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Enantioselective Organocatalytic Michael Addition to Unsaturated Indolyl Ketones

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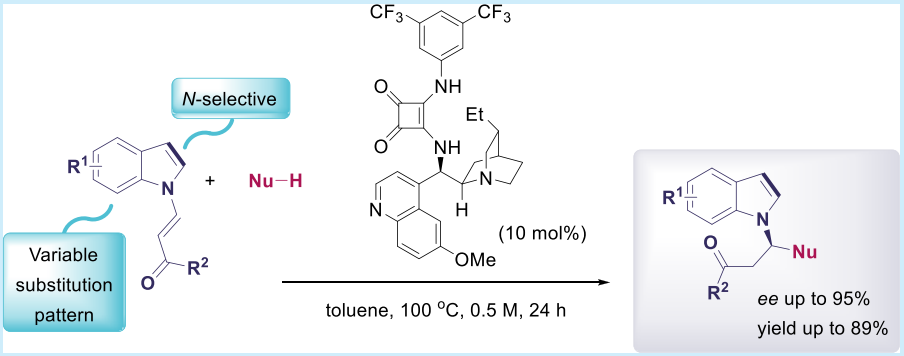

ABSTRACT: An efficient enantioselective organocatalytic method for the synthesis of *N*-alkylated indoles with α-branched alkyl substituents from the corresponding unsaturated indolyl ketones via a Michael addition has been developed. The resulting products were obtained in high enantioselectivities and in good yields. Various nucleophiles (nitroalkanes, malononitrile, malonic esters) can be used. The substitution pattern of the indole ring had no significant impact on the reaction outcome. Both electron-withdrawing and electron-donating substituents in any position of the heteroaromatic ring were well-tolerated.

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Molecules bearing indole scaffolds can be found in a wide range of natural products, pharmaceutical compounds, and agrochemicals.[1] Some biologically active indoles contain a stereogenic center at the α-position of the *N*-atom (Figure 1). Therefore, such compounds have recently gained wide interest in synthetic chemistry[2−4] and in medicinal chemistry.[5]

The stereoselective derivatization of indole at the nitrogen atom with electrophilic reagents is still challenging because the most reactive nucleophilic center of the indole core is at C3.[6] To avoid C3-alkylation and to achieve high *N*-selectivity, the third position of the ring can be protected by substitution or, alternatively, the *N*−*H* acidity and nucleophilicity of the nitrogen atom can be increased by substituents in different positions of the indole core. The application of these two additional conditions provides high regioselectivity of the nucleophilic attack but also changes electronic and steric properties of indole core and limits the scope of the synthetic methodologies.[7]

During the past two decades, the interest in new enantioselective methodologies for the synthesis of chiral *N*-substituted indoles with a branched alkyl substituent has increased considerably.[8] Both direct methods of the derivatization of the indole core and indirect methods starting from other nitrogen-containing heterocycles (isatin, indoline, dihydroindole, etc.) via metal-catalyzed or organocatalytic reactions have been used. Since Trost et al. demonstrated the first enantioselective synthesis of chiral indolocarbazole derivatives (Scheme 1, **I**),[9] several other strategies have been exploited. These methods generally consider indole to be a nucleophilic coupling fragment reacting with different electrophilic partners. However, difficulty in controlling regioselectivity is often a problem.

Recently, Buchwald et al. reported the first polarity reversal strategy where an indole derivative was used as an electrophile in the enantioselective ligand-controlled metal-catalyzed reaction to achieve *N*-alkylated products (Scheme 1, **II**).[10] The method is based on the CuH-catalyzed *N*-alkylation of *N*-(2,4,6-trimethylbenzoyloxy)indole with alkenes.

