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Dimeric Quinidine-Catalyzed Enantioselective Aminooxygenation of Oxindoles: An Organocatalytic Approach to 3-Hydroxyoxindole Derivatives

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3-Hydroxy-2-oxindoles are present in a variety of alkaloid natural products that have recently emerged as an important class of therapeutic compounds with a broad spectrum of biological activities.[1] Recent structure−activity relationship studies have shown that both the configuration of the hydroxy group and the substituent pattern at the C_3 position greatly affect the biological activities of these compounds.[1a] Therefore, development of synthetic routes to a C_3-hydroxy-bearing stereogenic center with control of the absolute configuration is of paramount importance. Catalytic procedures for the asymmetric synthesis of 3-hydroxy-2-oxindoles are limited, and most rely heavily on the use of transition-metal catalysis, particularly in the addition of an organometallic reagent to isatins, and in a rare case, the reaction of metal enolates derived from oxindoles with Davis' achiral oxaziridine.[2,3] Often, these metal-based reactions must be performed under an inert atmosphere in order to obtain optimal results. Few organocatalytic methods allowing access to these types of oxindoles via the additions of carbonyl compounds to isatins have been reported.[4] Only a single report describes asymmetric hydroxylation of oxindoles using phase-transfer catalysis.[5] Herein we describe a novel aminooxygenation of oxindoles with nitrosobenzene catalyzed by a newly designed quinidine dimer that affords the desired products in good yields with high enantioselectivities (Figure 1).[6] This metal-free catalytic process allows construction of a C−O bond at C_3 of oxindoles in a stereoselective manner, providing a new approach to the synthesis of optically active 3-hydroxy-2-oxindole derivatives.

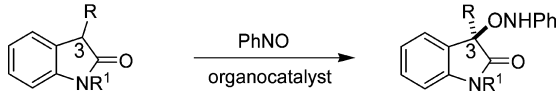

Figure 1. Synthetic route to 3-hydroxyoxindole derivatives.

Recently, we disclosed the first enantio- and diastereoselective Michael additions of oxindoles to nitroolefins and catalytic enantioselective α-aminations of oxindoles with diazo compounds.[7,8] We envisioned the reaction of oxindoles with nitrosobenzene as a way of constructing a C−O bond and simultaneously creating a tetrasubstituted stereogenic center at C_3 in a stereoselectively controlled manner when a chiral, nonracemic tertiary amine catalyst is employed. Control over the stereochemical outcome of this process was a challenge for several reasons. First was the loose, noncovalent interaction between the tertiary amine catalyst and the enolate derived from the oxindole substrate (Figure 2). Consequently, steric differentiation induced by the catalyst would not be large. Second, the enolate−catalyst complex must be highly reactive in order to overcome the steric encumbrance at C_3 while orchestrating the enantioselectivity of the aminooxygenation. Finally, although numerous enamine-based enantioselective processes involving nitrosobenzene and carbonyl compounds have been published,[6] the analogous transformation using oxindoles as nucleophiles, even in a racemic form, has not been reported.

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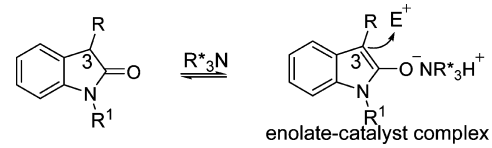
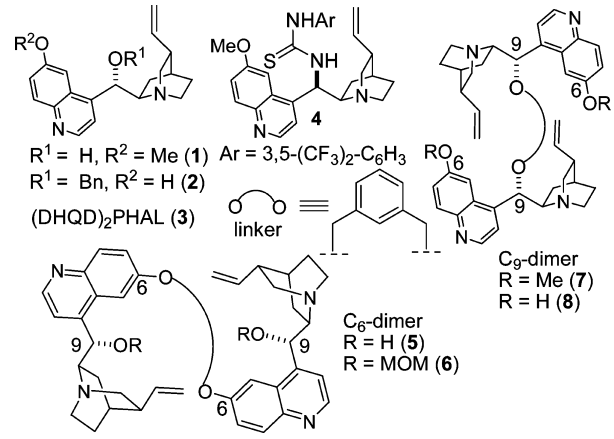


Figure 2. Noncovalent interaction between the enolate and catalyst.

