Organocatalysis

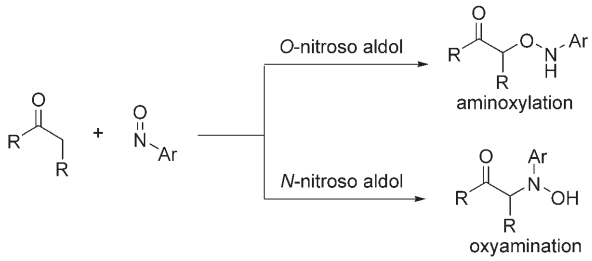
DOI: 10.1002/anie.200703001

Regio- and Enantioselective Direct Oxyamination Reaction of Aldehydes Catalyzed by α,α-Diphenylprolinol Trimethylsilyl Ether**

Claudio Palomo, Silvia Vera, Irene Velilla, Antonia Mielgo, and Enrique Gómez-Bengoa*

The nitroso function is recognized as a unique source to prepare nitrogen- and oxygen-containing molecules, and various catalytic asymmetric reactions of nitroso compounds[1] such as aminoxylation,[2] oxyamination,[3] and nitroso Diels–Alder reactions[4] have recently been developed which exploit their unique properties. Owing to the high reactivity of nitroso derivatives toward nucleophiles, controlling the regioselectivity of either the nitrogen or oxygen to preferentially react with the nucleophile is a challenge of fundamental importance. Investigations of the reaction of nitrosobenzene with a silyl or metal enolate have revealed that the O versus N selectivity is dependent on the nature of the enolate and the presence or absence of a Lewis acid catalyst.[5] Yamamoto and Momiyama reported the reaction between preformed enamines and nitrosobenzene in the presence of catalytic amounts of glycolic acid to preferentially afford the *O*-nitroso aldol product, while in the presence of TADDOL (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) the α-amino derivatives are exclusively obtained (Scheme 1).[6]

Organocatalyzed reactions of nitrosobenzene and carbonyl compounds with proline and its derivatives as catalysts to give α-oxygenated compounds as the major products have also been actively investigated.[2d–o,7] In sharp contrast, only two contributions on organocatalyzed direct nitrosoaldol reactions of carbonyl compounds that take place preferentially at the nitrogen have been reported.[2a,8] The first by Maruoka and co-workers[3a] described the asymmetric oxyamination reaction of aldehydes with nitrosobenzene catalyzed by the novel binaphthyl-based axially chiral secondary amine **1** (Figure 1). Although the preparation of the catalyst



Scheme 1. Possible products from the nitroso aldol reaction.

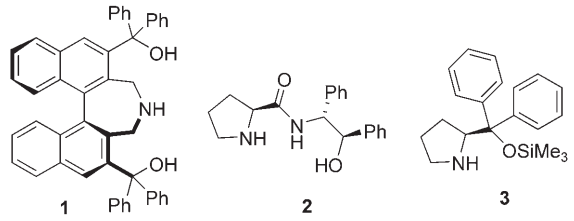


Figure 1. Developed organocatalysts for the *N*-nitroso aldol reaction of aldehydes (**1** and **2**) and a complementary alternative proposal (**3**).

requires several steps, high yields and excellent enantioselectivities were achieved. The second report implied the direct nitrosoaldol reaction of α-branched aldehydes in the presence of the L-prolinamide derivative **2** (Figure 1) as catalyst.[3b] In this case, the catalyst is structurally simple, but the reported enantioselectivities were modest. Here, we present our finding that prolinol ether derivatives are capable of efficiently promoting the oxyamination reaction of aldehydes with nitrosobenzene.

