Asymmetric Oxy-Michael Addition

Highly Diastereoselective Oxy-Michael Additions of Enantiopure δ-Lactol Anions to Nitroalkenes: Asymmetric Synthesis of 1,2-Amino Alcohols**

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The abundance of bioactive natural and unnatural products that contain the 1,2-amino alcohol motif continues to stimulate the development of new methods for their efficient asymmetric synthesis. Whereas 1,2-amino alcohols derived from proteinogenic amino acids are readily accessible, non-proteinogenic amino acid derived amino alcohols require efficient enantioselective routes.[1] Methods for the asymmetric synthesis of 1,2-amino alcohols with a stereogenic hydroxy-substituted carbon center are relatively uncommon, even though these materials and their derivatives are widespread in nature and routinely exploited in asymmetric synthesis.[2]

Stimulated by the utility of 1,2-amino alcohols and encouraged by the lack of a general synthetic approach to such compounds, we recently became interested in developing asymmetric methods for their synthesis. Although a logical retrosynthetic disconnection is based on an asymmetric nitroaldol reaction,[3] our approach relies on the stereoselective Michael addition of a chiral water equivalent **1** to readily available nitroalkenes **2**. As in many asymmetric catalytic processes, the levels of asymmetric induction in the nitroaldol reaction are substrate dependent, and in the worst cases there is no way of increasing the enantiopurity of the product. In the oxy-Michael addition approach the chirality in the nucleophile allows the separation of the diastereomeric products **3** and hence the isolation of enantiopure material after auxiliary removal. However, ideally the chirality of the nucleophile will induce high levels of stereoselectivity in the formation of the stereogenic center β to N, and subsequent nitro-group manipulation and nondestructive removal of the auxiliary will free the deprotected oxy-Michael product **4** (Scheme 1).

The strength of this concept was recognized previously by Enders et al.,[4] who used the sodium salt of *N*-formylnor-

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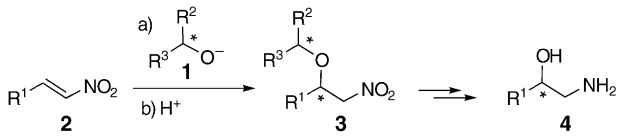


Scheme 1. The diastereoselective oxy-Michael addition to nitroalkenes for the asymmetric synthesis of 1,2-amino alcohols.

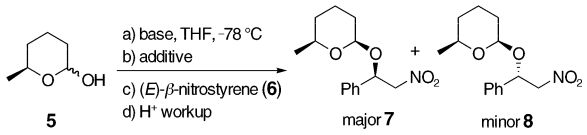
ephedrine as a chiral hydroxide equivalent in reactions with aliphatic nitroalkenes and observed excellent diastereoselectivities. However, when aryl nitroalkene acceptors were used, both the diastereoselectivities and the yields were low. Furthermore, the approach required a dissolving-metal Birch-type deprotection at the end of the sequence to free the amino alcohol products. This was not compatible with some aryl groups and led to partial reduction. Herein we report that enantiopure 6-substituted δ-lactols, when converted into the corresponding "naked" alkoxides, act as effective chiral water equivalents in Michael addition reactions to nitroalkenes, thus allowing the rapid synthesis of enantiomerically enriched 1,2-amino alcohols after subsequent manipulation of the nitro group and removal of the 6-methyltetrahydropyran (THP*) auxiliary.

The highly *cis*-selective O-alkylation and O-acylation of the anions of 6-substituted δ-lactols with bromoacetates and acid anhydrides has been reported previously.[5] This work and the availability of 6-alkyl δ-lactols in racemic and enantiopure form[5a,6] prompted us to test lactol anions in the oxy-Michael reaction and assess their potential as chiral water equivalents. Lactols such as these were attractive candidates from the outset, because the chirality source—the 6-substituted tetrahydropyran ring—is also an exceptional protecting group, which is used exhaustively in synthetic methodologies and total syntheses alike.[7]

