Synthetic Methods

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

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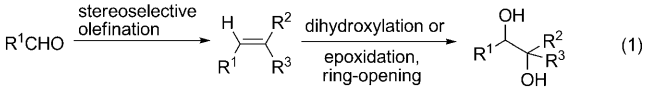
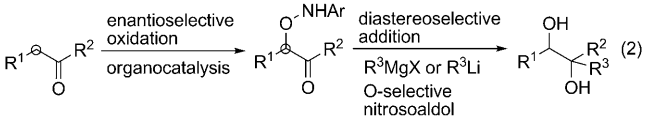
1,2-Diol units are frequently found in natural products, such as carbohydrates, polyketides, and alkaloids:[1] Meanwhile, chiral 1,2-diols are used as chiral ligands and auxiliaries in stereoselective syntheses.[2,3] Generally, chiral 1,2-diols are obtained either by oxidation of an olefin[4] or ring opening of an epoxide [Eq. (1)].[5] Although such a process can be



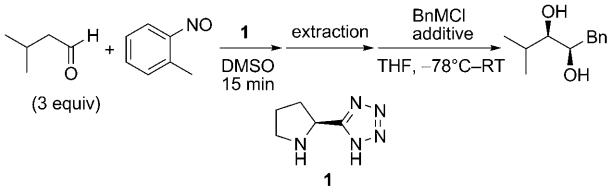
rendered asymmetric through the use of chiral catalyst, it either requires toxic transition-metal catalysts or suffers from lower regioselectivity. Furthermore, both methods require stereochemically pure olefins for high selectivity. We therefore considered a different strategy to prepare these 1,2-diols: one that makes use of organocatalytic oxidation of carbonyl compounds and subsequent Grignard additions [Eq. (2)].



Our previous research indicates that nitrosoaldol reaction give α-oxo or α-aza carbonyl derivatives with virtually complete stereoselectivity.[6,7] These species should subsequently undergo simple addition reaction with Grignard reagents. However, the actual execution of this strategy has some problem to overcome. Firstly, the intermediate aminoxycarbonyl compounds are usually unstable. In particular, aminoxy aldehydes are exceedingly unstable and difficult to handle. Thus, a one-pot procedure or sequential process is required. Secondly, the subsequent Grignard addition reaction should be highly diastereoselective; otherwise the diol product has to be purified, which is frequently rather difficult. Thirdly, the resulting product should be transformed into the 1,2-diol by cleavage of the N–O bond. Herein we report our successful procedure, which satisfies all these requirements.

By using L-proline-based tetrazole **1** as the catalyst,[7h] the reaction of 2-nitrosotoluene with isovaleraldehyde in DMSO gave the O-selective nitrosoaldol (O-NA) product in high yield within 15 minutes (Table 1). We discovered that the O-NA reaction proceeded much more cleanly with 2-nitrosotoluene than with nitrosobenzene, probably owing to the suppression of N–O bond cleavage.[8] As DMSO is not a suitable solvent for the successive alkylation, the product was extracted with pentane and used without purification. Benzyl additions to α-aminoxylated isovaleraldehyde were examined. Although the lithium[9] and Grignard reagents gave the desired 1,2-diol with good diastereoselectivity, the yields were poor because of rapid enolate formation (Table 1, entries 1 and 2). The addition of $ZnBr_2$ did not improve the yield of the Grignard reaction (Table 1, entry 3), however, the addition of $MnBr_2$ or the ate complex of $MnCl_2{\cdot}2\,LiCl$[10] increased the yield (Table 1, entries 4 and 5). Finally, in the presence of $CeCl_3{\cdot}2\,LiCl$ (an additive which favors the addition of Grignard reagents to carbonyl compounds)[11] benzylmagnesium chloride gave the product in 77% yield and >99:1 d.r. (Table 1, entry 6). Gratifyingly, under all reaction conditions where an additive was present the N–O bond is cleaved

