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A Rapid, Simple Route to Homochiral α,β-Epoxyketones

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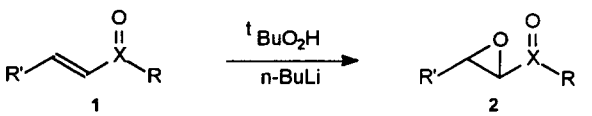
Abstract: *Substituted E- or Z-acrylylamides derived from a homochiral amine such as (R,R)-2,5-dimethylpyrrolidine or (S,S)-bis(2-phenylethyl)amine are readily epoxidised with complete stereocontrol with t-BuO$_2$Li to give two readily separated, enantiomerically pure diastereomeric epoxides. The easily separated epoxides are efficiently converted into α,β-epoxyketones by the action of organolithiums with 92->99% ee.*

We have shown that *t*-BuO$_2$Li, generated *in situ* from *t*-BuO$_2$H and BuLi, efficiently transforms α,β-unsaturated esters, amides, sulfones (**1**) etc. into the corresponding epoxides (**2**) with total stereocontrol[1]



X=O(R) = CO_2R'', $CONR''_2$, SO_2R'', SPhNPhO etc.

Scheme 1

(Scheme 1). This reaction has been used widely in synthesis. In one chiral example, an α,β-unsaturated sulfoximide, total diastereocontrol was also observed, though attempts to remove the chiral auxiliary were not successful.[1] α,β-Unsaturated esters derived from homochiral alcohols gave disappointing enantiocontrol under these conditions, the chiral centre being too remote from the site of epoxidation.[1] Since there is much current interest[2] in methods for the synthesis of homochiral epoxides we disclose our recent results utilising α,β-unsaturated homochiral amides herein.

In this note we demonstrate that α,β-unsaturated amides derived from homochiral secondary amines also show total stereocontrol on epoxidation, giving readily separated, enantiomerically pure diastereomeric epoxyamides **4** and **5** in about 2 : 1 ratio (Scheme 2). So far we have utilised amides based on (*R,R*)-2,5-dimethylpyrrolidine[3] and (*S,S*)-bis-α-phenylethylamine[4]. The reaction is equally effective for *E*- or *Z*-α,β-unsaturated amides. To illustrate their value, these separated amides were reacted with organolithiums to give the corresponding epoxyketones **6** and **7** in good yield, showing total chemospecificity for reaction at the amide carbonyl and high ee (Schemes 3 and 4). Yields and ee of ketones **6** and **7** are generally higher using bis(α-phenylethyl)amine-derived amides. Surprisingly, the de of the easily separated diastereomeric epoxyamides **4** or **5** are very similar whichever amide is utilised. The absolute configurations of the known epoxyketones (e.g. **6** and **7**, R' = Ph) concur with literature precedents.

The method has several further merits:

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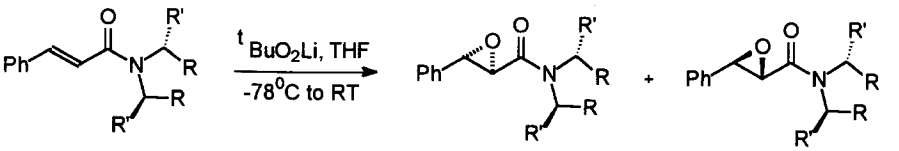
- In one case the chiral auxiliary is commercially available and can be recycled.[4]
- The products form with total predictability of chirality and are easily assayed by either chiral HPLC[5] or NMR shift reagent.[6]
- Both the amides and the product ketones are readily handled stable solids in most cases.
- The reaction is effective for a range of β-substituents on the α,β-unsaturated amide and for both *E* and *Z* isomers so far as we have studied them to date.