Preliminary studies were performed with readily available enantiopure (*S*)-6-methyl-δ-lactol (**5**) as the chiral water equivalent and commercially available (*E*)-β-nitrostyrene (**6**) as the Michael acceptor. Typically the reactions were carried out in THF at −78 °C with an excess of the lactol anion and were quenched at the same temperature with glacial acetic acid. Whereas high yields were obtained when the potassium or the sodium alkoxides were used, the observed stereoinduction at the center β to the nitro group was moderate in the former case and poor in the latter. Importantly however, only two of the possible four diastereoisomers, the *cis*-tetrahydropyranyl ether products **7** and **8**, were observed in the crude reaction mixtures. The use of the potassium salt of the lactol with toluene as the solvent also led to a decrease in the diastereoselectivity of the reaction, as well as in the yield, and led us to the conclusion that tight ion pairing of the metal and the alkoxide was detrimental to the reaction in all respects. Accordingly, 1 equivalent of [18]crown-6 was added to the potassium alkoxide in THF, and the reaction was performed as before. To our delight the selectivity at the center β to the nitro group for the *cis*-THP* isomer soared to ⩾99:1, as measured by ^{1}H NMR spectroscopy. Similarly, when the sodium salt of the alkoxide was treated with 1 equivalent of [15]crown-5 prior to the Michael addition, the observed selectivity at the β center was excellent[8] (Table 1).

To ascertain the generality of the reaction, a range of commercially available or readily prepared *E*-nitroalkene acceptors were treated with the "naked" lactol alkoxide formed from KHMDS (HMDS = hexamethyldisilazide) and [18]crown-6 (Table 2). When the β substituent was aryl, heteroaryl, or alkyl the observed selectivity at the β center and the yields of the reactions were uniformly excellent. The reaction products were readily purified by chromatography on silica gel, and the stereochemistry of the major isomer was established unambiguously by single-crystal X-ray diffraction

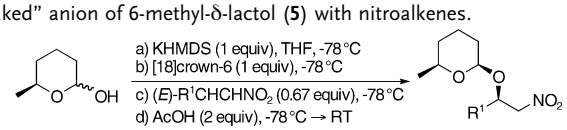
Table 1: Diastereoselective oxy-Michael addition reactions of 6-methyl-δ-lactol (**5**) with (*E*)-β-nitrostyrene (**6**) and variation in d.r. with metals and additives.

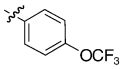


Entry	Base	Solvent	Additive	**7**/**8**[a]	Yield [%]
1	LiHMDS	THF	none	–	0
2	NaHMDS	THF	none	1:1	88
3	KHMDS	THF	none	4.2:1	89
4	KHMDS	THF	[18]crown-6	⩾99:1	99
5	NaHMDS	THF	[15]crown-5	56:1	97

[a] d.r. of the *cis*-THP* isomers **7** and **8**, determined by examination of ^{1}H NMR spectra of the crude product.

Table 2: Highly diastereoselective oxy-Michael addition reactions of the "naked" anion of 6-methyl-δ-lactol (**5**) with nitroalkenes.



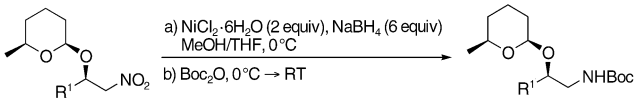
Entry	R^1	d.r.[a]	Product	Yield [%]
1		>99:1	**7**	99
2		>99:1	**9**[b]	81
3		>99:1	**10**	72
4		>99:1	**11**	82
5		52:1	**12**[c]	94
6		45:1	**13**	99
7		>40:1[d]	**14**	83

[a] d.r. of the *cis*-THP* isomers, determined by examination of the ^{1}H NMR spectrum of the crude product. [b] Configuration determined by single-crystal X-ray analysis. [c] Workup with ammonium chloride. [d] Approximated by peak-height measurements in the ^{13}C NMR spectrum of the crude product.

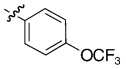
in the case of **9** and by chemical correlation methods for **12** and **13**.

