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Enantioselective *N*-alkylation of isatins and synthesis of chiral *N*-alkylated indoles†

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Asymmetric *N*-alkylations of isatins with enals were shown to be feasible *via* a prolinol-catalyzed iminium activation, and *N*-alkylated isatins were obtained in good yields and with excellent enantioselectivity. The biologically useful *N*-alkylated isatins also served as valuable synthetic precursors, and could be readily converted to chiral *N*-alkylated indole derivatives. The described method provides a novel entry to access optically enriched *N*-alkylated isatins and indole derivatives.

Functionalized chiral indole derivatives are extremely important structural units that are widely present in natural products and bioactive molecules.[1] Consequently, enormous efforts have been devoted to the development of new reactions for asymmetric functionalization of indoles.[2] Indoles most commonly act as carbon nucleophiles at the C3 position, and numerous reactions were focused on the asymmetric C3 alkylation of indoles.[3] Recently, a number of approaches for enantioselective C2 alkylation of indoles were also developed.[4] Chiral *N*-alkylated indoles are molecular architectures of great significance (Fig. 1).[5] However, catalytic enantioselective reactions at the indole N1 position have been investigated to a much less extent due to the low acidity of NH protons. Hartwig reported an iridium-catalyzed regioselective and enantioselective *N*-allylation of indoles.[6a] Trost disclosed a palladium catalyzed dynamic kinetic asymmetric alkylation of vinyl aziridines with substituted indoles.[6b] You designed an iridium-catalyzed allylic alkylation/oxidation of indolines to realize asymmetric *N*-allylation of indoles.[6c] A copper-catalyzed cascade C2-alkylation–*N*-hemiacetalization reaction of 3-substituted indoles was reported by Chen and Xiao.[6d] Very recently, Hartwig uncovered an iridium-catalyzed intermolecular hydroamination reaction of indoles with unactivated olefins.[6e] In addition to the above transition metal-mediated methods for indole N1 functionalization, a handful of non-metal based methods have also appeared. Intramolecular aza-Michael additions of indoles catalyzed by a phase-transfer-catalyst and a chiral phosphoric acid were reported by Bandini[7a] and You,[7b] respectively. There are a few reports dealing with more challenging non-metal-based intermolecular functionalization of N1 positions of indoles. Chen employed Morita–Baylis–Hillman (MBH) carbonates for asymmetric *N*-allylic alkylation of indoles, and *in situ* generated basic *tert*-butoxide is believed to deprotonate the NH of an indole substrate.[7c] By installing an electron-withdrawing indole-2-carbaldehyde, Enders[7d] and Wang[7e] independently developed organocatalytic domino reactions to enantioselectively functionalize the indole N1 position. Apparently, the necessity of *in situ* generated strong base and pre-installation of an aldehyde for activation in the above examples limited broad applications of the above methods. We thus set out to develop a mild and general organocatalytic approach to access chiral *N*-alkylated indoles.

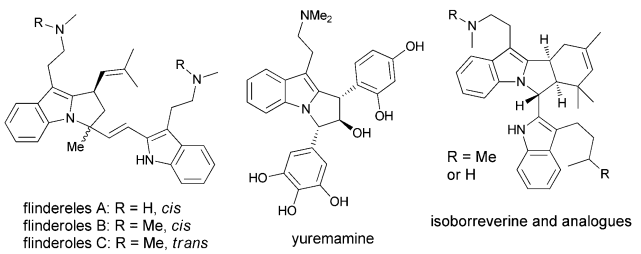

Fig. 1 Bioactive *N*-alkylated indole derivatives.

The low nucleophilicity of indole NH is intrinsic, which makes the indole *N*-alkylation unfavourable; we reasoned that judicious selection of an indole precursor may provide an easy solution to this challenging problem. In this context, we considered commercially available isatins as an excellent choice. The presence of the two carbonyl groups at C2 and C3 in isatin structures greatly enhances the acidity of the NH group; the p*K*a value of the NH proton is 10.3 for isatin, and that of indole NH is only 16.2. Whereas C2 and C3 alkylations of indoles are prevailing

