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Synthesis of *N*-Alkoxycarbonyl Ketimines Derived from Isatins and Their Application in Enantioselective Synthesis of 3-Aminooxindoles

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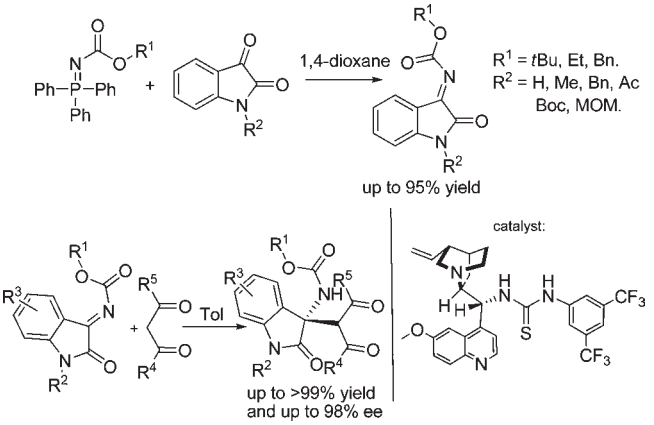
ABSTRACT



A simple and general method in the synthesis of *N*-alkoxycarbonyl ketimines derived from isatins has been described first. Generally, the enantioselective addition of 1,3-dicarbonyl compounds to this kind of ketimine affords chiral 3-amino oxindoles in high yield and excellent ee.

Chiral α-tertiary amines are important building blocks of naturally occurring and artificial biologically active molecules.[1] As one of the most important members, optically active 3-aminooxindoles have been recognized as the core structure in a variety of bioactive molecules.[2] Although there are catalytic asymmetric amination reactions to access these chiral compounds,[3] the asymmetric addition of carbon nucleophiles to ketimines, which can simultaneously construct a carbon skeleton and tetrasubstituted stereogenic center, is synthetically more efficient. To achieve this goal, several diastereoselective approaches could be found.[4] In the case of the catalytic enantioselective nucleophilic addition reaction using ketimines derived from isatins as substrates, there are only a few examples established.[5]

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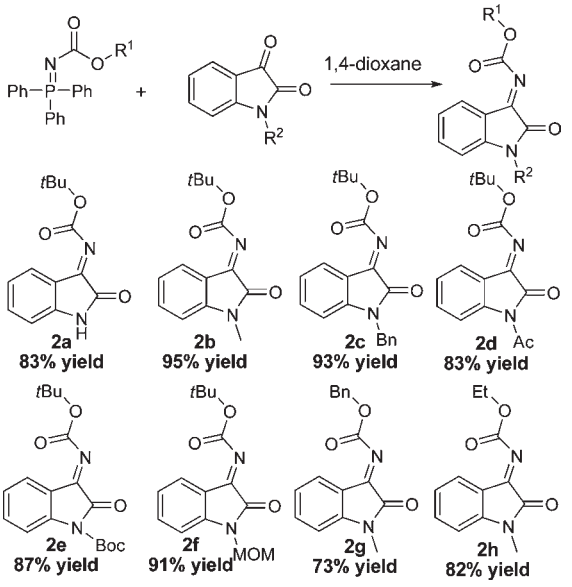
The result in the absence of the enantioselective addition of carbon nucleophiles to ketoimines derived from isatins was caused by the lack of appropriate ketimines. Although some *N*-aryl ketimines have been synthesized in the presence of an acid catalyst and water scavenger,[6] the low reactivity and tedious procedure of deprotection of the *N*-aryl group from the corresponding product limit the application of these known ketimines in synthesis. *N*-Alkoxy carbonyl groups such as *N*-Boc and *N*-Cbz are known as the most useful protecting groups in organic synthesis. Although one sample has been achieved by Hu's group in the presence of $Rh_2(OAc)_4$ and DDQ with moderate yield,[7] to date, there is no general method for the synthesis of *N*-alkoxycarbonyl ketimines derived from isatins, especially for those with readily cleavable *N*-Boc group.

