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The Quinine Thiourea-Catalyzed Asymmetric Strecker Reaction: An Approach for the Synthesis of 3-Aminooxindoles

Dong Wang,[a,c] Jinyan Liang,[a,c] Jingchao Feng,[a] Kairong Wang,[a] Quantao Sun,[a] Long Zhao,[a] Dan Li,[a] Wenjin Yan,[a,*] and Rui Wang[a,b,*]

[a] Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Life Sciences, School of Basic Medical Sciences, School of Pharmacy, State Key Laboratory of Applied Organic Chemistry and Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou 730000, People's Republic of China
Fax: (+86)-931-891-1255; e-mail: yanwj@lzu.edu.cn or wangrui@lzu.edu.cn

[b] State Key Laboratory of Chiroscience and Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong
E-mail: bcrwang@polyu.edu.hk

[c] These authors contributed equally to this work.

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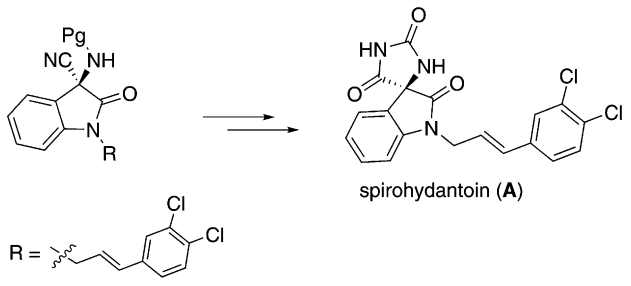
Abstract: An organocatalytic enantioselective Strecker reaction for the synthesis of 3-amino-3-cyanooxindoles has been developed. Employing a quinine-derived thiourea catalyst, the nucleophilic addition of trimethylsilyl cyanide to *N*-Boc-ketimines affords 3-amino-3-canooxindoles in good to excellent yields (78–98%) and very good enantioselectivities (up to 94%). Furthermore, to the best of our knowledge, this method also represents the first enantioselective organocatalyzed Strecker reaction with *N*-Boc-ketimines as electrophiles.

Keywords: 3-amino-3-cyanooxindoles; *N*-Boc-ketimines; organocatalysis; quaternary stereocenters; Strecker reaction

Introduction

Optically active α-amino nitriles are synthetically versatile intermediates for a wide range of natural products and pharmaceuticals.[1] As well-known α-amino acid precursors, these useful compounds also provide access to valuable α-amino aldehydes, ketones, β-amino alcohols and 1,2-diamines. Spurred on by the ever-increasing demand for these enantioenriched compounds, the asymmetric Strecker reaction has become one of the hottest topics in recent years.[2]



Scheme 1. Synthesis of spirohydantoin (**A**) from 3-amino-3-cyanooxindole.

Substituted 3-amino-2-oxindoles have been recognized as a core structure in a variety of bioactive molecules.[3] Among them, one classical example is the spirohydantoin (**A**) (Scheme 1) which was developed by AstraZeneca for potential use in the treatment of pain.[4] Experimentally, this useful compound could be achieved by the conversion of optically active 3-amino-3-cyanooxindoles (Figure 1). Considering the synthetic utility of this intermediate, Zhou's[5] and Sacchetti's[6] groups described the asymmetric addition of TMSCN to isatin ketimines, respectively, however, both with moderate yields and stereoselectivities.

Although there are several highly efficient catalytic enantioseletive systems for Strecker reaction with ketimines as the substrate,[7,8] to the best of our knowledge no related Strecker reactions of *N*-Boc-ketimines have been reported.[9] As part of our ongoing interest in the stereoselective synthesis of 3-aminooxindoles through the addition of carbon nucleophiles to isatin-derived ketimines,[10] we herein report a facile method for the construction of optically active 3-amino-3-cyanooxindoles.

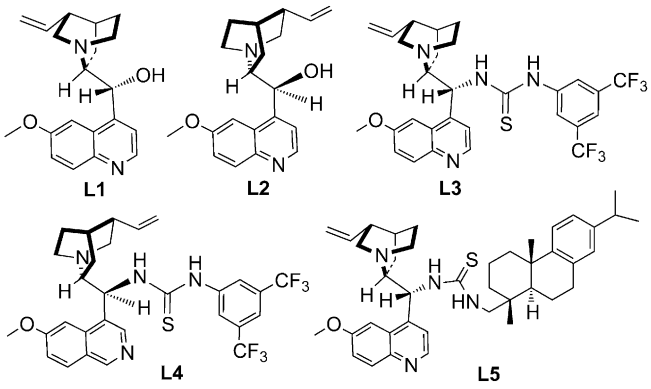


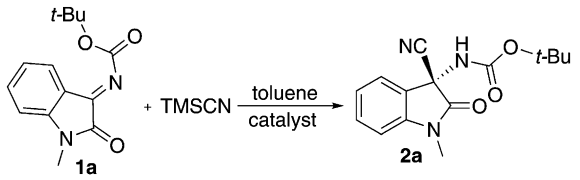
Figure 1. Catalysts for screening.

Results and Discussion

Our investigation began with the addition of TMSCN to ketimine **1a** using natural *Cinchona* alkaloids as catalysts. As expected, the reactions gave products in excellent yields respectively, however, both with lower *ee*. Furthermore, long reaction times, even more than 3 days, were needed (entries 1 and 2, Table 1). The catalysts quinine-thiourea **L3** and quinidine-thiourea **L4** were involved in the next investigation. To our delight, catalyst **L3** gave satisfactory results of 98% yield and 88% *ee*, and the enantiomer **2a′** could be achieved in a similar manner to **2a** with quinidine-thiourea **L4** as catalyst. As shown in Table 1, good yields and faster reaction rates were observed when catalyst **L5** was used, however, with moderate stereoselectivities.

Using **L3** as the selected catalyst, a reaction optimization was carried out with the addition of TMSCN to **1a** as the model reaction. The initial study focused on the influence of solvents. As presented in Table 2, although toluene, diethyl ether and 1,2-dichloroethane gave similar results (entries 1,4 and 6, Table 2), a relatively shorter reaction time was observed with 1,2-dichloroethane as solvent. When the reaction was carried out at 0 °C, the enantioselectivity improved slightly compared to that at room temperature (entry 10, Table 2). The Strecker product could be obtained in 98% yield and 93% *ee* when the reaction temperature was decreased to −25 °C (entry 11, Table 2). Meanwhile, we also found that further lowering the temperature could not improve the enantioselectivity (entry 12, Table 2). Then, the effects of molar ratio and concentration were investigated (entries 13–16, Table 2). The results indicated that satisfactory results could be obtained with 1.5 equiv. of TMSCN and in 1 mL of solvent. Aimed to test the reactivity, another efficient source CN^-, $NCCOOC_2H_5$, was also examined, but no adduct was found even after four days.

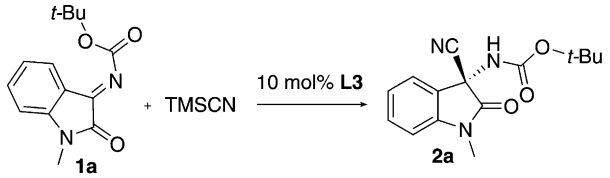
Table 1. Catalyst screening for the enantioselective Strecker reaction.[a]



Entry	Catalyst[b]	Time [h]	Yield [%]	*ee* [%][c]
1	**L1**	108	95	34
2	**L2**	96	83	18
3	**L3**	24	96	88
4	**L4**	24	96	−86
5	**L5**	17	94	63

[a] *Reaction conditions:* **1a** (0.1 mmol), TMSCN (0.15 mmol), $CH_3C_6H_5$ (1 mL) and at room temperature.
[b] Catalyst loading: 10 mol%.
[c] Determined by HPLC analysis.