A structural feature of catalysts **1** and **2** for the direct oxyamination of aldehydes is the presence of a weak hydrogen-bond donor (OH group), which apparently coordinates the oxygen atom of nitrosobenzene to facilitate the oxyamination pathway.[9] We hypothesized that the α-oxyamination of aldehydes could be promoted by catalysts which lack hydrogen-bond donors. As the reaction results in the production of hydroxylamine, either the product itself or water generated from formation enamine could activate the oxyamination reaction through hydrogen-bond coordination to the oxygen of nitrosobenzene. In a first instance and owing to the recent emergence of α,α-diarylprolinol ether derivatives as fairly general organocatalysts,[10] we considered that derivative **3**[11] (Figure 1) could be a reasonable candidate to evaluate the above assumption. Concordant with our expectations, product **6b** (Table 1, entry 3), obtained from the reaction of butanal with nitrosobenzene promoted by **3** in methylene chloride as solvent, was produced after subsequent reduction of the resulting oxyaminated intermediate, in good yield and, most remarkably, with essentially perfect regiose-

[*] Prof. Dr. C. Palomo, S. Vera, I. Velilla, Dr. A. Mielgo, Dr. E. Gómez-Bengoa
Departamento de Química Orgánica I
Facultad de Química
Universidad del País Vasco. Apdo. 1072
20080 San Sebastián (Spain)
Fax: (+34) 943-015-270
E-mail: claudio.palomo@ehu.es

[**] This work was financially supported by The University of the Basque Country (UPV/EHU) and the Ministerio de Educación y Ciencia (MEC, Spain). Predoctoral grants to S.V. (MEC) and to I. Velilla (UPV/EHU) are also acknowledged. We also thank the SGI/IZO-SGIker UPV/EHU for allocation of computational resources.

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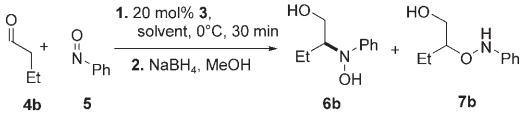
Table 1: Solvent screening in the oxyamination reaction of butanal with nitrosobenzene.[a]



Entry	Solvent	**6b**/**7b**	Yield [%][b]	*ee* [%][c]
1	toluene	>99:1	21	n.d.[d]
2	THF	>99:1	40	90
3	CH_2Cl_2	>99:1	65	90
4	CH_3CN	>99:1	50	85
5	H_2O	>99:1	25[e]	90

[a] Reactions were conducted with aldehyde (3 equiv) at 0 °C, with addition of the catalyst to a solution of the aldehyde and nitrosobenzene. [b] Isolated yield of product **6b** after column chromatography. [c] Determined by HPLC analysis. See Supporting Information for further details. [d] Not determined. [e] Nitrosobenzene shows poor solubility in water.

lectivity and very high enantioselectivity. Screening of other solvents for this reaction revealed that THF and acetonitrile are also efficient, although methylene chloride is somewhat superior.

Results with other aldehydes are shown in Table 2. The reactions were carried out by dropwise addition of catalyst **3** to a greenish solution of nitrosobenzene and the aldehyde in methylene chloride at 0 °C or room temperature, whereby an almost instantaneous decoloration was observed after the addition (Table 2, entries 1–3, 7–10). In general, the oxyamination reaction proceeded fast and the subsequent reduction with sodium borohydride provided the corresponding *N*-hydroxy β-aminoalcohols **6** in good yields over the two steps and with excellent enantioselectivities. Long-chain aldehydes afford at room temperature the expected adducts in somewhat lower yields (Table 2, entry 7). In these cases, the best results are obtained by carrying out the reaction at −20 °C overnight (Table 2, entries 4–6) in either methylene chloride or THF.

The absolute configuration of the resulted adduct in the reaction of pentanal with nitrosobenzene was determined by comparison of the value for the optical rotation with that previously described[3a] and was found to be *S*. This result is in accordance with the approach of the nitrosobenzene by the *Si* face of the enamine as shown in Figure 2.

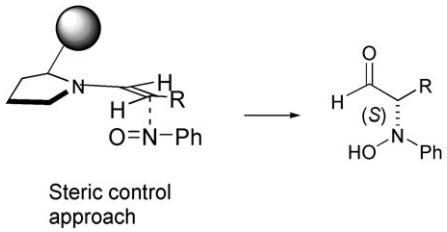


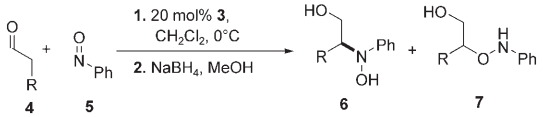
Figure 2. The approach of nitrosobenzene from the *Si* face of the enamine.

