Asymmetric Mukaiyama Aldol Reaction Catalyzed by C_2-Symmetric *N*,*N*′-Dioxide–Ni(II) Complex

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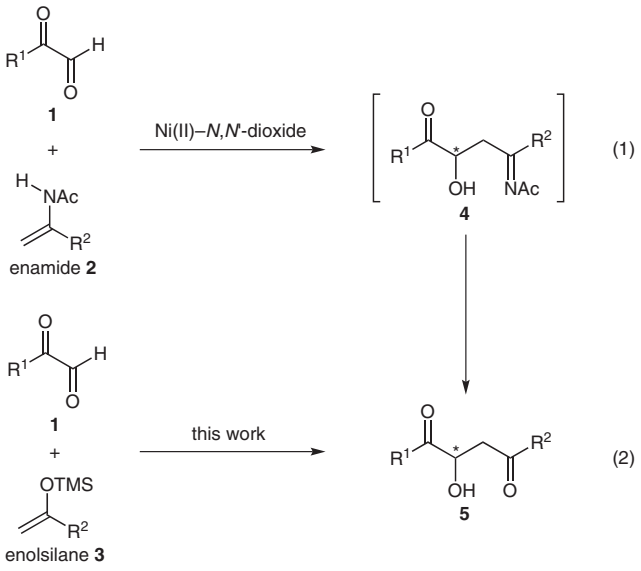
Abstract: The *N*,*N*′-dioxide–Ni(II) complex has been developed for the asymmetric Mukaiyama aldol reaction between glyoxal derivatives and enolsilane which produced the 2-hydroxy-1,4-dicarbonyl compounds in moderate to high yields (up to 95%) with excellent enantioselectivities (up to 95% ee). Based on the configuration of the product and X-ray structure of the catalyst, a possible transition state was proposed to explain the mechanism of the reaction.

Key words: asymmetric catalysis, *N*,*N*′-dioxides complex, nickel, Mukaiyama aldol reaction, glyoxal derivatives

The enantioselective aldol reaction of enolsilane with aldehyde and ketone (Mukaiyama aldol reaction) is one of the most important synthetic tools for C–C bond formations.[1] Since the pioneering work of Mukaiyama et al.,[2] a number of chiral catalysts have been developed for this reaction, including both metal complexes[3] and organocatalysts.[4] Thus far, the aldol reaction of 1,2-dicarbonyl compounds which led an approach for the formation of 2-hydroxy-1,4-dicarbonyl compounds was well investigated.[5] Since most of the studies focused on the reaction of pyruvates, the glyoxal derivatives, which could be easily synthesized from the corresponding ketones, have been rarely reported. Therefore, the development of a new catalyst system for this reaction is still interesting. As excellent chiral scaffold,[6,7] *N*,*N*′-dioxide could coordinate with many metals and exhibited great potential in many asymmetric reactions. Recently, we have reported the application of chiral Ni(II)-*N*,*N*′-dioxide complex in the aza-ene-type reaction between glyoxal derivatives **1** and enamide **2** (Scheme 1, eq. 1),[7b] and the Ni(II) complex showed good ability for the activation of glyoxal derivatives and strong asymmetry-inducing capability. As part of our ongoing program in exploring the application of *N*,*N*′-dioxides, we herein reported the catalytic asymmetric aldol reaction between glyoxal derivatives **1** and enolsilane **3** (Scheme 1, eq. 2). Excellent enantioselectivities (up to 95% ee) and moderate to high yields (up to 95%) were obtained for a range of substrates.

Initially, the reaction between phenylglyoxal (**1a**) and enolsilane **3a** was selected as a model reaction, and *N*,*N*′-dioxide **L1**–Ni(BF$_4$)$_2$·6H$_2$O complex showed good inducing potential with ee value of 58% (Table 1, entry 1). However, the exploration of counterions of the Ni(II)–**L1** complex failed to accelerate the reaction (Table 1, entries 2 and 3). Next, the electronic and steric effects of the ligand were examined. The results demonstrated that the ligand **L2** bearing electron-withdrawing group resulted in relatively low ee value (Table 1, entry 4). Electron-donating substituent at the *para* position of aromatic amide subunit had less improvement on the outcomes (Table 1, entry 5). While the appropriate steric hindrance of the substituent on aniline influenced the enantioselectivity dramatically, 88% ee was obtained with **L5** which was derived from 2,6-diethylaniline (Table 1, entry 7 vs. entries 1, 6 and 8).