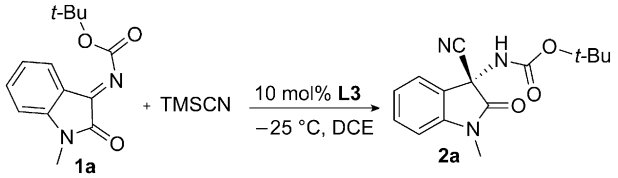
Table 2. Optimization of the reaction conditions.[a]



Entry	Solvent	Time [h]	Yield [%]	*ee* [%][b]
1	toluene	24	96	88
2	DCM	16	83	86
3	$CHCl_3$	16	98	84
4	DCE	12	98	88
5	THF	40	65	80
6	Et_2O	24	91	88
7	*t*-BuOMe	17	89	87
8	EtOAc	17	94	68
9	CH_3CN	17	98	83
10[c]	DCE	16	98	91
11[d]	DCE	24	96	93
12[e]	DCE	48	72	93
13[c,f]	DCE	48	94	93
14[c,g]	DCE	18	96	92
15[c,h]	DCE	36	91	92
16[c,i]	DCE	42	98	93
17[j]	DCE	–	–	–

[a] *Reaction conditions:* **1a** (0.1 mmol), TMSCN (0.15 mmol), in 1 mL solvent and at room temperature.
[b] Determined by HPLC analysis.
[c] At 0 °C.
[d] At −25 °C.
[e] At −40 °C.
[f] 2 mL DCM were used.
[g] 0.5 mL DCM was used.
[h] TMSCN (0.13 mmol) was used.
[i] TMSCN (0.17 mmol) was used.
[j] $CNCOOC_2H_5$ was used and no adduct was found.

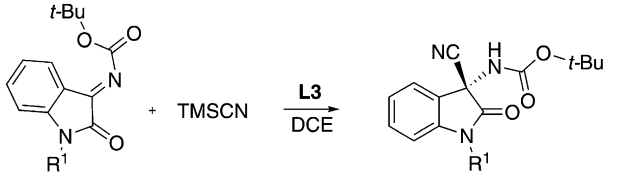
Table 3. Effect of sdditives in the reaction.[a]



Entry	Additive	Time [h]	Yield [%]	*ee* [%][b]
1	MeOH	18	83	93
2	EtOH	18	90	93
3	*i*-PrOH	18	96	93
4[c]	*i*-PrOH	60	–	–
5[d]	*i*-PrOH	18	94	−93

[a] *Reaction conditions:* **1a** (0.1 mmol), TMSCN (0.15 mmol), in 1 mL DCE, at −25 °C and with 0.15 mmol protic additive.
[b] Determined by HPLC analysis.
[c] With 1 mL *i*-PrOH as solvent.
[d] With **L4** as catalyst.

Table 4. Effect of substituent groups at ketimine 1-position.[a]



Entry	R^1	Time [h]	Product	Yield [%]	*ee* [%][b]
1	Me	18	**2a**	96	93
2	Bn	24	**3a**	98	93
3	MOM	18	**4a**	88	91
4[c]	H	12	**5a**	95	90
5	Ac	–	–	–	–
6	Boc	–	–	–	–

[a] *Reaction conditions:* **1a** (0.1 mmol), TMSCN (0.15 mmol), at −25 °C, with 0.15 mmol *i*-PrOH and with 10 mol% catalyst loading.
[b] Determined by HPLC analysis.
[c] The *ee* was determined by HPLC after a simple chemical conversion and see also ref.[13]

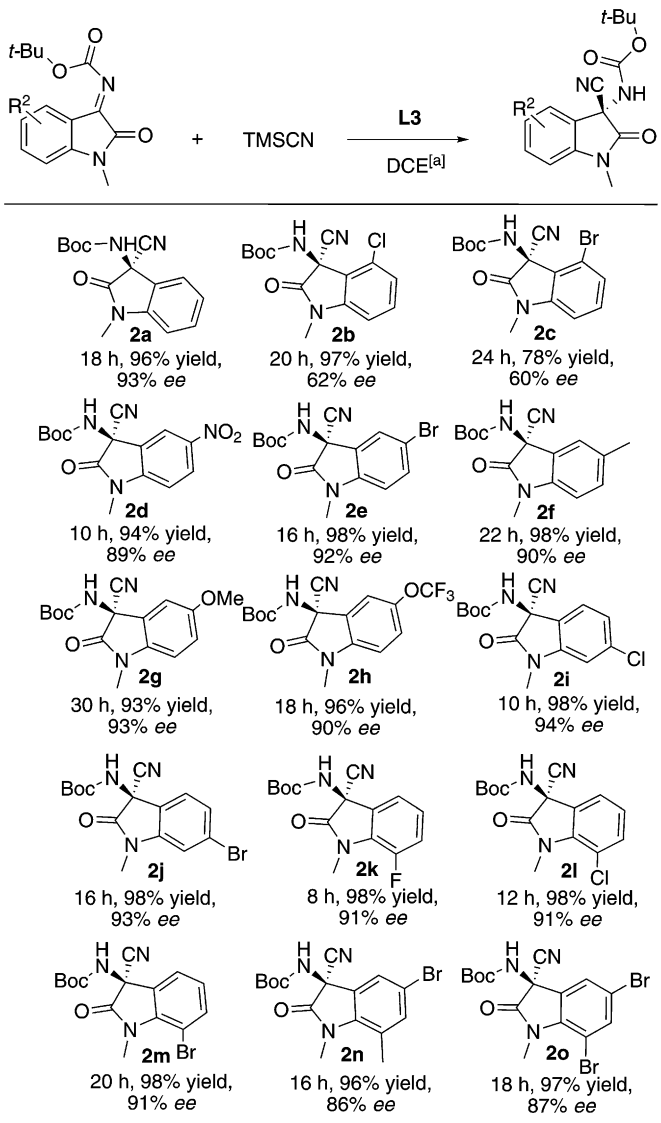
To further improve this addition reaction, a series of alcoholic additives was tested.[11] In general, the reaction rate was improved greatly with 0.15 mmol of a protic additive. And the reactions gave the products in similar enantioselectivity (entries 1–3, Table 3). In view of the best yield, *i*-PrOH was selected as the suitable additive for further investigation of the substrate scope. Partly because of the poor solubility of ketimine **1a** in *i*-PrOH, no adduct was observed even after 60 h with *i*-PrOH as solvent. In addition, the opposite enantiomer **2a′** of compound **2a** could be obtained in 94% yield and 93% *ee* under the optimal conditions with **L4** as catalyst.[12]

After the establishment of the optimal reaction protocol, the effect of the substituent groups at the 1-position of ketimines was investigated. As listed in Table 4, with CH_3, $CH_2C_6H_5$ and CH_2OCH_3 as the substituent group, the addition reactions were carried out smoothly and gave the products in high yields and excellent enantioselectivities, respectively (entries 1–3, Table 4). Although similar results were seen, a significantly slower reaction rate was observed with *N*-benzyl-Boc-ketimine as the substrate. It was noteworthy that the ketimine without the substituent group at the 1-position showed good reactivity in this addition reaction and gave the product **5a** in 95% yield and 90% *ee* (entry 4, Table 4).[13] At the same time, lost reactivity was observed with the bulky substituent Boc or an acetyl group at the 1-position of ketimine. The above-mentioned results indicated that a negative impact on the reactivity of ketimines was made by the increase of the size or electron-withdrawing ability of the substituent.