To gain more insight into our assumption, we computed by density functional theory (DFT) the different transition states for the formation of the C–N and C–O bonds in the reaction between propionaldehyde and nitrosobenzene in the absence of any added hydrogen-bonding source (non-functionalized pyrrolidine catalyst) and in the presence of water or *N*,*N*-dimethylhydroxylamine (**8**; mimicking product **6** or its precursor).[12] We found that the free activation energy $\Delta G^{\neq}$ for the non-catalyzed oxyamination is 25.6 kcal mol^{-1} (Figure 3 A). Water or *N*,*N*-dimethylhydroxylamine (**8**) catalyze the reaction with similar efficiency, reducing the activation barrier to 20.9 kcal mol^{-1} for water (Figure 3 B) and 20.3 kcal mol^{-1} for **8** (Figure 3 C).

In agreement with the experimentally encountered regioselectivity of over 99:1 in favor of the formation of **6**, the computed $\Delta G^{\neq}$ values for the non-catalyzed and catalyzed aminoxylation are in all cases over 3.0 kcal mol^{-1} higher than those of the oxyamination.

In summary, we have demonstrated that the direct and regioselective oxyamination reaction of aldehydes with nitrosobenzene can be successfully achieved in the presence of a structurally simple and readily accessible organocatalyst such as α,α-diphenylprolinol trimethylsilyl ether to afford the oxyaminated compounds in good yields and with excellent regio- and enantioselectivities.

Table 2: Enantioselective oxyamination of various aldehydes with nitrosobenzene.[a]



Entry	**6**,**7**	R	Solvent	*t* [min]	*T* [°C]	**6**/**7**[b]	Yield [%][c]	*ee* [%][d]
1	**a**	Me	CH_2Cl_2	5	RT	>99:1	70	94
2	**b**	Et	CH_2Cl_2	5	0	>99:1	65	99
3	**c**	*n*Pr	CH_2Cl_2	10	0	>99:1	60	96
4	**c**	*n*Pr	CH_2Cl_2	30	−20	>99:1	66	98
5	**d**	*n*-Pent	THF	16 h	−20	>99:1	74	98[e]
6	**e**	*n*-Hex	THF	16 h	−20	>99:1	75	98[e]
7	**e**	*n*-Hex	CH_2Cl_2	5	RT	>99:1	42	n.d.[f]
8	**f**	Bn	CH_2Cl_2	5	0	>99:1	70	94
9	**g**	2-$MeOC_6H_4CH_2$	CH_2Cl_2	5	RT	>99:1	40	91
10	**h**	*i*Pr	CH_2Cl_2	30	0	>99:1	60	99

[a] Reactions were conducted with aldehyde (3 equiv) at 0 °C or RT, with addition of the catalyst to a solution of the aldehyde and nitrosobenzene. See Experimental Section for the experimental procedure at −20 °C. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] Isolated yield of product **6** after column chromatography. [d] Determined by HPLC analysis. See Supporting Information for further details. [e] Determined by HPLC analysis of the benzoyl and naphthoyl derivatives. See Supporting Information for further details. [f] Not determined.

Experimental Section

General procedure for the oxyamination of aldehydes with nitrosobenzene: The catalyst (0.4 mmol, 20 mol %) was added

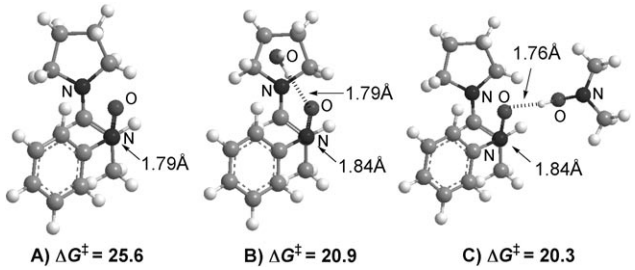


Figure 3. Computed transition states for the oxyamination reaction of propionaldehyde and nitrosobenzene: A) in the absence of any hydrogen-bonding source, B) in the presence of water, and C) in the presence of **8**. $\Delta G^{\ddagger}$ values are given in kcal mol^{-1}.

to a solution of the aldehyde (6 mmol, 3 equiv) in THF (1 mL) at −20 °C. A solution of nitrosobenzene (2 mmol, 1 equiv) in THF (1 mL) was then added dropwise to the reaction mixture, and the resulting solution was stirred at −20 °C for 16 h. EtOH (2 mL) and $NaBH_4$ (8 mmol) were successively added at the same temperature, and after stirring for 30 min the reaction was quenched with saturated NaCl (3 mL) and allowed to reach room temperature. After extraction with CH_2Cl_2 (3 × 4 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified over silica gel by flash column chromatography to afford the expected adducts.

