

Proline-Tetrazole-Catalyzed Enantioselective *N*-Nitroso Aldol Reaction of Aldehydes with In Situ Generated Nitrosocarbonyl Compounds**

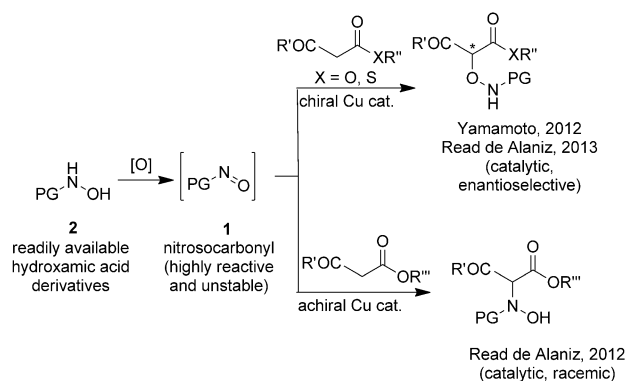
Biplab Maji* and Hisashi Yamamoto*

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: A highly enantioselective method (up to 98 % ee) for the preparation of β -amino alcohols was achieved by using the readily available proline-tetrazole as the catalyst for the *N*-nitroso aldol reaction of aldehydes with in situ generated nitrosocarbonyl compounds. The key to success of this reaction is the use of MnO_2 as an oxidant and catechol as a Brønsted acid additive.

Catalytic enantioselective oxidation, including hydroxylation and amination, in a complex molecular structure represents a central goal in organic synthesis.^[1] Stable aryl nitroso compounds^[2] have been widely utilized for this purpose as a useful source of oxygen^[3] and nitrogen^[4] functionalities. However, a limitation resulting from *N*-aryl bond cleavage has become apparent,^[5] and the search for a new source of nitroso compounds is in demand. The nitrosocarbonyl compounds **1** (Scheme 1), which can easily be manipulated, have turned out to serve this purpose.^[6] Because of their high reactivities, the transient nitrosocarbonyl species **1** are usually generated in situ by the oxidation of hydroxamic acid derivatives (**2**).^[7] The designs of catalytic enantioselective processes utilizing **1** are often made challenging by the incompatibility of the catalytic conditions with their formation. Recently, we introduced manganese dioxide as a mild oxidant in the copper-catalyzed enolate formation from 1,3-diketone compounds for the enantioselective *O*-nitroso aldol (*O*-NA) reaction.^[8] Read de Alaniz and co-workers utilized air as an oxidant for highly efficient copper-catalyzed racemic *N*-nitroso aldol (*N*-NA)^[5] and asymmetric *O*-NA reactions of β -ketoesters (Scheme 1).^[9]

Optically active α -amino acids, α -amino aldehydes, and β -amino alcohols represent valuable structural motifs because of their abundance in natural products and pharmaceutical



Scheme 1. Previous work with nitrosocarbonyl compounds. PG = protecting group.

compounds.^[10] They are also used as chiral ligands and auxiliaries in asymmetric synthesis.^[11] Hence, significant efforts have been devoted to developing enantioselective methods for their preparation.^[12] However, catalytic enantioselective methods for their syntheses were often complicated by the use of a suitable source of nitrogen and the need to avoid postreaction racemization of acid- or base-sensitive products.^[12] Herein, we report the utilization of in situ generated nitrosocarbonyl compounds **1** in *N*-NA reactions of aldehydes, catalyzed by proline-tetrazole, as a method for the synthesis of α -amino derivatives.^[13]

