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# Highly Enantioselective and Organocatalytic α-Amination of 2-Oxindoles

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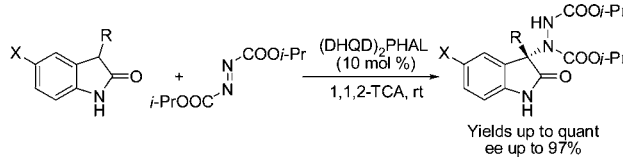
## ABSTRACT




**An effective method for the asymmetric synthesis of 3-amino-2-oxindoles was developed. The tetrasubstituted chiral carbon center was generated by asymmetric amination of *N*-unprotected 2-oxindoles with azodicarboxylate catalyzed by commercial biscinchona alkaloids in good to excellent yields with high enantioselectivities.**

As important substructures, chiral 3,3-disubstituted 2-oxindoles constitute a ubiquitous class of heterocycles found in numerous natural products, marketed drugs, and drug candidates.[1] Among them, 3-amino-2-oxindole compounds bearing a chiral quaternary carbon center have been investigated extensively and recognized as core structures in a variety of biologically active compounds, which exhibit significant pharmaceutical properties (Figure 1),[2] and challenging targets for medicinal chemistry and synthetic organic chemistry.

A plethora of different procedures have been developed to accomplish the synthesis of tetrasubstituted 3-amino-2-oxindoles, including cyclization of *o*-chlorinated anilines,[3] alkylation or addition of 2-oxindoles,[4] and other miscellaneous sequences.[5] However, these methods showed a lack of generality and gave variable yields, and most of them were hard to perform in a catalytic asymmetric manner.[3c,4a,e]

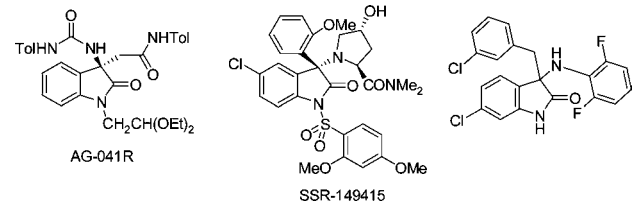



**Figure 1.** Bioactive disubstituted 3-amino-2-oxindoles.

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Recently, the catalytic asymmetric nucleophilic addition reaction of 2-oxindole has attracted considerable attention.[6,7] Since significant advances have been achieved in the metal-catalyzed or organocatalytic asymmetric α-amination of carbonyl compounds with azodicarboxylates,[8] we envisioned that the enantioselective electrophilic amination of 2-oxindole with azodicarboxylates would be a direct method for the synthesis of 3-amino-2-oxindole alkaloid compounds. However, to the best of our knowledge, the use of oxindoles as simple α-aryl amides has never been reported.

Herein we report the first enantioselective synthesis of the title compounds through the amination of various 2-oxindoles with azodicarboxylate catalyzed by commercial biscinchona alkaloids.[9,10] This appealing methodology, using readily available *N*-unprotected 3-monosubstituted 2-oxindoles as starting materials,[11] will undoubtedly provide effective method for the enantioselective synthesis of functionalized and complex 3,3′-disubstituted 3-amino-2-oxindole alkaloids.

Initially, the enantioselective amination reaction of 2-oxindole **1a** with 1.0 equiv of diethyl azodicarboxylate (DEAD, **2a**) in dichloromethane in the presence of natural cinchona alkaloids **4a**−**d** (10 mol %) (Figure 2) was carried out (Scheme 1).

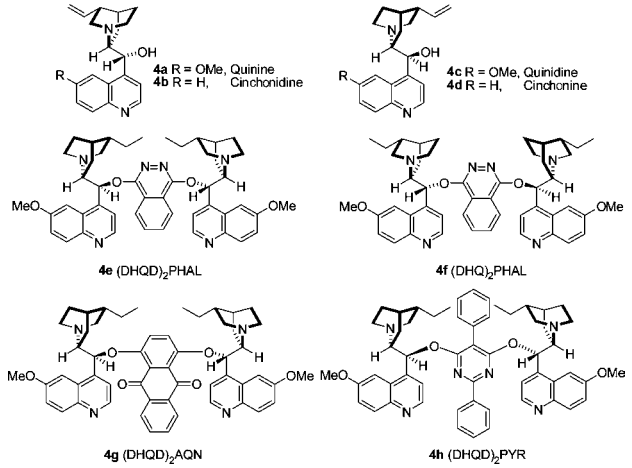


**Figure 2.** Catalysts for screening.

Although **1a** was smoothly converted to the adduct **3a** in moderate yields (45−69%), unfortunately, very poor enantioselectivities of the product were obtained (Table 1, entries 1−4). Various biscinchona alkaloids were screened for this

