., Br_2, $Br_2/PhI(OAc)_2$) provided complex mixtures of isomeric brominated products.

Attempts to carry out analogous iodination reactions of benzo[*h*]quinoline with NIS or $I_2/PhI(OAc)_2$[20a] were generally unsuccessful. Under all conditions screened for this transformation, only traces of unidentified isomers of iodinated product were obtained, with starting material remaining largely unconsumed. Because of the rigid planar nature of this substrate and the location of the C–H_{10} bond in a sterically congested portion of the molecule, steric constraints may prevent incorporation of the large iodine atom during these Pd-catalyzed reactions.

With optimal parameters for the chlorination and bromination of **1** in hand, we next focused our attention on the Pd-catalyzed halogenation of other organic substrates. Initial experimentation revealed that there was no universal set of reaction conditions for these transformations, and that varying the solvent (typically between MeCN and AcOH), temperature (ranging from 100 to 120 °C), and the oxidant



(1)

This initial result suggested that $PhICl_2$ was too reactive, leading to a faster rate of uncatalyzed backbone halogenation relative to chelate-directed C–H activation. As a result, we next examined a variety of alternative electrophilic halogenating reagents, anticipating that some might afford more competitive relative rates of the catalyzed to the uncatalyzed reaction. We were delighted to find that commercially available and inexpensive *N*-chlorosuccinimide provided the desired chlorination product **1-Cl** as a single regioisomer in 95% isolated yield (Eq. 1b) under standard reaction conditions (2 mol % of $Pd(OAc)_2$, 1.1 equiv NCS, MeCN, 100 °C, 3 days).[9d] In addition, further screening of oxidants revealed that $CuCl_2$ (in MeCN) and Chloramine-T (in AcOH) afforded comparable GC yields of **1-Cl** (81% and 85%, respectively) in much shorter times (~12 h). Notably, the control reaction of **1** with Chloramine-T (in the absence of Pd catalyst) provided mixtures of regioisomeric monochlorinated products, while the analogous controls with NCS and $CuCl_2$ returned unreacted starting material.

(between NXS and CuX_2) was necessary in order to obtain the optimal conditions for each substrate. Additionally, substrates with different substitution patterns on the aryl ring and with different directing groups showed dramatically different reactivities. In general, the substrates could be divided into four types based on their reactivity in the presence and absence of palladium as follows: (i) substrates for which the Pd-catalyzed reaction results in chelate-directed halogenation, while the control (without Pd catalyst) affords no halogenated products (*type 1*), (ii) substrates for which the Pd-catalyzed and control reactions afford different halogenated products (*type 2*), (iii) substrates for which the

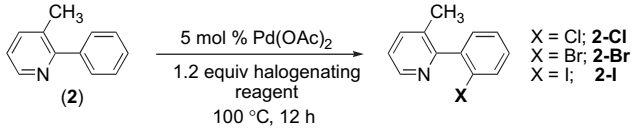
catalyzed and the uncatalyzed reactions afford the same product or mixtures of products (*type 3*), and (iv) substrates for which the similarity/difference in reactivity between the Pd-catalyzed and control reactions is dictated by the nature of the oxidant (*type 4*). A detailed discussion of each of these types of substrates follows below.

2.1. Type 1 substrates

The palladium-catalyzed halogenation of 3-methyl-2-phenylpyridine (**2**) was studied using a variety of electrophilic halogenating reagents in AcOH and MeCN (Table 1). Under all of the conditions examined, **2** exemplified a *type 1* substrate, affording <5% halogenated products in the absence of palladium catalyst. In contrast, in the presence of $Pd(OAc)_2$, most of the reagents screened afforded significant quantities of the *ortho*-halogenated products **2-Cl**, **2-Br**, or **2-I**. In general, the *N*-halosuccinimides proved to be superior oxidants, providing the highest isolated yields of **2-Cl** (65%), **2-Br** (56%), and **2-I** (79%).

Among the other oxidants examined, a number of notable observations were made. For example, unlike with benzo[*h*]-quinoline, the reaction of **2** with $PhICl_2$ afforded <5% of a mono-halogenated product in the absence of the catalyst. This is likely due to the low inherent reactivity of the relatively electron-deficient arene moiety of **2** toward electrophilic aromatic substitution. In the presence of the Pd catalyst, this iodine(III) reagent afforded the desired product **2-Cl**, albeit in only 32% GC yield (Table 1, entry 5). The low yield of this transformation can most likely be attributed to the instability of $PhICl_2$ at the elevated temperatures (100 °C) utilized for these transformations.[21]

Table 1. Palladium-catalyzed reaction of **2** with diverse electrophilic halogenating reagents



Entry	Halogenating reagent	Product	GC yield in AcOH (isolated) (%)	GC yield in MeCN (isolated) (%)
1	NCS	**2-Cl**	60 (65)[b]	56
2	$Pb(OAc)_4$/LiCl[c]	**2-Cl**	63	51
3	Chloramine-T	**2-Cl**	56	36
4	$K_2Cr_2O_7$/LiCl[c]	**2-Cl**	42	0
5	$PhICl_2$	**2-Cl**	32	15
6	$CuCl_2$	**2-Cl**	21[a]	30[a]
7	NBS	**2-Br**	53 (56)[b]	44
8	Br_2/$PhI(OAc)_2$	**2-Br**	39	24
9	$Pb(OAc)_4$/LiBr[c]	**2-Br**	32	42
10	$K_2Cr_2O_7$/LiBr[c]	**2-Br**	15	8
11	Br_2	**2-Br**	0	26
12	$CuBr_2$	**2-Br**	0[a]	15[a]
13	NIS	**2-I**	64	87 (79)
14	I_2/$PhI(OAc)_2$	**2-I**	64	71
15	$K_2Cr_2O_7$/LiI[c]	**2-I**	44	0
16	$Pb(OAc)_4$/LiI[c]	**2-I**	37	0
17	I_2	**2-I**	0	40

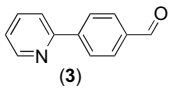
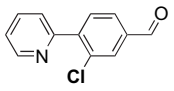
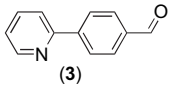
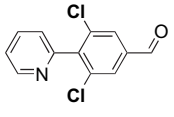
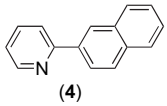
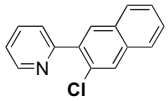
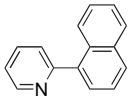
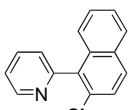
[a] Halogenating reagent (2.4 equiv).
[b] Isolated yields from reactions carried out at 120 °C.
[c] LiX (2 equiv).

Interestingly, neither Br_2 nor I_2 afforded substantial quantities of halogenated products (Table 1, entries 11 and 17, respectively), despite the fact that these reagents are highly effective for the stoichiometric halogenation of Pd^{II} alkyl,[16f] aryl,[16c,19] and vinyl[16a] species. This may be due to the decreased reactivity and/or solubility of PdX_2 (presumably formed in situ from the reaction of $Pd(OAc)_2$ with X_2) in these reactions.[20a] In contrast, $CuCl_2$ was an effective reagent for transforming **2** to **2-Cl** in 30% GC yield under standard conditions (Table 1, entry 6). This result is particularly remarkable because $CuCl_2$ could potentially be utilized in catalytic quantities with readily available and inexpensive dioxygen as the ultimate terminal oxidant.[22]

A number of other *type 1* substrates were identified, and the results of their Pd-catalyzed reactions with *N*-halosuccinimides are summarized in Tables 2–4. As discussed above, all these substrates afforded <5% of halogenated products in the absence of palladium. In general, the *type 1* substrates contain electron-withdrawing directing groups such as pyridines, oxime ethers, isoxazolines, quinolines, and tetrazoles; furthermore, the arene ring that undergoes halogenation is typically electron neutral or electron deficient (containing substituents such as halides, esters, enolizable oxime ethers, ketones, and aldehydes). Notably, substrates containing such structural motifs possess a wide range of potential applications. For example, isoxazolines serve as useful precursors to β-amino acids,[23] while pyridines and tetrazoles are important components of diverse drug molecules.[24] Tetrazole derivatives can also be used as trigger explosives and serve as components of mixed propellants.[24] In addition, the brominated 2-phenylpyridine derivatives are readily transformed into ligands that can be used to form a variety of late transition metal complexes.[15,25]

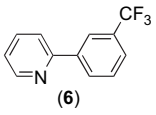
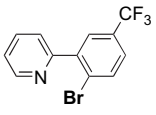
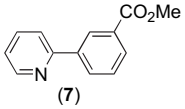
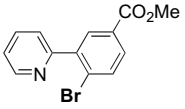
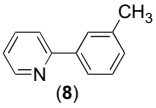
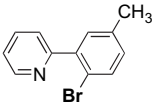
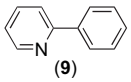
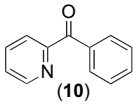
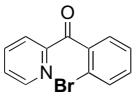
Importantly, all of these transformations (and those described throughout this paper) are completely tolerant of ambient air and moisture and were typically conducted on

Table 2. Palladium-catalyzed chlorination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (3)	 Cl	**3-Cl**, 57
2	 (3)	 Cl Cl	**3-Cl_2**, 72[b]
3	 (4)	 Cl	**4-Cl**, 82
4	 (5)	 Cl	**5-Cl**, 70

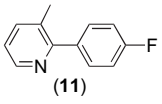
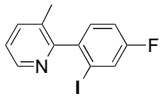
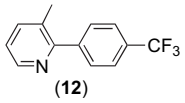
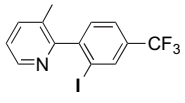
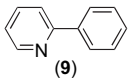
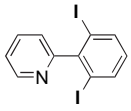
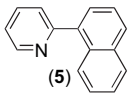
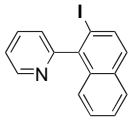
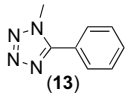
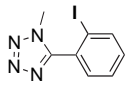
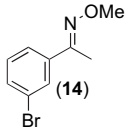
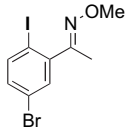
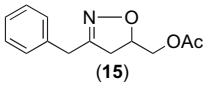
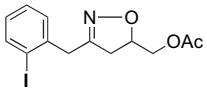
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.1–1.2 equiv NCS, 100–120 °C, 12 h, MeCN or AcOH.
[b] NCS (2.5 equiv).

Table 3. Palladium-catalyzed bromination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (**6**)		**6-Br**, 63
2	 (**7**)		**7-Br**, 70
3	 (**8**)		**8-Br**, 51
4	 (**9**)		**9-Br**, 63
5	 (**10**)		**10-Br**, 56

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.2–2.0 equiv NBS, 100–120 °C, 12 h, MeCN or AcOH.

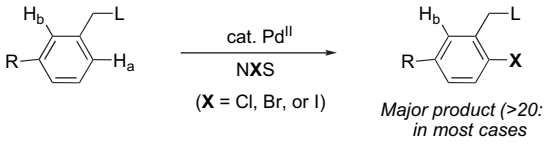
Table 4. Palladium-catalyzed iodination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (**11**)		**11-I**, 70
2	 (**12**)		**12-I**, 78
3	 (**9**)		**9-I_2**, 41
4	 (**5**)		**5-I**, 60[b]
5	 (**13**)		**13-I**, 41
6	 (**14**)		**14-I**, 57
7	 (**15**)		**15-I**, 54

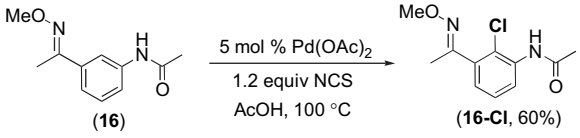
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.05–2.1 equiv NIS, 100–120 °C, 12 h, MeCN or AcOH.
[b] NIS (3.0 equiv).

the bench-top using commercial solvents and reagents. Furthermore, the safe and inexpensive nature of these transformations makes them easily scalable, and relatively large-scale reactions (11–82 mmol) typically afforded comparable yields to those carried out with 0.5–1.5 mmol of material. This is exemplified by substrate **8** (Table 3), for which the reactions performed at 17 mmol and 1.4 mmol scales afforded the product **8-Br** in nearly identical 51% isolated yield. In addition, the use of 1 mol % catalyst afforded comparable yields in similar reaction times to 5 mol % $Pd(OAc)_2$; for example, **2-Cl**, **2-Br**, and **2-I** were obtained in 71%, 54%, and 90% GC yields, respectively, after 12 h with 1 mol % Pd. Further reduction of the catalyst load (to 0.5 mol %) typically resulted in some (~20%) diminishment in yield. The easy and practical scale up along with the low catalyst loadings should make these halogenation reactions very attractive for diverse applications.

In *meta*-substituted arene substrates bearing two chemically inequivalent *ortho*-C–H bonds, the less hindered position was usually halogenated with high selectivity (Eq. 2).[9b] Both electron-deficient (Table 3, entries 1 and 2) and electron-rich arenes (Table 3, entry 3) exhibited a comparable preference for halogenation at the less congested position. Further, the site selectivity of these reactions was general for different directing groups. For example, the reaction of oxime ether **14** resulted in halogenation *para* to the *meta*-substituent (Table 4, entry 6). In napthyl substituted substrates **4** and **5**, the less sterically congested 3′ *ortho*-C–H bond was selectively halogenated, despite the fact that the 1′ position is more nucleophilic. This sensitivity to the steric environment of the arene ring appears to be general for a wide variety of Pd-catalyzed C–H activation/functionalization reactions.[9a,b,f] However, the *meta*-substituted oxime ether **16** (Eq. 3), which possesses three potential sites for directed C–H activation, presents an interesting exception. In contrast to the substrates discussed above, **16** underwent chlorination with extremely high (>20:1) selectivity for the more hindered 2-position of the arene. This may be the result of the cooperative coordination of both the amide and the oxime directing groups to the Pd-center during the C–H activation step of this reaction.[26] Notably, **16** is not technically a *type 1* substrate, as reaction with NCS in the absence of palladium afforded a complex mixture of isomeric chlorinated products.



(2)

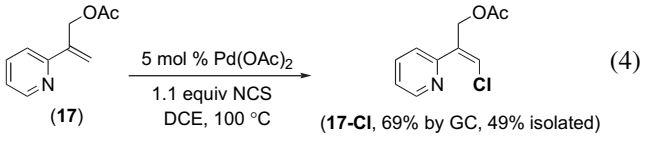


(3)

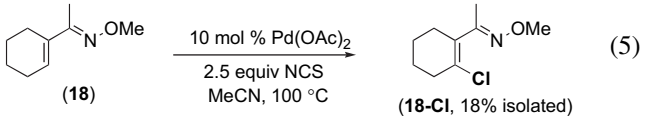
C–H activation/halogenation reactions of substrates containing two readily accessible, chemically equivalent C–H bonds generally led to modest yields of the mono-halogenated products due to competitive formation of the

corresponding difunctionalized compounds (e.g., see Table 2, entry 1). Tuning the stoichiometry of the oxidant in these systems allowed for the formation of dihalogenated products in good yields (e.g., Table 2, entry 2). Several approaches can be taken to attenuate the extent of dihalogenation in these systems if it is not desired. For example, as discussed above, the incorporation of a *meta*-substituent generally decreased the formation of dihalogenated side-products by reducing the rate of a second C–H activation at the more sterically hindered site. Additionally, dihalogenation could be minimized in phenylpyridine derivatives by placing a substituent at the 3-position of the pyridine moiety (e.g., substrate **2** in Table 1). The degree of dihalogenation in these systems decreases with increasing size of the halogen on the arene counterpart. This is illustrated by the fact that ~35% of the difunctionalized products were formed when **2-Cl** and **2-Br** were subjected to forcing reaction conditions (5 mol % $Pd(OAc)_2$, 2 equiv NXS, AcOH, 120 °C), while only traces (<5%) of the diiodinated product were observed in the analogous reaction of **2-I** with NIS. In these systems, the unfavorable steric interactions between the *ortho*-halogen of the mono-functionalized arene and the 3-substituent on the pyridine ring make it difficult to achieve coplanarity between the aryl rings, which is necessary for the second C–H activation/functionalization to occur.[27]

Preliminary results indicate that alkene derivatives can also act as *type 1* substrates in C–H bond halogenation reactions. For example, alkenyl pyridine **17** underwent $Pd(OAc)_2$-catalyzed reaction with NCS to afford the chlorinated product **17-Cl** in reasonable yield (69% by GC, 49% isolated) and with high stereochemical integrity (Eq. 4). Importantly, this product possesses a well-defined olefin geometry, presumably resulting from the selective functionalization of the alkene C–H bond proximal to the pyridine moiety.[28] Such stereochemically pure alkenes serve as important starting materials for many applications, including cross-coupling,[8] carbenoid transfer, and cycloaddition reactions.[29,30] Other alkenes, such as oxime ether **18** also reacted to form directed halogenation products (Eq. 5); however, in this case, the product was obtained in low yield under our standard reaction conditions. Ongoing work aims to optimize reaction conditions for the halogenation of this important class of substrates and to further probe the mechanisms of these transformations.[22e]



(4)



(5)

2.2. Type 2 substrates

Type 2 substrates undergo clean mono-halogenation both in the presence and absence of the Pd catalyst. However, in these cases there is a mismatch in the products favored by the catalyzed reaction versus by electrophilic aromatic substitution; therefore, the products obtained with Pd are different from and complementary to those obtained in the control reactions. Oxime ether substrate **19** exemplifies this class of substrates. The arene ring of **19** is activated at the 3-position toward traditional electrophilic aromatic substitution due to the electron-donating methoxy substituent, and, as a result, control reactions with NXS in AcOH cleanly afforded the 3-substituted products *iso*-**19-Cl**, *iso*-**19-Br**, and *iso*-**19-I** (Table 5, entry 1). However, in the presence of 5 mol % $Pd(OAc)_2$, the catalyzed reaction out-competed EAS such that the *ortho*-halogenated products **19-Cl**, **19-Br**, and **19-I** were formed exclusively, in yields ranging from 46% to 72% (Table 5, entry 1).

Similar results were observed in analogous substrates with different directing groups; for example, 3-methyl-2-(4-methoxyphenyl)pyridine (**20**) afforded **20-Cl** in 76% isolated yield in the Pd-catalyzed reaction, while only *iso*-**20-Cl** was obtained in the control (Table 5, entry 2). Substrate **23**, which contains methoxy substitution on the ring of the pyridine directing group, also showed comparable behavior. In the absence of Pd, a mixture of regioisomeric products was obtained, with Cl incorporated *ortho* (*iso*-**23-Cla**) and *para* (*iso*-**23-Clb**) to the methoxy substituent on the electron-rich pyridine ring. However, in the presence of 20 mol % $Pd(OAc)_2$, the directed chlorination product **23-Cl** was obtained cleanly in 71% yield (Table 5, entry 5).[31]

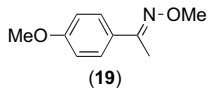
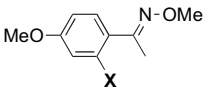
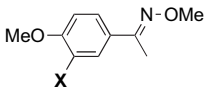
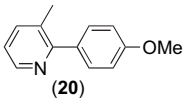
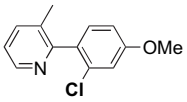
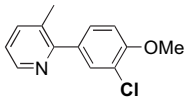
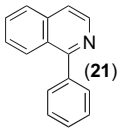
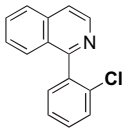
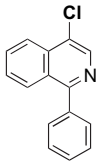
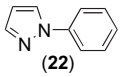
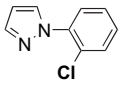
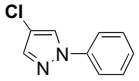
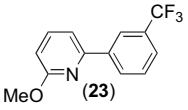
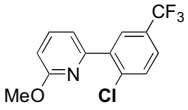
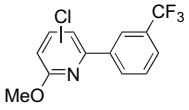
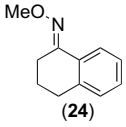
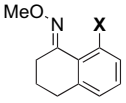
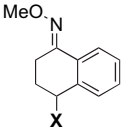
Other substrates that fall into *type 2* are those containing heterocyclic directing groups such as pyrazole and isoquinoline (Table 5, entries 3 and 4). Without added palladium, these substrates underwent chlorination on the heterocyclic ring; however, in the presence of 5 mol % $Pd(OAc)_2$, Pd-catalyzed directed C–H activation/chlorination out-competed EAS, and the *ortho*-chlorinated products **21-Cl** and **22-Cl** were obtained in 53% and 58% isolated yields, respectively.

A final example of a *type 2* substrate is oxime ether **24**. The 2° benzylic position of **24** is highly activated toward benzylic halogenation with NCS or NBS, and, in the absence of Pd catalyst, the benzylic halides *iso*-**24-Cl** and *iso*-**24-Br** were obtained as the major products (albeit in modest yields—Table 5, entry 6). However, in the Pd-catalyzed process, chelate-directed halogenation was fast relative to benzylic oxidation, and the haloarenes **24-Cl** and **24-Br** were obtained in 88% and 62% isolated yields, respectively.

2.3. Type 3 substrates

Type 3 substrates consist of compounds that favor the same product or mixtures of products both in the presence and absence of palladium. Hence, unless otherwise noted the use of a palladium catalyst offers no significant advantage in terms of the yield, purity or selectivity of reactions with these *type 3* substrates. Substrates such as **28–30**, containing highly electron-donating arene substituents (e.g., NMe_2, OMe) at the position *meta*- to the directing group, are representative members of this type. In these compounds, both the catalyzed and the uncatalyzed processes afforded halogenation

Table 5. Palladium-catalyzed halogenation of *type 2* substrates[a,b]

Entry	Starting material	Major product with Pd catalyst	Product #, yield (%)	Major product without Pd catalyst	Product #, yield (%)
1	 (**19**)		**19-Cl**, 58 **19-Br**, 72 **19-I**, 46		*iso*-**19-Cl**, 53 *iso*-**19-Br**, 69 *iso*-**19-I**, 47
2	 (**20**)		**20-Cl**, 76		*iso*-**20-Cl**, 95
3	 (**21**)		**21-Cl**, 53		*iso*-**21-Cl**, 56
4	 (**22**)		**22-Cl**, 58		*iso*-**22-Cl**, 83
5	 (**23**)		**23-Cl**, 71		*iso*-**23-Cl**, 82[c]
6	 (**24**)		**24-Cl**, 88 **24-Br**, 62		*iso*-**24-Cl**, 39 *iso*-**24-Br**, 29

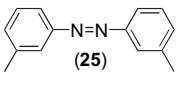
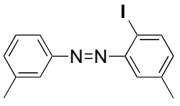
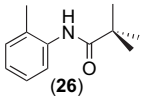
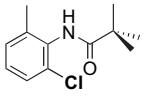
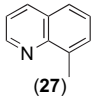
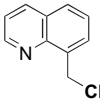
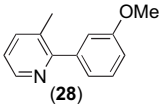
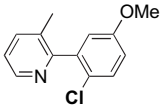
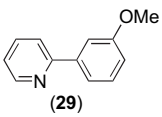
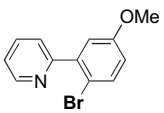
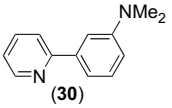
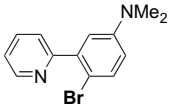
[a] Conditions without Pd: 1–2 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[b] Conditions with Pd: 5 mol % $Pd(OAc)_2$, 1–1.5 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[c] $Pd(OAc)_2$ (20 mol %).

para to the substituent. Hence, the use of a palladium catalyst was not necessary to obtain the 'chelate-directed' *ortho*-halogenated products **28-Cl**, **29-Br**, and **30-Br** in high yields (Table 6, entries 4–6).

Azobenzene **25** also falls under *type 3* as both the catalyzed and the uncatalyzed reactions afford the *ortho*-iodinated product as the major product. However, in this case, the use of palladium affords the desired chelate-directed product in higher yields because the reaction in the absence of palladium affords a 4:1 mixture of isomeric iodinated products. Similarly, reaction of pivalamide **26** with NCS afforded significant quantities of the *ortho*-chlorinated product **26-Cl** with or without palladium. However, in this case, the catalyzed reaction provided **26-Cl** in higher yield and selectivity, as it suppressed formation of a dichlorinated side-product, which was produced in ~50% yield in the control reaction. Thus for substrates **25** and **26**, the addition of Pd would be advantageous for applications where high material throughput and facile isolation/purification steps are necessary.