Scheme 1



Initially, the reaction of oxindole **1a** with nitrosobenzene in the presence of catalyst **1** (10 mol %) was examined (Scheme 1, Table 1). Under these conditions, the desired product **2a** was obtained in rather moderate yield and enantiomeric excess (ee) (entry 1). Quinidine derivative **2** was an unsatisfactory catalyst (entry 2). Bulky, dimeric hydroquinidine **3** was not effective for this transformation, nor was the bifunctional thiourea catalyst **4** (entries 3 and 4, respectively). Therefore, dimeric catalyst **5** was designed and synthesized by dimerization of quinidine at the C_6 position. With this new catalyst, remarkable improvements in yield and ee were observed (entry 5). Interestingly, with dimer **6**, a protected form of **5**, the yield and ee of product **2a** were low, indicating that the free hydroxyl groups at C_9 in **5** are crucial for overall catalytic efficiency (entry 5 vs entry 6). The yield and enantioselectivity were lower with catalysts **7** and **8** than with **5** (entry 5 vs entries 7 and 8); **7** and **8** were synthesized by dimerization of quinidine at C_9. The free hydroxyl groups at C_6 in **8** were not important for high selectivity (entry 7 vs entry 8). In addition, a significant decrease in ee was observed when the protecting group on the oxindole nitrogen atom was changed from benzyl to allyl (entry 5 vs entry 9). A survey of several solvents led to the identification of tetrahydrofuran (THF) as the optimal solvent for the reaction (entry 5 vs entries 9−13). An increase in temperature decreased the ee, but the yields were more or less comparable (entries 5 and 7 vs entries 14 and 15, respectively).

With the optimal conditions in hand, the scope of the aminooxygenation of oxindoles was investigated (Table 2). Oxindole products bearing methyl and benzyl substituents at the C_3 position were obtained in good yields and ee (entries 1−2). With an allyl

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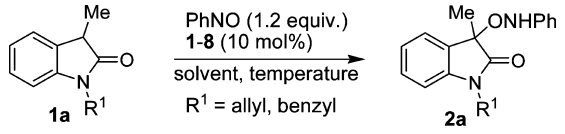
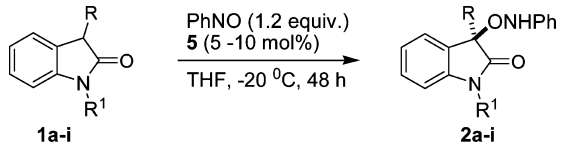
Table 1. Optimization Studies



entry	catalyst	solvent	temperature (°C)	yield (%)[a]	ee[b] (%)
1	**1**	THF	−20	41	48
2	**2**	THF	−20	58	51
3	**3**	THF	−20	60	12
4	**4**	THF	−20	51	13
5	**5**	THF	−20	85	92
6	**6**	THF	−20	65	77
7	**7**	THF	−20	70	83
8	**8**	THF	−20	87	50
9[c]	**5**	THF	−20	80	44
10[c]	**5**	Et_2O	−20	41	30
11	**5**	toluene	−20	20	18
12	**5**	CH_2Cl_2	−20	33	48
13[d]	**5**	THF/Et_2O	−20	87	76
14	**5**	THF	0	85	87
15	**7**	THF	0	83	73

[a] Isolated yields. [b] Determined by chiral-phase HPLC analysis. [c] *N*-Allyl-protected oxindole. [d] Reaction was performed in 1:1 THF/Et_2O.

