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# Enantioselective Organocatalyzed Direct α-Thiocyanation of Cyclic β-Ketoesters by *N*-Thiocyanatophthalimide

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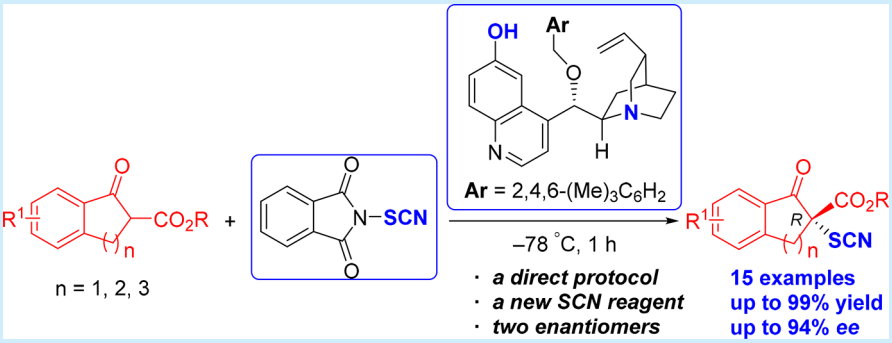
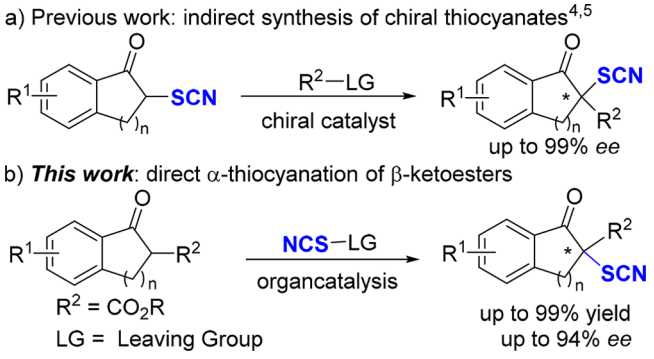
Supporting Information




**ABSTRACT:** A new electrophilic thiocyanation reagent, *N*-thiocyanatophthalimide, was synthesized and applied to the first example of catalytic asymmetric electrophilic α-thiocyanation of various cyclic β-ketoesters by the bifunctional cinchona alkaloid catalysis. Thus, a variety of chiral α-thiocyanato β-ketoesters with a quaternary carbon center have been achieved in excellent yields (up to 99%) and high enantioselectivities (up to 94% *ee*) in a convenient manner.

In recent decades, the development of significant strategies for the establishment of C−SCN bonds has recently received attention due to the fact that organic thiocyanates not only are efficient synthetic precursors to transform into diverse valuable sulfur-containing compounds, such as $-SCF_3$, $SCF_2H$ and thiotetrazole, but also have important functionality in natural marine sponges and alkaloids.[1] Tremendous effort has been devoted to developing the formation of C($sp^2$)−SCN and C($sp^3$)−SCN bonds by nucleophilic thiocyanate sources with different oxidants[2] or via the formation of a thiocyano radical.[3] For the asymmetric version, chiral quaternary α-cyanatoketones were prepared by the asymmetric Mannich reaction of thiocyanato-preassembled substrates (Scheme 1a).[4]

**Scheme 1. Asymmetric Synthesis of Thiocyanates**




Meanwhile, there have been few reports on the direct oxidative α-thiocyanation reactions[5a−d] or biomimetic SCN transfer,[5e,f] and the asymmetric ring-opening thiocyanation of epoxides to form a C($sp^3$)−SCN bond.[6a−c] To the best of our knowledge, there is only one example of asymmetric electrophilic α-thiocyanation by Evans' protocol.[7] Moreover, our group has been committed to the methodology to synthesize cyano-containing chemicals.[8] Herein, we report the effectively catalytic enantioselective α-thiocyanation of cyclic β-ketoesters using the cinchona alkaloid analogue catalyst (Scheme 1b) within 1 h.

In view of the direct thiocyanation reaction, only a few electrophilic thiocyanation reagents with high toxicity have been studied, such as thiocyanogen $(SCN)_2$[9] and thiocyanogen chloride (ClSCN).[10] Besides, *N*-thiocyanatosuccinimide (**1a**) was used in the electrophilic addition and substitution reactions leading to thiocyanates,[7] while the formation of thioperoxide species using a benziodoxole scaffold (**1b**) was initially disclosed by Buchwald.[11] In pursuit of the direct thiocyanation, a new reagent, *N*-thiocyanatophthalimide (**1c**), was prepared as a stable white solid by *N*-chlorophthalimide and CuSCN (Figure 1).[12]

With the electrophilic thiocyanating reagent **1c** in hand, indanone-derived β-ketoester **2a** was selected as the substrate to develop the catalytic enantioselective thiocyanation reaction. Initially, we carried out the asymmetric α-thiocyanation by

