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Scope and limitations of the catalytic asymmetric rearrangement of epoxides to allylic alcohols using chiral lithium amide bases/lithiated imidazoles

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Abstract—The catalytic asymmetric rearrangement of functionalised cyclohexene and cyclopentene oxides has been studied using sub-stoichiometric amounts of a chiral lithium amide in combination with a stoichiometric amount of three different lithiated imidazoles. 1-Methylimidazole that had been lithiated at the C-2 aryl position gave the highest enantioselectivity (82% ee). With 1,2-dimethylimidazole that had been lithiated at the C-2 methyl group, epoxide ring opening occurred as an unexpected and competing process. Ultimately, ring opening was suppressed using a more sterically hindered imidazole. In all catalytic examples, a racemic background reaction (presumably due to rearrangement by the lithiated imidazoles) was observed.

Chiral lithium amide bases are well established as useful, stoichiometric reagents for asymmetric deprotonation.[1] In contrast, the use of sub-stoichiometric amounts of these chiral bases together with achiral, regenerating (or bulk) bases is somewhat less successful.[2,3] The exception is found with the rearrangement of epoxides to allylic alcohols[2] for which a catalytic asymmetric version was first reported by Asami et al. in 1994.[4] Since then, further work by the Asami group[5] has been supplemented by the efforts of Alexakis,[6] Andersson,[7] Ahlberg[8] and Malhotra[9] and co-workers so that several catalytic systems capable of delivering allylic alcohols in high enantiomeric excess are now available. The Andersson system typically comprises 5 mol % of a chiral lithium amide together with stoichiometric LDA (1.5 equiv) and excess DBU (5 equiv) and is the most successful in terms of scope and enantioselectivity.[7b,d] However, since excess DBU is essential for the high enantioselectivity, we became interested in applying the more 'simple' catalytic systems (i.e., those that do not require the use of DBU as an additive) developed by Alexakis,[6] Ahlberg[8] and Malhotra[9] and co-workers for our own ongoing studies.[10] Of particular interest to us was the Ahlberg protocol using lithiated imidazoles since it utilised a norephedrine-derived chiral base that we had originally introduced.[11,12]

In 2001, Ahlberg and co-workers. reported the conversion of cyclohexene oxide **1** into allylic alcohol (*S*)-**2** (93% ee) using 0.2 equiv of the lithium amide base generated from diamine (1*R*,2*S*)-**3** and 2.0 equiv of lithiated imidazole **5** (generated from **4** that had been lithiated in situ at the C-2 position)[8a] or 2.0 equiv of lithiated imidazole **7** (produced from **6** by in situ lithiation at the C-2 methyl group)[8b] (Scheme 1). Perhaps surprisingly, these two quite different lithiated imidazoles gave identical results in terms of yield and enantioselectivity for the synthesis of (*S*)-**2**. However, with imidazole **4**, it took 198 h for the reaction to reach completion, 15 times longer than the reaction with imidazole **6**. Ahlberg provided NMR spectroscopic evidence for the formation of lithiated imidazoles **5** and **7** and suggested that a mixed dimer of lithium amide base from (1*R*,2*S*)-**3** and the appropriate lithiated imidazole was the reactive species.[8a,b,e]

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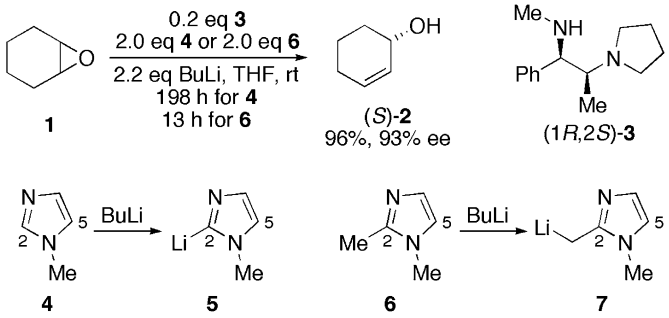
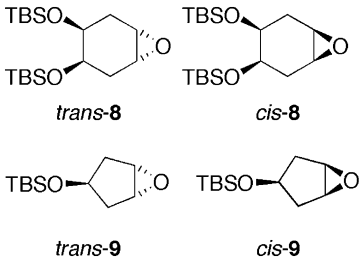


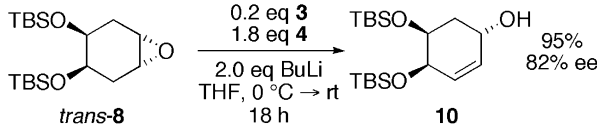
Scheme 1.

