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Sequential *O*-Nitrosoaldol and Grignard Addition Process: A New Enantio- and Diastereoselective Entry to Chiral 1,2-Diols**

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Abstract

Chiral 1,2-diols are prepared from chiral α -aminoxylated aldehydes or cyclohexanone and Grignard reagents in high diastereoselectivities (>87:13 *dr*) and high enantioselectivities (>93% *ee*). The presence of the *ate* complex of $\text{CeCl}_3 \cdot 2\text{LiCl}$ is essential for the high overall yields and high stereoselectivities. The N-O bond of α -aminoxylated carbonyl compound is cleaved by organometallic reagent.

Keywords

diastereoselective synthesis; chiral 1,2-diol synthesis; asymmetric *O*-nitrosoaldol reaction; $\text{CeCl}_3 \cdot 2\text{LiCl}$ *ate* complex

1,2-Diol units are frequently found in natural products, such as carbohydrates, polyketides and alkaloids,^[1] and chiral 1,2-diols are used as chiral ligands and auxiliaries in stereoselective syntheses.^[2, 3] Generally, chiral 1,2-diols are obtained either by oxidation of an olefin^[4] or ring opening of an epoxide [Eq. (1)].^[5] Although such a process can be rendered asymmetric through the use of chiral catalyst, it either requires toxic transition metal catalysts or suffers from lower regioselectivity. Furthermore, for high selectivity stereochemically pure olefins are required for both methods. We considered a very different strategy to prepare these 1,2-diols that makes use of organocatalytic oxidation of carbonyl compounds followed by Grignard additions [Eq. (2)].

(1)

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The carbonyl substrate is not limited to aldehyde. Aminoxylation of cyclohexanone with 2-nitrosotoluene gave the product in quantitative yield, which is better than that previously reported (77%).^[7e] When subjected to $\text{CeCl}_3 \cdot 2\text{LiCl}$ mediated Grignard reactions, the aminoxylation product gave the corresponding *cis*-1,2-diols in excellent *dr*, which makes the present procedure a suitable route to prepare a chiral quarternary carbon center (Table 3).^[15] These diols are difficult to prepare in high *ee* by known methods.^[4b]

The observed excellent diastereoselectivities of the 1,2-diol synthesis can be explained as follows (Figure 1). Chelation of the aminoxylated aldehyde or ketone with MX_n ($\text{M}=\text{Mg}$ or Ce) will cause the metallated R's species to approach the activated carbonyl group from the less hindered *Re* face, leading to the generation of the 1,2-diol. Single-electron transfer between the organometallic reagent and the aminoxylated aldehyde or ketone is believed to be the reason for the N-O bond cleavage: in the reactions using PhMgCl , biphenyl (50% yield) is separated, which is assumed to be formed from the coupling of phenyl radical.^[16]

In summary, we have opened a new asymmetric entry to 1,2-diols based on a completely different and flexible approach: using readily available carbonyl compounds and organometallic reagents as starting materials. The application of $\text{CeCl}_3 \cdot 2\text{LiCl}$ is essential to obtain high overall yields and high *dr* (up to >99:1) of the 1,2-diol products. In comparison with traditional methods of 1,2-diol synthesis from alkene, our method eliminates the stereoselective preparation of alkene and overcomes the regioselectivity problem of oxidation. The method will be further extended to the preparation of various 1,2-difunctional compounds including N,O- and N,N-derivatives with high selectivities, which is ongoing in our laboratory.

Experimental Section

General procedure for 1,2-diol synthesis: A dry Schlenk tube was charged with 5-[(2*S*)-2-pyrrolidinyl]-1*H*-tetrazole (**1**) or L-proline (0.2 mmol), 2-nitrosotoluene (242 mg, 2.0 mmol) and DMSO or CHCl_3 (3 mL). The aldehyde (6.0 mmol) was added in one portion via pipette. The mixture was stirred at the indicated temperature to give a clear solution (For temperature, solvent and reaction time, see Supporting Information). Cold water was added. The aqueous mixture was extracted with pentane or 1:1 pentane/ Et_2O (3×15 mL). The extracts were washed with H_2O (30 mL), dried over 4 Å MS (5 g), and concentrated at 10–20°C. The resulting yellow oil was dried under high vacuum (5 min) and dissolved in THF (10 mL). The solution (5 mL) of the aminoxylated aldehyde (~1.0 mmol) was added via syringe to a cooled mixture of $\text{R}'\text{MgCl}$ (5.0 mmol) and $\text{CeCl}_3 \cdot 2\text{LiCl}$ (5.0 mmol) at –78°C. The mixture was allowed to warm to RT over a period of 5 h, and stirred at RT overnight. Saturated aqueous NH_4Cl (10 mL) was added, followed by diluted hydrochloric acid (2 N, 4 mL). The organic layer was separated, and the aqueous layer extracted with AcOEt (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel using 4:1 and then 2:1 hexanes/ AcOEt as eluents. After concentration of the eluates, the yield of the 1,2-diol was determined and the *syn:anti* ratio analyzed by ^1H NMR.

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Figure 1.
Proposed transition state structure of the 1,2-diol synthesis.

Table 1Screening of metal reagents as nucleophiles to α -aminoxylated isovaleraldehyde.^[a-c]

Entry	BnMgCl	Additive	Yield [%] ^[d]	dr ^[e]
1	BnLi	-	30	91:9
2	BnMgCl	-	<15	93:7
3		ZnBr ₂	<15	87:13
4	BnMgCl	MnBr ₂	62	95:5
5		MnCl ₂ ·2LiCl	48	96:4
6		CeCl ₃ ·2LiCl	77	>99:1

^[a] 10 mol% **1** used.^[b] Pentane used for extraction.^[c] 5 equiv BnLi or BnMgCl and 5 equiv additive used.^[d] Isolated yield of two diastereomers. Based on nitrosotoluene.^[e] Determined by ¹H NMR.

Scope of aldehydes and Grignard reagents in 1,2-diol synthesis.^[a-f]

[f] Isolated yield of two diastereomers. Based on nitrosotoluene.

[g] R'Li used instead of R'MgCl.

[h] Arylmagnesium bromide used.

[i] Grignard reagent reacted with CeCl₃·2LiCl at RT.

[j] The addition reaction warmed to 0°C.

Table 3

Grignard additions to α -aminoxylated cyclohexanone.^[a, b]

3a ^[c] >99, 87:13, 89	3d >99, >99:1, 66	3g ^[c] >99, 92:8, 63
3b ^[d] >99, 92:8, 66	3e ^[e] >99, 92:8, 95	3h ^[c] >99, 91:9, 78
3c >99, 92:8, 91	3f ^[e] >99, >99:1, 62	

^[a] *cis* configuration and *dr* determined by ¹H NMR.^[b] Isolated yield of two diastereomers. Based on aminoxylated cyclohexanone.^[c] RMgBr used in the absence of CeCl₃·2LiCl.^[d] *n*-BuMgCl used in the absence of CeCl₃·2LiCl.^[e] RLi used instead of RMgCl.