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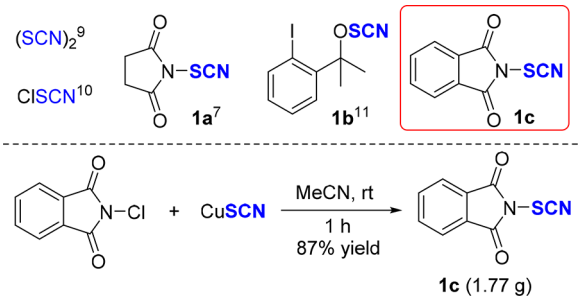



**Figure 1.** Electrophilic thiocyanation reagents.

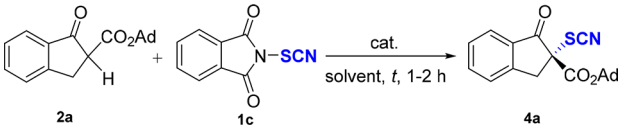
Lewis acid catalysis which was successful in the asymmetric electrophilic $\alpha$-cyanation of $\beta$-ketoesters in our previous studies.[8b,c] However, low enantioselectivities were obtained after a preliminary screening (see Scheme S1, Supporting Information (SI)). Considering the possible high activity of the electrophilic thiocyanating reagents,[8e] we moved to the organocatalysis by using the cinchona alkaloid derivatives.

Thus, cinchona alkaloid-derived catalysts **3a**–**k** were prepared and estimated at 0 °C by the model reaction between 1-adamantyl $\beta$-ketoester (**2a**) and thiocyanating reagent **1c**. Among the four naturally existing alkoloids, quinidine (**3d**) showed better catalytic performance (95% yield, −41% *ee* (Table 1, entry 4 vs entries 1−3). With protection of the $C_9$−OH by benzyl, **3f** lost its chiral inductivity (Table 1, entry 6 vs entry 4) while by deprotection of $C_{6'}$-OMe **3e** retained the chiral induction capacity giving improved enantioselectivity, 61% *ee*, with the opposite enantiomer as the major product (Table 1, entry 5 vs 6), indicating the crucial role of the OH group in the catalyst structure for high enantioselectivity. From intensive comparison of the results for **3d** and **3e**, in terms of enantioselectivity, it was noted that a $C_{6'}$−OH catalyst exhibits higher performance than a $C_9$−OH one (Table 1, entry 5 vs 4). Therefore, subsequent catalyst structure modification (**3g**–**k**) was focused on the protection of $C_9$−OH with a free $C_{6'}$−OH group. To our delight, 9-(2,4,6-trimethylbenzyl) protected catalyst **3j** gave the product **4a** in 95% yield and a higher 79% *ee* than more or less bulky **3g**–**i** and **3k** (Table 1, entry 10 vs entries 7−9 and entry 11).

To further investigate the catalytical capacity of **3j**, some reaction parameters were screened and optimized. Lowering the reaction temperature to −15 °C led to a higher *ee* value of 82% (Table 1, entry 12). Then various solvents were evaluated under −15 °C with **3j** (Table 1, entries 13−18). It showed that polar solvents such as THF and $CH_3CN$ decreased the enantioselectivity sharply (Table 1, entries 13 and 14), while nonpolar solvent toluene gave moderate enantioselectivity (Table 1, entry 15). Noteworthy, chlorinated alkane solvents showed an interesting effect. With increasing polarity of the solvent the enantioselectivity increased in the order of $CH_2Cl_2$, $ClCH_2CH_2Cl$, $CHCl_3$, and $CH_3CHCl_2$ (Table 1, entry 12, and entries 16−18). When the temperature was decreased further to −78 °C, $CH_3CHCl_2$ afforded the highest enantioselectivity, 94% *ee* (Table 1, entry 19). However, either increasing the substrate concentration or decreasing the amount of catalyst loading produced inferior *ee* values (Table 1, entries 20 and 21).

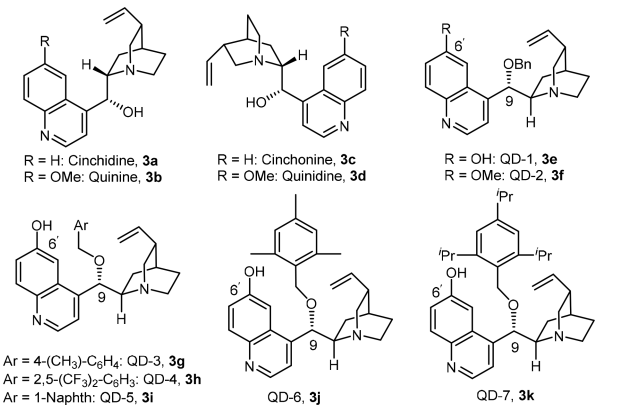
With the optimized reaction conditions in hand, the substrate scope of this protocol was investigated. As shown in Scheme 2, bulky *t*Bu ester **4c** was prepared in comparable 93% *ee*, which is higher than that for the ethyl ester **4b**. Other indanone-derived