Scheme 1 Mukaiyama aldol and ene reaction

Further studies on the chiral backbone moiety of the ligand revealed that the enantioselectivity of the reaction was improved to 92% ee, using L-proline-derived *N*,*N*′-dioxide **L7** instead of the (*S*)-pipecolic acid derivative **L5** (Table 1, entry 9 vs. 7).

To further improve the enantioselectivity of the reaction, several other reaction conditions such as solvent and temperature were explored. Instead of CH_2Cl_2, the use of DCE or $CHCl_3$ led to a significant drop in the yield with somewhat lower enantioselectivity (Table 1, entries 10

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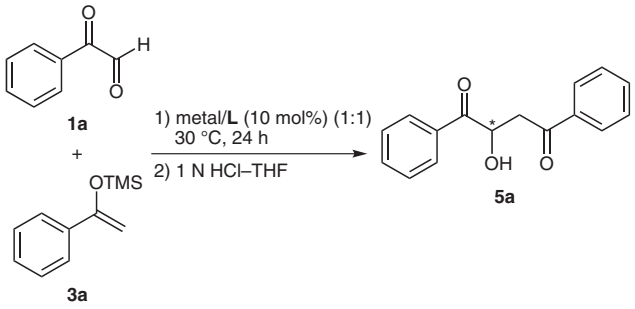
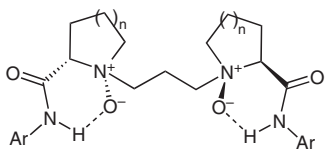
Table 1 Optimization of the Reaction Conditions[a]





L1 n = 2 Ar = Ph
L2 n = 2 Ar = 4-BrC_6H_4
L3 n = 2 Ar = 4-$MeOC_6H_4$
L4 n = 2 Ar = 2,6-$Me_2C_6H_3$
L5 n = 2 Ar = 2,6-$Et_2C_6H_3$
L6 n = 2 Ar = 2,6-*i*-$Pr_2C_6H_3$
L7 n = 1 Ar = 2,6-$Et_2C_6H_3$

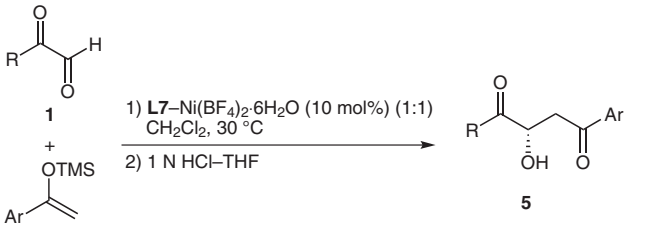
Entry	Metal	L	Solvent	Yield (%)[b]	ee (%)[c]
1	$Ni(BF_4)_2{\cdot}6H_2O$	**L1**	CH_2Cl_2	85	58
2	$Ni(ClO_4)_2{\cdot}6H_2O$	**L1**	CH_2Cl_2	84	53
3	$Ni(acac)_2$	**L1**	CH_2Cl_2	12	8
4	$Ni(BF_4)_2{\cdot}6H_2O$	**L2**	CH_2Cl_2	76	21
5	$Ni(BF_4)_2{\cdot}6H_2O$	**L3**	CH_2Cl_2	83	54
6	$Ni(BF_4)_2{\cdot}6H_2O$	**L4**	CH_2Cl_2	88	83
7	$Ni(BF_4)_2{\cdot}6H_2O$	**L5**	CH_2Cl_2	90	88
8	$Ni(BF_4)_2{\cdot}6H_2O$	**L6**	CH_2Cl_2	87	71
9	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	CH_2Cl_2	94	92
10	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	DCE	73	89
11	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	$CHCl_3$	67	85
12[d]	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	CH_2Cl_2	63	92
13[e]	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	CH_2Cl_2	61	92