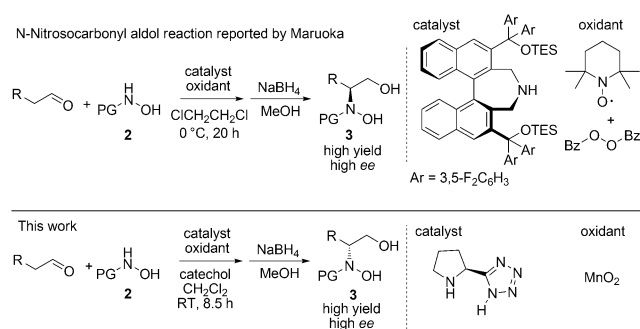
During the preparation of this manuscript Maruoka and co-workers reported a binaphthol-modified secondary amine catalyst for hydroxyamination of aldehydes with *N*-protected hydroxamic acids (**2**) as the nitrosocarbonyl precursor, and a combination of 2,2,6,6-tetramethylpiperidine *N*-oxyl and dibenzoyl peroxide as the oxidant (Scheme 2).^[14] Although the preparation of the catalyst requires several steps and the use of *N*-oxyl compounds and peroxides as oxidants requires additional precaution, high yield and enantioselectivities of the *N*-NA products **3** were achieved.

We envisioned that the development of a method for the *N*-NA reaction of aldehydes with relatively simple and commercially available proline-tetrazole as a catalyst, the *N*-protected hydroxylamine **2** as the nitrosocarbonyl precursor, and manganese dioxide as a mild oxidant^[15] would open a new direction for nitrosocarbonyl chemistry en route to a diverse range of α -amino compounds.

[*] Dr. B. Maji, Prof. Dr. H. Yamamoto
Molecular Catalyst Research Center, Chubu University
1200 Matsumoto-cho, Kasugai, Aichi 487-8501 (Japan)
E-mail: biplabmaji@isc.chubu.ac.jp
hyamamoto@isc.chubu.ac.jp
Homepage: <http://www3.chubu.ac.jp/catalyst/>

[**] This work is supported by a Grant-in-Aid for Scientific Research (No. 23225002), the Advance Catalytic Transformation Program for Carbon Utilization, the Uehara Memorial Foundation, Nippon Pharmaceutical Chemicals Co., Ltd, and Advance Electric Co., Inc. We thank Dr. M. Baidya and Dr. S. Bhadra for helpful discussions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201311069>.



Scheme 2. Enantioselective *N*-nitroso aldol reactions of aldehydes. Bz = benzoyl, TES = triethylsilyl.

To our delight, when a solution of commercially available *N*-CbzNHOH (**2a**) was added slowly by syringe pump to a mixture of 3-phenylpropanal, MnO₂, and 10 mol% of proline-tetrazole in CH₂Cl₂ at room temperature (23°C), the desired *N*-NA product **3a** was obtained in 65% yield and 88% *ee* after reduction with NaBH₄, and the undesired aminoxylated product was not observed by TLC (Table 1, entry 1).^[16] The structure of **3a** was confirmed by X-ray crystallography.^[17] Screening of other solvents resulted in diminished yields and enantioselectivities (entries 2–5). Gratifyingly, when *N*-BocNHOH (**2b**) was used as the source of nitrosocarbonyl compound, higher yield and enantioselectivity of the *N*-NA product **3b** was obtained while maintaining same level of regioselectivity (entry 6).

In our previous study with nitrosobenzene, we observed that the use of a Brønsted acid (BA) catalyst for the aldol

Table 1: Optimization of reaction conditions.^[a]

Entry	2	Solvent	Brønsted acid (BA)	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1 ^[d]	2a	CH ₂ Cl ₂	–	65	88
2 ^[e]	2a	THF	–	53	76
3 ^[e]	2a	1,4-dioxane	–	56	84
4	2a	(CH ₂ Cl) ₂	–	58	86
5 ^[e]	2a	THF/H ₂ O	–	33	13
6	2b	CH ₂ Cl ₂	–	67	91
7 ^[f]	2a	CH ₂ Cl ₂	(CH ₂ OH) ₂	58	83
8 ^[f]	2a	CH ₂ Cl ₂	(4 <i>S</i> ,5 <i>S</i>)-taddol	60	83
9 ^[f]	2a	CH ₂ Cl ₂	(<i>S</i>)-binol	61	91
10 ^[f]	2b	CH ₂ Cl ₂	(<i>S</i>)-binol	67	96
11	2b	CH ₂ Cl ₂	catechol	65	98
12	2b	CH ₂ Cl ₂	phenol	69	96

[a] Reaction of hydroxamic acids **2** (0.2 mmol) with 3-phenylpropanal (0.8 mmol) was carried out in the presence of proline-tetrazole (0.02 mmol), BA (0.02 mmol), and MnO₂ (1.0 mmol). [b] Yield of the isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] 79% hydrocinnamyl alcohol and 8% of an aldol dimer was isolated. [e] Used 0.04 mmol of the catalyst, and the THF/H₂O ratio was 5:1. [f] Used 0.04 mmol of BA. binol = 2,2'-dihydroxy-1,1'-binaphthyl, Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy, taddol = α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol, THF = tetrahydrofuran.

