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Cinchona Alkaloid-Derived Thiourea-Catalyzed Diastereo- and Enantioselective [3+2] Cycloaddition Reaction of Isocyanoacetates to Isatins: A Facile Access to Optically Active Spirooxindole Oxazolines

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Abstract: An efficient diastereo- and enantioselective [3+2] cycloaddition reaction of α-aryl isocyanoacetates to isatins catalyzed by a quinine-derived bifunctional amine-thiourea-bearing sulfonamide as multiple hydrogen-bonding donor catalyst has been investigated. The corresponding adducts, which bear a spirocyclic quaternary stereocenter at the C-3 position of the oxindole, were obtained in good yields (51–95%), high diastereoselectivities (up to >20:1 *dr*) and good to excellent enantioselectivities (up to 97% *ee*).

Keywords: cycloaddition; isatins; isocyanoacetates; organocatalysis; spiro compounds; synthetic methods

The oxindoles bearing a spirocyclic quaternary stereocenter at the C-3 position have emerged as attractive synthetic targets due to their appealing architectural complexity and their prevalence in numerous natural products and important biological active molecules.[1,2] While several methods exist for the enantioselective synthesis of different class of spirooxindoles, relying on nucleophilic addition or annulation with alkylidene oxindoles or isatins as a prochiral electrophilic oxindole,[1] methods for the enantioselective synthesis of spirooxindole oxazolines are rare.[3] Recently, Wang and Yuan et al. have reported a convenient method for the synthesis of spirobrassinin oxazoline analogues using organocatalyzed aldol/cyclization of α-isothiocyanao amides with isatins[3a,b] or 3-isothiocyanatooxindoles with simple ketones[3c] followed by alkylation of the thiocarbamates, leading to 2′-alkylthio-substituted spirooxindole oxazoline derivatives (Figure 1, *left*). Herein, we report an efficient catalytic stereoselective method to access 2′-unsubstituted spirooxindole oxazolines with two adjacent quaternary stereocenters (Figure 1, *right*) from readily available α-isocyanoacetates **3** and isatins **2**.

Isocyanides were found to be irreplaceable building blocks for the synthesis of numerous important classes of nitrogen heterocyclic compounds by the virtue of the fact that the unique divalent features of the isocyano group enable isocyanides to react smoothly with both electrophiles and nucleophiles.[4] Furthermore, isocyanide-involving multicomponent and cascade reactions have recently been developed.[5] Isocyanoacetate **3**, which combines several potential reaction centers, such as an isocyano group, an acidic CH fragment and a protected carboxylic acid, have shown exceptional reaction diversity and broad syn-

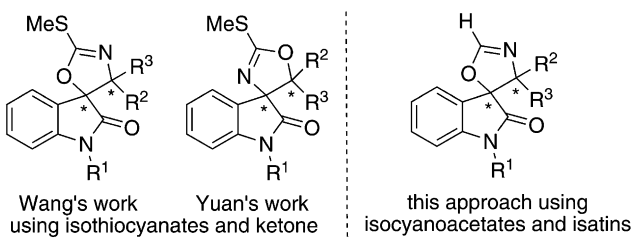


Figure 1. Enantioselective synthesis of spirooxindole oxazoline structures by different nucleophiles.

