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# RICH CHEMISTRY OF α-LITHIATED EPOXIDES AND AZIRIDINES

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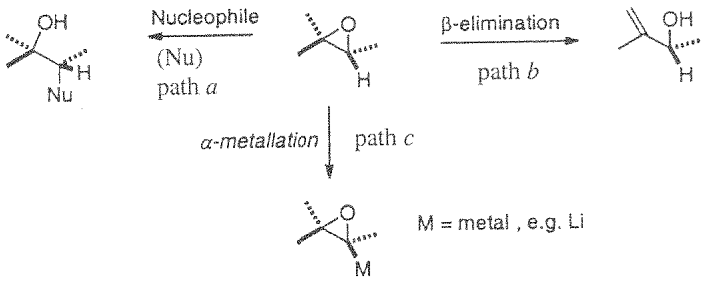
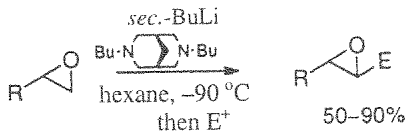
Epoxides and aziridines are widely utilized as synthetic intermediates, and the epoxide and aziridine functional groups are also found in a number of interesting natural products [1]. Much of the chemistry of epoxides and aziridines involves nucleophilic cleavage of the strained heterocyclic ring (Scheme 1, shown for epoxides, path *a*); however, another aspect of epoxide and aziridine chemistry is that which occurs upon reaction with a strong base, typically an organolithium or hindered lithium amide. As well as simple ring-opening, abstraction of β-proton can occur, which leads to the formation of allylic alcohols or amines (path *b*), a process known as β-elimination [2]. Due to the electron withdrawing effect of oxygen or nitrogen atoms and the acidifying nature of the strained ring, abstraction of an α-proton can also occur (path *c*) to give an α-metallated epoxide or aziridine [1, pp. 145–184, 3]



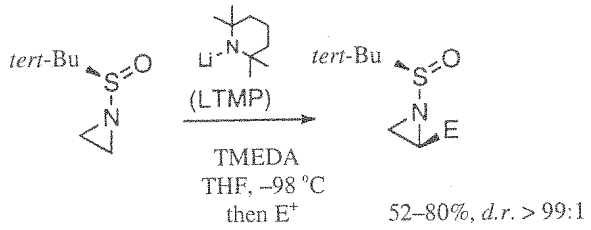

*Scheme 1.* Transformations of epoxides.

Exploring the selective generation and reactivity of α-metallated epoxides or aziridines, in the absence of an additional anion-stabilizing group at the α-metallated carbon atom, has led to a variety of potentially useful synthetic transformations [4, 5]. In this chemistry, the use of strongly basic and hindered reagents facilitates the clean generation of the desired carbanions.

Lithiation followed by electrophile trapping provides a stereocontrolled way to make more substituted small-ring heterocycles (Eqs. 1 and 2) [6–8].



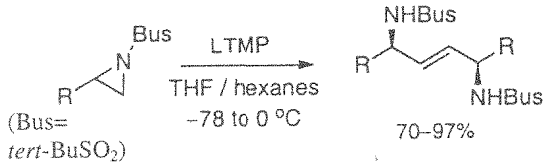

(1)



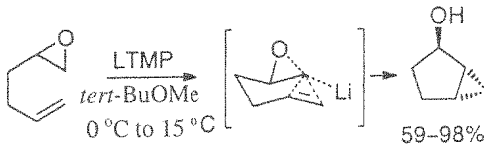

(2)

(TMEDA = tetramethylethylene diamine)

However, the α-lithiated intermediates are quite fragile, as they possess a heteroatom leaving group at the lithiated carbon atom and α-elimination would also relieve small-ring strain. Under suitable conditions the latter carbenoid character can be usefully harnessed, providing 2-ene-1,4-diamines (or diols) from dimerization (Eq. 3) [9–11], or cyclopropanation in the presence of tethered unsaturation (Eq. 4) [10, 12–16] The latter is especially valuable because of its completely stereocontrolled nature (proceeding through a chair-like transition state), and it has been carried out on process scale [17]. In this chemistry simple terminal epoxides and aziridines can be regarded as α-hydroxy- or α-amino carbene equivalents

