Novel Chiral C_2-Symmetric Bisimidazole-*N*-Oxides as Promising Organocatalysts for Enantioselective Allylation of Aromatic Aldehydes

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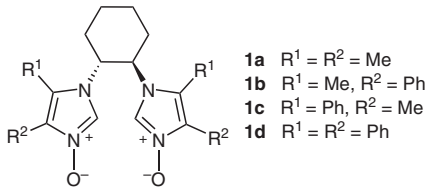
Abstract: A series of new, chiral Lewis bases containing imidazole-*N*-oxide moiety were tested for purposes of asymmetric catalysis. Bisimidazole-*N*-oxides derived from (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-1,2-diaminocyclohexane were used as catalysts in the allylation reaction of aromatic aldehydes with allyltrichlorosilane, which yielded homoallyl alcohols in good yields and with enantioselectivity up to 80% ee. Screening of catalysts revealed that the type of substituents and their location in imidazole ring has a crucial influence on enantioselectivity of the addition process.

Key words: allylation, asymmetric catalysis, chiral imidazole-*N*-oxides, nucleophilic addition, organocatalysis

One of the most important tasks of the modern asymmetric synthesis is the quest for novel catalysts useful for preparation of chiral compounds in high enantiomeric purity. In recent years, we observe rapidly growing interest in the development of asymmetric organocatalytic reactions,[1] including catalysis with organic Lewis bases.[2] Amine *N*-oxides and azaheterocyclic *N*-oxides are recognized as a group of very promising catalysts of this type, well documented by growing number of original papers[3,4] and review articles.[5] Diverse *N*-oxides were reported as more or less efficient catalysts for such reactions as asymmetric allylation of aldehydes, cyanosilylation of carbonyl and imine compounds, aldol-type reactions, and desymmetryzation of *meso*-epoxides.[5] To the best of our knowledge, chiral *N*-oxides derived from pyridine (and related heterocycles, e.g., quinoline)[3,5] or from tertiary amines (e.g., *N*-alkyl proline)[4,5] are only representatives reported, which found application in asymmetric catalysis until the present time. Herein, we report for the first time application of a new type of chiral catalysts based on the novel, 2-unsubstituted bisimidazole-*N*-oxides derived from *trans*-1,2-diaminocyclohexane.

Recently, we described a simple and efficient method for the preparation of diverse chiral imidazole *N*-oxides[6,7] including bisimidazole-*N*-oxides of type **1**[7] (Figure 1). Enantiomerically pure *trans*-1,10-(cyclohexane-1,2-diyl)bis(imidazole-*N*-oxides) **1a–d** were prepared via condensation of (1*R*,2*R*)- or (1*S*,2*S*)-*trans*-cyclohexane-1,2-bis(methylidenamine) (**2a**) with α-hydroxy-iminoketones **3a–d** in boiling EtOH or in glacial acetic acid at room temperature (Scheme 1).[8] In solution, the monomeric form **2a** exists in an equilibrium with the dimer identified as the eicosan derivative **2b**.[9] In average, yields of the isolated products were good or very good (62–85%) and could be reproduced with no problem. The optically active substrate **2** was easily obtained from the corresponding, enantiomerically pure *trans*-1,2-diaminocyclohexane and paraformalehyde.[7,8]



(1*R*,2*R*)-*trans*-**1a–d**

Figure 1 Chiral bisimidazole-*N*-oxides **1a–d**

The allylation of aromatic aldehydes **4** with allyltrichlorosilane was selected as a test reaction for the screening of catalysts of type **1**.[10] It is well known that highly nucleophilic amine *N*-oxides can act as efficient activators of organosilicon reagents.[5,11]

In the model reaction of benzaldehyde (**4a**) with allyltrichlorosilane (Scheme 2), the activities of four *N*-oxides **1a–d**, bearing Me and/or Ph substituents at C(4) and C(5) in imidazole ring, were compared. It turned out that the type of substituents and their positions in the imidazole ring have a crucial influence on enantioselectivities and the sense of asymmetric induction (Table 1). The presence of catalytic amount of **1a** with two Me groups at C(4) and C(5) resulted in the formation of product **5a** in moderate chemical yield and low enantioselectivity (entry 1). On the other hand, replacement of one Me group at C(4) with Ph substituent (catalyst **1b**) led to improvement of the yield of **5a** and better enantioselectivity (entry 2). The reaction carried out in the presence of the catalyst **1c** with reversed arrangement of Me and Ph substituents led to