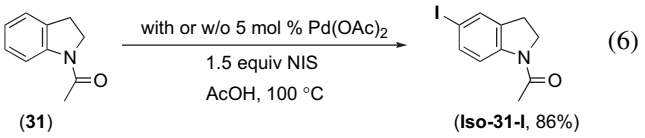
The indoline and the oxazolidinone substrates **31** and **32** are examples of *type 3* substrates in which EAS predominates, and the 'chelate-directed' product is not favored in either the Pd-catalyzed or the control reactions. For example, **31** and **32** reacted with NIS to afford the *para*-iodinated products *iso*-**31-I** and *iso*-**32-I**, respectively, in both the presence and absence of Pd (Eqs. 6 and 7). When analogous reactions were conducted with NCS and NBS, mixtures of

Table 6. Palladium-catalyzed halogenation of *type 3* substrates[a]

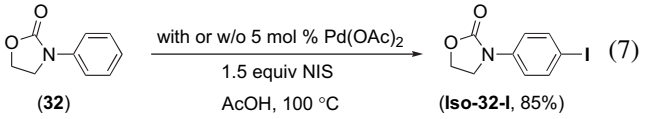
Entry	Starting material	Major product with and without Pd catalyst	Product #, yield (%)
1	 (**25**)		**25-I**, 41
2	 (**26**)		**26-Cl**, 67
3	 (**27**)		**27-Cl**, 86[b]
4	 (**28**)		**28-Br**, 95
5	 (**29**)		**29-Br**, 94
6	 (**30**)		**30-Br**, 99[c]

[a] Conditions: 1–1.2 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[b] $CuCl_2$ (4.0 equiv) with 5 mol % $Pd(OAc)_2$.
[c] 25 °C.

mono-halogenated compounds were formed; however, the addition of 5 mol % $Pd(OAc)_2$ did not alter the ratio of these compounds.



(6)



(7)

Type 3 substrates are not limited to those undergoing arene C–H functionalization. For example, 8-methylquinoline (**27**) reacts with NCS to afford the benzylic chloride **27-Cl** with or without palladium. However, interestingly, with $CuCl_2$ as the oxidant, this product is formed only in the Pd-catalyzed transformation, and not in the control. Hence, **27** represents a *type 3* substrate with NCS while it is a *type 1* substrate with $CuCl_2$.[32]

2.4. Type 4 substrates

Type 4 substrates are those in which there is a delicate balance between the catalyzed and uncatalyzed processes, such that the nature of the oxidant dictates which product predominates. In general, the chlorination of *type 4* substrates with NCS was most amenable to palladium catalysis, and they typically reacted to form different major monochlorinated products in Pd-catalyzed versus control reactions. In contrast, reactions of these substrates with NIS generally afforded identical results with and without Pd.

This *type 4* behavior is clearly illustrated by the reactivity profile of pyrrolidinone substrate **33**. As shown in Table 7, the control reaction with NCS afforded a ~1:1 mixture of *ortho* and *para*-chlorinated products (**33-Cl** and *iso*-**33-Cl**, respectively), while the *ortho*-chlorinated product **33-Cl** predominated in the Pd-catalyzed reaction. In contrast, the reaction of **33** with NBS provided a mixture of *ortho* and *para* brominated products **33-Br** and *iso*-**33-Br** both in the presence and absence of palladium. Finally, the reaction of **33** with NIS afforded exclusively the *para*-iodinated product *iso*-**33-I** in both the catalyzed and the uncatalyzed reactions.

Similarly, control reactions of pyrrolidinones **34**, **35**, and **36** as well as the acetanilide **37** with NCS afforded a mixture of chlorinated products, while the analogous Pd-catalyzed reactions afforded **34-Cl**, **35-Cl**, **36-Cl**, and **37-Cl** cleanly in 58%, 77%, 81%, and 70% isolated yields, respectively, along with only traces of the undesired isomeric products. Again, the corresponding bromination reactions of **33**, **34**, and **35** afforded approximately 3:1–4:1 mixture of regioisomeric brominated products both in the presence and absence of palladium.

The reactivity of *type 4* substrates represents a competition between the palladium-catalyzed reaction and uncatalyzed electrophilic aromatic substitution. The results in Table 7 clearly demonstrate that changing the oxidant changes the relative rates of these two competing processes, and current efforts in our group aim to delineate the effect of the oxidants on the relative contributions of the catalyzed versus the non-catalyzed pathways.

3. Conclusions

In summary, we have reported a full exploration of the palladium-catalyzed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides as terminal oxidants. In addition, preliminary results reported herein demonstrate that the halogenation of alkene and benzylic sp^3 C–H bonds can also be achieved using this methodology. These reactions were generally tolerant toward a variety of functional groups and showed wide scope with respect to directing groups. Furthermore, the reactivity trends of the various compounds greatly depended on the substitution pattern/electronics of the substrate as well as the ligand abilities of the directing group. Hence, the products obtained from these reactions are often different from and highly complementary to those obtained via traditional methods, such as electrophilic aromatic substitution and benzylic halogenation. The broad scope and often orthogonal nature of these Pd-catalyzed halogenation reactions should make them a valuable synthetic tool for accessing a more diverse array of halogenated organic molecules.

4. Experimental

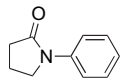
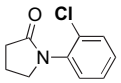
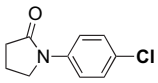
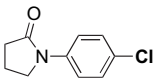
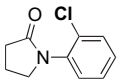
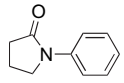
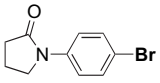
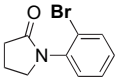
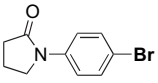
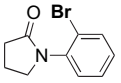
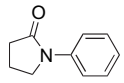
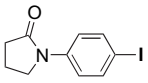
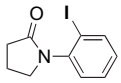
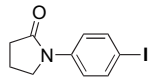
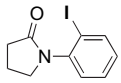
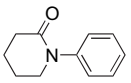
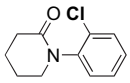
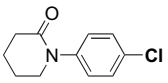
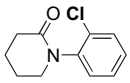
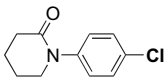
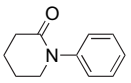
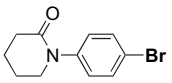
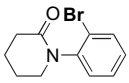
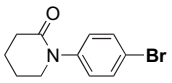
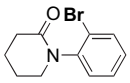
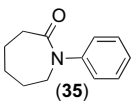
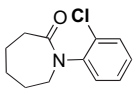
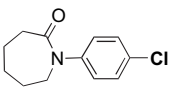
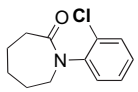
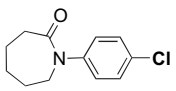
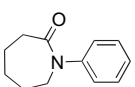
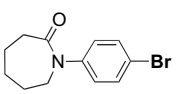
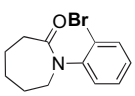
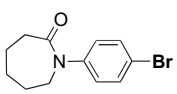
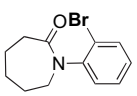
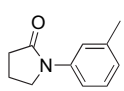
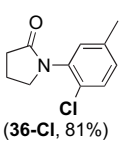
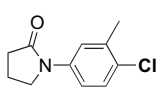
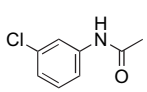
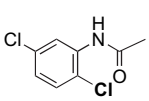
4.1. General

All reactions were performed with magnetic stirring in scintillation vials or thick-walled glass pressure-resistant vessels sealed with a Teflon bushing. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation and then at ca. 10 mTorr (vacuum pump). Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254.

4.2. Materials

Pyridine substrates **5**, **12**, **21**, **23**, and **29** were prepared by Suzuki coupling of the corresponding arylboronic acid with 2-bromo-3-picoline, 2-bromopyridine, or 1-chloroisoquinoline.[33] Substrate **30** was prepared in two steps by (i) Suzuki coupling of 3-aminophenylboronic acid with 2-bromopyridine followed by (ii) methylation of the amine using NaH and MeI. Substrates **7** and **8** were prepared by Stille coupling of 2-tributylpyridyltin with the corresponding aryl bromides.[34] Oxime substrates **16**, **18**, **19**, and **24** were prepared as previously reported,[9c] and tetrazole[35] and azobenzene[36] substrates **13** and **25** were prepared according to the literature procedures. Substrate **17** was prepared in two steps from 2-picoline.[37,38] Amide substrate **34** was synthesized via arylation of δ-valerolactam.[39] The remainder of the substrates were obtained from commercial sources (typically Acros Organics, Aldrich, or Lancaster) and were used without further purification. $Pd(OAc)_2$ was obtained from Pressure Chemical and used as received. NCS and NBS were obtained

Table 7. Palladium-catalyzed halogenation of *type 4* substrates[a]

Entry	Starting material	Oxidant	Major product with Pd catalyst	Minor product with Pd catalyst	Major product without Pd catalyst	Minor product without Pd catalyst
1	 (**33**)	NCS	 (**33-Cl**, 77%)	 (*Iso*-**33-Cl**, <5%)	 (*Iso*-**33-Cl**, 50%)[b]	 (**33-Cl**, 50%)[b]
2	 (**33**)	NBS	 (*Iso*-**33-Br**, 75%)[b]	 (**33-Br**, 17%)[b]	 (*Iso*-**33-Br**, 73%)[b]	 (**33-Br**, 19%)[b]
3	 (**33**)	NIS	 (*Iso*-**33-I**, 80%)	 (**33-I**, <5%)	 (*Iso*-**33-I**, 80%)	 (**33-I**, <5%)
4	 (**34**)	NCS	 (**34-Cl**, 57%)	 (*Iso*-**34-Cl**, <5%)	 (**34-Cl**, 45%)[b]	 (*Iso*-**34-Cl**, 41%)[b]
5	 (**34**)	NBS	 (*Iso*-**34-Br**, 63%)	 (**34-Br**, 37%)	 (*Iso*-**34-Br**, 81%)[b]	 (**34-Br**, 19%)[b]
6	 (**35**)	NCS	 (**35-Cl**, 77%)	 (*Iso*-**35-Cl**, <5%)	 (**35-Cl**, 41%)[b]	 (**35-Cl**, 28%)[b]
7	 (**35**)	NBS	 (*Iso*-**35-Br**, 60%)[b]	 (**35-Br**, 40%)[b]	 (*Iso*-**35-Br**, 77%)[b]	 (**35-Br**, 23%)[b]
8	 (**36**)	NCS	 (**36-Cl**, 81%)	 (*Iso*-**36-Cl**, <5%)	Complex mixture of products	
9	 (**37**)	NCS	 (**37-Cl**, 70%)	(*Iso*-**37-Cl**, 17%)	(**37-Cl**, 43%)	(*Iso*-**37-Cl**, 39%)

[a] NXS (1.5–1.8 equiv), 100 °C, 12 h, AcOH.
[b] Uncorrected yields as determined by GC and GC–MS.

from Acros, while NIS was obtained from Oakwood Products, and all were used without further purification. Solvents were obtained from Fisher Chemical and used as received. The synthesis of some substrates and characterization of the corresponding halogenated products (**1-Cl**, **1-Br**, **2-Cl**, **2-Br**, **2-I**, **3-Cl**, **3-Cl_2**, **4-Cl**, **6-Br**, **10-Br**, **11-I**, **14-I**, **15-I**, **20-Cl**, **20**-*iso*-**Cl**, **21-Cl**, **28-Cl**, **35-Cl**, and **36-Cl**) has been reported previously in preliminary communications of this work.[9d,g]

4.3. Instrumentation

NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F), or a Varian Mercury 300 (300.07 MHz for ^{1}H NMR, 75.45 MHz for ^{13}C; 282.35 MHz for ^{19}F) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), triplet of triplets (tt), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. HRMS data were obtained on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas chromatography

was performed on a Shimadzu GC-17A equipped with a Restek Rtx©-5 column (15 m, 0.25 mm ID, 0.25 μm df) and a FID detector. GC yields are reported as corrected GC yields based on a calibration curve against naphthalene as an internal standard. Typical errors associated with GC yields are approximately ±5%. GC–MS analysis was performed on a Shimadzu GCMS QP-5000 equipped with a Restek Rtx©-5 column (30 m, 0.25 mm ID, 0.25 μm df). Reactions with $CuCl_2$ were not conducive to GC analysis directly from the crude reaction mixture because a large amount of the desired product remained coordinated to the copper. To correct for this, pyridine was added to each crude reaction mixture (1/2 the total volume of the reaction for small-scale screenings) to liberate the product prior to GC analysis.

4.4. General procedures

Procedure A. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial or a larger pressure vessel. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The solvent was removed under vacuum, and the resulting residues were purified by chromatography on silica gel.

Procedure B. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL). An aqueous solution of Na_2CO_3 (10 mL) was then added dropwise to this mixture until the effervescence ceased. The organic and aqueous layers were separated. The aqueous layer was washed with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was then purified by chromatography on silica gel.

Procedure C. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (1×15 mL). The aqueous layer was washed with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.

Procedure D. A solution of the oxidant in the reaction solvent was added slowly with stirring to a solution of the substrate in the same solvent. The resulting mixture was stirred at room temperature for 1 h, then the solvent was evaporated. The crude residue was extracted between CH_2Cl_2 and H_2O to remove the succinimide by-product. The organic layer was washed with brine, filtered, and concentrated to afford the product.

Procedure E. The substrate and CuX_2 were dissolved in MeCN and heated to 120 °C for 12 h. After evaporation of the solvent, the resulting material was taken up in CH_2Cl_2 and washed several times with an equal volume of a solution of 5% pyridine in water, until the aqueous layer was no longer a bright blue color. The organic layer was then washed with brine, dried with $MgSO_4$, filtered, and condensed to give the crude product, liberated from most of the copper oxidant.

Procedure F. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with a solution of 5% pyridine in water (3×15 mL) followed by washing with brine (1×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.

4.4.1. 5-Chlorobenzo[*h*]quinoline (*iso*-1-Cl). Procedure A was followed, utilizing substrate **1** (215.5 mg, 1.2 mmol, 1 equiv), $PhICl_2$ (404.0 mg, 1.5 mmol, 1.3 equiv), and MeCN (10 mL) with no Pd needed. The product was isolated as an off-white solid (R_f=0.21 in 95% hexanes/5% EtOAc, mp=113.6–115.0 °C). Analytically pure material was isolated by further purification by HPLC (98% hexanes/2% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). Isolated yield was not determined due to difficulties in purification, but was ~38% by uncorrected GC ratios of the crude reaction mixture. Regiochemistry was assigned by analogy to *iso*-**1**-**Br** (see below). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (dt, *J*=8.0, 1.0 Hz, 1H), 9.05 (dd, *J*=4.5, 1.5 Hz, 1H), 8.65 (dd, *J*=8.5, 1.5 Hz, 1H), 7.94 (s, 1H), 7.85–7.83 (m, 1H), 7.76–7.69 (multiple peaks, 2H), 7.64 (dd, *J*=8.5, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 147.1, 133.2, 133.1, 130.7, 129.1, 129.0, 127.5, 127.3, 127.2, 124.9, 122.4 (two peaks are coincidentally overlapping). HRMS EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_8ClN$: 213.0345. Found: 213.0350.

4.4.2. 5-Bromobenzo[*h*]quinoline (*iso*-1-Br). Procedure E was followed, utilizing substrate **1** (1.0968 g, 6.1 mmol, 1 equiv), $CuBr_2$ (3.3578 g, 15.0 mmol, 2.5 equiv), and MeCN (50 mL). The crude residue was purified by column chromatography on silica gel (R_f=0.21 in 95% hexanes/5% EtOAc) and was isolated as a white solid (382.4 mg, 24% yield, mp=108.3–110.8 °C) contaminated with ~10% of an unidentified impurity by ^{1}H NMR. This was removed by further purification by preparative TLC (Whatman PK6F Silica gel, 60 Å, 500 μm thickness), eluting with 20% EtOAc in hexanes. Regiochemistry was confirmed by synthesis of an authentic sample of the 6-Br isomer[40] and comparison of the NMR spectral data to *iso*-**1**-**Br** (see below). For the **5**-**Br** isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (dt, *J*=8.0, 0.5 Hz, 1H), 9.01 (dd, *J*=4.0, 2.0 Hz, 1H), 8.60 (dd, *J*=8.5, 1.5 Hz, 1H), 8.15 (s, 1H), 7.83–7.81 (m, 1H), 7.77–7.74 (m, 1H), 7.72–7.68 (m, 1H), 7.62 (dd, *J*=8.5, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 147.0, 135.9, 133.8, 131.2, 131.1, 129.1, 127.7, 127.2, 125.9, 125.0, 122.7, 119.7. HRMS EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_8BrN$: 256.9840. Found: 256.9838. For the **6**-**Br** isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36–9.33 (m, 1H), 9.01 (dd, *J*=4.0, 2.0 Hz, 1H), 8.36–8.33 (m, 1H), 8.10 (dd, *J*=8.0, 2.0 Hz, 1H), 8.06 (s, 1H), 7.83–7.79 (multiple peaks, 2H), 7.54 (1H, dd, *J*=8.0, 4.5 Hz, 1H).

4.4.3. 2-(2-Chloronapthalen-1-yl)pyridine (5-Cl). Procedure A was followed, utilizing substrate **5** (100 mg, 0.487 mmol, 1 equiv), NCS (72 mg, 0.536 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **5-Cl** was isolated as a yellow solid (81 mg, 70% yield, mp=85.7–86.4 °C, R_f=0.11 in 95% toluene/5% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 8.80–8.79 (m, 1H), 8.03–7.97 (multiple peaks, 3H), 7.77 (d, J=8.9 Hz, 1H), 7.58–7.49 (multiple peaks, 3H), 7.43 (d, J=7.9 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H). ^{13}C NMR (100 MHz): δ 157.4, 150.6, 137.6, 137.3, 134.2, 133.1, 131.0, 130.7, 129.0, 128.1, 127.8, 127.1, 126.7, 126.6, 123.7. HRMS EI (m/z): [M^+] calcd for $C_{15}H_{10}ClN$, 239.0502. Found: 239.0499.

4.4.4. Methyl 4-bromo-3-(pyridin-2-yl)benzoate (7-Br). Procedure A was followed at 120 °C, utilizing substrate **7** (2.357 g, 11 mmol, 1 equiv), NBS (3.952 g, 22 mmol, 2 equiv), $Pd(OAc)_2$ (120.5 mg, 0.54 mmol, 5 mol %), and HOAc (200 mL). The crude residue was purified by chromatography on silica gel (R_f=0.04 in 90% hexanes/10% EtOAc). Material that was pure by GC was isolated as a yellow oil, which solidified upon standing (2.263 g, 70% yield). Analytically pure material (a white solid, mp=68.0–69.2 °C) was obtained after a second column. ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 2.0, 1.0 Hz, 1H), 8.17 (d, J=2.0 Hz, 1H), 7.89 (dd, J=8.5, 2.0 Hz, 1H), 7.77 (td, J=8.0, 2.0 Hz, 1H), 7.74 (d, J=8.5 Hz, 1H), 7.58 (dt, J=8.0, 1.0 Hz, 1H), 7.31 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 157.6, 149.7, 141.6, 136.1, 133.7, 132.5, 130.5, 129.7, 127.3, 124.7, 122.9, 52.4. IR (KBr): 1734, 1260, 753 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.18; H, 3.40; N, 4.71.

4.4.5. 2-(2-Bromo-5-methylphenyl)pyridine (8-Br). Procedure A was followed at 120 °C, utilizing substrate **8** (201 mg, 1.20 mmol, 1 equiv), NBS (254 mg, 1.40 mmol, 1.2 equiv), $Pd(OAc)_2$ (13.3 mg, 0.06 mmol, 5 mol %), and CH_3CN (7.7 mL). Product **8-Br** was isolated as a clear oil (151 mg, 51% yield, R_f=0.10 in 95% hexanes/5% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J=4.9 Hz, 1H), 7.75 (td, J=7.6, 1.8 Hz, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.36 (d, J=2.3 Hz, 1H), 7.29 (ddd, J=7.5, 4.9, 1.2 Hz, 1H), 7.07 (dd, J=8.1, 2.3 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 149.3, 140.8, 137.5, 135.7, 132.9, 132.1, 130.5, 124.8, 122.3, 118.3, 20.8. Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09; H, 4.06; N, 5.65. Found: C, 57.90; H, 3.90; N, 5.49.

4.4.6. 2-(2-Bromophenyl)pyridine (9-Br). Procedure A was followed at 120 °C, utilizing substrate **9** (2.17 g, 14.0 mmol, 1 equiv), NBS (2.99 g, 16.8 mmol, 1.2 equiv), $Pd(OAc)_2$ (156 mg, 0.70 mmol), and CH_3CN (200 mL). Product **9-Br** was isolated as a yellow oil (2.07 g, 63% yield, R_f=0.05 in 95% hexanes/5% EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 1.5, 1.0 Hz, 1H), 7.77 (td, J=8.0, 2.0 Hz, 1H), 7.68 (dd, J=8.0, 1.5 Hz, 1H), 7.61 (dt, J=8.0, 1.0 Hz, 1H), 7.54 (dd, J=7.5, 1.5 Hz, 1H), 7.41 (dt, J=7.5, 1.5 Hz, 1H), 7.30 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 7.27–7.24 (m (obscured by solvent), 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 149.5, 141.3, 135.9, 133.3, 131.5, 129.8, 127.6, 124.8, 122.5, 121.8. HRMS EI (m/z): [$M]^+$ calcd for $C_{11}H_8BrN$: 232.9840. Found: 232.9839.

4.4.7. 2-(2-Iodo-5-(trifluoromethyl)phenyl)-3-methylpyridine (12-I). Procedure B was followed, utilizing substrate **12** (150 mg, 0.633 mmol, 1 equiv), NIS (171 mg, 0.759 mmol, 1.2 equiv), $Pd(OAc)_2$ (7.1 mg, 0.032 mmol, 5 mol %), and CH_3CN (5.3 mL). Product **12-I** was isolated as a light yellow viscous oil with gradient elution from 100% CH_2Cl_2 to 95% CH_2Cl_2/5% EtOAc (179 mg, 78% yield, R_f=0.22 in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J=3.6 Hz, 1H), 8.19 (s, 1H), 7.71 (d, J=6.0 Hz, 1H), 7.64 (d, J=6.4 Hz, 1H), 7.38 (d, J=6.4 Hz, 1H), 7.30 (dd, J=6.2, 3.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.9, 146.8, 138.1, 135.8 (q, J_{CF}=4.4 Hz), 131.4 (q, J_{CF}=33 Hz), 131.1, 129.5, 125.2 (q, J_{CF}=3.6 Hz), 123.5, 122.8 (q, J_{CF}=272 Hz), 97.5, 18.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.7 (s). Anal. Calcd for $C_{13}H_9F_3IN$: C, 43.00; H, 2.50; N, 3.86. Found: C, 43.41; H, 2.57; N, 3.86.

4.4.8. 2-(2,6-Diiodophenyl)pyridine (9-I_2). Procedure A was followed, utilizing substrate **9** (150 mg, 0.966 mmol, 1 equiv), NIS (457 mg, 2.03 mmol, 2.1 equiv), $Pd(OAc)_2$ (10.8 mg, 0.048 mmol, 5 mol %), and AcOH (8.1 mL). Product **9-I_2** was isolated as a light brown solid (162 mg, 41% yield, mp=122.7–124.2 °C, R_f=0.29 in 90% hexanes/10% EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, J=4.5 Hz, 1H), 7.93 (d, J=8 Hz, 2H), 7.83 (t, J=8 Hz, 1H), 7.36 (m, 1H), 7.26 (d, J=8 Hz, 1H), 6.75 (t, J=8 Hz, 1H). ^{13}C NMR (100 MHz): δ 164.2, 149.2, 148.2, 139.0, 136.6, 131.1, 124.1, 123.2, 96.9. Anal. Calcd for $C_{11}H_7I_2N$: C, 32.46; H, 1.73; N, 3.44. Found: C, 32.71; H, 1.66; N, 3.50.

4.4.9. 2-(8-Iodonapthalen-1-yl)pyridine (5-I). Procedure A was followed, utilizing substrate **5** (100 mg, 0.487 mmol, 1 equiv), NIS (329 mg, 1.46 mmol, 3.0 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **5-I** was isolated as a yellow solid (97 mg, 60% yield, mp=85.9–87.0 °C, R_f=0.19 in 97.5% toluene/2.5% EtOAc). ^1H NMR (400 MHz, acetone-d_6): δ 8.78 (ddd, J=4.9, 1.8, 1.0 Hz, 1H), 8.03–7.97 (multiple peaks, 3H), 7.77 (d, J=8.9 Hz, 1H), 7.58–7.49 (multiple peaks, 2H), 7.44–7.42 (multiple peaks, 2H), 7.26 (d, J=8.5 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 161.8, 150.5, 144.4, 137.5, 136.3, 133.9, 131.1, 130.6, 129.0, 127.9, 127.4, 127.1, 126.3, 123.9, 97.1. HRMS EI (m/z): [M^+] calcd for $C_{15}H_{10}IN$, 330.9858. Found: 330.9857.