After the end of the reactivity assessment of substituent groups at the ketimine 1-position, we then evaluated different *N*-Boc-ketimines to define the scope of this Strecker reaction. As summarized in Scheme 2, the reactions of a variety of structurally diverse *N*-Boc-ketimines bearing electron-withdrawing, electron-neutral or electron-donating substituents in the aromatic ring, with TMSCN were tested. We were delighted to obtain the corresponding adducts for all ketimines with good to excellent yields (78–98%) under the optimized conditions. The general conclusion drawn from the results was that the steric effect on reactivity and stereoselectivity was more pronounced than the electronic effect. For example, the reactions of ketimines containing Cl or Br at the 4-position gave poorer enatioselectivities (see **2b** and **2c**), while the same substituents at the 6-position gave the products in higher yields and enantioselectivities (see **2i** and **2j**). With halogen substituents at the 7-position, the regular response was obtained (see **2k**, **2l** and **2m**).

As the increase of the substitutent's atomic radius, a downward trend of reactivity was shown (see **2k**, **2l** and **2m**). The effect of the electronic nature in the aromatic ring was also observed. With the change from electron-withdrawing to electron-donating group in the 5-position the corresponding reaction time increased, while the similar yields and enantioselectivities were afforded (see **2d**, **2e**, **2f**, **2g** and **2h**).

In addition, it turned out that this asymmetric addition of TMSCN to disubstituted ketimine also followed the same reaction pattern. When 7-methyl-5-bromoketimine was used as the substrate, the corresponding product was obtained in 96% yield and 86% *ee*. As to 5,7-dibromoketimine, 96% yield and 86% *ee* were observed.



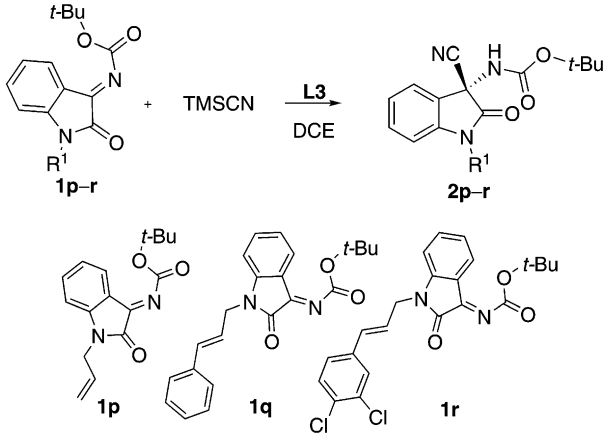
[a] *Reaction conditions:* ketimine (0.1 mmol), TMSCN (0.15 mmol), 0.15 mmol *i*-PrOH, in 1 mL DCE, at –25 °C and with 10 mol% catalyst loading.

Scheme 2. Scope of the enantioselective addition reaction.

In order to obtain the precursor of spirohydantoin (**A**), several ketimines with allyl group at the 1-position of isatin were synthesized. The result turned out that *N*-allylketimines could also be efficiently applied under the present reaction conditions. As shown in Table 5, with $-CH_2CH{=}CH_2$, and $-CH_2CH{=}CH_2C_6H_5$ as the substituent groups the addition reaction was carried out smoothly and gave the products in high yields and excellent enantioselectivities, respectively (entries 1 and 2, Table 5). To our delight, with ketimine **1r** as the substrate, the reaction gave the precursor of spirohydantoin (**A**) in 98% yield and 91% *ee*.

To explore the role of the thiourea and tertiary amine in this cyanation reaction, we first compared

Table 5. Cyanation reaction of *N*-allylketimines.[a]



Entry	Substrate	Time [h]	Product	Yield [%]	*ee* [%][b]
1	**1p**	16	**2p**	96	91
2	**1q**	16	**2q**	96	92
3	**1r**	16	**2r**	98	91

[a] *Reaction conditions:* ketimine (0.1 mmol), TMSCN (0.15 mmol), 0.15 mmol *i*-PrOH, in 1 mL DCE, at –25 °C and with 10 mol% catalyst loading.

[b] Determined by HPLC analysis.

the differences between the **L1**- and **L3**-catalyzed cyanation reactions. As demonstrated in Table 1, with quinine **L1** as catalyst, although the cyanation of ketimine **1a** was carried out smoothly, the lower reaction rate was shown. By contrast, with quinine-thiourea **L3** as catalyst, the reaction need only 24 h. The different reaction rate was caused by the difference of the group at the quinine 9-position. In view of this point, the extra H bond donation ability played an important role in the activation of thiourea to ketimines.

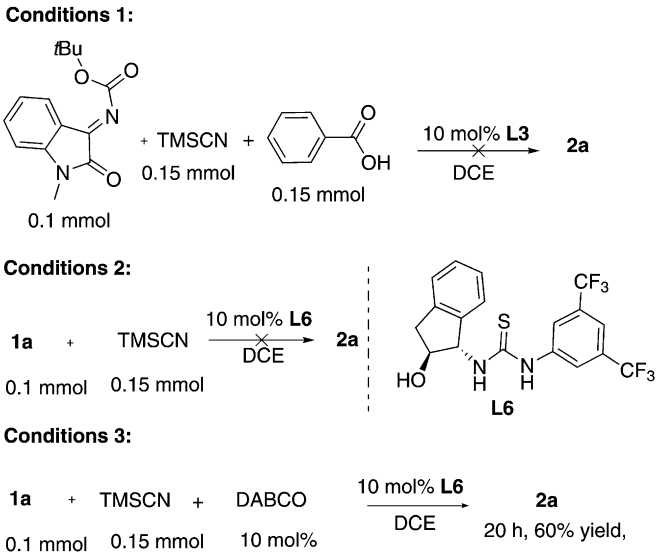


Figure 2. Conditions for exploration of the mechanism,

In the next step, we designed several reactions to discover the role of tertiary amine. As presented in Figure 2, taking cyanation of ketimine **1a** with TMSCN as the model reaction, quinine-thiourea **L3** combined with 0.15 mmol benzoic acid was employed as catalyst (conditions 1, Figure 2). Surprisingly, no adduct was observed after 72 h even at room temperature. This showed that the bonding of tertiary amine with H^+ made the catalyst **L3** lose catalytic activity. To verify this result, **L6**, which has no alkali atoms in the molecule was used as catalyst (conditions 2, Figure 2). However, the substrate ketimine was quantitatively recovered after 72 h. For further verification of the role of the tertiary amine, the combination of 10 mol% **L6** and 10 mol% DABCO was used as catalyst (conditions 3, Figure 2). The expected adduct **2a** was obtained in 60% yield. The above experiments shown that the tertiary amine played a critical role in the activation of TMSCN.

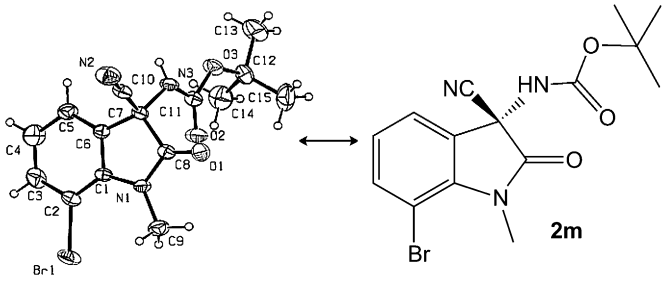


Figure 3. Absolute configuration of **2m**.

