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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of homochiral Baylis–Hillman products employing (*R*)-*N*-methyl-*N*-α-methylbenzyl amide

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Abstract

The conjugate addition of (*R*)-*N*-methyl-*N*-α-methylbenzyl amide to *tert*-butyl cinnamate followed by an asymmetric aldol reaction and subsequent *N*-oxidation/Cope elimination affords β-substituted homochiral Baylis–Hillman products in good yield.

The Baylis–Hillman reaction involves the condensation of an aldehyde and an acrylate ester, catalysed by the presence of a tertiary amine to afford α-methylene-β-hydroxy-esters.[1] These compounds have proven to be useful synthetic intermediates,[2] and have been shown to serve as useful synthons for stereoselective synthesis.[3] Various attempts have been made to develop an asymmetric version of this reaction to afford allylic alcohols in enantiomerically enriched form.[4] For example, Brzezinski et al. have reported an asymmetric Baylis–Hillman reaction which utilises Oppolzer's sultam auxiliary to generate adducts in >99% e.e.[5] This methodology is limited, however, to aldehydes unbranched at the α-position. Barrett et al. have probed the use of a chiral pyrrolizidine in promoting the coupling of vinyl ketones with aromatic aldehydes with poor to moderate levels of asymmetric induction (21–47% e.e.).[6] Similar levels of selectivity were also observed when using (*S*)-BINAP as a catalyst for the reaction of pyrimidine-5-carbaldehydes and acrylate esters.[7] All of these approaches are limited, however, to the use of acrylate derived systems, and we wish to address this structural limitation by developing methodology applicable to a wider range of substrates. We report herein on a protocol based on the diastereoselective conjugate addition of lithium amides to α,β-unsaturated esters,[8] which may be employed as a synthetic equivalent of an asymmetric Baylis–Hillman reaction.

We have previously demonstrated that β-amino ester **1** derived from conjugate addition of (*R*)-*N*-methyl-*N*-α-methylbenzyl amide **2** to *tert*-butyl (*E*,*E*)-hexa-2,4-dienoate **3** readily undergoes Cope elimination via *N*-oxide **4** when treated with MCPBA in $CHCl_3$ (Scheme 1).[9]

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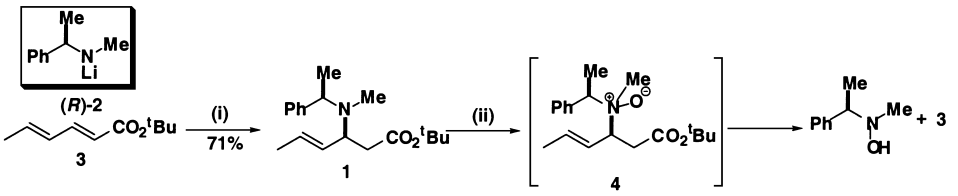
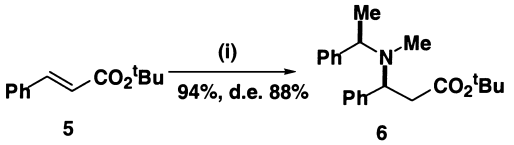


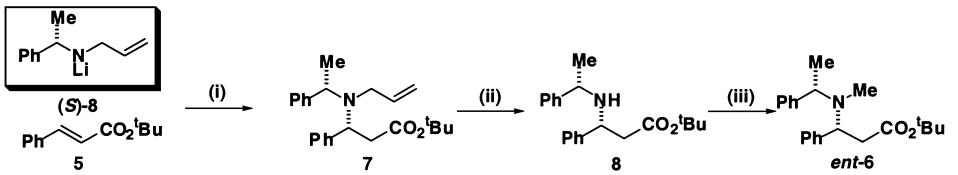
Scheme 1. *Reagents and conditions*: (i) 1.6 equiv. (*R*)-**2**, THF, –78°C; then NH_4Cl (aq); (ii) MCPBA, $CHCl_3$, rt

We wished to exploit this facile elimination process for the development of an asymmetric Baylis–Hillman reaction. It was proposed that this could be achieved via a three-step strategy involving the conjugate addition of lithium amide **2** to a Michael acceptor; an asymmetric aldol reaction and finally subsequent *N*-oxidation/Cope elimination. Accordingly, conjugate addition of lithium amide (*R*)-**2** to *tert*-butyl cinnamate **5** gave β-amino ester **6** in 88% d.e. and in excellent yield (Scheme 2).