4.4.10. 5-(2-Iodophenyl)-1-methyl-1*H*-tetrazole (13-I). Procedure A was followed, utilizing substrate **13** (150 mg, 0.936 mmol, 1 equiv), NIS (442 mg, 1.97 mmol, 2.1 equiv), $Pd(OAc)_2$ (20.9 mg, 0.094 mmol, 10 mol %), and AcOH (7.8 mL). Product **13-I** was isolated as a viscous milky white oil (111 mg, 41% yield, R_f=0.23 in 98.5% toluene/1.5% MeCN). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 41%. Note: the sample obtained from column chromatography was contaminated with approximately 50% of the starting material. Samples for HRMS, NMR analysis, and calibrated GC yields were obtained after further purification by HPLC (95% hexanes/5% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). Mp=71.8–72.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, J=7.8, 1.0 Hz, 1H), 7.73 (dd, J=7.8, 1.4 Hz, 1H), 7.46 (td, J=7.8, 1.6 Hz, 1H), 7.16 (td, J=7.8,

1.5 Hz, 1H), 4.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 140.7, 132.4, 131.2, 131.1, 128.2, 95.6, 39.7. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_8H_7IN_4$, 285.9715. Found: 285.9720.

4.4.11. *N*-(2-Chloro-3-(1-(methoxyimino)ethyl)phenyl)-acetamide (16-Cl). Procedure C was followed, utilizing substrate **16** (150 mg, 0.727 mmol, 1 equiv), NCS (116 mg, 0.872 mmol, 1.2 equiv), $Pd(OAc)_2$ (16.3 mg, 0.072 mmol, 10 mol %), and AcOH (6.1 mL). Product **16-Cl** was isolated as a light yellow solid as a 4:1 mixture of oxime isomers (105 mg, 60% yield, mp=123.9–125.3 °C, R_f=0.20 in 70% hexanes/30% EtOAc). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J*=8.1 Hz, 1H), 7.64 (br s, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 7.02 (d, *J*=7.5 Hz, 1H), 3.94 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz): δ 168.2, 155.4, 137.2, 135.0, 128.4, 127.5, 125.0, 121.7, 61.9, 24.9, 16.3. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J*=7.9 Hz, 1H), 7.67 (br s, 1H), 7.31 (t, *J*=7.7 Hz, 1H), 6.85 (d, *J*=7.7 Hz, 1H), 3.80 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H). IR (KBr): 1654 cm^{-1}. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{11}H_{13}ClN_2O_2$, 240.0666. Found: 240.0662. The reaction in the absence of palladium showed a complex mixture of isomeric chlorinated products by GC analysis.

4.4.12. (*E*)-3-Chloro-2-(pyridin-2-yl)allyl acetate (17-Cl). Procedure C was followed, utilizing substrate **17** (107.8 mg, 0.61 mmol, 1 equiv), NCS (88.6 mg, 0.66 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.6 mg, 0.029 mmol, 5 mol %), and 1,2-dichloroethane (10 mL). GC analysis of the crude reaction mixture afforded a calibrated yield of 69%. Product **17-Cl** was isolated as a tan oil (71.2 mg, contaminated with 12% of an inseparable dichlorinated product, 49% yield, R_f=0.04 in 90% hexanes/10% EtOAc). Samples for HRMS, NMR analysis, and calibrated GC yields were obtained after further purification by HPLC (90% hexanes/10% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (ddd, *J*=4.5, 2.0, 1.0 Hz, 1H), 7.73 (td, *J*=7.5, 2.0 Hz, 1H), 7.68 (dt, *J*=8.0, 1.0 Hz, 1H), 7.24 (ddd, *J*=7.0, 5.0, 1.5 Hz, 1H), 6.65 (t, *J*= 1.5 Hz, 1H), 5.09 (s, 2H), 2.01 (s, 3H). NOE: Irradiation of olefinic proton (at 6.65 ppm) produces a 1% enhancement of the methylene at 5.09 ppm and a trace enhancement of the methyl at 2.01 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 153.5, 149.6, 136.9, 136.1, 125.1, 123.1, 120.7, 65.6, 21.0. IR (thin film): 1743, 1226 cm^{-1}. HRMS EI (*m*/*z*): [M]$^+$ calcd for $C_{10}H_{10}ClNO_2$: 211.0400. Found: 211.0399.

4.4.13. 1-(2-Chlorocyclohex-1-enyl)ethanone *O*-methyl oxime (18-Cl). Procedure C was followed, utilizing substrate **18** (103.7 mg, 0.68 mmol, 1 equiv), NCS (226.0 mg, 1.7 mmol, 2.5 equiv), $Pd(OAc)_2$ (15.1 mg, 0.067 mmol, 10 mol %), and MeCN (10 mL). The product **18-Cl** was isolated as a colorless oil (23.1 mg, 18% yield, R_f=0.08 in 98% hexanes/2% EtOAc). The low isolated yield appears to be the result of incomplete conversion as well as the volatility of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 2.40–2.36 (m, 2H), 2.27–2.23 (m, 2H), 1.98 (s, 3H), 1.76–1.71 (m, 2H), 1.69–1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 131.9, 130.6, 61.7, 33.9, 30.2, 23.6, 22.1, 14.7. IR (thin film): 1722, 1435, 1052 cm^{-1}. HRMS EI (*m*/*z*): [M]$^+$ calcd for $C_9H_{14}ClNO$: 187.0764. Found: 187.0760.

4.4.14. (*E*)-1-(2-Chloro-4-methoxyphenyl)ethanone *O*-methyl oxime (19-Cl). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NCS (81.9 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-Cl** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (69 mg, 58% yield, R_f=0.20 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J*=8.8 Hz, 1H), 6.94 (d, *J*=2.5 Hz, 1H), 6.81 (dd, *J*=8.8, 2.5 Hz, 1H), 3.99 (s, 3H), 3.82 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 155.8, 133.4, 130.9, 129.3, 115.3, 112.8, 61.8, 55.6, 16.5. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J*=8.5 Hz, 1H), 6.96 (d, *J*=2.5 Hz, 1H), 6.84 (dd, *J*=8.5, 2.5 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 2.20 (s, 3H). HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}ClNO_2$, 213.0557. Found: 213.0563.

4.4.15. (*E*)-1-(3-Chloro-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-Cl). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NCS (89.4 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-Cl** was isolated as a white solid as a single oxime isomer (62 mg, 53% yield, mp=60.2–61.6 °C, R_f=0.25 in 60% hexanes/40% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J*=2.0 Hz, 1H), 7.50 (dd, *J*=8.8, 2.4 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.9, 130.0, 127.8, 125.4, 114.0, 111.5, 61.9, 56.2, 12.3. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}ClNO_2$, 213.0557. Found: 213.0562.

4.4.16. (*E*)-1-(2-Bromo-4-methoxyphenyl)ethanone *O*-methyl oxime (19-Br). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NBS (109 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-Br** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (105 mg, 72% yield, R_f=0.30 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.8 Hz, 1H), 7.12 (d, *J*=2.8 Hz, 1H), 6.85 (dd, *J*=8.4, 2.8 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.7, 131.3, 130.9, 122.2, 118.3, 113.3, 61.8, 55.6, 16.7. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0056. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J*=2.3 Hz, 1H), 7.00 (d, *J*=8.6 Hz, 1H), 6.87 (dd, *J*=8.6, 2.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.15 (s, 3H). HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0057.

4.4.17. (*E*)-1-(3-Bromo-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-Br). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NBS (119 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-Br** was isolated as a white solid as a single oxime isomer (99 mg, 69% yield, mp=70.2–71.1 °C, R_f= 0.30 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=2.4 Hz, 1H), 7.55 (dd, *J*=8.4, 2.4 Hz, 1H), 6.87 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 2.17

(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 152.9, 130.9, 130.4, 126.2, 111.7, 111.4, 61.9, 56.3, 12.3. HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0056.

4.4.18. (*E*)-1-(2-Iodo-4-methoxyphenyl)ethanone *O*-methyl oxime (19-I). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-I** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (78 mg, 46% yield, R_f=0.29 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J*=2.4 Hz, 1H), 7.15 (d, *J*=8.4 Hz, 1H), 6.89 (dd, *J*=8.8, 2.8 Hz, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.2, 135.2, 129.9, 124.7, 114.1, 96.0, 61.8, 55.6, 16.9. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J*=2.2 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 6.92 (dd, *J*=8.4, 2.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.14 (s, 3H). HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}INO_2$, 304.9913. Found: 304.9909.

4.4.19. (*E*)-1-(3-Iodo-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-I). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-I** was isolated as a light yellow solid as a single oxime isomer (81 mg, 47% yield, mp=65.0–66.4 °C, R_f=0.29 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J*=2.4 Hz, 1H), 7.59 (dd, *J*=8.4, 2.4 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 152.8, 137.0, 131.0, 127.3, 110.3, 86.0, 61.9, 56.4, 12.4. HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}INO_2$, 304.9913. Found: 304.9916.

4.4.20. 4-Chloro-1-phenylisoquinoline (*iso*-21-Cl). Procedure A was followed, utilizing substrate **21** (100 mg, 0.487 mmol, 1 equiv), NCS (130 mg, 0.974 mmol, 2.0 equiv), and AcOH (4.0 mL). Product *iso*-**21-Cl** was isolated as a white solid (66 mg, 56% yield, mp=129.7–130.3 °C, R_f=0.29 in 90% hexanes/10% CH_2Cl_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.65 (s, 1H), 8.28 (d, *J*=8.4 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.94 (dt, *J*=6.8, 1.2 Hz, 1H), 7.74 (dt, *J*=6.8, 1.2 Hz, 1H), 7.70–7.68 (multiple peaks, 2H), 7.58–7.53 (multiple peaks, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 160.5, 141.7, 139.9, 134.7, 132.3, 130.8, 129.6, 129.3, 129.1, 128.7, 128.2, 127.6, 124.1. Anal. Calcd for $C_{15}H_{10}ClN$: C, 75.16; H, 4.21; N, 5.84. Found: C, 74.48; H, 4.19; N, 5.65.

4.4.21. 1-(2-Chlorophenyl)-1*H*-pyrazole (22-Cl). Procedure B was followed, utilizing substrate **22** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), $Pd(OAc)_2$ (23.3 mg, 0.104 mmol, 10 mol %), and AcOH (8.7 mL). Product **22-Cl** was isolated as a clear oil (108 mg, 58% yield, R_f=0.12 in 60% hexanes/40% CH_2Cl_2). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 72%. Note: the sample obtained from column chromatography was contaminated with approximately 13% of the starting material. Samples for microanalysis were obtained after further purification by HPLC (98% hexanes/2% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=3.2 Hz, 1H), 7.75 (s, 1H), 7.58 (dd, *J*=10.4, 2.0 Hz, 1H), 7.52 (dd, *J*=10.2, 2.6 Hz, 1H), 7.42–7.30 (multiple peaks, 2H), 6.48 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 131.3, 130.6, 128.9, 128.3, 127.8, 127.6, 106.6. Two carbon resonances are coincidently overlapping. HRMS EI (*m*/*z*): [M^+] calcd for $C_9H_7ClN_2$, 178.0298. Found: 178.0299.

4.4.22. 1-(2-Chlorophenyl)-1*H*-pyrazole (*iso*-22-Cl). Procedure B was followed, utilizing substrate **22** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), and AcOH (8.7 mL). Product *iso*-**22-Cl** was isolated as a clear oil (154 mg, 83% yield, mp=72.5–74.3 °C, R_f=0.26 in 70% hexanes/30% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.64–7.62 (multiple peaks, 3H), 7.45 (t, *J*=7.4 Hz, 2H), 7.31(tt, *J*=7.4, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 139.4, 129.5, 126.9, 124.8, 118.9, 112.3. HRMS EI (*m*/*z*): [M^+] calcd for $C_9H_7ClN_2$, 178.0298. Found: 178.0297.

4.4.23. 2-(2-Chloro-5-(trifluoromethyl)phenyl)-6-methoxypyridine (23-Cl). Procedure B was followed, utilizing substrate **23** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), $Pd(OAc)_2$ (17.7 mg, 0.079 mmol, 20 mol %), and AcOH (3.3 mL). Product **23-Cl** was isolated as a clear oil (81 mg, 71% yield, R_f=0.35 in 98% hexanes/2% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.01–7.98 (m, 1H), 7.83 (dd, *J*=8.1, 7.2 Hz, 1H), 7.82–7.75 (multiple peaks, 2H), 7.37 (dd, *J*=10.0, 0.8 Hz, 1H), 6.86 (dd, *J*=11.0, 1.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 164.8, 153.4, 140.8, 140.1, 137.1, 132.3, 129.9 (q, J_{CF}=32.2 Hz), 129.3 (q, J_{CF}=4.05 Hz), 127.2 (q, J_{CF}=3.7 Hz), 124.9 (q, J_{CF}=272 Hz), 118.5, 111.4, 53.8. ^{19}F NMR (282 MHz, acetone-d_6): δ –63.1 (s) Anal. Calcd for $C_{13}H_9ClF_3NO$: C, 54.28; H, 3.15; N, 4.87. Found: C, 54.37; H, 3.01; N, 4.80.

4.4.24. 3-Chloro-2-methoxy-6-(3-(trifluoromethyl)-phenyl)pyridine and 3-chloro-6-methoxy-2-(3-(trifluoromethyl)phenyl)pyridine (*iso*-23-Cla) and (*iso*-23-Clb). Procedure B was followed, utilizing substrate **23** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), and AcOH (3.3 mL). GC analysis of the crude reaction mixture showed 3:1 mixture of regioisomeric mono-chlorinated products. Isomer *iso*-**23-Cla** was isolated as a clear oil (36 mg, 32% yield, R_f=0.18 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.44 (s, 1H), 8.40 (d, *J*=7.7 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.79–7.73 (multiple peaks, 2H), 7.68 (d, *J*=8.0 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 159.74, 151.80, 140.43, 139.86, 131.55 (q, J_{CF}=32 Hz), 131.17, 130.70, 125.37 (q, J_{CF}=271 Hz), 126.57 (q, J_{CF}=3.8 Hz), 124.03 (q, J_{CF}=3.8 Hz), 118.28, 115.13, 54.59. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.72 (s). HRMS EI (*m*/*z*): [M^+] calcd for $C_{13}H_9ClF_3NO$, 287.0325. Found: 287.0318. Isomer *iso*-**23-Clb** was isolated as a clear oil (57 mg, 50% yield, R_f=0.13 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.09 (multiple peaks, 2H), 7.73–7.64 (multiple peaks, 2H), 7.59 (t, *J*=7.7 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 151.8, 142.2, 140.1, 134.2, 130.8 (q, J_{CF}=32 Hz), 129.1, 126.9 (q, J_{CF}=3.7 Hz), 126.3

(q, J_{CF}=3.6 Hz), 125.3 (q, J_{CF}=271 Hz), 122.3, 112.8, 54.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.6 (s). HRMS EI (*m/z*): [M^+] calcd for $C_{13}H_9ClF_3NO$, 287.0325. Found: 287.0316.

4.4.25. (*E*)-8-Chloro-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (24-Cl). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol %), and AcOH (7 mL). Product **24-Cl** was isolated as a clear oil (179 mg, 88% yield, R_f=0.3 in 75% hexanes/25% CH_2Cl_2). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.32 (dd, J=7.8, 1.5 Hz, 1H), 7.23–7.13 (multiple peaks, 2H), 3.96 (s, 3H), 2.72 (t, J=6.6 Hz, 2H), 2.65 (t, J=6.0 Hz, 2H), 1.76–1.67 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 152.9, 144.8, 132.3, 130.3, 129.8, 129.7, 127.4, 62.3, 31.3, 25.3, 21.7. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.05; H, 5.83; N, 6.70.

4.4.26. (*E*)-4-Chloro-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (*iso*-24-Cl). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), and CH_3CN (7 mL). Product *iso*-**24-Cl** was isolated as a clear oil (70 mg, 39% yield, R_f=0.3 in 75% hexanes/25% CH_2Cl_2). Note: product *iso*-**24-Cl** was isolated in higher yield (66%) from the analogous reaction in AcOH; however, the isolated product from this reaction was contaminated with traces of isomeric chlorinated impurities. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.98 (d, J=7.6 Hz, 1H), 7.33 (t, J=6.4 Hz, 1H), 7.25–7.22 (m, 2H), 5.63 (t, J=2.8 Hz, 1H), 4.02 (s, 3H), 3.26–3.17 (m, 1H), 2.80–2.76 (m, 1H), 2.30–2.15 (multiple peaks, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 151.7, 138.3, 130.4, 129.8, 128.6, 127.3, 125.0, 62.8, 47.9, 30.7, 24.4. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.11; H, 5.88; N, 6.68.

4.4.27. (*E*)-4-Bromo-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (*iso*-24-Br). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NBS (160 mg, 0.899 mmol, 1.05 equiv), and AcOH (7.1 mL). Product *iso*-**24-Br** was isolated as a clear oil (64 mg, 29% yield, R_f=0.3 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J=7.8 Hz, 1H), 7.30–7.14 (multiple peaks, 3H), 5.63 (t, J=2.7 Hz, 1H), 4.06 (s, 3H), 3.34–3.27 (m, 1H), 2.76 (app d, J=16 Hz, 1H), 2.32–2.24 (m, 1H), 2.19–2.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 137.1, 129.5, 128.9, 127.7, 126.5, 124.5, 62.7, 37.9, 30.6, 25.3. HRMS EI (*m/z*): [M^+] calcd for $C_{11}H_{12}BrNO$, 253.0102. Found: 253.0106.

4.4.28. (*E*)-1-(2-Iodo-5-methylphenyl)-2-*m*-tolyldiazene (25-I). Procedure A was followed, utilizing substrate **25** (100 mg, 0.475 mmol, 1 equiv), NIS (160 mg, 0.713 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.3 mg, 0.024 mmol, 5 mol %), and AcOH (4.0 mL). Product **25-I** was isolated as an orange solid (65 mg, 41% yield, mp=64.6–66.0 °C, R_f=0.20 in 98% hexanes/2% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J=8.0 Hz, 1H), 7.81–7.79 (multiple peaks, 2H), 7.45–7.39 (multiple peaks, 2H), 7.32 (d, J=7.2 Hz, 1H), 7.01 (dd, J=8.0, 2.4 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 151.1, 139.4, 139.1, 139.0, 133.1, 132.3, 128.9, 123.9, 120.8, 117.8, 98.4, 21.4, 20.9. HRMS EI (*m/z*): [M^+] calcd for $C_{14}H_{13}IN_2$, 336.0123. Found: 336.0123. The reaction in the absence of palladium showed a 4:1 mixture of isomeric iodinated products.

4.4.29. *N*-(2-Chloro-6-methylphenyl)pivalamide (26-Cl). Procedure A was followed, utilizing substrate **26** (150 mg, 0.784 mmol, 1 equiv), NCS (126 mg, 0.941 mmol, 1.2 equiv), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol, 5 mol %), and AcOH (6.5 mL). Product **26-Cl** was isolated as a white solid (118 mg, 67% yield, mp=158.4–160.0 °C, R_f=0.20 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.31 (br s, 1H), 7.28 (dd, J=7.4, 2.4 Hz, 1H), 7.21–7.14 (multiple peaks, 2H), 2.22 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6): δ 176.9, 139.9, 135.4, 133.5, 129.7, 128.6, 127.7, 39.9, 27.9, 18.8. IR (KBr): 1654 cm^{-1}. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 63.71; H, 7.30; N, 5.84.

4.4.30. 8-Chloromethylquinoline (27-Cl). Procedure F was followed, utilizing substrate **27** (110 mg, 0.768 mmol, 1 equiv), $CuCl_2$ (413 mg, 3.07 mmol, 4.0 equiv), $Pd(OAc)_2$ (8.6 mg, 0.038 mmol, 5 mol %), and CH_2Cl_2 (6.4 mL). Product **27-Cl** was isolated as a yellow solid (118 mg, 86% yield, R_f=0.21 in 95% hexanes/5% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (dd, J=4.2, 1.8 Hz, 1H), 8.16 (dd, J=8.3, 1.8 Hz, 1H), 7.79–7.87 (multiple peaks, 2H), 7.53 (t, J=7.1 Hz, 1H), 7.44 (dd, J=8.3, 4.2 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 146.1, 136.6, 135.8, 130.3, 128.9, 128.5, 126.5, 121.7, 42.6. Anal. Calcd for $C_{10}H_8ClN$: C, 32.46; H, 1.73; N, 3.44. Found: C, 32.71; H, 1.66; N, 3.50.

4.4.31. 2-(2-Bromo-5-methoxyphenyl)pyridine (29-Br). Procedure A was followed, utilizing substrate **29** (2.879 g, 16 mmol, 1 equiv), NBS (2.770 g, 16 mmol, 1 equiv), and MeCN (200 mL). Product **29-Br** was isolated as a yellow-orange oil (3.861 g, 94% yield, R_f=0.18 in 80%, hexanes/20% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 1.5, 1.0 Hz, 1H), 7.77 (td, J=7.5, 2.0 Hz, 1H), 7.61 (d, J=7.5 Hz, 1H), 7.54 (d, J=9.0 Hz, 1H), 7.31 (ddd, J=7.5, 5.0, 1.5 Hz, 1H), 7.09 (d, J=3.0 Hz, 1H), 6.83 (dd, J=8.5, 3.0 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 158.2, 149.4, 142.0, 135.9, 134.0, 124.8, 122.5, 116.4, 116.3, 112.2, 55.6. IR (thin film): 1584, 1563, 1460 cm^{-1}. Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.60; H, 3.95; N, 5.36.

4.4.32. 2-(2-Bromo-5-dimethylaminophenyl)pyridine (30-Br). Procedure D was followed utilizing a solution of NBS (1.971 g, 11 mmol, 1 equiv, in 100 mL MeCN) and a solution of substrate **30** (2.180 g, 11 mmol, 1 equiv, in 50 mL MeCN). Product **30-Br** was isolated as a yellow oil (3.005 g, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (ddd, J=5.0, 2.0, 1.0 Hz, 1H), 7.75 (td, J=8.0, 2.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.29 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 6.86 (d, J=3.0 Hz, 1H), 6.63 (dd, J=9.0, 3.0 Hz, 1H), 2.96 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149.7, 149.1, 141.1, 135.6, 133.3, 124.7, 122.1, 115.0, 113.9, 107.5, 40.4. Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 56.60; H, 4.78; N, 9.97.

4.4.33. 1-(5-Iodoindolin-1-yl)ethanone (*iso*-31-I). *Procedure with palladium catalyst*: Procedure A was followed, utilizing substrate **31** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol, 5 mol %), and AcOH (5.2 mL). Product *iso*-**31-I** was isolated as a creamy white solid (154 mg, 86% yield, mp=139.6–140.2 °C, R_f=0.18 in 60% hexanes/40% EtOAc). *Procedure without palladium catalyst*: Procedure A was followed, utilizing substrate **31** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), and AcOH (5.2 mL). Product *iso*-**31-I** was isolated as a creamy white solid (154 mg, 86% yield, mp=139.6–140.2 °C, R_f=0.18 in 60% hexanes/40% EtOAc). The products with and without Pd were identical by GC and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.94 (d, J=8.4 Hz, 1H), 7.52 (s, 1H), 7.47 (d, J=8.4 Hz, 1H), 4.16 (t, J=8.8 Hz, 2H), 3.19 (t, J=8.4 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.4, 144.4, 136.7, 135.9, 134.4, 119.1, 85.9, 49.4, 28.2, 24.2. IR (KBr): 1654, 1475 cm^{-1}. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.83; H, 3.51; N, 4.88. Found: C, 42.00; H, 3.58; N, 4.78.

4.4.34. 3-(4-Iodophenyl)oxazolidin-2-one (*iso*-32-I). Procedure A was followed, utilizing substrate **32** (150 mg, 0.920 mmol, 1 equiv), NIS (248 mg, 1.10 mmol, 1.2 equiv), $Pd(OAc)_2$ (10.3 mg, 0.043 mmol, 5 mol %), and AcOH (7.7 mL). Product *iso*-**32-I** was isolated as a white solid (226 mg, 85% yield, mp=163.6–163.9 °C, R_f=0.25 in 70% hexanes/30% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=9 Hz, 2H), 7.46 (d, J=9 Hz, 2H), 4.52–4.48 (m, 2H), 4.14–4.10 (m, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 154.8, 139.1, 137.6, 119.9, 85.8, 61.4, 44.3. IR (KBr): 1726, 1416 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_9H_8INO_2$, 288.9600. Found: 288.9606.

4.4.35. 1-(2-Chlorophenyl)pyrrolidin-2-one (33-Cl). Procedure C was followed, utilizing substrate **33** (209 mg, 1.29 mmol, 1 equiv), NCS (208 mg, 1.55 mmol, 1.2 equiv), $Pd(OAc)_2$ (14.5 mg, 0.064 mmol, 5 mol %), and AcOH (8.4 mL). Product **33-Cl** was isolated as an off-white solid (197 mg, 77% yield, mp=40.9–42.4 °C, R_f=0.30 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.51 (d, J=7.3 Hz, 1H), 7.39–7.32 (multiple peaks, 3H), 3.77 (t, J=6.92 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.22 (q, J=6.9 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 174.7, 138.2, 132.9, 130.9, 130.8, 129.8, 128.7, 50.5, 31.4, 19.9. IR (KBr): 1698 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_{10}H_{10}ClNO$, 195.0451. Found: 195.0450.