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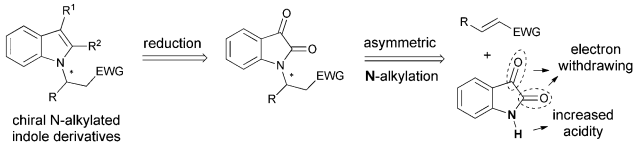
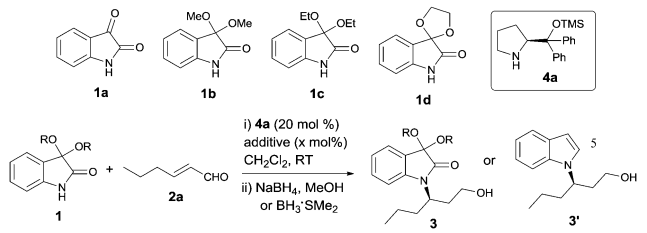


Scheme 1 Isatin as a precursor to derive chiral *N*-alkylated indoles.

reaction pathways when *N*-alkylation is concerned, the *N*-alkylation of isatins is exclusive. To the best of our knowledge, there was only one example of asymmetric *N*-allylation of isatins using MBH carbonates.[8] We envisioned that such a process may be realized with careful selection of suitable electrophilic partners and efficient catalytic systems. The chiral *N*-alkylated isatin derivatives can be readily converted to optically enriched *N*-alkylated indole products *via* a reduction[9] protocol (Scheme 1). Herein, we describe an enantioselective *N*-alkylation of isatins, and preparation of chiral *N*-alkylated indoles.

To provide a validation of our proposal, we chose enal as an electrophile to examine the potential NH functionalization of isatins. An enantioselective conjugate addition of isatins **1** to enal **2a** *via* iminium activation[10] was performed, and the results are summarized in Table 1. Prolinol **4a**[11] is a well-established effective catalyst in asymmetric enamine–iminium catalysis, we thus selected **4a** to investigate projected addition of isatins to enals in our initial studies. Unprotected isatin **1a** was first employed in the reaction. In the presence of 20 mol% of **4a**, the desired product was obtained with moderate enantioselectivity, but only in poor yield (entry 1). Addition of benzoic acid turned out to be detrimental to the reaction, and only a trace amount of the product was detected (entry 2). Effects of adding base additives were next examined. With a catalytic amount of the base, a slight increase in chemical yield and a decrease in enantioselectivity were observed (entries 3 and 4). Increasing

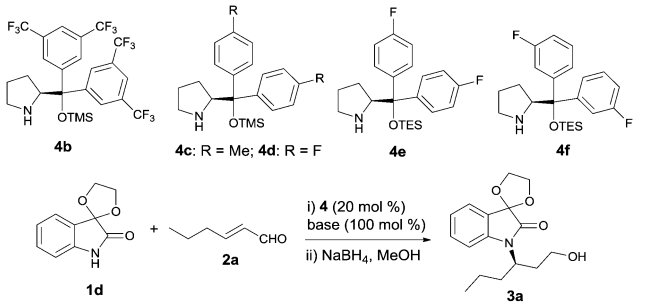
Table 1 Investigation of *N*-alkylation of isatin derivatives **1** with enal **2a**[a]



Entry	1	Additive/x	*t*/h	Product/yield[b] [%]	ee[c] [%]
1[d]	**1a**	None/—	12	**3′**/21	63
2[d]	**1a**	$PhCO_2H$/20	12	**3′**/trace	—
3[d]	**1a**	Et_3N/20	12	**3′**/25	49
4[d]	**1a**	DBU/20	12	**3′**/27	10
5[d]	**1a**	Et_3N/40	12	**3′**/30	49
6[d]	**1a**	Et_3N/100	12	**3′**/43	47
7[d]	**1a**	Et_3N/150	12	**3′**/41	47
8[e]	**1b**	Et_3N/100	48	**3**/69	78
9[e]	**1c**	Et_3N/100	48	**3**/56	77
10[e]	**1d**	Et_3N/100	48	**3**/78	79

[a] Reactions were performed with **1** (0.2 mmol) and **2a** (0.4 mmol). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $BH_3{\cdot}SMe_2$ was used. [e] $NaBH_4$ was used.

