

Highly Enantioselective Organocatalytic α -Amination Reactions of Aryl Oxindoles: Developing Designer Multifunctional Alkaloid Catalysts

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ABSTRACT



An enantioselective α -amination of aryl oxindoles catalyzed by a dimeric quinidine has been developed. The reaction is general, broad in substrate scope, and affords the desired products in good yields with good to excellent enantioselectivities. This study provides the first examples of a general organocatalytic method for the creation of nitrogen-containing, tetrasubstituted chiral centers at C₃ of various aryl oxindoles. Furthermore, new catalysts and insights into structural elements of the catalysts that significantly influence enantioselectivities are disclosed.

Catalyst design is instrumental to the development of new organic transformations, an endeavor that is important for the advancement of synthetic methodology. Although organocatalysts have been designed and developed, a detailed understanding of how they work often lags behind their extensive applications.¹ Recently, we disclosed a novel, dimeric quinidine catalyst and demonstrated its effectiveness in enantioselective aminoxygation of oxindoles.² This multifunctional catalyst, with its seemingly flexible 1,3-dibenzyl tether, was far more effective than other structurally rigid cinchona alkaloid dimers tested (Figure 1a).² These observations were counterintuitive from a catalyst design perspective and prompted us to explore the use of this catalyst in other asymmetric transformations, particularly in enantioselective α -amination reactions of aryl oxindoles. These reactions would provide access to optically

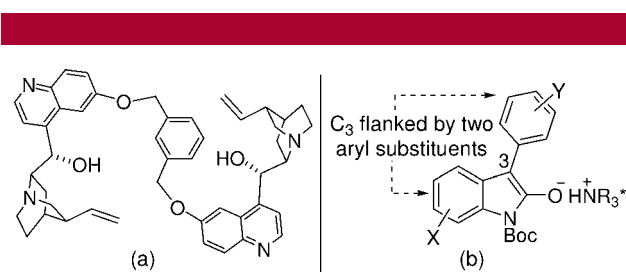


Figure 1. (a) Dimeric quinidine catalyst and (b) aryl oxindole enolates.

active 3-amino aryl oxindoles, common structural motifs present in a variety of bioactive molecules, including NITD609 and SSR-149415, which are drug candidates for the treatment of malaria and stress-related disorders, respectively.^{3,4}

To date, there is no general catalytic method for the asymmetric synthesis of 3-amino aryl oxindoles, especially those with readily cleavable diazo compounds such as di-*tert*-butyl

(1) Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis - From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Verlag GmbH & Co. KGaA, Weinheim, 2005.

(2) Bui, T.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2010**, *132*, 5574.

azodicarboxylates.^{4a,5–8} Several challenges arise when oxindoles bear an aryl substituent at the C₃ position. First, the aryl group renders the C₃ methine acidic, facilitating a background reaction to occur. Conversely, it sterically hinders this position, thereby limiting reactivity. Finally, it is difficult to differentiate the two enantiotopic faces of the oxindole enolate at C₃ when this position is flanked by two aryl groups of a similar size, one of which is the aryl oxindole ring (Figure 1b).

Herein, we report highly enantioselective α -amination reactions of aryl oxindoles with Boc-protected diazo electrophiles. We also provide insight into the role of the dimeric structure of the catalyst that has informed our design of novel multi-functional alkaloid catalysts for this reaction. The chemistry described herein provides the first examples of a general organocatalytic method for the synthesis of aryl oxindoles bearing a tetrasubstituted nitrogen-containing center at C₃.^{4a,5,6}

Initially, a model reaction using phenyl oxindole **1a** and di-*tert*-butyl azodicarboxylate was examined in the presence of cinchona alkaloid catalysts (Figure 2, Table 1). With 10 mol % of monomeric quinidine-derived catalyst **I**, **II**, or **III**, the α -amination reaction proceeded smoothly at $-20\text{ }^{\circ}\text{C}$ to afford product **3a** in good yields, albeit low enantiomeric excess (ee) (entries 1–3). Similarly, commercially available bulky hydroquinidine dimers **IV** and **V** also catalyzed the α -amination and provided products in moderate yields with low ee (entries 4