The absolute configuration of product **2m** was ascertained as (*R*) on the basis of an X-ray crystal structure analysis (Figure 3).[14] These data allowed us to propose a possible mechanism for the addition of TMSCN to Boc-ketimines derived from *N*-methylisatins. As shown in Figure 4, similar to the model suggested by Feng,[7e] the catalyst serves the dual function of activating both reaction partners. The tertiary amine of the catalyst promotes the formation of HCN, and then, through coordination, holds it in close proximity, while the thiourea moiety binds and activates the ketimine through hydrogen bonds. Following an enantioselective addition of CN to ketimine from the Re-face, the (*R*) configurated product was obtained.

To further demonstrate the synthetic utility of the present system, a gram-scale reaction was carried out. As shown in Scheme 3, with 2 mmol **1a** as the substrate, similar to the 0.1 mmol scale, the addition reaction gave the product **2a** in 97% yield and 93% *ee* under optimized conditions. The conversion of the cyano group into amide and ester groups, respectively, was explored next. As expected, the corresponding Boc-amino amide **2ab** and amino ester **2ac** were readily achieved without the loss of stereochemical purity.

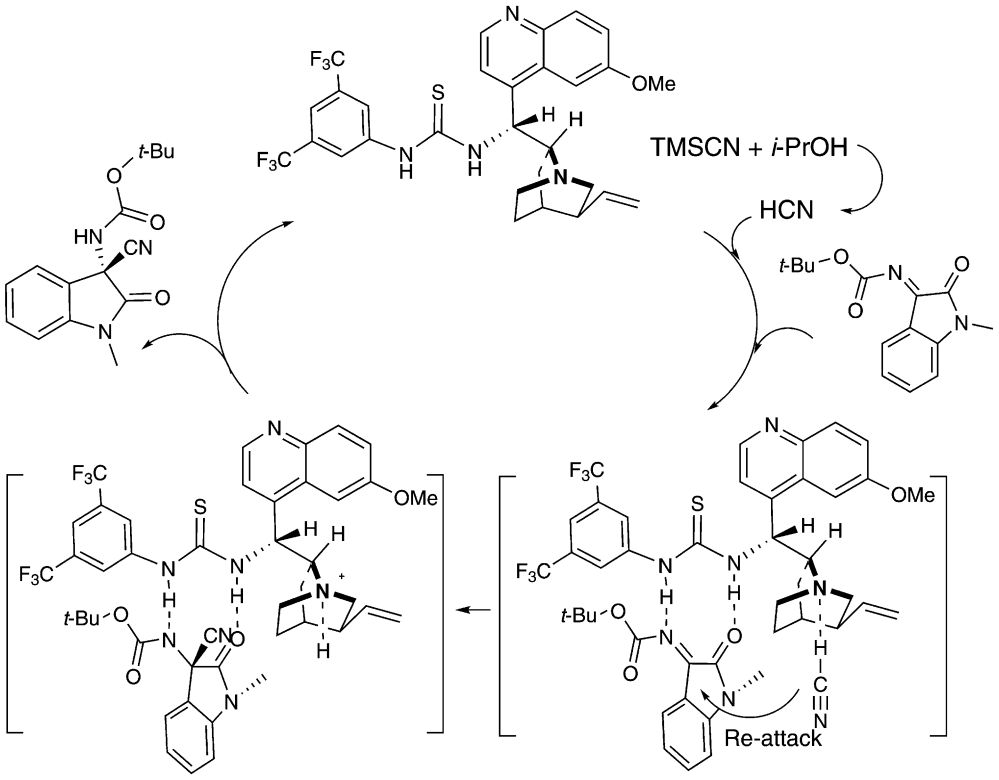
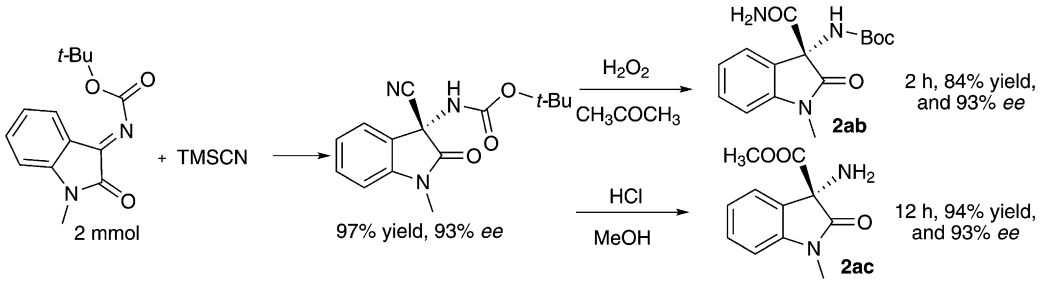


Figure 4. Proposed catalytic cycle for the Strecker reaction of ketimines.



Scheme 3. Demonstration of the synthetic utility.

Conclusions

In conclusion, we have developed a highly practical method for the asymmetric synthesis of 3-amino-3-canooxindoles through the addition of TMSCN to isatin-derived *N*-Boc-ketimines with the catalysis of quinine-thiourea. In addition, a variety of ketimines bearing electron-withdrawing and electron-donating substituents at different positions on the aromatic ring were tested. The reactions provided the expected products with good yields and enantioselectivities.

Experimental Section

General

All commercially available reagents were used without further purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica gel. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 75 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Data are presented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet) and coupling constant in Hertz (Hz). Dichloromethane and 1,2-dichloroethane was freshly distilled from CaH_2 before use; other solvents (THF, Et_2O, 1,4-dioxane, *t*-BuOMe and toluene) were freshly distilled from sodium. The thiourea catalysts were prepared according to the literature procedures.[10b][15]

General Procedure for the Synthesis of *N*-Boc-ketimines

The synthesis of *N*-Boc-ktimines was performed according to the literature procedure.[10b] Characterization data of three new substrates are presented as below.

(*E*)-*tert*-Butyl (1-allyl-2-oxoindolin-3-ylidene)carbamate (1p): Ketimine **1p** was obtained as a yellow solid; yield: 92%; mp 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 6.9 Hz, 1H), 7.46 (td, J = 7.8, 1.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 5.89–5.76 (m, 1H), 5.33–5.26 (m, 2H), 4.33 (d, J = 4.0 Hz, 2H), 1.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 156.9, 153.1, 147.4, 135.3, 130.5, 124.4, 123.5, 119.3, 118.5, 110.2, 83.5, 42.5, 28.0; IR (KBr): υ = 3434, 2980, 2933, 1740, 1722, 1681, 1613, 1469, 1371, 1350, 1249, 1164, 1146, 1097, 938, 763 cm^{-1}; HR-MS: m/z = 309.1209, calcd. for $C_{16}H_{18}N_2NaO_3$ $[M+Na]^+$: 309.1210.

(*E*)-*tert*-Butyl (1-cinnamyl-2-oxoindolin-3-ylidene)carbamate (1q): Ketimine **1q** was obtained as a yellow solid; yield: 91%; mp 130–132 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.0 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.36–7.25 (m, 5H), 7.09 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.16 (dt, J = 15.9, 6.0 Hz, 1H), 4.50 (d, J = 5.2 Hz, 2H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 157.0, 153.1, 147.4, 135.8, 135.4, 133.8, 128.7, 128.2, 126.5, 124.4, 123.5, 121.7, 119.4, 110.2, 83.6, 42.1, 28.1; IR (KBr): υ = 3432, 2985, 2935, 2361, 1740, 1719, 1680, 1618, 1470, 1348, 1251, 1154, 1098, 970, 750 cm^{-1}; HR-MS: m/z = 385.1523, calcd. for $C_{22}H_{22}N_2NaO_3$ $[M+Na]^+$: 385.1523.

