

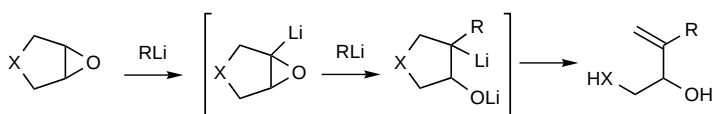
Enantioselective Alkylative Double Ring Opening of Epoxides: Synthesis of Enantioenriched Unsaturated Diols and Amino Alcohols**

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Enantioselective desymmetrization of achiral materials is an attractive and powerful concept in asymmetric synthesis.^[1] *meso*-Epoxides represent an important class of substrates for new desymmetrization methodologies,^[1,2] and base-induced enantioselective transformations of such epoxides are a focus of current interest.^[3,4]

Recently, we showed that epoxides derived from dihydrofuran and dihydropyrrole undergo organolithium-induced alkylative double ring opening, to give acyclic alkenediols and amino alcohols (Scheme 1, X = O or NBus (Bus = *tert*-butylsulfonyl)).^[5] Here we report the first example of enantioselective alkylative double ring opening of epoxides, especially the epoxides of oxa- and aza-bicyclic alkenes which lead to enantioenriched cyclic unsaturated diols and amino alcohols.

A preliminary screen of ligands known to mediate asymmetric deprotonations with (or additions of) organolithium compounds^[6] was carried out for the reaction of 3,4-epoxytetrahydrofuran with *n*BuLi.^[7] This study revealed that (–)-



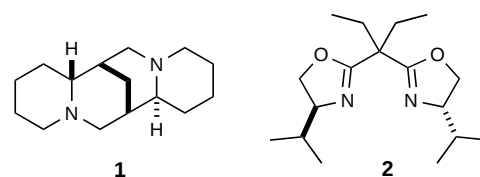
Scheme 1. Alkylative double ring opening of epoxides.

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sparteine (**1**) and bisoxazoline **2** (Scheme 2) gave the more encouraging levels of enantioenrichment in the current process (Table 1, entries 1 and 2), an observation which is in line with our previous results on enantioselective epoxide deprotonation/rearrangements.^[3,8]



Scheme 2. External chiral ligands used.

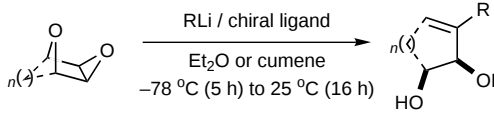
When this process was investigated with epoxides derived from oxabicyclo[*n*.2.1]alkenes (*n* = 2, 3),^[9] we were pleased to observe the formation of cycloalkenediols. The best results, with *n*BuLi and *i*PrLi (up to 85 % *ee*), were generally obtained when the reaction was conducted with **1** as the external ligand (entries 3–13). The method provides a new access to substituted cyclohexenediols (entries 3–7), arenediols (entries 8–10), and cycloheptenediols (entries 11–13), and in an enantioenriched form.

The product distribution arising from the alkylative double ring opening of 3,4-epoxytetrahydropyrroles (Scheme 1) was previously found to be dependant on the nitrogen protecting group.^[5b] In the current study, the use of the Bus protecting group^[10] was again found to result in superior yields of the amino alcohol (in comparison to using Boc (Boc = *tert*-butoxycarbonyl) protection) in the ligand-mediated process (Table 2, entries 1–4). However, significantly better results were observed through the use of Boc protection for epoxides derived from 7-azabicyclo[2.2.1]hept-2-ene (Table 2, entries 5–7).

The reaction of further Boc-protected azabicyclo[*n*.2.1]alkene-derived epoxides (*n* = 2, 3) with *n*BuLi or *i*PrLi in the presence of either **1** or **2** gave the corresponding amino cycloalkenols in generally good yields and *ee* values (Table 2, entries 7–17).^[11] Noteworthy is the introduction of the versatile allylsilane functionality (Table 2, entries 18–19), which is best effected using a mixed organolithium system.