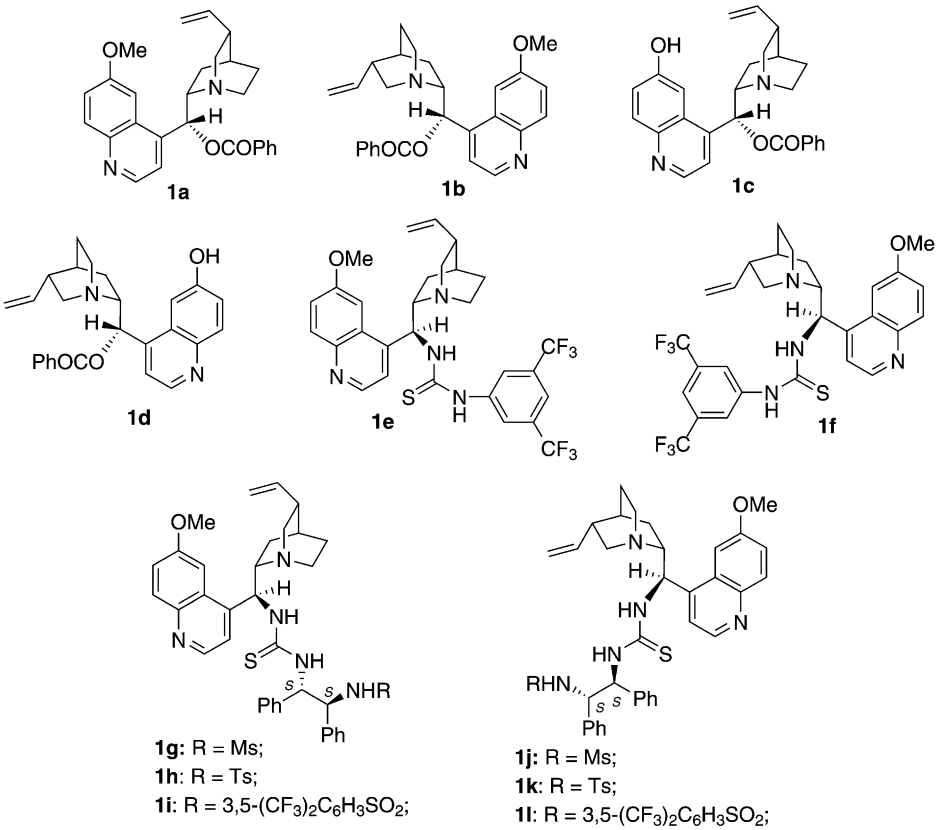


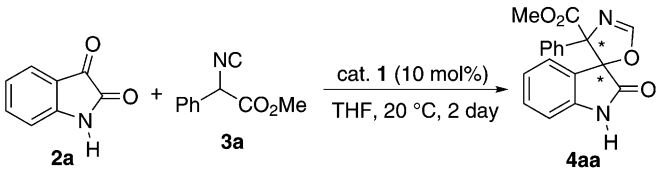
Figure 2. Catalysts screened.

thetic potential.[6] Stimulated by the pioneering works of Ito and Hayashi,[7] Gong[8] et al., organometallic or organo-catalyzed asymmetric additions between isocyanoacetates with many electrophiles, including nitroolefins,[8] aldehydes,[9] imines,[10] azodicarboxylates[11] and α,β-unsaturated carbonyl compounds,[12] have been intensively studied in recent years. In most cases, chiral cyclic compounds were obtained in good yields.

As a part of our ongoing interests in the asymmetric addition of isocyanoacetates, we have found that Ag(I)-*Cinchona* alkaloid squaramides cooperatively catalyzed the enantioselective formal [3+2] cycloaddition of isocyanoacetates to *N*-arylmaleimides.[12e] Considering that isatin derivatives have emerged as new electrophilic components for a variety of reactions due to their high electrophilicity and have been widely used in the synthesis of various spirooxindoles *via* addition and spirocyclization,[1a–c] we envisaged that the asymmetric addition of α-aryl isocyanoacetates with isatins could provide a facile access to optically active spirooxindoles with potential biological activity. To the best of our knowledge, there is no report on the organocatalyzed asymmetric addition of isocyanoacetates with isatin derivatives. Herein, we wish to report our initial results.

The addition reaction of isatin **2a** with isocyanoacetate **3a** in THF at room temperature was selected as our model reaction. A variety of *Cinchona* alkaloid-derived catalysts **1a–l** (Figure 2) was then tested in the model reaction and the results of these experiments are summarized in Table 1. *O*-Benzoyl-substituted *Cinchona* alkaloids, including BzQ (**1a**), BzQD (**1b**), *O*-Bz-cupreine (BzCPN, **1c**) and *O*-Bz-cupreidine (BzCPD, **1d**), are not suitable catalysts for this reaction, affording the corresponding product **4aa** in low yields along with low diastereoselectivities and enantioselectivities (Table 1, entries 1–4). Quinine- or quinidine-derived bifunctional tertiary amine-thiourea catalysts **1e** or **1f** gave much better results, higher yields with higher stereoselectivities (Table 1, entries 5 and 6). Further examination of *Cinchona* alkaloid-derived bifunctional amine-thiourea-bearing sulfonamides as multiple hydrogen-bonding donor catalysts **1g–l** revealed that quinine-derived catalyst **1g**, which has shown the best efficiency in the enantioselective Michael addition of 3-aryloxindoles to phenyl vinyl sulfone,[13] also exhibited higher catalytic activity in this reaction. The reaction proceeded smoothly in THF at room temperature to afford the desired adduct **4aa** in 75% yield, >20:1 *dr* along with 65% *ee* (Table 1, entry 7). Replacing the Ms group of **1g** with the sterically more bulky Ts and 3,5-$(CF_3)_2C_6H_3SO_2$