Epoxyamides by treatment of α,β-unsaturated amides with LiO_2Bu-*t*



3 **4** **5**

a, R–R = CH_2–CH_2, R' = Me; b, R = Me, R' = Ph

	Time (h)	Isolated Yield (%)	ee (%)*	$[\alpha]_D$ - CH_2Cl_2 (c)	m.p. °C
4a	0.5	49	>99	-105.4 (0.67)	160-162
5a	0.5	26	>99	+169.3 (0.67)	134-136
4b	12	43	>99	-98.8 (1.70)	176-178
5b	12	32	>99	-18.7 (1.70)	120-122

* As indicated by chiral HPLC [Chiralcel OD] and ^{1}H NMR with chiral shift reagent [$Eu(hfc)_3$]

Scheme 2

Some typical conditions for the above transformations are appended.[8] Since the proposed mechanism of the epoxidation involves chelate control,[1] the lithium being the strongly binding feature, we believe that the diastereochemical selectivity derives from the steric effect of the C_2-symmetric amine function. We are now examining a variety of amines with a view to producing high diastereoselectivity.

Acknowledgements
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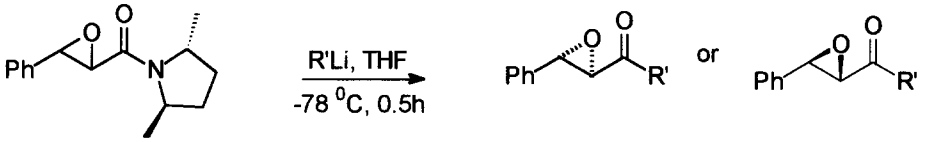
α,β-Epoxyketones by treatment of epoxyamides with RLi's



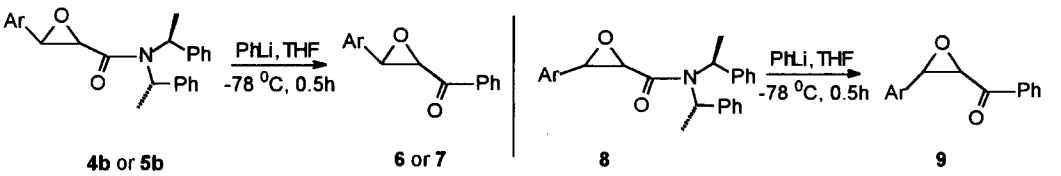
4a or **5a** **6** **7**

Substrate	R'	Product (%)	ee(%)	$[\alpha]^{22}_D$ $[CH_2Cl_2]$(conc)	m.p. °C
4a	Ph	**6** (82)	95[a]	-206.3 (1.43)	94-96
4a	Me	**6** (67)	93[b]	-87.7(1.32)	oil
4a	*n-Bu*	**6** (72)	95[b]	-80.3 (1.00)	47-49
4a	*sec*-Bu	**6** (75)	99[b]	-107.3 (1.37)	54-56
4a	*t*-Bu	**6** (78)	99[b]	-192.6 (1.21)	68-70
5a	Ph	**7** (88)	>99[a]	+227.6 (1.43)	94-96

[a] Determined by chiral HPLC (Chiralcel OD)[5] [b] Determined by $Eu(hfc)_3$ shift.

Scheme 3

α,β-Epoxyketones by treatment of epoxyamides with RLi's



4b or **5b** **6** or **7** **8** **9**

[**a**, *S,S*-epoxide; **b**, *R,R*-epoxide]

Substrate	Ar	Product (%)	ee(%)[a]	$[\alpha]^{22}_D$ $[CH_2Cl_2]$(conc)	m.p. °C
4b	Ph	**6**(93)	99	-213.4 (1.28)[b]	94-96
5b	Ph	**7**(92)	92	+208.7 (1.28)	94-96
4b	4-ClC_6H_4	**6**(88)	98	-207.8 (1.17)[c]	78-80
5b	4-ClC_6H_4	**7**(90)	99	+208.3 (1.17)	78-80
4b	2-$MeOC_6H_4$	**6**(92)	99	-40.8 (1.52)[d]	90-91
5b	2-$MeOC_6H_4$	**7**(92)	99	+39.9 (1.52)	90-91
8a	2-$MeOC_6H_4$	**9a**(91)	99	-41.2 (1.67)[d]	99-100
8b	2-$MeOC_6H_4$	**9b**(90)	99	+38.7 (0.67)	99-100