**Table 1. Optimization of the Reaction Conditions for the Asymmetric Thiocyanation**[a]




| entry | cat. | solvent | $t$ (°C) | yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | **3a** | $CH_2Cl_2$ | 0 | 91 | 20 |
| 2 | **3b** | $CH_2Cl_2$ | 0 | 92 | 31 |
| 3 | **3c** | $CH_2Cl_2$ | 0 | 94 | −20 |
| 4 | **3d** | $CH_2Cl_2$ | 0 | 95 | −41 |
| 5 | **3e** | $CH_2Cl_2$ | 0 | 94 | 61 |
| 6 | **3f** | $CH_2Cl_2$ | 0 | 91 | 0 |
| 7 | **3g** | $CH_2Cl_2$ | 0 | 91 | 62 |
| 8 | **3h** | $CH_2Cl_2$ | 0 | 89 | 41 |
| 9 | **3i** | $CH_2Cl_2$ | 0 | 90 | 61 |
| 10 | **3j** | $CH_2Cl_2$ | 0 | 95 | 79 |
| 11 | **3k** | $CH_2Cl_2$ | 0 | 96 | 76 |
| 12 | **3j** | $CH_2Cl_2$ | −15 | 90 | 82 |
| 13 | **3j** | THF | −15 | 90 | 0 |
| 14 | **3j** | $CH_3CN$ | −15 | 91 | 12 |
| 15 | **3j** | toluene | −15 | 85 | 67 |
| 16 | **3j** | $ClCH_2CH_2Cl$ | −15 | 94 | 85 |
| 17 | **3j** | $CHCl_3$ | −15 | 95 | 88 |
| 18 | **3j** | $CH_3CHCl_2$ | −15 | 95 | 90 |
| 19 | **3j** | $CH_3CHCl_2$ | −78 | 99 | 94 |
| 20[d] | **3j** | $CH_3CHCl_2$ | −78 | 99 | 80 |
| 21[e] | **3j** | $CH_3CHCl_2$ | −78 | 99 | 83 |

[a]Reaction conditions: **2a** (1.0 equiv), **1c** (1.5 equiv), cat. (10 mol %), 0.05 M, solvent, at corresponding temperature, 1−2 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]0.10 M solution of **2a**. [e]Using 5 mol % catalyst. Ad = 1-adamantyl.




$\beta$-ketoesters bearing various substituents on the phenyl ring such as halogens, methyl, phenyl, and alkynyl were tolerated in good to excellent enantioselectivities (**4d**–**m**, 74%–94% *ee*) and good to excellent yields (82%–99% yield), except bulky 3,3-dimethyl indanone-derived $\beta$-ketoester **4j** in 95% yield and 87% *ee*. However, when more-likely enolizable six- or seven-membered ring $\beta$-ketoesters were applied to the optimized reaction conditions, the corresponding thiocyanated products **4n** and **4o** were isolated with only moderate *ee* values. Nevertheless, acyclic $\beta$-ketoester **2p** was not suitable for this protocol. The absolute configuration (*R*) of the quaternary carbon center in products **4a**–**o** was determined by X-ray crystallographic analysis of a single crystal of **4e** (CCDC 1576837, Figure 2).



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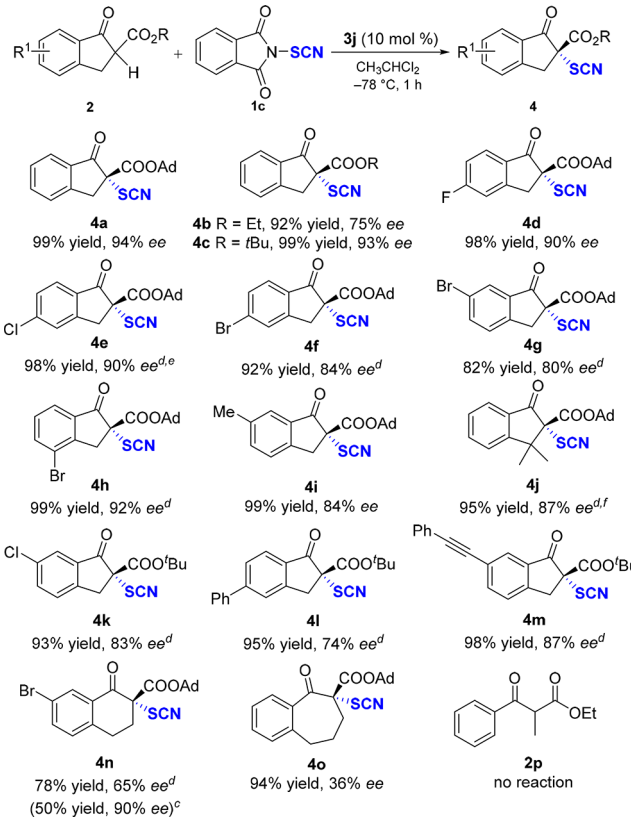
**Scheme 2. Scope of Substrates**[a,b]