Table 1. Catalysts screening for enantioselective [3+2] cycloaddition reaction of isocyanoacetate **3a** to isatin **2a**.[a]



2a 3a 4aa

Entry	Catalyst **1**	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1a**	20	20:1	13
2	**1b**	41	2:1	16[e]
3	**1c**	19	3:1	13
4	**1d**	28	1:1	31[e]
5	**1e**	72	>20:1	47
6	**1f**	74	15:1	45
7	**1g**	75	>20:1	65
8	**1h**	71	20:1	60
9	**1i**	66	16:1	39
10	**1j**	71	>20:1	54[e]
11	**1k**	65	5:1	63[e]
12	**1l**	64	9:1	36[e]

[a] Unless noted otherwise, all reactions were carried out with isatin **2a** (0.24 mmol), isocyanoacetate **3a** (0.20 mmol) and catalyst **1** (10 mol%) in THF (1.0 mL) at 20 °C for 2 days.
[b] Yield of isolated product.
[c] The *dr* of the purified product was determined by ^{1}H NMR spectroscopy.
[d] The *ee* was determined by HPLC on a chiral stationary phase.
[e] The opposite enantiomer was obtained.

groups gave the desired product **4aa** in relatively lower yields as well as lower diastereoselectivities and enantioselectivities, presumably due to the steric hindrance of the hydrogen-bonding donor site of the catalysts **1h** and **1i** (Table 1, entries 8 and 9). These results suggest that the strength and steric hindrance of the hydrogen bonding donor may play important roles in the level of enantioselectivity. Quinidine-derived catalysts **1j–l** also promoted the reaction, but gave **4aa** with opposite absolute configuration in much lower *dr* and *ee* values than the corresponding quinine-derived catalysts **1g–i** (Table 1, entries 10-12 vs 7-9).

Solvent effects were then extensively studied. It was found that although the reaction of isatin **2a** with isocyanoacetate **3a** proceeded smoothly in a wide range of solvents, the *ee* values obtained varied dramatically (Table 2). Among the various solvents screened, good *dr* and *ee* values were observed in ether solvents (Table 2, entries 1–3). Diethyl ether was found to be the best solvent for this reaction, affording **4aa** in up to 89% yield, 9:1 *dr* and 72% *ee* (Table 2, entry 2). In less polar solvents such as ethyl acetate, chlorinated solvents and aromatic hydrocarbon solvents, the reactions proceeded smoothly,

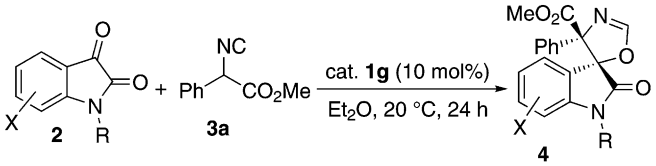
Table 2. Optimization of reaction conditions for the enantioselective [3+2] cycloaddition reaction of isocyanoacetate **3a** to isatin **2a** catalyzed by **1g**.[a]

Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	THF	20	48	75	>20:1	65
2	Et_2O	20	48	89	9:1	72
3	TBME	20	48	75	>20:1	52
4	EtOAc	20	48	70	10:1	56
5	DCM	20	48	81	18:1	37
6	$CHCl_3$	20	48	86	19:1	34
7	toluene	20	48	76	15:1	46
8	xylene	20	48	78	15:1	40
9	acetone	20	48	44	12:1	53
10	dioxane	20	48	80	5:1	52
11	CH_3CN	20	48	89	>20:1	44
12	MeOH	20	48	70	20:1	30
13[e]	Et_2O	20	10	63	13:1	70
14[f]	Et_2O	20	5	94	10:1	71
15[f,g]	Et_2O	20	1	96	>20:1	67
16[f,h]	Et_2O	20	2	87	>20:1	76
17[f,i]	Et_2O	20	24	93	>20:1	80
18[f,j]	Et_2O	20	36	88	>20:1	80
19[f,i]	Et_2O	0	55	75	4:1	70