[a] Using chiral HPLC as in Scheme 3; [b] Literature[7] value -205.4 (ee 96%); [c]Literature[10] value -253 (2.0) [ee 99]. [d] Literature value[10] -22 (2.0) [ee 76%].

Scheme 4

References and footnotes:

1. Meth-Cohn,O.; Moore,C.; Taljaard, H. C. *J. Chem. Soc. Perkin 1* **1988**, 2663-2674.
2. e.g. see Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem, Int. Ed. Engl.* **1980**, *19*, 929; Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 8090-8091; Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599-1602; Chen, W. P.; Roberts, S. M., *J. Chem. Soc. Perkin Trans. 1* **1999**, 103-105; Elston, C. L.,; Jackson, R. F. W.; MacDonald, S. F. J.; Murray, P. J. *Angew. Chem, Int. Ed. Engl.* **1997**, *36*, 410-412 and references therein.
3. Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755-1756.
4. From Fluka
5. Chiralcel OD columns were used at 254nm with hexane/IPA(95/5) as mobile phase at a flow rate of 1.0 mL/min. The racemic substrate was compared with the homochiral material. A Gilson HPLC system was employed.
6. NMR shifts reagent $Eu(hfc)_3$ was utilised.
7. Colonna, S.; Molinari, H.; Banfi, S. *Tetrahedron* **1983**, *39*, 1635-1641.
8. The epoxyamide and epoxyketone preparations utilised our earlier methodology[1] and are exemplified below:

Amide formation: A solution of the α,β-unsaturated acid chloride (0.011mol) in dichloromethane (20 mL) was added to a stirred mixture of (-)(*R,R*)-*2*,5-dimethylpyrrolidine or (-)(*S,S*)-bis(2-phenylethyl)amine (0.01mol) and sodium hydroxide (0.01mol) in water and dichloromethane (20 mL) at ~0 °C. The reaction mixture was stirred at room temperature for a further 30 min., poured into cold aqueous hydrochloric acid (2M, 50 mL) and the mixture extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was washed with further HCl, water and 5% $NaHCO_3$ solution and dried over $MgSO_4$. The solution was evaporated and the residue purified by flash chromatography (ethyl acetate/ light petroleum, 1:1).

Epoxidation: An anhydrous solution of *t*-butylhydroperoxide in toluene[8] (3.3M, 1.47mL) was added to freshly distilled dry THF (10mL) and cooled to -78 °C under nitrogen. To this stirred solution was added butyllithium in hexane (1.6M, 2.2mL) and after 5 min. the amide **3** (3.23 mmol) was added dropwise in dry THF (10 mL). The solution was then brought to room temperature and stirred overnight. Solid sodium sulfite (0.3g) was added and the mixture stirred for 15 min., ether added and the mixture filtered through Celite and the residue washed with ether. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (ethyl acetate/ light petroleum, 1:1). When 2-methoxycinnamides were epoxidised, 2.2 equivalents of *t*-BuO_2Li were utilised.

Epoxyketone formation: The epoxyamide (100mg) in dry THF (10mL) was treated dropwise with phenyllithium (1.8M, 1.5 equivalents) at -78 °C with stirring and after 30 min. further reaction, water and ether was added. The organic layer was separated and the aqueous layer re-extracted with ether. The combined organic layers were dried over $MgSO_4$, evaporated, and the residue purified by flash chromatography (light petroleum/ diethyl ether 3:1).

9. Hill,J. G.; Rossiter, B. E; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607-3608.
10. Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047-6049.