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



Entry	BnMCl	Additive	Yield [%][b]	d.r. *(syn/anti)*[c]
1	BnLi	–	30	91:9
2	BnMgCl	–	<15	93:7
3	BnMgCl	$ZnBr_2$	<15	87:13
4	BnMgCl	$MnBr_2$	62	95:5
5	BnMgCl	$MnCl_2{\cdot}2\,LiCl$	48	96:4
6	BnMgCl	$CeCl_3{\cdot}2\,LiCl$	77	>99:1

[a] Reaction conditions: **1** (10 mol%), Grignard reagent (5 equiv), and pentane was used for extraction. [b] Yield of the two isolated diastereomers was based on nitrosotoluene. [c] Determined by ^1H NMR spectroscopy. Bn = benzyl, DMSO = dimethyl sulfoxide, M = metal, THF = tetrahydrofuran.

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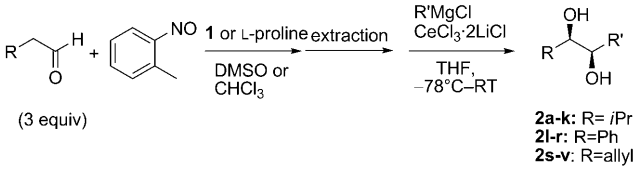
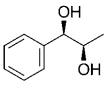
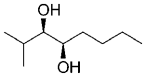
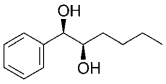
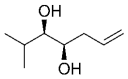
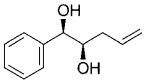
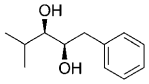
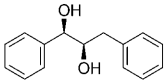
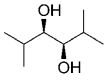
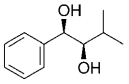
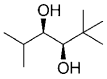
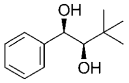
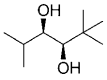
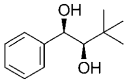
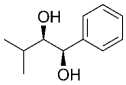
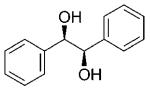
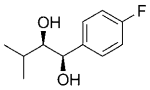
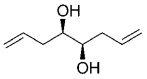
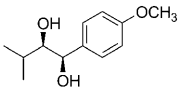
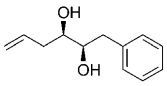
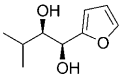
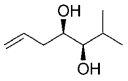
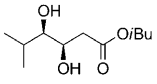
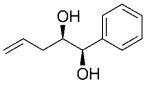
cleanly—a procedure which was previously accomplished by using copper (II) catalysis or catalytic hydrogenation.[7,12]

With the optimized procedure in hand, several aldehydes[13] and a wide range of Grignard reagents were examined using **1** or L-proline as the catalyst (Table 2). Not only tertiary alkyl Grignard reagents (→**2f**, **2q**) but also secondary (→**2e**, **2p**, **2u**) and primary (→**2b–d**, **2m–o**, **2s**, **2t**) alkyl Grignard reagents gave the 1,2-diols in excellent diastereoselectivity. Even a small nucleophile like methylmagnesium chloride produced **2a** and **2l** in high diastereoselectivity (Table 2, entries 1 and 13). Aryl Grignard reagents also gave the products **2g–j**, **2r**, and **2v** in good to excellent diastereoselectivity (Table 2, entries 8–11, 20, and 24). Electron-withdrawing (F) and -donating (OCH_3) groups on the phenyl ring were well tolerated (Table 2, entries 9 and 10). *t*BuLi/$CeCl_3$·2 LiCl could also be used for the synthesis of **2f** and **2q** (Table 2, entries 7 and 19), which in some cases (**2f**) provided better yields than with *t*BuMgCl/$CeCl_3$·2 LiCl

Table 2: Scope of aldehydes and Grignard reagents in the synthesis of 1,2-diols.[a]

