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Pyridine stabilized oxiranyl remote anions

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ABSTRACT

The chemistry of oxiranyl remote anions derived from α,β-epoxypyridines is investigated. Deprotonation of α,β-epoxy pyridines at the β-position and reactions of the corresponding anions with a variety of electrophiles are found to be highly regioselective, possibly as a consequence of stabilization from the chelation between lithium and the pyridine moiety in the form of a five-membered cyclic intermediate.

The chemistry of oxiranyl remote anions, although in its early stage, has received significant attention due to unique and fascinating chemical characteristics and its high potential as a new approach towards substituted epoxides, which are key precursors in natural products synthesis.[1,2] As revealed in the literature, the generation of oxiranyl remote anions and their reactions can be exemplified as shown in Scheme 1. It was suggested that the stability of the anions could be promoted by chelation between lithium and the carbonyl oxygen of ketone **2**,[3] ester **4**,[1] lactone or imide **6**,[4] or the nitrogen of oxazoline **8**.[2] These groups apparently used lone pair electrons to promote anion stabilization via chelation.

Pyridine is a fundamentally important heterocyclic aromatic compound which has been used as a directing group in coordination chemistry.[5] In principle, the pyridyl group attached to an epoxide would also serve as a lithium-chelator and thus stabilize the oxiranyl remote anion **10** (Scheme 1). To further extend the chemistry and synthetic utility of the oxiranyl remote anion intermediates, we report here our investigations on the pyridine stabilized oxiranyl remote anion and its reactions with electrophiles.

In analogy to compound **1**, epoxypyridine **9** in which the stabilizing group is pyridine instead of a ketone was prepared following the reaction summarized in Scheme 2. Treatment of 2-picoline **11** with *n*-BuLi then with PhCHO gave, after dehydration, alkene **13**. Two-step epoxidation of **13** with NBS in dioxane-H_2O (2:1), followed by base-induced epoxide ring closure gave the desired product **9**.

Treatment of epoxypyridine **9** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in the presence of a variety of electrophiles, including TMSCl, EtI, MeCOMe, $MeCONMe_2$ and cyclohexanone, gave the substituted products **14a–e** in moderate[6] to good yields as shown in Table 1. The regiochemistry of the substituted products **14**, wherein H_x was abstracted and replaced by an electrophile, could be deduced by HMBC in which the key correlations were those between H_y and pyridine carbons C3, C4 and C5 (Fig. 1).

In principle, two major factors that govern the regioselectivity of the deprotonation could be envisioned; (i) α-stabilization from the phenyl group[7] and/or (ii) β-stabilization through coordination between the pyridine nitrogen and lithium in the form of a five-membered cyclic chelate (intermediate **10**, Scheme 1). To substantiate the significance of each factor, the chemistry of the oxiranyl remote anion derived from epoxypyridine **15** of which the phenyl group was relocated to the α-position of the epoxypyridine was investigated.

Epoxypyridine **15** could be prepared straightforwardly via the Corey-Chaykovsky reaction between 2-benzoylpyridine and trimethylsulfoxonium iodide.[8] Treatment of epoxy-pyridine **15** with LTMP in the presence of a variety of electrophiles including TMSCl, PhCOPh, MeCOMe and $ClCO_2Et$ yielded substituted products **16a–d** as summarized in Table 2.

Interestingly, the reaction provided the products in which the substituents were oriented regioselectively *syn* to the pyridine group as confirmed by NOESY experiments (Fig. 2). For example, in the case of **16a**, correlations between a methyl of the TMS group and H_a and H_b of the pyridine ring as well as between H_y and H_A of the phenyl ring were observed. Moreover, the observation of the disubstituted product **16d**, entry 4, could be rationalized considering that the first deprotonation–substitution occurred at H_x (via the β-anion, governed by the pyridine moiety), followed by deprotonation–substitution at H_y (via the α-anion of the ester group).

The regiochemical outcomes of the aforementioned reactions unambiguously demonstrate the significance of the chelation effect from pyridine in the induction of the regioselectivity of β-deprotonation. However, the decrease in yield compared between the reaction of compounds **9** (Table 1) and **15** (Table 2) also alludes to participation in anion stabilization of the phenyl group.

