Asymmetric Catalysis

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Enantioselective Cyanoethoxycarbonylation of Isatins Promoted by a Lewis Base–Brønsted Acid Cooperative Catalyst**

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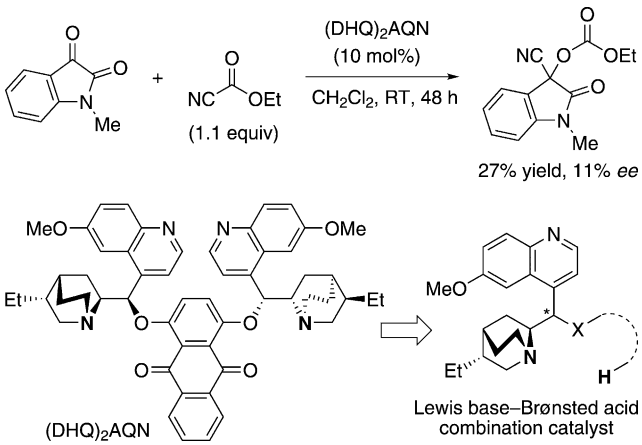
Oxindole is an important core structure found in many natural and synthetic bioactive compounds.[1] For the chemical synthesis of these useful bioactive compounds, much attention has been devoted to the development of stereoselective carbon–carbon bond-forming reactions at the C3 carbonyl carbon atom of isatins, and many enantioselective methods have been reported.[2] However, the enantioselective cyanation of isatins has not yet been reported. Enantioselective cyanation affords the corresponding cyanohydrin or its equivalent, which would be a useful chiral building block for the synthesis of these bioactive compounds.

The asymmetric cyanation of carbonyl compounds is an important reaction for the construction of tetrasubstituted carbon stereocenters.[3] Representative cyanation methods include hydrocyanation with hydrogen cyanide and silylcyanation with a silyl cyanide.[4] Although many chiral catalysts have been developed for asymmetric hydrocyanation and silylcyanation, these methods require a highly toxic cyanation reagent, and the corresponding cyanation products are rather unstable. In contrast, cyanocarbonylation with a less toxic acyl cyanide or alkyl cyanoformate[5] is also useful for the cyanation of carbonyl compounds, and the products are rather stable.

In 2001, Deng and Tian reported the first enantioselective cyanocarbonylation with $(DHQ)_2AQN$ as a chiral nucleophilic-base catalyst.[6,7] Although this pioneering method is highly efficient for the reaction of ketones, $(DHQ)_2AQN$ gave poor results in the reaction of *N*-methylisatin in our study, probably because *N*-methylisatin is much less reactive than ketones (Scheme 1). We envisioned that acid–base cooperative catalysts,[8] which have a Lewis basic site and a Brønsted acidic site, may be able to promote the enantioselective cyanocarbonylation of isatins. The Lewis basic site would activate the cyanocarbonylation reagent, and the Brønsted acidic site would simultaneously activate the carbonyl group of the isatin through hydrogen bonding to promote the reaction. We report herein the enantioselective cyanoethoxycarbonylation of isatins with acid–base cooperative organocatalysts.



Scheme 1. Organocatalytic enantioselective cyanoethoxycarbonylation of isatins.

On the basis of the findings of the Deng research group and our preliminary experiments, we chose the chiral quinuclidine moiety **B1** derived from cinchonidine as the Lewis basic site **B** in the acid–base cooperative catalyst **1**, and optimized the Brønsted acidic site **A** (Table 1). The reaction of *N*-methylisatin (R = Me) was conducted with ethyl cyanoformate (1.1 equiv) in CH_2Cl_2 in the presence of **1** (10 mol%) at ambient temperature. Catalyst **1a** containing sulfonamide **A1** as the Brønsted acidic site did not give any products, whereas the use of thiourea **A2** gave the desired product in moderate yield with moderate enantioselectivity (Table 1, entries 1 and 2). Upon further investigation of the Brønsted acidic site in catalyst **1**, we found that the introduction of a third Brønsted acid (in **A3**)[9,10] successfully improved both the yield and enantioselectivity to 73% and 65% *ee* (Table 1, entry 3). In contrast, the use of the diastereomeric chiral Lewis base **B2** and/or the enantiomeric chiral Brønsted acid **A4** led to decreased both yields and enantioselectivity (Table 1, entries 4–6). Therefore, we concluded that catalyst **1c** with the Lewis basic site **B1** and Brønsted acidic site **A3** was the optimal catalyst.

