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Cinchona Alkaloid Thiourea Mediated Asymmetric Mannich Reaction of Isocyanoacetates with Isatin-Derived Ketimines and Subsequent Cyclization: Enantioselective Synthesis of Spirooxindole Imidazolines

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Mei-Xin Zhao,*[a,b] Lei Jing,[a] Hao Zhou[a] and Min Shi[a,c]

We report the organocatalyzed asymmetric Mannich reaction of isocyanoacetates with isatin derived ketimines in good yields along with high stereoselectivities. The subsequent organocatalyzed cyclization of Mannich adducts is also investigated, emerging as a promising strategy for the synthesis of optically active spirooxindole imidazolines.

Introduction

Spirooxindoles have emerged as attractive synthetic targets given their appealing architectural complexity and their prevalence in many natural products and biological active molecules.[1,2] Consequently, many efficient organocascade strategies have been developed to build these structural motifs by using unsaturated oxindole derivatives, such as methyleneoxindole, isatin or isatinimine, 3-substituted oxindole or 3-unsubstituted oxindole with bis-nucleophilic center as substrates via addition-cyclization sequence over the last decade.[3] However, most studies focused on the catalytic asymmetric synthesis of spirooxindoles bearing an all carbon quaternary stereocenter at the C3-position of the oxindoles, such as spirocycloalkaneoxindole[4] and spiro[pyrrolidin-3,3'-oxindole],[5] the enantioselective synthesis of spiro[imidazolidin-4,3'-oxindole] which bearing a spiro imidazoline at the C3 position of the oxindoles was met with only limited success,[6] despite these motifs are found in many medicinally important compounds (Figure 1), such as a CRTH2 antagonist,[7] and tumour suppressor p53 with its negative regulator Hdm2 interaction inhibitor.[8] Thus, the development of highly enantioselective synthetic method for optically active spiro[imidazolidin-4,3'-oxindole] compounds is still very necessary.

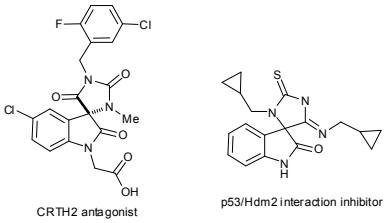


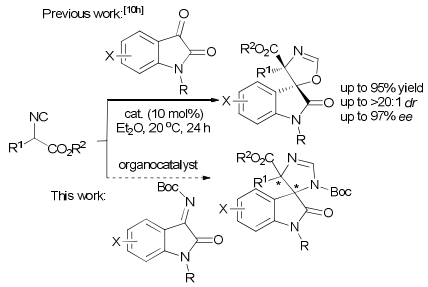
Figure 1. Examples of biologically active spirooxindole imidazolines

α-Isocyanoacetates are well-known irreplaceable building blocks for the synthesis of numerous important classes of nitrogen heterocyclic compounds by the organometallic- or organo-catalyzed asymmetric [3+2] cycloadditions with many electrophiles,[9] such as carbonyl compounds,[10] imines,[11] azodicarboxylates,[12] nitroolefins,[13] and α, β-unsaturated carbonyl compounds.[14] Among them, the catalytic asymmetric Mannich-type reaction of isocyanoacetates with imines, as a promising strategy for the synthesis of optically active imidazolines, had been received much attentions.[11] Although there are a few examples on the organometallic catalyzed asymmetric Mannich-type reaction of isocyanoacetates with ketimines very recently[11f,h] and we also reported that squaramide/Ag(I) cooperatively catalyzed asymmetric Mannich /cyclization cascade reaction of isocyanoacetates with cyclic trifluoromethyl ketimines,[11i] however, to the best of our knowledge, there is no report on the organocatalyzed Mannich-type reaction of isocyanoacetates with ketimines probably due to the lower reactivity of ketimines. As a part of our ongoing interests in the asymmetric addition of isocyanoacetates,[10h,11i,12c,14d,15] we have developed an efficient organocatalyzed diastereo- and enantioselective [3+2] cycloaddition reaction of α-aryl isocyanoacetates with isatins in good yields, high diastereoselectivities, and excellent enantioselectivities (Scheme 1).[10h] Considering that isatin derived ketimines are more reactive ketimines and had been