As part of our ongoing interest in developing new methods for the synthesis of optically active 3,3′-disubstituted oxindoles,[8] we herein report a general method for the synthesis of *N*-alkoxycarbonyl ketimines derived from isatins and their further application in the enantioselective nucleophilic addition of 1,3-dicarbonyl compounds catalyzed by a *Cinchona* alkaloid-derived thiourea.

Experimentally, we began our investigation with the synthesis of *N*-Boc ketimines derived from *N*-methyl isatin. After a series of depressing failures using traditional methods for the synthesis of *N*-alkoxycarbonyl ketimines,[9] an exciting result emerged by the employment of the aza-Wittig process, and the expected product was obtained in 95% yield (see Scheme 1).[10] Subsequently, several isatins with different substituted groups at the 1-position were involved in the evaluation of the generality of this synthetic method. As shown in Scheme 1, in general, the method was carried out with $-H$, $-CH_3$, $-CH_2C_6H_5$, $-CH_2OCH_3$, $-COCH_3$, and $-Boc$ as the substituted group, respectively, in high yield. The results combining the structural diversity of *N*-Boc ketimines with the further synthetic ketimines of **2g** and **2h** proved that the application of the aza-Witting process was a successful strategy in the synthesis of *N*-alkoxycarbonyl ketimines derived from isatins.

After obtaining the *N*-alkoxycarbonyl ketimines derived from isatins, we focused on examining the synthetic utility of these substrates. With the addition of pentane-2,4-dione to the ketimine **2b** as the model reaction, natural *cinchona* alkaloids (**L1**−**L4**) (Figure 1) were employed as the catalysts initially. In all cases, although the ketimine **2b** was converted smoothly to the adduct **3b** in high yield, poor enantioselectivities were obtained (entries 1−4, Table 1). Other representative catalysts derived from *cinchona* alkaloids (**L5**−**L7**) were used next (Figure 1).[11]

Scheme 1. Preparation of *N*-Alkoxycarbonyl Ketimines by Use of Aza-Witting Reaction



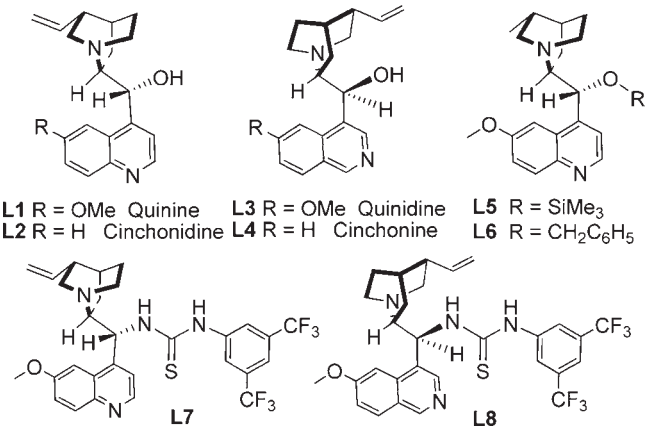
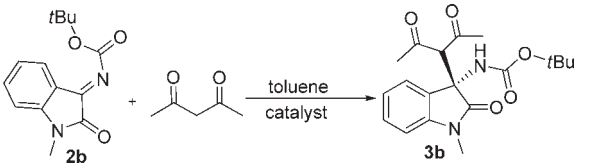


Figure 1. Catalysts for screening.

Table 1. Catalyst Screening for Enantioselectivity Addition of Pentane-2,4-dione to **2b**[a]



entry	catalyst[b]	time (h)	yield (%)	ee[c] (%)
1	**L1**	16	95	3
2	**L2**	17	83	0
3	**L3**	10	92	10
4	**L4**	11	85	10
5	**L5**	96	27	3
6	**L6**	60	60	67
7	**L7**	12	>99	92

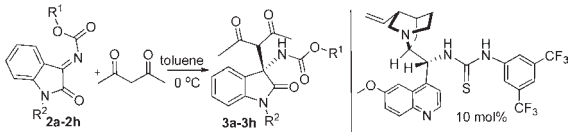
[a] Reaction conditions: **2b** (0.2 mmol), pentane-2,4-dione (0.22 mmol), $CH_3C_6H_5$ (1 mL), and at room temperature. [b] Catalyst loading (10 mol %). [c] Determined by HPLC analysis.

