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Organocatalytic Asymmetric α-Amination of Unprotected 3-Aryl and 3-Aliphatic Substituted Oxindoles using Di-*tert*-butyl Azodicarboxylate

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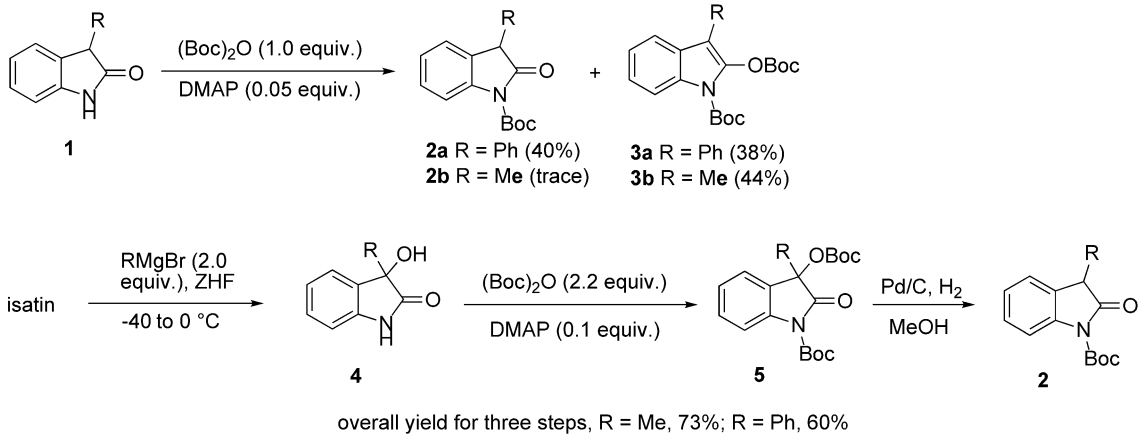
Abstract: The bifunctional quinine-derived thiourea catalyst **14** was found to catalyze the direct amination of unprotected 3-aryl and aliphatic substituted oxindoles with di-*tert*-butyl azodicarboxylate (DBAD) to construct a tetrasubstituted stereogenic carbon center at the C-3 position of oxindoles in good to excellent yield and enantioselectivity.

Keywords: 3-aminooxindoles; asymmetric catalysis; atom efficiency; organocatalysis; tetrasubstituted stereogenic carbon centers

To prepare products in an atom-economical manner is very important in modern organic synthesis.[1] As far as the catalytic asymmetric construction of tetrasubstituted carbon stereogenic centers is concerned,[2] a number of the current methods are not sufficiently atom-efficient as judged by the principles of "ideal synthesis" to maximize products and minimize by-products,[1b] although they are highly enantioselective. Because of the known challenges such as the low reactivity of precursors involved in the generation of tetrasubstituted carbon centers, the use of activating groups to make the substrates more reactive is a common strategy for reaction development. However, the introduction and removal of activating groups needs extra steps, consumes more time, labor and reagents, and generates more waste to get the desired products.[1]

This dilemma can be exemplified by the catalytic asymmetric direct amination of 3-prochiral oxindoles using azodicarboxylate,[3,4] which recently emerged as a promising method for the synthesis of 3-substituted 3-aminooxindoles.[5] Because of its presence in some natural bioactive products and pharmaceutically active compounds such as the potent gastrin/CCK-B receptor antagonist AG-041R[5f] and the vasopressin VIb receptor antagonist SSR-149415,[5g,h] the catalytic synthesis of enantioenriched 3-aminooxindoles is of current interest.[3,6] The reaction of unprotected 3-substituted oxindole **1** with diisopropyl or diethyl azodicarboxylate (DIAD or DEAD) could afford the desired products in excellent *ee*,[3a–d] but it was difficult to convert the corresponding products to synthetically useful 3-aminooxindoles.[7] In a previous study,[3b] we found that adducts obtained from DIAD or DEAD easily decomposed under all the reported conditions to remove the alkoxycarbonyl group for further N–N cleavage. The use of di-*tert*-butyl azodicarboxylate (DBAD) as amination reagent was favourable for the easy removal of the Boc group. However, since DBAD is less electrophilic than other azodicarboxylates,[8] the reaction of unprotected 3-substituted oxindoles and DBAD has not been developed up to now.