[a] *Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Mei Long Road, Shanghai, 200237, P. R. China. Fax: +86-21-34201699; E-mail: mxzhao@ecust.edu.cn.*
[b] *CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. China.*
[c] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China.*

† Electronic Supplementary Information (ESI) available: [General experimental procedure and characterization data of the products. Copies of NMR spectra and HPLC analysis spectra of compounds **4** and **5**, X-ray structural data (CIF) of compound **4p** (CCDC 1047214) and **5g** (1021346).]. See DOI: 10.1039/x0xx00000x

widely used in many enantioselective reactions for the synthesis of various enantioenriched isatin derived compounds,[16] we envisioned that the organocatalyzed Mannich-type reaction of isocyanoacetates and isatin derived ketimines will provide a facile protocol for the asymmetric construction of optically active spirooxindole imidazolines (Scheme 1). Herein, we wish to report our initial results.



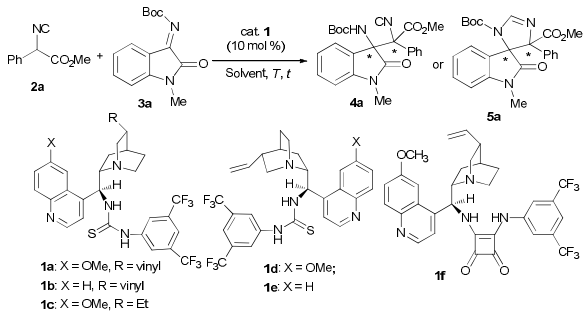
Scheme 1. Catalytic asymmetric synthesis of spirooxindoles from isocyanoacetates

Results and discussion

We began our studies by examining the reaction of isocyanoacetate **2a** with *N*-Boc isatinimine **3a** in the presence of quinine- or quinidine-derived thioureas **1a** and **1d** in THF at room temperature. Although the reaction proceed smoothly to give the corresponding spirooxindole imidazoline **5a** in high yields, but with low diastereo- and enantioselectivities (Table 1, entries 1 and 2). Interestingly, using cat. **1a** as catalyst, this organocatalyzed cascade Mannich/cyclization reaction can be stopped at the Mannich adduct stage by lowering the temperature to -15 °C, Mannich adduct **4a** rather than expected cyclization product **5a** was obtained as major product in high yield and excellent diastereoselectivity, albeit with moderate *ee* value (Table 1, entry 3). Encouraged by this result, a series of cinchona alkaloid derived thioureas **1b-e** and squaramide **1f** were then examined in this Mannich reaction and the results were summarized in Table 1 (Table 1, entries 4-8). Among the screened catalysts, quinidine-derived thiourea **1d** was the best for this reaction, affording Mannich product **4a** in 84% yield, >20:1 *dr* and up to 63% ee (Table 1, entry 6).

The solvent effect was next examined, and it was found that the choice of solvent impacted the enantioselectivity only, and chloroform was the most suitable one for this reaction (Table 1, entries 9-15). Further examination the temperature effect revealed that further lowering or elevating the reaction temperature led to a decrease in enantioselectivity or yield, respectively (Table 2, entries 16 and 17). Concerning both the yield and *ee* value, performing the reaction at -15 °C was the optimal choice. Additionally, increasing the reactant concentration could improve the enantioselectivity of **4a** without sacrificing the yield (Table 2, entries 18 and 19); the best enantioselectivity for **4a** was obtained in 0.4 M solution of isatin imine **3a**. It should be noted that a lower catalyst loading led to a significant decrease in both yield and enantioselectivity (Table 1, entry 20).

Table 1. Screening of the reaction conditions[a]