[a]Reaction conditions: **2** (1.0 equiv), **1c** (1.5 equiv), **3j** (10 mol %), in 0.05 M solution of $CH_3CHCl_2$ at −78 °C for 1 h. [b]Isolated yield; *ee* values were determined by chiral HPLC analysis. [c]After single recrystallization. [d]Using $CH_2Cl_2$ as the solvent. [e]Using 15 mol % of **3j**. [f]Using 20 mol % of **3j**.

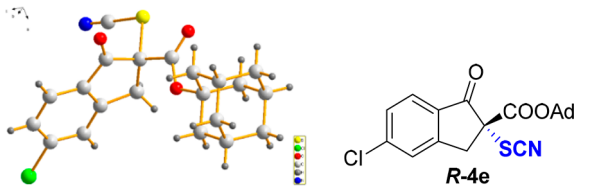
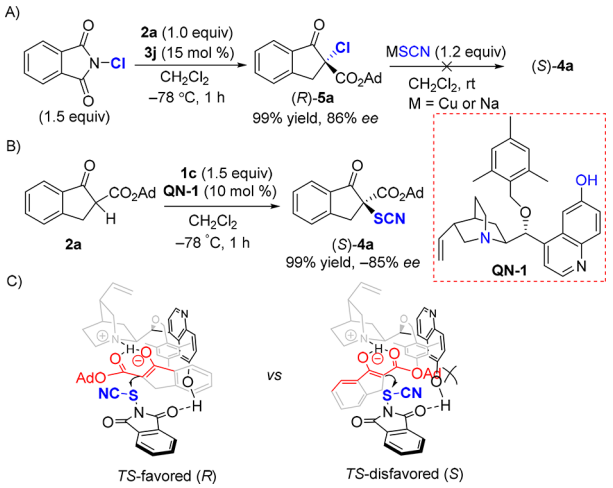



**Figure 2.** X-ray crystal structure of product **4e**.

In order to gain insight into this reaction,[13] a series of control experiments were conducted. Although the same configuration *α*-chloro-*β*-oxo ester **5a** was prepared with high enantiopurity (see Supporting Information), it was challenging for it to be tranformed into the corresponding *α*-thiocyanato-*β*-oxo ester **4a** via an $S_N2$ substitution stepwise process (Scheme 3A).[14] Nevertheless, using quinine derivative **QN-1** as the catalyst under similar conditions, the opposite (*S*)-**4a** was obtained in 99% yield and −85% *ee* (Scheme 3B). In consideration of the importance of $C_{6'}$−OH in the catalyst strucure (Table 1, entry 5 vs 6) and comprehensive applications of this type of alkoloid derivatives in organocatalysis,[15] and the similar trifluoromethyl sulfenylation,[16] a Wynberg ion pair-hydrogen bonding model to illustrate the stereochemistry outcome, was proposed in which the SCN transfers from the thiocyanating reagent to *β*-keto ester via an $S_N2$-like transition state (Scheme 3C). The bulky ester would prefer the transition state in favor of the formation of the (*R*)-enantiomer as the main product.

**Scheme 3. Control Experiments (A–B) and Proposed Transition State (C)**




In summary, the enantioselective direct *α*-thiocyanation of cyclic *β*-ketoesters was accomplished for the first time by a cinchona alkaloid bifunctional catalyst with *N*-thiocyanatophthalimide as the electrophilic thiocyanation reagent. Chiral quaternary *β*-ketoesters bearing a SCN group were achieved in excellent yields (up to 99% yield) and high enantioselectivities (up to 94% *ee*). Meanwhile, by employing quinidine and quinine derivatives, both (*R*)- and (*S*)-enantiomers could be obtained under similar reaction conditions. Further applications of *N*-thiocyanatophthalimide are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00342.

Experimental details, characterization data, NMR spectra, and HPLC chromatograms (PDF)

### Accession Codes

CCDC 1576837 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(12) See Supporting Information (SI) for details about the new electrophilic thiocyanation reagent *N*-thiocyanatophthalimide (**1c**).

(13) Initially, *N*-thiocyanatophthalimide (**1c**) was prepared by the reaction of *N*-chlorophthalimide with AgSCN in acetonitrile. However, when we used this reagent for asymmetric $\alpha$-thiocyanation, the results could not be reproduced smoothly. Sometimes the chlorinated byproduct **5a** could be isolated.

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