Table 2. Enantioselective Aminooxygenation of Oxindoles



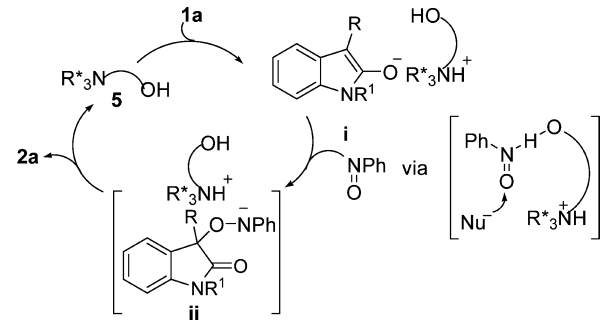
entry	R	R^1	product	yield (%)[a]	ee[b]
1	Me	Bn	**2a**	85	92
2	Bn	Bn	**2b**	80	87
3[c]	allyl	Bn	**2c**	86	87
4	allyl	4-MeO-Bn	**2d**	80	85
5	2-Me-allyl	Bn	**2e**	81	92
6[c]	1,1-Me_2-allyl	Bn	**2f**	65	86
7[c]	homoallyl	Bn	**2g**	78	73
8[c]	$-CH_2CCSiMe_3$	Bn	**2h**	85	96
9	$-CH_2CCSiMe_3$	4-MeO-Bn	**2i**	81	96

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] 5 mol % catalyst loading.

substituent, the reaction proceeded smoothly even with 5 mol% **5**, affording the desired product with good yield and ee. With a slight increase in catalyst loading (to 10 mol %), reaction of a *p*-methoxybenzyl (PMB)-protected oxindole provided the desired product in good yield (entry 4). The PMB protecting group is readily cleaved under oxidative conditions, and the allyl moiety provides a handle for further functional group manipulation. The substrate scope was expanded to oxindoles with more sterically hindered allyl substituents (entries 5 and 6). Although decreases in both yield and ee were observed with homoallyl-substituted substrates (entry 7), the enantioselectivities were excellent when PMB- and benzyl-protected alkynyl oxindoles were employed (entries 8 and 9). In most cases, the aminooxygenation was O-selective, providing the desired products in good yields.[9] The absolute configuration at the newly created center was determined to be *R* by analysis of an unprotected 3-hydroxyoxindole derived from **2d**.[10]

Although the mechanism of the dimeric quinidine-catalyzed enantioselective aminoxygenation has not been determined, we posit that the reaction proceeds through zwitterionic enolate **i**, which is generated by deprotonation of the C_3 methine protons of the oxindole (Scheme 2). This enolate then reacts with nitrosobenzene in an O-selective fashion, presumably as a result of the directing effect of a hydroxyl group of the catalyst.[11] Proton transfer from

Scheme 2



the protonated amine catalyst to species **ii** provides the product and releases the catalyst back into the cycle (see the Supporting Information).

In summary, we have demonstrated a novel enantioselective aminooxygenation of oxindoles catalyzed by a newly designed dimeric quinidine catalyst. The reaction is general, providing products in good yields and ee's. This work represents the first example of an organocatalytic method for the construction of a C−O bond and the creation of a tetrasubstituted chiral center at the C_3 position of oxindoles. Further studies of this dimeric bifunctional catalyst in other asymmetric transformations are being undertaken to broaden its utility and gain insight into its catalytic activity.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews of oxindoles and 3-hydroxyoxindoles: (a) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
(2) Nucleophilic additions to isatins using metal catalysis: (a) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. L. *Org. Lett.* **2006**, *8*, 2715. (b) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (c) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (d) Grant, C. D.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4485. (e) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (f) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283. (g) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744.
(3) Catalytic asymmetric hydroxylation of oxindoles using metal enolate chemistry: Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488.
(4) Organocatalytic additions of carbonyl compounds to isatins: (a) Luppi, G.; Monari, M.; Correa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, Q. B.; Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017. (b) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 14037. (c) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.
(5) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593.
(6) Reviews of the use of nitrosobenzene: (a) Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621. (b) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995.
(7) (a) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (b) Kato, Y.; Yurutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168. (c) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620.
(8) (a) Bui, T.; Borregan, M.; Barbas, C. F., III. *J. Org. Chem.* **2009**, *74*, 8935. (b) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874. (c) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753.
(9) N-addition products (<15%) were observed occasionally.
(10) Deprotection was achieved using Na in liquid ammonia to provide the product in 85% isolated yield (see the Supporting Information).
(11) Hydroxy-directing effects of cinchona alkaloid catalysts: (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (b) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

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