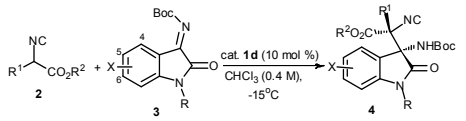
Entry	Cat.	solvent	*T* (ºC)	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**1a**	THF	25	**5a**, 99	1.4:1	40/48
2	**1d**	THF	25	**5a**, 99	1.2:1	-48/-44
3	**1a**	THF	-15	**4a**, 95	>20:1	50
4	**1b**	THF	-15	**4a**, 89	>20:1	43
5	**1c**	THF	-15	**4a**, 87	>20:1	55
6	**1d**	THF	-15	**4a**, 84	>20:1	-63
7	**1e**	THF	-15	**4a**, 96	>20:1	-55
8	**1f**	THF	-15	**4a**, 75	>20:1	20
9	**1d**	Et_2O	-15	**4a**, 90	>20:1	-71
10	**1d**	toluene	-15	**4a**, 85	>20:1	-73
11	**1d**	CH_2Cl_2	-15	**4a**, 77	>20:1	-83
12	**1d**	$CHCl_3$	-15	**4a**, 80	>20:1	-89
13	**1d**	$ClCH_2CH_2Cl$	-15	**4a**, 95	>20:1	-81
14	**1d**	CH_3CN	-15	**4a**, 89	>20:1	-42
15	**1d**	CH_3OH	-15	**4a**, 99	>20:1	-55
16[e]	**1d**	$CHCl_3$	-30	**4a**, 93	>20:1	-82
17	**1d**	$CHCl_3$	0	**4a**, 35	>20:1	-98
18[f]	**1d**	$CHCl_3$	-15	**4a**, 87	>20:1	-92
19[g]	**1d**	$CHCl_3$	-15	**4a**, 85	>20:1	-73
20[f,h]	**1d**	$CHCl_3$	-15	**4a**, 54	>20:1	-87

[a] All reactions were carried out with isocyanoacetate **2a** (0.30 mmol), imine **3a** (0.20 mmol) and catalyst **1** (10 mol%) in solvent (1.0 mL) for 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of purified product. [d] Determined by chiral HPLC analysis. [e] 48h. [f] 0.5 mL of $CHCl_3$. [g] 2.0 mL of $CHCl_3$. [h] 5 mol% of cat. **1d**

Having established the optimal reaction conditions for this Mannich reaction, we surveyed the scope of the reaction by varying the structure of isocyanoacetates **2** and isatinimines **3**. First, the substrate scope of isocyanoacetates was examined by varying the aryl substituent and ester moiety. The presence of electron-withdrawing and electron-donating substituents at the *para* and *meta* position of the phenyl ring is tolerated (Table 2, entries 2-8). However, those bearing an electron-withdrawing substituent (Table 2, entries 2-4 and 7) afford, in general, the Mannich adducts with a higher *ee* value than those having electron-donating group (Table 2, entries 5, 6 and 8). The benzyl and *tert*-butyl α-phenyl isocyanoacetates **2j-k** participated in the reaction efficiently to provide adducts **4j-k** in good yields and stereoselectivities (Table 2, entries 10 and 11). Limitation was observed with *ortho*-substituted aryl isocyanoacetate and α-alkyl substituted isocyanoacetate, which showed no conversion (Table 2, entries 9 and 12).

The substrate scope of isatin ketimines was also evaluated. In general, all of the *N*-Me substituted isatin ketimines, whether bearing electron-withdrawing or electron-donating group at the 4-, 5- or 6-position, readily undergo this reaction

Table 2. Substrate scope[a]



3a: X = H, R = Me; **3b**: X = 4-Cl, R = Me; **3c**: R^1 = 5-F, R = Me; **3d**: X = 5-Cl, R = Me; **3e**: X = 5-Br, R = Me; **3f**: X = 5-Me, R = Me; **3g**: X = 5-MeO, R = Me; **3h**: X = 6-Cl, R = Me; **3i**: X = 6-MeO, R = Me; **3j**: X = H, R = allyl; **3k**: X = H, R = Bn; **3l**: X = H, R = PMB; **3m**: X = H, R = Ph; **3n**: X = H, R = H.