[a] Unless noted otherwise, all reactions were carried out with isatin **2a** (0.24 mmol), isocyanoacetate **3a** (0.20 mmol) and catalyst **1g** (10 mol%) in solvent (1.0 mL).
[b] Yield of isolated product.
[c] The *dr* of the purified product was determined by ^{1}H NMR spectroscopy.
[d] The *ee* was determined by HPLC on a chiral stationary phase.
[e] The ratio of **2a/3a** was 2:1.
[f] The ratio of **2a/3a** was 1:2.
[g] 0.5 mL of Et_2O was used.
[h] 2.0 mL of Et_2O were used.
[i] 4.0 mL of Et_2O were used.
[j] 6.0 mL of Et_2O were used.

giving **4aa** in good yields with lower enantioselectivities (Table 2, entries 4–8). Other polar solvents gave poor results as well (Table 2, entries 9–12). Upon tuning the ratio of **2a**/**3a**, we found that the use of 2 equiv. of isocyanoacetate **3a** was necessary because decreasing the employed amount of **3a** led to a longer reaction time, lower yield and lower *ee* value (Table 2, entries 14 *vs.* 13 and 2). The examination of reactant concentration revealed that lowering the concentration could significantly improve the enantioselectivity of **4aa** without sacrificing the yield (Table 2, entries 15–18); the best enantioselectivity for **4aa** was obtained with a 0.05 M solution of isatin **2a** (Table 2, entry 17). The effect of temperature was also examined, and it was found that lowering the reaction temperature led to a decrease in enantioselectivity and yield (Table 2, entry 19). Thus, the optimal reaction conditions have been identified as carrying out the reaction with 1.0 equiv. of **2a** and 2.0 equiv. of **3a** in di-

Table 3. Substrate scope of isatin derivatives **2** for the enantioselective [3+2] cycloaddition reaction with isocyanoacetate **3a**.[a]



Entry	**2** [X, R]	**4**	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**2a** [H, H]	**4aa**	93	>20:1	80
2	**2b** [H, Bn]	**4ba**	74	12:1	86
3	**2c** [H, Me]	**4ca**	69	14:1	77
4	**2d** [H, Ph]	**4da**	95	20:1	70
5	**2e** [4-Cl, Bn]	**4ea**	71	5:1	95[e]
6	**2f** [4-Br, Bn]	**4fa**	95	2:1	93 (95)
7	**2g** [5-F, Bn]	**4ga**	95	>20:1	90
8	**2h** [5-Cl, Bn]	**4ha**	90	>20:1	88
9	**2i** [5-Br, Bn]	**4ia**	86	>20:1	80
10	**2j** [5-Me, Bn]	**4ja**	95	6:1	84
11	**2k** [5-OMe, Bn]	**4ka**	90	>20:1	73
12	**2l** [6-F, Bn]	**4la**	92	>20:1	82
13	**2m** [6-Cl, Bn]	**4ma**	88	>20:1	81
14	**2n** [6-OMe, Bn]	**4na**	90	>20:1	80
15[f]	**2o** [4-Cl, H]	**4oa**	82	15:1	97
16	**2p** [4-Br, H]	**4pa**	87	>20:1	94

[a] Unless noted otherwise, all reactions were carried out with isatins **2** (0.20 mmol), isocyanoacetate **3a** (0.40 mmol) and catalyst **1g** (10 mol%) in Et_2O (4.0 mL) at 20 °C for 24 h.
[b] Yield of isolated product.
[c] The *dr* of the purified product was determined by ^1H NMR spectroscopy.
[d] The *ee* was determined by HPLC on a chiral stationary phase; the value in parentheses is the *ee* of the minor isomer.
[e] Only for major isomer.
[f] For 48 h

ethyl ether (0.05 M for **2a**) at 20 °C using 10 mol% of **1g** as the catalyst.