An alternative method is to activate 3-substituted oxindoles to react with DBAD. Helpfully, introducing an electron-withdrawing group to the nitrogen moiety was able to lower down the pK_a value of 3-substituted oxindoles. For example, *N*-acetyloxindole has a pK_a value of 13.0, much lower than that of oxindole (18.2).[9] Accordingly, the more reactive *N*-Boc protected 3-substituted oxindole **2** was widely used for the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles.[10] Based on this strategy, Shibasaki and coworkers developed a highly enantioselective amination of *N*-Boc-protected 3-alkyloxindoles using DBAD, and applied it to the formal synthesis of AG-



Scheme 1. Synthesis of *N*-Boc-protected oxindoles **2**.

041R.[3e] Most recently, Barbas III et al. expanded the substrate scope to *N*-Boc-protected 3-aryloxindoles.[3f]

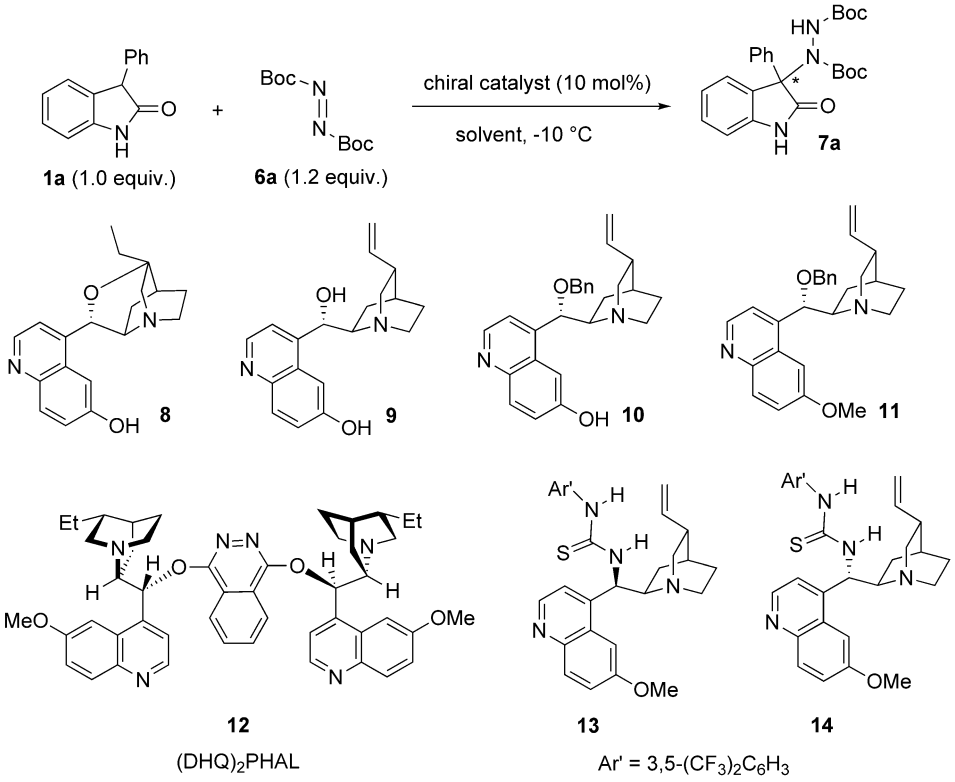
Despite these achievements, there is still room for further improvement. First, it would be more atom-economical to use unprotected 3-substituted oxindole **1** as the starting material, because it took three steps to prepare *N*-Boc-oxindole **2** from isatin with the sacrifice of one equivalent of $(Boc)_2O$.[11a] The direct protection of **1** using $(Boc)_2O$ was problematic due to the competitive *N*- and *O*-selectivity (Scheme 1).[11] In addition, there are no available methods for the highly enantioselective amination of both 3-aryl- and 3-alkyloxindoles using DBAD as yet. Accordingly, it is of great interest to develop an enantioselective amination reaction of both unprotected 3-aliphatic and aryl-substituted oxindoles using DBAD. In our efforts in the synthesis of 3,3-disubstituted oxindoles for biological evaluation,[3b,12] we started this research work, and here we wish to report our results.

