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COMMUNICATIONS

Published on Web 01/20/2007

Asymmetric Organocatalytic β-Hydroxylation of α,β-Unsaturated Aldehydes

Søren Bertelsen, Peter Dinér, Rasmus Lyng Johansen, and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Received December 13, 2006; E-mail: kaj@chem.au.dk

Over the past few years, a tremendous development has been seen in the field of organocatalysis.[1] Aminocatalysis[2] has proven to be a powerful procedure for the enantioselective transformations of carbonyl compounds and a large number of α-,[3] β-,[4] and γ-functionalizations[5] have been reported. Organocatalyzed enantioselective Michael-type β-functionalizations have recently been demonstrated for carbon-,[4a−c] hydrido-,[4d,e] sulfur-,[4f−i] nitrogen-,[4j,k] and to some extent, oxygen-nucleophiles.[4l,m] This paper presents the first highly chemo- and enantioselective, organocatalytic β-hydroxylation of α,β-unsaturated aldehydes (Scheme 1).

Chiral β-hydroxy carbonyl compounds and 1,3-diols are ubiquitously recurring motifs in natural products but also important building blocks for the synthetic chemists. Additionally, chiral carbonyl β-oxime ethers are highly interesting biological compounds, and several applications for their biological activity are seen in, e.g., sex pheromone analogues,[6] highly potent antiinflammatory agents,[7] and penicillin and cephalosporin analogues.[8]

A few reports have been made on the organocatalytic addition of oxygen-based nucleophiles to α,β-unsaturated aldehydes, but with the exception of salicyl aldehyde derivatives[4l,m] only racemic products have been reported from hydroxylation and alkoxylation reactions.[9] Another organocatalytic route to α-unsubstituted β-hydroxy carbonyl compounds has been the Mukaiyama-aldol reaction.[10]

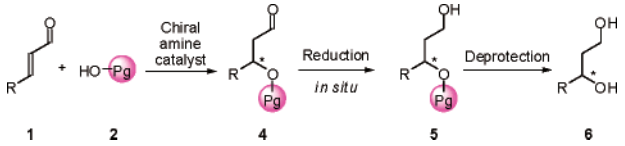
The difficulties encountered in the addition of the hard (HSAB) oxygen nucleophiles is due to the reversibility of the reaction and the affinity for acetal formation, which competes with the selective addition to the β-carbon atom (Scheme 2).

Oximes offer a class of oxygen-containing nucleophiles that partially circumvent these problems, and various additions of oximes to activated olefins have been reported.[11] A further advantage of oximes is the easy cleavage of the N−O bond, yielding the corresponding deprotected alcohols **6** (Scheme 1).[11c]

The recent success with the use of diarylprolinol ethers[12] prompted us to try the catalyst 2-[bis(3,5-bis-trifluoromethyl-phenyl)trimethyl-silanyloxymethyl]pyrrolidine, **3a**, for the enantioselective addition of (*E*)-benzaldehyde oxime, **2a**, to 2-*trans*-pentenal, **1a**. To our delight, **2a** reacted with **1a** within 20 min in CH_2Cl_2 to yield β-addition product **4a** in full conversion; after reduction with $NaBH_4$, the enantioselectivity was determined to be 89% ee. In order to find the optimal conditions for the reaction, a screening was performed using different amine catalysts **3a**−**e**, aromatic oximes **2a**−**c**, as well as other oxygen nucleophiles, solvents, and temperatures (see Table 1).

The screening of different solvents showed that the products formed in CH_2Cl_2 slowly racemize after completion of the reaction. Therefore, changing the solvent to a mixture of toluene/CH_2Cl_2 (4:1, Table 1, entry 2) or neat toluene (entry 3) led to an increase in the enantioselectivity but still gave full conversion into **4a**. The full conversion was generally observed for all the reactions in Table 1 except for entry 11. Performing the reaction in toluene at 4 °C

Scheme 1. Organocatalytic Asymmetric β-Hydroxylation and Formation of Diols



Scheme 2. Difficulties Faced when Attempting β-Hydroxylations of α,β-Unsaturated Aldehydes

