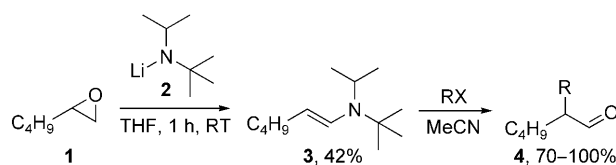


Asymmetric Synthesis of α -Alkylated Aldehydes using Terminal Epoxide-Derived Chiral Enamines**

David M. Hodgson* and Naeem S. Kaka

Access to chiral α -alkyl aldehydes is important, not only for potentially direct use in the fragrance industry,^[1] but also due to the diverse reactions they undergo [addition reactions with a vast range of nucleophiles (notably C–C bond formation) generating alcohols, imines, amine formation by reductive amination, olefination, etc.], which provide many possibilities for introducing asymmetry into molecules. However, the synthesis of enantioenriched mono- α -alkylated aldehydes remains a non-trivial problem and methods to directly access them are limited.^[2] Currently, the most popular method to generate enantioenriched aldehydes directly by an α -alkylation strategy, Enders' lithiated SAMP/RAMP hydrazone chemistry,^[3] typically involves very low temperatures (-80°C to -120°C) and a separate step (e.g. ozonolysis) is necessary to cleave the chiral auxiliary. Approaches involving alkylation at a higher (e.g. amide) oxidation level, such as Evans' oxazolidinone and Myers' pseudoephedrine chiral auxiliary-based protocols require further manipulation to give the aldehyde.^[4] In 2004, Vignola and List reported the intramolecular asymmetric α -alkylation of iodoalkyl aldehydes using a proline catalyst.^[5] The well-known issue of irreversible *N*-alkylation either at the free amine or, more problematically at the enamine stage is likely avoided in this case as the *trans*-enamine intermediate is unable to intramolecularly *N*-alkylate (due to geometric constraints). In 2006, Ibrahim and Córdova developed the α -allylation of aldehydes, using a combination of palladium- and organo-catalysis; asymmetric allylation was also reported (up to 87:13 e.r., but in 25 % yield).^[6] More recently, MacMillan and co-workers disclosed efficient enantioselective catalytic intermolecular α -allylation of aldehydes using allylsilanes (up to 97.5:2.5 e.r.), proceeding by one-electron oxidation of transient enamine species.^[7]

We recently reported the synthesis of enamines (e.g. **3**, Scheme 1) from terminal epoxides (e.g. **1**) and hindered lithium amides (e.g. **2**).^[8] In that work, lithium 2,2,6,6-tetramethylpiperidide (LTMP) derived enamines formed efficiently but did not satisfactorily react with electrophiles,



Scheme 1. Terminal epoxide-derived enamine synthesis and subsequent alkylation.^[8]

whereas the formation of acyclic lithium amide derived enamines such as **3** was less satisfactory, but the latter readily gave α -alkylated aldehydes **4** on reaction with electrophiles. Here, we describe the efficient preparation of a new class of hindered enamines from terminal epoxides, where this enamine class also undergoes synthetically viable *C*-alkylation, and with promising levels of asymmetric induction.

Attention focused on lithium 2,2,6-trisubstituted piperidide-derived enamines **5** (Figure 1). We envisaged that such

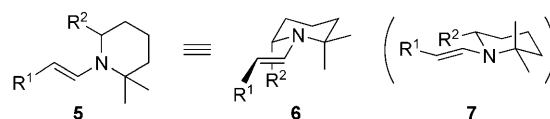


Figure 1. Enamine **5**.

lithium amides would, like LTMP, be basic and hindered enough to form enamines via α -lithiation of terminal epoxides in good yields (with minimal allylic alcohol/1,2-amino alcohol side products).^[8,9] Also however, we anticipated that unlike LTMP-derived enamines, such trisubstituted piperidide-derived enamines would undergo alkylation to generate α -alkylated aldehydes. In the latter analysis, the $n \rightarrow \pi^*$ overlap, essential for reactivity would be achievable by the single *C*-6 substituent (R^2 on the piperidine) residing axial to minimize $A^{1,3}$ strain (conformer **6**, Figure 1).^[10]

So as to examine the above strategy, lithium 2,2,6-trimethylpiperidide (LTriMP) **8a-Li** (readily accessed by dechloromethylation of *N*-chloro-2,2,6,6-tetramethylpiperidine,^[11,12] followed by reduction of the resulting imine and subsequent addition of *n*BuLi) was reacted with 1,2-epoxyhexane **1** giving enamine **5a** in good yield (76 %).^[13] The chemical shift difference between the two olefinic protons of enamine **5a** is 1.4 ppm, indicative of traditional enamine-like character^[8,14] and suggestive that reaction should be viable with a variety of activated and unactivated electrophiles; this was observed to be the case (Table 1).^[15] Not only addition to Michael acceptors, but also more significantly substitution using activated organohalides (α -bromoacetates, benzyl, allyl and propargyl bromide) gave the corresponding α -substituted

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Table 1: Synthesis and reaction of enamine **5a**.