[a] Unless otherwise noted, all reactions were carried out with phenylglyoxal (**1a**, 0.1 mmol) and enolsilane **3a** (0.15 mmol) at 30 °C under N_2 in CH_2Cl_2 (1.0 mL) for 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The reaction was performed at 0 °C for 30 h.
[e] Conditions: 5 mol% catalyst was used for 30 h.

and 11 vs. entry 9). Further lowering the temperature to 0 °C or reducing the catalyst loading to 5 mol%, the enantioselectivity was maintained, but the reactivity decreased obviously (Table 1, entries 12 and 13 vs. entry 9). Extensive screening shown that the optimal conditions were 10 mol% **L7**–$Ni(BF_4)_2{\cdot}6H_2O$ complex (molar ratio = 1:1), 0.1 mmol of phenylglyoxal (**1a**) and 0.15 mmol of enolsilane **3a** in 1.0 mL of CH_2Cl_2 at 30 °C.[9]

Under the optimal reaction conditions, substrate scope was investigated, and the corresponding products were gained in moderate to high yields with excellent ee values in the range of 90–95% (Table 2). A variety of glyoxal derivatives proved to be excellent aldol acceptors in this catalyst system. Both the electronic and steric substituent in the substrates had no obvious effect on the enantioselectivity (Table 2, entries 1–9). The heteroaromatic glyoxal could also be converted to the desired product in moderate yield with excellent enantioselectivity (Table 2, entry 10). Moreover, glyoxylate proceeded smoothly with **3a** in 93% yield with 94% ee (Table 2, entry 11). In addition, the substituted enolsilane **3b** was also proved to be an effective nucleophile, affording the adduct in 92% ee (Table 2, entry 12).

Table 2 Substrate Scope for the Catalytic Asymmetric Mukaiyama Aldol Reaction[a]



3a Ar = Ph
3b Ar = 4-ClC_6H_4

Entry	R	3	Product	Yield (%)[b]	ee (%)[c]
1	Ph	**3a**	**5a**	94	92
2	2-MeC_6H_4	**3a**	**5b**	88	92
3	3-MeC_6H_4	**3a**	**5c**	95	93
4	4-MeC_6H_4	**3a**	**5d**	65	90
5	3-$MeOC_6H_4$	**3a**	**5e**	74	93
6	3-ClC_6H_4	**3a**	**5f**	74	93
7	4-ClC_6H_4	**3a**	**5g**	70	91
8	4-FC_6H_4	**3a**	**5h**	85	92
9	4-BrC_6H_4	**3a**	**5i**	77	95 (*S*)[d]
10	2-furyl	**3a**	**5j**	63	91
11	OEt	**3a**	**5k**	93	94 (*S*)[d]
12	Ph	**3b**	**5l**	67	92

[a] All reactions were carried out with glyoxal derivatives **1** (0.1 mmol) and enolsilane **3** (0.15 mmol) at 30 °C under N_2 in CH_2Cl_2 (1.0 mL) for 20–28 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The absolute configuration of **5i**[7b] and **5k**[8] were determined to be *S* by comparison with literature data.

On the basis of the absolute configuration of the product and the X-ray structure of **L6**–Ni(II) complex which have been reported by our group,[7b] a possible transition state was proposed.[3c,f] As shown in Figure 1, the ligand provided the carbonyl oxygens and *N*-oxides for coordination. Meanwhile, the glyoxal derivative tends to chelate to the nickel by carbonyl groups in bidentate fashion. The **TS1** was considered as the favorable transition state in which

the aldehyde moiety of glyoxal was bound in the equatorial position. Enolsilane attacked from the less hindered *Si*-face to afford the corresponding *S* product, since the 2,6-diethylphenyl group on the ligand effectively shielded the other face. While in **TS2**, the ketone group located at the equatorial position which resulted in the steric hindrance between R of the substrate and the 2,6-diethylphenyl group of the ligand.

