Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of N-Chiral Amine Oxides

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Abstract: *Direct asymmetric synthesis of N-chiral amine oxides was accomplished (up to 91:9 e.r.) by means of a bimetallic titanium catalyst. A hydroxy group situated at the γ-position of the N stereocenter enables the desired N-oxidation through dynamic kinetic resolution of the trivalent amine substrates. The method was further extended to the kinetic resolution of racemic γ-amino alcohols with a preexisting stereocenter, giving an important class of enantioenriched (up to 99.9:0.1 e.r.) building blocks that are otherwise difficult to synthesize.*

Optically active chiral sulfoxides, phosphine oxides, and amine oxides are frequently found in biologically relevant compounds. In addition, these molecules have been used both as chiral ligands in metal-catalyzed reactions and as organocatalysts.[1] The development of catalytic methods leading to these molecules are of fundamental importance. Whereas, the asymmetric syntheses of optically active sulfoxides and phosphine oxides are well established, the synthesis of amine oxides has not been satisfactorily developed. The potential pitfall of the direct synthesis of N-chiral amine oxides originates from the fact that the starting tertiary amine enantiomers are always in equilibrium as a result of a rapid pyramidal inversion on the stereogenic nitrogen atom of the substrates. A literature survey demonstrates that N-chiral *N*,*N*-dialkylarylamine oxides are primarily accessed through various resolution methods.[2–4] Thus the direct asymmetric oxidation of tertiary amines to the corresponding N-chiral amine oxides remained unsolved except by using an enzymatic process that has rather low enantioselectivity and efficiency.[5,6] A powerful catalytic asymmetric route to N-chiral amine oxides is reported herein.

Recently we have introduced a new concept based on bimetallic catalysis for various asymmetric oxidation processes, including epoxidation of homoallylic alcohols and 2-allylic phenols, and sulfoxidation of γ-hydroxypropyl sulfides.[7,8] In the new approach, one of the two independent metal centers inside the bimetallic catalyst scaffold holds the hydroxy substrate in close proximity to the other metal center, which enantioselectively transfers the oxidant to the reactive site. We envisaged that this approach could be used to position a hydroxy group at an appropriate distance from the N center to confer enantioselectivity on the N-oxidation. We herein report direct access to N-chiral amine oxides starting from the corresponding unsymmetrical tertiary amino alcohols through bimetallic catalysis (Figure 1).

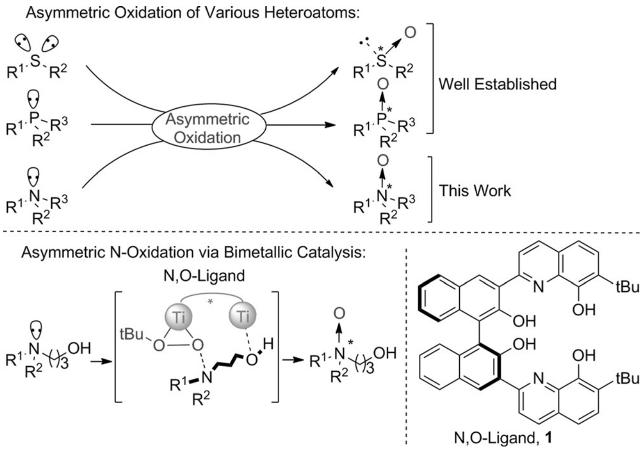

Figure 1. Asymmetric N-oxidation.

We started our investigation for a suitable asymmetric N-oxidation method with various amino alcohol substrate classes (for details see Table 1 and Tables S1, S2 in the Supporting Information). The desired N-oxidation of the β-amino alcohol gave the corresponding N-oxide **2** as a racemic mixture in good yield when using a 2:1 complex of Ti and N,O-ligand **1** in the presence of 70 % aqueous *tert*-butyl hydroperoxide solution (TBHP) at room temperature.[8] Gratifyingly, we observed that the title reaction for the γ-amino alcohol provided the N-oxide **3a** in reasonably good yield and enantioselectivity (69 %, 70:30 e.r.; entry 2). The stereoselectivity was further improved when the reaction was carried out at −20 °C. A 2:1 metal-to-ligand ratio was crucial; the use of a 1:1 metal-to-ligand ratio had a deleterious effect. The presence of the γ-hydroxy group was the key for successful N-oxidation, since the reaction does not proceed in its absence, thus confirming that the hydroxy group acts as an anchor for the Ti catalyst (entry 3). However, as expected, the N-oxidation was not effective for other substrate classes, including δ-amino alcohols, hydroxymethylaniline, and aminophenols (see Table S1).