Entry ^[a]	Electrophile [RX]	T [°C]	Product	Yield [%]
1	methyl acrylate ^[b]	82	4a	80
2	acrylonitrile ^[b]	82	4b	70
3	MeO ₂ CCH ₂ Br	RT	4c	89
4	<i>t</i> BuO ₂ CCH ₂ Br	RT	4d	69
5	PhCH ₂ Br	RT	4e	98
6	CH ₂ =CHCH ₂ Br	RT	4f	96
7	HC≡CCH ₂ Br	RT	4g	87
8	MeI ^[c]	40	4h	67
9	EtI	65	4i	71
10	PrI	75	4j	67
11	BuI	82	4k	67
12	C ₁₀ H ₂₁ I ^[b]	94	4l	62
13	<i>i</i> PrI ^[d]	94	4m	61

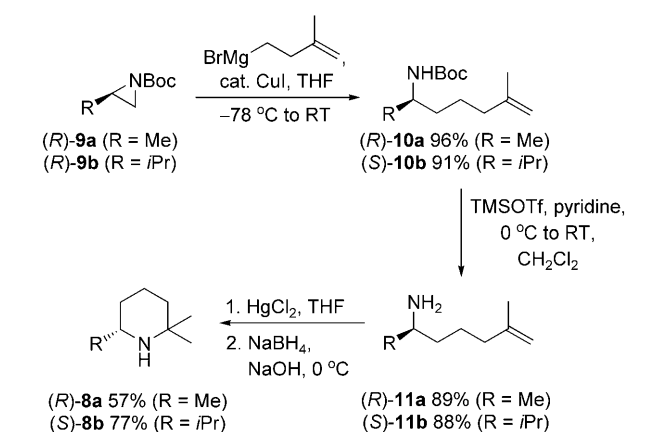
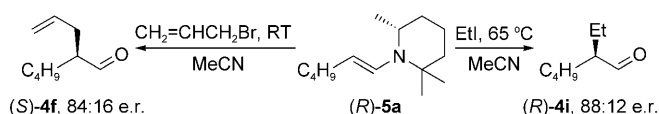
[a] 16 h reaction time in sealed tube with 2 equivalents of electrophile, unless otherwise stated. [b] 20 h reaction time. [c] 3 equivalents used. [d] 42 h reaction time.

aldehydes in good to excellent yields (Table 1, entries 1–7). Alkylation with propargyl bromide yielded only the propargyl-substituted aldehyde with none of the corresponding allene observed; this result shows that *N*-alkylation followed by [3,3] sigmatropic rearrangement is not occurring.^[14] Importantly, a range of short-, longer-chain and secondary unactivated alkyl iodides also proved viable (Table 1, entries 8–13).

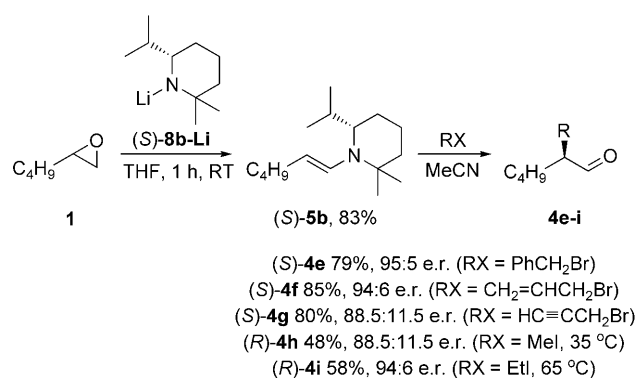
Standard work-up of representative alkylations (Table 1, entries 6 und 9), but using deuterated materials (AcOD/NaOAc/D₂O) resulted in no deuterium incorporation at the α -position of the alkylated aldehyde, suggesting that if an enantiopure enamine underwent completely stereoselective alkylation, then enantiopure aldehydes should be obtained on hydrolysis of the iminium intermediate. So as to ascertain how effective 2,2,6-trimethylpiperidine (TriMP) **8a** would be in this context, (*R*)-TriMP (*R*)-**8a** (>99.5:0.5 e.r.) was synthesized by copper-catalyzed Grignard ring-opening of enantiopure 2-substituted aziridine (*R*)-**9a**^[16] (available from aminolytic kinetic resolution of the corresponding racemic epoxide),^[17] followed by formal intramolecular hydroamination (Scheme 2).