To establish that the regioselectivity of deprotonation in **9** was indeed a consequence of the stabilization effect from pyridine through chelation, *cis*-epoxide **20** was prepared. As shown in

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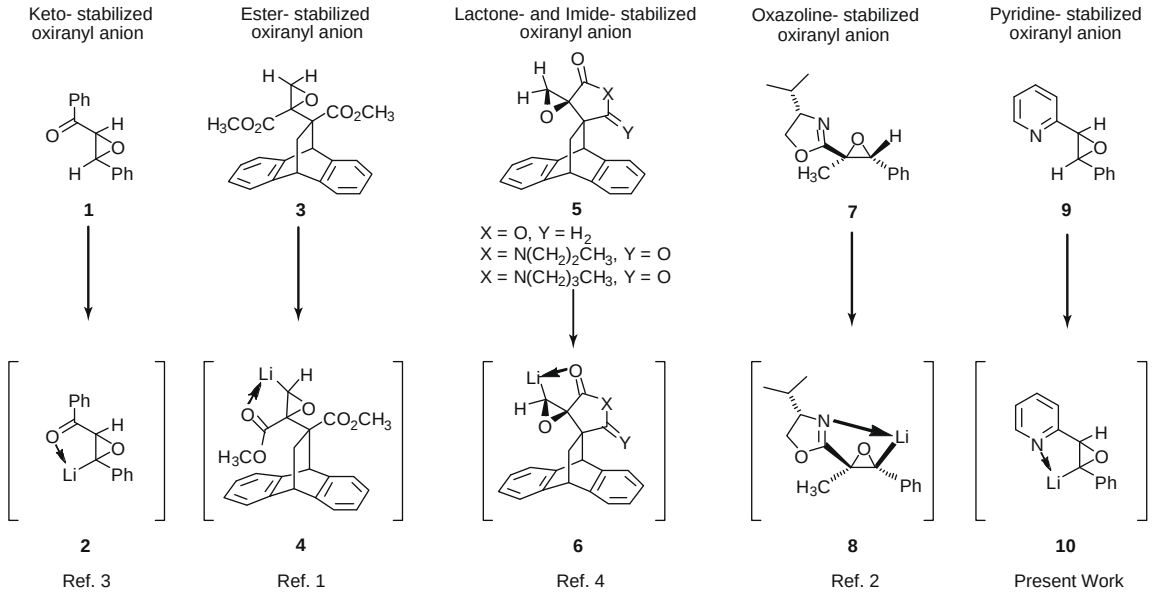
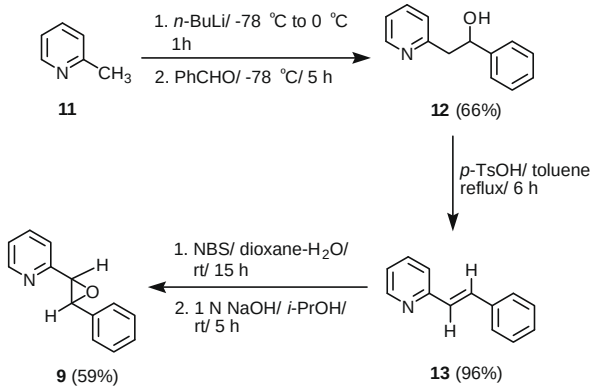


Scheme 1. Formation of remote stabilized oxiranyl anions.

Scheme 3, Wittig reaction of **18** with 2-pyridinecarboxaldehyde yielded *cis*-adduct **19** in 64% yield. Alkene **19** was then subjected to epoxidation with NBS, dioxane-H_2O (2:1) and finally, base-catalyzed epoxide ring closure, to afford the desired product **20** in 33% yield.

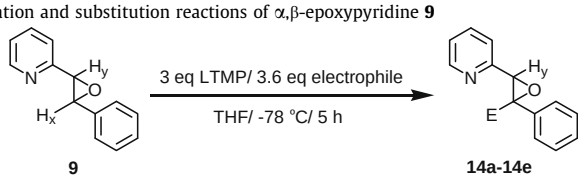
Treatment of epoxide **20** with LTMP and then quenching with CD_3OD yielded ketone **21** exclusively, without any deuterium incorporation (Scheme 4). The regiochemistry of the product was assigned by HMBC experiments of which correlations between the α-methylene proton and the phenyl carbons were observed exclusively (Fig. 3).