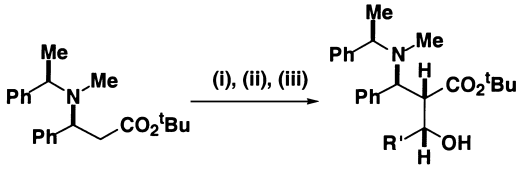
Scheme 2. *Reagents and conditions*: (i) 1.6 equiv. (*R*)-**2**, THF, –78°C; then NH_4Cl (aq)

Purification to homogeneity of β-amino ester **6** proved problematic since repeated chromatography did not enhance the diastereomeric excess from 88% and therefore the minor diastereoisomer remained as an impurity in the product. The configuration of the new stereogenic centre at C(3) of **6** was assigned as (*S*). This assignment is based on the transition state model previously developed for the addition of this class of lithium amide to Michael acceptors, which demonstrated that the facial selectivity for these conjugate additions is controlled by the stereogenic centre of the α-methylbenzyl fragment of the lithium amide.[10] This assignment was confirmed by comparison with authentic *ent*-**6** which was prepared from the known β-amino ester **7** according to the protocol described in Scheme 3. Therefore, conjugate addition of (*S*)-*N*-allyl-*N*-α-methylbenzyl amide **8** to *tert*-butyl cinnamate **5** gave β-amino ester **7** which was deallylated with Wilkinson's catalyst to give monoprotected β-amino ester **8**.[11] Subsequent treatment of **8** with MeI gave *ent*-**6**.



Scheme 3. *Reagents and conditions*: (i) 1.6 equiv. (*S*)-**8**, THF, –78°C; then NH_4Cl (aq); (ii) $(PPh_3)_3RhCl$, $MeCN/H_2O$ (5:1), Δ; (iii) MeI, neat, rt

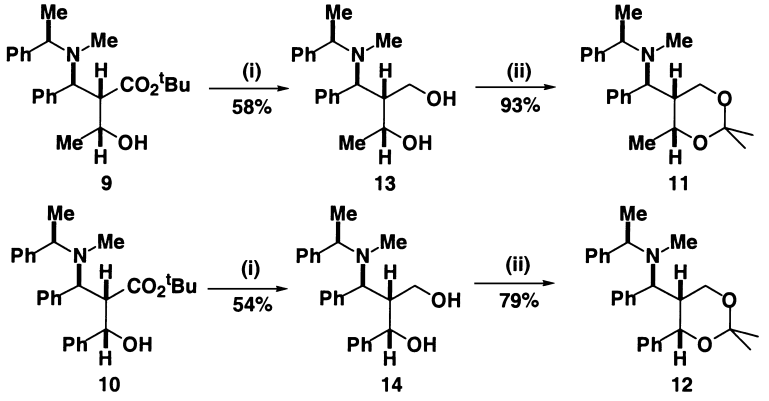
β-Amino ester **6** (d.e. 88%) was then subjected to an asymmetric aldol reaction, whereby deprotonation with LDA followed by transmetallation with trimethyl borate afforded a boron enolate which reacted with either acetaldehyde or benzaldehyde to afford the desired aldol products **9** and **10** in good d.e.[12] The major diastereoisomeric aldol product in each case could be easily purified to homogeneity by flash chromatography at this stage (Scheme 4).



	R'	d.s.	Yield (%)†	$[\alpha]_D^{22}$
9	Me	93:7	76	+56.5 (c 1.28, $CHCl_3$)
10	Ph	92:8	62	+68.0 (c 0.95, $CHCl_3$)

Scheme 4. *Reagents and conditions*: (i) 3 equiv. LDA, THF, –78°C; (ii) $B(OMe)_3$, THF, –78°C; (iii) MeCHO or PhCHO, THF, –78°C.† Yield refers to isolated yield of pure major diastereomer.