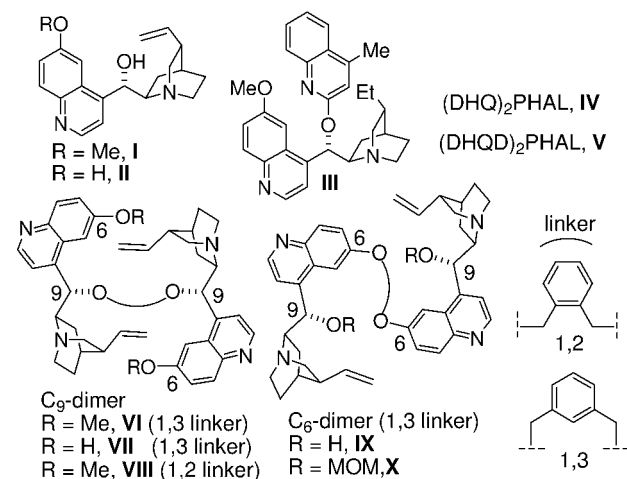


Figure 2. Catalyst screen.

Table 1. Optimization Studies^a

entry	catalyst	solvent	temp ($^{\circ}\text{C}$)	yield ^b (%)	ee ^c (%)
1	I	THF	-20	86	45
2	II	THF	-20	74	27
3	III	THF	-20	81	14
4	IV	THF	-20	77	0
5	V	THF	-20	51	35
6	VI	THF	-20	96	5
7	VII	THF	-20	94	41
8	VIII	THF	-20	84	35
9	IX	THF	-20	93	53
10	IX	THF	-50	87	83
11	IX	THF	-70	78	88
12	IX	CH_2Cl_2	-70	89	79
13	IX	Et_2O	-70	72	92
14	IX	toluene	-70	87	95
15 ^d	IX	toluene	-70	93	98
16	IX	<i>m</i> -xylene	-70	73	83
17 ^d	X	toluene	-70	86	83

^a Unless otherwise noted, all reactions were run for 24 h. Reactions in entries 1–8 employed 10 mol % of catalyst; entries 9–17 employed 5 mol %. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d Reactions run for 48 h.

and 5). Interestingly, these dimers were not as effective as **I** (entry 1 vs entries 4–5). Previously developed dimeric catalysts **VI**–**VIII** from our laboratory were also tested, but they did not give satisfactory results with respect to ee (entries 6–8).² These catalysts were synthesized by dimerization of quinidine at the C₉ position using different dibromo benzyl linkers. Notably, catalyst **VII** with a free hydroxyl group at C₆ provided product in higher ee than catalyst **VI** (entry 7 vs entry 6). The catalyst with the 1,3-dibenzyl linker was more effective than

(3) (a) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagona, T. T. *Science* **2010**, *329*, 1175. (b) Griebel, G.; Simiand, J.; Gal, C. S.-L.; Wagnon, J.; Pascal, M.; Scatton, B.; Maffrand, J.-P.; Soubrie, P. *Proc. Natl. Acad. Sci.* **2002**, *99*, 6370. (c) Leugn, C.; Tomaszewski, M.; Woo, S. (Astrazeneca AB, Swed.). U.S. Pat. Appl. Publ. (2007), CODEN: USXXCO US 2007185179 A1 20070809 Patent written in English. Application: US 2007–671153 20070205.

(4) Recent reviews on oxindoles and their biological activities: (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (b) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (d) Martí, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(5) Bui, T.; Borregan, M.; Barbas III, C. F. *J. Org. Chem.* **2009**, *74*, 8935.

(6) Organocatalytic α -amination of alkyl oxindoles: (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874. (b) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753. In ref 1a, there is one example of α -amination of an aryl oxindole using di-isopropyl azodicarboxylate to afford product in 74% yield with 63% ee. For the Lewis acid-based approach: (c) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (d) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem.–Eur. J.* **2010**, *16*, 6632 (in this reference there is one example concerning an aryl oxindole). (e) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, 4040. For the chiral auxiliary-based approach: (f) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537. (g) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559.