Catalyst **L5** was not suitable for this enantioselective addition reaction, while **L6** gave the product in moderate ee (entries 5 and 6, Table 1). To our delight, the enantioselectivity was dramatically improved to 92% ee when quinine–thiourea **L7** was used as the catalyst.

With the satisfactory catalyst **L7** in hand, we then assessed the influence of solvents, temperature, and additives in the addition of pentane-2,4-dione to the ketimine **2b**. As shown in the Supporting Information, the best result was obtained in toluene at 0 °C and without the addition of molecular sieves.

Having established the optimal reaction protocol, we then evaluated the reactivities of different ketimines **2a**–**h** in this catalytic enantioselective nucleophilic addition reaction. As shown in Table 2, the results revealed that the substituted groups at ketimine 1-position had a significant effect both on the enantioselectivity and the reactivity of ketimines. The reactions preceded smoothly with $-CH_3$, $-CH_2C_6H_5$ and $-CH_2OCH_3$ as the substituted groups at the ketimine 1-position and gave the products in high yields and excellent enantioselectivities, respectively (entries 2, 3, and 6, Table 2). It was noteworthy that the ketimine without the substituted group at 1-position showed good reactivity in this addition reaction and gave the product **3a** in 86% yield and 87% ee (entry 1, Table 2), while lower reactivity was observed with the bulk-substituted Boc group and offered the product with no enantioselectivity (entry 5, Table 2). Meanwhile, the ketimine with acetyl at the 1-position lost reactivity in the addition reaction (entry 4, Table 2). Furthermore, with results similar to those for **3b**, the enantimer **3b′** could also be obtained under these conditions using quinidine-derived thiourea **L8** as the catalyst.

Table 2. Reactivities Evoluation of Ketimines **2a**–**h**[a]



entry	ketimine	product	time (h)	yield (%)	ee[b] (%)
1	**2a**	**3a**	60	86	87
2	**2b**	**3b**	18	>99	95
3	**2b**	**3b′**	18	>99	−95
4	**2c**	**3c**	8	95	94
5[c]	**2d**				
6[d]	**2e**	**3e**	80	95	0
7	**2f**	**3f**	24	95	97
8	**2g**	**3g**	24	84	90
9	**2h**	**3h**	24	90	97

[a] Reaction condition: ketimine (0.2 mmol), pentane-2,4-dione (0.22 mmol), toluene (1 mL), at 0 °C. [b] Determined by HPLC analysis. [c] No adduct was found. [d] At room temperature.