Our plan was to extend Ahlberg's sub-stoichiometric chiral base conditions with imidazoles **4** and **6** to more functionalised epoxides such as *trans*-**8**, *cis*-**8**, *trans*-**9** and *cis*-**9**. Due to unexpected epoxide ring opening using imidazole **6** with epoxides **8** and **9** (vide infra), we elected to modify the structure of the imidazoles. In this letter, we report the scope and limitations of the catalytic asymmetric rearrangement of these epoxides using the lithium amide base from (1*R*,2*S*)-**3** and three different lithiated imidazoles.



Epoxides *trans*-**8**,[10b] *cis*-**8**,[10b] *trans*-**9**[13] and *cis*-**9**,[13] together with diamine (1*R*,2*S*)-**3**,[12] were prepared according to the literature procedures; 1-methylimidazole **4** and 1,2-dimethylimidazole **6** are commercially available. To start with, we reacted each of the four epoxides under standard Ahlberg conditions using imidazoles **4** and **6**. Typical reaction conditions involved lithiation of 0.2 equiv of diamine (1*R*,2*S*)-**3** and 1.8 equiv of imidazole **4** or **6** using 2.0 equiv of *n*-BuLi in THF at 0 °C. Then, the epoxide was added and the solution was allowed to warm to room temperature over 2 or 4 h. The reactions were then stirred at room temperature to give total reaction times of 18–64 h. The results of these reactions are summarised in Schemes 2 and 3.

Using imidazole **4**, epoxides *cis*-**8**, *trans*-**9** and *cis*-**9** did not generate any of the expected allylic alcohols and only high yields of recovered starting epoxides were obtained. In contrast, epoxide *trans*-**8** was successfully transformed into allylic alcohol **10** in 95% yield and 82% ee (Scheme 2). This catalytic reaction proceeds with lower enantioselectivity than the corresponding stoichiometric version (≥95% ee using 2 equiv of (1*R*,2*S*)-**3**).[10c] A competing background racemic rearrangement reaction could be invoked to explain the lower enantioselectivity since reaction of epoxide *trans*-**8** with 2 equiv of imidazole **4**/*n*-BuLi alone gave a 43% yield of allylic alcohol **10** (with 52% recovered starting material) under otherwise identical conditions. Such a background reaction was not observed with cyclohexene oxide and has not been commented on previously.[8a]

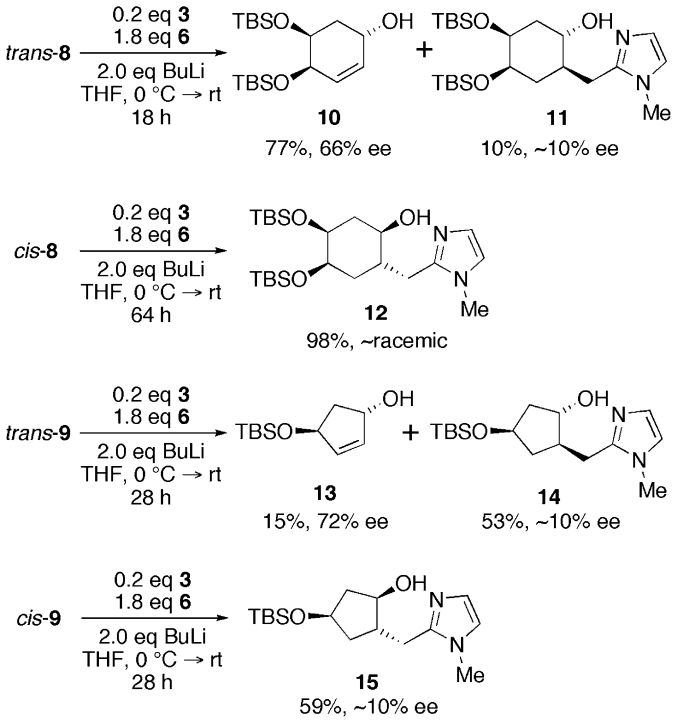


Scheme 2.