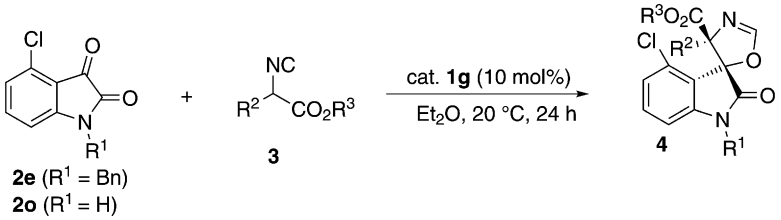
The substrate scope of isatin derivatives was then examined under the optimized reaction conditions and the results of these experiments are summarized in Table 3. In general, all of the isatin derivatives readily undergo this reaction to afford the desired adducts in moderate to high yields (69–95%) along with good to excellent stereoselectivities (up to >20:1 *dr*, 70–97% *ee*). The electronic and steric properties of the substituent on the nitrogen and the aromatic ring both played important roles in determining the reaction outcomes. Isatin **2a** and *N*-benzyl-substituted isatin **2b** gave much better results than the corresponding *N*-methyl- and *N*-phenyl-substituted isatins **2c** and **2d**; *N*-benzyl-substituted isatin **2b** afforded the best enantioselectivity (Table 3, entries 1–4). In the case of 4-substituted isatin derivatives **2e**, **2f**, **2o** and **2p**, the corresponding products **4ea**, **4fa**, **4oa** and **4pa** were obtained in good yields along with excellent enantioselectivities, albeit with lower diastereoselectivities for *N*-benzyl-substituted substrates **2e** and **2f** (Table 3, entries 5, 6, 15 and 16). Other isatin derivatives, whether bearing electron-withdrawing or electron-donating groups at the 5- or 6-positions, gave the desired products in moderate to good yields and stereoselectivities, albeit isatins with electron-withdrawing groups could give the corresponding products with much better results than those of the corresponding isatins with electron-donating groups (Table 3, entries 7–9 and 12–13 *vs.* entries 10, 11 and 14). It should be noted that 5-methoxyisatin (**2k**) led to an unexpected lower enantioselectivity than that of isatin **2a** (Table 3, entry 11).

The substrate scope of various α-substituted isocyanoacetates was also evaluated (Table 4). For *N*-benzyl-substituted isatin **2e**, isocyanoacetates with either an electron-withdrawing or electron-donating group at the *para* position of the aromatic ring gave their corresponding products in excellent yields and enantioselectivities, but with low diastereoselectivities (Table 4, entries 1 and 2). However, in the case of *N*-unsubstituted isatin **2o**, the substituents on phenyl ring have a great impact on the enantioselectivities. Isocyanoacetates bearing either an electron-withdrawing or electron-donating groups at *para*- or *meta*-positions afforded the desired products with good yields (up to 63–95%), excellent diastereoselectivities (up to >20:1 *dr*) and lower enantioselectivities (85–94% *ee*) than those of isocyanoacetate **3a** (Table 4, entries 3–9). A limitation was observed with an *ortho*-substituted aryl group, which showed no conversion (Table 4, entry 10). Variation on the ester moiety was then considered. Compared with methyl isocyanoacetate **3a**, *tert*-butyl and benzyl isocyanoacetate **3j** or **3k** reacted smoothly with isatin **2o** to afford the desired products in comparable yields and stereoselectivities, whereas **3j** gave the desired product in only moderate yield (Table 4, entries 11 and 12). The use of aliphatic isocyanoacetates such as α-benzyl and unsubstituted isocyanoacetates **3m** and **3n** was also successful, albeit with lower stereoselectivities. Using α-isopropyl isocyanoacetate **3l** as the reactant, no reaction occurred under the standard conditions (Table 4, entries 13–15).

The absolute and relative configurations of **4** were unambiguously assigned by X-ray crystallographic analysis of the optically pure compound **4pa**,[14] which was obtained by recrystallization from a mixture of dichloromethane and hexanes (Table 3, entry 16). The structure enabled the (3*R*,4′*S*) assignment of the newly formed stereogenic centers in **4pa** (Figure 3). The configurations of other adducts **4** were then assigned by analogy.