In order to establish the absolute stereochemistry of the two new stereogenic centres formed in the aldol reaction, **9** and **10** were converted into the acetonides **11** and **12**, respectively, via a protocol involving reduction with lithium aluminium hydride in THF and treatment of the resulting diol **13** and **14** with dimethoxypropane and CSA in acetone (Scheme 5).

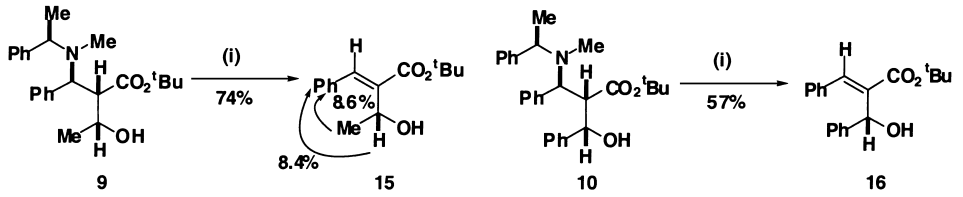


Scheme 5. *Reagents and conditions*: (i) $LiAlH_4$, THF, rt; (ii) $(MeO)_2CMe_2$, CSA, acetone, Δ

^{1}H NMR spectroscopic analysis of acetonides **11** and **12** confirmed the relative stereochemistries of the newly formed stereogenic centres of the aldol products **9** and **10**. The absolute configurations of these centres follow from the known stereochemistry of substrate **6** and the established stereochemical bias observed for aldol reactions of (*E*)-β-amino ester enolates.[13]

Treatment of **9** with MCPBA in $CHCl_3$ resulted in *N*-oxidation and Cope elimination to afford the Baylis–Hillman adduct **15** as a single diastereoisomeric product in 74% yield. ^{1}H NMR spectroscopic analysis via NOE difference experiments was indicative of the (*E*) geometry of the double bond. This assignment is consistent with the well-documented *syn*-elimination of *N*-oxides

during Cope elimination and follows from the known stereochemistry of aldol product **9**.[14] Similar treatment of **10** afforded its Baylis–Hillman product **16** also as a single diastereoisomer in 57% yield. Authentic scalemic samples of **15** and **16** were obtained for comparative purposes via repetition of this three stage protocol using a 2:1 (*R*):(*S*) mixture of lithium *N*-methyl-*N*-α-methylbenzyl amide **2** in the initial conjugate addition. This enabled the enantiomeric excess of **15** and **16** to be determined as >99% e.e. via chiral HPLC analysis using a Chiralpak OD stationary phase (Scheme 6).



	e.e. (%)	Yield (%)	$[\alpha]_D^{22}$
15	>99	74	+93.7 (c 0.75, $CHCl_3$)
16	>99	57	+209.3 (c 0.61, $CHCl_3$)

Scheme 6. *Reagents and conditions*: (i) 2 equiv. MCPBA, $CHCl_3$, rt

In conclusion, we have demonstrated that (*R*)-*N*-methyl-*N*-α-methylbenzyl amide **2** is an efficient chiral auxiliary for the asymmetric synthesis of homochiral Baylis–Hillman products. Our novel synthetic approach involves conjugate addition of lithium amide **2** to *tert*-butyl cinnamate to afford β-amino ester **6**, reaction of the boron enolate of **6** with either acetaldehyde or benzaldehyde and subsequent *N*-oxidation/Cope elimination to afford the desired homochiral Baylis–Hillman products **15** and **16**. Importantly, deploying the enantiomer of lithium amide (*R*)-**2** in the initial conjugate addition step will allow simple access to *ent*-Baylis–Hillman products. The extension of this methodology to α,β-unsaturated acceptors other than cinnamate esters is currently under investigation.

Acknowledgements

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