(*E*)-*tert*-Butyl {1-[(*E*)-3-(3,4-dichlorophenyl)allyl]-2-oxoindolin-3-ylidene}carbamate (1r): Ketimine **1r** was obtained as a yellow solid; yield: 94%; mp 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$); δ = 7.69 (d, J = 7.1 Hz, 1H), 7.47 (td, J = 7.8, 1.1 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.18–7.09 (m, 2H), 6.87 (d, J = 7.9 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.18 (dt, J = 16.0, 5.8 Hz, 1H), 4.49 (d, J = 4.9 Hz, 2H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 157.0, 152.9, 147.1, 135.9, 135.4, 132.8, 131.8, 131.2 130.6, 128.2, 125.6, 124.6, 123.9 123.7 119.4, 109.9, 83.7 41.8, 28.0; IR (KBr): υ = 3436, 2980, 1738, 1350, 1253, 1151, 1100, 965, 752 cm^{-1}; HR-MS: m/z = 453.0739, calcd. for $C_{22}H_{20}Cl_2N_2NaO_3$ $[M+Na]^+$: 453.0743.

General Procedure for the Strecker Reaction of TMSCN with *N*-Boc-ketimines

In a 5-mL vial, *N*-Boc-ketimine (0.1 mmol) and quinine-derived thiourea catalyst **L3** 5.9 mg (0.01 mmol, 10 mol%) were placed. After an injection of 1,2-dichloroethane (1 mL), the reaction mixture was cooled to −25 °C, then, 20 μL (0.15 mmol) TMSCN were added, followed by the addition of 11.5 μL *i*-PrOH. After that the mixture was stirred until complete disappearance of the ketimine. The mixture was purified by flash chromatography (silica gel, hexane/ethyl acetate) and afforded the resulting products as described below.

(*R*)-*tert*-Butyl (3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2a): According to the general procedure, compound **2a** was obtained as a pale yellow solid; yield: 27.6 mg (96%); mp 176–177 °C. 93%. The *ee* was determined by

HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 60: 40, 1.0 mL min^{-1}); retention times: t_{major} = 10.4 and t_{minor} = 14.2 min. $[\alpha]_D^{26}$: +68 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.5 Hz, 1H), 7.44 (td, *J* = 7.8, 1.2 Hz, 1H), 7.19 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.62 (s, 1H), 3.29 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.9, 153.6, 143.0, 131.4, 126.2, 124.7, 124.3, 114.6, 109.3, 82.3, 54.6, 28.1, 27.3; IR (KBr): υ = 3315, 2978, 2927, 2247, 1742, 1719, 1612, 1492, 1473, 1369, 1255, 1160, 755 cm^{-1}; HR-MS (ESI): *m/z* = 310.1164, calcd. for $C_{15}H_{17}N_3NaO_3$ $[M+Na]^+$: 310.1168.

(*S*)-*tert*-Butyl (3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2a′): According to the general procedure, except for using **L4** as the catalyst, compound **2a′** was obtained as a pale yellow solid; yield: 27.0 mg (94%); mp 157–158 °C. 93% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 60: 40, 1.0 mL min^{-1}): retention times: t_{major} = 10.5 and t_{minor} = 14.4 min. $[\alpha]_D^{26}$: −66 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.4 Hz, 1H), 7.44 (td, *J* = 7.8, 1.3 Hz, 1H), 7.18 (td, *J* = 7.7, 1.0 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.62 (s, 1H), 3.29 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 153.6, 143.0, 131.4, 126.2, 124.7, 124.3, 114.6, 109.3, 82.3, 54.6, 28.1, 27.3; IR (KBr): υ = 3310, 2977, 2928, 2247, 1741, 1719, 1612, 1492, 1473, 1369, 1254, 1159, 755 cm^{-1}; HR-MS (ESI): *m/z* = 310.1163, calcd. for $C_{15}H_{17}N_3NaO_3$ $[M+Na]^+$: 310.1162.

(*R*)-*tert*-Butyl (1-benzyl-3-cyano-2-oxoindolin-3-yl)carbamate (3a): According to the general procedure, compound **3a** was obtained as a yellow solid; yield: 35.6 mg (98%); mp 190–192 °C. 93% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 96: 4, 1.0 mL min^{-1}); retention times: t_{major} = 19.9 and t_{minor} = 18.5 min. $[\alpha]_D^{26}$: +46 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.5 Hz, 1H), 7.37–7.27 (m, 6H), 7.13 (td, *J* = 7.7, 0.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.72 (s, 1H), 4.96 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 153.6, 142.2, 134.2, 131.2, 129.0, 128.1, 127.2, 126.3, 124.7, 124.3, 114.6, 110.3, 82.4, 54.8, 44.9, 28.1; IR (KBr): υ = 3218, 2979, 2928, 2247, 1720, 1611, 1487, 1370, 1278, 1255, 1160, 754, 700 cm^{-1}; HR-MS (ESI): *m/z* = 386.1481, calcd. for $C_{21}H_{21}N_3NaO_3$ $[M+Na]^+$: 386.1481.

(*R*)-*tert*-Butyl [3-cyano-1-(methoxymethyl)-2-oxoindolin-3-yl]carbamate (4a): According to the general procedure compound **4a** was obtained as a pale yellow solid; yield: 27.9 mg (88%); mp 149–151 °C. 91% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 95: 5, 1.0 mL min^{-1}): retention times: t_{major} = 11.3 and t_{minor} = 14.6 min. $[\alpha]_D^{26}$: +62 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 1H), 7.43 (td, *J* = 7.8, 1.2 Hz, 1H), 7.21 (td, *J* = 7.7, 0.9 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 5.79 (s, 1H), 5.19 (s, 2H), 3.40 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 153.3, 141.4, 131.5, 125.6, 124.7, 124.1, 114.5, 110.8, 82.4, 72.4, 56.8, 55.1, 28.1. IR (KBr): υ = 3220, 2979, 2932, 2248, 1752, 1719, 1612, 1487, 1368, 1343, 1282, 1252, 1160, 1097, 756 cm^{-1}; HR-MS (ESI): *m/z* = 340.1272, calcd. for $C_{16}H_{19}N_3NaO_4$ $[M+Na]^+$: 340.1273.

(*R*)-*tert*-Butyl (3-cyano-2-oxoindolin-3-yl)carbamate (5a): According to the general procedure compound **5a** was obtained as a yellow solid; yield: 26.0 mg (95%); mp 88–90 °C. $[\alpha]_D^{26}$: +55 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.35 (td, *J* = 7.8, 1.2 Hz, 1H), 7.15 (td, *J* = 7.7, 0.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.91 (s, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 153.6, 140.3, 131.4, 125.9, 125.0, 124.2, 114.3, 111.2, 82.7, 55.0, 28.1; IR (KBr): υ = 3289, 2979, 2928, 2249, 1746, 1620, 1474, 1369, 1254, 1158, 753 cm^{-1}; HR-MS (ESI): *m/z* = 296.1006, calcd. for $C_{14}H_{15}N_3NaO_3$ $[M+Na]^+$: 296.1006.