Based on the approach where an indole derivative was applied as a non-nucleophile,[11] we decided to employ the electrophilic activation mode of the α-carbon of the nitrogen atom by converting an indole to a Michael acceptor (Scheme

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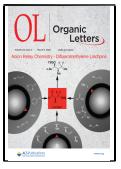

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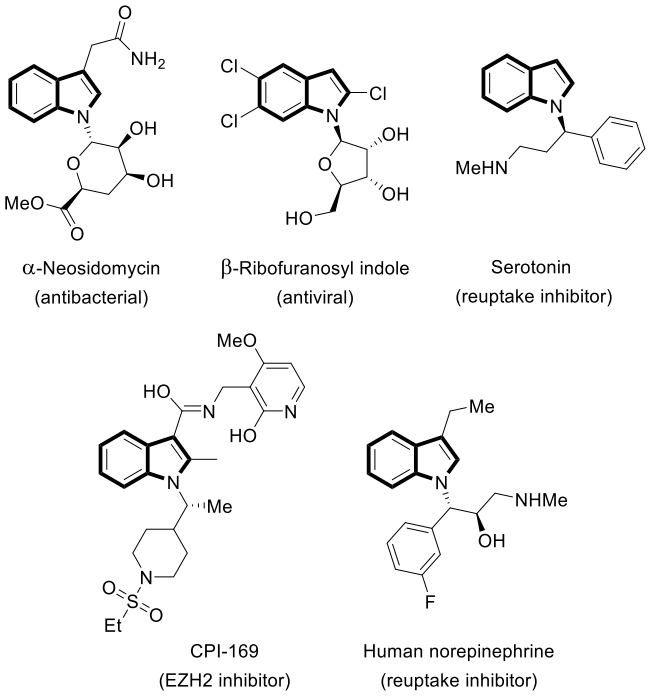
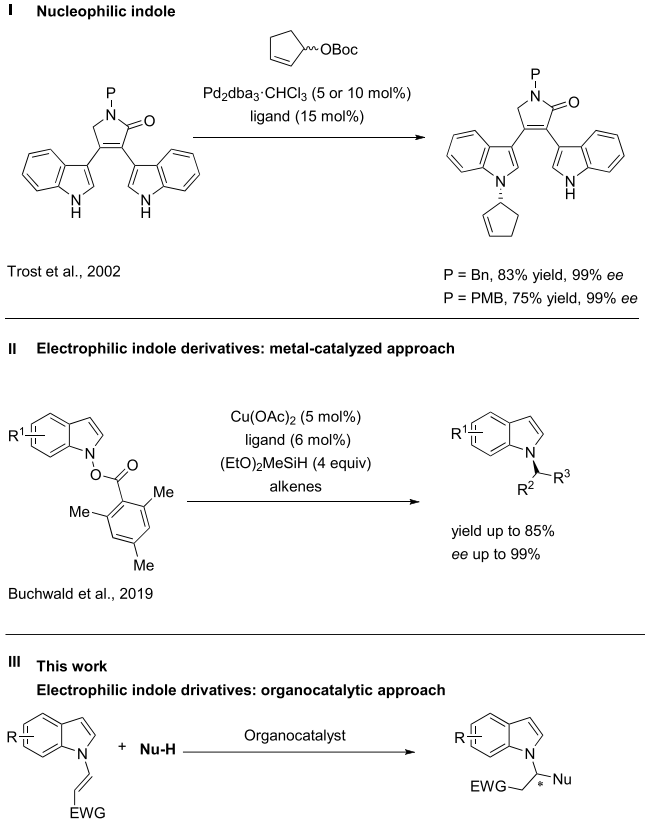


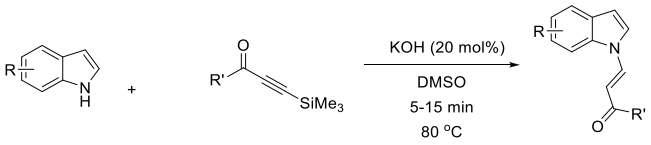
Figure 1. Selected biologically active enantiomeric *N*-substituted indoles.