With an effective reaction system in hand, we subsequently studied the scope of the asymmetric N-oxidation for various γ-amino alcohols (Scheme 1). A range of (*N*,*N*-benzylalkyl)amino alcohols were converted into the corresponding N-chiral oxide in satisfactory yields and with moderate to good enantioselectivity (**3a**–**3j**). The presence

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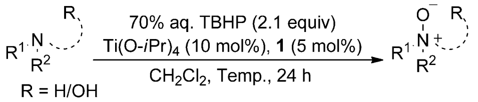
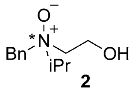
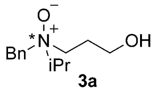
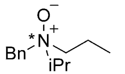
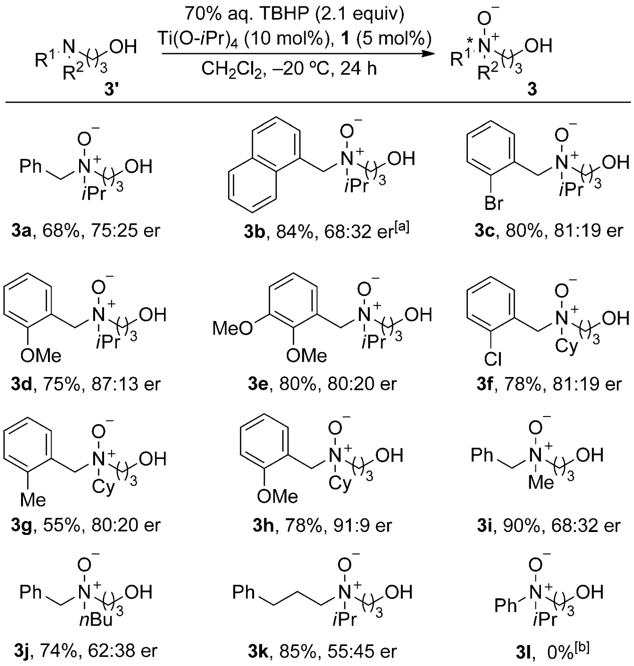
Table 1: Identification of the appropriate amino alcohol for the asymmetric N-oxidation.[a]



Entry	N-Oxides	*T*	Yield [%], e.r. [%]
1	 **2**	RT	85, 1:1
2	 **3a**	RT	67, 70:30
		−20 °C	68, 75:25
		−78 °C	45, 60:40
		−20 °C	60, 67:33[b]
		−20 °C	30, 58:42[c]
3	 **4**	RT	0

[a] *Reaction Conditions:* 0.15 mmol amino alcohol (1 equiv), 2.1 equiv 70 % aq TBHP, 10 mol % Ti(O-*i*Pr)$_4$, 5 mol % **1**, in 4 mL CH$_2$Cl$_2$ at a given temperature for 24 h. Yields of isolated product are shown, and the e.r. values were determined by HPLC with a chiral stationary phase. [b] With 5 mol % Ti(O-*i*Pr)$_4$ and 2.5 mol % **1**. [c] With 5 mol % Ti(O-*i*Pr)$_4$ and 5 mol % **1**.



Scheme 1. Scope of the asymmetric N-oxidation. Reaction Conditions: 0.15 mmol **3′** (1 equiv), 2.1 equiv 70 % aq TBHP, 10 mol % Ti(O-*i*Pr)$_4$, 5 mol % **1**, in 4 mL CH$_2$Cl$_2$ at −20 °C for 24 h. Yields of isolated product are shown, and the e.r. values were determined by HPLC with a chiral stationary phase. [a] At 0 °C. [b] With 3.5 equiv 70 % aq. TBHP, and for 72 h.

of a bulky substituent at the N stereocenter facilitated the formation of more enantioenriched products (**3a**–**3h**). Unfortunately, however, the enantioselectivity drops in the presence of a less bulky substituent (**3i**–**3j**) or a simple alkyl side chain instead of the benzyl group at the N center (**3k**). Further, γ-(*N*,*N*-isopropylphenyl)amino alcohol did not undergo oxidation under the optimized conditions (**3l**).