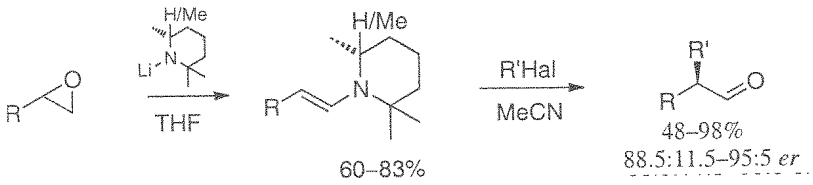



(3)



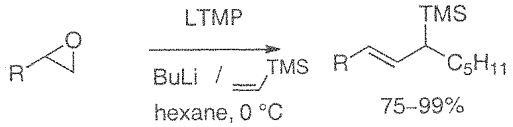

(4)

With terminal epoxides and lithium tetramethylpiperidide (LTMP) in THF, the lithiated intermediate can be intercepted by a second equivalent of the base, the latter remarkably acting as a nucleophile despite its hindered nature. Following *in situ* elimination of $Li_2O$, this process allows access to hindered enamines (Eq. 5) [18, 19] The use of enantiopure 2,2,6-trisubstituted piperidines provides the first direct asymmetric method for the direct generation of aldehydes by C-alkylation involving nucleophilic substitution with alkyl halides [20].



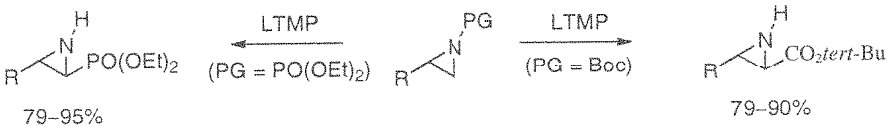

(5)

With terminal epoxides, using LTMP in combination with organolithium or Grignard reagent allows the latter organometallics to act as nucleophiles on the intermediate lithiated epoxides, followed again by *in situ* elimination of $Li_2O$ (Eq. 6) [21–23]. This results in a stereocontrolled convergent alkene synthesis, in which the terminal epoxide functions as a vinyl cation equivalent.




(6)

With terminal aziridines, variation of the protecting group at nitrogen atom can profoundly affect the fate of the α-lithiated intermediate. As indicated in Eq. 3, N-sulfonyl protection leads to carbenoid reactivity similar to epoxides, whereas ester and phosphonate functionality lead to 1,2-migration chemistry (Eq. 7), resulting in simultaneous C-functionalization and N-deprotection [10, 24]




(7)

In conclusion, the above studies broaden the conventional use of aziridines and epoxides as electrophiles in ring opening reactions to now include their use as nucleophiles and carbenoid species. The increasing availability of epoxides and aziridines as single enantiomers [25, 26] promises to heighten the impact of the above methodology in asymmetric synthesis.