(*R*)-*tert*-Butyl (4-chloro-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2b): According to the general procedure compound **2b** was obtained as a white solid; yield: 31.2 mg (97%); mp 194–195 °C. 62% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 22.0 and t_{minor} = 19.6 min. $[\alpha]_D^{26}$: +38 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 8.1 Hz, 1H), 7.10 (dd, *J* = 8.3, 0.5 Hz, 1H), 6.82 (dd, *J* = 7.9, 0.5 Hz, 1H), 5.89 (s, 1H), 3.30 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1, 152.4, 145.2, 132.4, 131.2, 124.4, 120.3, 112.8, 107.7, 82.3, 54.9, 28.0, 27.6; IR (KBr): υ = 3307, 2979, 2927, 2249, 1751, 1707, 1607, 1459, 1290, 1122, 1033, 764 cm^{-1}. HR-MS (ESI): *m/z* = 344.0778, calcd. for $C_{15}H_{16}ClN_3NaO_3$ $[M+Na]^+$: 344.0778.

(*R*)-*tert*-Butyl (4-bromo-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2c): According to the general procedure compound **2c** was obtained as a yellow solid; yield: 28.6 mg (78%); mp 211–212 °C. 60% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention time: t_{major} = 27.0 and t_{minor} = 23.2 min. $[\alpha]_D^{26}$: +29 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 2H), 6.86 (dd, *J* = 7.2, 1.4 Hz, 1H), 5.92 (s, 1H), 3.30 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 152.3, 145.4, 132.6, 127.4, 122.0, 119.2, 112.7, 108.3, 82.3, 56.0, 28.0, 27.6; IR (KBr): υ = 3306, 2979, 2926, 2247, 1747, 1708, 1603, 1457, 1363, 1287, 1157, 1113, 1025, 781, 756 cm^{-1}; HR-MS (ESI): *m/z* = 388.0271, calcd. for $C_{15}H_{16}BrN_3NaO_3$ $[M+Na]^+$: 388.0273.

(*R*)-*tert*-Butyl (3-cyano-1-methyl-5-nitro-2-oxoindolin-3-yl)carbamate (2d): According to the general procedure compound **2d** was obtained as a yellow solid; yield: 31.2 mg (94%); mp 94–95 °C. 89% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}); retention times: t_{major} = 12.4 and t_{minor} = 20.3 min. $[\alpha]_D^{26}$: +50 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 2.2 Hz, 1H), 8.42 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 5.85 (d, *J* = 7.9 Hz, 1H), 3.39 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 153.2, 148.5, 144.4, 128.1, 125.2, 121.5, 113.3, 109.2, 83.2, 54.2, 28.1, 27.9; IR (KBr): υ = 3320, 2979, 2927, 2374, 1756, 1719, 1528, 1493, 1340, 1159, 756 cm^{-1}; HR-MS (ESI): *m/z* = 355.1019, calcd. for $C_{15}H_{16}N_4NaO_5$ $[M+Na]^+$: 355.1018.

(*R*)-*tert*-Butyl (5-bromo-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2e): According to the general procedure compound **2e** was obtained as a pale yellow solid; yield: 35.9 mg (98%); mp 175–177 °C. 92% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 8.4 and t_{minor} = 13.4 min. $[\alpha]_D^{26}$: +54 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1H), 7.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.65 (s, 1H), 3.28 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 153.5, 142.1, 134.3,

129.4, 126.2, 116.8, 114.0, 110.8, 82.7, 54.4, 28.1, 27.5. IR (KBr): υ = 3315, 2977, 2927, 2249, 1747, 1609, 1487, 1358, 1255, 1160, 759 cm^{-1}; HR-MS (ESI): *m/z* = 388.0271, calcd. for $C_{15}H_{16}BrN_3NaO_3$ $[M+Na]^+$: 388.0273.

(*R*)-*tert*-Butyl (3-cyano-1,5-dimethyl-2-oxoindolin-3-yl)-carbamate (2f): According to the general procedure compound **2f** was obtained as a yellow solid; yield: 29.5 mg (98%); mp 204–205 °C. 90% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 6.8 and t_{minor} = 6.2 min. $[\alpha]_D^{26}$: +75 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.26–7.19 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.57 (s, 1H), 3.26 (s, 3H), 2.37 (s, 3H), 1.44 (d, *J* = 9.6 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 153.6, 140.6, 134.2, 131.6, 126.8, 124.7, 114.7, 109.0, 82.2, 54.7, 28.1, 27.3, 21.1; IR (KBr): υ = 3313, 2955, 2925, 2246, 1741, 1720, 1610, 1501, 1364, 1253, 1162 cm^{-1}; HR-MS (ESI): *m/z* = 324.1324, calcd. for $C_{16}H_{19}N_3NaO_3$ $[M+Na]^+$: 324.1324.

(*R*)-*tert*-Butyl (3-cyano-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (2g): According to the general procedure compound **2g** was obtained as a white solid; yield: 29.5 mg (93%); mp 158–159 °C. 93% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 17.2 and t_{minor} = 14.1 min. $[\alpha]_D^{26}$: +67 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 6.96 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.64 (s, 1H), 3.82 (s, 3H), 3.26 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 157.0, 153.7, 136.2, 125.8, 116.3, 114.6, 112.9, 109.9, 82.3, 56.0, 54.9, 28.1, 27.4; IR (KBr): υ = 3312, 2977, 2930, 2248, 1738, 1607, 1500, 1366, 1285, 1162, 756 cm^{-1}. HR-MS (ESI): *m/z* = 340.1273, calcd. for $C_{16}H_{19}N_3NaO_4$ $[M+Na]^+$: 340.1273.

(*R*)-*tert*-Butyl [3-cyano-1-methyl-2-oxo-5-(trifluoromethoxy)indolin-3-yl]carbamate (2h): According to the general procedure compound **2h** was obtained as a pale yellow solid; yield: 35.6 mg (96%); mp 133–134 °C. 90% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 5.4 and t_{minor} = 8.3 min. $[\alpha]_D^{26}$: +55 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.33 (ddd, *J* = 8.6, 2.4, 0.8 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 5.71 (s, 1H), 3.31 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 145.6, 141.7, 125.9, 124.6, 122.1, 120.4, 118.7, 113.9, 110.0, 82.8, 54.5, 28.0, 27.5; IR (KBr): υ = 3314, 2980, 2928, 2250, 1748, 1721, 1621, 1498, 1368, 1258, 1218, 1165, 759 cm^{-1}; HR-MS (ESI): *m/z* = 394.0990, calcd. for $C_{16}H_{16}F_3N_3NaO_4$ $[M+Na]^+$: 394.0991.

(*R*)-*tert*-Butyl (6-chloro-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2i): According to the general procedure compound **2i** was obtained as a yellow solid; yield: 31.5 mg (98%); mp 148–150 °C. 94% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 9.5 and t_{minor} = 15.4 min. $[\alpha]_D^{26}$: +65 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.16 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 5.69 (s, 1H), 3.28 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 153.5, 144.2, 137.4, 127.2, 124.2, 122.9, 114.1, 110.1, 82.6, 54.2, 28.1, 27.5; IR (KBr): υ = 3318, 2979, 2928, 2249, 1747, 1720, 1610, 1493, 1368, 1253, 1160, 1073, 736 cm^{-1}; HR-MS (ESI): *m/z* = 344.0777, calcd. for $C_{15}H_{16}ClN_3NaO_3$ $[M+Na]^+$: 344.0778.