**Scheme 1**

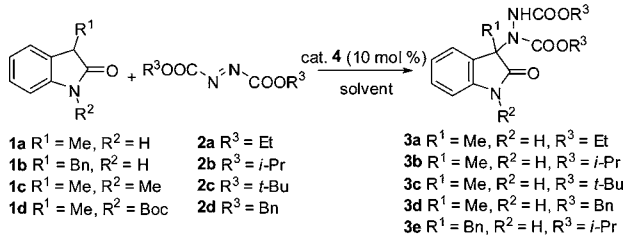


**Table 1.** Catalyst Screening for Enantioselective α-Amination of 2-Oxindoles **1a** with **2**[a]

| entry | **2** | catalyst[b] | products | yield[c] (%) | ee of **3**[d] (%) |
|---|---|---|---|---|---|
| 1 | **2a** | **4a** | **3a** | 45 | 7 |
| 2 | **2a** | **4b** | **3a** | 63 | 5 |
| 3 | **2a** | **4c** | **3a** | 50 | 1 |
| 4 | **2a** | **4d** | **3a** | 69 | 7 |
| 5 | **2a** | **4e** | **3a** | 47 | 33 |
| 6 | **2a** | **4f** | **3a** | 48 | −31 |
| 7 | **2b** | **4e** | **3b** | quant | 57 |
| 8 | **2c** | **4e** | **3c** | 85 | 39 |
| 9 | **2d** | **4e** | **3d** | 58 | <10 |

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $CH_2Cl_2$ (0.2 mL), room temperature. [b] Catalyst loading: 10 mol %. [c] Isolated yields. [d] Determined by chiral HPLC analysis.

reaction (Figure 2).[12,13] While the catalysts **4g**,**h** were not suitable for the enantioselective amination of **1a** with **2a** (yields 13−17%, ee 1−40%), by using $(DHQD)_2PHAL$ **4e** and $(DHQ)_2PHAL$ **4f** as catalysts, the adduct **3a** was produced in 47−48% yield with moderate enantioselectivities (ee 31−33%) (Table 1, entries 5 and 6). Catalysts **4e** and **4f** showed nearly equal reactivity and enantioselectivity with opposite configuration.

Next, we assessed the influence of the alkyl group $R^3$ at the azodicarboxylate. To our great delight, the enantioselectivity was dramatically improved to 57% ee when **2b** (DIAD, $R^3$ = *i*-Pr) was used as an amination reagent (Table 1, entry 7). Interestingly, when more steric hindered **2c** (DTAD, $R^3$ = *t*-Bu) was applied, the ee value of the product **3c** decreased to 39% (entry 8), while **2d** (DBAD, $R^3$ = Bn) afforded a product mixture with very poor enatioselectivity (entry 9).

The influence of solvents was extensively studied. Interestingly, though the reaction of **1a** and **1b** with **2a** could proceeded to completion in a wide range of solvents, a large variation of enantioinduction was observed (Table 2).[13]

The reaction performed in $Et_2O$, a high dielectric constant oxygenated solvent, which was utilized in the highly enan-

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**Table 2.** Solvent Effect on the α-Amination of 2-Oxindoles **1a** and **1b** with **2b**[a]

| entry | 1 | solvent | products | yield[b] (%) | ee of 3[c] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | $Et_2O$ | **3b** | 99 | 39 |
| 2[d] | **1b** | $Et_2O$ | **3e** | 83 | 53 |
| 3 | **1a** | toluene | **3b** | quant | 55 |
| 4 | **1a** | hexane | **3b** | trace | |
| 5 | **1a** | DCE | **3b** | quant | 62 |
| 6[d] | **1b** | DCE | **3e** | 88 | 90 |
| 7[d] | **1a** | 1,1,2-TCA | **3b** | quant | 78 |
| 8[d] | **1b** | 1,1,2-TCA | **3e** | 99 | 93 |
| 9[d,e] | **1b** | 1,1,2-TCA | **3e** | 95 | 91 |
| 10[d,f] | **1b** | 1,1,2-TCA | **3e** | 90 | 90 |
| 11[d,g] | **1b** | 1,1,2-TCA | **3e** | 99 | −91 |