(7) For related amine-catalyzed α -amination of aldehydes and ketones: (a) Kumaragurbaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (b) Bøgevig, A.; Juhl, K.; Kumaragurbaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (c) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (d) Chowdari, N. S.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 867. (e) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448. (f) Dahlin, N.; Bøgevig, A.; Adolfsen, H. *Adv. Synth. Catal.* **2004**, *346*, 1101. For organocatalytic enantioselective α -amination of β -ketoesters and derivatives thereof: (g) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, *12*, 2115. (h) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (i) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (j) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044.

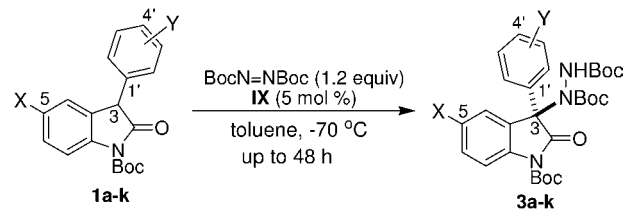
that with the 1,2-dibenzyl linker (entry 8 vs entry 6). Not surprisingly, C₆ quinidine dimer **IX** (5 mol %) was most effective among the catalysts examined. These results mirrored those obtained from previously reported catalytic, enantioselective aminoxygenations of aryl oxindoles.²

The moderate enantioselectivity obtained with catalyst **IX** warranted further investigation. We discovered that Boc-protected aryl oxindole **1a** was highly reactive, and a competing nonselective reaction occurred (due to the inherent reactivity of aryl oxindoles *vide supra*), thereby compromising the enantioselectivity. This problem was solved by performing the α -amination reaction at low temperature (entry 9 vs entry 10). However, the ee increased only marginally when the temperature was lowered from -50 to -70 °C (entry 10 vs entry 11). A survey of solvents resulted in conditions that provided excellent yield and ee: the optimal results were obtained when the α -amination was performed in toluene at -70 °C for 48 h (entry 15). The long reaction time was required to ensure good yield and ee of the desired product (24 h, entry 14 vs 48 h, entry 15). As previously observed, the free hydroxyl groups in catalyst **IX** were important for high yield and enantioselectivity (entry 15 vs entry 17). These results suggest that these hydroxyl groups might direct or orient the incoming azadicarboxylate electrophile via weak hydrogen bonding before C–N bond formation takes place.^{2,9}

(8) For selected related C–C bond-forming reactions involving oxindoles in organocatalysis: (a) Bui, T.; Syed, S.; Barbas, C. F., III *J. Am. Chem. Soc.* **2009**, *131*, 8756. (b) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559. (c) Galzerano, P.; Bencivenni, G.; Pesciaoli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.–Eur. J.* **2009**, *15*, 7846. (d) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14. (e) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (f) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (g) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583. (h) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (i) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (j) Bencivenni, G.; Wu, L.; Mazzanti, A.; Giannichi, B.; Pesciaoli, F.; Song, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (k) Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. *Chem.–Eur. J.* **2009**, *15*, 7913. (l) Deng, J.; Zhang, S.; Ding, P.; Jiang, H.; Wang, W.; Li, J. *Adv. Syn. Catal.* **2010**, *352*, 833. (m) Zhu, Q.; Lu, Y. *Angew. Chem., Int. Ed.* **2010**, DOI: 10.1002/anie.201003837. Selected references for C–C bond-forming reactions of oxindoles involving transition metal catalysis: (n) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168. (o) Doumay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261. (p) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (q) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (r) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (s) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (t) Kozłowski, M. C.; Linton, E. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162. Synthesis of oxindoles via organocatalytic additions of carbonyl compounds to isatins: (u) 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. (v) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 14037. (w) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854. Asymmetric synthesis of oxindoles via nucleophilic additions to isatins using metal catalysis: (x) Toullec, P. Y.; Jagt, R. B.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. L. *Org. Lett.* **2006**, *8*, 2715. (y) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (z) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (aa) Grant, C. D.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4485. (bb) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (cc) Lai, H.; Huang, Z.; Wu, Q.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 283. (dd) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744.