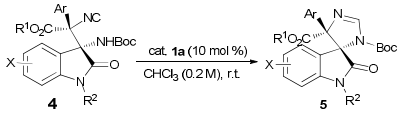
Entry	**2** (R^1, R^2)	**3**	**4**, Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**2a** (Ph, Me)	**3a**	**4a**, 87	>20:1	92
2	**2b** (4-FC_6H_4, Me)	**3a**	**4b**, 76	>20:1	98
3	**2c** (4-ClC_6H_4, Me)	**3a**	**4c**, 48(75)[e]	>20:1	96(90)[e]
4	**2d** (4-BrC_6H_4, Me)	**3a**	**4d**, 25(71)[f]	>20:1	97(90)[f]
5	**2e** (4-MeC_6H_4, Me)	**3a**	**4e**, 83	>20:1	88
6	**2f** (4-$MeOC_6H_4$, Me)	**3a**	**4f**, 90(75)[g]	>20:1	81(86)[g]
7	**2g** (3-FC_6H_4, Me)	**3a**	**4g**, 38(51)[h]	>20:1	97(95)[h]
8	**2h** (3-MeC_6H_4, Me)	**3a**	**4h**, 84	>20:1	87
9	**2i** (2-BrC_6H_4, Me)	**3a**	**4i**, n.r.	n.d.	n.d.
10	**2j** (Ph, t-Bu)	**3a**	**4j**, 93	>20:1	93
11	**2k** (Ph, Bn)	**3a**	**4k**, 70	>20:1	87
12	**2l** (Bn, Me)	**3a**	**4l**, n.r.	n.d.	n.d.
13	**2a** (Ph, Me)	**3b**	**4m**, 65	>20:1	85
14	**2a** (Ph, Me)	**3c**	**4n**, 74	>20:1	90
15	**2a** (Ph, Me)	**3d**	**4o**, 55	>20:1	90
16	**2a** (Ph, Me)	**3e**	**4p**, 47(65)[h]	>20:1	95(92)[h]
17	**2a** (Ph, Me)	**3f**	**4q**, 90	>20:1	93
18	**2a** (Ph, Me)	**3g**	**4r**, 82(73)[g]	>20:1	83(92)[g]
19	**2a** (Ph, Me)	**3h**	**4s**, 65	>20:1	90
20	**2a** (Ph, Me)	**3i**	**4t**, 83	>20:1	82
21	**2a** (Ph, Me)	**3j**	**4u**, 84	>20:1	83
22	**2a** (Ph, Me)	**3k**	**4v**, 57	>20:1	74
23	**2a** (Ph, Me)	**3l**	**4w**, 80	>20:1	69
24	**2a** (Ph, Me)	**3m**	**4x**, 90	>20:1	95
25	**2a** (Ph, Me)	**3n**	**4y**, n.r.	n.d.	n.d.

[a] All reactions were carried out with isocyanoacetate **2** (0.30 mmol), imine **3** (0.20 mmol) and cat. **1d** (10 mol%) in $CHCl_3$ (0.5 mL) at -15ºC for 24 h. Data in parenthesis were the results in different reaction time. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of purified product. [d] Determined by chiral HPLC analysis. [e] 4h. [f] 8h. [g] 32h. [h] 16h.

to afford the desired adducts in moderate to high yields along with good stereoselectivities (up to >20:1 *dr*, 83-93% *ee*), albeit isatinimines with electron-withdrawing or weak electron-donating groups could give the corresponding adducts in much better results than those of imines with strong electron-donating groups (Table 2, entries 13-17 and 19 *vs* entries 18 and 20). The electronic properties of the substituent on the nitrogen also played important roles in determining the reaction outcomes. *N*-Me and *N*-phenyl substi- tuted isatinimines **3a** and **3m** gave much better results than the corresponding *N*-allyl, *N*-Bn and *N*-PMB substituted isatinimines **3j-l**; Using *N*-H substituted isatinimine **3n** as the reactant, no reaction occurred under the standard conditions (Table 2, entries 21-25).

Furthermore, we interestingly found that moderate yields along with excellent enantioselectivities were obtained for some more reactive substrates bearing electron-withdrawing groups, accompanying with some cyclization products **5** generation; Whereas high yields and good *ee* value were