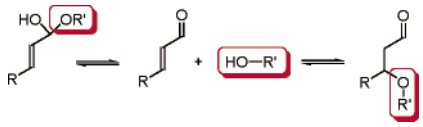
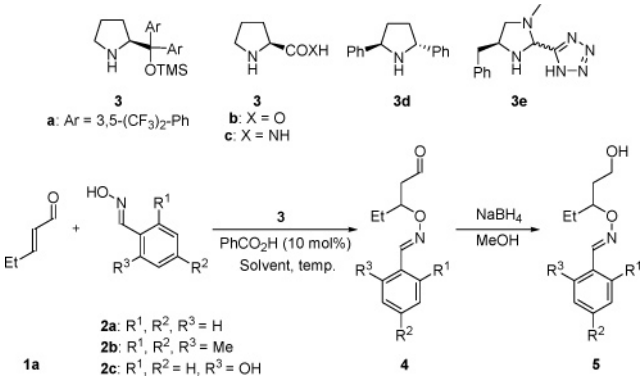


Table 1. Screening of Various Reaction Conditions for the Addition of Aromatic Oximes **2a**−**c** to 2-Pentenal, **1a**, Using Catalysts **3**[a]



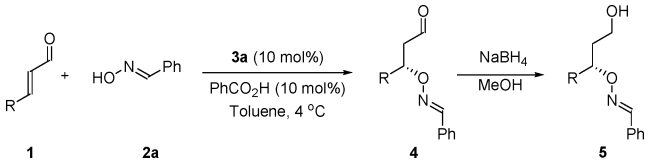
entry	solvent	cat.	nuc	*t* (°C)	ee (%)[b]
1	CH_2Cl_2	**3a**	**2a**	rt	89
2	Tol/CH_2Cl_2	**3a**	**2a**	rt	90
3	toluene	**3a**	**2a**	rt	93
4	toluene	**3a**	**2a**	4	95
5	toluene	**3a**	**2b**	rt	90
6	toluene	**3a**	**2c**	rt	<25
7	Tol/CH_2Cl_2	**3b**	**2a**	4	9
8	Tol/CH_2Cl_2	**3c**	**2a**	4	14
9	Tol/CH_2Cl_2	**3d**	**2a**	4	0
10	Tol/CH_2Cl_2	**3e**	**2a**	4	7
11	toluene	**3a**	TMSiOK	rt	n.r.

[a] Performed with **1a** (0.25 mmol), **2** (0.75 mmol), **3** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene (0.125 mL). [b] Determined by chiral HPLC.

increased the enantiomeric excess from 93% to 95% ee (entries 3, 4). Using different aromatic oximes as the oxygen nucleophile, such as mesitylaldehyde oxime **2b** and salicyl aldehyde oxime **2c**, led to lower conversion and longer reaction times as shown in entries 5 and 6, respectively, and in the case of oxime **2c**, the enantioselectivity decreased drastically compared to those of oximes **2a** and **2b**. We have also tested other oxygen nucleophiles, such as

10.1021/ja068908y CCC: $37.00

Table 2. Scope of the Organocatalytic β-Hydroxylation of α,β-Unsaturated Aldehydes **1a**−**h** Using (*E*)-Benzaldehyde Oxime, **2a**[a]



1 2a 4 5

entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	Et	1	**5a** − 72	95
2	Me	1	**5b** − 72	95
3	Pr	1	**5c** − 75	95
4	Bu	1	**5d** − 75	93
5	Hep	1	**5e** − 64	95
6	*i*-Pr	1.5	**5f** − 62	97
7	Hex−3-enyl	1	**5g** − 68	95
8	CO_2Et	8	**5h** − 60	88

[a] Performed with **1** (0.25 mmol), **2a** (0.75 mmol), **3a** (0.025 mmol), and $PhCO_2H$ (0.025 mmol) in toluene at 4 °C. [b] Purified by flash chromatography. [c] Determined by chiral HPLC.

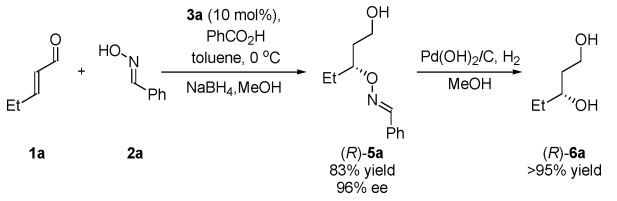
potassium trimethylsilanol salt, but no β-addition product was observed (entry 11).

L-Proline **3b**, proline amide **3c**, the C_2-symmetric catalyst **3d**, and the imidazoline tetrazoline **3e** (Table 1, entries 7−10) also catalyzed the β-hydroxlation reaction and gave full conversion, but only with a modest enantioselectivity.