Scheme 1. Different Approaches to the Enantioselective Synthesis of *N*-Substituted Indoles with Branched Substituents



1, **III**). An appropriate starting material can be prepared by the hydroamination of the corresponding silyl alkynes with an indole (Scheme 2).[12] It is a specific reaction where the only

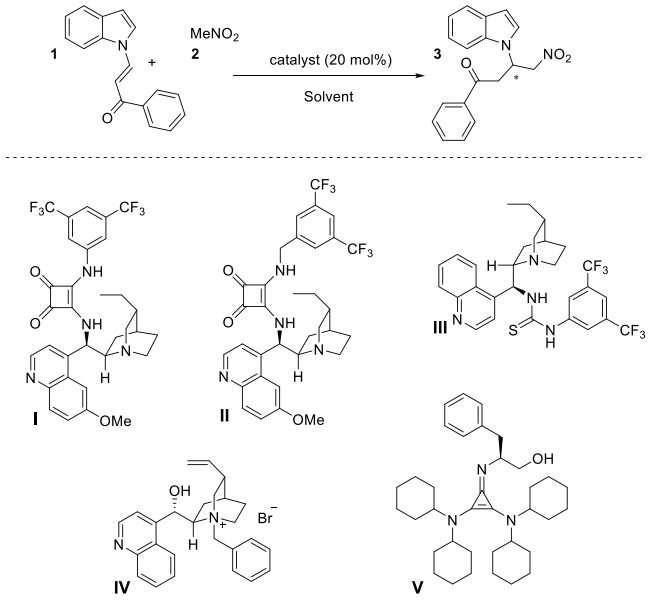
Scheme 2. Hydroamination of Indoles



reaction center in the indole ring is the *N*-atom. The simple synthetic route provides easy access to enaminones possessing indole core and Michael acceptor moiety. An asymmetric 1,4-conjugate addition to the acceptor provides a direct entry to the enantioselective synthesis *N*-substituted indoles with a branched alkyl substituents. This two-step sequence totally excludes the formation of C3-side product due to the application of indole *N*-adducts as electrophiles.

Here, we describe the first enantioselective organocatalytic formal *N*-alkylation of indoles using an indole derivative as a Michael acceptor. To test our hypothesis, compound **1** was synthesized and used as a model compound in a reaction with nitromethane **2** in the presence of organocatalysts (Table 1). For the stereoselective conjugate addition of nitroalkanes to electron-deficient alkenes, various catalysts have been used.[13] The screening of the catalyst was started with hydrogen

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	time (h)	temp (°C)	solvent	conv[b] (%)	ee[c] (%)
1	**I**	48	rt	DCM	nr	nd
2	**I**	48	80	DCE	71	92
3	**II**	48	80	DCE	traces	nd
4	**III**	48	80	DCE	12	−88
5[d]	**IV**	1	rt	DCE	99	*rac*
6	**V**	24	rt	DCE	31	*rac*
7	**I**	48	80	1.4-dioxane	69	94
8	**I**	48	80	toluene	82	94
9	**I**	48	100	toluene	85	94
10[e]	**I**	48	100	toluene	93	92

[a]Reaction conditions: 0.1 mmol scale, 1 equiv of **1**, 10 equiv of **2**, 20 mol % of catalyst, solvent (0.5 mL). [b]Conversion was determined by ^{1}H NMR from the crude mixture. [c]Determined by chiral HPLC analysis. [d]1 equiv of Rb_2CO_3 was added. [e]Toluene (0.2 mL).