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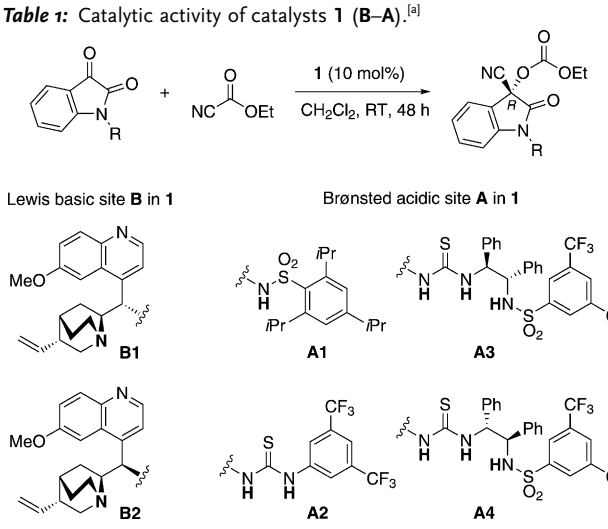
Table 1: Catalytic activity of catalysts **1** (**B**–**A**).[a]



Entry	**1** (**B**–**A**)	R	Yield [%][b]	*ee* [%]
1	**1a** (**B1**–**A1**)	Me	0	–
2	**1b** (**B1**–**A2**)	Me	34	33
3	**1c** (**B1**–**A3**)	Me	73	65
4	**1d** (**B1**–**A4**)	Me	30	20
5	**1e** (**B2**–**A3**)	Me	22	−18[c]
6	**1f** (**B2**–**A4**)	Me	42	−55[c]
7	**1c** (**B1**–**A3**)	Bn	71	72
8	**1c** (**B1**–**A3**)	*p*-methoxybenzyl	41	61
9	**1c** (**B1**–**A3**)	*p*-nitrobenzyl (PNB)	59	82
10[d]	**1c** (**B1**–**A3**)	*p*-nitrobenzyl (PNB)	87	95
11[d,e]	**1c** (**B1**–**A3**)	*p*-nitrobenzyl (PNB)	98	95
12[e,f]	**1c** (**B1**–**A3**)	*p*-nitrobenzyl (PNB)	94	95

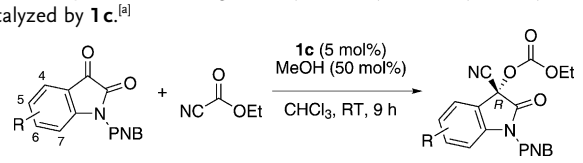
[a] Reaction conditions: N-protected isatin (0.50 mmol), EtOCOCN (1.1 equiv), **1** (10 mol%), CH_2Cl_2, ambient temperature, 48 h. [b] Yield of the isolated product. [c] The negative values indicate that the major enantiomer had the *S* configuration. [d] The reaction was conducted with EtOCOCN (2.2 equiv) in the presence of **1c** (5 mol%) in $CHCl_3$ for 6 h. [e] The reaction was conducted with MeOH (50 mol%). [f] The reaction was conducted on a 5 mmol scale with EtOCOCN (2.2 equiv) in the presence of **1c** (5 mol%) in $CHCl_3$ for 24 h. Bn = benzyl.

With this optimized catalyst in hand, we turned our focus to the protecting group of the amide group of isatin. We found that the use of a benzyl group improved the enantioselectivity (Table 1, entry 7). Interestingly, the use of a benzyl group substituted with an electron-donating methoxy group led to a decrease in enantioselectivity (Table 1, entry 8), whereas the introduction of an electron-withdrawing *p*-nitrobenzyl (PNB) substituent led to an increase in enantioselectivity, and the product was obtained with 82% *ee* (entry 9). During further optimization of the reaction conditions, we found that the use of chloroform as the solvent and 2.2 equivalents of ethyl cyanoformate improved both the reactivity and the enantioselectivity (87% yield, 95% *ee*; Table 1, entry 10). Furthermore, the addition of MeOH (50 mol%) improved the reactivity remarkably: the reaction reached completion in only 2 h under the optimized conditions (Table 1, entry 11). The results of ^{1}H NMR spectroscopic analysis suggested that catalyst **1c** largely existed as a less active oligomeric species in $CHCl_3$. The addition of MeOH might dissociate the oligomer to give the active monomer[11] and thus promote the reaction.

The protocol of the present reaction was very simple: the substrate, reagent, and catalyst were stirred together at ambient temperature in simple glassware. Thus, this reaction could be applied to a large-scale synthesis without any difficulties. When the reaction of *N*-PNB-protected isatin (1.4 g, 5 mmol) was conducted in the presence of **1c** (5 mol%) under the optimized reaction conditions, 1.8 g of the product was obtained (94% yield; Table 1, entry 12).[12]