Table 2 Chiral prolinol silyl ether-catalyzed conjugate addition of isatin **1d** to enal **2a**[a]

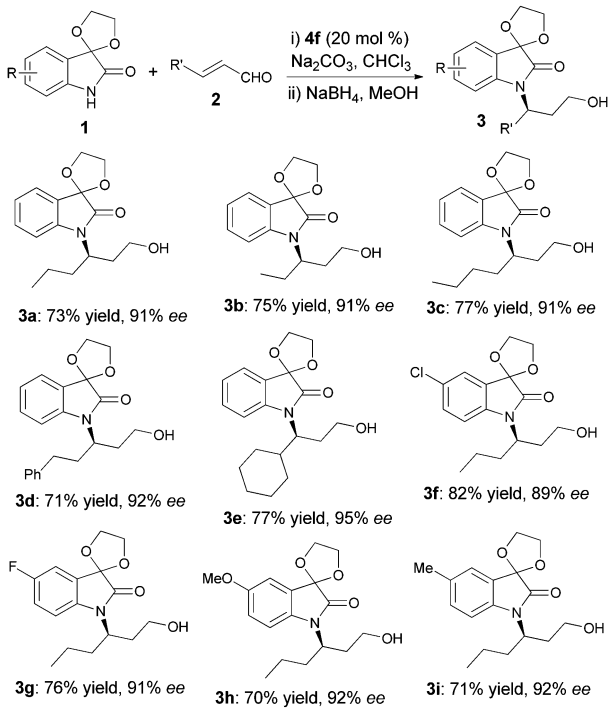


Entry	4	Solvent	Base	*t*/d	Yield[b] [%]	ee[c] [%]
1	**4a**	$CHCl_3$	Et_3N	2	72	84
2	**4a**	DCE	Et_3N	2	64	79
3	**4a**	Toluene	Et_3N	2	55	84
4	**4a**	THF	Et_3N	2	Trace	n.d.
5	**4a**	MeOH	Et_3N	2	Trace	n.d.
6	**4b**	$CHCl_3$	Et_3N	2	42	67
7	**4c**	$CHCl_3$	Et_3N	2	70	84
8	**4d**	$CHCl_3$	Et_3N	2	75	85
9	**4e**	$CHCl_3$	Et_3N	2	77	86
10	**4f**	$CHCl_3$	Et_3N	2	77	87
11	**4f**	$CHCl_3$	DIPEA	2	78	83
12	**4f**	$CHCl_3$	nBu_3N	2	75	75
13	**4f**	$CHCl_3$	Proton sponge	2	<20	n.d.
14	**4f**	$CHCl_3$	$NaHCO_3$	4	37	91
15	**4f**	$CHCl_3$	Na_2CO_3	3	73	91
16	**4f**	$CHCl_3$	K_2CO_3	3	<20	n.d.
17	**4f**	$CHCl_3$	Cs_2CO_3	1	Messy	n.d.

[a] Reactions were performed with **1d** (0.2 mmol) and **2a** (0.4 mmol). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

the amount of base resulted in limited improvement of the reaction (entries 5–7). Suspecting the high electrophilicity of the 3-carbonyl group of isatins may pose problems to the reaction; we then employed protected isatins for further investigations. Gratifyingly, isatin 3-ketals were found to be superior donors, and much improved chemical yields and enantioselectivities were attainable, although the reactivities were lower than those of isatins (entries 8–10). When ethylene glycol protected isatin **1d** was employed, the desired product was obtained in good chemical yield and high enantioselectivity.

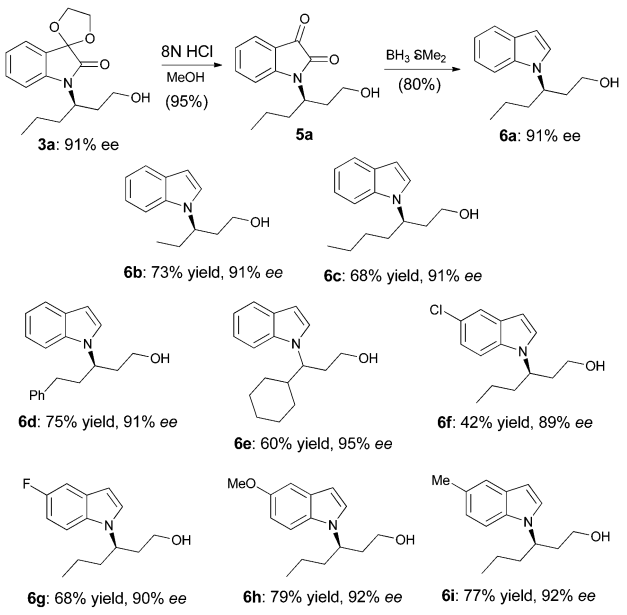
Having established the feasibility of the projected *N*-alkylation of isatins, we next focused on optimizing the reaction conditions to make the process highly enantioselective, and the results are summarized in Table 2. Solvent screening revealed that chloroform was the solvent of choice (entries 1–5). A number of prolinol silyl ethers were prepared and their catalytic effects were examined. Catalyst **4b** containing 3,5-CF_3-Ph substituents was less effective (entry 6). Prolinols with mono-substituted phenyl rings showed similar catalytic activities, and catalyst **4f** was chosen since it led to slightly better results (entries 7–10). Different bases were also examined as additives. While organic bases efficiently promoted the reaction (entries 10–12), inorganic bases were tested for further improvements. Upon adding $NaHCO_3$, the desired product was obtained with high enantioselectivity, however, the yield was low (entry 14). With the employment of Na_2CO_3,