Enantioselective nucleophilic ring opening of unsaturated oxa- and (to a lesser extent) aza-bicyclic compounds, which is principally being developed by Lautens et al.,^[12] results in cycloalkenes bearing the nucleophile in an allylic position. The results described herein represent, to the best of our knowledge, the first enantioselective generation–intermolecular nucleophilic trapping of a lithium carbenoid^[13] (see Scheme 1). The reaction proceeds by double ring opening and comprises an intermolecular C–C bond-forming reaction with cogeneration of unsaturation and two functional group reorganizations, which leads to nucleophile incorporation at a vinylic position as well as synthetically valuable 1,2-diol and 1,2-amino alcohol functionality. The method provides a new and enantioselective access to sought-after cyclic unsaturated diols and amino alcohols^[14] in a regio-, stereo-, and enantio-controlled fashion, and thus has the potential to be a powerful method for organic synthesis.

Table 1. Formation of enantioenriched diols.

					
Entry ^[a]	Epoxide	RLi/ligand	Product ^[b]	Yield [%] ^[c]	ee [%] ^[d]
1		<i>n</i> BuLi/ 1		16	43
2		<i>n</i> BuLi/ 2		44	–42
3		<i>n</i> BuLi/ 1		46	34
4		<i>n</i> BuLi/ 2		34	–40
5		<i>i</i> PrLi/ 1		34	63
6		<i>n</i> BuLi/ 2		57	27
7		<i>i</i> PrLi/ 1		49	59
8		<i>n</i> BuLi/ 2		50	51
9		<i>i</i> PrLi/ 1		44	74
10		<i>i</i> PrLi/ 2		42	56
11		<i>i</i> PrLi/ 1		44	85
12		<i>i</i> PrLi/ 1		46	69
13		<i>i</i> PrLi/ 1		54	84

[a] Entries 1–10 carried out in Et₂O; entries 11–13 carried out in cumene. [b] Absolute configuration of predominant enantiomer obtained with (–)-sparteine (**1**) is shown (assigned by analogy with the sense of asymmetric induction in deprotonations of other *meso*-epoxides).^[3] Bisoxazoline **2** preferentially produced the opposite configuration. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase. TBDMS = *tert*-butyldimethylsilyl.

Experimental Section

Typical procedure for enantioselective alkylative double ring-opening reaction (Table 2, entry 7): *i*PrLi (1.4 M in petroleum ether, 3.0 mL, 4.1 mmol) was added dropwise to a solution of (–)-sparteine (**1**; 0.95 mL, 4.1 mmol) in Et₂O (4 mL) at –78 °C. After stirring the mixture at –78 °C for 1 h, a solution of *N*-*tert*-butyloxycarbonyl-3-oxa-8-azatricyclo[3.2.1.0^{2,4}]octane^[11] (0.25 g, 1.2 mmol) in Et₂O (10 mL) was added dropwise. The mixture was stirred at –78 °C for 5 h and then allowed to warm to 25 °C over 16 h. 1.0 M HCl (10 mL) was added and the aqueous layer extracted with Et₂O (3 × 20 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO₂, Et₂O/petroleum ether (1/1)) gave *N*-*tert*-butyloxycarbonyl-6-amino-2-isopropylcyclohex-2-enol as a white solid (0.24 g, 78%); *R*_f: 0.22 (Et₂O/petroleum ether (1/1)); m.p. 77.5–80.5 °C (Et₂O/petroleum ether). Elemental analysis calcd (%) for C₁₄H₂₅NO₃: C 65.85, H 9.9, N 5.5; found: C 65.8, H 9.8, N 5.5. [α]_D²⁴ –65 (*c* = 1.00 in CHCl₃) IR (KBr): 3437, 2960, 1691, 1501, 1367 cm^{–1}; ¹H NMR(CDCl₃, 500 MHz): δ = 5.56 (t, *J* = 3.5 Hz, 1H), 5.15 (d, *J* = 8.0 Hz,