The reaction of 3-phenyloxindole **1a** and DBAD **6a** was chosen for optimization, using THF as the solvent at −10 °C in the presence of 10 mol% chiral catalyst. We first focused on the use of bifunctional Brønsted acid-base catalysts, with the base moiety[13] for deprotonative activation of oxindole and the acid moiety[14] to interact with DBAD. Hatakeyama's catalyst **8**, with a phenol group as the Brønsted acid moiety, worked well to afford the desired product in moderate yield and 56% *ee* (entry 1, Table 1). This result encouraged us to try other bifunctional catalysts, and bifunctional urea catalyst **14**[15] turned out to be the most effective, which could promote the reaction in 82% yield with 87% *ee* (entry 7). For comparison, Brønsted base catalysts **11** and **12** were also tried, but both proved to be less enantioselective (entries 4 and 5). The solvent effect was further examined using catalyst **14**, and 1,2-dichloroethane (DCE) was found to be the best, which afforded the product **7a** in up to 90% *ee*, but the reactivity was unsatisfactory (entry 13). Considering that the use of additives to improve both the enantioselectivity and reactivity is a fruitful method in asymmetric catalysis,[16] we tried different additives to improve the reactivity. To our delight, we found that the addition of powdered MS 5 Å could obviously accelerate the reaction to finish the products within three days, with only a slight decrease in *ee* (entry 14). The role of MS 5 Å to accelerate the reaction is now under investigation.

The DBAD was found to be crucial for the high *ee* of this amination reaction. As shown in Scheme 2, the alkyl group R at azodicarboxylates **6** significantly influenced the *ee* of product **7**. DBAD, with bulkyl *tert*-butyl group, afforded the corresponding adduct **7a** in the highest *ee*. In contrast, DIAD or DEAD enabled the reaction to be obviously faster but the desired product **7b** or **7c** was obtained in much lower *ee*. The absolute configuration of product **7b** was assigned to be *S* by comparing its HPLC performance with the literature report,[3a] and that of compound **7a** was tentatively assigned by comparing the sign of its optical rotations to that of **7b**.

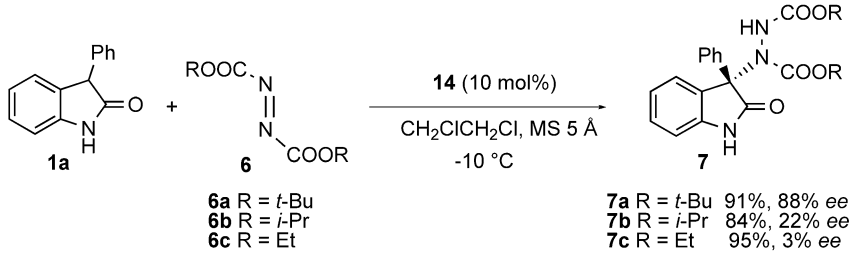
Then a variety of unprotected 3-aryloxindoles **1a**–**m** were examined using catalyst **14** and DCE as the solvent, and the results were shown in Table 2. All the reactions were run on a 0.25-mmol scale at −10 °C with the addition of powdered MS 5 Å. Generally, the electron-donating substituents had a positive influence on the selectivity of the reaction, irrespectuive of whether on the oxindole framework or on the phenyl ring at the C-3 position of oxindole, and the desired products were all obtained in excellent *ee* (entries 2–5, 9, 10 and 13). The methoxy group on the C-5 position of the oxindole greatly slowed down the reaction so that 20 mol% of catalyst was used to ensure a high yield of product **7l** (entry 10). On the other hand, the presence of electron-withdrawing groups on the phenyl group at C-3 position improved the reactivity but decreased the *ee* of the products **7h** and **7i**

Table 1. Catalyst screening and solvent effect.