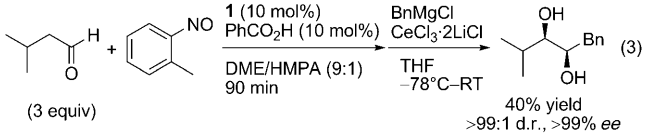


Entry	Product	Config.[b]	Yield [%][c]	*ee* [%][d]	d.r. (*syn*/*anti*)[e]	Entry	Product	Config.[b]	Yield [%][c]	*ee* [%][d]	d.r. (*syn*/*anti*)[e]
1	**2a** 	*R*,*R*	63	97	93:7	13	**2l** 	*R*,*R*	66	98	93:7
2	**2b** 	–	62	96	95:5 (97:3)	14	**2m** 	–	62	>99	95:5
3	**2c** 	*R*,*R*	73	96	91:9 (94:6)	15	**2n** 	*R*,*R*	76	99	96:4
4	**2d** 	–	77	>99	>99:1	16	**2o** 	*R*,*R*	72	>99	>99:1
5	**2e** 	*R*,*R*	75	98	95:5 (94:6)	17	**2p** 	*R*,*R*	64	98	>99:1
6	**2f** 	–	24	97	>99:1	18	**2q** 	–	57	>99	>99:1
7	**2f**[f] 	–	75	97	>99:1	19	**2q**[f] 	–	61	>99	>99:1
8	**2g** 	*R*,*R*	65	96	>99:1	20	**2r** 	*R*,*R*	61	98	96:4
9	**2h**[g] 	–	74	96	95:5	21	**2s** 	*R*,*R*	70	98	92:8 (97:3)
10	**2i**[g,h] 	–	71	97	96:4	22	**2t** 	–	65	96	>99:1
11	**2j**[g,h] 	–	65	97	94:6	23	**2u** 	*R*,*R*	65	96	91:9 (92:8)
12	**2k**[f,i] 	–	45	93	95:5	24	**2v** 	*R*,*R*	70	98	96:4

[a] Reaction conditions: **1** (10 mol%) or L-proline (10 mol%), Grignard reagent (5 equiv), and $CeCl_3$·2 LiCl (5 equiv). [b] Determined by comparison of specific rotation with literature data. [c] Yield of the two isolated diastereomers was based on nitrosotoluene. [d] Determined by GC or HPLC analysis on a chiral stationary phase. [e] Determined by ^{1}H NMR spectroscopy. Ratios in parentheses were determined by GC analysis. [f] R′Li was used instead of R′MgCl. [g] Arylmagnesium bromide was used. [h] Grignard reagent reacted with $CeCl_3$·2 LiCl at room temperature. [i] The addition reaction was warmed to 0°C.

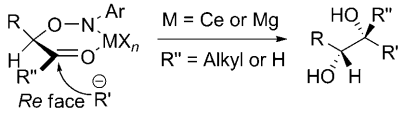
(Table 2, entry 6). In addition, lithium *tert*-butyl acetate gave **2k** in good diastereoselectivity and with a high *ee* value (Table 2, entry 12). The reactions involving 4-pentenal (Table 2, entries 21–24) or allyl (Table 2, entries 3, 15, and 21) Grignard reagents gave the 1,2-diols with terminal olefin groups, which are complementary products to those obtained by asymmetric dihydroxylation reactions (as reported by Sharpless). The *ee* values of the diols were excellent; we believe this to be a result of complete transfer from the α-aminoxylated aldehydes.

If necessary, the 1,2-diol can be synthesized in one pot. The aminoxylation of isovaleraldehyde was conducted in DME/HPMA (9:1),[14] and the mixture was subsequently exposed to benzyl Grignard reagent to give the desired product as a single diastereomer in 40% yield and >99% *ee* [Eq. (3); DME = 1,2-dimethoxyethane, HPMA = hexamethyl phosphoramide].