(*R*)-*tert*-Butyl (6-bromo-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2j): According to the general procedure compound **2j** was obtained as a yellow solid; yield: 35.9 mg (98%); mp 90–91 °C. 93% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 8.4 and t_{minor} = 11.7 min. $[\alpha]_D^{26}$: +59 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 5.65 (s, 1H), 3.28 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 153.5, 144.3, 127.5, 127.2, 125.3, 123.4, 114.0, 112.9, 82.6, 54.3, 28.1, 27.5; IR (KBr): υ = 3316, 2978, 2928, 2249, 1748, 1605, 1491, 1367, 1253, 1159, 759 cm^{-1}; HR-MS (ESI): *m/z* = 388.0272, calcd. for $C_{15}H_{16}BrN_3NaO_3$ $[M+Na]^+$: 388.0273.

(*R*)-*tert*-Butyl (3-cyano-7-fluoro-1-methyl-2-oxoindolin-3-yl)carbamate (2k): According to the general procedure compound **2k** was obtained as a white solid; yield: 29.9 mg (98%); mp 124–125 °C. 91% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 90: 10, 1.0 mL min^{-1}); retention times: t_{major} = 6.8 and t_{minor} = 7.7 min. $[\alpha]_D^{26}$: +63 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.0 Hz, 1H), 7.21–7.08 (m, 2H), 5.71 (s, 1H), 3.50 (d, *J* = 2.8 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 153.3, 149.4, 146.2, 130.0, 129.9, 127.0, 124.9, 124.8, 121.6, 119.5, 119.2, 114.1, 82.5, 54.6, 30.0, 29.9, 28.1; IR (KBr): υ = 3319, 2980, 2929, 2251, 1750, 1720, 1631, 1487, 1367, 1246, 1161, 758, 734 cm^{-1}; HR-MS (ESI): *m/z* = 328.1074, calcd. for $C_{15}H_{16}FN_3NaO_3$ $[M+Na]^+$: 328.1073.

(*R*)-*tert*-Butyl (7-chloro-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2l): According to the general procedure compound **2l** was obtained as a yellow solid; yield: 31.5 mg (98%); mp 153–154 °C. 91% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 90: 10, 1.0 mL min^{-1}): retention times: t_{major} = 6.8 and t_{minor} = 7.9 min. $[\alpha]_D^{26}$: +85 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.3 Hz, 1H), 7.36 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.10 (dd, *J* = 8.2, 7.6 Hz, 1H), 5.75 (s, 1H), 3.66 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 153.3, 139.1, 133.6, 127.1, 124.9, 124.3, 116.6, 114.0, 82.6, 54.4, 31.0, 28.1; IR (KBr): υ = 3320, 2979, 2928, 2250, 1747, 1607, 1464, 1365, 1255, 1160, 1109, 759, 737 cm^{-1}; HR-MS (ESI): *m/z* = 344.0777, calcd. for $C_{15}H_{16}ClN_3NaO_3$ $[M+Na]^+$: 344.0778.

(*R*)-*tert*-Butyl (7-bromo-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2m): According to the general procedure compound **2m** was obtained as a white solid; yield: 35.9 mg (98%); mp 163–164 °C. 91% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 7.6 and t_{minor} = 9.2 min. $[\alpha]_D^{26}$: +50 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.1, 7.6 Hz, 1H), 5.77 (s, 1H), 3.67 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 153.3, 140.5, 137.0, 127.4, 125.3, 124.8, 114.0, 103.3, 82.6, 54.3, 31.2, 28.1; IR (KBr): υ = 3320, 2956, 2927, 2250, 1747, 1606, 1459, 1365, 1255, 1160, 1105, 737 cm^{-1}; HR-MS (ESI): *m/z* = 388.0273, calcd. for $C_{15}H_{16}BrN_3NaO_3$ $[M+Na]^+$: 388.0273.

(*R*)-*tert*-Butyl (5-bromo-3-cyano-1,7-dimethyl-2-oxoindolin-3-yl)carbamate (2n): According to the general procedure compound **2n** was obtained as a pale yellow solid; yield:

36.5 mg (96%); mp 204–205 °C. 86% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 80: 20, 1.0 mL min^{-1}): retention times: t_{major} = 7.0 and t_{minor} = 10.0 min. $[\alpha]_D^{28}$: +52 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 1.5 Hz, 1H), 7.32 (dd, J = 2.0, 0.6 Hz, 1H), 5.60 (s, 1H), 3.54 (s, 3H), 2.55 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 153.3, 140.0, 137.5, 126.8, 126.7, 122.9, 116.5, 114.1, 82.6, 54.2, 30.9, 28.1, 18.8; IR (KBr): υ = 32316, 2957, 2926, 2250, 1740, 1720, 1602, 1463, 1342, 1257, 1161, 745 cm^{-1}; HR-MS (ESI): m/z = 402.0432, calcd. for $C_{16}H_{18}BrN_3NaO_3$ $[M+Na]^+$: 402.0424.

(*R*)-*tert*-Butyl (5,7-dibromo-3-cyano-1-methyl-2-oxoindolin-3-yl)carbamate (2o): According to the general procedure compound **2o** was obtained as a white solid; yield: 43.2 mg (97%); mp 205–206 °C. 87% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 95: 5, 1.0 mL min^{-1}); retention times: t_{major} = 11.5 and t_{minor} = 13.5 min. $[\alpha]_D^{26}$: +59 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 1.3 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 5.77 (s, 1H), 3.65 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 153.2, 139.79, 138.9, 128.5, 127.9, 117.0, 113.5, 103.9, 83.0, 54.2, 31.2, 28.1; IR (KBr): υ = 3312, 2956, 2925, 2377, 1750, 1719, 1460, 1370, 1335, 1253, 1159, 1112, 759, 740 cm^{-1}; HR-MS (ESI): m/z = 465.9375, calcd. for $C_{15}H_{15}Br_2N_3NaO_3$ $[M+Na]^+$: 465.9372.

(*R*)-*tert*-Butyl (1-allyl-3-cyano-2-oxoindolin-3-yl)carbamate (2p): According to the general procedure compound **2p** was obtained as a pale yellow solid; yield: 27.5 mg (96%); mp 138–140 °C. 91% *ee* was determined by HPLC analysis (Daicel Chiralcel OJ-H column, hexane/2-propanol 90:10, 1.0 mL min^{-1}): retention times: t_{major} = 10.1 and t_{minor} = 12.5 min. $[\alpha]_D^{23}$: +50 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.5 Hz, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.17 (td, J = 7.7, 0.8 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 5.91–5.78 (m, 1H), 5.65 (s, 1H), 5.35–5.27 (m, 2H), 4.39 (d, J = 1.8 Hz, 2H), 1.43 (s, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 153.6, 142.2, 131.2, 129.9, 126.3, 124.7, 124.2, 118.6, 114.6, 110.1, 82.3, 54.6, 43.4, 28.1; IR (KBr): υ = 3295, 2957, 2925, 1739, 1711, 1611, 1487, 1466, 1369, 1280, 1254, 1160, 1019, 755 cm^{-1}; HR-MS (ESI): m/z = 336.1321, calcd for $C_{17}H_{19}N_3NaO_3$ $[M+Na]^+$: 336.1319.