Having established the optimal reaction conditions, we began to investigate the scope of the α -amination reaction with respect to oxindole substrates (Table 2). The reaction was general in

Table 2. Enantioselective α -Aminations of Aryl Oxindoles



entry	X	Y	product	yield ^a (%)	ee ^b (%)
1	H	H	3a	93	98
2	OMe	H	3b	96	95
3	H	4'-Me	3c	71	96
4	H	3'-OMe	3d	95	97
5	H	4'-tBu	3e	76	96
6	H	4'-F	3f	87	96
7	OMe	4'-Me	3g	94	98
8	OMe	3'-OMe	3h	92	97
9	OMe	4'-F	3i	91	73
10	OCF ₃	3'-OMe	3j	93	93
11	F	3'-OMe	3k	87	87

^a Isolated yields. ^b Determined by chiral HPLC analysis.

scope, tolerating aryl oxindoles of different electronic natures and with different aromatic substitution patterns. For example, oxindoles bearing electron-neutral and electron-rich substituents at C₅ afforded the desired products in excellent yields and ee's (entries 1–2). Moreover, reactions with substrates with various aryl groups at the C₃ position also provided products in moderate to good yields with excellent ee's (entries 3–6). It is noteworthy that oxindole **3f**, which contains a fluorine atom, was obtained in good yield and high ee (entry 6). Enantiomerically enriched syntheses of fluorine-containing molecules are of importance in drug discovery and development.¹⁰ Under our optimized conditions, oxindoles with various substituents at C₅ and different substitution patterns on the C₃-substituted aryl ring were all viable substrates (entries 7–11). The yields and ee's of the desired products were high for most of these substrates. The absolute configuration at the newly created center was determined to be *R* by comparison with a known oxindole derivative of **3a**.¹¹ Finally, we demonstrated that product **3a** could be converted into the corresponding, free amino aryl oxindole in good yield with excellent optical purity.¹¹

To determine the role of the dimeric structure and the quinidine units in catalysis by **IX**, analogues were synthesized and examined in the enantioselective α -amination of **1a** (Table 3). Catalysts **XI** and **XII** had only one quinuclidine moiety within the catalyst

(9) 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.

(10) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.

(11) See Supporting Information.

Table 3. Insight into the Role of the Dimeric Structure

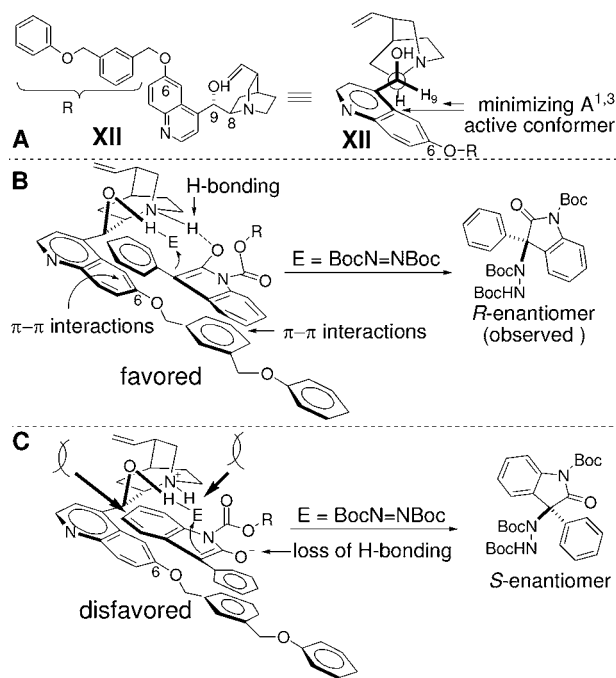
entry	catalyst	product	yield ^a (%)	ee ^b
1	IX	3a	93	98
2	XI	3a	94	98
3	XII	3a	89	98
4	XIII	3a	89	94
5	I	3a	85	79

