

Studies in the Asymmetric Ring Opening of an Oxabicyclic Compound. Catalytic Asymmetric Induction using (–)-Sparteine

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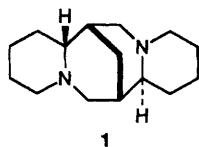
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Oxabicyclo[3.2.1]octenes have been found to undergo enantioselective ring opening in the presence of a catalytic quantity of the chiral amine sparteine.

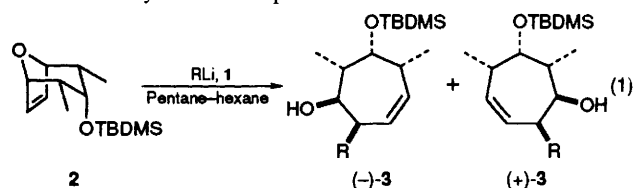
We have described ring-opening reactions of oxabicyclo[3.2.1] and [2.2.1] compounds with organocuprate, organolithium and hydric reagents and the application of this reaction to subunits of ionomycin and rifamycin.^{1–3} Regioselective ring opening of unsymmetrical oxabicyclic compounds has also been observed.⁴

The appeal of this strategy would be enhanced if enantiomerically enriched products were produced rather than racemic mixtures. One solution to this problem is to prepare the starting oxabicyclic compounds as single enantiomers *via* an asymmetric cycloaddition⁵ or using a classical resolution.⁶ However, these strategies are not applicable to the *meso* oxabicyclic compounds, which are the primary focus of our investigations. The most attractive approach is the development of an asymmetric ring opening promoted by a chiral catalyst. This report describes our results which were designed to render the nucleophilic organolithium reagent chiral by complexation to a suitable ligand.

In earlier studies we had noted a significant increase in the rate of the ring opening reaction upon addition of tetramethylethylenediamine (TMEDA).^{2c} This led us to examine chiral chelating diamines.⁷ (–)-Sparteine **1** represents a readily available ligand which has demonstrated potential for modifying organometallic reagents to achieve enantioselective deprotonation, polymerization, and carbonyl addition reactions.⁸



Oxabicyclic compound **2** was chosen for this investigation since the ring-opening reaction with BuⁿLi is extremely efficient and convenient (>80% yield, 4–5 h in diethyl ether at 0 °C) providing (±)-**3**, eqn. (1).^{2b} Initial experiments involving addition of (–)-sparteine to this mixture gave minimal asymmetric induction. Changing the solvent from ether to pentane gave much improved results. We observed that the presence of even stoichiometric amounts of ether led to significant reduction in the enantiometric excess (e.e.) in contrast to the report of Beak where diethyl ether improved the e.e.s in asymmetric deprotonations.^{8g}

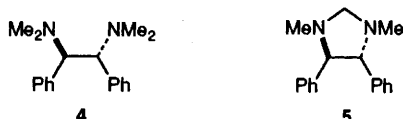


Further experimentation led to a procedure in which the lithium reagent and freshly prepared sparteine (1:1 ratio) were premixed in pentane–hexane at –78 to –40 °C. A white precipitate formed as the reaction was stirred. Addition of the substrate prior to the formation of the precipitate gave no ring-opened product. We then established that the reaction was less capricious and gave reproducible and marginally higher e.e.s if the lithium–sparteine mixture was warmed to 0 °C, stirred for 15 min, then recooled to the desired temperature before addition of the substrate. The lithium reagent was typically used in fivefold excess compared with the substrate and reactions occurred over 24–48 h. The e.e. was

Table 1 Effect of temperature on the e.e. of the ring opening of **1** with BuⁿLi^a

Entry	Temp.	Sparteine : Bu ⁿ Li : Substrate	E.e. (%)	Yield (%)
1	Room temp.	5 : 5 : 1	26	77
2	0 °C	5 : 5 : 1	35	79
3	-40 °C	5 : 5 : 1	40	52
4	-78 °C	5 : 5 : 1	20 ^b	36
5	-78 °C	25 : 5 : 1	52	69

