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The asymmetric alkylation of dimethylhydrazones; intermolecular chirality transfer using sparteine as chiral ligand†

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The asymmetric alkylation of ketones represents a fundamental transformation in organic chemistry. Chiral auxiliaries have been used almost exclusively for this transformation. Herein we describe a strategy for the generation of enantiomerically enriched α-alkylated ketones up to an er of 83 : 17, using a chiral ligand protocol.

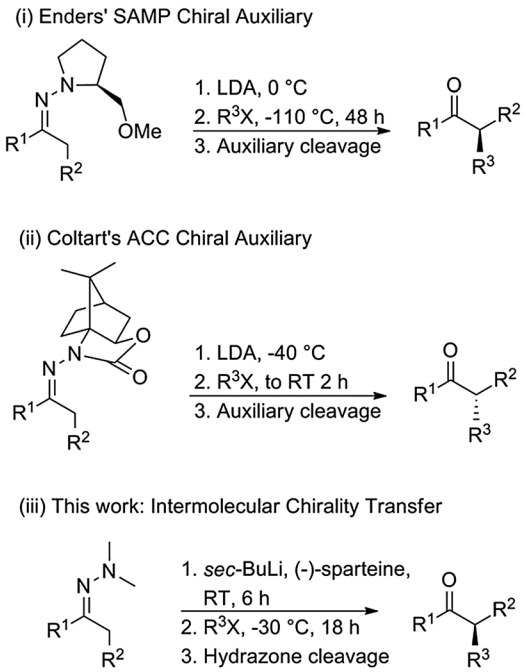
A large number of optically active drugs and natural products contain α-functionalized ketones, or simple derivatives there-of. Furthermore, chiral α-alkylated ketones are very useful synthons and have found widespread use in total synthesis.[1] Thus, the asymmetric alkylation of ketones represents a very useful transformation in organic chemistry. Surprisingly however, only one effective methodology is available for acyclic systems, and this involves the use of chiral auxiliaries.

The well-known, proline derived, SAMP/RAMP auxiliaries (Scheme 1(i)) have found numerous applications in asymmetric alkylation.[1c] For example, Nicolaou *et al.* applied the SAMP auxiliary of 3-pentanone in an asymmetric alkylation en route to swinholide A.[2] More recently Coltart has introduced *N*-amino cyclic carbamate (ACC) chiral auxiliaries (Scheme 1(ii)).[3] These auxiliaries do not require the extremely low alkylation temperatures used with SAMP/RAMP hydrazones. The ACC methodology has already been utilized in the synthesis of several biologically important compounds.[4]

Moreover, it is worth noting that despite the advances in the use of homo chiral lithium amide bases,[5] transition metal catalysis[6] and organocatalysis,[7] none of these areas of research have managed to achieve the asymmetric α-alkylation of acyclic ketones.

Our approach to chiral α-alkylated ketones involves the use of simple non-chiral dimethylhydrazones and effecting their asymmetric alkylation using a chiral diamine ligand (Scheme 1(iii)).

The use of lithium bases to furnish small aliphatic α-alkylated ketones, often proceeds in poor yield.[8] In light of this, we chose the dimethylhydrazone methodology.[9] Additionally, we postulated that deprotonation using an alkyl lithium–chiral diamine system would furnish a highly structured azaenolate benefiting from added chelation of the dimethylamino group (Scheme 2). Subsequent alkylation with high facial selectivity could provide chiral, alkylated dimethylhydrazones.



Scheme 1 Comparison of previously used methodology and our work.

Of the numerous chiral diamines available,[10] (−)-sparteine ((−)-sp) was chosen due to its efficiency and breadth of application.[11] For example, (−)-sp/lithium systems have proven useful in a number transformations involving asymmetric deprotonations and substitutions.[12] O'Brien and co-workers have used (−)-sp in the catalytic asymmetric deprotonation of *N*-Boc pyrrolidine.[13]

Firstly, 3-pentanone dimethylhydrazone **1**, 4-heptanone dimethylhydrazone **2** and cycloheptanone dimethylhydrazone