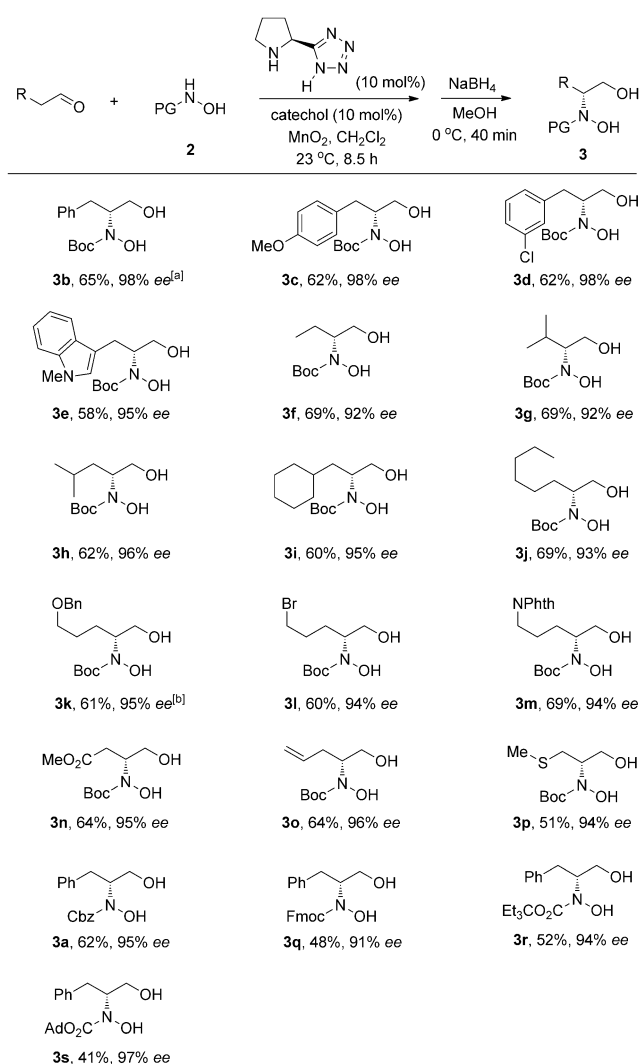
reaction of preformed enamines with nitrosobenzene was not only important to control the regioselectivity but also enantioselectivity.^[3] To test whether BA affected our catalytic system we performed the proline-tetrazole-catalyzed *N*-NA reactions in the presence of several BAs (Table 1, entries 7–12). While aliphatic alcohols are not efficient (entries 7 and 8), the use of aromatic alcohols as a BA additive resulted in improved enantioselectivities and maintained similar yields and regioselectivities (entries 9–12). We were pleased to find that catechol could serve as an optimal BA additive for this reaction as it gave 65% of the desired *N*-NA product with 98% *ee*.^[18]

With the optimal reaction conditions in hand, we examined the scope of this novel C–N bond-forming protocol and the results are shown in Scheme 3. With 10 mol% of the readily available proline-tetrazole catalyst, catechol as a BA additive, and MnO₂ as oxidant, this protocol accommodates a wide range of substituents on the aldehyde component, including aromatics, alkane chains of various steric bulk, ethers, halides, amines, esters, alkenes, and readily oxidizable thioethers (51–69% yield and 92–98% *ee*). However, more sterically demanding 3,3-dimethylbutanal, phenylacetaldehyde, and α-branched aldehydes were not useful substrates in this transformation. Other *N*-protected hydroxy amines were also tolerated in this reaction, thus providing the corresponding *N*-NA products in 41–62% yields and 91–97% *ee*.