## REFERENCES


1. Aziridines and Epoxides in Organic Synthesis. Ed. by A.K. Yudin. Wiley-VCH, Weinheim, 2006.
2. *Hodgson D.M., Humphreys P.G.* In: Science of Synthesis: Houben–Weyl Methods of Molecular Transformations. Vol. 36. Ed. by J.P. Clayden. Thieme, Stuttgart, 2007, 583–665.
3. *Hodgson D.M., Gras E.* Synthesis, 2002, 1625.
4. *Hodgson D.M., Bray C.D., Humphreys P.G.* Synlett, 2006, 1.
5. *Hodgson D.M., Humphreys P.G., Hughes S.P.* Pure Appl. Chem., 2007, **79**, 269.
6. *Hodgson D.M., Kirton E.H.M., Miles S.M., Norsikian S.L.M., Reynolds N.J., Coote S.J.* Org. Biomol. Chem., 2005, **3**, 1893.
7. *Hodgson D.M., Humphreys P.G., Ward J.G.* Org. Lett., 2005, **7**, 1153.
8. *Hodgson D.M., Hughes S.P., Thompson A.L., Heightman T.D.* Org. Lett., 2008, **10**, 3453.
9. *Hodgson D.M., Miles S.M.* Angew. Chem. Int. Ed., 2006, **45**, 935.
10. *Hodgson D.M., Humphreys P.G., Miles S.M., Brierley C.A.J., Ward J.G.* J. Org. Chem., 2007, **72**, 10009.
11. *Hodgson D.M., Bray C.D., Kindon N.D.* Org. Lett., 2005, **7**, 6870.
12. *Hodgson D.M., Chung Y.K., Paris J.-M.* J. Am. Chem. Soc., 2004, **126**, 8664.
13. *Hodgson D.M., Chung Y.K., Paris J.-M.* Synthesis, 2005, 2264.
14. *Hodgson D.M., Chung Y.K., Nuzzo I., Freixas G., Kulikiewicz K.K., Cleator E., Paris J.-M.* J. Am. Chem. Soc., 2007, **129**, 4456.
15. *Hodgson D.M., Salik S.* Synlett, 2009, 1730.
16. *Hodgson D.M., Humphreys P.G., Ward J.G.* Org. Lett., 2006, **8**, 995.
17. *Alorati A.D., Bio M.M., Brands K.M.J., Cleator E., Davies A.J., Wilson R.D., Wise C.S.* Org. Process Res. Dev., 2007, **11**, 637.

18. *Hodgson D.M., Bray C.D., Kindon N.D.* J. Am. Chem. Soc., 2004, **126**, 6870.
19. *Hodgson D.M., Bray C.D., Kindon N.D., Reynolds N.J., Coote S.J., Um J.M., Houk K.N.* J. Org. Chem., 2009, **74**, 1019.
20. *Hodgson D.M., Kaka N.S.* Angew. Chem. Int. Ed., 2008, **47**, 9958.
21. *Hodgson D.M., Fleming M.J., Stanway S.J.* J. Am. Chem. Soc., 2004, **126**, 12250.
22. *Hodgson D.M., Fleming M.J., Stanway S.J.* J. Org. Chem., 2007, **72**, 4763.
23. *Hodgson D.M., Humphreys P.G., Fleming M.J.* Org. Synth., 2008, **85**, 1.
24. *Hodgson D.M., Humphreys P.G., Xu Z., Ward J.G. Angew.* Chem. Int. Ed., 2007, **46**, 2245.
25. *Hodgson D.M., Kloesges J., Evans B.* Org Lett., 2008, **10**, 2781.
26. *Hodgson D.M., Kloesges J., Evans B.* Synthesis, 2009, 1923.

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**α-LITIJĒTU EPOKSĪDU UN AZIRIDĪNU BAGĀTĀ ĶĪMIJA**

KOPSAVILKUMS

Pētījums paplašina aziridīnu un epoksīdu pielietošanas iespējas organiskajā sintēzē. Ja līdz šim aziridīni un epoksīdi pazīstami kā efektīvi elektrofili reaģenti gredzena atvēršanas reakcijās, tad tagad ieteikts tos lietot arī kā nukleofilus reaģentus un karbenoīdas vielas. Epoksīdu un aziridīnu pieaugošā pieejamība atsevišķu enantiomēru veidā atļauj paaugstināt izstrādātās metodoloģijas nozīmi asimetriskajā sintēzē.

**Д.М. Ходжсон**

**БОГАТАЯ ХИМИЯ α-ЛИТИИРОВАННЫХ ЭПОКСИДОВ И АЗИРИДИНОВ**

РЕЗЮМЕ

Данное исследование расширяет поле применения азиридинов и эпоксидов в органическом синтезе. Если до сих пор азиридины и эпоксиды известны в качестве эффективных электрофилов в реакции раскрытия кольца, то теперь предложено их применять и в качестве нуклеофилов и карбеноидных веществ. Возрастающая доступность эпоксидов и азиридинов в виде раздельных энантиомеров позволяет повысить значение разработанной методологии в асимметрическом синтезе.