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Conjugate reduction-initiated tandem cyclization of a chiral α,β,χ,ψ–unsaturated bisphosphine oxide

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Abstract—Conjugate reduction-initiated cyclization of a chiral α,β,χ,ψ-unsaturated bisphosphine oxide was developed by treating with lithium tri-siamylborohydride (LS-selectride®) as a reducing agent to afford efficiently and selectively a carbocycle bearing bisphosphine appendage.

Construction methodology of a functionalized carbocycle has been a topic of recent synthetic organic chemistry.[1] We have been engaged in this field for a number of years and succeeded in Michael–Aldol tandem cyclization of a ψ-oxoenoate[2,3] and Michael–Michael tandem cyclization of a α,β,χ,ψ-unsaturated bisphosphonate.[4,5] A recent report from this laboratory proved the versatile utility of the process in providing an efficient methodology for synthesis of a chiral carbocycle bearing bisphosphine appendages.[6] Upon treatment with LDA a chiral bisphosphine oxide **1a** (R = Me) underwent lithiation to **2** and subsequent Michael cyclization through **3** to give **4** as a major product in 60% yield (Scheme 1). Reduction of an olefin moiety of **4** with lithium aluminium hydride or diimide gave stereoselectively *trans*- and *cis*-**5a**, respectively. Subsequent deoxygenation of **5a** afforded the chiral bisphosphine **5b** applicable as a chiral ligand in an efficient catalytic asymmetric hydrogenation. However, conceptual drawback of the carbocycle synthesis lies on a stepwise formation of **5a**. Simultaneous reduction of **1** and generation of α-anion **7** provide a more efficient way than the separate stepwise procedure starting from **1** to **4** via **2**. We describe herein that the reaction of **1b** (R = Bn) with lithium tri-siamylborohydride (LS-selectride®) directly and stereoselectively afforded the corresponding reduction-Michael tandem cyclization products **8**.[7]

We chose a benzyl ether **1b** (R = Bn) as a starting bisphosphine oxide because a benzyl protecting group is easily removal and hence convertible to another group. The chiral **1b** was conveniently prepared in 48% yield through partial reduction of a dibenzyl ether of ethyl L-tartrate **6b**[8] with DBALH to a dialdehyde and subsequent Horner–Wadsworth–Emmons olefination.[6]

We began our study with evaluation of a variety of hydride reagents as a reduction and carbanion-forming agent. Treatment of **1b** with a molar equivalent of $LiAlH_4$ in THF at 0°C for 5 min afforded, after aqueous workup and purification by silica gel column chromatography, all of possible four 5-membered carbocycles **8a–d** in 53% combined yield. Over reduction product and reduced-but-not-cyclized product were not isolated in this reaction. The ratio of these carbocycles **8a–d** was determined by isolation and ^{31}P NMR analysis of the crude product to be 58:23:16:3 (Table 1, entry 1). The relative stereochemistry of **8a–d** was assigned based on the NOESY analysis.[6]

Other aluminium hydride, Red-Al ($Na(O(CH_2)_2OMe)_2$-AlH_2), was not reactive enough to afford **8** in 26% yield (entry 2). Although DIBAL-H gave a relatively good 60% combined yield of **8**, the selectivity was not high, giving all four isomers in nearly equal amounts (entry 3). Fortunately, borane-based hydrides behaved satisfactorily affording stereoselectively **8**. Thus, superhydride® ($LiEt_3BH$) reduced **1b** in THF to give **8a** and **8b** as major two diastereomers in good yield (entry 4).