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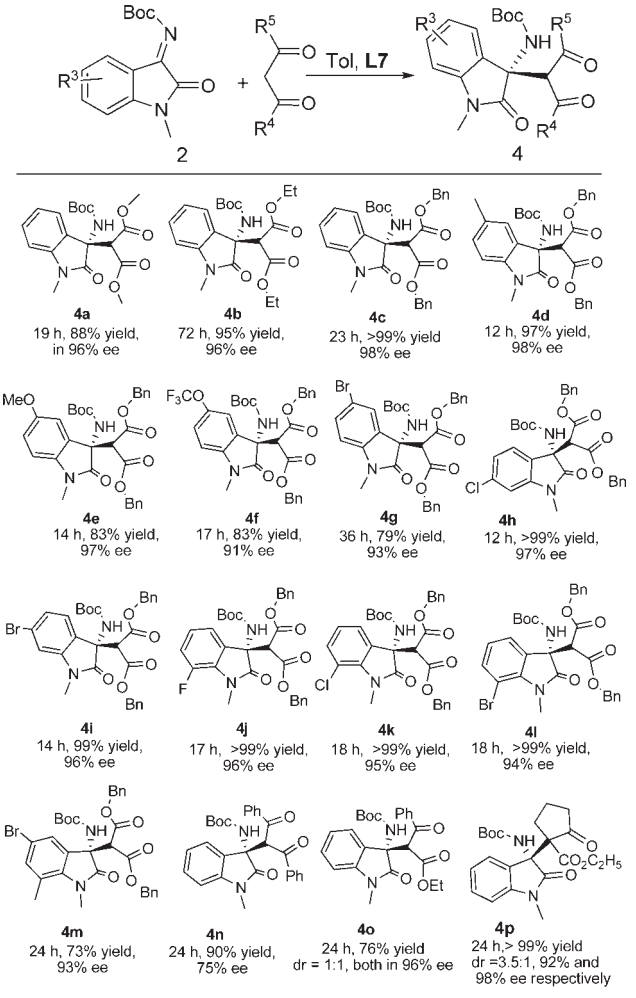
After the end of the reactivity assessment of ketimines **2a**–**h**, we evaluated the different *N*-Boc ketimines derived from various substituted *N*-methylisatins via a reaction with malonates to define the scope of the reaction and the further synthetic utility of this kind of ketimines. As summarized in Scheme 2, the addition of dimethyl malonate and diethyl malonate to ketimine **2b** preceded smoothly and gave the products both in 96% ee. Notably, using dibenzyl malonate as the nucleophile the reaction gave the adduct in quantitative yield and up to 98% ee. A variety of 1-methyl *N*-Boc ketimines were then involved in the following examination, and generally, high to excellent enantioselectivities were obtained in the addition of dibenzyl malonate to these ketimines. These results indicated that the ketimines with the substituted group at the

Scheme 2. Reaction Scope of Enantioselective Additions[a]



[a] Reaction condition: ketimine (0.2 mmol), nucleophilic reagent (0.22 mmol), toluene (1 mL), at room temperature. The reaction time required for each substrate is given. The ee's were determined by HPLC analysis.

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5-position giving the products in lower yields than those with the substituted group at the 6- and 7-position. In addition, it turned out that this asymmetric addition of dibenzyl malonates to disubstitued ketimine also followed the same reaction pattern, which afforded the addition product in 73% yield and 94% ee.

Furthermore, some other 1,3-dicarbonyl compounds were also explored. The addition of 1,3-diphenylpropane-1,3-dione to ketimine **2b** offered the product **4n** in 90% yield and 75% ee. With ethyl 2-oxocyclopentanecarboxylate as the nucleophile compound, **4o** was obtained with 76% yield, 1:1 dr, and 96% ee. Additionally, as expected, the catalytic system also proved to be efficient for prochiral cyclic β-ketoester, leading to **4p** with $>99\%$ yield, 3.5:1 dr, and in 92% ee and 98% ee respectively.

On the basis of X-ray crystal structure analysis of product **4i** (Supporting Information), a potential transition-state structure was proposed. As shown in Figure 2, similar to the model suggested by Takemoto,[12] catalyst serves the dual function of activating both reaction partners. The tertiary amine of catalyst deprotonates the malonate and, through coordination, holds it in close proximity, while the thiourea moiety binds and activates the ketimine through hydrogen bonds.

In conclusion, we have described a general strategy for the synthesis of *N*-alkoxycarbonyl ketimines derived from isatins in high yield under very simple reaction conditions. The reactivity has been demonstrated in the synthesis of chiral 3-aminooxindoles by the enantioselective addition of 1,3-dicarbonyl compounds. In general, the corresponding adducts were obtained in high yields and excellent ee.

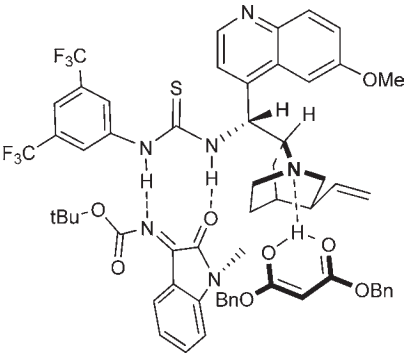

Figure 2. Proposed transition state.

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Supporting Information Available. Experimental procedures and characterization of the products. Crystallographic data for compound of **4i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.