^a The substrate was added to a mixture of sparteine and BuⁿLi in pentane and stirred for 24–48 h. ^b The reaction was carried out in diethyl ether.



measured by conversion of the mixture of alcohols to the Mosher's esters and analysis by ¹⁹F NMR spectroscopy.⁹

The effect of reaction temperature on the e.e. is presented in Table 1. As expected, the e.e.s decreased as the temperature was increased, probably owing (in part) to competing non-sparteine catalysed ring opening at higher temperature (0 °C and room temp.). At very low temperatures (-78 °C), the ratio of sparteine to lithium reagent was increased to 5 : 1 in order to maintain a reasonable rate of reaction. E.e.s up to 52% were obtained under the optimized conditions. Diamines **4** and **5** were briefly examined as ligands which gave e.e.s of 4 and 20%, respectively.†

The nature of the white precipitate was briefly investigated by comparing the reactivity of the precipitate and the clear supernatant. Upon removal of the supernatant, the precipitate was resuspended in pentane, the solution was cooled to -78 °C and **2** was added. Under these conditions alcohol **3** was formed in 57% yield and 54% e.e. The supernatant was totally unreactive with **2** up to 0 °C. Quenching experiments indicated that approximately 5% of the BuⁿLi and sparteine remained in the supernatant.‡

While these results were encouraging, we sought to avoid the large excess of sparteine compared with substrate. We reasoned that an efficient catalytic cycle would be possible if conditions were found where no ring opening occurred until the organolithium reagent had formed the activated complex with sparteine and formation of this complex was reasonably rapid.¹⁰ This analysis proved to be correct and we can now report a ring-opening reaction that is catalytic in sparteine. Our studies were all carried out at -40 °C since no ring-opening reaction occurred in the absence of sparteine, and yet precipitate formation occurred at a reasonable rate. We found that as little as 15 mol% sparteine (based on oxabicyclic) can be used with no effect in e.e. or yield compared with the stoichiometric process, Table 2. Efforts to further reduce the amount of catalyst gave reduced e.e.s, entry 8. Thus, the ligand plays the dual role of accelerating the ring opening and generating a chiral environment for the nucleophile, which gives rise to diastereoisomeric transition states for the ring opening.

In conclusion, we have observed the first asymmetric ring opening reaction of an oxabicyclic compound. More significantly, catalytic asymmetric induction has been realized. Improvement in the e.e.s will be pursued by examination of

† Diamines **4** and **5** were prepared by asymmetric osmylation of *trans*-stilbene,¹⁰ mesylation of the diol, displacement with azide and reductive amination with formaldehyde and formic acid.

‡ Benzaldehyde was added to the supernatant to determine the amount of BuⁿLi. The amount of sparteine was determined by recovery from the supernatant.

Table 2 Effect of % sparteine on the e.e. of the ring opening of **1** with BuⁿLi

Entry	T/°C	Sparteine : Bu ⁿ Li : Substrate	E.e. (%)	Yield (%)
1	-40	25 : 5 : 1 ^a	48	69
2	-40	5 : 5 : 1 ^a	40	52
3	-40	2.5 : 5 : 1 ^a	44	69
4	-40	0.5 : 5 : 1 ^a	48	66
5	-40	0.25 : 5 : 1 ^b	51	61
6	-40	0.2 : 5 : 1 ^b	50	63
7	-40	0.15 : 5 : 1 ^b	52	60
8	-40	0.03 : 5 : 1 ^a	30	60

^a Sparteine and BuⁿLi were stirred at -40 °C for 15 min prior to addition of the substrate. ^b Sparteine and BuⁿLi were mixed at -40 °C, warmed to 0 °C, stirred for 15 min and recooled to -40 °C prior to addition of the substrate.

other chiral diamines or amino alcohols. Work along these lines is now in progress.

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