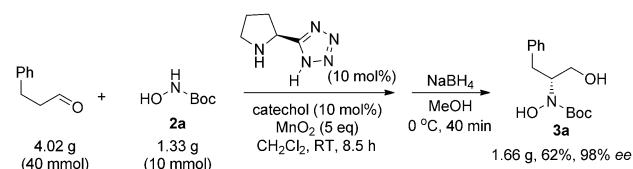
To test the synthetic utility of the present hydroxyamination of aldehydes we performed the reaction on a multigram scale (10 mmol). With 10 mol% of the catalyst under the optimized reaction conditions the *N*-NA reaction proceeded smoothly and the corresponding hydroxy amino alcohol **3a** was obtained in 62% yield (1.66 g) and 98% *ee* (Scheme 4).

To further demonstrate the synthetic utility of this protocol, we have illustrated a representative procedure to convert these enantioenriched *N*-NA products into the corresponding *N*-Boc-protected 1,2-amino alcohol **4** and 1,2-hydroxyamino alcohol **5** (Scheme 5). Thus, [Mo(CO)₆] treatment of **3a** cleanly cleaved the N–O bond and provided **4** in excellent yield with complete retention of the enantioselectivity.^[19] In contrast, when a dichloromethane solution of **3a** was treated with TFA, **5** was obtained in good yield without affecting the enantioselectivity. The absolute configuration of **4** (and hence **3a**) was established to be *R* by comparing the optical rotation of **4** with that reported in the literature.^[20] The absolute configurations of the compounds in Scheme 3 were assigned by analogy to the absolute configuration of **3a**.

In conclusion, we have developed an organocatalytic method to the *N*-nitroso aldol reaction of aldehydes with *N*-protected hydroxamic acid using easily handled MnO₂ as the oxidant and commercially available proline-tetrazole as the catalyst. This facile and robust method provides access to β-amino alcohols in moderate to good yields with excellent enantioselectivities. A detailed mechanistic study, including the beneficial effect of Brønsted acids on enantioselectivities, and further investigations aimed at applying this method to the synthesis of complex target structures containing a chiral amine fragment is underway in this laboratory.



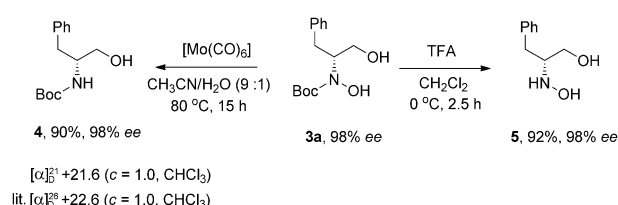
Scheme 3. Scope of enantioselective *N*-nitroso aldol reaction. Reaction conditions: **2** (0.2 mmol), aldehyde (0.8 mmol), proline-tetrazole (0.02 mmol), catechol (0.02 mmol), MnO_2 (1.0 mmol). Yield of isolated products are given. The *ee* value was determined by HPLC using a chiral stationary phase. [a] 76% hydrocinnamyl alcohol and 9% of an aldol dimer were isolated. [b] 74% 5-(benzyloxy)pentan-1-ol and 8% of an aldol dimer were isolated. Ad = 1-adamantyl, Fmoc = 9-fluorenylmethoxycarbonyl, NPhth = 1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl.



Scheme 4. Scale-up of the *N*-nitroso aldol reaction.

Experimental Section

General procedure of the *N*-nitroso aldol reaction: A solution *N*-protected hydroxamic acid (0.2 mmol) in CH_2Cl_2 (2 mL) was added by syringe pump, over a 7.5 h period at room temperature (23 °C), to a stirred suspension of the proline-tetrazole (0.02 mmol), catechol (0.02 mmol), MnO_2 (1.0 mmol), and aldehyde (0.8 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for an additional 1 h before it was



Scheme 5. Synthesis of the *N*-Boc-protected 1,2-amino alcohol **4** and 1,2-hydroxyamino alcohol **5**. TFA = trifluoroacetic acid.

placed into an ice bath. MeOH (2 mL) and NaBH_4 (1.6 mmol) was added and the mixture was stirred vigorously for another 40 min. The reaction was quenched with saturated NH_4Cl solution (0.2 mL) and filtered through a small pad of MgSO_4 and celite. After concentrating, the residue was purified by silica gel flash chromatography to afford the *N*-NA product.