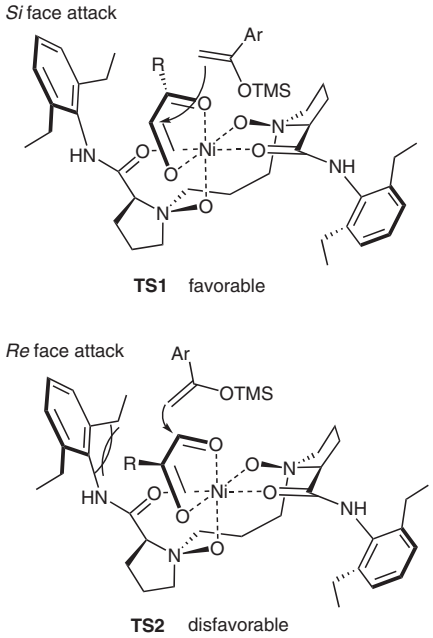


Figure 1 Proposed transition state for Mukaiyama aldol reaction

In summary, we have developed an efficient chiral **L7**–Ni(II) complex catalyst for the enantioselective Mukaiyama aldol reaction of glyoxal derivatives as well as glyoxylate. Excellent enantioselectivities (up to 95% ee) and moderate to high yields (up to 95%) were obtained for a range of substrates. Meanwhile, a proposed transition state was depicted. Further efforts are being devoted to applying the catalyst to other reactions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) For reviews, see: (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (c) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (d) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 36. (e) Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 7506. (f) Adachi, S.; Harada, T. *Eur. J. Org. Chem.* **2009**, 3661. (g) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131.

(2) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

(3) For selected examples, see: (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (d) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (e) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (f) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (g) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292. (h) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097. (i) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. (j) Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 4267. (k) Kiyooka, S.; Matsumoto, S.; Shibata, T.; Shinozaki, K. *Tetrahedron* **2010**, *66*, 1806; and references therein.

(4) For selected examples, see: (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (b) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405. (c) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (d) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130. (e) Adachi, S.; Harada, T. *Org. Lett.* **2008**, *10*, 4999. (f) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 776. (g) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363. (h) Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476; and references therein.

(5) (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (c) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375. (d) Langner, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5984. (e) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532. (f) Engers, J. L.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 6109. (g) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 904.

(6) For reviews on *N*-dioxides in the asymmetric catalysis, see: (a) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29.

(7) For examples of our recent work, see: (a) Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770. (b) Zheng, K.; Liu, X. H.; Zhao, J. N.; Yang, Y.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2010**, *46*, 3771. (c) Xie, M. S.; Chen, X. H.; Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3799. (d) Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Cai, Y. F.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4290. (e) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2010**, *132*, 8532.

(8) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4122.

(9) **General Procedure for the Asymmetric Mukaiyama Aldol Reaction between Glyoxal Derivative 1a and Enolsilane 3a**:
Ligand **L7** (0.01 mmol) and $Ni(BF_4)_2 \cdot 6H_2O$ (0.01 mmol) were dissolved in CH_2Cl_2 (0.5 mL) and stirred at 30 °C for 1 h. Then the solvent was removed and glyoxal derivative **1a** (0.1 mmol) was added. After adding CH_2Cl_2 (1.0 mL) and enolsilane **3a** (0.15 mmol), the mixture was stirred at 30 °C for 24 h under N_2 atmosphere. Then, THF (2.0 mL) and 1 N HCl (1.0 mL) were added to the reaction mixture. After stirring at r.t. for 30 min, this solution was poured into a separatory funnel and diluted with Et_2O (5.0 mL) and H_2O (1.0 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with sat. aq $NaHCO_3$ (5.0 mL) and brine (5.0 mL). The resulting ether layer was dried over anhyd $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel to give the desired adduct **5a**: 94% yield; 92% ee {determined by HPLC analysis with a Chiral OJ-H column, hexane–2-PrOH (80:20), 1.0 mL/min, UV = 254 nm; t_{R1} = 18.6 min, t_{R2} = 20.5 min); $[\alpha]_D^{25}$ +11.9 (*c* 0.454, in CH_2Cl_2}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37–3.49 (m, 2 H), 4.04 (d, *J* = 6.0 Hz, 1 H), 5.68–5.73 (m, 1 H), 7.46–7.55 (m, 4 H), 7.58–7.66 (m, 2 H), 7.95–8.01 (m, 4 H) ppm.