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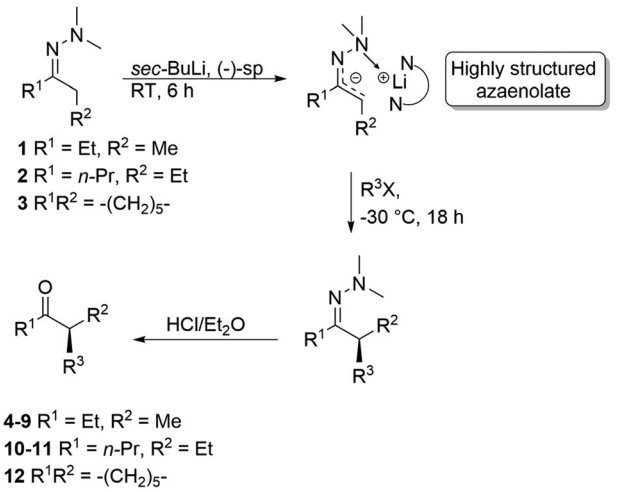


Scheme 2 General scheme for asymmetric alkylations *via* intermolecular chirality transfer.

Table 1 Solvent optimization studies on the dimethylhydrazones of 3-pentanone

Entry	Ligand	R^3X	Solvent	Yield[a] (%)	Ketone	er[c] *R* : *S*
1	(−)-sp	BnBr	THF	40	**4**	Racemic
2	(−)-sp	BnBr	Toluene	57	**4**	24 : 76
3	(−)-sp	BnBr	Cumene	62[b]	**4**	25 : 75
4	(−)-sp	BnBr	Benzene	45	**4**	31 : 69
5	(−)-sp	BnBr	Cyclohexane	23	**4**	31 : 69
6	(−)-sp	*n*-PeI	Toluene	34	**5**	17 : 83
7	(−)-sp	*n*-PeI	MTBE	32	**5**	33 : 67
8	(+)-sp	*n*-PeI	Et_2O	43	**5**	78 : 22

[a] Isolated yields over 2 steps after purification by column chromatography. [b] Yield determined using NMR and 1,3,5-trimethoxybenzene as internal standard. [c] er determined by chiral GC and absolute configuration assigned based on the optical rotation data of **4** and inferred for the others.

3 were prepared in near quantitative yields using dimethylhydrazine in the presence of a catalytic amount of AcOH. We focused our initial studies on establishing an optimum solvent for these reactions. Hydrazone **1** was subjected to (−)-sp/*sec*-BuLi deprotonation (room temperature for 6 h) and alkylated with either benzyl bromide or 1-iodopentane (−30 °C for 18 h), in a range of solvents (Table 1). The resultant alkylated hydrazones were hydrolysed using a biphasic 4 M HCl–diethyl ether system and the enantiomeric excess of the ketones **4** and **5** determined.[14] The enantioselectivity showed a high solvent dependence. The use of THF as solvent, afforded ketone **4** with no enantioenrichment (entry 1), probably due to competing coordination with (−)-sp to lithium.[15] Cumene as solvent gave good conversion to alkylated ketone (62% NMR yield over 2 steps) (entry 3).[16] The use of benzene, cyclohexane and MTBE gave poor enantioselectivity (entries 4, 5 and 7, Table 1). Diethyl ether afforded ketone **5** in good enantioselectivity (78 : 22 er) and moderate yield (43%) over 2 steps (entry 8). In this case, to demonstrate the accessibility of both enantiomers of the chiral ketone, (+)-sp was utilised.

Toluene was found to be the prime solvent for these reactions giving the best enantioenrichment of both **4** and **5**, 24 : 76 er (entry 2) and 17 : 83 er (entry 6), respectively. While conversion to product in toluene was high, yields remained moderate, most likely due to the high volatility of the resulting ketones.[17]

Table 2 Substrate scope in asymmetric alkylations using sparteine as chiral ligand