Enamine (*R*)-**5a** was found to undergo alkylation with allyl bromide and EtI in 84:16 e.r. and 88:12 e.r., respectively, with the sense of asymmetric induction as shown in Scheme 3.^[12]

Given the encouraging e.r. values obtained using (*R*)-TriMP, we next sought an amine with a sterically more demanding group at C-6 in order to examine if this would lead to higher stereoselectivity. An isopropyl substituent should still not be prevented from residing axial (*A* values for Me and *i*Pr-substituted cyclohexane are 7.3 and 9.3 kJ mol⁻¹, respectively),^[18] however, with the methine C–H of this group pointing inward (to minimize 1,3-diaxial interactions), it was considered that one of the two methyl groups at the branch


Scheme 2. Asymmetric synthesis of 6-alkyl-2,2-dimethylpiperidines (*R*)-**8a** and (*S*)-**8b**.

Scheme 3. Asymmetric alkylation of enamine (*R*)-**5a**.

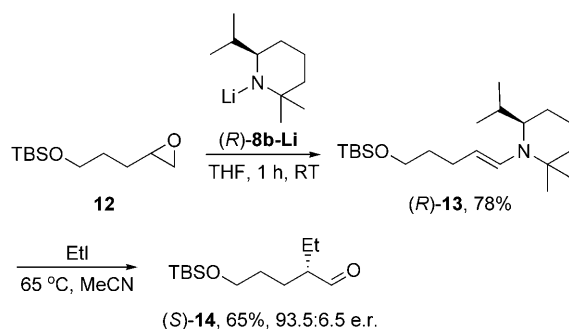
point should provide more efficient impediment to electrophile approach from the lower face [conformer **6** (*R*² = *i*Pr), Figure 1]. (*S*)-6-Isopropyl-2,2-dimethylpiperidine (*S*)-**8b** was synthesized by a similar sequence to that for (*R*)-TriMP (Scheme 2). Reaction of the corresponding lithiated amide (*S*)-**8b**-Li gave the enamine (*S*)-**5b** in very good yield (83%, Scheme 4). Although the difference in chemical shift between


Scheme 4. Synthesis and asymmetric alkylation of enamine (*S*)-**5b**.

the two olefinic protons of enamine (*S*)-**5b** was only 0.3 ppm (0.5 ppm was found for the corresponding unreactive LTMP-derived enamine),^[8] enamine (*S*)-**5b** underwent reaction with strongly electrophilic benzyl, allyl, and propargyl bromides in very good yields and with short chain alkyl iodides, MeI and EtI, in satisfactory yields. These data suggest that whilst the preferred conformer of enamine (*S*)-**5b** may resemble **7** (*R*² = *i*Pr, Figure 1), access to reactive conformer **6** (*R*² = *i*Pr) is achievable. Significantly, improved levels of asymmetric

induction, compared with TriMP-derived enamine (*R*)-**5a** were observed (up to 95:5 e.r.).

So as to exemplify the above methodology with a functionalized terminal epoxide, aldehyde (*S*)-**14**, an intermediate in Nicolaou's synthesis of the ionophore antibiotic indanomycin (X-14547A)^[19] was generated in good yield (65%) and 93.5:6.5 e.r. from the corresponding chiral enamine (*R*)-**13** (Scheme 5); the latter being obtained from terminal epoxide **12**^[20] and (*R*)-**8b-Li** in very good yield (78%).



Scheme 5. Asymmetric synthesis of aldehyde (*S*)-**14** using enamine (*R*)-**13**.

In summary, we describe the first lithium amides capable of efficiently converting terminal epoxide into enamine functionality, where the latter demonstrate effective *C*-alkylation activity. With chiral lithium amides, the corresponding enamines provide the first direct access to α -alkylated aldehydes with high asymmetric induction by intermolecular nucleophilic substitution.

Experimental Section

Representative procedure for enamine alkylation: a solution of enamine (1 mmol) and electrophile (2 mmol) in MeCN (1 mL) was stirred in a sealed tube at the stated temperature for the indicated time. A solution of AcOH (0.125 g), NaOAc (0.125 g) in water (0.25 mL) was then added and the mixture allowed to stir at room temperature for 10 min, before being partitioned between water (10 mL) and Et₂O (10 mL). The aqueous phase was washed with Et₂O (10 mL) and the combined organic layers were washed with brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography gave the aldehyde.

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