Under the optimized reaction conditions, isatin derivatives bearing a variety of substituents were converted into the corresponding products in high yields with excellent enantioselectivity (Table 2). For example, isatin derivatives with electron-donating methyl, methoxy, and trifluoromethoxy groups and electron-withdrawing nitro, fluoro, chloro, bromo, and iodo groups at the 5-position were converted into the corresponding products in up to 98% yield with 88–98 *ee* (Table 2, entries 1–10). Furthermore, reactions of isatins bearing a bromine substituent proceeded with excellent enantioselectivity regardless of the position of the bromine substituent (Table 2, entries 10–13). The absolute configuration of the 5-brominated product was determined to be *R* by X-ray single-crystal analysis.[13,14]

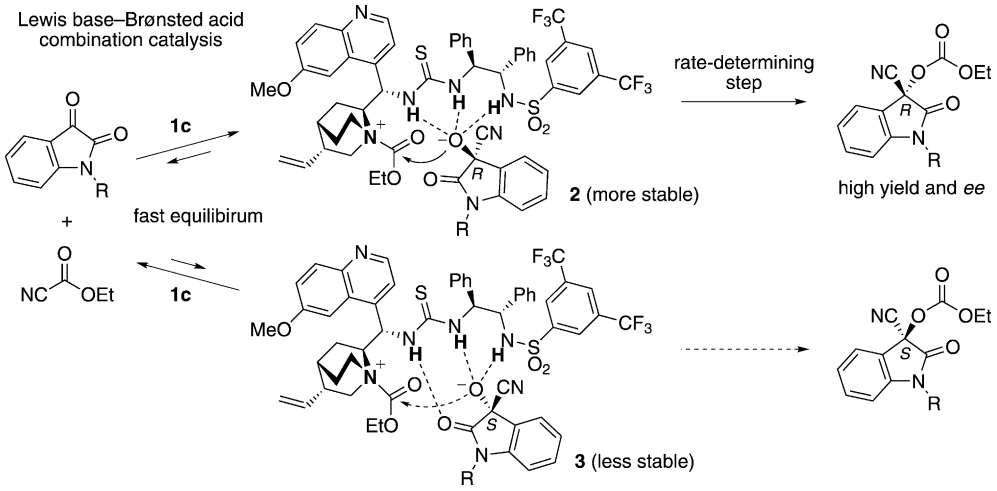
Table 2: Exploration of the generality of the cyanoethoxycarbonylation catalyzed by **1c**.[a]



Entry	R	Yield [%][b]	*ee* [%]
1	5-Me	96	95
2	5,7-Me_2	70	94
3	5-MeO	88	95
4	5,6-$(MeO)_2$	61	88
5	5-CF_3O	97	96
6	5-NO_2	85	98
7	5-F	96	96
8	5-Cl	97	97
9	5-I	94	97
10	5-Br	98	96
11	4-Br	96	99
12	6-Br	91	95
13	7-Br	87	94
14	5,7-Br_2	67	96
15	7-CF_3	94	95

[a] Reaction conditions: *N*-PNB-isatin (0.5 mmol), ethyl cyanoformate (2.0 equiv), **1c** (5 mol%), MeOH (50 mol%), $CHCl_3$ (2.5 mL), ambient temperature, 9 h. [b] Yield of the isolated product.

A proposed mechanism for the enantioselective cyanoethoxycarbonylation of isatins is shown in Scheme 2. The cyanoethoxycarbonylation is a two-step reaction: the first step is a reversible cyanation of the carbonyl group, and the second step is the irreversible acylation of the cyanohydrin alkoxide intermediate. Kinetic studies of the present **1c**-catalyzed cyanoethoxycarbonylation of isatins showed that the initial reaction rate did not depend on the concentration of the substrate or EtOCOCN.[14] Furthermore, the *ee* value of

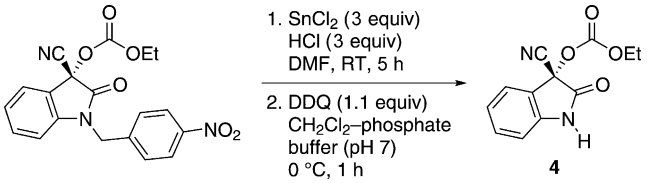


Scheme 2. Proposed mechanism for the **1c**-catalyzed cyanoethoxycarbonylation of isatins.

the product was completely independent of the conversion of the reaction.[14,15] These results suggested that the first cyanation step was a rapid equilibrium and the second acylation step was rate-determining.