1H), 4.03 (d, *J* = 2.5 Hz, 1H), 3.62–3.58 (m, 1H), 2.38 (sept., *J* = 6.5 Hz, 1H), 2.19–2.08 (m, 2H), 1.81–1.69 (m, 1H), 1.60–1.51 (m, 1H), 1.45 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H); ¹³C NMR(CDCl₃, 125 MHz): δ = 155.5, 144.1, 122.9, 79.2, 67.0, 50.8, 32.1, 28.4, 24.7, 22.9, 22.6, 21.6; *m/z* (CI) 256 [*M*⁺ + H⁺], 5%), 156 (5), 138 (100); The *ee* value was determined to be 87% by HPLC on a chiral stationary phase (Chiralpak AD column, EtOH/hexane (1:1), flow rate 1.0 mL min^{–1}, retention times 4.0 min (major) and 10.0 min (minor)) following derivatization as the 2,4-dinitrobenzoate.

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Table 2. Formation of enantioenriched amino alcohols.

Entry ^[a]	Epoxide	RLi/ligand	Product ^[b]	Yield [%] ^[c]	ee [%] ^[d]
1		<i>n</i> BuLi/ 1		69	24
2		<i>n</i> BuLi/ 2		79	–45
3		<i>n</i> BuLi/ 1		25	45
4		<i>n</i> BuLi/ 2		0	–
5		<i>n</i> BuLi/ 1		52	40
6		<i>i</i> PrLi/ 1		42	64
7		<i>i</i> PrLi/ 1		78	87
8		<i>i</i> PrLi/ 1		44	71
9		<i>n</i> BuLi/ 1		83	41
10		<i>n</i> BuLi/ 2		60	–67
11		<i>i</i> PrLi/ 1		59	65
12		<i>n</i> BuLi/ 1		68	79
13		<i>n</i> BuLi/ 1		84	66
14		<i>n</i> BuLi/ 2		71	–67
15		<i>i</i> PrLi/ 1		85	71
16		<i>i</i> PrLi/ 2		72	–75
17		<i>i</i> PrLi/ 1		69	82
18		TMSCH ₂ Li/ 1		61	57
19		mixed ^[e] / 1		66 ^[f]	64

[a] Quenched at 25°C, apart from entries 9–11 and 18, 19 (–5°C), entry 12 (–78°C), entries 13–16 (–30°C), and entry 17 (–50°C). [b] See Table 1 footnote [b]. [c] Yield of isolated product. [d] Determined by HPLC or GC on a chiral stationary phase. [e] *i*PrLi (1.1 equiv) and TMSCH₂Li (2.5 equiv). [f] Allylsilane major product, 7% of *i*Pr incorporation additionally observed. TMS = trimethylsilyl.

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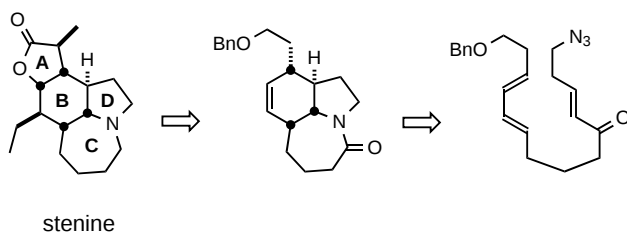
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A Combined Intramolecular Diels–Alder/Intramolecular Schmidt Reaction: Formal Synthesis of (±)-Stenine**