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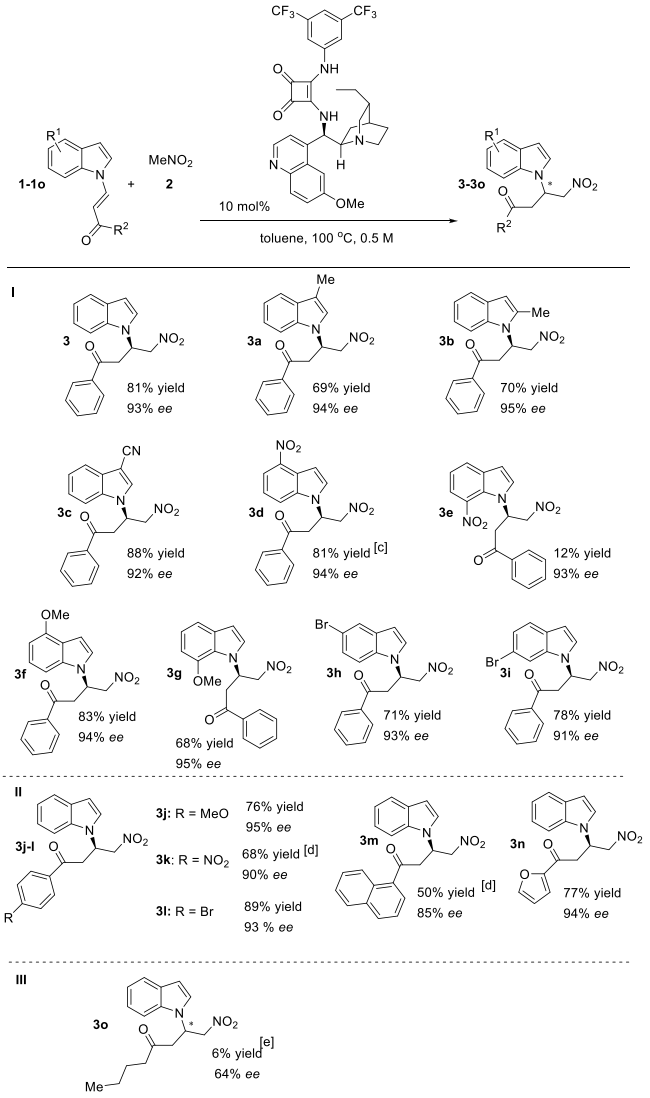
bonding catalysts. Bifunctional cinchona alkaloid-based squaramides **I**, **II**, and thiourea **III** are widely used with nitro-group containing Michael donors.[14,15] The reaction did not take place in the presence of catalyst **I** at room temperature in DCM, although increasing the temperature to 80 °C led to moderate conversion (71%) and afforded product in high ee (92%) in DCE in 2 days (Table 1, entries 1 and 2). Only traces of the product were detected in the presence of the catalyst **II** under the same conditions (Table 1, entry 3). The reaction in the presence of quinine-based thiourea **III** afforded product in high enantioselectivity but the conversion was unreasonably low (Table 1, entry 4). According to our previous experience with indole chemistry with phase-transfer catalysis,[7a] PTC **IV** was used (Table 1, entry 5). Full conversion was achieved at room temperature but the formed product was racemic. Next, cyclopropenimines as enantioselective Brønsted base catalysts were applied.[16] With the catalyst **V**, low conversion of the starting material and obtained racemic product were characteristic (Table 1, entry 6). Next, a brief screening of the solvents with the most selective catalyst **I** revealed that toluene was the best solvent in terms of both yield and enantioselectivity (Table 1, entry 8). A slightly higher reactivity was achieved when the temperature was raised to 100 °C (Table 1, entry 9). Moreover, almost full conversion was reached by increasing the concentration from 0.2 to 0.5 M without a significant impact on the stereoselectivity (Table 1, entry 10).

Additionally, the influence of the catalyst amount on the reaction rate was examined (see, Figure S1). There was no significant difference when 10 or 20 mol % of the catalyst was used. However, the experiment with 5 mol % of the catalyst was inefficient demonstrating a considerable decline in reaction rate and the conversion was only 78% in 26 h. Notably, the catalyst amount did not affect the enantioselectivity of the reaction, and the ee value remained constant and high during the entire experiment.