The results obtained using imidazole **6** with epoxides *trans*-**8**, *cis*-**8**, *trans*-**9** and *cis*-**9** are shown in Scheme 3. With epoxide *trans*-**8**, allylic alcohol **10** was produced in 77% yield and 66% ee for the catalytic reaction. The mass balance was accounted for by 5% recovered epoxide *trans*-**8** and a 10% yield of essentially racemic hydroxy imidazole **11** resulting from nucleophilic ring opening of the epoxide by the lithiated imidazole. As observed with imidazole **4**, the reduced % ee compared to the stoichiometric reaction appears to be the result of a competing background racemic reaction: treatment of epoxide *trans*-**8** with 2 equiv of imidazole **6**/*n*-BuLi afforded allylic alcohol **10** (24% yield) and hydroxy imidazole **11** (66% yield). The other three epoxides were far more susceptible to the ring opening process and hydroxy imidazoles **12** (98% yield), **14** (53% yield) and **15** (59% yield) were the main or only products (Scheme 3).[14,15]

Full characterisation of **11**, **12**, **14** and **15** identified that they were products of substitution at the C-2 methyl group of **6**. This was important since lithiation of imidazole **6** and subsequent trapping (e.g., with ketones) has been reported to give products functionalised at the C-2 methyl group or at the conjugated C-5 position on the ring.[16] The epoxide ring opening reaction that we observe is precedented in one isolated example with ethylene oxide.[17] No allylic alcohols were detected from the reactions of epoxides *cis*-**8** and *cis*-**9**.

Although allylic alcohol **13** was obtained as the minor product (15% yield), we were encouraged that it was generated with 72% ee since reaction with 2 equiv of (1*R*,2*S*)-**3** gave **13** of 78% ee (62% yield) and these are comparable with the best enantioselectivity for such

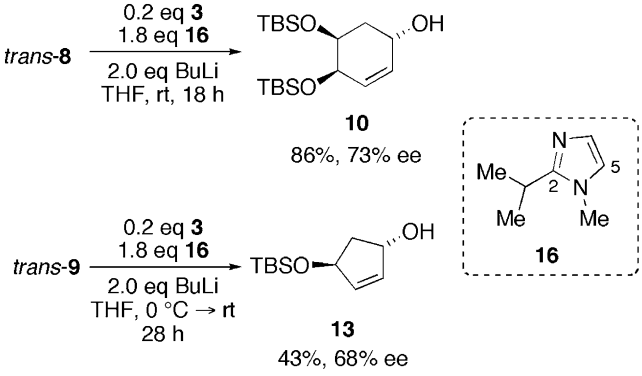


Scheme 3.

substituted *trans*-cyclopentene oxides.[10a,13] Indeed, the similar % ee of allylic alcohol **13** for the stoichiometric and catalytic reactions suggested that there was no background reaction. This was verified using 2 equiv of imidazole **6**/*n*-BuLi with epoxide *trans*-**9** which gave hydroxy imidazole **14** only (54% yield).

At this stage, a direct comparison of the results with epoxides *trans*-**8**, *cis*-**8**, *trans*-**9** and *cis*-**9** with those obtained using cyclohexene and cyclopentene oxide was carried out. For reactions in the absence of diamine (1*R*,2*S*)-**3**, we found that lithiated 1,2-dimethylimidazole **6** ring-opened cyclohexene and cyclopentene oxides to give the corresponding hydroxy imidazoles in 49% and 45% isolated yields, respectively. With cyclopentene oxide under typical catalytic conditions using diamine (1*R*,2*S*)-**3** and 1,2-dimethylimidazole **6**, a 20% yield of the hydroxy imidazole was obtained; for cyclohexene oxide, under identical conditions, a 7% yield of the hydroxy imidazole was isolated. Thus, even with these simple epoxides, some ring opening by the lithiated imidazole does occur under the catalytic conditions.