^a Isolated yield. ^b Determined by chiral HPLC analysis.

molecule. In **XI**, the 1,3-dibenzyl linker was attached to an electron-rich π -quinoline ring, and in **XII**, it was attached to a simple phenyl ring. If π - π interactions between the two quinoline units in **IX** and **XI** were critical for catalysis, one would expect that **XII** would be a less effective catalyst.¹² In catalyst **XIII**, the linker was a single benzyl group. The molecular weight and complexity of catalyst **IX** is greater than those of analogues **XI**, **XII**, and **XIII**. Significantly, catalysts **IX**, **XI**, and **XII** provided the desired product in similar yields with excellent ee's (Table 3, entries 1–3). Interestingly, when monomeric catalyst **XIII** was used, the ee was lower (entry 4 vs entries 1–3). The drop in ee was even more significant when the 1,3-dibenzyl linker was replaced by a methyl group in catalyst **I** (entry 5). The effects of the C₆-alcohol protecting group on ee were striking. This effect was not expected as this group is distal to the quinuclidine nitrogen atom where the reactive oxindole enolate is presumably generated. These observations provide valuable information that will aid future catalyst design and development. Our hypothesis is that the hydroxy protecting group at C₆ affects the conformation of quinidine; this conformation impacts the stereochemistry-determining step and ultimately the enantioselectivity of the α -amination reaction (Figure 3, A–C).^{12,13} Our proposed transition state structures are consistent with the following experimental observations: (a) the importance of a π -rich moiety that protects the C₆ hydroxyl group in the catalyst to maintain high selectivity (Figure 3B), (b) the free hydroxyl group at C₉ to ensure high yield and ee, and (c) the same sense of asymmetric induction is observed for both aminoxygenation and α -amination of oxindoles.^{2,11}

(12) We believe that the electron-rich π -systems of the two quinoline moieties in **IX** are likely to participate in π - π interactions with the oxindole substrate. See: (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

(13) (a) Studies of the active conformation of cinchona alkaloid catalysts: Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L. *Proc. Natl. Acad. Sci.* **2010**, DOI: 10.1073/pnas.1004439107, Early Edition. (b) Calculation of the lowest-energy conformation of cinchona alkaloids: Caner, H.; Biedermann, P. U.; Agranat, I. *Chirality* **2003**, *15*, 637.

**Figure 3.** Proposed active conformer (A) and proposed transition state structures with catalyst **XII** (B and C).

In summary, we have developed dimeric and designer quinidine-catalyzed enantioselective α -aminations of aryl oxindoles to afford the desired products in good yields with good to excellent enantioselectivities. These reactions are general and provide entry to a broad range of aryl oxindoles including those that contain fluorine atoms. The organocatalytic method employs readily cleavable Boc-protected diazo electrophiles for the α -amination and allows access to optically active 3-amino aryl oxindoles with minimal functional group manipulation under mild conditions. The reactions reported here provide the first examples of a general organocatalytic approach to the generation of tetrasubstituted nitrogen-containing centers at the C₃ position of a variety of aryl oxindoles. Our experiments revealed important and somewhat unexpected structural elements of the catalyst that are crucial for high enantioselectivities. These insights allowed for the design and development of practical, multifunctional catalysts that possess Bronsted acidic, Lewis basic, and π -stacking sites, that together enable effective catalysis of the α -amination reaction. These catalysts will be investigated in other asymmetric transformations, and the results of these studies will be reported in due course.

Acknowledgment. We thank the Skaggs Institute for Chemical Biology for funding.

Supporting Information Available: General experimental, general procedures, spectroscopic data for catalysts **IX** and **XI–XII**, synthetic route to **3I** [(*R*)-3-amino-3-phenyloxindole], determination of the absolute configuration, HPLC chromatograms, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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