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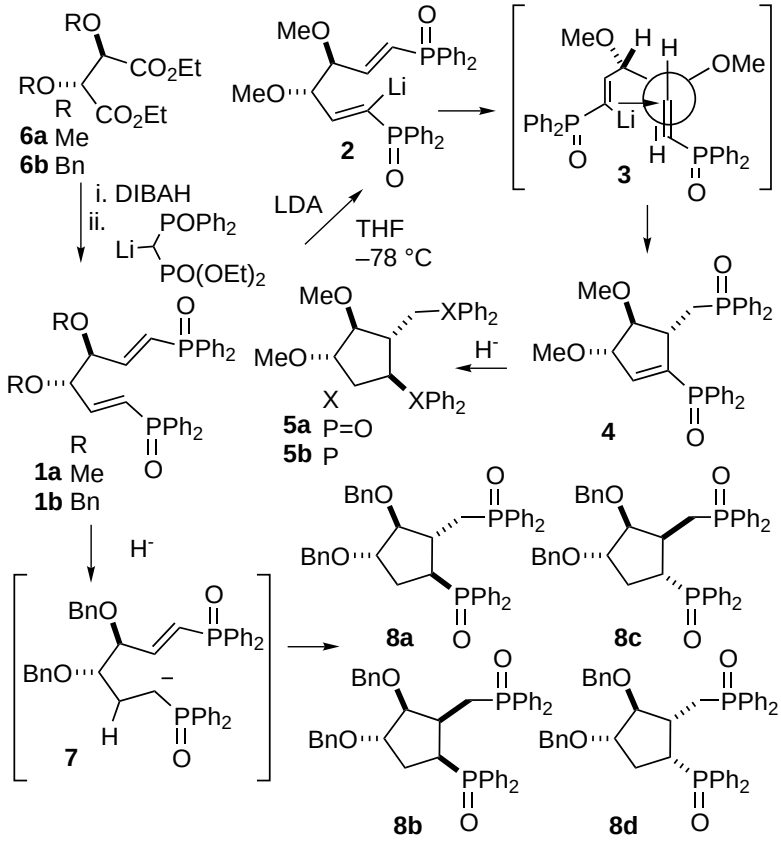

Scheme 1. Hydride and LDA-mediated cyclization of **1**.

Table 1. Reduction-Michael cyclization of **1b** in THF

Entry	Reagents	Temp. (°C)	Time (min)	Yield (%)[f]	Ratio of **8**[g] **a**:**b**:**c**:**d**
1	$LiAlH_4$	0	5	53	58:23:16:3
2	$Na(O(CH_2)_2OMe)_2AlH_2$[a]	0	5	26	54:13:33:0
3	*i*-Bu_2AlH[b]	0	5	60	42:14:23:21
4	$LiEt_3BH$[c]	0	10	70	61:37:2:0
5	$LiEt_3BH$[c]	−40	30	83	58:41:1:0
6	$LiEt_3BH$[c,d]	0	10	80	56:43:1:0
7	Li(*sec*-Bu)$_3BH$[c]	0	60	75	66:34:0:0
8	Na(*sec*-Bu)$_3BH$[c]	0	60	53	67:17:16:0
9	K(*sec*-Bu)$_3BH$[c]	60	60	30	54:9:37:0
10	Li(siamyl)$_3BH$[c]	0	60	88	68:32:0:0
11	$Zn(BH_4)_2$[e]	Reflux	540	64	36:34:17:13

[a] A 65% toluene solution.
[b] A 1 M hexane solution.
[c] A 1 M THF solution.
[d] Toluene was used as a solvent
[e] A 0.15 M THF solution prepared from $NaBH_4$ and $ZnCl_2$.
[f] Combined yield of the mixture.
[g] Determined by ^{31}P NMR (202 MHz, $CDCl_3$) analysis δ: **8a** (30.2 and 34.5), **8b** (30.8 and 31.2), **8c** (31.4 and 37.4), **8d** (29.9 and 32.2).

Lower temperature (–40°C) and toluene solvent did not affect greatly the yield and selectivity (entries 5 and 6). Bulkier lithium trialkylborohydride, L-selectride® (Li(*sec*-Bu)$_3$BH) improved the selectivity to afford a 66:34 mixture of **8a**,**b** in 75% yield (entry 7). Sodium and potassium versions, N-Selectride® and K-Selectride®, however, decreased the selectivity giving a mixture of three diastereomers **8a**,**b**,**c** in a decreased yield (entries 8 and 9). Although a non-alkaline metal hydride, zinc borohydride,[9] gave **8** under reflux for 9 h, the selectivity was almost negligible giving possible all carbocycles (entry 11). Finally we found that LS-selectride® (Li(siamyl)$_3$BH) behaved best to give a 68:32 mixture of **8a**,**b** in 88% yield without formation of **8c**,**d** (entry 10).

Although borane and aluminium-based hydride reagents were applicable in a conjugate reduction-initiated tandem cyclization, the selectivity was dependent on the type of a metal cation. Especially, a lithium cation is superior to sodium, potassium, and zinc, as shown in Table 1.

The initial step of the tandem cyclization involves a conjugate reduction of **1b** to a carbanion **7** (Scheme 1). The regio- and stereochemical courses of this first step were examined by reducing **1b** with $LiAlD_4$ under the conditions of entry 1, giving **8a**,**b**,**c-D** in 34, 17, and 9% isolated yields. ^1H NMR analysis of these deuterated **8D** clearly indicated stereoselective α-side introduction of deuterium in the conjugate addition manner as shown by the spectra of **8a** and **8aD** (Fig. 1),[10] being the same stereochemical course with those of lithium thiolate addition to a carboxylate version.[3a,11] A carbanion **7** is thus generated and undergoes intramolecular Michael addition to a α,β-unsaturated phosphine oxide moiety.

