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Formation and reaction of 2-metalated *N*-Boc-4,4-dimethyl-1,3-oxazolidines in the presence of (−)-sparteine: new chiral formyl anion equivalents

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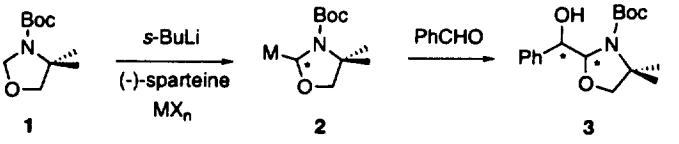
Abstract

Lithiation of *N*-Boc-4,4-dimethyl-1,3-oxazolidine with *s*-BuLi and the following reaction with benzaldehyde was carried out in the presence of (−)-sparteine. The reaction was not diastereoselective (*syn*:*anti*=46:54), but each isomer of the adducts was obtained enantioselectively (*syn*: 90% ee, *anti*: 88% ee). Addition of $MgBr_2$ to the reaction mixture increased the diastereoselectivity to *syn*:*anti*=90:10.

Chiral formyl anion equivalents are useful reagents for asymmetric homologation of aldehydes. Although a variety of chiral formyl anion equivalents have been developed so far, these are based on chiral pool and chiral auxiliary methods employing chiral derivatives of dithioacetals,[1,2] hemithioacetals,[3] 1,3-dioxolanes,[4] and 1,3-oxazolidines.[5] On the other hand, chiral ligand methods with (−)-sparteine have recently been reported for formation of chiral anions adjacent to oxygen[6,7] and nitrogen atoms.[8–10] We report herein 2-metalation of *N*-Boc-4,4-dimethyl-1,3-oxazolidine **1** and subsequent reaction with benzaldehyde in the presence of (−)-sparteine (Scheme 1). To our knowledge, this is the first example of chiral formyl anion equivalents based on chiral external ligand methodology.



1 **2** **3**

Scheme 1.

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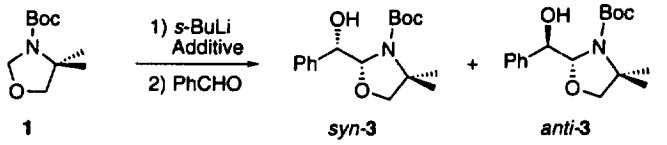
Table 1
Diastereoselective addition of **2** to benzaldehyde

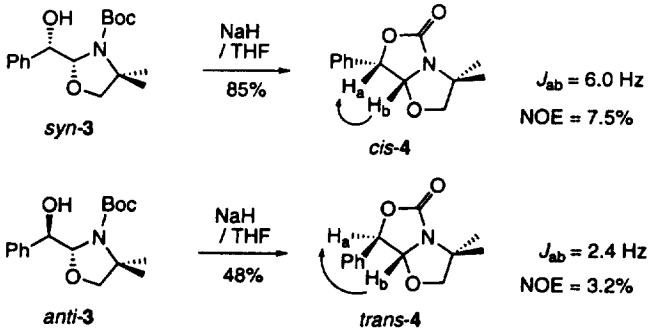


entry	solvent	additive	% yield of 3[a]	*syn*/*anti* of 3[b]
1	THF	none	78	47/53
2	Et_2O	none	57	48/52
3	Et_2O	TMEDA	73	46/54
4	THF-Et_2O	$MgBr_2$	85	90/10

a) Isolated yields. b) Determined by isolation with flash column chromatography.

First, we examined formation of 2-lithiated *N*-Boc-4,4-dimethyl-1,3-oxazolidine **2** (M=Li) and its reaction with benzaldehyde (Table 1, entry 1). Treatment of **1**‡ with 1.2 equiv. of *s*-BuLi at −78°C in THF for 3 h followed by addition of benzaldehyde (1.2 equiv.) gave the adduct **3** with a 47:53 (*syn*:*anti*) dr (diastereomeric ratio) in 78% yield. Use of Et_2O as a solvent and addition of TMEDA (1.2 equiv.) did not improve the dr of **3** (entries 2 and 3). Addition of $MgBr_2$ (1.2 equiv.) to the reaction mixture, however, increased the dr (*syn*:*anti*) to 90:10 (entry 4).

The stereochemistry of each diastereomer of **3** was determined by ^1H NMR spectrum analysis of cyclic carbamate **4**, prepared from **3** by refluxing with NaH in THF for 30 min (Scheme 2). The isomer showing the larger coupling constant and NOE between H_a and H_b is assigned to be *cis*-**4**.[11]

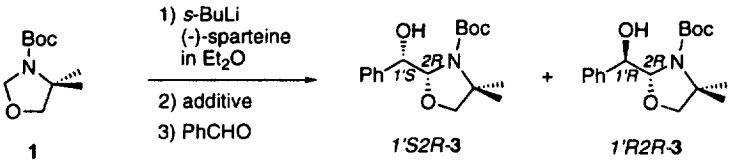


Scheme 2.

