ORGANIC LETTERS

2011
Vol. 13, No. 4
600–603

Highly Enantioselective Synthesis of Tetrahydroquinolines via Cobalt(II)-Catalyzed Tandem 1,5-Hydride Transfer/Cyclization

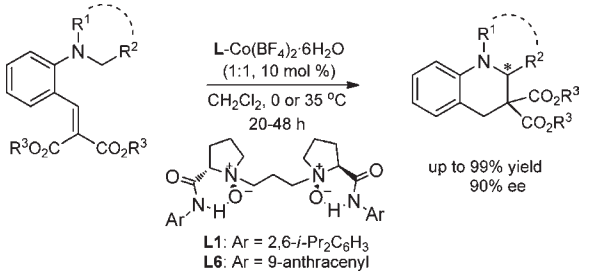
Weidi Cao, Xiaohua Liu, Wentao Wang, Lili Lin, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China

xmfeng@scu.edu.cn

Received November 22, 2010

ABSTRACT



A chiral catalyst prepared from *N,N'*-dioxide and $Co(BF_4)_2 \cdot 6H_2O$ was applied in the asymmetric hydride transfer initiated cyclization reaction, giving optically active tetrahydroquinolines in good yields with high enantioselectivities under mild reaction conditions. Meanwhile, in light of the absolute configuration of the product, a possible working model was proposed to explain the origin of the activation and asymmetric induction.

Optically pure tetrahydroquinoline derivatives are widely used in organic synthesis and pharmaceutical chemistry due to their significant building blocks and intriguing biological activities.[1] Traditional methodologies for the formation of these lichipins mainly include the Povarov reaction[2] and reduction of quinolines.[3] As an alternative straightforward approach to afford tetrahydroquinolines, the intramolecular tandem hydride transfer/cyclization[4] process (Scheme 1), which undergoes a zwitterionic intermediate formed by a 1,5-hydride transfer, has been developed in recent years. To the best of our knowledge, only two asymmetric examples have been described subsequently by the Seidel group and Kim group. Bis(oxazoline)-$Mg(OTf)_2$ catalyst[5] and

(1) (a) Barton, D. H.; Nakanishi, K.; Meth-Cohn, O. *Comprehensive Natural Chemistry*; Elsevier: Oxford, 1999; Vols. 1−9. (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(2) (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137. (c) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (d) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (e) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327.

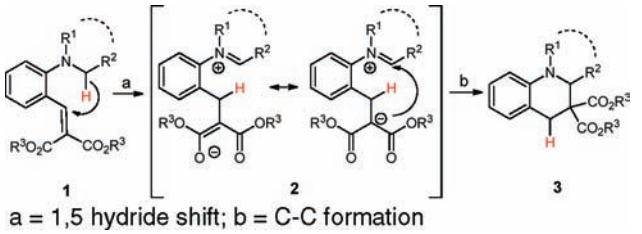
(3) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (b) Zhou, Y. G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Mršić, N.; Lefort, L.; Boogers, J. A. F.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2008**, *350*, 1081. (d) Guo, Q. S.; Du, D. M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759. (e) Wang, X. B.; Zhou, Y. G. *J. Org. Chem.* **2008**, *73*, 5640. (f) O'Byrne, A.; Evans, P. *Tetrahedron* **2008**, *64*, 8067.

(4) For racemic examples: (a) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (b) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136–3138. (c) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (d) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (e) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (f) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (g) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (h) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (i) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (j) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (k) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (l) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732.

(5) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226.

10.1021/ol1028282
Published on Web 01/10/2011

Scheme 1. Mechanistic Concept for the α-Alkylation of Amines via 1,5-Hydride Transfer/Cyclization



organocatalyst[6] were used to promote the intramolecular asymmetric tandem 1,5-hydride transfer/cyclization with excellent enantioselectivities. However, high temperature (80 °C) or a long reaction time (4−12 days) was involved in these cases. Thus, searching for new catalyst systems that could achieve high reactvity and enantioselectivity under mild reaction conditions and extending the substrate scope are still challenging and desirable. Herein, we wish to report a highly enantioselective intramolecular tandem hydride transfer/cyclization of *o*-dialkylamino-substituted alkylidene malonates, which could be tolerated under a chiral *N,N*′-dioxide-Co(II) complex catalyst system, delivering the corresponding optically active tetrahydroquinolines in excellent yields (up to 99%) with high enantioselectivities (up to 90% ee).