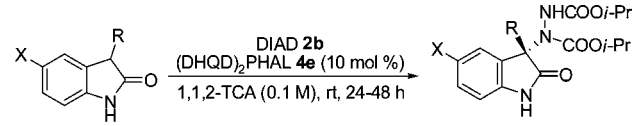
[a] Reaction conditions (unless otherwise noted): **1** (0.2 mmol), **2b** (0.2 mmol), **4e** (0.02 mmol, 10 mol %), solvent (0.2 mL), room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Solvent (2 mL). [e] Catalyst loading: 5 mol %. [f] Catalyst loading: 2 mol %. [g] **4f** was used as the catalyst.

tioselective aldol-type reaction of oxindoles with ethyl trifluoropyruvate catalyzed by the same cinchona alkaloid $(DHQD)_2PHAL$ **4e**,[6a] did not give desirable selectivity (entries 1 and 2). The use of nonpolar solvents, such as toluene and hexane, did not improve the results either (entries 3 and 4). However, the use of aprotic dipolar chlorinated alkanes as solvents in the reaction provided facile product isolation and the corresponding adducts was obtained in significantly improved enantioselectivities (entries 5−7).

The best solvent for this reaction was found to be 1,1,2-TCA (1,1,2-trichloroethane), and the enantioselectivity of **3e** was further increased up to 93% by performing the reaction in a dilute concentration (0.1 M) (entry 8), which required no additional additives and enabled milder reaction conditions. Lowering the catalyst loading led to a decrease of yield and enantioselectivity of the product, and a longer reaction time was required (entries 9−10). Most importantly, the amination catalyzed by $(DHQ)_2PHAL$ **4f** also proceeded in excellent yield and enantioselectivity (entry 11), which demonstrated that both enantiomers could be synthesized upon the selection of the appropriate cinchona alkaloid.

Encouraged by these results, the generality of this addition reaction was next examined. As summarized in Table 3,

**Table 3.** Asymmetric Organocatalytic Addition of 2-Oxindoles **1** with DIAD **2b**[a]




**1a-b, e-r** **3b, e-s**

| entry | 1 | X | R | 3 | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | H | Me | **3b** | quant | 78 |
| 2 | **1b** | H | $CH_2Ph$ | **3e** | 99 | 93 |
| 3 | **1e** | H | $CH_2$-$C_6H_4$-4-Cl | **3f** | 80 | 96 |
| 4 | **1f** | H | $CH_2$-$C_6H_4$-4-Br | **3g** | 97 | 90 |
| 5 | **1g** | H | $CH_2$-$C_6H_4$-4-OMe | **3h** | 80 | 93 |
| 6 | **1h** | H | $CH_2$-$C_6H_4$-4-Me | **3i** | 65 | 97 |
| 7 | **1i** | H | $CH_2$-$C_6H_4$-2-Br | **3j** | 54 | 96 |
| 8 | **1j** | H | $CH_2$-$C_6H_4$-2-$CF_3$ | **3k** | 79 | 93 |
| 9 | **1k** | H | $CH_2$-$C_6H_4$-2-OMe | **3l** | 87 | 90 |
| 10 | **1l** | H | $CH_2$-$C_6H_4$-2-Me | **3m** | 83 | 91 |
| 11 | **1m** | H | $CH_2$-$C_6H_3$-2,6-$(Me)_2$ | **3n** | quant | 88 |
| 12 | **1n** | H | $CH_2$-$C_6H_3$-3,4-$OCH_2O$ | **3o** | 90 | 89 |
| 13 | **1o** | H | $CH_2$-2-thiophene | **3p** | quant | 94 |
| 14 | **1p** | Cl | $CH_2Ph$ | **3q** | 71 | 88 |
| 15 | **1q** | Br | Me | **3r** | 96 | 85(99)[d] |
| 16 | **1r** | H | Ph | **3s** | 74 | 63 |

[a] Reaction conditions: **1** (0.2 mmol), **2b** (0.2 mmol), 1,1,2-TCA (2 mL), $(DHQD)_2PHAL$ **4e** (10 mol %), room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The value in parentheses refer to the single crystal.

under the optimized reaction conditions, the asymmetric addition of 2-oxindoles (**1e**−**r**) to DIAD **2b** catalyzed by $(DHQD)_2PHAL$ **4e** was then evaluated, which exhibited a broad substrate scope and tolerance toward the presence of various substituents.