Reductive manipulation of the nitro group and non-destructive removal of the THP* group was necessary to confirm the effectiveness of this reaction as an asymmetric method for the synthesis of amino alcohols. It was eventually found that the most reliable way to reduce the nitro group was a one-pot nickel boride reduction[9] with concomitant in situ *tert*-butyloxycarbonyl (Boc) protection. The THP* group functions as both a protecting group and a stereochemical marker: Any epimerization of the newly formed stereogenic center would be observable in the ^{1}H NMR spectra of the products. Gratifyingly, no epimerization was observed, and the *N*-Boc-protected amine products **15**–**21** were afforded in good to excellent yields in all cases (Table 3).

Table 3: Nickel boride reduction and in situ *N*-Boc-protection of the oxy-Michael adducts **7** and **9**–**14**.



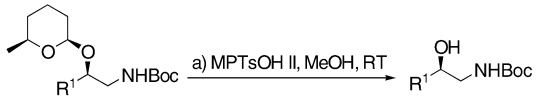
7, 9–14 **15–21**

Entry	R^1	Product	Yield [%]
1		**15**	98
2		**16**	57
3		**17**	80
4		**18**	81
5		**19**	85
6		**20**	90
7		**21**	83

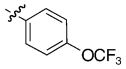
Removal of the THP* group in the presence of methanol and polymer-bound acid resin (MPTsOH II) was straightforward and afforded the *N*-Boc-protected amino alcohol products **22**–**28** in good to excellent yields in all cases following filtration and concentration in vacuo. Owing to the high efficiency of the reaction and high volatility of the 6-methyltetrahydropyranyl methyl ether side products, no further purification was required. The *ee* values of the products were determined by derivatization as their Mosher esters[10] and were found to be superior to or equivalent to the diastereomeric ratios obtained in the oxy-Michael addition reactions (Table 4).

In summary, the "naked" alkoxide of 6-methyl-δ-lactol, formed by deprotonation with KHMDS and sequestering with [18]crown-6, undergoes highly diastereoselective oxy-Michael additions to a range of nitroalkene acceptors to give the *O*-protected Henry products in good yields. Subsequent reduction of the nitro group and acidic methanolysis of the THP* group affords the desired enantiomerically enriched 1,2-amino alcohols. Further studies to ascertain the origin of stereoselectivity and the scope of the reaction are ongoing.

Table 4: Acid-mediated methanolysis of the THP* auxiliary and production of amino alcohols **22**–**28**.



15–21 **22–28**

Entry	R^1	Product	Yield [%]	*ee* [%]	$[\alpha]_D^{25}$ (*c*)[a]
1		**22**	97	>98	−57.5 (1.01)
2		**23**	94	>98	−19.9 (1.45)
3		**24**	99	>98	−20.0 (1.00)
4		**25**	84	>98	−37.8 (1.03)
5		**26**	74	>97	−27.4 (1.06)[b]
6		**27**	84	>96	−19.2 (1.00)[c]
7		**28**	99	>97	−10.2 (1.00)

[a] Measured in $CHCl_3$. [b] Ref. $[\alpha]_D^{25} = -28.8$ ($CHCl_3$, $c = 1.19$)[4b]. [c] Ref. $[\alpha]_D^{25} = -19.4$ ($CHCl_3$, $c = 0.94$)[4b].