We speculate that the asymmetric N-oxidation proceeds via dynamic kinetic resolution at the N center of the chiral racemic γ-amino alcohol.[9] The enantioselectivity of the product was induced by our new bimetallic catalysis approach. Although the reaction mechanism is not clear at this point, the stereodiscrimination should take place during the N-oxidation stage at one of the titanium centers of the bimetallic catalyst.

Encouraged by these promising results, we became interested in applying this strategy to the practical synthesis of optically active γ-amino alcohols via kinetic resolution (KR) of the racemates through formation of the corresponding N-oxide. The synthesis of optically active γ-amino alcohols and amine oxides is of profound significance given their abundance in bioactive natural products and pharmaceutical agents, and their increasing use as chiral ligands (Figure 2).[10,11] While the racemic γ-amino alcohols are simply accessible, only a handful of straightforward synthetic routes to the optically active variants have been reported, including transition-metal-catalyzed asymmetric reduction of the corresponding amino ketones,[12] stereoselective addition of dialkyl zinc to aldehydes,[13] and the recently reported Buchwald's hydroamination reactions.[14] Nonetheless, various classes of amino alcohols remain that cannot be synthesized with excellent enantioselectivity.

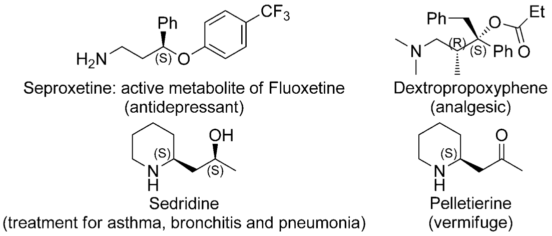
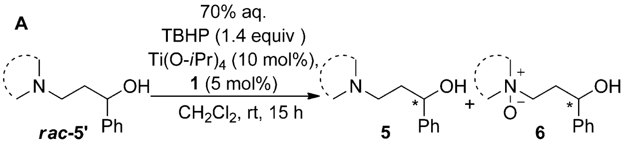
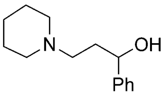
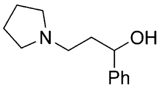
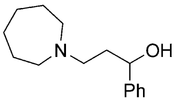
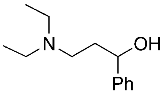


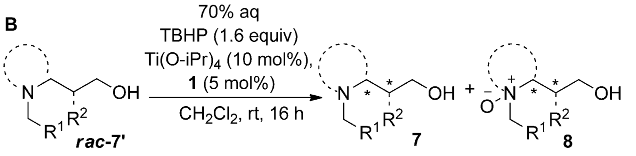
Figure 2. Some optically active γ-amino alcohol derivatives.

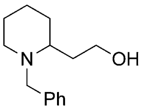
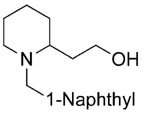
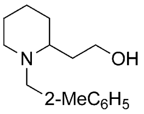
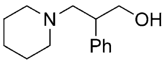
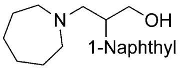
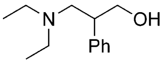
We predicted that our N-oxide formation strategy could be utilized for a kinetic resolution (KR) of γ-amino alcohols that contain a preexisting stereogenic center, a transformation that has failed to be achieved through the Sharpless method.[15] After a quick survey of various reaction parameters (see Table S3, S4), it turned out that the quantity of TBHP is crucial to achieve excellent enantioselectivity. To our delight we found that when the racemic secondary alcohol **5′a** was subjected to oxidation with 1.4 equiv of 70 % aq. TBHP in the presence of the optimized catalyst system, the optically active γ-amino alcohol **5a** was obtained at room temperature in virtually enantiopure form (> 99 % *ee*). The KR may proceed via the formation of a stereocongested transition state driven by the crowded secondary hydroxy group of the substrate. In this way, an array of optically active *sec*-γ-amino alcohols and the corresponding N-oxides were obtained in good yields and with excellent enantioselectivity (Table 2 A). Next, we studied the KR of primary γ-amino alcohols with

Table 2: Kinetic resolution of γ-amino alcohols.