Regardless of the electronic or steric nature of the substituents on the benzylic rings at C-3 position, the asymmetric α-amination of 2-oxindoles consistently gave good yields (up to quant) and very high enantioselectivities (up to 97%) (entries 3−12). This transformation tolerated significant functionalization in the aromatic rings, both of electron-donating (OMe, $OCH_2O$, Me) and electron-withdrawing groups (Cl, Br, $CF_3$), including *ortho*- or *para*-substitutions, can be accommodated.

The variation of the C-3 benzylic substituent to an heteroaryl group (thiephene) was also possible to give the expected product **3p** in quantitative yield with 94% ee (entry 13). We were pleased to find that the catalytic system was also effective for the asymmetric amination of 5-halogenated-2-oxindoles, which gave the adducts with good enantioselectivities (entries 14 and 15).

However, 3-phenyl-2-oxindole **1r** afforded the product **3s** in acceptable yield with moderate enantioselectivity, which

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(12) For reviews on modified cinchona alkaoids, see: (a) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. For some pioneering work using biscinchona alkaloids, see: (c) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (d) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338. (e) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900.

(13) See the Supporting Information for details.

might be due to its high activity toward electrophiles (entry 16). Thus, we have developed an efficient enantioselective α-amination of *N*-unsubstituted 2-oxindoles with broad generality, which is operationally convenient and could be performed without exclusion of air or moisture.

It should be indicated that the *N*-H subunit of oxindole is necessary for the reaction of 2-oxindole with azodicarboxylates.[11,14] Low conversions and poor enantioselectivities were observed in the direct amination of *N*-protected oxindoles (**1c**, $R^2$ = Me and **1d**, $R^2$ = Boc) with **2b**.[13]

The absolute configuration of the newly created chiral quaternary carbon center in the reaction adducts was deduced as (*S*) by X-ray single-crystal analysis of **3r** after recrystallization.[13]

Cinchona alkaloid derivatives are conformationally flexible in solution;[15a,c] however, in the present state, the transition state for the formation of (*S*)-3-amino-2-oxindoles under the catalysis of $(DHQD)_2PHAL$ **4e** was presumably through an open conformation, in which the deprotonated enolated 2-oxindole was supposed to be locked in the open U-shaped cleft where the aromatic PHAL ring formed the bottom while two quinoline rings from DHQD alkaloids formed the walls (Figure 3).[6a,15]

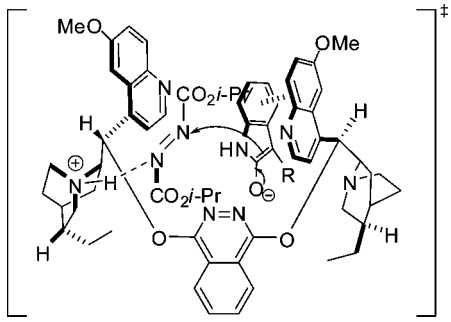


**Figure 3.** Proposed transition state for the enantioselective amination of 2-oxindoles to give (*S*)-enantiomers.

The enolated 2-oxindole was deprotonated by the quinuclidine nitrogen of one alkaloid and then stabilized by potential $\pi-\pi$ stacking with the other alkaloid. The N═N double bond in azodicarboxylate, which was activated by hydrogen bonding through protonated quinuclidine nitrogen, was attacked preferably from the uncovered *Si*-face of oxindole, while the (*S*)-enantiomers were generated predominately. Nevertheless, further studies should be required to elucidate the mechanism.

In conclusion, the first organocatalytic enantioselective amination reaction of *N*-unprotected 2-oxindoles was developed by using dialkyl azodicarboxylate as an amination reagent in the presence of biscinchona alkaloid catalysts. The catalytic system was applied to the formation of (*S*)-3-amino-2-oxindoles in excellent yields and enantioselectivities. Application of the present method for the synthesis of natural and bioactive compounds is currently under investigation.

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**Supporting Information Available:** Experimental procedures, characterization data, chiral chromatographic analysis for all new compounds, and single-crystal structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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