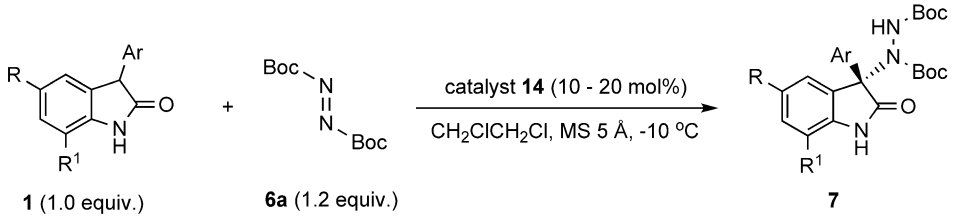
Entry[a]	Catalyst	Time [days]	Solvent	Yield[b] [%]	*ee*[c] [%]
1	**8**	5	THF	51	56
2	**9**	5	THF	64	26
3	**10**	5	THF	58	15
4	**11**	5	THF	56	3
5	**12**	5	THF	55	0
6	**13**	4	THF	19	74[d]
7	**14**	4	THF	82	87
8	**14**	4	toluene	25	71
9	**14**	4	CH_2Cl_2	64	89
10	**14**	4	acetone	68	81
11	**14**	4	CH_3CN	72	60
12	**14**	4	Et_2O	10	46
13	**14**	4	CH_2ClCH_2Cl	58	90
14[e]	**14**	3	CH_2ClCH_2Cl	91	88

[a] On a 0.1-mmol scale.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Opposite enantiomer.
[e] Powdered MS 5 Å as the additive.



Scheme 2. Effect of the alkyl group R at azodicarboxylates **6**.

Table 2. Substrate scope of 3-aryloxindoles with catalyst **14**.



1 (1.0 equiv.) **6a** (1.2 equiv.) **7**

Entry[a]	Substrate **1**	Product **7**	Time [days])	Yield [%][b]	*ee*[c] [%]
1	**1a**: R = R^1 = H, Ar = Ph	**7a**	3	91	88
2	**1b**: R = R^1 = H, Ar = *o*-MeC$_6$H$_4$	**7d**	5	67	94
3	**1c**: R = R^1 = H, Ar = *m*-MeC$_6$H$_4$	**7e**	5	83	90
4	**1d**: R = R^1 = H, Ar = *p*-MeC$_6$H$_4$	**7f**	5	88	93
5[d]	**1e**: R = R^1 = H, Ar = *p*-MeOC$_6$H$_4$	**7g**	5	75	95
6	**1f**: R = R^1 = H, Ar = *p*-ClC$_6$H$_4$	**7h**	3	83	82
7	**1g**: R = R^1 = H, Ar = *p*-BrC$_6$H$_4$	**7i**	3	89	83
8	**1h**: R = R^1 = H, Ar = *2*-naphthyl	**7j**	5	74	87
9	**1i**: R = Me, R^1 = H, Ar = Ph	**7k**	5	65	91
10[e]	**1j**: R = MeO, R^1 = H, Ar = Ph	**7l**	5	81	95
11[e]	**1k**: R = F, R^1 = H, Ar = Ph	**7m**	2	61	84
12[e]	**1l**: R = Cl, R^1 = H, Ar = Ph	**7n**	2	86	81
13	**1m**: R = Me, R^1 = Me, Ar = Ph	**7o**	5	97	96

[a] On a 0.25-mmol scale.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] THF as the solvent without MS 5 Å.
[e] 20 mol% catalyst.

(entries 6 and 7). In the case of oxindoles **1k** and **1l**, we found that the use of 20 mol% of catalyst could improve the *ee* of the products **7m** and **7n**, which were obtained in above 80% *ee* (entries 11 and 12). An oxindole bearing a 2-naphthyl group at the C-3 position was also examined, and the corresponding product **7j** was obtained in 87% *ee* (entry 8).