4.4.36. 1-(4-Chlorophenyl)pyrrolidin-2-one (*iso*-33-Cl). Procedure C was followed, utilizing substrate **33** (203 mg, 1.26 mmol, 1 equiv), NCS (202 mg, 1.51 mmol, 1.5 equiv), and AcOH (8.1 mL). Product *iso*-**33-Cl** was isolated as a white solid (142 mg, 58% yield, mp=95.5–96.6 °C, R_f=0.44 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 3.84 (t, J=7.2 Hz, 2H), 2.62 (t, J=8 Hz, 2H), 2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 137.9, 129.4, 128.7, 120.8, 48.6, 32.6, 17.8. IR (KBr): 1679 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_{10}H_{10}ClNO$, 195.0451. Found: 195.0445.

4.4.37. 1-(4-Bromophenyl)pyrrolidin-2-one (*iso*-33-Br). Procedure A was followed, utilizing substrate **33** (150 mg, 0.930 mmol, 1 equiv), NBS (199 mg, 1.12 mmol, 1.2 equiv), $Pd(OAc)_2$ (10.4 mg, 0.046 mmol, 5 mol %), and AcOH (7.7 mL). Product *iso*-**33-Br** was isolated as a white solid (156 mg, 70% yield, R_f=0.30 in 60% hexanes/40% EtOAc). The NMR data were identical to that reported previously for this compound.[41]

4.4.38. 1-(4-Iodophenyl)pyrrolidin-2-one (*iso*-33-I). *Procedure with palladium catalyst*: Procedure A was followed, utilizing substrate **33** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol, 5 mol %), and AcOH (5.2 mL). Product *iso*-**33-I** was isolated as a light yellow solid (141 mg, 80% yield, mp=140.0–141.6 °C, R_f=0.28 in 60% hexanes/40% EtOAc). *Procedure without palladium catalyst*: Procedure A was followed, utilizing substrate **33** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), and AcOH (5.2 mL). Product *iso*-**33-I** was isolated as a light yellow solid (141 mg, 80% yield, mp=140.0–141.6 °C, R_f=0.28 in 60% hexanes/40% EtOAc). The products with and without Pd were identical by GC and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 3.81 (t, J=7.2 Hz, 2H), 2.59 (t, J=8.1 Hz, 2H), 2.19–2.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 139.1, 137.7, 121.5, 87.9, 48.4, 32.7, 17.8. IR (KBr): 1684 cm^{-1}. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.83; H, 3.51; N, 4.88. Found: C, 41.82; H, 3.62; N, 4.71.

4.4.39. 1-(2-Chlorophenyl)piperidin-2-one (34-Cl). Procedure C was followed, utilizing substrate **34** (100 mg, 0.571 mmol, 1 equiv), NCS (114 mg, 0.856 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.39 mg, 0.028 mmol, 0.05 mol equiv), and AcOH (8.4 mL). Product **34-Cl** was isolated as an off-white solid (68.0 mg, 57% yield, mp=55.9–56.9 °C, R_f=0.18 in 90% CH_2Cl_2/10% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J=7.6, 1.3 Hz, 1H), 7.32 (td, J=7.5, 1.5 Hz, 1H), 7.29–7.25 (multiple peaks, 2H), 3.60 (m, 1H), 3.49 (m, 1H), 2.64–2.52 (multiple peaks, 2H), 2.02–1.93 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 140.6, 132.2, 130.4, 129.4, 128.9, 127.9, 50.9, 32.5, 23.4, 21.4. IR (KBr): 2921, 1652 cm^{-1}. HRMS EI (m/z): [M+Na$^+$] calcd for $C_{11}H_{12}ClNO$, 232.0505. Found: 232.0505.

4.4.40. *N*-(2,5-Dichlorophenyl)acetamide (37-Cl). Procedure A was followed, utilizing substrate **37** (150 mg, 0.884 mmol, 1 equiv), NCS (212 mg, 1.59 mmol, 1.8 equiv), $Pd(OAc)_2$ (9.90 mg, 0.044 mmol, 5 mol %), and AcOH (7.4 mL). Product **37-Cl** was isolated as a white solid (126 mg, 70% yield, mp=133.4–133.9 °C, R_f=0.28 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.74 (br s, 1H), 8.35 (d, J=2.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.14 (dd, J=8.4, 2.4 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.7, 137.6, 133.3, 131.3, 125.3, 123.l, 122.8, 24.3. IR (KBr): 1666 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_8H_7Cl_2NO$, 202.9905. Found: 202.9896.

4.4.41. *N*-(3,4-Dichlorophenyl)acetamide (*iso*-37-Cl). Procedure A was followed, utilizing substrate **37** (150 mg, 0.884 mmol, 1 equiv), NCS (142 mg, 1.06 mmol,

1.2 equiv), and AcOH (7.4 mL). Product **37-Cl** was isolated as a white solid (77 mg, 43% yield, mp=133.4–133.9 °C, R_f=0.28 in 80% hexanes/20% EtOAc). The NMR data were identical to that reported above for the reaction with palladium. The product *iso*-**37-Cl** was isolated as a white solid (70 mg, 39% yield, mp=121.9–123.3 °C, R_f=0.24 in 60% hexanes/40% EtOAc).^{1}H NMR (400 MHz, acetone-d_6): δ 7.78 (br s, 1H), 7.73 (d, J=1.8 Hz, 1H), 7.35–7.29 (multiple peaks, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 137.3, 132.7, 130.4, 127.5, 121.6, 119.1, 24.5. IR (KBr): 1665 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_8H_7Cl_2NO$, 202.9905. Found: 202.9904.

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A general organic catalyst for asymmetric addition of stabilized nucleophiles to acyl imines

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Abstract—Cinchona alkaloid-derived thiourea catalysts promote nucleophilic additions to acyl imines for the asymmetric synthesis of secondary amine adducts. The hydroquinine-derived thiourea catalyst efficiently promotes the aza-Henry reaction of nitroalkane with acyl imines, affording β-nitroamines in good yields with enantioselectivities of 90–98% ee and diastereoselectivities up to 97%. The scope of the reaction also includes dimethyl malonate as a nucleophile to access β-amino esters in high enantiopurity. Under the optimized reaction conditions, secondary amine adducts of high enantiopurity are generated based on various aromatic and α,β-unsaturated acyl imines.

1. Introduction

Organocatalysis is an expanding area of research in asymmetric organic synthesis.[1] Catalysts of organic origin are an appealing option versus the metal catalysts often used to achieve high enantio- and diastereoselectivities. Urea and thiourea catalysts, first noted for their catalytic utility in 1988 and widely used since, have been shown to be capable hydrogen bond donors, enabling selectivity in reactions.[2] Their stabilization of reaction components has allowed for the development of many asymmetric urea and thiourea catalyzed transformations, including the Strecker[3] and nitro-Michael reactions,[4] the Morita–Baylis–Hillman reaction,[5] and conjugate addition reactions,[6] to name a few.

Two important and useful organic reactions that have been highly studied are the Mannich[7] and nitro-Mannich[8] (aza-Henry) additions of carbon nucleophiles to electrophilic imines. Utilizing dicarbonyls and nitroalkanes as nucleophiles, respectively, these reactions allow for the formation of secondary amine adducts, which can be easily converted to a variety of synthetically useful products such as α- and β-amino acids, 1,2-diamines, and cyclic amines.[9]

Several systems have been designed to asymmetrically catalyze each separate reaction, with a recent surge in the development of organocatalytic methods to achieve high enantio- and diastereoselectivities.[1c,2e,f,4e,10] List et al. developed the first organocatalyzed direct Mannich reaction, using L-proline to synthesize Mannich products in high enantio- and chemoselectivities.[10] Barbas et al. later extended this work to include other amino acid derivatives.[11] Our laboratory developed the asymmetric Mannich reaction of β-keto esters to acyl imines using cinchona alkaloids, producing enantioenriched dihydropyrimidones and α-amino alcohols.[12] Recently, Deng et al. used a chiral cinchona alkaloid-derived thioureas to promote the reaction of acyl imines with different malonate nucleophiles.[13]

The asymmetric nitro-Mannich reaction using organocatalysts has recently received much attention.[14] Takemoto first used a chiral thiourea with an *N*,*N*-dimethylamino group to enantioselectively catalyze the addition of nitromethane to various *N*-phosphinoylimines, further expanding the reaction scope by enantioselectively adding various nitroalkanes.[14,16] Jørgensen used a chiral copper(II) bisoxazoline complex, combined with cinchona alkaloids, to catalyze the reaction of *p*-methoxyphenylimino ethyl esters with tertiary nitroalkanes to form products in high enantioselectivities (Fig. 1).[15] Using chiral thiourea catalysts in the presence of an external base, Jacobsen and Yoon developed another variation of the nitro-Mannich reaction.[16] Ricci et al. utilized a phase-transfer catalyst to promote the nitro-Mannich reaction of *N*-carbamoyl imines generated from in situ α-amido sulfones.[17] Following this work, they screened a variety of cinchona organocatalysts to catalyze the addition of nitromethane to a variety of protected imines, synthesizing products in satisfactory yields and enantioselectivities.[18]

Due to the previous work completed in our laboratory using cinchona alkaloids as tertiary amine catalysts to asymmetrically catalyze direct Mannich reactions,[10,19] we initially attempted to extend the methodology to the nitro-Mannich

Keywords: Cinchona alkaloids; Thiourea; Organic catalysis; Imines; Mannich reaction; Aza-Henry reaction.
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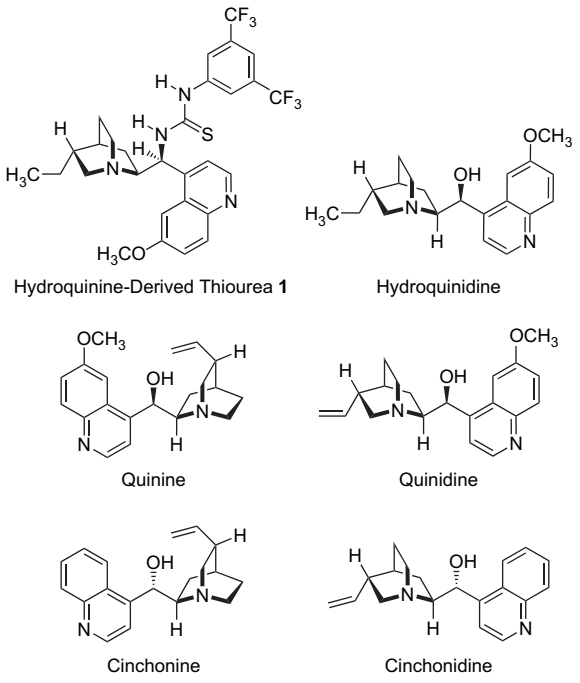


Figure 1. Cinchona alkaloid catalysts.

reaction. In the reactions of benzylidene methyl carbamate, nitromethane, and 10 mol % of a variety of cinchona alkaloids in CH_2Cl_2, we were able to synthesize secondary amine products in high yields (>90%). However, our progress was stymied by low enantioselectivities (<55%). Nevertheless, these preliminary results led us to further investigate the nature of cinchona alkaloids as catalysts, and possible modifications that could lead to greater success.

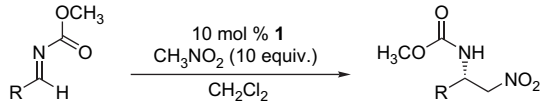
Our attention turned to the cinchona alkaloid-derived thiourea catalyst **1** used by Connon and Soos.[6b,g] Thiourea compounds have often been used in organic chemistry to efficiently enhance reaction rates, and have been known to catalyze nucleophilic addition reactions.[2,6]

2. Results and discussion

The reaction of methyl benzylidenecarbamate **2a** with nitromethane and 10 mol % hydroquinine-derived thiourea **1** in CH_2Cl_2 yielded the corresponding β-nitroamine **3a** in 91% isolated yield and in 93% ee after 24 h at −10 °C (Table 1, entry 1). Compared to the trifluoromethylated thiourea, the dimethyl-substituted catalyst gave **3a** in a comparable yield, yet with lower enantioselectivity (most likely due to the weaker electron-withdrawing capabilities of the methyl groups, affecting the hydrogen-bonding ability of the thiourea portion). In contrast, the cinchona alkaloid-derived thiourea was quite an efficient catalyst for this nitro-Mannich reaction.

The asymmetric nitro-Mannich reaction catalyzed by the hydroquinine-derived thiourea was found to be successful with other imines of varying electronics, both more electron-rich and electron-poor acyl imines (Table 1, entries 2–6). The reactions of electron-rich and electron-poor imine substrates yielded the corresponding β-nitroamines **3b**–**3f** in high enantioselectivities (90–98%) and yields (60–98%).

Table 1. Asymmetric nitro-Mannich additions of nitromethane[a]



2a–f **3a–f**

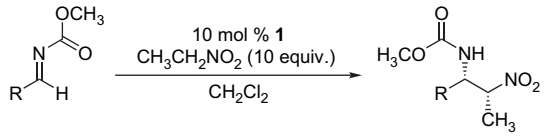
Entry	R	Adduct	Yield (%)[b]	ee (%)[c]
1[d]	**2a**: Ph	**3a**	91	93
2	**2b**: 3-MeC_6H_4	**3b**	98	91
3	**2c**: 3-FC_6H_4	**3c**	98	98
4	**2d**: cinnamyl	**3d**	80	90
5	**2e**: 2-furyl	**3e**	60	92
6	**2f**: 2-furyl-propenyl	**3f**	97	98

[a] Nitro-Mannich additions were carried out using 5 mmol of nitromethane, 0.5 mmol of imine in CH_2Cl_2 (0.5 M) at −10 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of nitro-Mannich addition products.
[c] Determined by chiral HPLC analysis.
[d] Reaction was run for 24 h.

While cinchona alkaloid-derived thioureas have previously been utilized to study the nitro-Mannich addition of nitromethane to acyl imines, there has yet to be a thorough investigation using nitroethane as a carbon nucleophile. We attempted to extend the scope of our work by investigating nitroethane additions to the substrates used in Table 1. The same general reaction conditions proved to be useful for nitroethane additions, affording *syn*-addition products of similar yields (73–98%) and enantioselectivities (90–97%) (Table 2, entries 1–6). The nitroethane additions produced β-nitroamines **5a**–**5f** with adjacent stereocenters and established that the alkaloid-derived thiourea also catalyzed with high diastereoselectivity (ranging from 82 to 97%). Lower yields were obtained for the more electrophilic acyl imines **5d** and **5e**; however, there was no compromise in enantio- or diastereoselectivity.

A further expansion of the methodology was investigated upon the enantio- and diastereomeric success of the nitro-Mannich nucleophiles. The Mannich reaction parallels the nitro-Mannich in both the electrophilic substrate (acyl imine) and the nucleophilic additive (carbon nucleophile); it was

Table 2. Asymmetric nitro-Mannich additions of nitroethane[a]

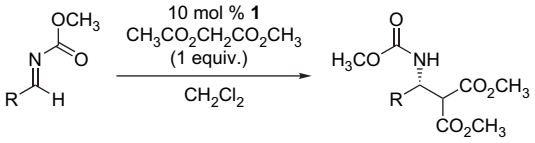


4a–f **5a–f**

Entry	R	Adduct	Yield (%)[b]	ee (%)[c]	de (%)[d]
1[e]	**4a**: Ph	**5a**	96	94	83
2	**4b**: 3-MeC_6H_4	**5b**	98	97	90
3	**4c**: 3-FC_6H_4	**5c**	98	91	97
4	**4d**: cinnamyl	**5d**	80	90	92
5	**4e**: 2-furyl	**5e**	73	97	82
6	**4f**: 2-furyl-propenyl	**5f**	90	97	83

[a] Nitro-Mannich additions were carried out using 5 mmol of nitroethane and 0.5 mmol of imine in CH_2Cl_2 (0.5 M) at −10 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of nitro-Mannich addition products.
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR analysis.
[e] Reaction was run for 24 h.

Table 3. Asymmetric Mannich additions of dimethyl malonate[a]



6a–f **7a–f**

Entry	R	Adduct	Yield (%)[b]	ee (%)[c]
1[d]	**6a**: Ph	**7a**	98	92
2	**6b**: 3-MeC_6H_4	**7b**	97	86
3	**6c**: 3-FC_6H_4	**7c**	98	90
4	**6d**: cinnamyl	**7d**	97	90
5[e]	**6e**: 2-furyl	**7e**	65	94
6[e]	**6f**: 2-furyl-propenyl	**7f**	96	90

[a] Mannich reactions were carried out using 0.5 mmol of dimethyl malonate and 0.5 mmol of imine in CH_2Cl_2 at −35 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of Mannich products.
[c] Determined by chiral HPLC analysis.
[d] Reaction was run for 24 h.
[e] Reactions were run at −50 °C.

believed that this parallel should allow the HQ-derived thiourea to asymmetrically catalyze direct Mannich additions as well. To test this hypothesis, methyl benzylidenecarbamate **6a**, hydroquinine-derived thiourea catalyst, and dimethyl malonate in CH_2Cl_2 were reacted at −35 °C to produce the corresponding Mannich adduct **7a** in 98% yield and 92% ee (Table 3). With this encouraging result, the same substrates were employed in the reaction and similar good results were obtained, with yields ranging from 65 to 98% and enantioselectivities from 86 to 94%. The more electrophilic substrates **6e** and **6f** required lower reaction temperatures to achieve the same levels of enantioselectivity. These results highlight the utility of the cinchona alkaloid-derived thioureas, and the broad range of reaction conditions that may be used.

The relative stereochemistry and absolute stereochemistry of the products obtained were determined via optical rotation comparisons to known literature compounds.[20] The absolute stereochemistry of products **3a**–**3f** and **7a**–**7f** was determined to be (*S*) while the nitroethane addition was determined to be (1*S*,2*R*) by analogy with the corresponding allyl carbamates.

Aside from the reported utilities of the nitro-Mannich additions, we have also developed a method for transforming the Mannich products into their corresponding β-amino esters. Dixon et al. reported a decarboxylation via reflux in toluene for 12 h.[14d] We successfully transformed the malonate addition products to the β-amino esters using microwave irradiation, drastically reducing the previously reported reaction time, with only slight racemization of the resultant ester (Fig. 2).

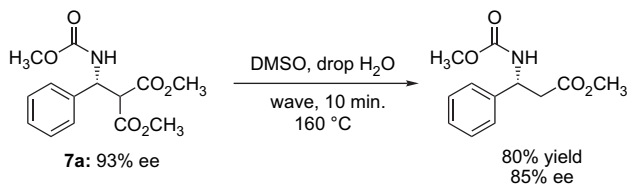


Figure 2. Decarboxylation of Mannich product **7a**.

3. Modeling

Catalyst **1** is capable of promoting the addition of stabilized anions to acyl imines with high levels of enantiodiscrimination. The high degree of selectivity observed in these reactions indicates a catalyst-associated complex with a high degree of coordination.[10a,b] We have developed a model that accounts for the observed diastereo- and enantioselectivity (Fig. 3). We modeled both nitromethane anion and malonate anion complex with thiourea catalyst **1**. A MMFF conformation search[21] identified the lowest energy conformer for each complex with the quinoline ring blocking one face of the nucleophile and the thiourea moiety forming a hydrogen bond with the nucleophile.[21a,22] The aromatic ring of the thiourea forms an edge-face contact with the nucleophile. Modeling of the methyl benzylidenecarbamate *re*-face attack of the nucleophile-catalyst complex provides a model of selectivity for the reactions.[23] The approach of the electrophile places the hydrogen of the energy-minimized *Z*-aldimine in line with the catalyst. Also depicted in Figure 3, the benzylidene aromatic ring forms an edge-face interaction with the thiourea arene. The nitromethane catalyst complex depicted in Figure 3A was modeled with *re*- and *si*-facial attack of the nucleophile. The calculated energy difference between the two binding modes was found to be 1.6 kcal/mol in favor of *si*-facial attack of the nucleophile. While the energy difference is modest, the model is in agreement with the preferred sense of selectivity (Table 2). These models illustrate the important interactions of the nucleophile with the catalyst. They also provide some insight into the factors that result in a selective reaction and how this class of thiourea catalysts is selective for such a wide-range of reactions.

4. Conclusion

In summary, hydroquinine-derived thiourea **1** was found to catalyze nucleophilic additions of nitroalkanes and dimethyl malonate to methyl carbamate acyl imines with good yields and high enantioselectivities. Catalyst **1** is a representative from a class of cinchona alkaloid-derived thiourea catalysts that promote a wide-range of reactions asymmetrically. The generality of these catalysts guarantees their use in the catalytic reaction methodology development. Future work includes the expansion of the methodology to different substrates and investigation of the synthetic utility of the addition products.

5. Experimental

5.1. General procedure for nitro-Mannich addition of nitroalkanes to acyl imines

5.1.1. Synthesis of product 3a: ((*S*)-2-nitro-1-phenylethyl)-carbamic acid methyl ester. To an oven-dried reaction vessel under argon were added acyl imine **2a** and thiourea catalyst **1** in CH_2Cl_2, (0.5 M). The mixture was cooled to −10 °C and then nitromethane (10 equiv) was added. The reaction was run to completion (24 h) and the crude mixture was run through a silica gel plug, eluted with ethyl acetate (5 mL). The filtrate was concentrated under

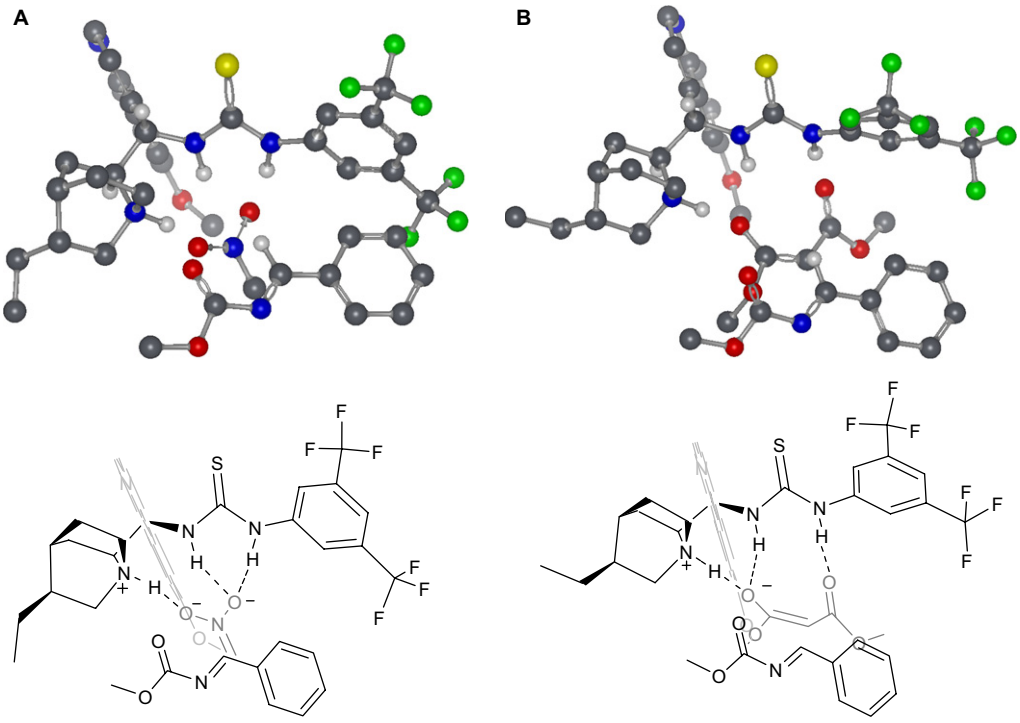


Figure 3. Proposed catalytically active thiourea **1** complexes (MMFF) approaching the *re*-face of methyl benzylidenecarbamate. (A) Nitromethane complex. (B) Malonate complex.

reduced pressure and the crude product was purified by flash chromatography over silica gel (eluted with 15–30% ethyl acetate in hexanes) to afford the nitro-Mannich adduct.

5.2. General procedure for Mannich addition of dimethyl malonate to acyl imines

5.2.1. Synthesis of product 7a: 2-((*R*)-methoxycarbonyl-amino-phenyl-methyl)-malonic acid dimethyl ester. To an oven-dried reaction vessel under argon were added acyl imine **2a** and thiourea catalyst **1** in CH_2Cl_2 (0.5 M). The mixture was cooled to −35 °C and dimethyl malonate (1 equiv) was added. The reaction was run to completion (24 h) and the crude mixture was run through a silica gel plug, eluted with ethyl acetate (5 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography over silica gel (eluted with 15–30% ethyl acetate in hexanes) to afford the Mannich adduct.

Please refer to table footnotes for specific reaction times and temperature of each respective product.