Table 3. Quinine derived thiourea **1a** catalyzed cyclization of adducts **4**



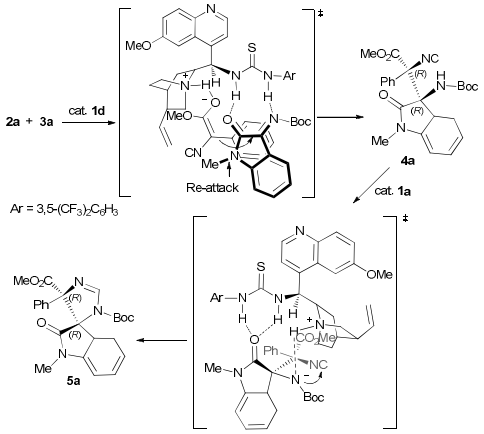
Entry	**4** (X, Ar, R^1, R^2) (*ee* %)	*t* (h)	**5**	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	**4a** (H, Ph, Me, Me) (92)	8	**5a**	95	>20:1	92
2	**4b** (H, 4-FC_6H_4, Me, Me) (98)	8	**5b**	89	>20:1	97
3	**4d** (H, 4-BrC_6H_4, Me, Me) (90)	24	**5c**	87	>20:1	90
4	**4g** (H, 3-FC_6H_4, Me, Me) (95)	8	**5d**	76	>20:1	93
5	**4h** (H, 3-MeC_6H_4, Me, Me) (87)	8	**5e**	86	>20:1	90
6	**4j** (H, Ph, t-Bu, Me) (93)	8	**5f**	68	>20:1	95
7	**4p** (5-Br, Ph, Me, Me) (92)	8	**5g**	89	>20:1	92
8	**4x** (H, Ph, Me, Ph) (95)	8	**5h**	99	>20:1	95

[a] All reactions were carried out with Mannich adduct **4** (0.1 mmol) and cat. **1a** (10 mol%) in $CHCl_3$ (0.5 mL) at r.t. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of purified product. [d] Determined by chiral HPLC analysis

obtained for the substrates bearing electron-donating groups under the optimized reaction conditions (Table 2, entries 3, 4, 7 and 16 vs 6 and 18). We postulated that quinidine-derived thiourea **1d** can preferentially promote the minor adduct *ent*-**4** to undergo further cyclization and a highly efficient cyclization reaction could be developed by exploring the chirality match relationship between the Mannich adduct and organocatalysts. Thus, we became interested in examining the organocatalyzed cyclization of Mannich adducts **4** for the synthesis of enantiomerically enriched spirooxindole imidazolines **5** (for details, see the Supporting Information Table S1). Eventually, we identified that quinine derived thiourea **1a** is the optimal catalyst for the cyclization of adduct **4a**, affording **5a** in 95% yield with the retention of *ee* value at room temperature for 8h (Table 3, entry 1). Other Mannich adducts **4**, whether bearing electron-withdrawing or electron-donating substituents on the phenyl ring of the isocyanoacetates and ketimines, all gave the corresponding spirooxindole imidazolines **5** in high yields and without loss of enantioselectivities (Table 3, entries 2-8).

The relative and absolute configurations of the major diastereomers of **4p** and **5g** were assigned as (*R,R*) by single crystal X-ray analysis[17] (see Figure S1 and S2 in the SI), and the other products were deduced by an analogue assuming a common reaction pathway. The stereochemical outcome of the asymmetric Mannich reaction catalyzed by **1d** and the subsequent cyclization catalyzed by **1a** could be rationalized by a proposed transition-state model (Scheme 2). The isocyanoacetate was deprotonated by the quinuclidine nitrogen of catalyst **1d** and holds it in close proximity through coordination, while the thiourea moiety binds and activates the ketimine through hydrogen bonds, which make the enolic isocyanoacetate much more easily attack the isatin ketimine from the *Re*-face and lead to formation of two newly generated stereocenters with (*R, R*)-configuration. Additionally, a *5-endo-dig* cyclization would take place by an intramolecular reaction between the deprotonated amino group and the

isocyano group with the assistance of cat. **1a** to afford the observed spirocyclic product **5a**.



Scheme 2. Proposed transition-state model

Conclusions

In conclusion, we have developed cinchona alkaloid thiourea catalyzed highly diastereo- and enantioselective Mannich reaction of α-aryl isocyanoacetates with isatin derived ketimines and subsequent cyclization for the synthesis of enantiomerically enriched 3,3-disubstituted oxindoles **4** and spirooxindole imidazolines **5**. A wide variety of α-aryl isocyanoacetates and isatinimins, with different electronic and steric properties, were tolerated in these reactions, leading to the corresponding Mannich adducts **4** and spirooxindole imidazoline derivatives **5** in good yields along with good to excellent stereoselectivities (up to >20:1 *dr*, up tp 98% *ee*). Investigations on developing more effective addition reactions of isocyanoacetates with other electrophiles are ongoing.

Acknowledgements

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17 CCDC 1047214 (for **4p**) and CCDC 1021346 (for **5g**) contain 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.