Received: December 20, 2013

Published online: February 19, 2014

Keywords: aldol reaction · amino alcohol · organocatalysis · oxidation · synthetic methods

- [1] For an excellent review, see: S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943–2989.
- [2] For reviews, see: a) P. Merino, T. Tejero, *Angew. Chem.* **2004**, *116*, 3055–3058; *Angew. Chem. Int. Ed.* **2004**, *43*, 2995–2997; b) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364–4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292–4300; c) B. Plietker, *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459; d) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514–3525; e) H. Yamamoto, M. Kawasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607.
- [3] For selected examples of catalytic asymmetric *O*-nitroso aldol reactions with nitroso benzene, see: a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039; b) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379–4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250; c) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; d) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. J. Shoji, *J. Org. Chem.* **2004**, *69*, 5966–5973; e) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673–3684; f) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374–5378; g) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963; h) Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435–1439; i) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189–4191; j) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080–1081; k) M. Kawasaki, P. Li, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 3855–3857; *Angew. Chem. Int. Ed.* **2008**, *47*, 3795–3797; l) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu, G. Zhong, *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563; m) P. Jiao, M. Kawasaki, H. Yamamoto, *Angew. Chem.* **2009**, *121*, 3383–3386; *Angew. Chem. Int. Ed.* **2009**, *48*, 3333–3336; n) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem.* **2008**, *120*, 10341–10345; *Angew. Chem. Int. Ed.* **2008**, *47*, 10187–10191; o) A. Yanagisawa, S. Takeshita, Y. Izumi, K. Yoshida, *J. Am. Chem. Soc.* **2010**, *132*, 5328–5329.
- [4] For selected examples of catalytic asymmetric *N*-nitroso aldol reaction with aryl nitroso compounds, see: a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361; b) ref. [3];