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[1] a) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576; b) N. Kise, N. Inakoshi, Y. Matsumura, *Tetrahedron Lett.* **1995**, *36*, 909–912; c) G. B. Fisher, C. T. Goralski, L. W. Nicholson, D. L. Hasha, D. Zakett, B. Singaram, *J. Org. Chem.* **1995**, *60*, 2026–2034; d) R. E. Marti, J. Heinzer, D. Seebach, *Liebigs Ann.* **1995**, 1193–1215; e) D. Enders, U. Reinhold, *Liebigs Ann.* **1996**, 11–26; f) D. Enders, U. Reinhold, *Angew. Chem.* **1995**, *107*, 1332–1334; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1219–1222; g) T. Wirth, *Angew. Chem.* **1996**, *108*, 65–67; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 61–63; h) G. K. S. Prakash, M. Mandal, S. Schweizer, N. A. Petasis, G. A. Olah, *J. Org. Chem.* **2002**, *67*, 3718–3723; i) W. Oppolzer, O. Tamura, G. Sundarababu, M. Signer, *J. Am. Chem. Soc.* **1992**, *114*, 5900–5902; j) M. Brunner, L. Mußmann, D. Vogt, *Synlett* **1993**, 893–894; k) C. E. Harris, G. B. Fisher, D. Beardsley, L. Lee, C. T. Goralski, L. W. Nicholson, B. Singaram, *J. Org. Chem.* **1994**, *59*, 7746–7751; l) H.-T. Chang, K. B. Sharpless, *Tetrahedron Lett.* **1996**, *37*, 3219–3222; m) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421–431; n) J. L. Leighton, E. N. Jacobsen, *J. Org. Chem.* **1996**, *61*, 389–390; o) C. H. Senanayake, R. D. Larsen, L. M. DiMichele, J. Liu, P. H. Toma, R. G. Ball, T. R. Verhoeven, P. J. Reider, *Tetrahedron: Asymmetry* **1996**, *7*, 1501–1506; p) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449–452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454; q) A. V. Gontcharov, H. Liu, K. B. Sharpless, *Org. Lett.* **1999**, *1*, 783–786; r) K. L. Reddy, K. R. Dress, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 3667–3670; s) Z. P. Demko, M. Bartsch, K. B. Sharpless, *Org. Lett.* **2000**, *2*, 2221–2223; t) L. J. Goossen, H. Liu, K. R. Dress, K. B. Sharpless, *Angew. Chem.* **1999**, *111*, 1149–1152; *Angew. Chem. Int. Ed.*

1999, *38*, 1080 – 1083; u) C. T. Goralski, D. L. Hasha, L. W. Nicholson, D. Zakett, G. B. Fisher, B. Singaram, *Tetrahedron Lett.* **1994**, *35*, 3251 – 3254.
[2] See, for example: J. M. Klunder, S. Y. Ko, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 3710 – 3712.
[3] a) H. Sasai, N. Itoh, T. Suzuki, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 855 – 858; b) H. Sasai, T. Suzuki, N. Itoh, S. Arai, M. Shibasaki, *Tetrahedron Lett.*, **1993**, *34*, 2657 – 2660; c) R. Chinchilla, C. Nájera, P. Sanchez-Agulló, *Tetrahedron: Asymmetry* **1994**, *5*, 1393 – 1402; d) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290 – 1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236 – 1256; e) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388 – 7389; f) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621 – 2623.
[4] a) D. Enders, A. Haertwig, G. Raabe, J. Runsink, *Angew. Chem.* **1996**, *108*, 2540 – 2542; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2388 – 2390; b) D. Enders, A. Haertwig, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1771 – 1792; c) D. Enders, A. Haertwig, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1793 – 1802.
[5] a) M. F. Buffet, D. J. Dixon, S. V. Ley, E. W. Tate, *Synlett* **1998**, 1091 – 1092; b) D. J. Dixon, S. V. Ley, E. W. Tate, *Synlett* **1998**, 1093 – 1095; c) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2665 – 2667.
[6] a) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3125 – 3126; b) D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2385 – 2394.
[7] *Protective Groups in Organic Synthesis, Vol. 3* (Eds.: T. W. Greene, P. G. M. Wuts), Wiley, New York, **1999**, pp. 49 – 55.
[8] For a related system with an oxazolidinone chiral nucleophile, see: a) D. Lucet, L. Toupet, T. Le Gall, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 2682 – 2683; b) S. Sabelle, D. Lucet, T. Le Gall, C. Mioskowski, *Tetrahedron Lett.* **1998**, *39*, 2111 – 2114; c) D. Lucet, S. Sabelle, O. Kostelitz, T. Le Gall, C. Mioskowski, *Eur. J. Org. Chem.* **1999**, 2583 – 2591; d) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894.
[9] a) A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1981**, *29*(4), 1159 – 1161; b) A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1988**, *36*(4), 1529 – 1533; c) A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1989**, *37*(3), 816 – 818; d) J. O. Osby, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 6413 – 6416.
[10] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.