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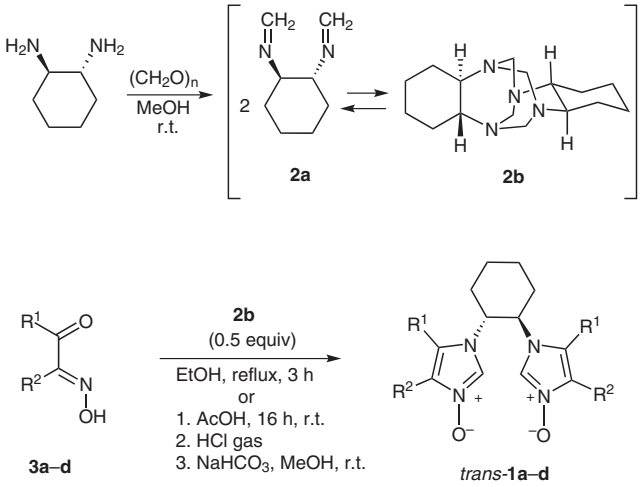
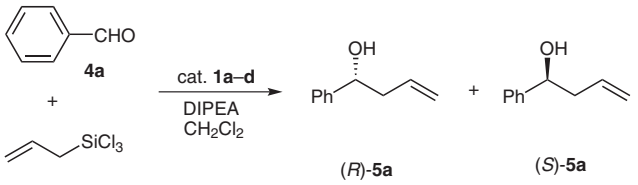


Scheme 1 Short synthesis of chiral bisimidazole-*N*-oxides



Scheme 2 The model reaction

Table 1 Screening of Catalyst in the Reaction of Benzaldehyde and Allyltrichlorosilane[a]

Entry	Catalyst	R^1	R^2	Yield of **5a** (%)[b]	ee (%)[c]	Config.[d]
1	(1*R*,2*R*)-**1a**	Me	Me	55	18	*R*
2	(1*R*,2*R*)-**1b**	Me	Ph	85	43	*R*
3	(1*R*,2*R*)-**1c**	Ph	Me	54	5	*S*
4	(1*R*,2*R*)-**1d**	Ph	Ph	86	53	*S*
5	(1*S*,2*S*)-**1d**	Ph	Ph	84	52	*R*

[a] Reactions were performed using 5 mol% of catalyst **1a**–**d**, 0.5 mmol of benzaldehyde, 1.5 mmol of DIPEA, and 0.6 mmol of allyltrichlorosilane in 1.0 mL of CH_2Cl_2 initially at 0 °C (ca. 10 min) and then at 20 °C (20 h).
[b] Yields of isolated product by column chromatography on silica gel.
[c] The ee were determined by HPLC on chiral stationary phases (OD-H).
[d] Absolute configuration assigned by measurement of optical rotation and comparison with the literature data.

formation of **5a** via opposite sense of induction and with clear drop of efficiency (entry 3). Finally, the best enantioselectivity (53% ee) was achieved using the catalytic amount of **1d** bearing two phenyl groups at C(4) at C(5), respectively (entries 4 and 5). The comparison of the results summarized in Table 1 leads to the conclusion, that the best results in terms of both, yield and enantioselectivity, were achieved using (1*R*,2*R*)-**1b** and (1*R*,2*R*)-**1d** as the catalysts. Interestingly to note, that the sense of asymmetric induction was in these two entries just the opposite.

The optimization study was performed using the most promising catalyst **1d**. The influence of the type of solvents, catalyst loading, and temperature were also investigated. Among typical solvents used in the study (THF, MeCN, DMF, toluene, CH_2Cl_2), dichloromethane turned out to be the best in terms of enantioselectivity and chemical yields. Experiments showed that the mode of loading of the catalyst **1d** has also a significant influence on asymmetric induction (Table 2, entries 1–3). Moreover, lower temperature of the reaction mixture led to substantial increase of enantioselectivity up to 72%. However, in these cases the yield remarkably dropped. The reaction conditions with 10 mol% concentration of **1d** and temperature kept at 0 °C during the addition of allyltrichlorosilane seem to be optimal in terms of the yield of **5a** and enantiomeric excess (entry 3).[12]