5.2.2. Compound 3a: ((*S*)-2-nitro-1-phenyl-ethyl)-carbamic acid methyl ester. Yield: 0.102 g (91%), white solid; ee: 93%; HPLC analysis, t_R minor: 9.72 min, t_R major: 15.91 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.28 (m, 5H), 5.42 (m, 2H), 4.84 (br s, 1H), 4.70 (m, 1H), 3.69 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 136.7, 129.1, 128.7, 126.3, 78.6, 53.1, 52.6; IR (thin film, cm^{-1}): 3322, 2954, 1686, 1534, 1256, 1049; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{10}H_{12}N_2O_4Na$: 247.0695, found: 247.0695; $[\alpha]_D^{23}$ +26.7 (*c* 1.00, $CHCl_3$).

5.2.3. Compound 3b: ((*S*)-2-nitro-1-*m*-tolyl-ethyl)-carbamic acid methyl ester. Yield: 0.035 g (98%), white solid; ee: 91%; HPLC analysis, t_R minor: 4.16 min, t_R major: 9.58 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.06 (m, 5H), 5.38 (m, 1H), 4.82 (br s, 1H), 4.70 (m, 2H), 3.68 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 138.8, 136.6, 129.4, 128.9, 127.0, 123.2, 78.5, 76.6, 53.1, 52.4. 21.3; IR (thin film, cm^{-1}): 3316, 3025, 2956, 1702, 1554, 1454, 1378, 1261, 1060, 913, 781; HRMS calcd for $(M+H)^+$ $C_{11}H_{14}N_2O_4$: 238.0948, found 239.1031; $[\alpha]_D^{23}$ −9.4 (*c* 1.10, $CHCl_3$).

5.2.4. Compound 3c: ((*S*)-1-(3-fluoro-phenyl)-2-nitro-ethyl)-carbamic acid methyl ester. Yield: 0.036 g (98%), light yellow solid; ee: 98%; HPLC analysis, t_R minor: 8.56 min, t_R major: 13.55 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.22 (m, 2H), 7.08–6.92 (m, 3H), 6.14 (d, *J*=8.4 Hz, 1H), 5.54 (br s, 1H), 5.37 (m, 2H), 5.09 (m, 1H), 3.69 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 164.3, 161.2, 155.9, 130.1, 122.3, 117.6, 113.7, 83.7, 55.6, 53.7; IR (thin film, cm^{-1}): 3659, 3323, 2924, 1705, 1595, 1533, 1354, 1258, 1058, 775; HRMS calcd for $(M+H)^+$ $C_{10}H_{11}N_2O_4$: 242.0697, found: 243.0781; $[\alpha]_D^{23}$ +13.9 (*c* 1.00, $CHCl_3$).

5.2.5. Compound 3d: ((*E*)-(*S*)-1-nitromethyl-3-phenyl-allyl)-carbamic acid methyl ester. Yield: 0.029 g (80%), light yellow solid; ee: 90%; HPLC Analysis, t_R minor: 9.27 min, *t* major: 17.92 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 6.63 (d, *J*=6.8 Hz, 1H), 6.14 (dd, *J*=6.4, 6.8 Hz, 1H), 5.38 (br s, 1H), 4.96–4.94 (m, 1H), 4.70–4.60 (m, 2H), 3.71 (s, 3H); ^{13}C NMR

(75.0 MHz, $CDCl_3$): δ 156.0, 133.7, 128.6, 128.41, 127.9, 127.1, 126.5, 123.3, 80.9, 52.7, 51.4; IR (thin film, cm^{-1}): 3325, 2955, 2926, 1717, 1550, 1520, 1449, 1538, 1246, 1065, 969, 748; HRMS calcd for $(M+H)^+$ $C_{12}H_{14}N_2O_4$: 250.0954, found: 251.1032; $[\alpha]_D^{23}$ +38.9 (*c* 0.77, $CHCl_3$).

5.2.6. Compound 3e: ((*R*)-1-furan-2-yl-2-nitro-ethyl)-carbamic acid methyl ester. Yield: 0.039 g (60%), orange solid; ee: 92%; HPLC analysis, t_R minor: 9.04 min, t_R major: 9.92 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J*=1.6 Hz, 1H), 6.33 (dd, *J*=3.4, 1.6 Hz, 1H), 6.30 (d, *J*=2.8 Hz, 1H), 5.49 (m, 1H), 5.43 (br s, 1H), 4.86 (dd, *J*=16.0, 8.0 MHz, 1H), 4.72 (dd, *J*=13.2, 5.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.0, 149.0, 143.0, 110.7, 107.9, 76.3, 52.7, 47.5; IR (thin film, cm^{-1}): 3311, 3127, 2954, 2933, 1702, 1553, 1265; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_8H_{10}N_2O_5Na$: 237.0644, found: 237.0487; $[\alpha]_D^{23}$ +30.3 (*c* 0.60, $CHCl_3$).

5.2.7. Compound 3f: ((*S*)-3-furan-2-yl-1-nitromethyl-allyl)-carbamic acid methyl ester. Yield: 0.035 g (97%), yellow solid; ee: 98%; HPLC analysis, t_R minor: 12.55 min, t_R major: 18.37 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*=2.0 Hz, 1H), 6.45 (d, *J*=16.0 Hz, 1H), 6.35 (dd, *J*=3.2, 2.0 Hz, 1H), 6.28 (d, *J*=3.2 Hz, 1H), 6.07 (dd, *J*=16.0, 6.4 Hz, 1H), 5.25 (br s, 1H), 4.92 (m, 1H), 4.66 (m, 1H), 4.59 (dd, *J*=12.8, 4.8 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.0, 151.0, 142.7, 121.9, 121.5, 111.5, 109.9, 78.0, 52.6, 51.0; IR (thin film, cm^{-1}): 3313, 2956, 2924, 2853, 1700, 1550, 1378, 1256; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{10}H_{12}N_2O_5Na$: 263.0800, found: 263.0644; $[\alpha]_D^{23}$ +36.9 (*c* 1.00, $CHCl_3$).

5.2.8. Compound 5a: ((1*S*,2*R*)-2-nitro-1-phenyl-propyl)-carbamic acid methyl ester. Yield: 0.107 g (96%), white solid; ee: 94%, de: 83%; HPLC analysis, t_R minor: 18.82 min, t_R major: 23.16 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=90:10, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 3H), 7.22–7.20 (m, 2H), 5.72 (br s, 1H, minor), 5.49 (br s, 1H, major), 5.22 (dd, *J*=9.0, 5.8 Hz, 1H, major), 5.13 (s, 1H, minor), 4.92 (m, 1H), 3.67 (s, 3H), 1.52 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 136.2, 128.9, 128.7, 126.7, 85.5, 57.8, 52.5, 15.1; IR (thin film, cm^{-1}): 3311, 2924, 2853, 1691, 1544, 1291, 1018; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{11}H_{14}N_2O_4Na$: 261.0954, found: 261.0851; $[\alpha]_D^{23}$ +40.1 (*c* 1.00, $CHCl_3$).

5.2.9. Compound 5b: ((1*S*,2*R*)-2-nitro-1-*m*-tolyl-propyl)-carbamic acid methyl ester. Yield: 0.037 g (98%), white solid; ee: 97%, de: 90%; HPLC analysis, t_R minor: 11.91 min, t_R major: 19.11 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.21 (m, 2H), 7.13–7.11 (m, 1H), 7.03–6.98 (m, 2H), 5.42 (m, 1H), 4.18 (m, 1H), 4.89 (br s, 1H), 3.67 (s, 3H), 2.32 (s, 3H), 1.51 (d, *J*=6.4 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 138.5, 129.2, 128.7, 128.5, 126.8, 123.6, 85.57, 57.7, 52.7, 21.3, 21.2; IR (thin film, cm^{-1}): 3326, 2954, 2857, 1732, 1547, 1449, 1355, 1243, 1027, 913, 783, 731; HRMS calcd for $(M+H)^+$ $C_{12}H_{16}N_2O_4$: 252.1105, found: 253.1188; $[\alpha]_D^{23}$ +17.9 (*c* 0.86, $CHCl_3$).

5.2.10. Compound 5c: ((1*S*,2*R*)-1-(3-fluoro-phenyl)-2-nitro-propyl)-carbamic acid methyl ester. Yield: 0.037 g (98%), light yellow solid; ee: 91%, de: 97%; HPLC analysis, t_R minor: 9.92 min, t_R major: 14.12 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 2H), 7.04–6.93 (m, 3H), 5.50 (br s, 1H), 5.22 (m, 1H), 4.89 (m, 1H), 3.68 (s, 3H), 1.53 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 164.5, 161.2, 156.2, 130.6, 122.5, 115.6, 114.1, 85.3, 57.3, 52.7, 15.1; IR (thin film, cm^{-1}): 3316, 3067, 2955, 1703, 1593, 1550, 1452, 1357, 1248, 1026, 877, 786; HRMS calcd for $(M+H)^+$ $C_{11}H_{13}FN_2O_4$: 256.0854; found: 257.0938; $[\alpha]_D^{23}$ +51.0 (*c* 0.90, $CHCl_3$).

5.2.11. Compound 5d: ((*E*)-(*S*)-1-((*R*)-1-nitro-ethyl)-3-phenyl-allyl)-carbamic acid methyl ester. Yield: 0.032 g (80%), light yellow solid; ee: 90%, de: 92%; HPLC analysis, t_R minor: 12.30 min, t_R major: 21.25 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09–6.91 (m, 5H), 6.37 (d, *J*=16.4 Hz, 1H), 5.81 (dd, *J*=7.2, 7.6 Hz, 1H), 5.04 (br s, 1H), 4.59 (m, 1H), 4.44 (m, 1H), 3.46 (s, 3H), 1.31 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 135.9, 132.4, 128.5, 127.2, 126.6, 126.9, 85.1, 55.3, 52.5, 29.6; IR (thin film, cm^{-1}): 3323, 2954, 2927, 1731, 1547, 1519, 1296, 1247, 1197, 1049, 968, 744; HRMS calcd for $(M+H)^+$ $C_{13}H_{16}N_2O_4$: 263.1110, found: 264.1010; $[\alpha]_D^{23}$ +58.6 (*c* 0.52, $CHCl_3$).

5.2.12. Compound 5e: ((1*R*,2*R*)-1-furan-2-yl-2-nitro-propyl)-carbamic acid methyl ester. Yield: 0.025 g (73%), light yellow solid; ee: 97%, de: 82%; HPLC analysis, t_R minor: 7.38 min, t_R major: 8.18 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J*=1.2 Hz, 1H), 6.31 (dd, *J*=3.4, 1.8 Hz, 1H), 6.27 (d, *J*=3.2 Hz, 1H), 5.55 (br s, 1H, minor), 5.45 (br s, 1H, major), 5.35 (dd, *J*=9.0, 6.0 Hz, 1H, major), 5.27 (br m, 1H, minor), 5.04 (m, 1H, minor), 4.88 (m, 1H, major), 3.70 (s, 3H), 1.57 (d, *J*=9.2 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 148.7, 143.0, 110.6, 108.6, 84.2, 52.8, 52.1, 15.3; IR (thin film, cm^{-1}): 3310, 2955, 2924, 1701, 1550, 1235, 1013, 743; HRMS (*m*/*z*) $(M+Na)^+$ calcd for $C_9H_{12}N_2O_5Na$: 251.0487, found: 251.0644; $[\alpha]_D^{23}$ +49.6 (*c* 0.50, $CHCl_3$).

5.2.13. Compound 5f: ((*S*)-3-furan-2-yl-1-((*R*)-1-nitro-ethyl)-allyl)-carbamic acid methyl ester. Yield: 0.065 g (90%), yellow oil; ee: 97%, de: 83%; HPLC analysis, t_R minor: 22.91 min, t_R major: 30.38 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=95:5, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*=1.6 Hz, 1H), 6.43 (d, *J*=16.0 Hz, 1H), 6.35 (dd, *J*=3.2, 2.0 Hz, 1H), 6.27 (d, *J*=3.6 Hz, 1H), 5.98 (dd, *J*=15.6, 7.6 Hz, 1H), 5.26 (d, *J*=8.4 Hz, 1H), 4.79 (m, 1H), 4.67 (m, 1H), 3.69 (s, 3H), 1.56 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 151.1, 142.6, 123.0, 121.4, 111.4, 108.8, 85.0, 56.0, 52.6, 15.9; IR (thin film, cm^{-1}): 3375, 2958, 2921, 2850, 1709, 1550, 1259, 733; HRMS (*m*/*z*) $(M+Na)^+$ calcd for $C_{11}H_{14}N_2O_5Na$: 277.0746, found: 277.0800; $[\alpha]_D^{23}$ +5.3 (*c* 1.00, $CHCl_3$).

5.2.14. Compound 7a: 2-((*R*)-methoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester. Yield: 0.145 g (98%), white solid; ee: 92%; HPLC analysis, t_R

minor: 12.42 min, t_R major: 15.11 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 6.36 (d, J=8.0 Hz, 1H), 5.48 (m, 1H), 3.90 (d, J=5.6 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.6, 167.6, 156.5, 139.3, 128.9, 128.0, 126.4, 56.7, 54.1, 53.2, 52.8, 52.5; IR (thin film, cm^{-1}): 3274, 2954, 2924, 1754, 1739, 1688, 1550, 1434, 1290, 1263, 1149; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{14}H_{17}NO_6Na$: 318.0954, found: 318.0954; $[\alpha]_D^{23}$ −1.4 (*c* 1.00, $CHCl_3$).

5.2.15. Compound 7b: 2-((*R*)-methoxycarbonylamino-*m*-tolyl-methyl)-malonic acid dimethyl ester. Yield: 0.045 g (97%), white solid; ee: 86%; HPLC analysis, t_R minor: 9.21 min, t_R major: 11.57 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.17 (m, 3H), 7.07–7.06 (m, 2H), 6.36 (d, J=7.2 Hz, 1H), 5.46 (br s, 1H), 3.88 (br s, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.2, 167.2, 156.2, 138.9, 138.2, 128.5, 128.4, 126.8, 123.0, 56.3, 53.8, 52.8, 52.4, 52.1, 21.3; IR (thin film, cm^{-1}): 3287, 2955, 2926, 1748, 1693, 1545, 1438, 1354, 1293, 1194, 1149, 1049, 1013, 913, 786; HRMS calcd for (M+H)$^+$ $C_{17}H_{21}NO_6$: 335.1369, found 336.2093; $[\alpha]_D^{23}$ −1.7 (*c* 1.10, $CHCl_3$).

5.2.16. Compound 7c: 2-((*R*)-(3-fluoro-phenyl)-methoxycarbonylamino-methyl)-malonic acid dimethyl ester. Yield: 0.092 g (98%), light yellow solid; ee: 90%; HPLC analysis, t_R minor: 16.67 min, t_R major: 20.19 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 7.06–6.91 (m, 3H), 6.42 (d, J=8.4 Hz, 1H), 5.48 (d, J=4.4 Hz, 1H), 3.89 (d, J=1.3 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.9, 167.4, 164.5, 161.2, 142.1, 130.2, 122.0, 114.7, 113.5, 63.7, 62.3, 52.8, 52.5; IR (thin film, cm^{-1}): 3316, 3067, 2955, 1703, 1593, 1550, 1452, 1357, 1248, 1026, 877, 786; HRMS calcd for (M+H)$^+$ $C_{16}H_{18}FNO_6$: 339.1118, found: 340.0278; $[\alpha]_D^{23}$ −15.4 (*c* 1.46, $CHCl_3$).

5.2.17. Compound 7d: 2-((*E*)-(*S*)-1-methoxycarbonylamino-3-phenyl-allyl)-malonic acid dimethyl ester. Yield: 0.046 g (97%), light yellow solid; ee: 90%; HPLC analysis, t_R minor: 9.18 min, t_R major: 11.35 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 6.57 (d, J=16.0 Hz, 1H), 6.18 (dd, J=6.8, 6.8 Hz, 1H), 5.86 (br s, 1H), 5.02 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.2, 156.2, 136.0, 132.4, 128.5, 127.9, 126.6, 125.9, 55.3, 52.8, 52.6, 52.3; IR (thin film, cm^{-1}): 3376, 2955, 2854, 1735, 1511, 1442, 1354, 1240, 1197, 1069, 1034, 970, 785; HRMS calcd for (M)$^+$ $C_{16}H_{19}NO_6$: 321.1212, found: 321.1110; $[\alpha]_D^{23}$ +4.5 (*c* 0.66, $CHCl_3$).

5.2.18. Compound 7e: 2-((*R*)-furan-2-yl-methoxycarbonylamino-methyl)-malonic acid dimethyl ester. Yield: 0.022 g (65%), light yellow oil; ee: 94%; HPLC analysis, t_R minor: 5.96 min, t_R major: 6.57 min [Chiralcel OD chiral column, hexanes:IPA=90:10, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J=1.8, 0.6 Hz, 1H), 6.28 (dd, J=3.4, 1.8 Hz, 1H), 6.21 (dd, J=3.2, 1.2 Hz, 1H), 6.09 (d, J=8.8 Hz, 1H), 5.56 (dd, J=9.4, 4.2 Hz, 1H), 4.02 (d, J=4.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.1, 167.0, 156.3, 151.8, 142.2, 110.5, 106.9, 53.8, 53.0, 52.7, 52.4, 48.7; IR (thin film, cm^{-1}): 3357, 2923, 2852, 1725, 1503, 1436, 1230, 1147; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{12}H_{15}NO_7Na$: 308.0746, found: 308.0746; $[\alpha]_D^{23}$ +12.7 (*c* 1.00, $CHCl_3$).

5.2.19. Compound 7f: 2-((*S*)-3-furan-2-yl-1-methoxycarbonylamino-allyl)-malonic acid dimethyl ester. Yield: 0.033 g (96%), a yellow oil; ee: 97%; HPLC analysis, t_R minor: 12.16 min, t_R major: 24.21 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J=1.6 Hz, 1H), 6.40 (d, J=15.2 Hz, 1H), 6.33 (dd, J=3.2, 2.0 Hz, 1H), 6.23 (d, J=3.2 Hz, 1H), 6.09 (dd, J=15.4, 6.6 Hz, 1H), 5.85 (d, J=10.4 Hz, 1H), 4.99 (br s, 1H), 3.74 (s, 6H), 3.66 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 167.3, 151.4, 142.1, 124.2, 124.2, 120.4, 111.2, 108.8, 55.0, 52.6, 52.4, 52.1; IR (thin film, cm^{-1}): 3379, 2956, 2852, 1724, 1511, 1436, 1232, 729; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{12}H_{15}NO_7Na$: 334.0903, found: 334.0903; $[\alpha]_D^{23}$ +5.6 (*c* 1.00, $CHCl_3$).

Acknowledgements

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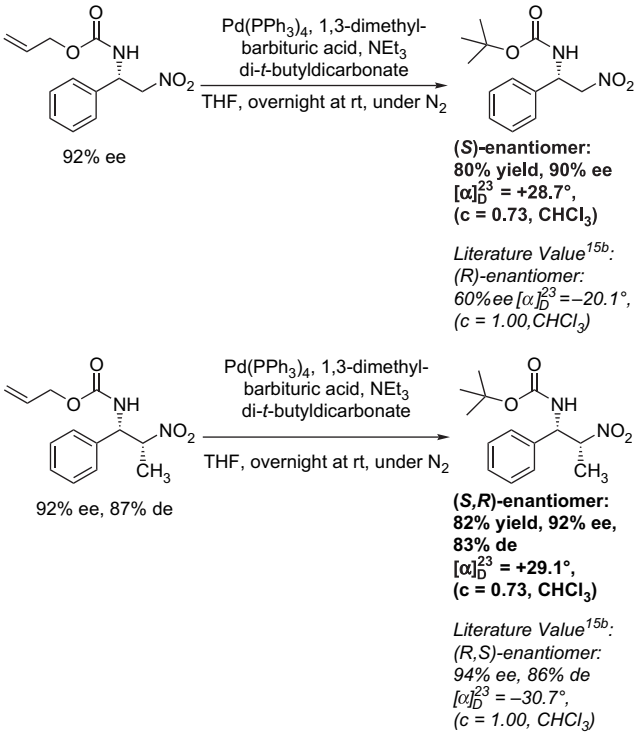

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Asymmetric ammonium ylid rearrangements: the effect of nitrogen asymmetry

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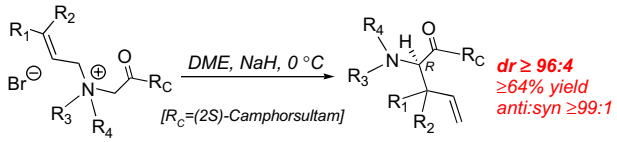
Abstract—[2,3]-Sigmatropic rearrangements of allylic ammonium ylids derived from glycinoylcamphorsultams are highly selective in terms of relative *and* absolute stereocontrol only when acyclic alkenes are present. When chiral esters of ylids derived from *N*-methyltetrahydropyridine ('NMTP') undergo rearrangement, the reactions show exclusive cis-stereoselectivity but the products are obtained with virtually no absolute stereocontrol. These observations support the notion that sigmatropic rearrangements of *N*-chiral ammonium ylids are controlled by nitrogen stereogenicity.

1. Introduction

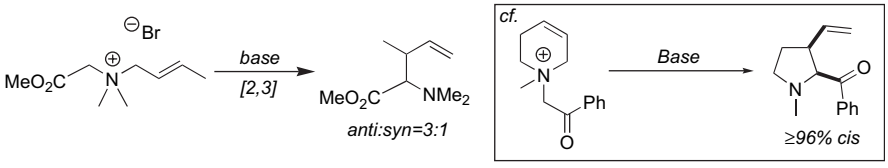
We have recently described our studies on the asymmetric [2,3]-sigmatropic rearrangements of allyl ammonium ylids derived from *N*-glycinoylcamphorsultam, which proceed with high levels of stereoselectivity (Scheme 1).[1]



Scheme 1.

[2,3]-Rearrangements of ammonium ylids derived from *N*-methyltetrahydropyridine ('NMTP') are inherently more stereoselective than nonasymmetric rearrangements of acyclic allylic ylids, due to the preference of a rigid *endo*-configured transition state (Scheme 2).[2]

Furthermore, NMTP ylids contain a stereogenic nitrogen atom[†] (yet, to our knowledge, simple[‡] enantiomerically-enriched ammonium ylids have never been prepared); though there is a paucity of examples of sigmatropic rearrangements of ammonium ylids involving N→C chirality transfer, the work of Hill and Chan[3] has shown that an asymmetric nitrogen atom *can* lead to enantioselective rearrangement reactions, which suggested in turn that nitrogen in NMTP ylids should exert a powerful stereotopic influence. However, the preparation of enantiomerically-pure NMTP ylids is currently an inaccessible goal, and we, therefore, initially sought to carry out stereoselective N-alkylations of chiral derivatives of NMTP as a means of preparing *diastereomerically* enriched ylids. We were also cognizant of the fact that, even if these alkylations proved unselective, the presence of two chiral elements in, say, sultam ylids **1** could in theory leads to an internal double asymmetric induction and a concomitant kinetic resolution to give only one of the two possible pyrrolidine products of rearrangement, plus a single diastereoisomer of unreacted salt precursor (Scheme 3).



Scheme 2.

* Corresponding author. E-mail: j.b.sweeney@rdg.ac.uk
† *N*-chiral ammonium salts are historic compounds, having been prepared and used to greatly effect during the famous debate concerning the 'quinquevalence' of nitrogen: see, for instance, Pope, W. J.; Peachey, S. J. *J. Chem. Soc.*, **1899**, 1127.
‡ i.e., ammonium ylids where nitrogen is the only asymmetric component.

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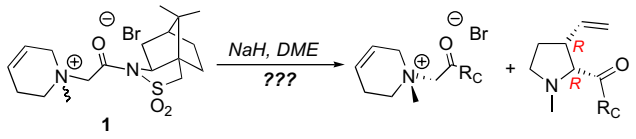
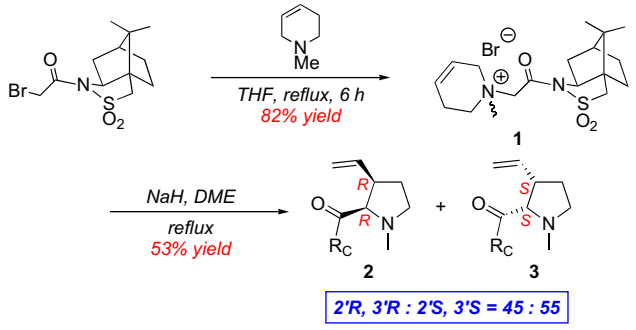


Scheme 3.

We report here that the [2,3]-rearrangements of diastereomeric NMTP ylids are highly diastereoselective, but proceed with little control of absolute stereochemistry, indicating that the asymmetric nitrogen atom completely dominates the stereochemical course of the reaction.