Amino Alcohol 5′	**5** e.r.[a] [% Yield][b]	**6** e.r.[a] [% Yield][b]	C[c]	s[d]
	**5a** 99.5:0.5 [43]	**6a** 97.7:2.3 [48]	51	213
	**5b** 98.9:1.1 [40]	**6b** 80:20 [50]	62	17
	**5c** 99.9:0.1 [45]	**6c** 90:10 [49]	56	54
	**5d** 97.4:2.6 [44]	**6d** 97:3 [48]	50	139



Amino Alcohol 7′	**7** e.r.[a] (% Yield)[b]	**8** e.r.[a] (% Yield)[b]	C[c]	s[d]
	**7a** 97.5:2.5 [45]	**8a** 93.7:6.3 [52]	52	56
	**7b** 97.7:2.3 [44]	**8b** 95.7:4.3 [48]	51	87
	**7c** 99.7:0.3 [39]	**8c** 95.9:4.1 [48]	52	133
	**7d** 95:5 [48]	**8d** 80.3:19.7 [48]	60	12
	**7e** 99.1:0.9 [43]	**8e** 79:21 [53]	63	16
	**7f** 82:18 [57]	**8f**[e] 64:36 [38]	70	3

[a] The e.r. values were determined by HPLC with a chiral stationary phase. [b] Yield of isolated product. [c] Conversion, $C = ee_S/(ee_S + ee_P)$. [d] The selectivity factor s was calculated as $s = \ln[(1-C)(1-ee_S)]/\ln[(1-C)(1+ee_S)]$. [e] For 24 h.

diverse substitution patterns, which represent a more challenging but important substrate class (Table 2B). The 2-hydroxyalkyl-substituted piperidines and their derivatives constitute a framework that is frequently found in the structure of drug candidates.[16] We were pleased to find that when using our new KR method, 2-piperidineethanol-derived γ-amino alcohols (**7a**–**7c**) were obtained with excellent enantiopurity, along with their N-oxides (**8a**–**8c**) in diastereomerically pure form and with satisfactory enantiomeric excess. The KR was further extended successfully to other primary γ-amino alcohols with different substituents in the γ-amino alcohol chain (**7d**–**7f**). The N-oxides thus formed can be transformed into the corresponding γ-amino alcohols of opposite configuration through various reduction methods.[17] However the KR did not proceed for the γ-amino tertiary alcohols with a geminal dialkyl substituents.

In conclusion, we have developed a catalytic asymmetric N-oxidation of unsymmetrical γ-hydroxy tertiary amines that proceeds via dynamic kinetic resolution, leading to N-chiral amine oxides. A hydroxy group located at the γ-position with respect to the N stereocenter is key to the success of this approach. The concept of hydroxy-directed N-oxidation was further extended to the KR of racemic γ-amino alcohols with a preexisting stereogenic center. These oxidative transformations based on bimetallic catalysis approach provide a new platform for "catalyst-controlled" chemical reactions, and further investigation is currently ongoing in our laboratory.

Experimental Section

General procedure for the asymmetric N-oxidation of γ-amino alcohols: To the ligand **1** (5.2 mg, 0.0075 mmol, 5 mol%) in 3 mL dicloromethane, $Ti(O\text{-}iPr)_4$ (4.5 μL, 0.015 mmol, 10 mol%) was added at room temperature with a microlitre syringe under nitrogen atmosphere. The resulting yellow solution almost immediately turned red and was stirred for additional 2 h. Next, 70% aq. *t*BuOOH solution (31 μL, 0.315 mmol, 2.1 equiv) was added and stirred for an additional 10 min before cooling to −20°C. The γ-amino alcohol (0.15 mmol, 1 equiv) in 1 mL CH_2Cl_2 was then added dropwise with a syringe. The reaction mixture was stirred at the same temperature for the required time (TLC). It was then directly subjected to column chromatography over silica gel using CH_2Cl_2 and MeOH as eluents to obtain the corresponding N-oxide.

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Angew. Chem. **2016**, *128*, 13237–13240

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[1] For an overview see: a) *Asymmetric Synthesis, Vol. 4* (Eds.: J. D. Morrison, J. W. Scott), Academic Press, New York, **1983**; b) K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375–1411; c) N. V. Dubrovina, A. Boerner, *Angew. Chem. Int. Ed.* **2004**, *43*, 5883–5886; *Angew. Chem.* **2004**, *116*, 6007–6010; d) H. B. Kagan in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, pp. 1–29; e) M. Carmen Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129–6144; f) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2012**, *23*, 1–46; g) S. Liao, I. Čoric, Q. Wang, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 10765–10768; h) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.*

2014, *114*, 6081 – 6129; i) B. M. Trost, M. Rao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5026 – 5043; *Angew. Chem.* **2015**, *127*, 5112 – 5130.