In view of the requirement of effective activation as well as the proper stereoinduction of the substrate by coordinating with a chiral *N,N*′-dioxide−metal complex,[7,8] alkylidene malonate derivative **1a** was selected as a model substrate which could bind to the central metal with dicarbonyl groups. Initiatlly, various metal salts such as Mg^{II}, Fe^{II}, Ni^{II}, and Co^{II} chelated with L-proline-derived *N,N*′-dioxide **L1** (Figure 1) were used to catalyze this tandem 1,5-hydride transfer cyclization (Table 1, entries 1−4). Gratifyingly, moderate enantioselectivity (51% ee) and high yield were obtained using cobalt(II) as the central metal. Then, the influence of counterions was investigated (Table 1, entries 5−7), and a better result was obtained with $Co(BF_4)_2 \cdot 6H_2O$ (Table 1, entry 7). Next, a series of

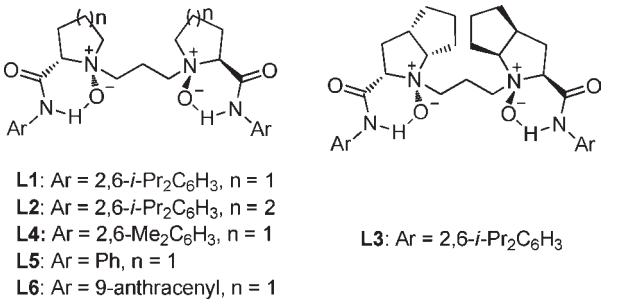
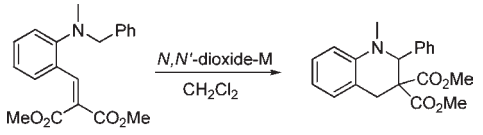


Figure 1. Chiral ligands used in this study.

Table 1. Evaluation of Reaction Parameters[a]



entry	ligand	metal	yield (%)[b]	ee (%)[c]
1	**L1**	$Mg(OTf)_2$	86	35
2	**L1**	$Fe(BF_4)_2 \cdot 6H_2O$	NR[e]	–
3	**L1**	$Ni(ClO_4)_2 \cdot 6H_2O$	63	50
4	**L1**	$Co(ClO_4)_2 \cdot 6H_2O$	92	51
5	**L1**	$Co(AcAc)_2$	NR[e]	–
6	**L1**	$Co(OAc)_2$	NR[e]	–
7	**L1**	$Co(BF_4)_2 \cdot 6H_2O$	95	57
8	**L2**	$Co(BF_4)_2 \cdot 6H_2O$	87	20
9	**L3**	$Co(BF_4)_2 \cdot 6H_2O$	80	37
10	**L4**	$Co(BF_4)_2 \cdot 6H_2O$	90	39
11	**L5**	$Co(BF_4)_2 \cdot 6H_2O$	93	7
12	**L6**	$Co(BF_4)_2 \cdot 6H_2O$	99	87
13[d]	**L6**	$Co(BF_4)_2 \cdot 6H_2O$	35	90

[a] Unless otherwise noted, reactions were carried out with ligand (10 mol %), metal (10 mol %), and **1a** (0.1 mmol) in CH_2Cl_2 (0.2 mL) at 35 °C for 30 h. [b] Isolated yield. [c] Determined by HPLC using chiral IC column. [d] Reaction was performed at 20 °C. [e] NR = No reaction.