2. Results and discussion

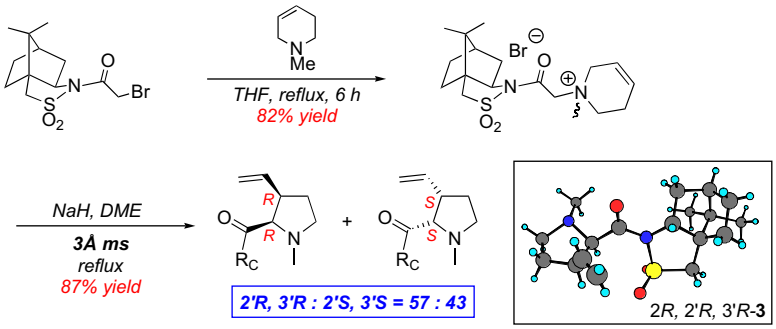
(2*S*)-Camphorsultam-NMTP salt **1** was synthesized in a routine manner from *N*-bromoacyl camphorsultam,[4] by alkylation with NMTP in THF at reflux (Scheme 3). Though many different conditions for this reaction were examined, we were unable to prepare this salt as anything more than a ~50:50 mixture of diastereoisomers (as judged from ^{1}H NMR spectra), indicating that the asymmetric auxiliary has little or no effect upon the diastereoselectivity of the N-alkylation reaction. In addition, to date we have found no means of separating the diastereomeric salts using a range of chromatographic and crystallization methods. When **1** was treated with stoichiometric[§] NaH in DME at 0 °C, no reaction occurred and starting material was recovered quantitatively; when the process was carried out in the same solvent at reflux (Scheme 4), [2,3]-rearrangement proceeded to give a pair of diastereomeric pyrrolidine carboxylate derivatives, **2** and **3**, which were tentatively assigned cis-stereochemistry by analogy with the racemic reactions previously carried out in our labs. These isomers were obtained in approximately equal amounts, indicating that virtually no selectivity had been induced in the absolute configuration of the products during the rearrangement reaction.



Scheme 4.

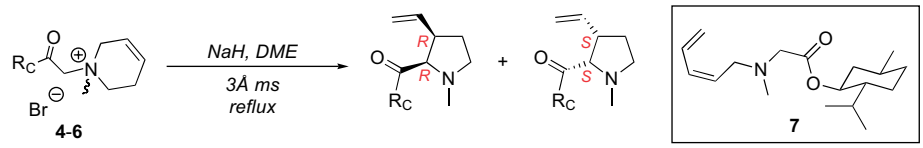
The rearrangement reaction could not be persuaded to proceed at lower temperatures for salts derived from either antipode of camphorsultam, though the yield of the process could be improved by the addition of 3 Å molecular sieves to the reaction medium. X-ray analysis of 2*R*,2′*R*,3′*R*-product of rearrangement confirmed the original conclusion that the pyrrolidine carboxylates obtained were cis-configured (Scheme 5).

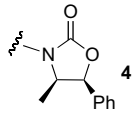
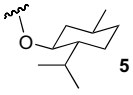
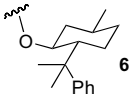
These initial data indicated two facts: firstly, the stereoselective N-alkylation of bromoacyl sultams is not feasible and, secondly, the NMTP ylids of either absolute configurations at nitrogen will undergo efficient rearrangement. We next investigated the preparation of NMTP salts by a reverse sequence of alkylation events, i.e., by acylmethylating tetrahydropyridine itself, and then carrying out a methylation reaction. However, under all of the conditions we have examined (using alkyl halides [with or without silver salts or other activators] or other electrophiles [triflates, oxonium salts, etc.]) the low or ambient-temperature alkylations of 2-(1′-tetrahydropyridinyl)acylsultams proceeded at a rate too slow to be practical (typically ≤5% yield of the salts would be obtained after 21 days reaction time). Furthermore, the very small amounts of salts isolated from these reactions did not seem to be enriched with either absolute configurations at nitrogen (though the deliquescent nature of the salts often precluded detailed analysis). Forced to consider, in the light of this experimental evidence, that perhaps the sultam auxiliary was too hindered, we next turned to other auxiliaries. Thus, oxazolidinone and menthyl derivatives of NMTP ylids were prepared using a range of alkylative procedures; once again, the only practical method to obtain the ylid precursors was by the alkylation of NMTP with the corresponding bromoacetylated auxiliaries. When these salts (**4**–**6**) were deprotonated and reacted in an analogous manner to the sultam ylids shown above, it was found that only the menthyl derivatives underwent efficient rearrangement; the oxazolidine-derived salt underwent preferential cleavage to give the parent heterocycle, even when the reaction was



Scheme 5.

[§] Reactions using *sub*-stoichiometric base are inefficient, and to date we have seen no evidence for kinetic resolution.



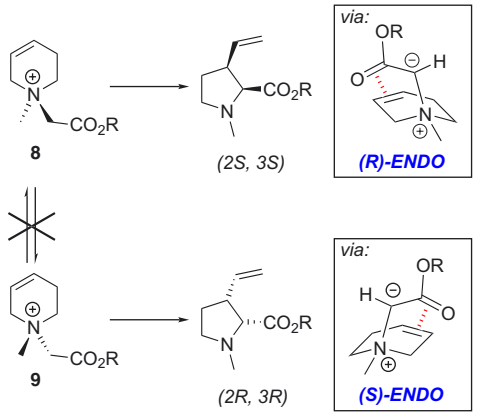
R_C	Yield/%	Dr (2'R, 3'R : 2'S, 3'S)
 4	0[a]	-
 5	53	51:49
 6	54	55:45

[a] (4R, 5S)-4-Methyl-5-phenyloxazolidinone obtained

Scheme 6.

carried out in the presence of desiccants (such as molecular sieves) (Scheme 6). Even where rearrangement did occur, side reactions were observed, such as the obtention of elimination product **7**[5] from the rearrangement reaction of menthyl salt **5**.

Thus, it is clear from these data that nitrogen stereogenicity dominates the course of the rearrangements of NMTP ylids; N_R-isomers **8** will lead to 2*S*,3*S*-pyrrolidines, whilst the N_S-isomers **9** will give 2*R*,3*R*-products (Scheme 7). Moreover, the effect of any chiral auxiliary is so small as to preclude any kinetic resolution and both ylid diastereoisomers undergo efficient rearrangement. Given the dominant effect of nitrogen chirality, these data also provide the tantalizing prospect that enantiomerically pure NMTP ylids can indeed be used to prepare enantiomerically enriched pyrrolidine carboxylates.



Scheme 7.

3. Conclusion

The [2,3]-sigmatropic rearrangements of NMTP ylids are not rendered stereoselective, in terms of absolute stereocontrol, by the attachment of chiral substituents at the periphery of the molecules. In addition, the diastereoselective alkylation of tetrahydropyridine derivatives has proved to be an elusive transformation. The pursuit of methods to prepare simple enantiomerically-enriched *N*-chiral ylids continues to dominate our aspirations and we shall report in due course the results of our further studies in this arena.

4. Experimental

4.1. General

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[6] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl, toluene from sodium and dichloromethane from calcium hydride. Other chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded on Perkin–Elmer 881 or Paragon 1000 spectrophotometers. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on VG9090 or Fisons Autospec mass spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-250 or AX-400 spectrometers. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as parts per million downfield from tetramethylsilane and in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (*J*) are quoted in hertz.

Reactions involving chemicals or intermediates sensitive to air or moisture were conducted under a nitrogen or argon atmosphere in oven- or flame-dried apparatus. Flash chromatography was performed using Merck Kieselgel 60 or Fluka

Kieselgel 60 silica gel. Analytical thin-layer chromatography was performed using either precoated Merck Kieselgel 60 F_{254} glass-backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and was visualized under UV at 254 nm and by staining with iodine and/or an acidic ammonium molybdate dip.

4.2. *N*′-Methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide 1

A solution of *N*-methyl-1,2,3,6-tetrahydropyridine hydrochloride (5.0 g, 37.4 mmol) in 2 M aqueous sodium hydroxide (56.1 ml, 112.2 mmol, 3 equiv) was extracted with pentane (4×25 ml). The combined organic extracts were dried ($MgSO_4$) and removal of solvent in vacuo gave *N*-methyl-1,2,3,6-tetrahydropyridine as a colourless liquid (2.98 g, 82%), which was used without further purification. *N*-Bromoacetyl-(1*R*,2*S*)-bornane-10,2-sultam (1.73 g, 5.15 mmol) dissolved in THF (10 ml) was added dropwise over 5 min to a stirred solution of *N*-methyl-1,2,3,6-tetrahydropyridine (0.50 g, 5.15 mmol) in THF (10 ml) under nitrogen atmosphere. The reaction mixture was refluxed for 6 h during which the product began to precipitate. Once cooled, the mixture was triturated with petrol, the precipitate was collected over a glass sinter, washed with a small amount of methanol and the solvents were removed in vacuo to give *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)-methyl-1,2,3,6-tetrahydropyridinium bromide (1.82 g, 82%) as a colourless deliquescent solid; $[\alpha]_D^{20}$ +84.8 (*c* 1, $CHCl_3$); mp 178.2–180.5 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1697, 1603, 1342, 1170; δ_H (250 MHz, $CDCl_3$) 0.99 (3H, s), 1.15 (3H, s), 1.39–1.59 and 1.78–2.04 (7H, br m), 2.23 (1H, br m), 2.48 (1H, br m), 3.46 (2H, m), 3.55 (2H, m), 3.66 (1.5H, s), 3.69 (1.5H, s), 4.17 (1H, m), 4.53 (1H, br m), 4.65 (1H, br m), 4.83 (1H, br m), 5.37 (1H, br m), 5.74 (1H, br m), 6.03 (1H, br m); δ_C (62.5 MHz, $CDCl_3$) 20.2, 21.5, 21.8, 26.5, 33.3, 38.6, 45.4, 48.6, 49.8, 49.9, 53.1, 57.9, 58.6, 61.7, 65.1, 119.8, 125.0, 163.8; *m*/*z* (CI) 353.1878 (M^+-Br, $C_{18}H_{29}N_2O_3S$ requires 353.1899), 353 (11%), 339 (57), 110 (16), 96 (100), 82 (13), 42 (11).

4.3. (2′*R*,3′*R*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine 2 and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine 3

4.3.1. Method 1. Sodium hydride (27.6 mg, 1.15 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (0.50 g, 1.15 mmol) in DME (20 ml), under nitrogen atmosphere. The reaction mixture was heated at reflux for 16 h, after which it was cooled and diethyl ether (15 ml) was added. This mixture was then filtered through a small pad of Celite®, supported on a glass sinter, and washed well with further diethyl ether (2×10 ml). Solvents were removed in vacuo to give a solid, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to give (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (119 mg, 29%) and (2′*R*,3′*R*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (98 mg, 24%) as colourless crystalline solids.

(2′*R*,3′*R*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **2**: R_f 0.24 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ +135.4 (*c* 1, $CHCl_3$); mp 211.9–213.2 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1702, 1642, 1331, 1165; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, s), 1.05 (3H, s), 1.20–1.47 and 1.63–1.87 (5H, m), 1.93 (1H, m), 1.98 (1H, m), 2.00–2.12 (2H, m), 2.29 (3H, s), 2.32 (1H, ddd, *J* 7.6, 8.5, 8.7), 3.09 (1H, ddd, *J* 2.0, 8.5, 8.7), 3.15 (1H, dddd, *J* 7.5, 7.9, 8.0, 8.7), 3.36 (1H, d, *J* 13.8), 3.43 (1H, d, *J* 13.8), 3.71 (1H, d, *J* 8.4), 3.87 (1H, dd, *J* 5.2, 7.5), 4.84 (1H, dd, *J* 1.9, 9.9), 4.94 (1H, ddd, *J* 0.7, 1.9, 17.0), 5.70 (1H, ddd, *J* 9.7, 9.9, 17.0); δ_C (62.5 MHz, $CDCl_3$) 20.3, 21.3, 26.8, 31.5, 33.3, 38.9, 40.7, 45.0, 47.1, 48.0, 48.6, 53.7, 55.7, 65.7, 71.8, 116.3, 138.9, 171.3; *m*/*z* (CI) 353.1889 (MH^+, $C_{18}H_{29}N_2O_3S$ requires 353.1898), 353 (20%), 110 (100).

(2′*S*,3′*S*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **3**: R_f 0.32 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ +49.6 (*c* 1, $CHCl_3$); mp 154.6–156.5 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1693, 1642, 1334, 1165; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, s), 1.10 (3H, s), 1.20–1.29 and 1.72–1.87 (5H, m), 1.89 (1H, m), 1.98 (1H, m), 2.02–2.16 (2H, m), 2.31 (3H, s), 2.47 (1H, ddd, *J* 7.1, 8.7, 8.8), 3.01 (1H, ddd, *J* 2.5, 8.7, 8.8), 3.12 (1H, dddd, *J* 8.4, 8.5, 8.5, 8.6), 3.37 (1H, d, *J* 13.8), 3.46 (1H, d, *J* 13.8), 3.85 (1H, dd, *J* 5.4, 7.2), 3.85 (1H, d, *J* 8.4), 4.90 (1H, ddd, *J* 0.7, 1.9, 10.1), 4.98 (1H, ddd, *J* 1.0, 1.9, 17.1), 5.77 (1H, ddd, *J* 8.5, 10.1, 17.1); δ_C (62.5 MHz, $CDCl_3$) 20.3, 21.4, 26.7, 31.6, 33.4, 39.3, 40.5, 45.2, 46.6, 48.1, 48.8, 53.7, 55.8, 65.9, 71.5, 116.1, 139.1, 171.4; *m*/*z* (CI) 353.1877 (MH^+, $C_{18}H_{29}N_2O_3S$ requires 353.1898), 353 (30%), 110 (100).

4.3.2. Method 2. Sodium hydride (55 mg, 2.30 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (1.00 g, 2.30 mmol) in DME (40 ml) containing molecular sieves, under nitrogen atmosphere. The reaction mixture was heated at reflux for 16 h, after which it was cooled and diethyl ether (30 ml) was added. This mixture was then filtered through a small pad of Celite® supported on a glass sinter, and washed well with further diethyl ether (2×15 ml). Solvents were removed in vacuo to give a solid, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to give (2′*R*,3′*R*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)-carbonyl-3′-ethenylpyrrolidine **2** (278 mg, 34%) and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **3** (352 mg, 43%) as a colourless crystalline solids (data as previously recorded).

4.4. *N*′-Methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (*ent*-1)

Following the method described above, *N*-bromoacetyl-(1*S*,2*R*)-bornane-10,2-sultam (1.73 g, 5.15 mmol) dissolved in THF (10 ml) was added to a stirred solution of *N*-methyl-1,2,3,6-tetrahydropyridine (0.50 g, 5.15 mmol) in THF (10 ml) to give *N*′-methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (1.78 g, 80%) as a colourless deliquescent solid; $[\alpha]_D^{20}$ −79.7 (*c* 1, $CHCl_3$), other physical data as for **1**.

4.5. (2′*R*,3′*R*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine

Following method 2 described above, sodium hydride (27.6 mg, 1.15 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (0.50 g, 1.15 mmol) in DME (20 ml) over molecular sieves to give the crude product, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to furnish (2′*R*,3′*R*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (198 mg, 49%) and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (152 mg, 38%) as a colourless crystalline solids.

(2′*R*,3′*R*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine: R_f 0.34 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ −47.8 (*c* 1, $CHCl_3$), other physical data are identical to **3**.

(2′*S*,3′*S*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine: R_f 0.23 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ −136.0 (*c* 1, $CHCl_3$), other physical data are identical to **2**.

4.6. *N*-Methyl-*N*-((4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidone-*N*-carbonylmethyl)-3,4-didehydropiperidinium bromide 4

(4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidone-*N*-bromoacetate (1.0 g, 3.35 mmol [prepared using an adaptation of the method used to prepare bromoacyl sultams[4] and utilized without further purification]) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.33 g, 3.35 mmol) in THF (20 ml) under argon. The reaction mixture was heated under reflux for 6 h, resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×25 ml) to give *N*-methyl-*N*-((4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone-*N*-carbonylmethyl)-3,4-didehydropiperidinium bromide **4** (1.01 g, 76%) as a colourless deliquescent solid and a 50:50 mixture of diastereoisomers; mp 120.9–121.1 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 1781, 1709; δ_H ($CDCl_3$) 0.93 (1.5H, d), 0.94 (1.5H, d), 2.41 (1H, m), 2.52 (1H, m), 3.62 (1.5H, s), 3.62 (1.5H, s), 4.15 (1H, m), 4.22 (0.5H, m), 4.31 (0.5H, m), 4.47 (0.5H, br d, *J* 16.9), 4.57 (0.5H, br d, *J* 16.9), 4.69 (0.5H, br d, *J* 16.9), 4.81 (0.5H, m), 4.84 (1H, m), 5.44 (1H, d, *J* 17.9), 5.59 (1H, d, *J* 17.9), 5.74 (1H, m), 5.98 (1H, d), 6.14 (1H, m), 7.27–7.42 (5H, m); δ_C ($CDCl_3$) 15.1, 21.5, 21.7, 42.8, 47.5, 47.8, 55.5, 58.2, 58.5, 60.5, 60.7, 64.5, 64.7, 119.6, 119.9, 124.4, 124.8, 126.2, 129.0, 129.1, 133.2, 153.1, 164.5; *m*/*z* (CI) 315.1712 (M^+−Br, $C_{18}H_{23}N_2O_3$ requires 315.1709), 298 (24%), 220 (75), 178 (100), 134 (26), 96 (72), 98 (21).

4.7. *N*-Methyl-*N*-((1*S*)-menthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide 5

(1*S*,2*R*,5*S*)-Menthol bromoacetate (1.0 g, 3.61 mmol) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.35 g, 3.61 mmol) in THF (20 ml) under argon. The reaction mixture was heated under reflux for 6 h resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×25 ml) to give *N*-methyl-*N*-((1*S*)-menthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide **5** (1.2 g, 92%) as a colourless deliquescent solid; mp 172.1–172.6 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 2955, 2933 and 2868, 1734; δ_H ($CDCl_3$) 0.68 (1.5H, d, *J* 6.9), 0.69 (1.5H, d, *J* 6.9), 0.79 (1H, m), 0.82–0.86 (6H, m), 0.97 (1H, m), 1.03 (1H, m), 1.34 (1H, m), 1.40 (1H, m), 1.61 (1H, m), 1.65 (1H, m), 1.76 (1H, m), 1.90 (1H, m), 2.37 (1H, br d, *J* 17.2), 2.50 (1H, br d, *J* 17.2), 3.62 (1.5H, s), 3.63 (1.5H, s), 4.04 (1H, m), 4.14 (1H, m), 4.48 (1H, br m), 4.64 (1H, d, *J* 17.07), 4.73 (1H, m), 4.82 (1H, m), 4.98 (1H, d, *J* 17.07), 5.67 (1H, d, *J* 10.4), 5.96 (1H, d, *J* 10.4); δ_C ($CDCl_3$) 16.5, 21.2, 21.8, 22.4, 23.5, 23.6, 26.5, 26.7, 31.9, 34.3, 40.9, 41.0, 47.0, 47.1, 49.1, 49.4, 57.5, 57.8, 60.0, 60.4, 60.5, 60.8, 78.0, 119.8, 119.9, 124.9, 164.8, 164.8; *m*/*z* (CI) 294.2431 (M^+−Br, $C_{18}H_{32}NO_2$ requires 294.2433), 280 (100%), 156 (9), 142 (33), 110 (23), 96 (72), 82 (11), 69 (19), 42 (8).

4.8. (2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine and (1*S*)-menthyl-3-aza-3-methyl-octa-5,7-dienoate 7

Sodium hydride (33.3 mg, 1.39 mmol) was added to a suspension of *N*-methyl-*N*-((1*S*,2*R*,5*S*)-menthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide (0.50 g, 1.39 mmol) in DME (20 ml), vigorously stirred under argon. The reaction mixture was heated under reflux for 16 h, after which it was cooled and quenched by careful addition of methanol. Solvents were removed in vacuo to give a solid, which was partitioned between water (20 ml) and diethyl ether (20 ml). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (4×20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave a yellow solid, which was purified by column chromatography, eluting with diethyl ether/petrol, to give a mixture of (2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*,2*R*,5*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine (210 mg, 53%) and (1*S*,2*R*,5*S*)-menthyl-3-aza-3-methyl-octa-5,7-dienoate **7** (27 mg, 7%) both as colourless oils.

(2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*,2*R*,5*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.36 (diethyl ether/petrol 2:1); ν_{max}/cm^{-1} 2955, 2869 and 2786 (NR_3), 1743 and 1725; δ_H ($CDCl_3$) 0.70 (1.5H, d, *J* 6.9), 0.76 (1.5H, d, *J* 6.9), 0.86 (3H, d, *J* 6.9), 0.88 (1.5H, d, *J* 6.9), 0.89 (1.5H, d, *J* 6.9), 0.92–1.05 (3H, m), 1.39 (1H, m), 1.44–1.52 (1H, m), 1.65 (1H, m), 1.68 (1H, m), 1.82 (1H, m), 1.90 (1H, m), 1.96 (1H, m), 2.05 (1H, m), 2.36 (1.5H, s), 2.37 (1.5H, s), 2.41 (1H, m), 3.05 (1H, m), 3.12 (0.5H, d, *J* 8.06), 3.14 (0.5H, d, *J* 8.4), 3.17 (1H, m), 4.69 (0.5H, ddd, *J* 4.4, 10.9, 10.9), 4.77 (0.5H, ddd, *J* 4.4, 10.9, 10.9), 4.95 (0.5H, dd, *J* 1.8, 9.9), 4.96 (0.5H, dd, *J* 1.8, 9.9), 5.02 (0.5H, dd, *J* 1.8, 16.8), 5.03 (0.5H, dd, *J* 1.8, 16.8), 5.77 (0.5H, ddd, *J* 9.2, 9.9, 16.8), 5.79 (0.5H, ddd, *J* 9.5, 9.9, 16.8); δ_C ($CDCl_3$) 15.7, 16.1, 20.70, 20.8, 22.0, 22.8, 23.2, 25.5, 26.2, 30.6, 30.7, 31.3,34.2, 40.3, 40.3, 41.1, 41.1, 46.1, 46.3, 46.6, 46.8, 55.2, 71.9, 72.4, 74.2, 74.7,

115.8, 115.9, 138.4, 171.0, 171.1; *m/z* (CI) 294.2421 (M^++H, $C_{18}H_{32}NO_2$ requires 294.2433), 156 (14%), 131 (12), 110 (100), 69 (7).

(1*S*,2*R*,5*S*)-Menthyl-3-aza-3-methyl-octa-5,7-dienoate: R_f 0.46 (diethyl ether/petrol 1:2); ν_{max}/cm^{-1} 2955, 2923 and 2871 (NR_3), 1736, 1686 and 1643; δ_H ($CDCl_3$) 0.75 (3H, d, *J* 6.9), 0.86 (3H, d, *J* 6.9), 0.88 (3H, d, *J* 6.9), 0.95–1.05 (2H), 1.11 (1H, m), 1.27 (1H, m), 1.31 (1H, m), 1.59 (1H, m), 1.66 (1H, m), 1.84 (1H, m), 1.97 (1H, m), 2.41 (3H, s), 3.26 (2H, s), 3.35 (2H, d, *J* 7.3), 4.76 (1H, ddd, *J* 4.4, 10.9, 10.9), 5.16 (1H, d, *J* 10.09), 5.25 (1H, d, *J* 16.8), 5.55 (1H, dt, *J* 10.6, 7.3), 6.18 (1H, dd, *J* 10.6, 11.2), 6.65 (1H, dddd, *J* 10.09, 11.2, 16.8, 1.1); δ_C ($CDCl_3$): 16.2, 20.7, 22.0, 23.3, 26.2, 31.4, 34.2, 40.9, 42.3, 46.9, 53.4, 57.7, 74.4, 118.7, 128.2, 131.7, 132.5, 170.4; *m/z* (CI) 294.2443 (M^++H, $C_{18}H_{32}NO_2$ requires 294.2433), 156 (13%), 110 (64), 96 (53), 67 (12).

