Asymmetric Baylis–Hillman reactions: catalysis using a chiral pyrrolizidine base

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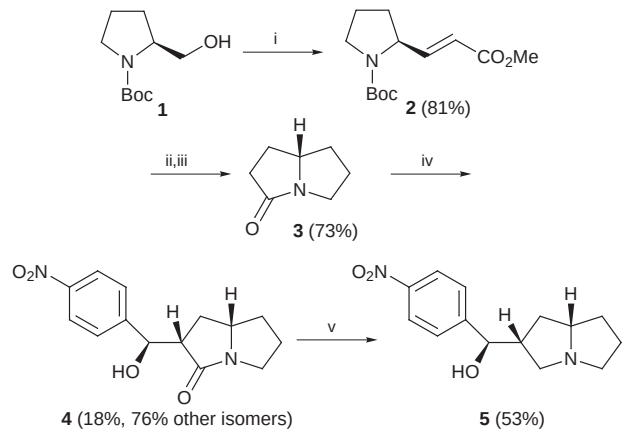
Received (in Liverpool, UK) 3rd August 1998, Accepted 16th October 1998

A novel chiral pyrrolizidine base 5 derived from L-proline promotes the Baylis–Hillman reaction of ethyl and methyl vinyl ketones with electron deficient aromatic aldehydes with moderate levels of enantiomeric excess.

The Baylis–Hillman reaction is a convenient process for the preparation of a β-hydroxy-α-methylene ketone, nitrile, ester, *etc*. in one step from an α,β-unsaturated ketone, acrylonitrile or an acrylic ester and an aldehyde.[1] The reaction is mediated by a tertiary amine, and DABCO (diazabicyclo[2.2.2]octane) is the most common catalyst employed. Whilst the Baylis–Hillman reaction of chiral aldehydes or chiral Michael acceptors has been shown to proceed, in some cases, with high diastereoselectivities, the development of chiral catalysts for the Baylis–Hillman reaction is less well developed. Hirama and Markó have respectively reported the use of chiral derivatives of diazabicyclo[2.2.2]octane[2] and of quinidine or cinchonine[3] as enantioselective catalysts. However, these authors observed only modest levels of enantioselectivities (11–47 and 6–45% ee, respectively) and the requirement to use elevated pressures (3–10 Kbar) to ensure acceptable conversions. We have previously published a two step procedure to effect the enantioselective (50–96% ee) Baylis–Hillman reaction of an aldehyde with an α-methylene ketone *via* a tandem Michael addition–aldol reaction of (phenylthio)- or (phenylselenyl)-trimethylsilane catalysed by a chiral borane Lewis acid followed by oxidative elimination.[4] Recently, Soai and co-workers reported the use of (*S*)-BINAP as a catalyst for the enantioselective (9–44% ee) Baylis–Hillman reaction of pyrimidine-5-carbaldehydes with acrylate esters.[5] This work has prompted us to report the use of pyrrolizidine (1-azabicyclo-[3.3.0]heptane) derivatives as alternative chiral catalysts. We considered that such amines may function as efficient catalysts for the Baylis–Hillman reaction on account of their enhanced basicity relative to common tertiary amines[6] and the accessibility of the nitrogen lone pair. We were concerned, in our design, to seek to alleviate the known slow kinetics of the DABCO catalysed Baylis–Hillman reaction.

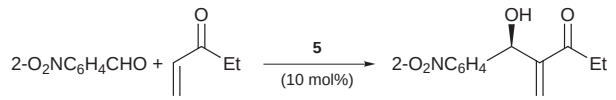
Swern oxidation of Boc-L-prolinol[7] **1** and direct Wittig homologation gave ester **2**[8] (81%) (Scheme 1). Subsequent hydrogenation over Raney nickel, deprotection of the Boc group, under acidic conditions, and lactamisation gave the pyrrolizidinone[9] **3** (73%). Aldol reaction of lactam **3** with 4-nitrobenzaldehyde in the presence of $BF_3{\cdot}OEt_2$ gave a mixture of four β-hydroxy lactams (94%). The less polar component consisted of a single crystalline diastereoisomer **4**†‡ which was readily isolated in 16% yield. The remaining three diastereoisomers co-chromatographed and were not separable at the lactam oxidation stage. Finally, $BH_3{\cdot}SMe_2$ mediated reduction gave the desired pyrrolizidine **5** which was initially isolated as the robust borane adduct but which could be converted into the free base following sequential reflux with methanolic TsOH and K_2CO_3.