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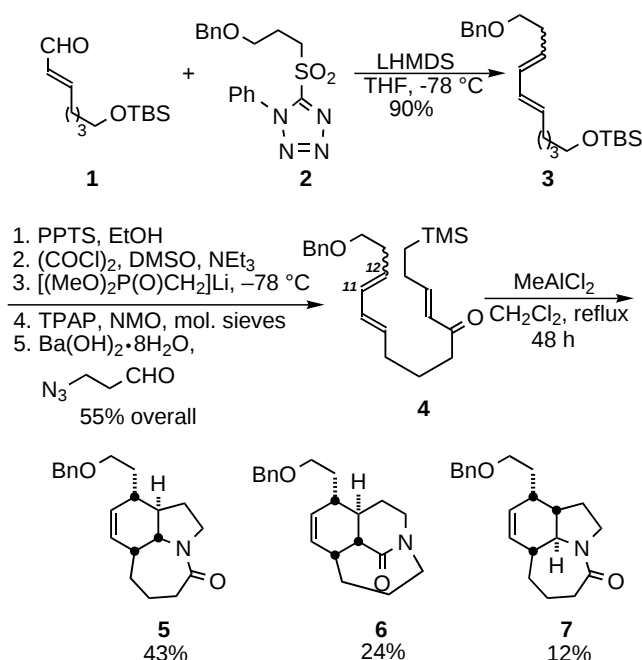
One hallmark of an attractive synthetic strategy is the efficient assembly of advanced intermediates. One way of achieving this goal has been the development of cascade reactions.^[1] An objective of this laboratory has been to advance the utility of the intramolecular Schmidt reaction of azides and ketones in total synthesis.^[2] Herein, we describe the combination of an intramolecular Schmidt reaction with an intramolecular Diels–Alder process—two efficient reactions that benefit from Lewis-acid promotion. The specific context of this work is the formal total synthesis of stenine, shown retrosynthetically in Scheme 1.

Stenine and related alkaloids^[3–11] have drawn considerable attention from synthetic chemists, partly because of the historical use of root extracts of stemonaceous plants in Japanese and Chinese folk medicine.^[6] Efforts in this area



Scheme 1. Retrosynthesis of (±)-stenine.

have already culminated in four total syntheses of stenine by teams led by Hart,^[7] Wipf,^[8] Morimoto,^[9] and, most recently, Padwa.^[10] The first three of these syntheses feature the stepwise construction of the ABD ring substructure followed by final formation of the C ring. Additionally, routes developed by Hart and Morimoto utilize a Diels–Alder reaction as the key step, and both subsequently implement a Curtius rearrangement to install a nitrogen atom adjacent to the carbonyl group. While the present work was in progress, Jung and co-workers^[11] published a partial synthesis, in which a Diels–Alder reaction similar to that shown in Scheme 1 was used, followed by a four-step Beckmann rearrangement/N-alkylation sequence to form the BCD ring skeleton. We now report an approach in which all three rings of a key intermediate and four of the stereocenters were formed in a single chemical step beginning with the acyclic precursor **4** (Scheme 2).



Scheme 2. Construction of the ABD-ring framework of stenine. TBS = *tert*-butyldimethylsilyl, LHMDS = lithium bis(trimethylsilyl)amide, PPTS = pyridinium 4-toluenesulfonate, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

The cascade reaction substrate **4** was prepared by using standard methodology (Scheme 2). Diene **3** was generated in 90% yield from a modified Julia coupling^[12] between aldehyde **1** and sulfone **2** to afford an inseparable 85:15-mixture of isomers at the new double bond.^[13] Removal of the silyl group of **3**, followed by Swern oxidation, gave an aldehyde that was treated with the lithium anion of dimethyl methylphosphonate. This provided a β -hydroxyphosphonate that was subsequently oxidized with TPAP/NMO. The resulting β -oxophosphonate was subjected to a Horner–Wadsworth–Emmons reaction^[14] with 3-azidopropanal^[15] to afford triene **4** in 55% yield from **3**.

Treatment of **4** with MeAlCl_2 in refluxing dichloromethane afforded tricyclic lactams **5**, **6**, and **7** in 79% overall yield and

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