Next, we carried out lithiation of **1** and the following reaction of **2** (M=Li) with benzaldehyde in the presence of (−)-sparteine in Et_2O (Table 2, entry 1). The adduct **3** was obtained with a 46:54 (*syn*:*anti*) dr in 71% yield. The ee values were determined to be 90 and 88% for *syn*- and *anti*-**3**, respectively, by chiral HPLC analysis. The absolute configurations of each isomer of **3** were confirmed to be 1'*S*,2*R* for *syn* and 1'*R*,2*R* for *anti* by their conversion to known alcohols **6**: lit.[12] $[\alpha]^{25}_D$ −53.9 (c 1.5, $CHCl_3$) for (*R*)-**6** (Scheme 3). The ee values of **6** were measured by ^1H NMR analysis with Eu(hfc)$_3$ and demonstrated

‡ *N*-Boc-4,4-dimethyl-1,3-oxazolidine (**1**) was prepared from the reaction of 2-amino-2-methyl-1-propanol with formaldehyde and subsequent treatment with di-*tert*-butyldicarbonate and DMAP in 48% yield (two steps).

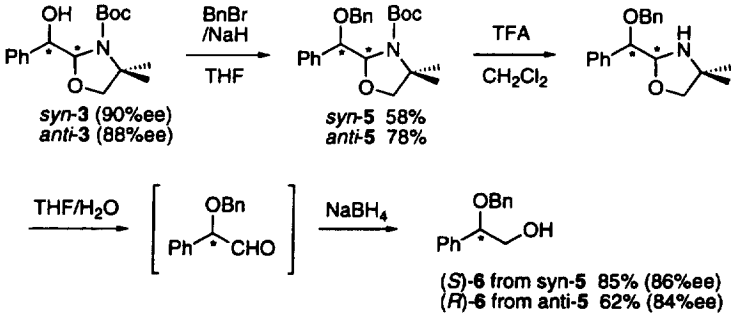
Table 2
Enantioselective addition of **2** to benzaldehyde



entry	additive	% yield of **3**[a]	*syn*/*anti* of **3**[b]	% ee of *syn*-**3**[c]	% ee of *anti*-**3**[c]
1	none	71	46/54	90	88
2	$MgBr_2$	67	90/10	86	83

a) Isolated yields. b) Determined by isolation with flash column chromatography.
c) The ee of each isomer of **3** was determined by HPLC analysis of its 2,4-dinitrophenyl carbamate which was prepared by treatment of **3** with 3,5-dinitrophenylisocyanate and pyridine in toluene. Carbamate of *syn*-**3**: CHIRALPAK AS (DALCEL CHEMICAL IND., LTD.), hexane/ethanol = 60/1. Carbamate of *anti*-**3**: SUMICHIRAL OA-4700 (Sumika Chemical Analysis Service, Ltd.), hexane/1,2-dichloroethane/ethanol = 300/40/1.

that only marginal racemization occurred during hydrolysis and reduction steps. Addition of $MgBr_2$ to the reaction mixture remarkably increased the dr (*syn*:*anti*=90:10) in a similar manner to the above results, but slightly decreased the ee of each isomer (entry 2). The experimental procedure is as follows. To a solution of (−)-sparteine (0.56 g, 2.4 mmol) in Et_2O (5 mL) at −78°C was added a solution of 1.0 M *s*-BuLi in cyclohexane (2.4 mL, 2.4 mmol). After stirring for 10 min, a solution of **1** (403 mg, 2.0 mmol) in Et_2O (2 mL) was added at −78°C and the reaction mixture was stirred for 3 h. To the mixture were added THF (5 mL) and a solution of freshly prepared $MgBr_2$[13] (2.4 mmol) in Et_2O (3 mL) successively at −78°C. The mixture was allowed to warm to 0°C, stirred for 30 min at this temperature, and then recooled to −78°C. Benzaldehyde (0.24 mL, 2.4 mmol) was added dropwise to the mixture. After stirring for an additional 3 h at −78°C, the mixture was allowed to reach 25°C. The mixture was quenched with H_2O (20 mL) and extracted with Et_2O (3×10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc=10:1) to give *syn*-**3** (371 mg) and *anti*-**3** (41 mg) as colorless oils (67% yield). Each isomer gave satisfactory spectroscopic data and elemental analysis: *syn*-**3** (86% ee): $[\alpha]^{20}_D$ +87.1 (c=1.16, $CHCl_3$); *anti*-**3** (83% ee): $[\alpha]^{20}_D$ +73.2 (c=1.05, $CHCl_3$).



Scheme 3.

The reaction of **2** with benzaldehyde proceeds with high stereoselectivity to give the 2*R* configuration of adducts **3**. According to previous studies,[6–10] it is likely that asymmetric deprotonation of **1** with *s*-BuLi/(−)-sparteine forms (*R*)-**2** and the following addition to benzaldehyde takes place with retention of stereoconfiguration at the C-2 position selectively. The high diastereoselectivity in the reaction of magnesium salts cannot be explained clearly. Their reaction mechanisms seem to be different from that of lithium salts as mentioned by Gawley.[14]

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