Received: July 5, 2007
Revised: July 18, 2007
Published online: September 12, 2007

Keywords: aldehydes · enantioselectivity · organocatalysis · oxyamination · regioselectivity

[1] For reviews on nitroso compounds, see: a) P. Zuman, P. Shap, *Chem. Rev.* **1994**, *94*, 1621 – 1641; b) L. Soghyuk, C. Li, H. W. Ann, *Chem. Rev.* **2002**, *102*, 1019 – 1066; c) H. Yamamoto, M. Kawasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595 – 607. For a review on catalytic, enantioselective α-aminations and oxygenations, see: d) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364 – 4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292 – 4300.

[2] For reviews, see: a) P. Merino, T. Tejero, *Angew. Chem.* **2004**, *116*, 3055 – 3058; *Angew. Chem. Int. Ed.* **2004**, *43*, 2995 – 2997; b) B. Plietker, *Tetrahedron: Asymmetry* **2005**, *16*, 3453 – 3459; c) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514 – 3525. For L-proline as catalyst, see: d) Z. Zhong, *Angew. Chem.* **2003**, *115*, 4379 – 4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247 – 4250; e) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808 – 10809; f) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. J. Shoji, *J. Org. Chem.* **2004**, *69*, 5966 – 5973; g) K. Huang, Z.-Z. Huang, Y.-L. Li, *J. Org. Chem.* **2006**, *71*, 8320 – 8323; h) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673 – 3684. For a proline-based tetrazole derivative, see: i) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374 – 5378; j) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189 – 4191; k) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962 – 5963; l) S. G. Kin, T.-H. Park, *Tetrahedron Lett.* **2006**, *47*, 9067 – 9071. For *trans*-4-*tert*-butyldimethylsilyloxy-L-proline, see: m) Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435 – 1439. For a polymer-supported proline derivative, see: n) D. Font, A. Bastero, S. Salayero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 1943 – 1946. For a pyrrolidine sulfonamide catalyst, see: o) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235 – 7238.

[3] a) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046 – 6047; b) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Ghong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429 – 431.

[4] a) Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 4128 – 4129; b) Y. Yamamoto, H. Yamamoto, *Angew. Chem.* **2005**, *117*, 1508 – 1511; *Angew. Chem. Int. Ed.* **2005**, *44*, 7082 – 7085.

[5] a) N. Momiyama, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3459 – 3461; *Angew. Chem. Int. Ed.* **2002**, *41*, 2986 – 2988; b) N. Momiyama, H. Yamamoto, *Org. Lett.* **2002**, *4*, 3579 – 3582; c) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038 – 6039.

[6] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080 – 1081.

[7] For the origins of selectivities in proline-catalyzed α-aminoxylations, see: a) P. H.-Y. Chong, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 13912 – 13913; b) S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem.* **2004**, *116*, 3379 – 3383; *Angew. Chem. Int. Ed.* **2004**, *43*, 3317 – 3321.

[8] For reviews on organocatalytic enantioselective α-heterofunctionalisation of carbonyl compounds, see: a) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465 – 1492; b) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001 – 2011.

[9] It has also been reported recently that a pyrrolidine-based tetrazole catalyst also promotes the oxyamination. In this instance, lower levels of regio- and enantioselectivities, are produced; see Ref. [2l] for details.

[10] a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042 – 8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876 – 7880. For a recent review on asymmetric aminocatalysis, see: b) B. List, *Chem. Commun.* **2006**, 819 – 824, and references therein.

[11] Y. Hayashi, H. Gotog, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215.

[12] All the calculations were performed at the standard 6-31G* basis set (see Supporting Information for details). Further studies at higher level involving the actual catalyst **3**, as suggested by one referee, are currently underway.