[2] a) J. Meisenheimer, *Chem. Ber.* **1908**, *41*, 3966 – 3976; b) J. Meisenheimer, H. Glawe, H. Greeske, A. Schorning, E. Vieweg, *Justus Liebigs Ann. Chem.* **1926**, *449*, 188 – 213; c) J. Meisenheimer, *Justus Liebigs Ann. Chem.* **1922**, *428*, 252 – 285.

[3] F. Toda, K. Mori, Z. Stein, I. Goldberg, *Tetrahedron Lett.* **1989**, *30*, 1841 – 1844.

[4] J. Drabowicz, B. Dudziński, M. Mikołajczyk, S. Colonna, N. Gaggero, *Tetrahedron: Asymmetry* **1997**, *8*, 2267 – 2270.

[5] F. A. Davis, J. R. H. Jenkins in *Asymmetric Synthesis*, *Vol. 4* (Eds.: J. D. Morrison, J. W. Scott), Academic Press, New York, **1983**.

[6] S. Colonna, N. Gaggero, J. Drabowicz, P. Lyzwa, M. Mikolajczyk, *Chem. Commun.* **1999**, 1787 – 1788.

[7] For reviews, see: a) *Multimetallic Catalysts in Organic Synthesis* (Eds.: M. Shibasaki, Y. Yamamoto), Wiley-VCH, Weinheim, **2004**; b) S. Matsunaga, M. Shibasaki, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60 – 75; c) S. Matsunaga, M. Shibasaki, *Chem. Commun.* **2014**, *50*, 1044 – 1057; d) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis* (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**.

[8] S. Bhadra, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2015**, *137*, 15612 – 15615.

[9] The barrier to pyramidal inversion at the N center in amines is 6–7 kcal mol^{-1} at room temperature; For details, see Ref. [5].

[10] An overview on chiral amines: a) *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; For applications of chiral *N*-oxide ligands see: b) M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419 – 6420; c) M. Nakajima, Y. Sasaki, H. Iwamoto, S.-i. Hashimoto, *Tetrahedron Lett.* **1998**, *39*, 87 – 88; d) B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353 – 354; e) M. Saito, M. Nakajima, S. Hashimoto, *Chem. Commun.* **2000**, 1851 – 1852; f) M. Nakajima, M. Saito, M. Uemura, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 8827 – 8829; g) T. Shimada, A. Kina, S. Ikeda, T. Hayashi, *Org. Lett.* **2002**, *4*, 2799 – 2801; h) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29 – 36; i) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574 – 587, and references therein.

[11] a) G. T. Rice, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11707 – 11711; b) H. Ren, W. D. Wulff, *Org. Lett.* **2013**, *15*, 242 – 245.

[12] a) D. Liu, W. Gao, C. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 1687 – 1689; *Angew. Chem.* **2005**, *117*, 1715 – 1717; b) J. M. M. Verkade, P. J. L. M. Quaedflieg, G. K. M. Verzijl, L. Lefort, F. L. van Delft, J. G. de Vries, F. P. J. T. Rutjes, *Chem. Commun.* **2015**, *51*, 14462 – 14464, and references therein.

[13] C. Lutz, V. Lutz, P. Knochel, *Tetrahedron* **1998**, *54*, 6385 – 6402.

[14] S.-L. Shi, Z. L. Wong, S. L. Buchwald, *Nature* **2016**, *532*, 353 – 356.

[15] Although a Ti-based catalyst reported by Sharpless et al. enables the KR of β-hydroxy amines, it does not allow a similar transformation of γ-hydroxy amines. For details, see: a) S. Miyano, L. D.-L. Lu, S. M. Viti, K. B. Sharpless, *J. Org. Chem.* **1983**, *48*, 3608 – 3611; b) S. Miyano, L. D.-L. Lu, S. M. Viti, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 4350 – 4360.

[16] a) G. M. Strunzand, J. A. Finlay in *The Alkaloids*, *Vol. 26* (Ed.: A. Brossi), Academic Press, New York, **1985**; b) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701 – 1729.

[17] H. P. Kokatla, P. F. Thomson, S. Bae, V. R. Doddi, M. K. Lakshman, *J. Org. Chem.* **2011**, *76*, 7842 – 7848.

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