Formation of diastereoisomers **8a**,**b**,**c-D** bearing stereospecifically substituted α-D suggests that intramolecular Michael reaction of a carbanion is not directly related to stereoselectivity of a hydride reagent attack. Stereoselective formation of **4** is ascribable to the sterically favorable conformation **3** (Scheme 1). Straightforward extension to the Newman presentation **A** and **A′** predicts the preferred formation of **8a** over other three isomers (Scheme 2). On the other hand, **D**, **D′**, and **D″** are the most sterically demanding structures and predict the least favorable production of **8d**, which is the most minor isomer observed. The conformation presentations **B** and **B′** suggest steric superiority to **C**, **C′**, and **C″**. Other controlling factors involve chelate formation of two phosphine oxides with a metal cation, especially a lithium cation. A chelate formation of two oxygen atoms of bisphosphine oxide with lithium cation is responsible for the high selectivity with use of lithium reagents other than sodium, potassium, and zinc hydride reagents.[12] These analyses predict well and explain the preferred formation of the isomer in the order of **8a**, **8b**, **8c**, and **8d** by the reaction of **1b** with lithium trialkylborohydride.

In summary, a conjugate reduction-initiated tandem cyclization of a chiral α,β,χ,ψ-unsaturated bisphosphine oxide afforded stereoselectively and in a single step a five-membered carbocycle in 60% yield by using lithium trialkylborohydride as a hydride source as well as a carbanion forming agent. The methodology is useful for the convenient synthesis of a chiral bisphosphine ligand.

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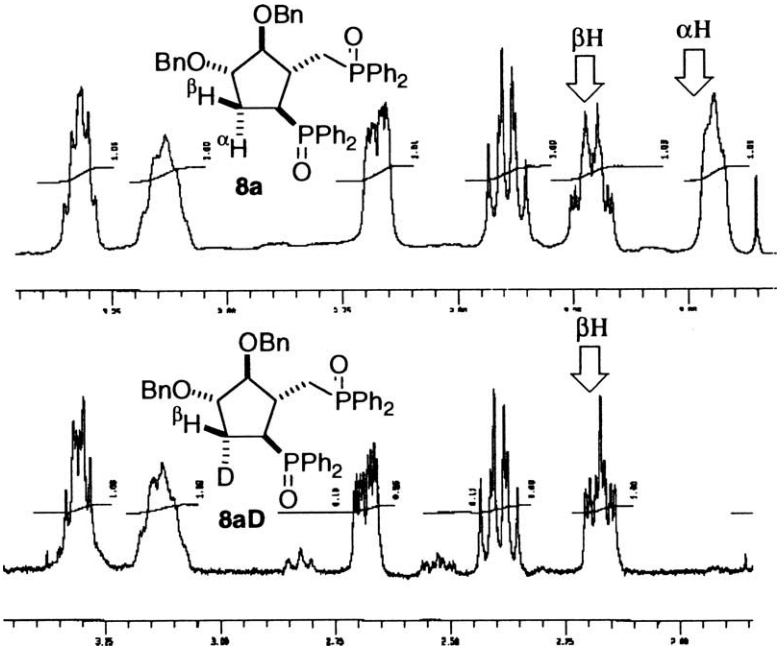
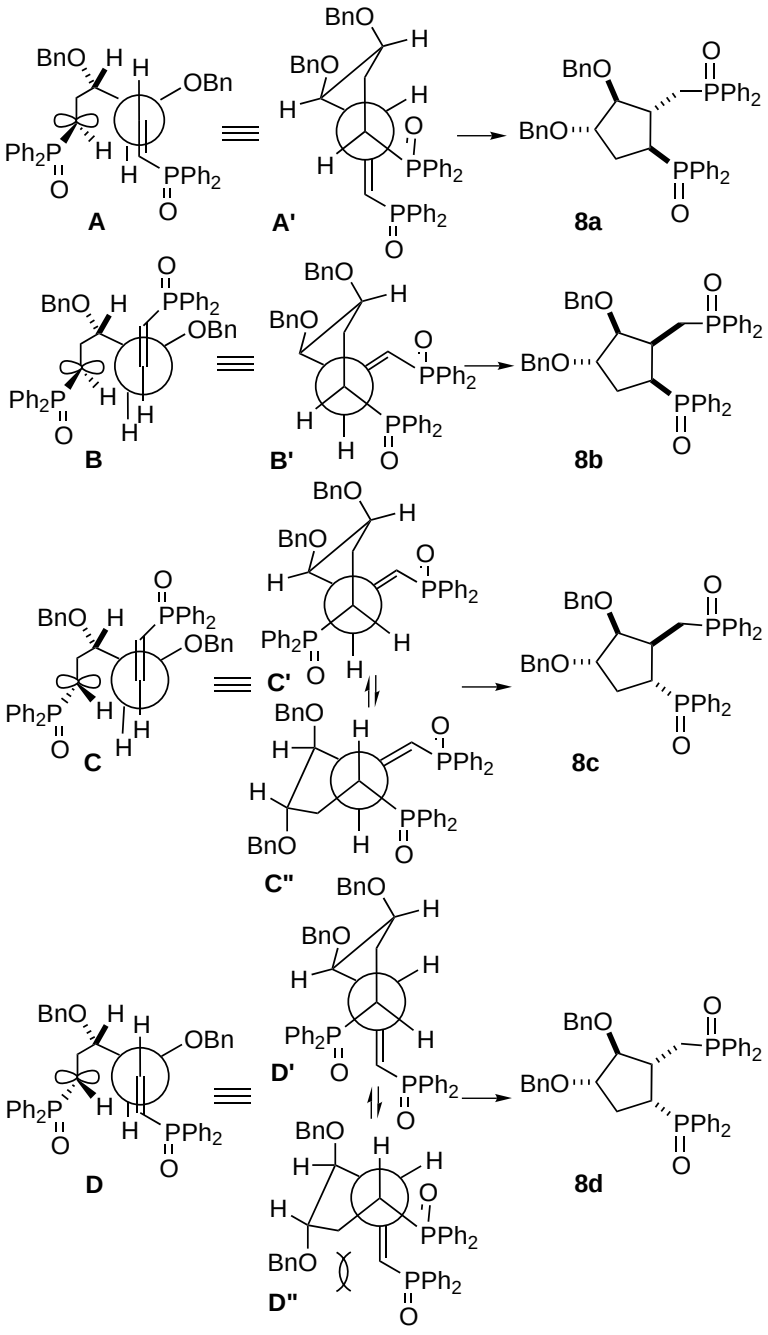