4.9. *N*-Methyl-*N*-((1*R*)-8-phenylmenthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide 6

(1*R*,2*S*,5*R*)-8-Phenylmenthyl bromoacetate (0.5 g, 1.41 mmol) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.14 g, 1.41 mmol) in THF (10 ml) under argon. The reaction mixture was heated under reflux for 12 h resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×15 ml) under argon to give *N*-methyl-*N*-(8-phenylmenthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide **6** (503 mg, 79%) as a colourless deliquescent solid; mp 169.9–170.2 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 2958, 2935 and 2875, 1735, 1685, 1653 and 1636 (aromatic C=C); δ_H ($CDCl_3$) 0.87 (1.5H, d, *J* 6.9), 0.91 (1.5H, d), 0.97 (1H, m), 1.09 (1H, m), 1.18 (3H, m), 1.23 (1H, m), 1.29 (3H, m), 1.47 (1H, m), 1.71 (1H, m), 1.85 (1H, m), 1.94 (1H, m), 2.16 (1H, m), 2.33 (1H, br m), 2.50 (1H, br m), 3.49 (3H, s), 3.87 (1H, m), 3.98 (1H, m), 4.14 (1H, br m), 4.29 (1H, m), 4.38 (1H, m), 4.44 (1H, d, *J* 17.9), 4.86 (1H, m), 5.69 (1H, br m), 6.01 (1H, br m), 7.17 (1H, m), 7.31 (2H, m), 7.34 (2H, m); δ_C ($CDCl_3$) 21.1, 21.2, 21.5, 22.2, 22.5, 22.5, 25.9, 26.0, 28.1, 28.9, 30.1, 30.3, 34.0, 41.1, 41.2, 48.4, 48.7, 49.2, 49.3, 56.9, 57.7, 58.8, 59.2, 59.3, 60.2, 118.8, 119.1, 124.3, 124.6, 125.1, 125.2, 125.3, 128.2, 151.6, 151.8, 163.4, 163.5; *m/z* (CI) 370.2763 (M^+−Br, $C_{24}H_{36}NO_2$ requires 370.2746), 156 (19%), 110 (100).

4.10. (2*R*,3*R*)-*N*-methyl-2-(1*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine and (2*S*,3*S*)-*N*-methyl-2-(1*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine 6

Sodium hydride (26.6 mg, 1.11 mmol) was added to a suspension of *N*-methyl-*N*-((1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide (0.50 g, 1.11 mmol) and powdered molecular sieves (200 mg) in THF (20 ml), vigorously stirred under argon. The reaction mixture was heated under reflux for 16 h, after which it was cooled and quenched by careful addition of methanol. Solvents were removed in vacuo to give a solid, which was partitioned between water (20 ml) and diethyl ether (20 ml). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (4×20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave a yellow oil, which was purified by column chromatography, eluting with diethyl ether/petrol (1:2), to give (2*R*,3*R*)-*N*-methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine (120 mg, 29%) and (2*S*,3*S*)-*N*-methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine (99 mg, 24%) both as colourless oil.

(2*S*,3*S*)-*N*-Methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.33 (diethyl ether/petrol 1:2); $[\alpha]_D^{20}$ −13.04 (*c* 1.3, CH_2Cl_2); ν_{max}/cm^{-1} 2955, 2876 and 2789 (NR_3), 1735, 1684 and 1653; δ_H ($CDCl_3$) 0.78 (1H, m), 0.84 (3H, d, *J* 6.2), 0.88 (1H, m), 0.96 (1H, m), 1.22 (3H, s), 1.34 (3H, s), 1.43 (1H, m), 1.50 (1H, m), 1.83 (1H, m), 1.92 (1H, m), 1.95 (1H, m), 2.07 (2H, m), 2.33 (3H, s), 2.48 (1H, m), 2.92 (1H, m), 2.96 (1H, m), 3.07 (1H, m), 4.74 (1H, ddd, *J* 4.03, 10.9, 10.9), 5.03 (1H, dd, *J* 1.8, 9.9), 5.07 (1H, dd, *J* 1.8, 17.2), 5.67 (1H, ddd, *J* 9.4, 9.9, 17.2), 7.15 (1H, m), 7.26 (2H, m), 7.28 (2H, m); δ_C ($CDCl_3$) 21.2, 24.3, 27.2, 29.0, 30.3, 31.3, 34.6, 40.2, 41.8, 46.1, 50.5, 54.9, 71.6, 74.4, 116.3, 125.2, 125.7, 128.0, 138.4, 151.1, 171.9; *m/z* (CI) 370.2744 (M^++H, $C_{24}H_{36}NO_2$ requires 370.2740), 282 (9%), 197 (11), 156 (15), 110 (100), 69 (12).

(2*R*,3*R*)-*N*-Methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.17 (diethyl ether/petrol 1:2); $[\alpha]_D^{20}$ −10.77 (*c* 0.9, CH_2Cl_2); ν_{max}/cm^{-1} 2955, 2876 and 2789 (NR_3), 1735, 1684 and 1653; δ_H ($CDCl_3$) 0.82 (1H, m), 0.84 (3H, d, *J* 6.5), 0.87 (1H, m), 1.06 (1H, m), 1.31 (3H, s), 1.43 (3H, s), 1.57 (1H, m), 1.59 (1H, m), 1.67 (1H, m), 1.72 (1H, m), 1.87 (1H, m), 2.01 (2H, m), 2.34 (3H, s), 2.43 (1H, m), 2.94 (1H, m), 2.96 (1H, m), 3.14 (1H, m), 4.82 (1H, ddd, *J* 4.3, 10.7, 10.7), 4.89 (1H, dd, *J* 1.8, 10.1), 4.94 (1H, dd, *J* 1.8, 17.0), 5.67 (1H, ddd, *J* 9.6, 10.1, 17.03) 7.15 (1H, m), 7.27 (2H, m), 7.34 (2H, m); δ_C ($CDCl_3$) 15.3, 21.8, 26.7, 29.7, 30.3, 31.2, 34.6, 39.8, 42.1, 45.9, 50.1, 55.2, 70.8, 74.6, 115.7, 125.0, 125.4, 128.1, 138.9, 151.7, 170.5; *m/z* (CI) 370.2744 (M^++H, $C_{24}H_{36}NO_2$ requires 370.2740), 282 (9%), 197 (11), 156 (15), 110 (100), 69 (12).

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Palladium-catalysed intramolecular enolate *O*-arylation and thio-enolate *S*-arylation: synthesis of benzo[*b*]furans and benzo[*b*]thiophenes

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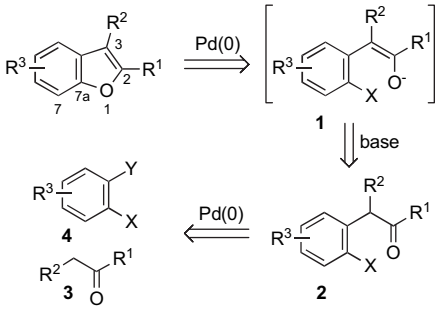
Abstract—Enolates derived from α-(*ortho*-haloaryl)-substituted ketones undergo palladium-catalysed C–O bond formation to deliver benzofuran products in good yield. A catalyst generated from $Pd_2(dba)_3$ and the ligand DPEphos effects the key bond formation to deliver a variety of substituted products from both cyclic and acyclic precursors. The analogous thio-ketones undergo C–S bond formation using identical reaction conditions and are converted to benzothiophene products. A cascade sequence that produces the required α-aryl ketones in situ has also been developed, although the substrate scope is more restricted.

1. Introduction

Benzofurans and benzothiophenes are two of the most common and consequently most studied classes of aromatic heterocycle.[1] The occurrence of these heterocycles in a significant number of medicinal agents, active in a variety of disease areas, has led to an enduring interest in the development of new methods for their synthesis.[2] Methods that utilise new classes of precursor are particularly valuable. Amongst the many syntheses available, transition metal catalysed processes[3] and palladium-mediated methods in particular[4] feature heavily. Syntheses based on palladium-catalysed cyclisations of appropriately substituted alkenyl or alkynyl phenols, or thiophenols, are particularly versatile and have been used on many occasions.[5] Related tandem processes involving catalysed C–C bond formation, usually employing Sonogashira type reactions, before construction of the key C–O or C–S bond have also been developed.[6] The crucial bond-forming event in these processes is intramolecular attack of a nucleophilic oxygen or sulfur atom onto a palladium-activated C–C multiple bond, resulting in formation of the $X–C_2$ bond of the heterocycle. We wished to develop an alternative synthesis involving formation of the $X–C_{7a}$ bond and employing the intramolecular attack of a nucleophilic oxygen or sulfur atom onto a palladium-activated aryl ring; crucially, the nucleophilic heteroatom would be embedded in an enolate or thio-enolate, generated from the corresponding ketone or thio-ketone, respectively. Such a synthesis would open the use of α-(*ortho*-haloaryl)-substituted ketones and thio-ketones as new benzofuran and benzothiophene precursors.[7]

2. Results and discussion

A retrosynthetic scheme representing our proposed route to benzofurans is shown in Scheme 1. The key palladium-catalysed C–O bond formation is represented by the disconnection of $O–C_{7a}$ bond of the benzofuran to generate enolate **1**. In turn, the enolate would be generated from α-aryl ketone **2**. The use of the thio-ketone corresponding to ketone **2** would allow access to the corresponding thio-enolate and ultimately to the benzothiophene. Therefore, α-aryl ketones **2**



Scheme 1.

Keywords: Benzofuran; Benzothiophene; Palladium catalysis; Enolate.
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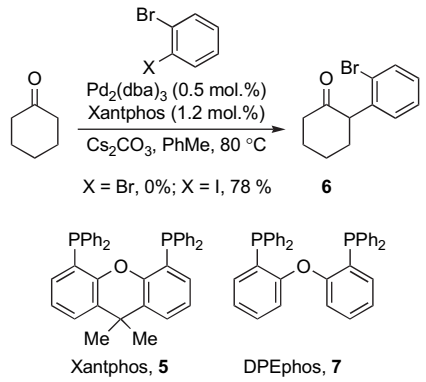
become common intermediates for the synthesis of both classes of heterocycle. Although there are a number of methods for the synthesis of α-arylated ketones,[8] we wished to employ a second palladium-catalysed transformation involving the α-arylation of a simple ketone **3** with a 1,2-dihaloarene **4**.

Over recent years palladium-catalysed intermolecular C-arylation of enolates[9] and similar C-nucleophiles has been developed as a useful synthetic tool.[10] Although the use of 1,2-dihaloarenes to access the required α-(*ortho*-haloaryl)ketones had not been documented, precedent existed for the use of *o*-substituted aryl halides. The preparation of α-(*o*-bromophenyl)cyclohexanone **6** is used as an illustrative example for substrate preparation (Scheme 2). Application of literature conditions,[10a,b] involving combining the substrates with Cs_2CO_3, $Pd_2(dba)_3$ and the ligand Xantphos (**5**),[11] to the coupling of cyclohexanone and 1,2-dibromobenzene, resulted in no reaction. However, the use of 1-bromo-2-iodobenzene under identical reaction conditions delivered the α-arylated ketone **6** in 78% yield. Variations of this protocol were used to prepare all of the α-arylated ketones employed in this study.[12]

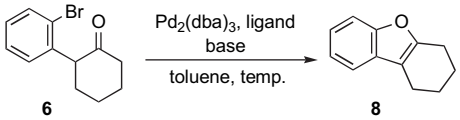


Scheme 2.

With a route to the required 2-(haloaryl)-ketones established, we turned our attention to the key benzofuran-forming transformation. Palladium-catalysed aryl C–X bond formations, and C–N constructions in particular, are now reliable and well established methods, with growing numbers of applications appearing in the literature.[13] Intramolecular versions of these reactions, leading to the formation of a variety of heterocycles, are also well known.[13] Although a diverse range of nucleophiles have been employed in these reactions, the use of *O*- and *S*-enolates as hetero-nucleophiles is rare.[14] Substituted cyclohexanone **6** was selected for initial study (Table 1). Although we had detected trace amounts of benzofuran **8** during the preparation of arylated ketone **6**, when we resubjected ketone **6** to a Xantphos derived catalyst in combination with Cs_2CO_3 we could only isolate small amounts of the benzofuran product (entry 1). The use of the same catalyst system with a stronger base was similarly unsuccessful (entry 2). However, the use of the structurally similar ligand DPEphos[11] **7** with Cs_2CO_3 as base at 100 °C provided benzofuran **8** in 95% yield (entry 3). Lowering the reaction temperature simply resulted in poorer conversions (entries 4 and 5).

With conditions to effect the key intramolecular *O*-enolate aryl-coupling was established using a test system, we next

Table 1. Catalyst optimisation[a]



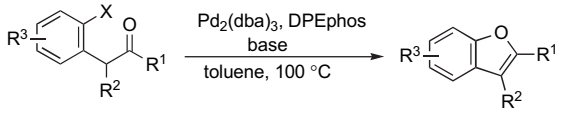
Entry	Ligand	Base	*T* (°C)	Time (h)	Yield (%)[b]
1	Xantphos	Cs_2CO_3	110	20	<5
2	Xantphos	NaO^{t}Bu	110	20	0
3	DPEphos	Cs_2CO_3	110	20	95
4	DPEphos	Cs_2CO_3	80	24	52
5	DPEphos	Cs_2CO_3	50	30	0

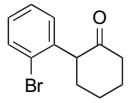
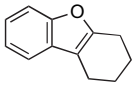
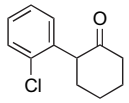
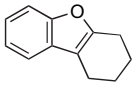
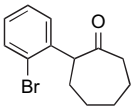
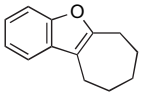
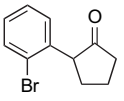
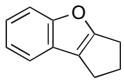
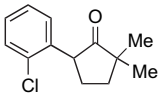
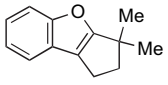
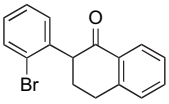
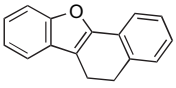
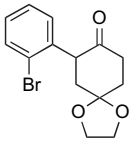
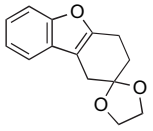
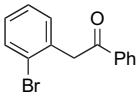
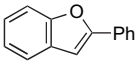
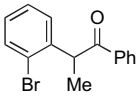
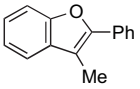
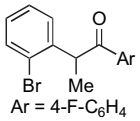
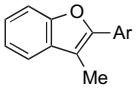
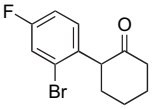
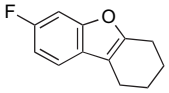
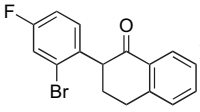
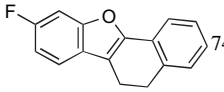
[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %), base (2.2 equiv).
[b] Isolated yields.

explored the scope of the process (Table 2). All of the examples shown below employ the standard catalyst: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %). Entries 1–3 provide a comparison between the use of bromo- and chloro-substituents on the aryl ring. With the bromo-substrate, the use of the base Cs_2CO_3 was sufficient to achieve an excellent yield of the benzofuran. Application of these conditions to the chloro-substrate resulted in only a low conversion to product, however, the use of the alternative base NaHMDS delivered the benzofuran in 94% yield. The ability to employ Cl-substituted arenes significantly adds to the appeal of the process given the greater numbers of aryl chlorides that are commercially available.[15] Variation of the base used in the following cyclisations was important in achieving optimal yields. Although the cycloheptanone-derived substrate delivered the corresponding benzofuran as expected (entry 4), the cyclopentanone system was unreactive (entry 5). The use of a variety of base and temperature combinations also failed to deliver the benzofuran. We were concerned that competing aldol processes may have been occurring with the stronger bases, however, the use of the *gem*-dimethyl-substituted variant shown in entry 6 was also unsuccessful. It appears that ring-closure to form a cyclopentane-fused benzofuran is not possible using the current methodology.[16] Entries 7–11 demonstrate that benzo- and ketal substituents are possible on the ketone fragment and that acyclic as well as cyclic substrates can also be employed. The remaining examples show that variation of the arene fragment is also tolerated with F-substituents and a pyridyl ring all delivering the target benzofurans. While ring-closure to the corresponding benzofurans was possible without the use of a palladium catalyst for the pyridyl example, there was a significant reduction in reaction time if a catalyst was employed. Although the same catalyst was employed for all of the examples in Table 2, it can also be seen that some variation in the choice of base is needed.

Having demonstrated that *O*-enolates can perform as competent hetero-nucleophiles with a variety of intramolecular coupling partners we were interested as to whether the process could be extended to *S*-enolates. Although examples of palladium-catalysed C–S bond formation are known,[17,18] they are much less common than the corresponding C–N and C–O examples. To test the ability of *S*-enolates to participate in the desired cyclisation reactions we first needed to convert the α-(*ortho*-haloaryl)-ketone substrates into the corresponding thio-ketones. This was achieved in a straightforward manner using P_2S_5.[19] Pleasingly, treatment of the

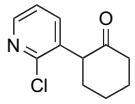
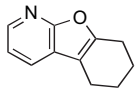
Table 2. Scope of benzofuran formation[a]



Entry	Substrate	Base	Product	Yield (%)[b]
1		Cs_2CO_3		95
2		Cs_2CO_3		54
3		NaHMDS		94
4		NaHMDS		95
5		Cs_2CO_3		0
6		Cs_2CO_3		0
7		NaO^{t}Bu		81
8		NaO^{t}Bu		73
9		NaO^{t}Bu		50
10		NaO^{t}Bu		80
11	 Ar = 4-F-C_6H_4	NaO^{t}Bu		68
12		NaO^{t}Bu		81
13		NaO^{t}Bu		74

(*continued*)

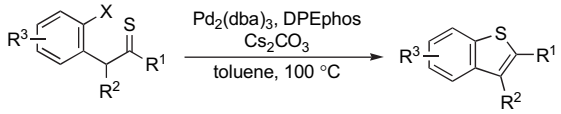
Table 2. (*continued*)

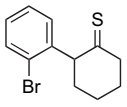
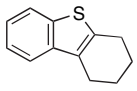
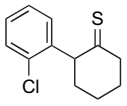
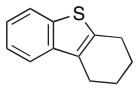
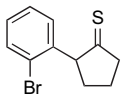
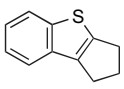
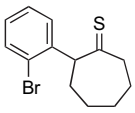
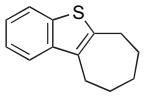
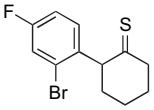
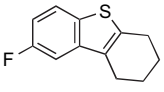
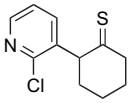
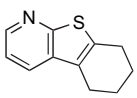
Entry	Substrate	Base	Product	Yield (%)[b]
14		NaO^{t}Bu		86[c]

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %), base (2.2 equiv).
[b] Isolated yields.
[c] In the absence of catalyst a 40% conversion is achieved after 20 h.

cyclohexanone-derived thio-ketone with the standard benzofuran-forming reaction conditions delivered benzothiophene in 74% yield (Table 3, entry 1). The aryl chloride variant also underwent cyclisation, although similar to the corresponding ketone example when using Cs_2CO_3, in a reduced yield (entry 2). In contrast to the equivalent ketone, reaction of the cyclopentanethione derived substrate delivered the expected benzothiophene (entry 3). This difference in reactivity between ketone and thio-ketone may be due to the increased nucleophilicity of the *S*-atom or the longer C–S bond. In line with the ketone examples, entries 4 and 5 demonstrate that further variation in both the ketone and aryl fragments are possible. One class of substrate not amenable to the catalysed

Table 3. Benzothiophene formation[a]

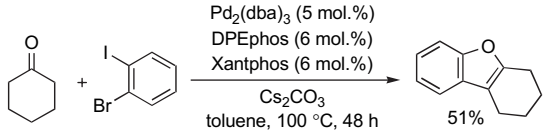


Entry	Thio-ketone	Yield (%) *S*-ketone	Product	Yield (%)[b]
1		71		74
2		40		44
3		38		52
4		40		57
5		53		57
6[c]		0		67

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %), Cs_2CO_3 (2.2 equiv), toluene, 100 °C.
[b] Isolated yields.
[c] Attempted formation of thio-ketone lead directly to cyclised product.

S-enolate reaction are the pyridyl-substituted variants; attempted conversion of the ketone to the thio-ketone lead directly to the benzothiophene product (entry 6).

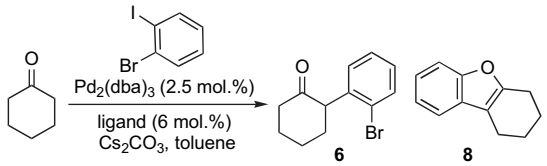
The benzofuran and benzothiophene syntheses as presented consist of two independent palladium-catalysed reactions leading to the efficient preparation of the individual heterocycles. The similarity of the reaction conditions, particularly the ligand choice, for the two independent reactions suggested that a one-pot cascade process might be achievable. Unfortunately, even though there is significant structural homology between the two optimal ligands for each separate reaction (Xantphos for the *C*-arylation, DPEphos for benzofuran/benzothiophene formation), neither ligand would effect the alternate reaction. One solution to this was to combine both ligands in a single reaction:[20] Scheme 3 illustrates the process for the direct preparation of the cyclohexane-fused benzofuran from cyclohexanone and 1-bromo-2-iodobenzene.



Scheme 3.

Although a 51% yield of benzofuran could be obtained from the mixed-ligand reaction we sought a single ligand system capable of achieving the desired cascade sequence. The number of ligands reported to facilitate palladium-catalysed coupling processes is ever increasing and this combined with the number of additional variables (base, Pd source, solvent, temperature) makes a complete evaluation of reaction conditions a prohibitively complex exercise. As a compromise we elected to simply vary the ligand choice while keeping all other variables constant. The coupling of cyclohexanone and 1-bromo-2-iodobenzene was again selected as an appropriate test system. Table 4 documents these studies: as already stated, the ligands Xantphos and DPEphos were not effective for the desired cascade transformation, neither was (*rac*)-BINAP (entries 1–3). The biphenyl-based phosphine ligands developed by Buchwald have been shown to be effective for a number of palladium-mediated transformations, however, the use of ligands **9** or **10** were similarly ineffective (entries 4 and 5).[21] Recently, ferrocene-based ligands have appeared in the literature with more frequency and have shown success in a number of palladium-catalysed *C–O* bond-forming reactions.[22] Unfortunately, application of the bis-chelating isopropyl **11** and phenylphosphino variants **12** gave none of the desired products (entries 6 and 7). However, the *tert*-butyl analogue **13** promoted both steps in the sequence producing 9% of the arylated ketone and 7% of the benzofuran (entry 8). The respective conversions both increased to 25% when the catalyst loading was increased to 5 mol % Pd and 6 mol % ligand (entry 9). Although the bulky tri-isopropyl-substituted dicyclohexylphosphine ligand **14**[23] gave poor conversion to the benzofuran product it gave complete cyclisation of the arylated ketone (entry 10). The *tert*-butyl analogue **15** showed decreased activity (entry 11). Use of the dimethoxy-substituted dicyclohexylphosphine ligand **16**[24] provided the arylated ketone in 9% with 20% conversion to the benzofuran product (entry 12).

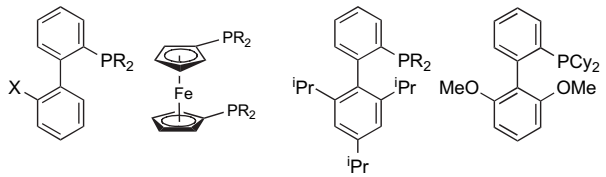
Table 4. Development of a single-ligand cascade reaction[a]



6 **8**

Entry	Ligand	Aryl ketone conv. (%)[b]	Benzofuran conv. (%)[b]
1	Xantphos	78[c]	<5
2	DPEphos	0	0
3	BINAP	0	0
4	**9**	0	0
5	**10**	9	0
6	**11**	0	0
7	**12**	0	0
8	**13**	9	7
9[d]	**13**	25	25
10	**14**	0	9
11	**15**	0	0
12	**16**	9	20
13[d]	**16**	0	91
14[e]	**16**	0	100

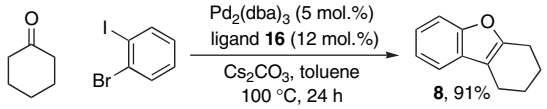
[a] Conditions: 1-bromo-2-iodobenzene (1.0 equiv), cyclohexanone (1.2 equiv), toluene, 80 °C, 24 h.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] $Pd_2(dba)_3$ (5 mol %), ligand (6 mol %), 100 °C.
[e] $Pd_2(dba)_3$ (5 mol %), ligand (12 mol %), 100 °C.



9, R = ^{t}Bu, X = H
10, R = Cy, X = NMe_2
11, R = Ph
12, R = ^{i}Pr
13, R = ^{t}Bu
14, R = ^{t}Bu
15, R = Cy
16

Increasing the palladium loading to 5 mol % significantly increased the conversion to benzofuran (entry 13), and finally, simultaneously increasing the ligand loading to 12 mol % resulted in complete conversion to benzofuran (entry 14).

A preparative scale reaction using these optimised conditions delivered benzofuran **8** in 91% yield (Scheme 4). Unfortunately, these conditions were not transferable to alternative substrates, with only low yields of mixtures of arylated ketone and benzofuran being obtained in almost all cases. For example, reactions involving the coupling of 2-bromo-iodobenzene with either cycloheptanone or α-tetralone were unsuccessful. It appears that it would be necessary to develop an optimised catalyst system for individual substrates. The effort needed to optimise for individual substrates in cascade processes suggests that the use of multi-ligand systems may offer advantages, in that it is often more convenient to optimise for a single one-step transformation using a single ligand and then apply this information to the cascade sequence.



Scheme 4.