Table 2 Optimization of the Model Reaction with the Catalyst **1d**[a]

Entry	Catalyst **1d** (mol%)	Temp (°C)	Yield of **5a** (%)	ee (%)
1	2	0 to 20	70	35
2	5	0 to 20	86	53
3	10	0	90	64
4	10	–10	65	68
5	5	–78 to –25	34	72

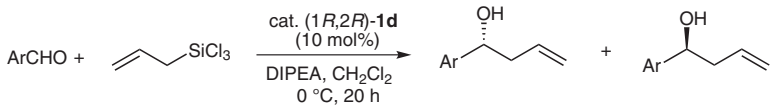
[a] Reactions were performed using 2–10 mol% of catalyst **1d**, 0.5 mmol of **4a**, 1.5 mmol of DIPEA, and 0.6 mmol of allyltrichlorosilane in 1.0 mL of CH_2Cl_2, 20 h.

Finally, in order to estimate the scope of aldehyde substrates, which can be applied in the enantioselective allylation reactions catalyzed by **1d**, differently substituted aromatic aldehydes were examined as substrates (Table 3).[12]

The reaction occurred efficiently with different aromatic aldehydes **4**, and the enantiomeric excesses were determined, ranging from 39–80% (Table 3). Application of the catalyst (1*R*,2*R*)-**1d** led to the formation of *S*-configured homoallyl alcohols **5**. The best enantioselectivities (76–80%) were observed in the case of furan-2-carbaldehyde (**4k**) and thiophen-2-carbaldehyde (**4l**). On the other hand, lower enantioselectivities were determined for products obtained in reactions with *para*-substituted benzaldehydes **4b**, **4d**, and **4f** (57–72% ee). The presence of electron-withdrawing substituents, such as Cl attached to aromatic ring (in **4f**–**h**), seems to contribute to the drop of enantioselectivity (57–39% ee). Finally, *ortho*-substituted analogues gave substantially lower ee (below 51%). All these observations lead to the conclusion that the substitution pattern in the molecule of aldehydes **4** strongly influences the enantioselectivity of formation of the corresponding alcohols **5**.

In summary, preliminary results presented in the paper showed, that the novel, easy in handling, and readily

Table 3 Scope of Aromatic Aldehydes **4** in the Allylation Reaction Catalyzed by (1*R*,2*R*)-**1d**[a,12]



4a–l (*R*)-**5a–l** (*S*)-**5a–l**

Entry	Products **5a–l** (Ar =)		Yield (%)[b]	ee (%)[c]	Config.[d]
1	**5a**	Ph	90	64	(–)-*S*
2	**5b**	4-MeC_6H_4	78	70	(–)-*S*
3	**5c**	2-MeC_6H_4	76	51	(–)-*S*
4	**5d**	4-MeOC_6H_4	72	72	(–)-*S*
5	**5e**	2-MeOC_6H_4	85	48	(–)-*S*
6	**5f**	4-ClC_6H_4	76	57	(–)-*S*
7	**5g**	2-ClC_6H_4	82	40	(–)
8	**5h**	3-ClC_6H_4	81	39	(–)-*S*
9	**5i**	β-naphthyl	75	62	(–)-*S*
10	**5j**	α-naphthyl	69	39	(–)-*S*
11	**5k**	furan-2-yl	50	76	(–)-*S*
12	**5l**	thien-2-yl	64	80	(–)-*S*

[a] Reactions were performed using 10 mol% of catalyst **1a–d**, 0.5 mmol of **4**, 1.5 mmol of DIPEA, and 0.6 mmol of allyltrichlorosilane in 1.0 mL of CH_2Cl_2 at 0 °C, 20 h (see ref. 12).
[b] Yields of isolated product by column chromatography on silica gel.
[c] The ee were determined by HPLC on chiral stationary phases (OD-H or AS-H).
[d] Absolute configuration assigned by measurement of optical rotation and comparison with the literature data.

available chiral bisimidazole-*N*-oxides of type **1**, derived from *trans*-1,2-diaminocyclohexane, can be considered as promising organocatalysts for enantioselective allylation of aromatic aldehydes **4** and, very likely, also for other stereocontrolled reactions. The chiral bisimidazole *N*-oxide **1d** turned out to be the most efficient catalyst; the expected alcohols **5** were obtained in good chemical yields and in fair enantioselectivities up to 80% ee. The obvious advantage of the catalysis with imidazole-*N*-oxides of type **1** is their straightforward synthesis and possible modification of the substitution pattern within the imidazole ring. However, further studies are needed to determine the scope and limitation for the possible exploration of imidazole-*N*-oxides of type **1** as catalysts for purposes of enantio- and diastereoselective synthesis.