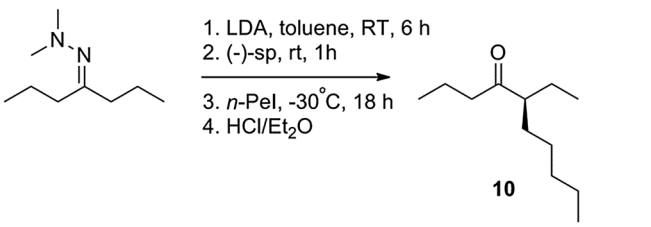
Entry[a]	Ligand	Hydrazone	R^3X	Yield[b] (%)	Ketone	er[c] *R* : *S*
1	(−)-sp	**1**	*n*-PeI	34	**5**	17 : 83
2	(+)-sp	**1**	*n*-PeI	31	**5**	81 : 19
3	(−)-sp	**1**	BnBr	57	**4**	24 : 76
4	(−)-sp	**1**	$C_6H_5CH{=}CHCH_2Br$	30	**6**	21 : 79
5	(+)-sp	**1**	$2\text{-}CH_3C_6H_4CH_2Br$	54	**7**	76 : 24
6	(+)-sp	**1**	$C_6(CH_3)_5CH_2Br$	60	**8**	81 : 19
7	(+)-sp	**1**	$4\text{-}t\text{-}BuC_6H_4CH_2Br$	62	**9**	71 : 29
8	(−)-sp	**2**	*n*-PeI	39	**10**	18 : 82
9	(+)-sp	**2**	*n*-HexI	53	**11**	80 : 20
10	(+)-sp	**3**	AllylBr	19	**12**	68 : 32[d]

[a] All reactions were performed in anhydrous toluene using optimized conditions as shown in Scheme 2. [b] Isolated yields over 2 steps after purification by column chromatography. [c] er determined by chiral GC. [d] Absolute configuration not determined.

Next we probed the scope of the reaction with a range of simple alkyl halides (Table 2). A clear trend is apparent, with the long chain alkyl halides proving less reactive (entries 1, 2, 8 and 9) compared with benzyl bromides (entries 3 and 5–7). Introduction of *n*-pentyl and *n*-hexyl moieties require an iodide leaving group. However, these slower reacting electrophiles did result in products (**5**, **10**, **11**) displaying the highest enantioenrichment.

The introduction of a methyl group at the 2-position of benzyl bromide (entry 5) had no effect on enantioselectivity in comparison to the unsubstituted benzyl bromide (entry 3), but the use of pentamethyl benzyl bromide showed a distinct increase in enantioselectivity (entry 6) in the final ketone. Also increased yields were observed for electrophiles resulting in less volatile ketone products (entries 6 and 7). Finally, cycloheptanone dimethylhydrazone was subjected to the standard conditions. The resulting allylated ketone **12** was isolated in 19% yield with an er of 68 : 32.

Interestingly, deprotonation of hydrazone **2** with LDA, followed by subsequent addition of (−)-sp, *n*-iodopentane and hydrolysis gave **10** in an er of 21 : 79 (Scheme 3). Significantly, only a slight drop in enantiomeric excess and yield is noticed in comparison to reaction when (−)-sp is added prior to deprotonation (entry 8, Table 2). In light of this we postulate that



Scheme 3 Deprotonation prior to (−)-sp addition.

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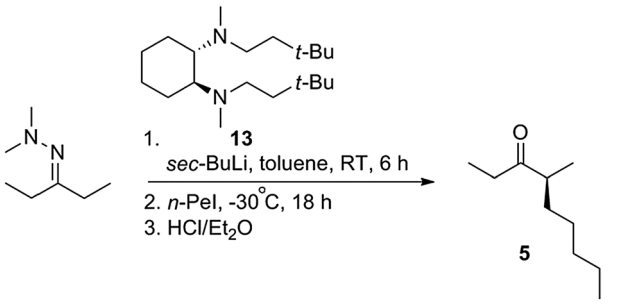

Scheme 4 Use of an easily-prepared chiral diamine.

asymmetric alkylation rather than (or at least in addition to) asymmetric deprotonation is operative.[18] Interestingly, the low nucleophilicity of LDA indicates that this methodology could be extended to the α-substitution of hydrazones derived from aldehydes, and esters.

Preliminary investigations show that easily-prepared chiral diamines such as **13**[19] can mediate these transformations also (Scheme 4). In contrast to sparteine, these ligands can be easily modified. Optimisation of ligands such as **13** and application to asymmetric alkylation reactions are currently underway.

In summary, to the best of our knowledge this report details the first example of asymmetric alkylation to a non-chiral acyclic aza(enolate). Optimisation studies involving the use of other chiral diamines are ongoing and will be reported in due course.

We thank Science Foundation Ireland (09/RFP/CHS2353) and the Irish Research Council for funding.

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