3. Conclusion

We have demonstrated that a simple catalyst comprising $Pd_2(dba)_3$ and the ligand DPEphos effects the cyclisation of α-(*ortho*-haloaryl)-substituted ketones and thio-ketones to benzofurans and benzothiophenes, respectively. The process tolerates variations in both the ketone and aryl fragments to deliver the heterocyclic products in good yields. The key cyclisation reaction involves the coupling of enolate and thio-enolate heteroatoms to palladium-activated aryl halides. Although it is possible to construct a cascade reaction sequence, involving the in situ preparation of the arylated ketones, the process is less general and requires optimsation for individual substrates. Applications of similar enolate-heteroatom cyclisations to the synthesis of alternative heterocycles are underway.

4. Experimental

4.1. General

The preparation of several of the α-arylated ketones and the corresponding benzofuran products has been previously described.[7,12]

4.1.1. General procedure (A) for the preparation of α-arylated ketones. Exemplified by the preparation of 2-(2-bromophenyl)-cyclohexanone 6. Caesium carbonate (4.570 g, 14.00 mmol) was added to a flask charged with $Pd_2(dba)_3$ (0.030 g, 0.033 mmol) and Xantphos (0.040 g, 0.080 mmol) under nitrogen. The reagents were suspended in anhydrous dioxane (6.4 mL) and 1-bromo-2-iodobenzene (1.80 g, 6.370 mmol, 0.82 mL) and cyclohexanone (1.25 g, 12.74 mmol, 1.3 mL) were added under nitrogen and the reaction was heated to 80 °C for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (5–10% diethyl ether/petrol) to yield ketone **6** (1.26 g, 78%) as a white solid: mp 57–58 °C (MeOH) (lit. 58–59 °C).[1] ν_{max} (Nujol™)/cm^{-1} 2920, 2855, 1709, 1566 (w), 1462, 1377, 1281, 1196, 1121, 1070, 1027, 977, 940, 769, 746, 722, 674; δ_H (300 MHz, $CDCl_3$) 1.71–2.10 (4H, m, CH_2), 2.15–2.35 (2H, m, ArCHCH_2), 2.51–2.89 (2H, m, CH_2CO), 4.11 (1H, app. dd, *J* 12.4 and 5.3, Ar–C*H*), 7.12 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar–*H*), 7.21 (1H, dd, *J* 7.9 and 1.9, Ar–*H*), 7.31 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.56 (1H, td, *J* 7.9 and 1.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 25.1, 27.1, 33.6, 41.8, 56.0, 124.6, 126.8, 127.8, 128.9, 132.1, 137.8, 208.3; *m/z* LRMS (CI^+, NH_3) 270 $[M+NH_4]^+$, 253 $[M+H:^{79}Br]^+$, 173 $[M-^{79}Br]^+$, 145 $[M-^{79}Br-CO]^+$, 115 $[M-^{79}Br-CO-C_2H_4]^+$; HRMS (ES^+) calcd for $C_{12}H_{14}BrO$: 253.0223 $[M+H]^+$, found: 253.0225 $[M+H]^+$.

4.1.1.1. Preparation of 5-(2-chlorophenyl)-2,2-dimethylcyclopentanone (Table 2, entry 6 substrate). General procedure A was followed employing 1-bromo-2-chlorobenzene (159 mg, 0.830 mmol, 0.10 mL), 2,2-dimethylcyclopentanone (112 mg, 0.997 mmol, 0.13 mL) and 2-dicyclohexylphosphino-2′-methylbiphenyl (18 mg, 0.049 mmol) as the ligand, heating at 110 °C for 17 h. The product was purified via flash column chromatography (5–10% diethyl ether/petrol) to yield the *ketone* (90 mg, 50%) as a creamy/white solid: mp 63–64 °C. ν_{max} (KBr)/cm^{-1} 2961, 2867, 1736, 1478, 1460, 1437, 1381, 1360, 1329, 1258, 1190, 1128, 1089, 1062, 1031, 767, 753; δ_H (300 MHz, $CDCl_3$) 1.15 (3H, s, C(CH_3)$_2$), 1.20 (3H, s, C(CH_3)$_2$), 1.81–2.07 (3H, m, CH_2 and ArCHCH_2), 2.42–2.53 (1H, m, ArCHCH_2), 3.85–3.97 (1H, m, Ar–C*H*), 7.03 (1H, dd, *J* 7.5 and 2.1, Ar–*H*), 7.18 (1H, td, *J* 7.5 and 1.9, Ar–*H*), 7.23 (1H, td, *J* 7.5 and 1.9, Ar–*H*), 7.38 (1H, dd, *J* 7.5 and 2.1, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 24.2, 25.5, 28.1, 37.0, 45.8, 53.1, 127.5, 128.6, 129.6, 130.0, 135.0, 137.9, 221.5; *m/z* LRMS (CI^+, NH_3) 242 $[M:^{37}Cl]^+$, 240 $[M:^{35}Cl]^+$, 206 $[M-^{35}Cl]^+$, 204 $[M-^{37}Cl]^+$; HRMS (ES^+) calcd for $C_{13}H_{19}ClNO$: 240.1150 $[M+NH_4]^+$, found: 240.1153 $[M+NH_4]^+$. $C_{13}H_{15}ClO$ requires C 70.11, H 6.79%, found C 69.80, H 6.78%.

4.1.1.2. Preparation of 2-(2-bromophenyl)-1-phenylethanone (Table 2, entry 9 substrate).[25] General procedure A was followed employing 1-bromo-2-iodobenzene (2.000 g, 7.070 mmol, 0.91 mL) and acetophenone (1.020 g, 8.480 mmol, 0.99 mL) using $HP^tBu_3BF_4$ (90 mg, 0.320 mmol) as the ligand and sodium *tert*-butoxide (1.600 g, 16.560 mmol) as the base, heating at 60 °C for 9 h. The product was purified via flash column chromatography (5% diethyl ether/petrol) to yield the *ketone* (1.19 g, 51%) as a white crystalline solid: mp 66–67 °C. ν_{max} (Nujol™)/cm^{-1} 3057, 1691, 1585, 1581, 1567, 1470, 1447, 1427, 1407, 1331, 1277, 1219, 1202, 1174, 1156, 1025, 990, 756, 690, 666, 650, 575; δ_H (300 MHz, $CDCl_3$) 4.46 (2H, s, Ar–CH_2CO), 7.15 (1H, ddd, *J* 7.9, 6.8 and 2.3, Ar–*H*), 7.22–7.32 (2H, m, Ar–*H*), 7.47 (2H, tt, *J* 8.1 and 1.5, Ar–*H*), 7.55–7.62 (2H, m, Ar–*H*), 8.05 (2H, d, *J* 7.2, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 45.8, 125.1, 127.5, 128.3, 128.7, 131.7, 132.8, 133.3, 133.8, 134.9, 136.6, 196.3; *m/z* LRMS (CI^+, NH_3) 294 $[M+NH_4:^{81}Br]^+$, 292 $[M+NH_4:^{79}Br]^+$, 277 $[M+NH_3:^{81}Br]^+$, 275 $[M+NH_3:^{79}Br]^+$; HRMS (ES^+) calcd for $C_{14}H_{15}BrNO$: 292.0332 $[M+NH_4:^{79}Br]^+$, found: 292.0331 $[M+NH_4:^{79}Br]^+$; $C_{14}H_{11}OBr$ requires C 61.11, H 4.03%, found C 61.10, H 4.01%.

4.1.2. General procedure (B) for the preparation of benzofurans from α-arylated ketones. Exemplified by the preparation of 1,2,3,4-tetrahydro-dibenzofuran (Table 2, entry 1). Caesium carbonate (180 mg, 0.560 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.009 mmol) and DPEphos (13 mg, 0.022 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1 mL) prior to the addition of ketone **6** (100 mg, 0.40 mmol) and the reaction heated to 100 °C for 20 h. After cooling the reaction mixture was filtered through a plug of Celite and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (64 mg, 95%) as a colourless oil. Data consistent with that reported in the literature.[26]

4.1.3. General procedure (C) for the preparation of thioketones. Exemplified by the preparation of 2-(2-bromophenyl)-cyclohexanethione (Table 3, entry 1 substrate). 2-(2-Bromophenyl)-cyclohexanone (500 mg, 1.981 mmol) was added to a flask charged with phosphorus pentasulfide (220 mg, 0.489 mmol) under nitrogen and the reaction

mixture suspended in anhydrous toluene (2.50 mL). The mixture was stirred at room temperature for 10 min prior to the addition of hexamethyldisiloxane (550 mg, 3.360 mmol, 0.71 mL) and heated to 90 °C for 21 h. After cooling, the reaction mixture was filtered through a plug of silica and the filtrate reduced in vacuo to yield the *thio-ketone* (375 mg, 71%) as a colourless oil. The product was used without further purification. ν_{max} (NaCl)/cm^{-1} 3050, 2924, 2855, 1642, 1587, 1559, 1466, 1435, 1334, 1258, 1243, 1136, 1115, 1078, 1050, 1027, 1014, 821, 799, 751, 724, 688; δ_H (300 MHz, $CDCl_3$) 1.63–1.80 (4H, m, CH_2), 1.95–2.12 (1H, m, ArCHCH_2), 2.24–2.38 (3H, m, ArCHCH_2 and CH_2CS), 2.39 (1H, br s, Ar–C*H*), 7.03–7.10 (2H, m, Ar–*H*), 7.24 (1H, td, *J* 7.9 and 1.4, Ar–*H*), 7.53 (1H, dd, *J* 7.9 and 1.4, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.0, 32.0, 34.1, 123.4, 125.9, 128.2, 129.0, 130.6, 133.4, 133.7, 143.8; *m/z* LRMS (EI$^+$) 271 [M:^{81}Br]$^+$ (53%), 270 [M−H:^{81}Br]$^+$ (52%), 269 [M:^{79}Br]$^+$ (100%), 268 [M−H:^{79}Br]$^+$ (48%), 189 [M−Br]$^+$ (40%); (CI$^+$, NH_3) 288 [M+NH_3:^{81}Br]$^+$, 286 [M+NH_3:^{79}Br]$^+$, 272 [M+H:^{81}Br]$^+$, 271 [M:^{81}Br]$^+$, 270 [M+H:^{79}Br]$^+$, 269 [M:^{79}Br]$^+$; HRMS (EI) calcd for $C_{12}H_{13}BrS$: 267.9916 [M]$^+$, found: 267.9917 [M]$^+$.

4.1.3.1. Preparation of 2-(2-chlorophenyl)-cyclohexanethione, (Table 3, entry 2 substrate). General procedure C was followed employing the relevant ketone (180 mg, 1.318 mmol) to yield the *thio-ketone* (119 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3645, 3055, 2925, 2857, 2833, 2661, 2571, 2318, 1799, 1722, 1643, 1590, 1564, 1470, 1428, 1335, 1260, 1174, 1121, 1078, 1059, 1034, 1016, 941, 862, 801, 753, 728, 709, 650; δ_H (300 MHz, $CDCl_3$) 1.69–1.86 (4H, m, CH_2), 2.02–2.19 (2H, m, ArCHCH_2), 2.31–2.44 (2H, m, CH_2CS), 2.46 (1H, br s, Ar–C*H*), 7.15 (1H, dd, *J* 7.2 and 2.3, Ar–*H*), 7.24 (1H, app. qd, *J* 7.2 and 2.3, Ar–*H*), 7.41 (1H, dd, *J* 7.2 and 2.3, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.1, 31.9, 34.2, 126.0, 127.5, 128.9, 130.2, 130.6, 132.2, 133.2, 141.8; *m/z* LRMS (EI$^+$) 224 [M:^{35}Cl]$^+$ (34%), 189 [M−^{35}Cl]$^+$ (100%), 188 [M−H−^{35}Cl]$^+$ (62%), 187 [M−^{37}Cl] (33%); HRMS (ES$^+$) calcd for $C_{12}H_{14}ClS$: 225.0499 [M+H]$^+$, found: 225.0498 [M+H]$^+$.

4.1.3.2. Preparation of 2-(2-bromophenyl)-cyclopentanethione, (Table 3, entry 3 substrate). General procedure C was followed employing relevant ketone (200 mg, 0.837 mmol) to yield the *thio-ketone* (80 mg, 38%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3062, 2923, 2848, 1742 (vs), 1634, 1559, 1467, 1429, 1317, 1262, 1204, 1115, 1057, 1028, 752, 722, 699; δ_H (300 MHz, $CDCl_3$) 1.93–2.05 (2H, m, CH_2), 2.57–2.71 (5H, m, Ar–C*H*, ArCHCH_2 and CH_2CS), 7.04–7.14 (2H, m, Ar–*H*), 7.21–7.27 (1H, m, Ar–*H*), 7.53 (1H, dd, *J* 7.9 and 0.8, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI$^+$) 256 [M+H:^{79}Br]$^+$ (95%), 254 [M−H:^{79}Br]$^+$ (100%); (CI$^+$, NH_3) 272 [M+NH_3:^{79}Br]$^+$, 258 [M+H:^{81}Br]$^+$, 257 [M:^{81}Br]$^+$, 256 [M+H:^{79}Br]$^+$, 255 [M:^{79}Br]$^+$, 254 [M−H:^{79}Br]$^+$; HRMS (EI) calcd for $C_{11}H_{11}BrS$: 253.9759 [M]$^+$, found: 253.9756 [M]$^+$.

4.1.3.3. Preparation of 2-(2-bromophenyl)-cycloheptanethione, (Table 3, entry 4 substrate). General procedure C was followed employing relevant ketone (430 mg, 1.619 mmol) to yield the *thio-ketone* (181 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3049, 2923, 2848, 2569, 1630, 1587, 1558, 1466, 1446, 1432, 1356, 1343, 1269, 1148, 1026, 979, 750, 726, 685; δ_H (300 MHz, $CDCl_3$) 1.61–1.90 (5H, m, CH_2), 2.27–2.69 (5H, m, ArCHCH_2, CH_2CS and CH_2), 2.70 (1H, br s, Ar–C*H*), 7.08–7.17 (2H, m, Ar–*H*), 7.30 (1H, app. td, *J* 7.2 and 1.5, Ar–*H*), 7.61 (1H, app. dd, *J* 7.9 and 1.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 26.6, 26.8, 32.1, 35.9, 38.5, 122.9, 128.3, 128.7, 130.4, 131.0, 133.5, 137.3, 146.3; *m/z* LRMS (EI$^+$) 284 [M:^{81}Br]$^+$ (12%), 282 [M:^{79}Br]$^+$ (12%), 203 [M−Br]$^+$ (52%), 202 [M−^{81}Br]$^+$ (54%), 201, 173, 160, 147; (CI$^+$, NH_3) 300 [M+NH_3]$^+$, 286 [M+H_2:^{81}Br]$^+$, 285 [M+H:^{81}Br]$^+$, 284 [M:^{81}Br]$^+$, 283 [M+H:^{79}Br]$^+$, 204 [M−^{79}Br]$^+$, 203 [M+H−^{81}Br]$^+$, 202 [M−^{81}Br]$^+$, 201 [M−H−^{81}Br]$^+$; HRMS (EI) calcd for $C_{13}H_{15}BrS$: 282.0072 [M:^{79}Br]$^+$, found: 282.0072 [M:^{79}Br]$^+$.

4.1.3.4. Preparation of 2-(4-fluoro-2-bromophenyl)-cyclohexanethione, (Table 3, entry 5 substrate). General procedure C was followed employing relevant ketone (200 mg, 0.738 mmol) to yield the *thio-ketone* (113 mg, 53%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 2962, 2932, 2858, 2833, 1715, 1644, 1596, 1577, 1483, 1446, 1384, 1336, 1260, 1198, 1016, 872, 815, 666; δ_H (300 MHz, $CDCl_3$) 1.70–1.88 (4H, m, CH_2), 2.00–2.14 (1H, m, ArCHCH_2), 2.41–2.27 (3H, m, ArCHCH_2 and CH_2CS), 2.43 (1H, s, Ar–C*H*), 7.03 (1H, td, *J* 8.4 and 2.5, Ar–*H*), 7.11 (1H, dd, *J* 8.4 and 6.2, Ar–*H*), 7.35 (1H, dd, *J* 8.4 and 2.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.0, 32.1, 34.2, 115.4 (d, J_{CF} 24.2), 126.9, 120.5 (d, J_{CF} 21.1), 131.5 (d, J_{CF} 8.1), 132.8, 139.8 (d, J_{CF} 3.7), 160.1, 163.5; *m/z* LRMS (EI$^+$) 288 [M:^{81}Br] (87%), 286 [M:^{79}Br] (100%); (CI$^+$, NH_3) 208 [M−^{79}Br]$^+$, 207 [M+H−^{79}Br]$^+$, 206 [M−^{81}Br]$^+$, 205 [M−H−^{81}Br]$^+$; HRMS (EI) calcd for $C_{12}H_{12}BrFS$: 285.9822 [M:^{79}Br]$^+$, found: 285.9826 [M:^{79}Br]$^+$.

4.1.4. General procedure (D) for the preparation of benzothiophenes. Exemplified by the preparation of 1,2,3,4-tetrahydro-dibenzothiophene (Table 3, entry 1). Caesium carbonate (180 mg, 0.557 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.009 mmol) and DPEphos (13 mg, 0.022 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.5 mL) prior to the addition of 2-(2-bromophenyl)-cyclohexanethione (100 mg, 0.372 mmol) and the reaction heated to 100 °C for 20 h. After cooling, the reaction mixture was filtered through a plug of Celite and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzothiophene* (52 mg, 74%) as a colourless oil.

4.1.4.1. Preparation of 2,3-dihydro-1*H*-benzo(β)cyclopenta(δ)thiophene (Table 3, entry 3). General procedure D was followed employing the relevant thio-ketone (50 mg, 0.196 mmol) to yield the *benzothiophene* (17 mg, 52%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3058, 2923, 2851, 1699, 1571, 1467, 1428, 1378, 1319, 1296, 1258, 1152, 1066, 1017, 800, 750, 728; δ_H (300 MHz, $CDCl_3$) 2.51–2.62 (2H, m, CH_2), 2.86–2.93 (2H, m, CH_2C═CS), 2.98–3.07 (2H, m, CH_2C═CS), 7.24 (1H, td, *J* 7.5 and 1.3, Ar–*H*), 7.32 (1H, td, *J* 7.5 and 1.3, Ar–*H*), 7.56 (1H, d, *J* 7.5, Ar–*H*),

7.76 (1H, dt, *J* 7.5 and 1.3, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI^+) 174 $[M]^+$ (18%), 173 $[M-H]^+$ (39%); (CI^+, NH_3) 173 $[M]^+$; HRMS (EI) calcd for $C_{11}H_9S$: 173.0419 $[M-H]^+$, found: 173.0415 $[M-H]^+$.

4.1.4.2. Preparation of 6,7,8,9-tetrahydro-5*H*-10-oxabenzothiazulene (Table 3, entry 4).[27] General procedure D was followed employing the relevant thio-ketone (100 mg, 0.369 mmol) to yield the *benzothiophene* (42 mg, 57%) as a yellow solid: mp 65–66 °C. ν_{max} (NaCl)/cm^{-1} 3059, 2921, 2838, 1442, 1435, 1359, 1311, 1262, 1223, 1151, 1090, 1019, 823, 800, 750, 725, 667; δ_H (300 MHz, $CDCl_3$) 1.68–1.82 (4H, m, C*H*$_2$), 1.90–1.99 (2H, m, C*H*$_2$), 2.87–2.96 (4H, m, C*H*$_2$C=CS and C*H*$_2$CS=C), 7.25 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.34 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.62 (1H, d, *J* 7.9, Ar–*H*), 7.75 (1H, dt, *J* 7.9 and 1.1, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 26.0, 26.8, 28.7, 29.3, 31.3, 119.8, 121.1, 122.1, 122.6, 133.2, 137.0, 139.6, 139.9; *m/z* LRMS (EI^+) 202 $[M]^+$ (100%), 173 $[M-C_2H_5]$ (90%), 160 $[M-C_3H_6]$ (45%), 147 $[M-C_4H_7]^+$ (58%); (CI^+, NH_3) 203 $[M+H]^+$, 202 $[M]^+$; HRMS (EI) calcd for $C_{13}H_{14}S$: 202.0811 $[M]^+$, found: 202.0810 $[M]^+$.

4.1.4.3. Preparation of 8-fluoro-1,2,3,4-tetrahydro-dibenzothiophene (Table 3, entry 5). General procedure D was followed employing the relevant thio-ketone (100 mg, 0.369 mmol) to yield the *benzothiophene* (43 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3063, 2932, 2857, 2840, 1603, 1556, 1470, 1446, 1401, 1376, 1349, 1338, 1314, 1298, 1250, 1201, 1150, 1136, 1111, 1069, 1050, 1022, 979, 951, 894, 848, 822, 804, 790, 701, 600, 534; δ_H (300 MHz, $CDCl_3$) 1.85–1.98 (4H, m, C*H*$_2$), 2.69–2.77 (2H, m, C*H*$_2$C=CS), 2.80–2.87 (2H, m, C*H*$_2$CS=C), 7.07 (1H, td, *J* 8.9 and 2.4, Ar–*H*), 7.42–7.51 (2H, m, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.9, 26.0, 30.1, 108.9 (d, J_{CF} 25.4), 112.8 (d, J_{CF} 23.6), 121.5 (d, J_{CF} 8.7), 129.4, 136.7, 137.0, 159.0, 162.1; *m/z* LRMS (EI^+) 206 $[M]^+$ (73%), 205 $[M-H]^+$ (24%), 178 $[M-C_2H_4]^+$ (100%); (CI^+, NH_3) 207 $[M+H]^+$, 206 $[M]^+$; HRMS (EI) calcd for $C_{12}H_{11}FS$: 206.0560 $[M]^+$, found: 206.0561 $[M]^+$.

4.1.4.4. Preparation of 5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3,*β*]pyridine (Table 3, entry 6). The starting ketone (Table 3, entry 6 substrate, 200 mg, 0.738 mmol) was added to a flask charged with phosphorus pentasulfide (82 mg, 0.184 mmol) under nitrogen and the reaction mixture suspended in anhydrous toluene (0.74 mL). The mixture was stirred at room temperature for 10 min prior to the addition of hexamethyldisiloxane (204 mg, 1.250 mmol, 0.27 mL) and heated to 90 °C for 18 h. After cooling the reaction mixture was filtered through a plug of silica and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzothiophene* (113 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3047, 2924, 2855, 2359, 1728, 1584, 1537, 1456, 1392, 1368, 1350, 1336, 1304, 1261, 1240, 1218, 1156, 1136, 1122, 1094, 1069, 1023, 972, 950, 848, 791, 748, 733, 672; δ_H (300 MHz, $CDCl_3$) 1.87–2.01 (4H, m, C*H*$_2$), 2.69–2.77 (2H, m, C*H*$_2$C=CS), 2.84–2.93 (2H, m, C*H*$_2$CS=C), 7.25 (1H, dd, *J* 7.9 and 4.9, Ar–*H*), 7.81 (1H, dd, *J* 7.9 and 1.5, Ar–*H*), 8.46 (1H, d, *J* 3.8, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.6, 23.7, 26.1, 30.1, 119.4, 127.7, 128.2, 138.2, 145.6, 161.2; *m/z* LRMS (EI^+) 189 $[M]^+$ (65%), 161 $[M-C_2H_4]$ (100%); (CI^+, NH_3) 190 $[M+H]^+$; HRMS (ES^+) calcd for $C_{11}H_{12}NS$: 190.0685 $[M+H]^+$, found: 190.0686 $[M+H]^+$.

4.1.4.5. Preparation of 1,2,3,4-tetrahydro-dibenzofuran using a one-pot two-ligand cascade reaction (Scheme 3). Caesium carbonate (1.727 g, 5.301 mmol) was added to a flask charged with $Pd_2(dba)_3$ (81 mg, 0.088 mmol), Xantphos (61 mg, 0.106 mmol) and DPEphos (57 mg, 0.106 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (2.00 mL) and 1-bromo-2-iodobenzene (0.500 g, 1.767 mmol, 0.23 mL) and cyclohexanone (0.260 g, 2.651 mmol, 0.28 mL) were added under nitrogen and the reaction heated to 100 °C for 48 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (0.223 g, 51%) as a colourless oil.

4.1.4.6. Preparation of 1,2,3,4-tetrahydro-dibenzofuran using a one-pot one-ligand cascade reaction (Scheme 4). Caesium carbonate (691 mg, 2.212 mmol) was added to a flask charged with $Pd_2(dba)_3$ (32 mg, 0.035 mmol) and ligand **16** (17 mg, 0.042 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1.00 mL) and 1-bromo-2-iodobenzene (200 mg, 0.707 mmol, 0.09 mL) and cyclohexanone (80 mg, 0.848 mmol, 0.09 mL) were added under nitrogen and the reaction heated to 100 °C for 48 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (0.111 g, 91%) as a colourless oil.

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