On the basis of the above results and commonly accepted mechanisms, a plausible transition-state model

Table 4. Substrate scope of isocyanoacetates **3** for the enantioselective [3+2] cycloaddition reaction with isatins **2e** or **2o**.[a]



Entry	2	3 [R^2, R^3]	4	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**2e**	**3c** [4-ClC_6H_4, Me]	**4ec**	94	7:1	95 (95)
2	**2e**	**3e** [4-MeC_6H_4, Me]	**4ee**	95	3:1	96 (97)
3	**2o**	**3b** [4-FC_6H_4, Me]	**4ob**	90	>20:1	94
4	**2o**	**3c** [4-ClC_6H_4, Me]	**4oc**	88	>20:1	92
5	**2o**	**3d** [4-BrC_6H_4, Me]	**4od**	90	>20:1	92
6	**2o**	**3e** [4-MeC_6H_4, Me]	**4oe**	95	>20:1	91
7[e]	**2o**	**3f** [4-$MeOC_6H_4$, Me]	**4of**	95	>20:1	85
8	**2o**	**3g** [3-FC_6H_4, Me]	**4og**	93	>20:1	92
9	**2o**	**3h** [3-MeC_6H_4, Me]	**4oh**	63	>20:1	91
10	**2o**	**3i** [2-MeC_6H_4, Me]	**4oi**	–	–	n.d.
11[f]	**2o**	**3j** [Ph, *t*-Bu]	**4oj**	51	>20:1	85
12[e]	**2o**	**3k** [Ph, Bn]	**4ok**	80	15:1	91
13	**2o**	**3l** [*i*-Pr, Me]	**4ol**	–	–	n.d.
14[g]	**2o**	**3m** [Bn, Me]	**4om**	92	>20:1	80
15	**2o**	**3n** [H, Et]	**4on**	87	2:1	27 (36)

[a] Unless noted otherwise, all reactions were carried out with isatins **2** (0.20 mmol), isocyanoacetates **3** (0.40 mmol) and catalyst **1g** (10 mol%) in Et_2O (4.0 mL) at 20 °C for 24 h.
[b] Yield of isolated product.
[c] The *dr* of the purified product was determined by ^1H NMR spectroscopy.
[d] The *ee* was determined by HPLC on a chiral stationary phase; the data in parentheses are the *ee* values for the minor isomers.
[e] For 48 h.
[f] For 168 h.
[g] For 96 h.

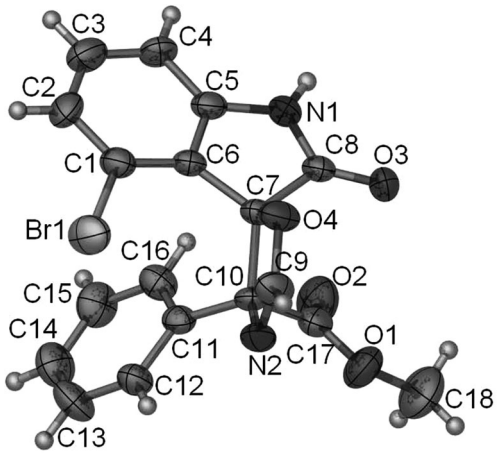
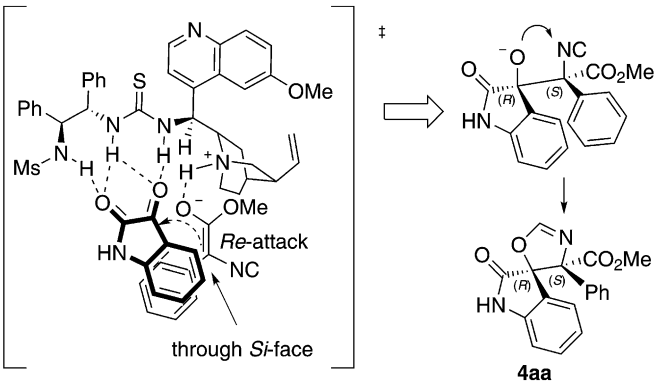


Figure 3. ORTEP drawing of **4pa**.

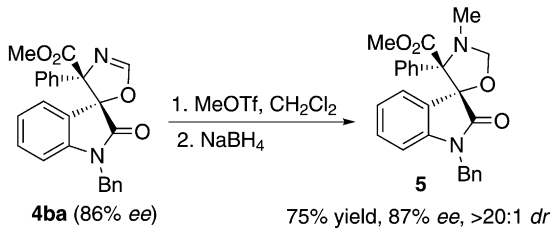


Scheme 1. Proposed transition state model.

is proposed as shown in Scheme 1. The isocyanoacetate is deprotonated by the quinuclidine nitrogen of catalyst **1g**, resulting in a single H-bonding interaction between the OH group of the enolized isocyanoacetate and the tertiary amine. Simultaneously, hydrogen bonds are formed between the two carbonyl groups of isatin and the multi-hydrogen bonding donor thiourea moiety of the catalyst to activate the carbonyl group toward enolate attack and direct the orientation of isatin. Additionally, the π–π stacking interac-

tion between the phenyl group of isocyanoacetate and the isatin moiety might be formed concurrently, which enables the enolized isocyanoacetate to attack much more easily the isatin from the *Re*-face, leading to the formation of two newly generated stereocenters with (3*R*,4′*S*)-configuration. Subsequently, a *5-endo-dig* cyclization would take place by an intramolecular reaction between the hydroxy group of the resulting aldol intermediate and the isocyano group to afford the observed spirocyclic product **4aa**.