The structure of the amination adduct **7m** was further confirmed by single-crystal X-ray diffraction analysis (Figure 1).[17]

We were pleased to find that unprotected 3-alkyloxindoles also worked well under these conditions. This result was really interesting, because unprotected 3-alkyloxindoles were less reactive, with a pK_a value that can be expected to be substantially higher than 18.2 (oxindole).[9] The reaction was run at 0 °C. 3-Benzyloxindole worked well to give the desired product **7p** in 72% yield with 88% *ee* (entry 1, Table 3). Electron-withdrawing substituents at the C-5 position accelerated the reaction, so that products **7q** and **7r** could be obtained in up to 90% *ee* with high yield, using only 10 mol% of catalyst (entries 2 and 3). The 5-bromo-substituted product **7s** was obtained in 84% *ee* in the presence of 20 mol% catalyst **14** (entry 4). On the other hand, a methyl group on the C-5 position obviously slowed the reaction, although the product **7t** could be obtained in 95% *ee* (entry 5). Different aryl substituents on the C-3 benzyl group of oxindole **1** were also examined, and the corresponding products **7u–y** were all obtained in excellent *ee* (entries 6–10). Interestingly, even 5-bromo-3-methyloxindole could afford the corresponding product **7z** in 85% *ee*, although 30 mol% of catalyst **14** was used (entry 11).

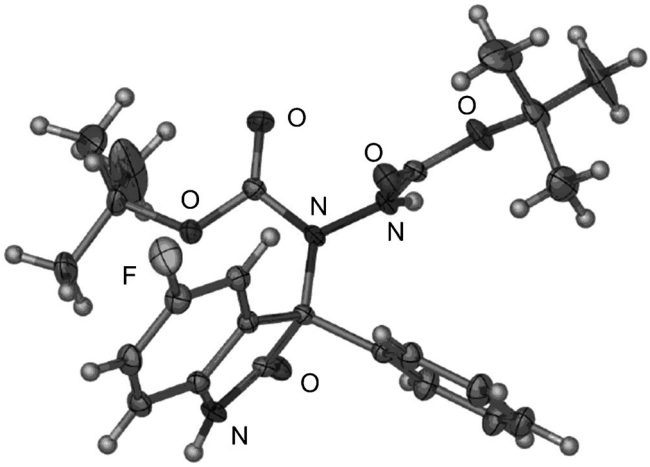
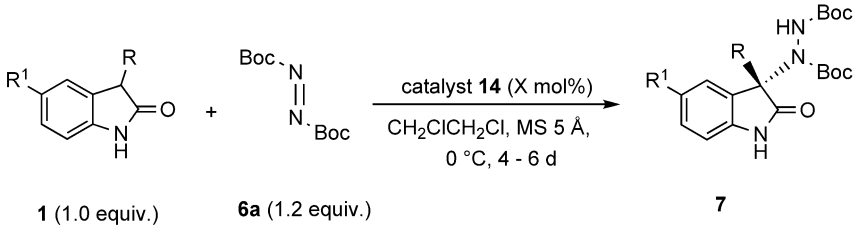


Figure 1. X-ray structure of amination adduct **7m**.

During the catalyst screening, we observed that the pseudo-enantiomeric quinidine-derived bifunctional

Table 3. Substrate scope of 3-alkyloxindoles with catalyst **14**.

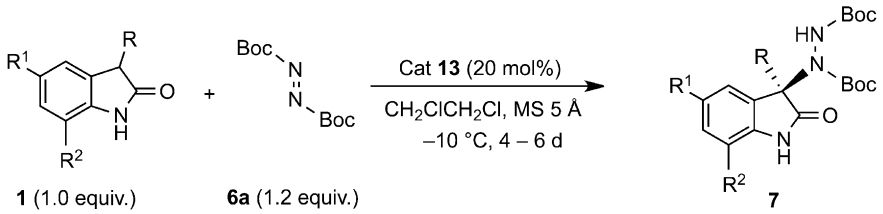


Entry[a]	R^1	R	X	Product **7**	Yield[b] [%]	*ee*[c] [%]
1	H	Bn	20	**7p**	72	88
2	F	Bn	10	**7q**	70	86
3	Cl	Bn	10	**7r**	83	90
4	Br	Bn	20	**7s**	92	84
5	Me	Bn	20	**7t**	47 (86)[d]	95
6	H	*p*-$ClC_6H_4CH_2$	20	**7u**	67	90
7	H	*p*-$CF_3C_6H_4CH_2$	20	**7v**	80	93
8	H	*p*-$MeOC_6H_4CH_2$	30	**7w**	56 (71)[d]	98
9	H	*o*-$FC_6H_4CH_2$	20	**7x**	60	89
10	H	*m*-$MeC_6H_4CH_2$	20	**7y**	56 (88)[d]	90
11	Br	Me	30	**7z**	60	85

[a] On a 0.25-mmol scale.
[b] Isolated yield.
[c] By chiral HPLC analysis.
[d] Yield based on recovery of oxindole **1**.