The Baylis–Hillman reaction of ethyl vinyl ketone with 2-nitrobenzaldehyde was examined in MeCN or EtCN solution in the presence of pyrrolizidine **5** (10 mol%) at variable temperatures (−75 to 25 °C). All reactions gave rise to the corresponding β-hydroxy-α-methylene ketone **6** (R^1 = 2-$O_2NC_6H_4$, R^2 = Et) (Table 1) which was formed in variable yield and enantioselectivity.§ The yield of the reaction was significantly improved by cooling and no significant decrease in rate was observed until −50 °C. Leahy has reported unusual temperature dependence on conversions in the DABCO mediated Baylis–Hillman reaction of acrylate esters with aldehydes.[10] Although, the yield of the reaction was optimum at −40 °C, enantioselectivities were superior at higher temperatures with a maximum value at −20 °C (47% ee). Since Aggarwal has reported rate enhancements on the use of lanthanide triflates in the Baylis–Hillman reaction,[11] a series of Lewis acid co-catalysts were examined in the synthesis of **6**. Amongst diverse metal salts examined, those of the alkali metals, in particular sodium, were the most effective additives. A series of aldehydes were allowed to react with ethyl or methyl vinyl ketone in the presence of amine **5** (10 mol%) and 1 M $NaBF_4$ or $NaBPh_4$¶ in MeCN at −20 °C (Table 2). The



Scheme 1 *Reagents and conditions*: i, Swern oxidation, CH_2Cl_2, then $Ph_3P{=}CHCO_2Me$; ii, Raney Ni, H_2 (40 psi), MeOH; iii, HCl, EtOAc, 0 °C, then NaOMe, MeOH; iv, Lithium 2,2,6,6-tetramethylpiperidide, THF, −78 to −30 °C, then 4-$O_2NC_6H_4CHO$, $BF_3{\cdot}OEt_2$, −78 to −20 °C; v, $BH_3{\cdot}SMe_2$, THF, reflux, then TsOH, MeOH, reflux, then K_2CO_3, MeOH, reflux.

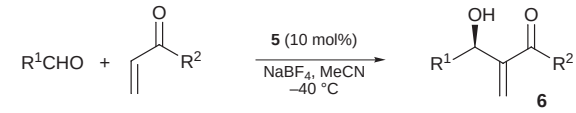
Table 1 Temperature variation in the Baylis–Hillman reaction of 2-nitrobenzaldehyde with ethyl vinyl ketone



T/°C	Yield (%)	Ee (%)	*t*/d	Solvent
25	27	37	3	MeCN
4	21	42	3	MeCN
−10	57	30	3	MeCN
−20	50	47	2	MeCN
−30	53	31	2	MeCN
−40	93	26	2	MeCN
−75	9[a]	21	3	EtCN

[a] This slow reaction was stopped before reaching completion.

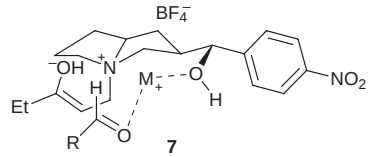
Table 2 Baylis–Hillman reactions of aldehydes with ethyl or methyl vinyl ketones



R^1	R^2	Yield (%)	Ee (%)[a]	*t*/h
2-$O_2NC_6H_4$	Et	71	67	18
2-$O_2NC_6H_4$	Me	71	53	18
2-FC_6H_4	Et	31	63	48
2-ClC_6H_4	Et	58	72	14
2-BrC_6H_4	Et	63	71	72
3-$O_2NC_6H_4$	Et	51	37	18
2-Pyridyl	Et	83	21	14
3-Pyridyl	Et	93	49	12
4-Quinolinyl[b]	Et	63	70	18
4-$O_2NC_6H_4$	Et	17	39	48