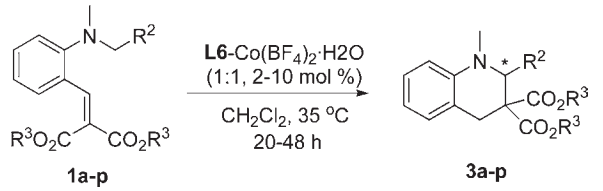
N,N′-dioxides were examined (Figure 1). It was found that the chiral backbone strongly affected both yield and enantioselectivity. L-Proline derived **L1** could achieve better results than L-pipecolic acid derived **L2** and L-ramipril derived **L3** (Table 1, entry 7 vs 8 and 9). Moreover, the steric effect of the amide moiety played a crucial role; bulkier groups at the *o*-position of aniline were superior to smaller ones (Table 1, entries 7 and 10−12). High enantioselectivity (87% ee) was achieved using the **L6**−$Co(BF_4)_2 \cdot 6H_2O$ complex (Table 1, entry 12). Lowering the reaction temperature to 20 °C further enhanced the enantioselectivity to 90% ee but led to an obvious loss in yield (Table 1, entry 13). Therefore, the optimal conditions were as follows: the **L6**−$Co(BF_4)_2 \cdot 6H_2O$ complex (10 mol %; molar ratio **L6**/$Co(BF_4)_2 \cdot 6H_2O$ = 1/1), alkylidene malonate (0.1 mmol) in CH_2Cl_2 (0.2 mL) at 35 °C.

(6) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847.

(7) (a) Wang, L. J.; Liu, X. H.; Dong, Z. H.; Fu, X.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8670. (b) Liu, Y. L.; Shang, D. J.; Zhou, X.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2009**, *15*, 2055. (c) Chen, D. H.; Chen, Z. L.; Xiao, X.; Yang, Z. G.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2009**, *15*, 6807.

(8) (a) Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770. (b) Yu, Z. P.; Liu, X. H.; Dong, Z. H.; Xie, M. S.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1308. (c) Wang, W. T.; Liu, X. H.; Cao, W. D.; Wang, J.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 1664. (d) Shen, K.; Liu, X. H.; Zheng, K.; Li, W.; Hu, X. L.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 3736. (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. (f) 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. (g) 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. (h) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160.

Table 2. Substrate Scope for the Catalytic Asymmetric Intramolecular 1,5-Hydride Transfer/Cyclization of Acyclic Compounds[a]



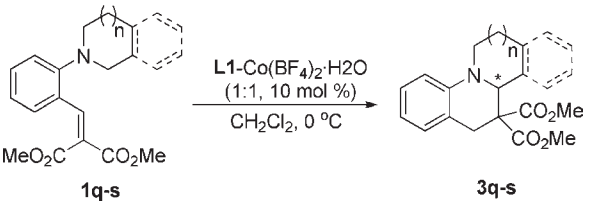
entry	R^2	R^3	prod.	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	Me	**3a**	30	99	87
2	Ph	Et	**3b**	48	60	84
3	Ph	Bn	**3c**	24	93	86
4	2-MeC_6H_4	Me	**3d**	32	95	90
5	3-MeC_6H_4	Me	**3e**	48	83	87
6	4-MeC_6H_4	Me	**3f**	40	84	83
7	2-$MeOC_6H_4$	Me	**3g**	24	97	82
8[d]	2-$MeOC_6H_4$	Me	**3g**	28	95	82
9	3-$MeOC_6H_4$	Me	**3h**	40	85	85
10	4-$MeOC_6H_4$	Me	**3i**	24	96	83
11	4-FC_6H_4	Me	**3j**	48	86	86
12	4-ClC_6H_4	Me	**3k**	48	81	86
13	4-BrC_6H_4	Me	**3l**	48	73	84
14	2,3-$(MeO)_2C_6H_3$	Me	**3m**	40	89	83
15[e]	1-naphthyl	Me	**3n**	24	97	87(*S*)
16	2-naphthyl	Me	**3o**	20	97	86
17	2-thienyl	Me	**3p**	48	90	79

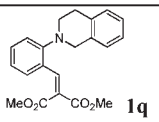
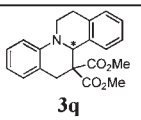
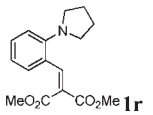
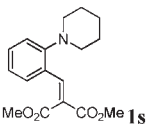
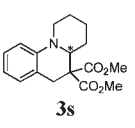
[a] Unless otherwise noted, reactions were carried out with **L6** (10 mol %), $Co(BF_4)_2 \cdot 6H_2O$ (10 mol %), and **1** (0.1 mmol) in CH_2Cl_2 (0.2 mL) at 35 °C. [b] Isolated yield. [c] Determined by HPLC using chiral IC column. [d] 2 mol % catalyst was used. [e] The absolute configuration was determined to be *S* by X-ray crystallographic analysis.