Figure 1. ^1H NMR of **8a** and deuterated **8aD** in C_6D_6.



Scheme 2. The Newman presentation of **7** leading to **8**.

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10. ^{1}H NMR (500 MHz) presented in δ (ppm). J_{1H-31P} was completely decoupled by irradiation of ^{31}P (IRSET: 124 808 Hz). **8a** (in C_6D_6,): 1.94 (1H, dd, $J=13.1$, 8.0 Hz, α-H), 2.20 (1H, ddd, $J=13.1$, 11.3, 4.9 Hz, β-H), 2.40 (1H, dd, $J=15.3$, 11.0 Hz, 1′-H), 2.69 (1H, dd, $J=15.3$, 2.5 Hz, 1′-H), 3.14 (1H, m, 2-H), 3.32 (1H, ddd, $J=11.3$, 8.0, 8.0 Hz, 1-H), 3.92 (1H, s, 4-H), 4.18 and 4.43 (each 1H, ABq, $J=11.6$ Hz, Bn), 4.33 and 4.61 (each 1H, ABq, $J=11.6$ Hz, Bn), 4.96 (1H, s, 3-H), 7.00–7.80 (30H, m, Ph). **8b** (in $CDCl_3$): 1.57 (1H, dd, $J=13.5$, 7.0 Hz, 5-H$^{\alpha}$), 2.36 (1H, ddd, $J=13.5$, 11.3, 4.6 Hz, 5-H$^{\beta}$), 2.69 (1H, d, $J=14.7$ Hz, 1′-H), 3.14 (1H, dd, $J=14.7$, 11.9 Hz, 1′-H), 3.20 (1H, ddd, $J=11.3$, 10.4, 7.0 Hz, 1-H), 3.25 (1H, ddd, $J=11.9$, 10.4, 4.9 Hz, 2-H), 3.83 (1H, d, $J=4.6$ Hz, 4-H), 4.19 (1H, d, $J=4.9$ Hz, 3-H), 4.28 and 4.23 (each 1H, ABq, $J=11.9$ Hz, Bn), 4.36 and 4.40 (each 1H, ABq, $J=11.9$ Hz, Bn), 4.96 (1H, s, 3-CH), 7.20–7.85 (30H, m, Ph).
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