Surprised by the observation of a background reaction for epoxide *trans*-**8** and epoxide ring opening for all four epoxides *trans*-**8**, *cis*-**8**, *trans*-**9** and *cis*-**9**, we turned our attention to the use of an alternative lithiated imidazole. With the idea that increased steric hindrance in the imidazole would reduce the amount of ring opening (and hence improve the yield of allylic alcohol), the use of substituted imidazole **16** in the rearrangement of epoxides *trans*-**8** and *trans*-**9** was investigated (Scheme 4). Imidazole **16** is known[18] (although not fully characterised) and was prepared by *N*-alkylation of the parent NH imidazole using the literature conditions.[18b]



Scheme 4.

To our delight, use of imidazole **16** in place of imidazole **6** led to improved yields of allylic alcohols **10** and **13** and no epoxide ring opening. Thus, epoxide *trans*-**8** gave allylic alcohol **10** in 86% yield and 73% ee and epoxide *trans*-**9** gave allylic alcohol **13** in 43% yield and 68% ee (Scheme 4). As with imidazole **6**, there was no background racemic rearrangement with the cyclopentene oxide *trans*-**9** and the enantioselectivity was similar to the stoichiometric result. In contrast, reaction of epoxide *trans*-**8** with 2 equiv of imidazole **6**/*n*-BuLi alone gave an 11% yield of allylic alcohol **10** suggesting the presence of a background racemic rearrangement.

In summary, the results presented here show that rearrangement of functionalised cyclopentene and cyclohexene oxides such as *trans*-**8**, *cis*-**8**, *trans*-**9** and *cis*-**9** to allylic alcohols is accompanied by other reaction manifolds, not previously noted for cyclohexene oxide.[8b,d] These include epoxide ring opening to give hydroxy

imidazoles with imidazole **6** and racemic rearrangement as a background reaction for cyclohexene oxide *trans*-**8** with imidazoles **4**, **6** and **16**. By modifying the imidazole structure, we have shown that epoxide ring opening for both epoxides *trans*-**8** and *trans*-**9** can be minimised whilst maintaining satisfactory enantioselectivity. Thus, using imidazole **16**, *trans*-**8** gave allylic alcohol **10** in 86% yield and 73% ee whereas *trans*-**9** gave allylic alcohol **13** in 43% yield and 68% ee. For the catalytic rearrangement of epoxide *trans*-**8**, the use of imidazole **4** was optimal: allylic alcohol **10** was obtained in 95% yield and 82% ee in a relatively short reaction time (18 h). Unfortunately, we were unable to extend the use of this imidazole to other epoxides. Our results indicate the importance of imidazole structure on the yield and enantioselectivity of epoxide rearrangement under Ahlberg's catalytic conditions.