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References and Notes

(1) For reviews on asymmetric organocatalysis, see: (a) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**. (b) List, B., Ed. *Chem. Rev.* **2007**, *107*, 5413–5883. (c) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. C. *Drug Discov. Today* **2007**, *12*, 8. (d) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A.; Gröger, H., Eds.; Wiley-VCH: Weinheim, **2004**. (e) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

(2) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227. (c) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (d) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(3) For recent examples of asymmetric reactions catalyzed by chiral pyridine-derived *N*-oxides, see: (a) Malkov, A. V.; Westwater, M.-M.; Gutnov, A.; Ramírez-López, P.;

Friscourt, F.; Kadlčíková, A.; Hodačová, J.; Rankovic, Z.; Kotora, M.; Kočovský, P. *Tetrahedron* **2008**, *64*, 11335. (b) Malkov, A. V.; Ramírez-López, P.; Biedermannová, L. (née Bendová); Rulíek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský, P. *J. Am. Chem. Soc.* **2008**, *130*, 5341. (c) Hrdina, R.; Boyd, T.; Valterova, I.; Hodacova, J.; Kotora, M. *Synlett* **2008**, 3141. (d) Hrdina, R.; Dracinsky, M.; Valterova, I.; Hodacova, J.; Cisarova, I.; Kotora, M. *Adv. Synth. Catal.* **2008**, *350*, 1449. (e) Takenaka, N.; Sarangthem, S. R.; Captain, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708. (f) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574. (g) Hrdina, R.; Valterova, I.; Hodacova, J.; Cisarova, I.; Kotora, M. *Adv. Synth. Catal.* **2007**, *349*, 822. (h) Chelucci, G.; Belmonte, N.; Benaglia, M.; Pignataro, L. *Tetrahedron Lett.* **2007**, *48*, 4037. (i) Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006**, *71*, 1458. (j) Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, *47*, 8611. (k) Denmark, S. E.; Yu, F. *Tetrahedron: Asymmetry* **2006**, *17*, 687.

(4) For recent examples of asymmetric reactions catalyzed by chiral *N*-oxides derived from tertiary amines, see: (a) Simonini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, 1061. (b) Wen, Y.; Gao, B.; Fu, Y.; Dong, S.; Liu, X.; Feng, X. *Chem. Eur. J.* **2008**, *14*, 6789. (c) Qin, B.; Liu, X.; Shi, J.; Zheng, K.; Zhao, H.; Feng, F. *J. Org. Chem.* **2007**, *72*, 2374.

(5) For reviews on application of chiral *N*-oxides in asymmetric catalysis, see: (a) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2008**, *252*, 492. (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. (c) Chelucci, G.; Marineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (d) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737. (e) Nakajima, M. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 1081.

(6) (a) Jasinski, M.; Mloston, G.; Mucha, P.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2007**, *90*, 1765. (b) Mloston, G.; Mucha, P.; Urbaniak, K.; Broda, K.; Heimgartner, H. *Helv. Chim. Acta* **2008**, *91*, 232. (c) Jasinski, M.; Mloston, G.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2008**, *91*, 1916. (d) Mloston G., Romanski J., Jasinski M., Heimgartner H.; *Tetrahedron: Asymmetry;* **2009**, *20*, 1073.

(7) Mucha, P.; Mloston, G.; Jasinski, M.; Linden, A.; Heimgartner, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1600.