(*R,E*)-*tert*-Butyl (1-cinnamyl-3-cyano-2-oxoindolin-3-yl)-carbamate (2q): According to the general procedure compound **2q** was obtained as a colorless amorphous solid; yield: 34.7 mg (96%); 92% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 90:10, 1.0 mL min^{-1}): retention times: t_{major} = 23.0 and t_{minor} = 26.1 min. $[\alpha]_D^{23}$: +40 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.5 Hz, 1H), 7.41–7.24 (m, 6H), 7.17 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 16.0 Hz, 1H), 6.18 (dt, J = 15.9, 5.8 Hz, 1H), 5.69 (s, 1H), 4.54 (d, J = 5.5 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 153.6, 142.3, 135.8, 133.9, 131.3, 128.6, 128.2, 126.6, 126.3, 124.7, 124.3, 121.1, 114.6, 110.2, 82.4, 54.7, 43.1, 28.1; IR (KBr): υ = 3408, 3311, 2958, 2925, 1744, 1711, 1611, 1487, 1467, 1364, 1281, 1223, 1162, 1018, 755,531 cm^{-1}; HR-MS (ESI): m/z = 412.1637, calcd. for $C_{23}H_{23}N_3NaO_3$ $[M+Na]^+$: 412.1632.

(*R,E*)-*tert*-Butyl {3-cyano-1-[3-(3,4-dichlorophenyl)allyl]-2-oxoindolin-3-yl}carbamate (2r): According to the general procedure compound **2r** was obtained as a colorless amorphous solid; yield: 42.1 mg (98%). 91% *ee* was determined by HPLC analysis (Daicel Chiralcel IA column, hexane/2-propanol 60:40, 1.0 mL min^{-1}): retention times: t_{major} = 6.8 and t_{minor} = 6.1 min. $[\alpha]_D^{23}$: +15 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.5 Hz, 1H), 7.43–7.34 (m, 3H), 7.19 (t, J = 7.8 Hz, 2H), 6.91 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.20 (dt, J = 16.0, 5.4 Hz, 1H), 5.78 (s, 1H), 4.55 (qd, J = 16.6, 5.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 153.4, 142.1, 136.0, 132.7, 131.7, 131.4, 131.0, 130.5, 128.4, 125.9, 125.6, 124.6, 124.4, 123.1, 114.5, 109.9, 100.0, 82.4, 54.8, 42.7, 28.1; IR (KBr): υ = 3318, 2957, 2926, 2853, 1741, 1718, 1612, 1471, 1369, 1279, 1255, 1160, 1026, 755 cm^{-1}; HR-MS (ESI): m/z = 480.0860, calcd. for $C_{23}H_{21}Cl_2N_3NaO_3$ $[M+Na]^+$: 480.0852.

Synthesis of 2ab from 2a

In a 25-mL round-bottom flask, 143.5 mg **2a** (0.5 mmol) were placed. After an injection of 5 mL acetone, the mixture was stirred for 10 min. Then, 1.5 mL aqueous solution of Na_2CO_3 (1 N, 3 equiv.) was added, followed by the addition of 1.6 mL of H_2O_2 (30%, 27 equiv.). After that the mixture was stirred for 2 h. After an evaporation of the volatile organic solvents, the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate), giving the product **2ab** as a white solid; yield: 128 mg (84%); mp 163–164 °C. 93% *ee*, as determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 90:10, 1.0 mL min^{-1}): retention times: t_{major} = 28.5 and t_{minor} = 23.7 min. $[\alpha]_D^{26}$: −14 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (td, J = 7.7, 1.2 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.39 (s, 1H), 5.82 (s, 1H), 5.53 (s, 1H), 3.27 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 167.0, 153.5, 144.0, 130.2, 127.5, 123.7, 123.6, 109.0, 80.6, 66.1, 28.0, 27.0; IR (KBr): υ = 3385, 3326, 3195, 2958, 2926, 2291, 1718, 1695, 1617, 1471, 1367, 1250, 1164, 1125, 753 cm^{-1}; HR-MS (ESI): m/z = 328.1272, calcd. for $C_{15}H_{19}N_3NaO_4$ $[M+Na]^+$: 328.1268,.

Synthesis of 2ac from 2a

In a 25-mL round-bottom flask, 143.5 mg **2a** (0.5 mmol) were placed. After an injection of 5 mL absolute methanol, the mixture was cooled to 0 °C. Then, dried HCl was bubbled slowly. This process lasted for 15 min. After that, the resulting solution stirred at room temperature over ight. After an evaporation of the volatile organic solvents, 5 mL water were added followed by the addition of 2 mL saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate), compound **2ac** was obtained as a yellow solid; yield: 103.5 mg (94%); mp 109–110 °C. 93% *ee* was determined by HPLC analysis (Daicel Chiralcel AD-H column, hexane/2-propanol 60: 40, 1.0 mL min^{-1}): retention times: t_{major} = 8.9 and t_{minor} = 10.5 min. $[\alpha]_D^{26}$: −122 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (td, J = 7.8, 1.2 Hz, 1H), 7.30 (dd, J = 7.4, 0.7 Hz, 1H), 7.09 (td, J = 7.6, 0.9 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 3.68 (s, 3H), 3.25 (s, 3H), 2.28 (s, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.7$, 170.7, 144.2, 130.1, 128.9, 123.29, 123.26, 108.8, 65.2, 53.3, 26.7; IR (KBr): $\upsilon =$ 3372, 3304, 2955, 2926, 1749, 1720, 1612, 1494, 1470, 1374, 1242, 1126, 1083, 1001, 755 cm^{-1}; HR-MS (ESI): $m/z =$ 243.0746, calcd. for $C_{11}H_{12}N_2NaO_3$ $[M+Na]^+$: 243.0746.

Synthesis of 5ab from 5a

In a 5-mL round-bottom flask, 10 mg NaH (0.25 mmol, 60% in mineral oil, 2.5 equiv.) were placed, after an injection of 0.5 mL THF, the mixture was cooled to 0 °C, 26 mg compound **5a** in 1 mL THF were dropwise added. The resulting solution was stirred 15 min, and 20 μL MOMCl were added. After that, the resulting solution stirred at room temperature overnight. Then, the solution was neutralized by the addition of a saturated aqueous solution of NH_4Cl and then the volatile organic solvents were removed under vacuum. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer obtained was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate), compound **5ab** was obtained as a colorless oil; yield: 23 mg (64%). 90% *ee* was determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol 95: 5, 1.0 mL min^{-1}): retention times: $t_{major} = 7.3$ and $t_{minor} =$ 8.3 min. $[\alpha]_D^{26}$: −5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 7.5$ Hz, 1H), 7.42 (td, $J = 7.8$, 1.2 Hz, 1H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.10 (d, $J = 7.9$ Hz, 1H), 5.31 (d, $J = 11.1$ Hz, 1H), 5.24 (d, $J = 11.0$ Hz, 1H), 5.13 (s, 1H), 5.05 (d, $J = 11.1$ Hz, 1H), 3.48 (s, 3H), 3.43 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.9$, 152.2, 141.6, 135.8, 131.0, 124.4, 124.3, 113.7, 110.4, 83.4, 78.6, 72.5, 60.6, 56.8, 56.0, 27.8; IR (KBr): $\upsilon = 3288$, 2955, 2925, 1752, 1711, 1610, 1465, 1369, 1298, 1154, 1095, 757 cm^{-1}; HR-MS (ESI): $m/z = 384.1530$, calcd. for $C_{18}H_{23}N_3NaO_5$ $[M+Na]^+$: 384.1530.

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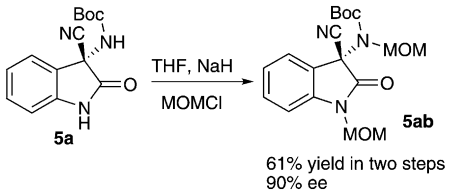

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