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References and notes

1. (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439; (b) Gibson (née Thomas), S. E.; Reddington, E. G. *Chem. Commun.* **2000**, 989; (c) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.
2. Eames, J. *Eur. J. Org. Chem.* **2002**, 393.
3. (a) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 8195; (b) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron* **1997**, *53*, 16987; (c) Amedjkouh, M. *Tetrahedron: Asymmetry* **2004**, *15*, 577.
4. Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793.
5. (a) Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **1997**, *38*, 6425; (b) Asami, M.; Seki, A. *Chem. Lett.* **2002**, 160; (c) Asami, M.; Seki, A. *Tetrahedron* **2002**, *58*, 4655.
6. (a) Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019; (b) Equey, O.; Alexakis, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1069.
7. (a) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760; (b) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610; (c) Gayet, A.; Bertilsson, S.; Andersson, P. G. *Org. Lett.* **2002**, *4*, 3777; (d) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Org. Chem.* **2002**, *67*, 1567; (e) Bertilsson, S. K.; Andersson, P. G. *Tetrahedron* **2002**, *58*, 4665; (f) Liu, D.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4757.
8. (a) Amedjkouh, M.; Pettersen, D.; Nilsson Lill, S. O.; Davidsson, O.; Ahlberg, P. *Chem. Eur. J.* **2001**, *7*, 4368; (b) Nilsson Lill, S. O.; Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3054; (c) Pettersen, D.; Amedjkouh, M.; Nilsson Lill, S. O.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1397; (d) Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron* **2002**, *58*, 4669; (e) Pettersen, D.; Dinér, P.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1607.
9. Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 645.
10. (a) Oxenford, S. J.; O'Brien, P.; Shipton, M. R. *Tetrahedron Lett.* **2004**, *45*, 9053; (b) O'Brien, P.; Pilgram, C. D. *Org. Biomol. Chem.* **2003**, *1*, 523; (c) de Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron* **2002**, *58*, 4643; (d) Barrett, S.; O'Brien, P.; Steffens, H. C.; Towers, T. D.; Voith, M. *Tetrahedron* **2000**, *56*, 9633.
11. de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423.
12. Colman, B.; de Sousa, S. E.; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175.
13. Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402.
14. The enantioselectivity of formation of hydroxy imidazoles **11**, **12**, **14** and **15** was low ($\leqslant$10% ee) and the absolute stereochemistry of the major enantiomer has not been determined.
15. *Representative procedure for catalytic asymmetric rearrangement of epoxides*: *n*-Butyllithium (0.66 mL of a 1.88 M solution in hexanes, 1.24 mmol, 2 equiv) was added dropwise to a stirred solution of diamine (1*R*,2*S*)-**3** (26 mg, 0.12 mmol, 0.2 equiv) and imidazole **6** (108 mg, 1.12 mmol, 1.8 equiv) in THF (4 mL) at 0 °C under N_2. The resulting solution was stirred at 0 °C for 30 min and then a solution of epoxide *trans*-**8** (222 mg, 0.62 mmol) in THF (1 mL) was added via a cannula. The reaction mixture was then allowed to warm to room temperature over 4 h and stirred at room temperature for 14 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2×10 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (15 mL), brine (15 mL) and water (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 4:1 petrol–EtOAc and then 9:1 EtOAc–MeOH as eluent gave known[10c] allylic alcohol **10** (171 mg, 77%, 66% ee by Mosher's ester formation) as a colourless oil, $[\alpha]_D$ −84.8 (*c* 1.0 $CHCl_3$) {lit.,[10c] $[\alpha]_D$ −100.8 (*c* 1.0, $CHCl_3$) for >95% ee}, recovered epoxide *trans*-**8** (11 mg, 5%) as a colourless oil and hydroxy imidazole **11** (28 mg, 10%, ~10% ee by Mosher's ester formation, absolute stereochemistry not assigned) as a pale yellow solid, $[\alpha]_D$ −7.5 (*c* 1.0, $CHCl_3$); mp 200–205 °C; IR ($CHCl_3$) 3269, 2916, 1655, 1537, 1363, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.89 (d, $J = 1.0$, 1H), 6.78 (d, $J = 1.0$, 1H), 3.93–3.90 (m, 1H), 3.78 (app. td, $J = 11.0$, 4.5, 1H), 3.62 (ddd, $J = 13.5$, 4.5, 2.5, 1H), 3.59 (s, 3H), 2.81 (dd, $J = 16.0$, 8.0, 1H), 2.72 (dd, $J = 16.0$, 3.5, 1H), 2.07 (app. dt, $J = 13.5$, 4.5, 1H), 1.98–1.91 (m, 1H), 1.83 (app. q, $J = 11.0$, 1H), 1.50–1.41 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.044 (s, 3H), 0.041 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 148.0, 126.2, 120.5, 73.0, 71.4, 70.3, 41.4, 41.1, 34.9, 32.8, 32.2, 26.0, 25.8, 18.3, 18.1, −4.4, −4.5, −4.7, −4.9; MS (CI, NH_3) *m*/*z* 455 $[(M+H)^+]$; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{46}N_2O_3Si_2$ $(M+H)^+$ 455.3125, found 455.3122.
16. (a) Iddon, B.; Lim, B. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 271; (b) Noyce, D. S.; Stowe, G. T.; Wong, W. *J. Org. Chem.* **1974**, *39*, 2301; (c) Iddon, B.; Ngochindo, R. I. *Heterocycles* **1994**, *38*, 2487.
17. Sundberg, R. J.; Van Nguyen, P. *Med. Chem. Res.* **1997**, *7*, 123.
18. (a) Lissel, M. *Liebigs Ann. Chem.* **1987**, 77; (b) Lissel, M.; Schmidt, S.; Neumann, B. *Synthesis* **1986**, 382.