Under the optimized reaction conditions, a series of substrates (**1a**−**p**) were investigated. As summarized in Table 2, the ester group of malonate derivatives had little influence on the enantioselectivity (Table 2, entries 1−3). Regardless of the electronic properties or steric hindrance of the substituents on the aromatic ring, the corresponding ring-fused tetrahydroquinolines were obtained in good yields (73−99%) with high enantioselectivities (82−90% ee; Table 2, entries 4−7 and 9−13) within less than 48 h. The electrodonating groups on aromatic substrates exhibited higher reactivity (Table 2, entries 4−10 vs 11−13), and for the *o*-methoxy substrate **1g**, the enantioselectivity was still maintained even as the catalyst loading was decreased to 2 mol % (Table 2, entry 8). Furthermore, disubstituted, condensed-ring, and heteroaromatic substrates were also well tolerated (Table 2, entries 14−17).

To extend the application of this protocol, further examination of the substrates was focused on forming polycyclic compounds. Under the same reaction conditions (Table 2, entry 1), the desired product **3q** was obtained in 70% ee. To our delight, after a slight modification of ligand, by altering the ligand **L6** to **L1** and decreasing the reaction temperature to 0 °C, a higher ee value (88% ee) of **3q** was obtained (Table 3, entry 1). Moreover, products incorporating five- and six-membered

Table 3. Substrate Scope for the Catalytic Asymmetric Intramolecular 1,5-Hydride Transfer/Cyclization of Polycyclic Compounds[a]



entry	substrate	product	yield (%)[b]	ee (%)[c]
1	 **1q**	 **3q**	90	88
2	 **1r**	 **3r**	93	80
3	 **1s**	 **3s**	90	82

[a] Reactions were carried out with **L1** (10 mol %), $Co(BF_4)_2 \cdot 6H_2O$ (10 mol %), and **1** (0.1 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C for 48 h. [b] Isolated yield. [c] Determined by HPLC using chiral OJ-H column.

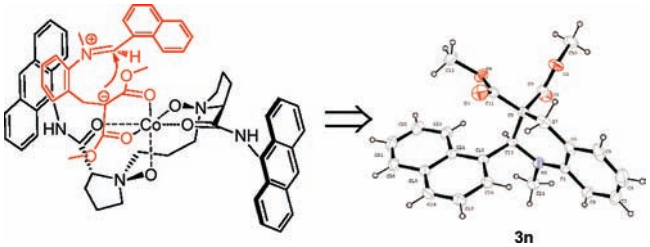


Figure 2. Proposed transition-state model and the absolute configuration of **3n** determined by X-ray crystallographic analysis.

azacycles were also gained with promising yields and enantioselectivities (Table 3, entries 2−3).

To gain insight into the mechanism, the relationship between the enantiomeric excess of the product **3q** and *N*,*N*′-dioxide **L1** was studied under the optimal conditions (Table 3). A linear effect[9] was observed, which manifested that the monomeric catalyst may be the main catalytically active species.[10] On the basis of the absolute configuration of product **3n**,[11] a possible transition-state

(9) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456.

(10) See Supporting Information for more details.

(11) CCDC-798879 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.

model was proposed (Figure 2), in which the oxygens of *N,N′*-dioxide, amide oxygens, and the alkylidene malonate coordinated to cobalt(II) in a hexadentate manner. The carbanion prefers to attack the *Re* face rather than the *Si* face of the imine because the latter is strongly shielded by the nearby anthracenyl ring, which results in the *S*-configured product.

In summary, we have developed a highly enantioselective intramolecular 1,5-hydride transfer/cyclization of *o*-dialkylamino-substituted alkylidene malonates using a 10 mol % *N,N′*-dioxide−Co(II) complex, which facilitated the asymmetric synthesis of biologically interesting tetrahydroquinolines. Various tetrahydroquinolines were obtained in good yields with high enantioselectivities (up to 90% ee) under mild conditions. Meanwhile, a transition-state model was proposed to explain the origin of the asymmetric induction. This catalyst system may provide a new entry for other asymmetric hydride transfer cyclization reactions. Further application of the current method is currently underway.

Acknowledgment. We appreciate the National Natural Science Foundation of China (Nos. 20732003 and 21021001) and the Basic Research Program of China (973 Program: 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR and X-ray analysis.

Supporting Information Available. Experimental procedures, spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.