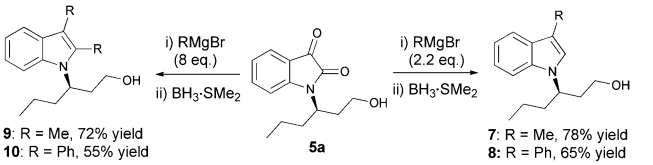
Scheme 2 *N*-Alkylated isatin derivatives.

the *N*-alkylation product was obtained in 73% yield and with 91% ee (entry 15).

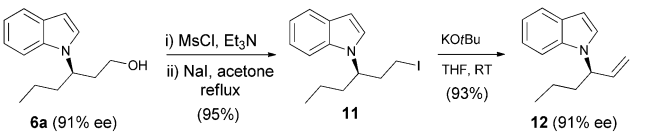
The generality of the reaction was next evaluated by employing various enals and isatin 3-ketals (Scheme 2). Aliphatic enals with a linear chain were well tolerated (**3a–3c**). Aryl substituted linear enal and branched enal were also suitable substrates (**3d** and **3e**). Different substitutions at the 5-position of the isatin motif also worked well, and the products were obtained in high yields and



Scheme 3 Preparation of chiral *N*-alkylated indoles.



Scheme 4 Facile synthesis of 2,3-substituted indoles from isatin **5a**.



Scheme 5 Preparation of branched *N*-allyl indole.

with high ee values (**3f–3i**). However, aryl enals were found to be unsuitable for the reaction.[12]

We then established effective conversion of chiral *N*-alkylated isatin 3-ketals to optically enriched indole derivatives. Isatin **3a** was first deprotected to the corresponding isatin **5a** under acidic conditions. *N*-Alkylated indole derivative **6a** was readily obtained in high yield after reduction of isatin **5a** with borane. The ee value was maintained throughout the deprotection–reduction process. With this protocol in hand, a range of chiral *N*-alkylated indole derivatives were readily prepared, in moderate to good chemical yields and excellent enantiomeric excesses (Scheme 3).

In addition to simple indole derivatives, the *N*-alkylated isatins can also be converted into various C2/C3-substituted *N*-alkylated indole derivatives (Scheme 4). When isatin **5a** was treated with 8 equivalents of Grignard reagent, nucleophilic additions to both carbonyl groups of isatin took place, and 2,3-disubstituted *N*-alkylated chiral indole products were obtained. Alternatively, if 2.2 equivalents of Grignard reagent were employed, the nucleophilic addition only occurred at the more electrophilic C3 position, subsequent reduction then afforded 3-mono-substituted indoles bearing an *N*-alkyl group (Scheme 4).

Since optically enriched *N*-allylated indoles create an entry into bioactive indole derivatives,[13] we illustrated an easy manipulation of our products to such useful structural motifs (Scheme 5). Indole **6a** was converted to iodide **11** in high yield, and *N*-allyl indole derivative **12** was obtained in excellent yield upon the elimination of iodide. The absolute configuration of **12** was determined to be *R* by comparison with the known compound reported in the literature[6c] (see the ESI† for details).

In summary, we devised a novel approach to access chiral *N*-alkylated isatins and indole derivatives. We demonstrated that isatin 3-ketals could undergo efficient *N*-alkylations with enals *via* prolinol-catalyzed iminium activation to afford *N*-alkylated isatins in good yields and excellent enantioselectivities. The *N*-alkylated isatins are not only biologically significant molecules,[14] but also could serve as useful synthetic intermediates, and were readily converted to (2,3-disubstituted) chiral indole derivatives bearing an *N*-alkyl group in high yields. It is noteworthy that this is the first time that isatins are used as activated indole precursors for the preparation of chiral *N*-alkylated indoles. Given the easy availability of isatins, as well as the enormous value of indole derivatives

in biological sciences and medicinal chemistry, the described approach should have immediate, general applications, and we are currently investigating along this line.

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