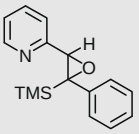
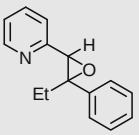
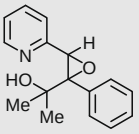
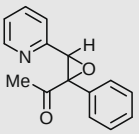
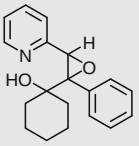
Formation of **21** could take place via a mechanism similar to that reported by Hodgson et al.,[9] as shown in Scheme 5. In this case, due to the diminishing chelation by the pyridine moiety, the regioselectivity of the deprotonation was thus influenced by the acidity of protons H_x and H_y. Because of its greater acidity,[10] proton abstraction from epoxide **20** occurred at the α-position to the pyridine group (H_y-abstraction). The lithiated species then directed the addition of LTMP to the epoxide regioselectively at the carbon adjacent to the pyridine group, leading to the epoxide ring opening to afford dianion **22**. Elimination of Li_2O from dianion **22** gave enamine **23**. Upon normal work-up, ketone **21**, in which the carbonyl group is adjacent to the pyridine group was thus obtained. This finding confirmed that the highly regioselective deprotonation at H_x of epoxypyridine **9** was the result of the chelation effect from the pyridine and lithium in the form of five-membered cyclic intermediate, instead of the acidity of protons H_x or H_y.

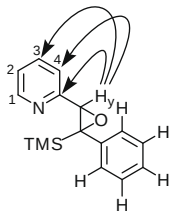


Scheme 2. Preparation of epoxypyridine **9**.

Table 1
Lithiation and substitution reactions of α,β-epoxypyridine **9**



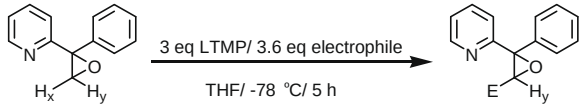
Entry	Electrophile	Product (%yield)	
1	TMSCl		**14a** (94)
2	EtI		**14b** (44)
3	MeCOMe		**14c** (55)
4	$MeCONMe_2$		**14d** (56)
5	Cyclohexanone		**14e** (67)



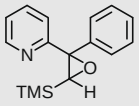
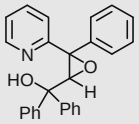
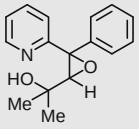
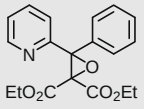
14a

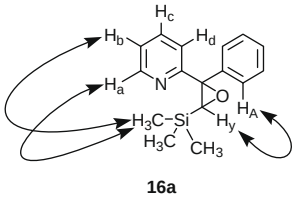
Figure 1. Key HMBC correlations in compound **14a**.

Table 2
Lithiation and substitution reactions of α,β-epoxypyridine **15**



15 **16a-16d**

Entry	Electrophile	Product (%yield)		
1	TMSCl		**16a**	(73)
2	PhCOPh		**16b**	(77)
3	MeCOMe		**16c**	(29)
4	$ClCO_2Et$		**16d**	(16)

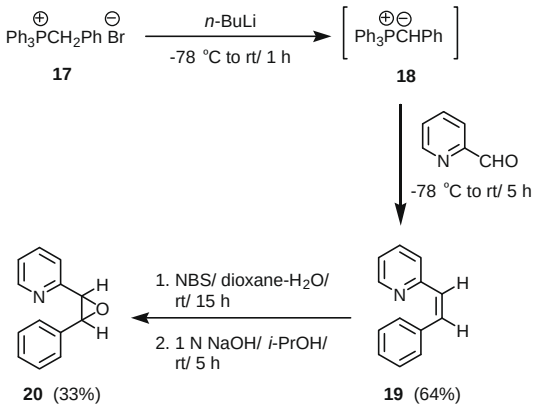


16a

Figure 2. Key NOE correlations in compound **16a**.