- c) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Ghong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2006**, 429–431; d) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046–6047; e) C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2007**, *119*, 8200–8202; *Angew. Chem. Int. Ed.* **2007**, *46*, 8054–8056; f) J. López-Cantarero, M. B. Cid, T. B. Poulsen, M. Bella, J. L. G. Ruano, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 7062–7065; g) K. Shen, X. Liu, G. Wang, L. Lin, X. Feng, *Angew. Chem.* **2011**, *123*, 4780–4784; *Angew. Chem. Int. Ed.* **2011**, *50*, 4684–4688; h) L.-N. Jia, J. Huang, L. Peng, L.-L. Wang, J.-F. Bai, F. Tian, G.-Y. He, X.-Y. Xu, L.-X. Wang, *Org. Biomol. Chem.* **2012**, *10*, 236–239; i) A. Yanagisawa, T. Fujinami, Y. Oyokawa, T. Sugita, K. Yoshida, *Org. Lett.* **2012**, *14*, 2434–2437.
- [5] D. Sandoval, C. P. Frazier, A. Bugarin, J. Read deAlaniz, *J. Am. Chem. Soc.* **2012**, *134*, 18948–18951.
- [6] For pioneering work on nitrosocarbonyl compounds, see: a) G. W. Kirby, J. G. Sweeny, *J. Chem. Soc. Chem. Commun.* **1973**, 704–705; b) G. W. Kirby, *Chem. Soc. Rev.* **1977**, *6*, 1–24; For reviews on nitrosocarbonyl Diels–Alder reactions, see: c) J. Streith, A. Defoin, *Synthesis* **1994**, 1107–1117; d) C. Kibayashi, S. Aoyagi, *Synlett* **1995**, 873–879; e) P. E. Vogt, M. J. Miller, *Tetrahedron* **1998**, *54*, 1317–1348; f) Y. Yamamoto, H. Yamamoto, *Eur. J. Org. Chem.* **2006**, 2031–2043; g) B. S. Bodnar, M. J. Miller, *Angew. Chem.* **2011**, *123*, 5746–5764; *Angew. Chem. Int. Ed.* **2011**, *50*, 5630–5647; For reviews on nitrosocarbonyl ene reactions, see: h) W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131–4146; i) S. Iwasa, A. Fakhruddin, H. Nishiyama, *Mini-Rev. Org. Chem.* **2005**, *2*, 157–175; j) M. Baidya, H. Yamamoto, *Synthesis* **2013**, *45*, 1931–1938.
- [7] For selected oxidation methods with periodate, see: a) Ref. [6a]; b) For Swern oxidation, see: S. F. Martin, M. Hartmann, J. A. Josey, *Tetrahedron Lett.* **1992**, *33*, 3583–3586; c) For lead and silver oxide, see: L. H. Dao, J. M. Dust, D. Mackay, K. N. Watson, *Can. J. Chem.* **1979**, *57*, 1712–1719; d) For Dess–Martin periodinane, see: N. E. Jenkins, R. W., Jr. Ware, R. N. Atkinson, S. B. King, *Synth. Commun.* **2000**, *30*, 947–953; e) For oxidations using peroxides in combination with transition metals, see: S. Iwasa, A. Fakhruddin, Y. Tsukamoto, M. Kameyama, H. Nishiyama, *Tetrahedron Lett.* **2002**, *43*, 6159–6161; f) J. A. K. Howard, G. Ilyashenko, H. A. Sparkes, A. Whiting, A. R. Wright, *Adv. Synth. Catal.* **2008**, *350*, 869–882; g) For aerobic oxidation, see: D. Chaiyaveij, L. Cleary, A. S. Batsanov, T. B. Marder, K. J. Shea, A. Whiting, *Org. Lett.* **2011**, *13*, 3442–3445; h) C. P. Frazier, J. R. Engelking, J. Read deAlaniz, *J. Am. Chem. Soc.* **2011**, *133*, 10430–10433; i) C. P. Frazier, A. Bugarin, J. R. Engelking, J. Read deAlaniz, *Org. Lett.* **2012**, *14*, 3620–3623; j) For photooxidation, see: Y. C. Teo, Y. Pan, C. H. Tan, *ChemCatChem* **2013**, *5*, 235–240.
- [8] M. Baidya, K. A. Griffin, H. Yamamoto, *J. Am. Chem. Soc.* **2012**, *134*, 18566–18569.
- [9] C. P. Frazier, D. Sandoval, L. I. Palmer, J. Read deAlaniz, *Chem. Sci.* **2013**, *4*, 3857–3862.
- [10] a) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284–287; b) *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2000**; c) *Amino Group Chemistry: From Synthesis to the Life Sciences* (Ed.: A. Ricci), Wiley-VCH, Weinheim, **2008**; d) R. M. Williams in *Synthesis of Optically Active α -Amino Acids*, Pergamon, Oxford, **1989**.
- [11] For an excellent review, see: a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876.
- [12] a) ref. [10]; b) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868–1871; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793; c) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5657–5658; d) Y.-W. Zhong, Y.-Z. Dong, K. Fang, K. Izumi, M.-H. Xu, G.-Q. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 11956–11957; e) H. Konishi, T. Y. Lam, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2010**, *12*, 2028–2031; f) G. Cecere, C. M. Kønig, J. L. Alleva, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 11521–11524.
- [13] a) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834; b) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, *3*, 558–560; c) H. Torii, M. Nakadaï, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986.
- [14] T. Kano, F. Shirozu, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 18036–18039.
- [15] E. Brill, *Experientia* **1974**, *30*, 835.
- [16] Use of L-proline as a catalyst resulted in lower catalytic activity (37% yield and 51% ee of **3a**). See Table S1 in the Supporting Information for screening of other secondary amine catalysts.
- [17] CCDC 981058 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] See the Table S1 in the Supporting Information for detailed screening of other BAs.
- [19] S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. D. Sarlo, *Tetrahedron Lett.* **1990**, *31*, 3351–3354.
- [20] T. Vilaivan, *Tetrahedron Lett.* **2006**, *47*, 6739–6742.