[a] Determined by HPLC analyses (Chiralcel OD-H and AD). [b] Reaction carried out using $NaBPh_4$ not $NaBF_4$.

corresponding β-hydroxy-α-methylene ketones **6** were isolated in modest to excellent yields (17–93%) and with acceptable levels of enantioselectivity (21–72% ee).‖ The absolute configuration of ketone **6** (R^1 = 2-$O_2NC_6H_4$, R^2 = Me) was determined to be *R* by comparison of the sign of its specific rotation with that of the antipodal ketone.** The absolute stereochemistry of the other β-hydroxy-α-methylene ketones **6** were assigned by analogy since all were laevorotatory. It is reasonable to speculate that the reaction may proceed *via* the intermediate **7** rather than the more sterically congested system **8**. The importance of hydroxy substitution on enhancing the rate



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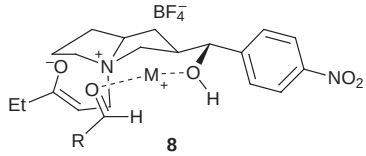

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of Baylis–Hillman reactions is well known[1] and is exemplified by the fact that 3-hydroxyquinuclidine is a superior catalyst to quinuclidine. Such an effect may also be of significance in both the catalysis by pyrrolizidine **5** and the enhancement of enantioselectivity in the presence of sodium ions. Further studies of this variant of the Baylis–Hillman reaction are now being investigated in our laboratory.

We thank Zeneca, Chiroscience, the EPSRC and the DTI for generous support under the Link Asymmetric Scheme; Glaxo-Wellcome Research Ltd for the most generous endowment (to A. G. M. B.); the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College; and George O'Doherty, Oswy Pereira and D. Christopher Braddock for helpful discussions.

Notes and references

† All new compounds were fully authenticated by spectroscopic data and microanalysis and/or HRMS.

‡ The structure of **4** and related β-hydroxy lactams and pyrrolizidines, which were confirmed by X-ray crystallography, will be reported elsewhere.

§ Enantioselectivities of all reactions were determined by HPLC analyses on Chiralcel OD-H and AD columns and, in some cases, by ^{1}H NMR spectroscopy in the presence of the chiral the shift reagent Eu(tfc)$_3$.

¶ For the use of lithium salts to enhance the rate of reactions proceeding *via* ionic intermediates, see ref. 12.

‖ *General experimental procedure* (Table 2, entry 4): **6** (R^1 = 2-ClC_6H_4, R^2 = Et)·$NaBF_4$ (27 mg, 0.25 mmol) followed by 2-chlorobenzaldehyde (26 μl, 0.22 mmol) were added to a stirred suspension of amine **5** (5 mg, 0.019 mmol) in MeCN (0.25 ml) under nitrogen at –40 °C. The reaction mixture was stirred for a further 10 min when ethyl vinyl ketone (19 μl, 0.19 mol) was added and stirring continued for 24 h. The mixture was concentrated *in vacuo* and the residue chromatographed (1:6 EtOAc–hexanes, R_f 0.3) to yield the title compound **6** (R^1 = 2-ClC_6H_4, R^2 = Et) (24.8 mg, 58%) as a colourless oil.

** The absolute stereochemistry of the major adduct **6** (R^1 = 2-$O_2NC_6H_4$, R^2 = Me) was determined by comparison of the sign of the specific rotation with literature data on (4*R*)-4-hydroxy-3-methylene-4-(2-nitrophenyl)butan-2-one, which was prepared by an enantioselective Baylis–Hillman reaction (11–42% ee) and by the partial kinetic resolution of the racemic compound by Sharpless epoxidation using L-(+)-diethyl tartrate (see ref. 2).

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Communication 8/06115G