The carbonyl substrate is not limited to an aldehyde. Aminoxylation of cyclohexanone with 2-nitrosotoluene gave the product in quantitative yield (Table 3, entries 1–8), which is better than previously reported (77% yield).[7e] When subjected to Grignard reactions mediated by $CeCl_3 \cdot 2\,LiCl$, the aminoxylation product gave the corresponding *cis*-1,2-diols in excellent diastereoselectivity. This result makes the present procedure a suitable route for the preparation of a chiral quaternary carbon center (Table 3).[15] These diols are difficult to prepare with high *ee* values by other methods.[4b]

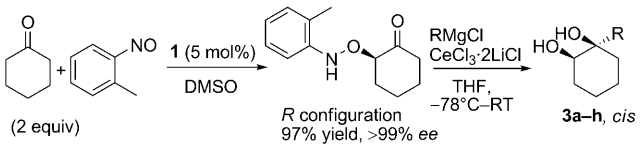
The excellent diastereoselectivities observed for the synthesis of our 1,2-diols can be explained using the proposed transition-state model (Scheme 1). Chelation of the aminoxylated aldehyde or ketone with MX_n (M = Mg or Ce) will cause the metalated R′ species to approach the activated carbonyl group from the less hindered *Re* face, thus leading to the generation of the 1,2-diol. It is believed that single-electron transfer between the organometallic reagent and the aminoxylated aldehyde or ketone causes cleavage of the N–O bond: in the reactions using PhMgCl, biphenyl (50% yield) was recovered, which we assume was formed from the coupling of phenyl radicals.[16]



Scheme 1. Proposed transition state model for the synthesis of 1,2-diols.

In summary, we have opened a new asymmetric entry to 1,2-diols based on a completely different and flexible approach by using readily available carbonyl compounds and organometallic reagents as starting materials. The application of $CeCl_3 \cdot 2\,LiCl$ is essential to obtain high overall yields and high diastereoselectivity (up to >99:1) of the 1,2-diol. In comparison with traditional methods of 1,2-diol synthesis from an alkene, our method eliminates the stereoselective preparation of alkenes and overcomes the regioselectivity problem of oxidation. Continuing work focuses on further extending our methodology to include the preparation

Table 3: Grignard additions to α-aminoxylated cyclohexanone.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]	d.r. (*cis*/*trans*)[d]	Entry	Product	Yield [%][b]	*ee* [%][c]	d.r. (*cis*/*trans*)[d]
1	**3a**[e]	89	>99	87:13	5	**3e**[g]	95	>99	92:8
2	**3b**[f]	66	>99	92:8	6	**3f**[g]	62	>99	>99:1
3	**3c**	91	>99	92:8	7	**3g**[e]	63	>99	92:8
4	**3d**	66	>99	>99:1	8	**3h**[e]	78	>99	91:9

[a] All products have a *cis* configuration. [b] Yield of the two isolated diastereomers was based on aminoxylated cyclohexanone. [c] Determined by GC or HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy. [e] RMgBr was used in the absence of $CeCl_3 \cdot 2\,LiCl$. [f] *n*BuMgCl was used in the absence of $CeCl_3 \cdot 2\,LiCl$. [g] RLi was used instead of RMgCl.

of various 1,2-difunctional compounds with high selectivities, including N,O- and N,N-derivatives.

Experimental Section

General procedure for the preparation of 1,2-diols: 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) before the aldehyde (6.0 mmol) was added in one portion by pipette. The reaction mixture was stirred at the indicated temperature to give a clear solution (see the Supporting Information for temperature, solvent, and reaction time). Cold water was added and the aqueous mixture was extracted with pentane or pentane/Et_2O (1:1; 3×15 mL). The organic extracts were washed with H_2O (30 mL), dried over molecular sieves (4 Å; 5 g), and the solvent was removed at 10–20 °C. The resulting yellow oil was dried under high vacuum (5 min) and dissolved in THF (10 mL). To a cooled mixture of R′MgCl (5.0 mmol) and $CeCl_3\cdot2\,LiCl$ (5.0 mmol) at −78 °C was added the solution of the aminoxylated aldehyde (5 mL, ≈1.0 mmol) by syringe. The reaction mixture was then allowed to warm to room temperature over a period of 5 hours, and then stirred at room temperature overnight. The mixture was diluted with saturated aqueous NH_4Cl (10 mL), and diluted hydrochloric acid (2 N, 4 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (4:1→2:1 hexanes/AcOEt) afforded the 1,2-diol. The *syn*/*anti* ratio was determined by ^{1}H NMR spectroscopy.

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