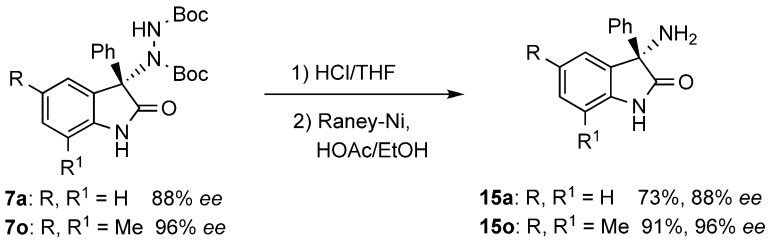
catalyst **13** could deliver the opposite enantiomer of product **7a** in 74% *ee* when using THF as the solvent, although at a much slower rate (entry 6, Table 1). Under the optimized conditions, we further examined the potency of catalyst **13** for the synthesis of the opposite enantiomers of products **7**. To our delight, when the reaction was carried out at −10 °C in 1,2-dichloroethane in the presence of MS 5 Å, the use of 20 mol% catalyst **13** could afford the desired opposite enantiomers of product **7** in reasonable yields and *ee* (Table 4). It also should be pointed out that the pseudo-enantiomeric catalyst **13** was less reactive and enantioselective than catalyst **14**.

Table 4. Substrate scope of 3-alkyloxindoles with catalyst **13**.



Entry[a]	R^1	R^2	R	Product **7**	Yield[b] [%]	*ee*[c] [%]
1	H	H	Ph	**7a**	69	86
2	H	H	*p*-MeC_6H_4	**7f**	67	90
3	H	H	*p*-BrC_6H_4	**7i**	61	80
4	Me	H	Ph	**7k**	36 (62)[d]	89
5	Me	Me	Ph	**7o**	76	97
6[e]	Cl	H	Bn	**7r**	71	82

[a] On a 0.25-mmol scale.
[b] Isolated yield.
[c] By chiral HPLC analysis, opposite enantiomer.
[d] Yield based on recovery of oxindole **1**.
[e] 0 °C.



Scheme 3. Product elaboration.

The thus obtained amination adducts can be readily transformed to the desired 3-amino-3-aryloxindoles. For example, compounds **7a** and **7o** can be converted to the corresponding aminooxindoles **15a** and **15o** in good yield without loss of *ee*, after the removal of Boc group by HCl and the cleavage of N–N bond by Raney Ni (Scheme 3). By comparing its HPLC data with the literature report, the absolute configuration of product **15a** was also assigned to be *S*.[3f]

In summary, we have developed the first example of highly enantioselective direct amination of both unprotected 3-aryl- and 3-alkyloxindoles using DBAD. Simple and easily available bifuntional catalyst **14** was identified as a powerful catalyst for this reaction. The use of unprotected 3-substituted oxindoles is very impressive because they can be easily accessed. The use of DBAD allows the facile transformation of amination adducts to synthetically useful 3-aminooxindoles without loss of enantioselectivity. The application of this method for the total synthesis of related bioactive compounds is now in process in our laboratory.

Experimental Section

To a 5-mL vial were added catalyst **14** (0.025 mmol), oxindole **1** (0.25 mmol), 2.5 mL of anhydrous 1,2-dichloroethane and MS 5 Å (250 mg). After the reaction mixture had been stirred at −10 °C for half an hour, DBAD **6a** (0.3 mmol) was added. The resulting mixture was stirred at −10 °C until almost full conversion of **1** by TLC analysis. The reaction mixture was directly subjected to column chromatography (5–10% EtOAc in DCM) to afford the desired product **7**.

Acknowledgements

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[17] CCDC 795614 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.