(8) **Typical Procedure for the Preparation of Bisimidazole *N*-Oxides – Synthesis of (1*R*,2*R*)-1d**
To a stirred soln of (1*R*,2*R*)-*trans*-1,2-diamonocyclohexane (114.0 mg, 1.0 mmol) in MeOH (3 mL), a portion of paraformaldehyde (63.0 mg, 2.1 mmol) was added and the soln was stirred overnight at ambient temperature. After evaporation of the solvent in vacuum, the resulting, viscous oil was dissolved in glacial acid (7 mL) containing 473 mg (2.1 mmol) α-benzil monoxime **3d** and the soln obtained thereby was stirred overnight at ambient temperature. Next day, a gentle stream of gaseous HCl was bubbled through the soln for ca. 1.5 h, and the separated colorless bisimidazole *N*-oxide hydrochloride was filtered off and dried in vacuum exsiccator. The crude hydrochloride was suspended in MeOH (ca 25 mL) and 1 g of the solid $NaHCO_3$ was added; stirring was continued for ca.1.5 h until evolution of CO_2 was complete. Precipitated solid of inorganic salts was filtered off, and the filtrate was evaporated to dryness. The colorless solid material was triturated with a little portion (ca. 5 mL) of a $CHCl_3$–MeOH (2:1) mixture. Suspended, solid material was separated, and the filtrate was evaporated to dryness. Crude product was washed with little amount of dry acetone to yield analytically pure sample of (1*R*,2*R*)-*trans*-1,1′-(cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole)-3,3′-dioxide [(*R*,*R*)-**1d**]; yield 342 mg (62%); colorless crystals; mp(dec) 208–210 °C. IR (KBr): ν = 3424–2867 (vs, br), 1635 (m), 1570 (m), 1506 (m), 1484 (m), 1446 (m), 1405 (m), 1339 (s), 1222 (m), 1193 (m), 767 (s), 711 (s), 658 (m), 636 (m) cm^{-1}. ^1H NMR (CD_3OD): δ = 8.08 [s, 2 H, HC(2), HC(2′) imidazole], 7.65–7.50 (m, 4 H, 4 arom. H), 7.38–7.23 (m, 12 H, 12 arom. H), 7.18–7.07 (m, 4 H, 4 arom. H), 4.37–4.26 (m, 2 H, 2CH, *c*Hex), 2.38–1.40 (m, 8 H, $4CH_2$, *c*Hex). ^{13}C NMR (CD_3OD): δ = 131.8, 131.4, 131.2, 130.8, 129.9, 129.7 [6 d, 20 arom. CH, C(2), C(2′) imidazole], 131.0, 129.6, 127.3 [3 s, 4 arom. C, C(4), C(4′), C(5), C(5′) imidazole], 61.4 (d, 2 CH, *c*Hex), 34.0, 25.3 (2 t, 4 CH_2, *c*Hex). ESI-MS: *m/z* = 575 (100) $[M + Na]^+$. ESI-HRMS: m/z calcd for $C_{36}H_{32}N_4O_2Na$ $[M + Na]^+$: 575.2423; found: 575.2422. $[\alpha]_D^{20}$ +6.0 (*c* 1.02; MeOH). For X-ray structure determination of (1*R*,2*R*)- and (1*S*,2*S*)-**1d**, see: Mloston G., Mucha P., Tarka R., Urbaniak K., Linden A., Heimgartner H.; *Polish J. Chem.;* **2009**, *83*, 1105.

(9) Edward, J. T.; Chubb, F. L.; Gilson, D. F. R.; Hynes, R. C.; Sauriol, F.; Wisenthal, A. *Can. J. Chem.* **1999**, *77*, 1057.

(10) For reviews on asymmetric allylation of carbonyl compounds, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167.

(11) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

(12) **General Allylation Procedure**
To a stirred soln of the catalyst **1d** (27.7 mg, 0.05 mmol) in dry CH_2Cl_2 (1 mL) the corresponding aldehyde **4** (0.5 mmol) and dry diisopropylethylamine (260 μL, 1.5 mmol) were added. After 5 min. magnetic stirring at 0 °C, allyltrichlorosilane (90–95 μL, 0.6 mmol) was added to the reaction mixture. Stirring was continued at 0 °C for another 20 h, and after this time the mixture was firstly diluted with Et_2O, quenched with aq $NaHCO_3$ (1 mL) and next shaken with H_2O. Organic layer was separated and the aqueous soln was extracted again with Et_2O (2 × 10 mL); combined ethereal soln were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography. Yields refer to the isolated amount of alcohol **5**. The ee was determined using HPLC technique with chiral column (Chiralcel OD-H or Chiralpak AS-H); mixture of 2-PrOH–hexane was applied as an eluent.