Under optimized reaction conditions (toluene, 100 °C, 10 mol % of catalyst **I**, and reaction time 24 h), the substrate scope of the reaction was investigated. Initially, variations on the indolyl scaffold were evaluated (Scheme 3, **I**). The reaction was run with monosubstituted indole derivatives that differentiated from each other in the position and nature of the substituent. The incorporation of the methyl group into the C2- or C3-position did not have a significant impact on the reaction yield or on the enantioselectivity. Substrates with electron-withdrawing substituents at the C3- or C4-positions tolerated the reaction well, providing the products **3c** and **3d** in good yields (88 and 81%) and high *ee*-s (92% and 94%). A drastic decline in the reaction yield was detected (most probably a retro-Michael reaction occurred) when the 7-nitro-substituted Michael acceptor **1e** was used (yield 12%). However, the *ee* value of the product **3e** remained high (93%). The tolerance toward electron-donating groups (and also the substituent at the seventh position) on the indolyl ring was well represented by 4- and 7-metoxy-substituted *N*-functionalized indoles. The electron-donating groups did not affect the reactivity, and the desired products **3f** and **3g** were isolated in good yields (83% and 68%) and excellent enantioselectivities (94% and 95%). Halogen-substituted C5- and C6-unsaturated *N*-indolyl ketones reacted smoothly, affording *N*-alkylated indoles **3h** and **3i** in good yields (71% and 78%) and high ee's (93% and 91%). Thus, the substitution pattern of the indole ring is not essential and the method is applicable to the monosubstituted indole derivatives possessing

Scheme 3. Scope and Limitations of the Reaction with Nitromethane[a]



[a]Reaction conditions: 0.2 mmol scale, 1 equiv of **1**−**1o**, 10 equiv of nitromethane, 10 mol % of catalyst **I**, in 0.4 mL of toluene (0.5 M), 24 h. [b]ee was determined by chiral HPLC analysis. [c]0.2 M. [d]0.1 mmol scale. [e]Reaction time 7 days.

substituents in any position. The absolute stereochemistry of product **3g** was unambiguously assigned by single-crystal X-ray diffraction (see the SI), and other compounds in the series were assigned based on the analogy.

Next, we turned our attention to the scope of Michael acceptors with parent indolyl scaffolds (Scheme 3, **II**). Both electron-withdrawing and electron-donating substituents at the *para*-position of a phenyl ring did not have a significant impact on the reaction yield (68% and 76%), but slightly better enantioselectivity (95%) was achieved in the case of methoxy-substituted substrate **1j**. The *p*-bromo-substituted product **3l** was isolated in high yield (89%), and the achieved ee was comparable with the model compound **3**. The bulky 1-naphthyl substituent of **1m** led to a moderate yield (50%) and slightly decreased the *ee* value (85%). Heteroaromatic furyl derivative **3n** was obtained in high yield and ee (77% and 94%, respectively). Notably, the reaction rate and stereoselectivity dropped drastically when the substrate **1o** with the aliphatic

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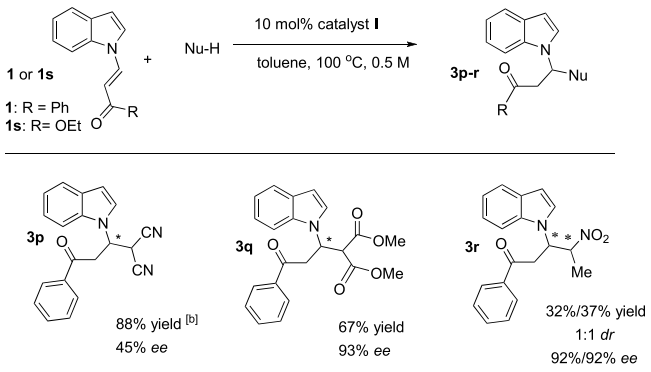
butyl chain was used instead of a phenyl ring (Scheme 3, **III**). The reaction was unacceptably slow, indicating the importance of $\pi-\pi$ interactions. The product **3o** was isolated after 7 days in only 6% yield.