Deng and Tian reported that asymmetric induction in the Lewis base catalyzed cyanoethoxycarbonylation of ketones arose from kinetic resolution of the cyanohydrin alkoxy anion intermediates through asymmetric acylation, since the *ee* values of the cyanohydrin intermediates were much lower than those of the cyanoethyoxycarbonylation products.[6] In contrast, in the present **1c**-catalyzed cyanoethoxycarbonylation of isatins, a theoretical calculation showed that ion pair **2** of the *R* alkoxy anion (Figure 1) was 3 kcal mol^{-1} more stable than ion pair **3** of the *S* alkoxy anion.[14,16] In ion pair **2**, the three acidic hydrogen atoms of **1c** act as an "oxyanion hole"[17,18] and stabilize the oxyanion through three hydrogen-bonding interactions. These results implied that asymmetric induction would arise not only from the kinetic resolution of the cyanohydrin alkoxy anion intermediate in the second step, but also from the cyanation of the isatin in the first step.[19] It is conceivable that when a Lewis base such as $(DHQ)_2AQN$ is used as a catalyst for the cyanoethoxycarbonylation of isatins, the first-step equilibrium greatly favors the starting materials, in contrast to the **1c**-catalyzed reaction, and that the $(DHQ)_2AQN$-catalyzed cyanoethoxycarbonylation of isatins showed poor reactivity for this reason (Scheme 1).

We next investigated the removal of the PNB group in the products. Since the carbonate moiety is rather unstable under strongly acidic and basic conditions, deprotection should be conducted under weakly acidic or basic conditions. Therefore, we attempted deprotection by DDQ oxidation, which is generally conducted under nearly neutral mild conditions. Since electron-deficient benzyl groups are less reactive toward oxidation with DDQ, we had to convert the electron-withdrawing nitro group into an electron-donating group to make the benzyl group electron-rich. We first selectively reduced the PNB nitro group with tin(II) chloride to an electron-donating amino group (Scheme 3). Subsequent DDQ oxidation of the electron-rich *p*-aminobenzyl group successfully gave the deprotected compound **4** in 78% yield.



Scheme 3. Removal of PNB protection. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide.

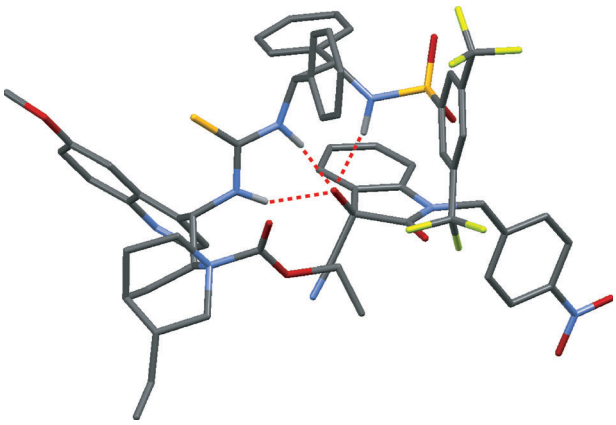
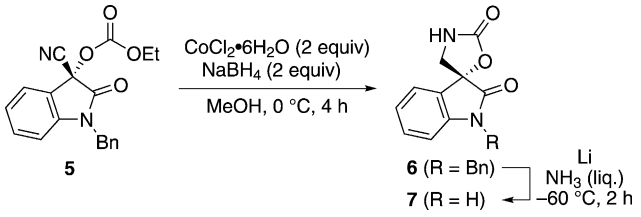


Figure 1. Optimized geometry (B3LYP/6-31G(d)) of ion pair **2** (R = PNB) of the *R* alkoxy anion intermediate.[21,22] Hydrogen atoms, except for those in the thiourea and sulfonamide groups, are omitted for clarity.

The spiro-fused compound **6** was obtained by the selective reduction of the cyano group of **5**, which was obtained from **4** by benzylation of the amide group (Scheme 4). Reduction of the cyano group with cobalt(II) chloride and sodium borohydride[20] gave the corresponding primary amine, which underwent simultaneous cyclization with the carbonate moiety to give cyclic carbamate **6** without any loss of optical purity. Removal of the benzyl group under Birch conditions gave **7** in 52% yield. Compound **7** is a promising chiral building block for the synthesis of various bioactive oxindoles.

In conclusion, we have developed the first enantioselective cyanoethoxycarbonylation of isatins by using the Lewis base–Brønsted acid cooperative catalyst **1c**. The Lewis basic site of **1c** caused nucleophilic activation of ethyl cyanoformate, and the Brønsted acidic, deep, and flexible cavity simultaneously stabilized and selectively recognized the *R*



Scheme 4. Synthesis of the spiro-fused compound **7**.

alkoxy anion intermediate to promote asymmetric acylation. Furthermore, the use of a *p*-nitrobenzyl protecting group successfully improved the enantioselectivity. The protocol was very simple, all the reagents could be used without purification, and the reaction could be readily applied to a large-scale synthesis without any difficulties.

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[12] The catalyst was recovered in 98% yield after flash column chromatography.

[13] CCDC 925315 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.

[14] See the Supporting Information for details.

[15] Deng and Tian also observed that the *ee* value of the product only depended slightly on the conversion in the Lewis base catalyzed cyanoethyoxycarbonylation of ketones.[6]

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[22] All optimized structures of complexes and calculation data are described in the Supporting Information.