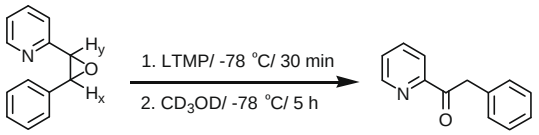
In conclusion, this investigation has described the highly regioselective formation of oxiranyl remote anions derived from α,β-epoxypyridines. It was also found that the stabilization from the chelation between the lithium and the pyridine moiety in the form of a five-membered cyclic intermediate played a key role in the regioselectivity. In addition, the phenyl group at the β-position of the α,β-epoxypyridine could also facilitate the formation of the oxiranyl anion, thus enhancing the yields of the substituted products.

General procedure for lithiation and substitution reactions of α,β-epoxypyridine **9**. To a solution of LTMP (1.52 mmol, generated in situ from *n*-BuLi (1.33 N in hexanes, 1.14 mL, 1.52 mmol) and 2,2,6,6-tetramethylpiperidine (0.32 mL, 1.90 mmol) in THF (7 mL)) was added a solution of *trans*-2-(3-phenyloxiran-2-yl)pyridine **9** (100.0 mg, 0.51 mmol) and freshly distilled trimethylsilyl chloride (0.23 mL, 1.82 mmol) in THF (3 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 5 h before quenching with saturated ammonium chloride solution. The crude mixture was extracted with 20 mL CH_2Cl_2 thrice and the combined organic layer was washed with H_2O, dried over Na_2SO_4 and the mixture was



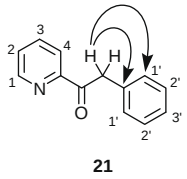
17 **18** **20** (33%) **19** (64%)

Scheme 3. Preparation of epoxypyridine **20**.



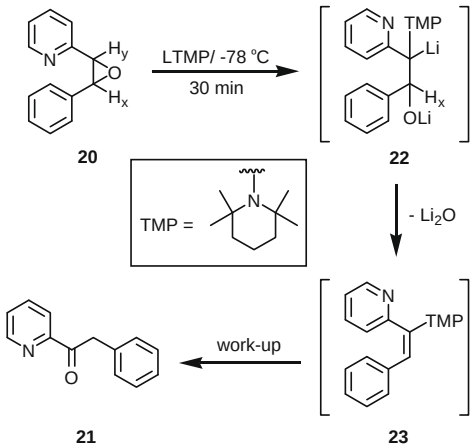
20 **21** (75%)

Scheme 4. Deprotonation of epoxypyridine **20** with LTMP.



21

Figure 3. Key HMBC correlations in ketone **21**.



20 **22** **21** **23**

Scheme 5. Proposed mechanism for the generation of ketone **21**.

evaporated to dryness. Purification by preparative thin layer chromatography (SiO_2; 5% EtOAc/hexane) gave 2-(3-phenyl-3-(trimethylsilyl)oxiran-2-yl)pyridine **14a** (129.5 mg, 0.48 mmol, 94% yield) as a white solid. mp 48–51 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.10 (s, 9H, $Si(CH_3)_3$), 4.24 (s, 1H, H_x), 7.32–7.39 (m, 2H, 1ArH, H_b), 7.42–7.47 (m, 2H, 2ArH), 7.53–7.59 (m, 3H, 2ArH, H_d), 7.80 (td, J = 7.68, 1.46 Hz, 1H, H_c), 8.74 (d, J = 4.87 Hz, 1H, H_a); ^{13}C NMR (75 MHz, $CDCl_3$): δ −2.0, 63.2, 65.5, 121.6, 122.6, 126.0, 126.5, 128.0, 136.1, 142.7, 148.9, 156.9; IR (cm^{-1}): 3057, 3023, 2900, 1590, 1568, 1494, 1471, 1446, 1432, 1247, 839, 776, 755, 703; exact mass: m/z [M+H$^+$] found 270.1141.

Acknowledgements

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds **9**, **14a**–**e**, **15**, **16a**–**d**, **20** and **21** are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.106.

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6. Aside from TMSCl, the decrease in yield could also reflect the low-compatibility nature of electrophiles with LTMP.
7. For selected references on phenyl stabilized oxiranyl anions, see: (a) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942. and references cited therein; (b) Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, 1359–1369; (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642; (d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448.
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10. Although the pK_a of both H_x and H_y in this particular system has not been reported, it could be postulated, based on the pK_a of 2-methylpyridine and toluene, that H_y is more acidic than H_x Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232–3234.