Next, the scope of Michael donors and acceptors was studied briefly (Scheme 4). The reaction with malononitrile

Scheme 4. Scope of Michael Donors and Acceptors[a]

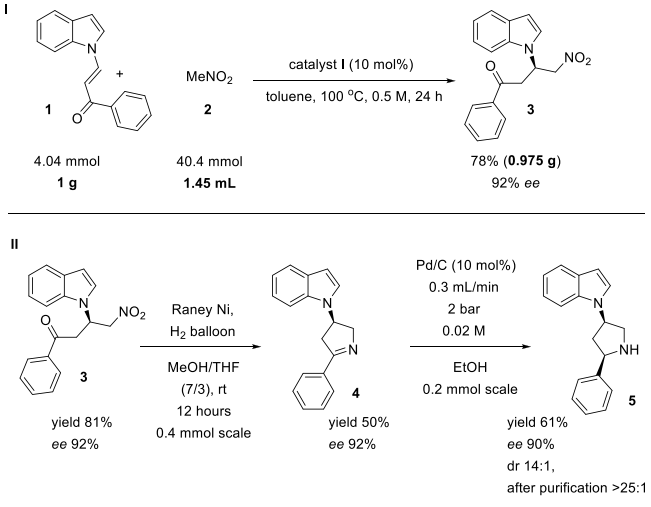


[a]Reaction conditions: 0.2 mmol scale, 1 equiv of **1** or **1o**, 10 equiv of nucleophile, 10 mol % of catalyst **I**, in 0.4 mL of toluene (0.5 M), 24 h. [b]Reaction time 1 h.

was complete with 1h but the enantiomeric purity of the product **3p** was considerably lower. There was no reaction with acetonitrile. Malonic ester reacted smoothly affording product **3q** in 67% yield and 93% ee. A 1:1 mixture diastereomers **3r** was obtained with nitroethane in high ee's (92%/92%). To our delight, the diastereomers of **3r** were chromatographically separable. The reaction with 2,4-pentanedione led to the mixture of products. The substitution of the phenyl ring with an alkoxycarbonyl group in the indole-based Michael acceptor (compound **1s**) led to the substantial decrease of the reactivity and no reaction was detected with nitromethane.

To evaluate the synthetic potential of the current methodology, a gram-scale experiment was performed with substrate **1** (Scheme 5, **I**). The scale-up of the reaction did not affect either the reaction yield or enantioselectivity (78% yield, 92% ee). Furthermore, the synthetic transformation of compound **3** was

Scheme 5. Demonstration of Synthetic Utility



explored. It was converted to a 5-HT_6 receptor modulator analogue precursor **5**.[17] The treatment of compound **3** with Raney nickel induced the reduction of the nitro group to an amino group followed by intramolecular cyclization, affording the corresponding chiral imine **4** without the loss of enantioselectivity (Scheme 5, **II**). The imine **4** was later easily hydrogenated in a flow reactor with Pd/C cartridge providing chiral pyrrolidine derivative **5** in high dr ratio (14:1) and good yield (62%). The *cis*-configuration of the substituents in the pyrrolidine ring was determined by selective NOESY (details in the SI). The diastereomeric ratio of the product **5** was improved after the purification of the reaction (>25:1).

In summary, we have developed the first enantioselective organocatalytic method for the synthesis of *N*-alkylated indoles starting from unsaturated indolyl ketones. The main feature of our method is exploiting an indole derivative as an electrophile totally avoiding the regioselectivity problems common with other *N*-alkylation methods. A wide range of electrophilic indole *N*-adducts bearing various substituents provide exclusively *N*-alkylated indoles with a branched substitutents in good yields (up to 89%) and high to excellent ee values (up to 95%). The enantioselectivity of the reaction does not depend on the substitution pattern of the indole ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00222.

Synthesis of starting compounds, copies of ^{1}H and ^{13}C spectra, and HPLC chromatograms (PDF)

Accession Codes

CCDC 2054770 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.

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