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Enantioselective Rearrangement of *exo*-Norbornene Oxide to Nortricyclanol

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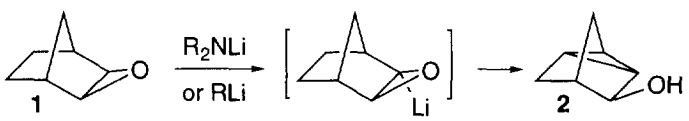
Abstract: The enantioselective α-deprotonation-rearrangement of *exo*-norbornene oxide **1** to (–)-nortricyclanol **2** in up to 52% *ee* using a nonracemic lithium amide, or an organolithium in the presence of (–)-sparteine, is described. Copyright © 1996 Elsevier Science Ltd

We recently reported the enantioselective α-deprotonation-rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived *meso*-epoxides using organolithiums in the presence of (–)-sparteine, which gave bicyclic alcohols in good yields and *ees*.[2] Here we communicate our preliminary results concerning the application of this new strategy for asymmetric synthesis to the desymmetrisation of *exo*-norbornene oxide **1** to give nortricyclanol **2** (Eq. 1).[3]



(1)

exo-Norbornene oxide **1** was selected for study as being representative of a class of prochiral epoxides derived from bicycloalkenes which could generate tricyclic alcohols in an enantioselective manner by α-deprotonation-rearrangement. The conformational rigidity of the norbornyl skeleton was also expected to facilitate analysis of factors governing enantiotopic proton selection. At the outset it was recognised that epoxides such as **1** differ from those in our medium-ring study in that they are significantly more strained and that this may offer competing reaction pathways such as organolithium addition. In addition, consideration of the fact that epoxides such as **1** could not suffer from competing elimination to generate allylic alcohols led us to first examine the transformation using nonracemic lithium amides.[4] It is not obvious that nonracemic lithium amides would be capable of enantioselective desymmetrisation by α-deprotonation since, unlike β-deprotonation (or α-deprotonation using organolithiums), this process has been demonstrated to be reversible using simple lithium amides.[5] Reversible α-deprotonations occur when the rate of reprotonation from the generated amine is competitive with the insertion step. From an asymmetric synthesis viewpoint, since enantioselectivity would be determined by kinetically controlled enantiotopic α-proton selection *via* diastereomeric transition states, then reversible deprotonation could compromise *ee*.

In the event, treatment of *exo*-norbornene oxide **1** in ether from –78° C to 25° C with bases which can effect the rearrangement of epoxides to allylic alcohols in high *ees* {lithium (*S*)-2-[(pyrrolidin-1-yl)methyl]pyrrolidide[4] (1.8 equiv.) or dilithiated (1*R*,2*S*)-norephedrine (3 equiv.)}[6] gave nortricyclanol **2** in poor yields (22% and 29% respectively) and low *ees* (1% and 8% respectively).[7] However, using lithium

(*S,S*)-bis(1-phenyl)ethylamide **3** (1.8 equiv.) in ether from 0 °C to 25° C gave the (–)-alcohol **2** in 49% *ee* (Table 1). Commencing the reaction with **3** in ether at –78° C, rather than at 0° C, gave essentially the same result possibly suggesting that the reaction does not operate below 0° C. The use of other solvents with **3** was less satisfactory. The presence of lithium halides, which have been shown to improve enantioselectivity in other lithium amide reactions,[8] did not alter enantioselectivity in the present case. Evaluation of RLi (1.4 equiv.) / (–)-sparteine **4** (1.45 equiv.) indicated that it was a viable reagent combination for the desymmetrisation of norbornene oxide **1** (Table 1, entries 7-11). Improved yields and *ee*s were found when reducing the temperature of the reaction from 0 °C to –78 °C in ether; yields were further improved in pentane without degradation of *ee*.

Table 1. Effect of Experimental Conditions on the Yields and Enantioselectivities of Formation of Alcohol **2** from Epoxide **1** using Lithium (*S,S*)-bis(1-phenyl)ethylamide **3** or RLi / (–)-Sparteine **4**.

Entry	base	Solvent	T/°C	Yield	*Ee*	Entry	base	Solvent	T/°C	Yield	*Ee*
1	**3**	ether	0 to 25	73%	49%	7	Bu^sLi/**4**	ether	0 to 25	16%	34%
2	**3**	ether	-78 to 25	65%	47%	8	Bu^sLi/**4**	ether	-78 to 25	43%	49%
3	**3**	benzene	0 to 25	76%	31%	9	Bu^sLi/**4**	benzene	0 to 25	67%	24%
4	**3**	pentane	-78 to 25	64%	25%	10	Bu^sLi/**4**	pentane	-78 to 25	73%	52%
5	**3** / LiCl	ether	-78 to 25	68%	45%	11	Pr^iLi/**4**	ether	-78 to 25	63%	46%
6	**3** / LiBr	ether	-78 to 25	59%	46%						

The absolute stereochemistry of the major enantiomer of the alcohol **2** obtained with either lithium (*S,S*)-bis(1-phenyl)ethylamide **3** or RLi / **4** was the same, is as shown in Eq. 1, and was established by comparison of the direction of the optical rotations with those of the known alcohol **2**.[9] The sense of asymmetric induction with RLi / **4** parallels that observed in our medium-ring study.[2]

In summary, this work establishes that norbornene oxide, as a representative bicycloalkene-derived prochiral epoxide, can be desymmetrised with a reasonable level of *ee* by enantioselective α-deprotonation-rearrangement. This can be achieved using the combination of an organolithium with a nonracemic ligand or, significantly, using a nonracemic lithium amide. Further studies on the scope of this process are in progress and will be reported in due course.

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