To further explore the synthetic utility of the [3+2] cycloaddition products **4**, we next explored their transformation to the corresponding amino acid derivatives by hydrolysis or reduction with oxazolines.[9] However, an isatin rather than an amino acid derivative was obtained due to the decomposition of adduct, probably owing to the instability of spirooxazoline in the presence of various acids and reductive reagents.[15] However, spirooxindole oxazolidine **5** can be obtained from adduct **4ba** by Meyers *N*-methylation–reduction procedure (MeOTf-$NaBH_4$) in high yield and without influencing the enantioselectivity (Scheme 2).[16]



Scheme 2. Synthetic transformation of cycloaddition adduct **4ba**.

In conclusion, we have developed an efficient diastereo- and enantioselective [3+2] cycloaddition reaction of α-aryl isocyanoacetates to isatins catalyzed by a quinine-derived bifunctional amine-thiourea-bearing multiple hydrogen-bonding donor catalyst. A wide variety of substituted isatins and α-aryl isocyanoacetates, with different electronic and steric properties, was tolerated in this catalytic enantioselective [3+2] cycloaddition reaction, leading to optically active 2-oxo-4′*H*-spiro[indoline-3,5′-oxazole] derivatives in high yields (51–95%) along with good to excellent diastereo- and enantioselectivities (up to >20:1 *dr*, up to 97% *ee*). Investigations aimed at fully understanding the reaction mechanism and developing more effective addition reactions of isocyanoacetates with other electrophiles are ongoing.

Experimental Section

General Procedure for the Enantioselective [3+2] Cycloaddition Reaction of Isocyanoacetates 3 with Isatins 2 under the Catalysis of 1g

To the solution of isatin **2** (0.2 mmol) and catalyst **1g** (0.02 mmol) in diethyl ether (4.0 mL) was added isocyanoacetate **3** (0.4 mmol) at 20 °C. The resulting mixture was stirred at 20 °C for 1–7 days until the reaction completed (monitored by TLC). After concentration, the residue was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1–4:1 or dichloromethane/ethyl acetate = 10:1 as eluent) to furnish the corresponding cycloaddition product **4**.

(3*R*,4′*S*)-Methyl 2-oxo-4′-phenyl-4′*H*-spiro[indoline-3, 5′-oxazole]-4′-carboxylate (4aa): Yield: 59.8 mg (93%); >20:1 *dr*; white solid; mp 89.3–93.2 °C; $[\alpha]_D^{25}$: −31.9 (*c* = 0.5, CH_2Cl_2) (80% *ee*); HPLC (Chiralpak AD-H, hexane/2-propanol = 80/20, 0.9 mL min^{-1}, 254 nm): t_{major} = 16.68 min, t_{minor} = 31.01 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1H), 7.54 (s, 1H), 7.33–7.27 (m, 5H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.58 (t, *J* = 7.6 Hz, 1H), 5.68 (d, *J* = 7.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 170.8, 155.5, 142.6, 134.5, 131.0, 128.8, 128.1, 127.2, 127.0, 122.7, 122.0, 110.6, 88.3, 85.6, 53.3; IR (film): ν = 3288, 1751, 1645, 1616, 1590, 1449, 1251, 1179, 1095, 1014 cm^{-1}; MS (EI): *m*/*z* = 322 (M^+, 21%), 279 (13), 175 (100), 148 (93), 104 (60), 77 (18); HR-MS (EI); *m*/*z* = 322.0956, calcd. for $C_{18}H_{14}N_2O_4$ (M^+): 322.0954.

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[15] Isatin was obtained in low yields when treating the adduct **4** with $SOCl_2$-MeOH, HCl-MeOH, silica gel, wet chloroform, etc. Moreover, a complex reaction mixture was obtained in the presence of $LiAlH_4$ or Pd/C.

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