With the optimized condition, several α,β-unsaturated aldehydes **1a**−**h** were reacted with (*E*)-benzaldehyde oxime **2a** using catalyst **3a**, yielding products **5a**−**h** after reduction with $NaBH_4$ (Table 2, entries 1−8). The results show that several different linear α,β-unsaturated aldehydes (entries 1−5) reacted smoothly and gave the optically active oxime addition products in high yields (up to 75%) and high enantioselectivities (up to 95% ee). The incorporation of a branched alkyl substituent, such as an isopropyl group, increases the ee to 97% (entry 6), and nearly similar results were also obtained (95% ee, entry 7) for α,β-unsaturated aldehydes having an extra double bond. Also the α,β-unsaturated aldehyde having an ester functionality in the β-position (**1h**) (entry 8) was converted to the optically active *O*-protected α-hydroxy carboxylic acid **5h**, with high stereocontrol and good yields. This latter product might be of importance for a number of further transformations. It should be noted that α,β-unsaturated aldehydes having aromatic substitutents did not react under these reaction conditions.

In order to broaden the scope for the reaction, we also wanted to show that the reaction could be performed at larger scales, demonstrating that the catalyst **3a** could be suitable for scale-up chemistry. Therefore, we were pleased to find that catalyst **3a** in 10 mol % catalyzed the reaction between 2-*trans*-pentenal, **1a** (7 mmol), and (*E*)-benzaldehyde oxime, **2a** (21 mmol), in high yield and enantioselectivity (83%, 96% ee) at 0 °C, yielding the optically active **5a** in a gram scale (Scheme 3). From the β-addition product **5a**, the deprotected 1,3-diol **6a** was easily accessed by hydrogenation with $Pd(OH)_2/C$ in MeOH. The absolute configuration of the products was determined by comparison of the optical rotation of **6a** as previously reported in literature.[13] Lowering the catalyst loading to 2 mol % of **3a** gave full conversion into product **5a** in 92% ee in 16 h with full recovery of excess of oxime **2a**.

Scheme 3. Gram-Scale Reaction and Deprotection to the 1,3-Diol



In conclusion, we have presented the first catalytic, highly stereoselective β-hydroxylation of α,β-unsaturated aldehydes using aromatic oximes as the hydroxylating agent. After reduction, the optically active products were isolated in good to excellent yield and enantiomeric excess.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation. P.D. thanks the Wenner-Gren Foundation for financial support.

Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews on organocatalysis see e.g.: (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2004. (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) *Acc. Chem. Res.* **2004**, *37* (8), special issue on organocatalysis. (e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. C. *Drug Discovery Today* **2007**, *2*, 8.

(2) See e.g.: List, B. *Chem. Commun.* **2006**, 819.

(3) (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.

(4) See e.g.: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M. Jørgensen, K. *A. Angew. Chem., Int. Ed.* **2006**, *45*, 4305. (c) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 6853. (d) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. (e) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (f) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (g) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**; *128*, 10354. (h) Rios, R.; Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 8547. (i) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (j) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (k) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**. Published online: http://dx.doi.org/10.1039/b613410f. (l) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (m) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Cordova, A. *Chem. Eur. J.* **2007**, *13*, 574.

(5) Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

(6) Martin, D.; Weber, B. *J. Chem. Eco.* **1994**, *20*, 1063.

(7) Balsamo, A.; Bertini, S.; Gervasi, G.; Lapucci, A.; Nencetti, S.; Orlandini, E.; Rapposelli, S.; Rossello, A.; Soldani, G. *Eur. J. Med. Chem.* **2001**, *36*, 799 and refences therein.

(8) Balsamo, A.; Broccali, G.; Lapucci. A.; Macchia, F.; Orlandini, E.; Rossello, A. *J. Med. Chem.* **1989**, *32*, 1398.

(9) See e.g.: (a) Ramachary, D. B.; Mondal, R. *Tetrahedron Lett.* **2006**, *47*, 7689. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 3039.

(10) For a diastereoselective version, see e.g.: Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48 and references therein.

(11) For recent examples see, e.g.: (a) Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis* **2003**, 1018. (b) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (c) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631. (d) Bhuniya, D.; Gujjary, S.; Sengupta, S. *Synth. Commun.* **2006**, *36*, 151.

(12) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(13) Yang, D.; Zhang, Y.-H.; Zhang, D.-W. *J. Org. Chem*. **2004**, *69*, 7577.

JA068908Y