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Remote Activation of the Nucleophilicity of Isatin

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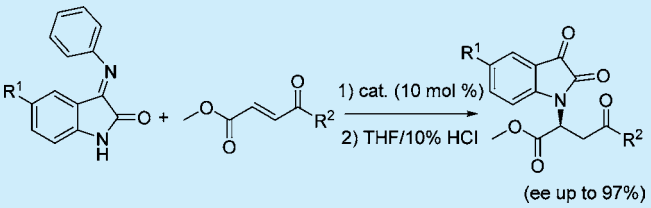
Supporting Information

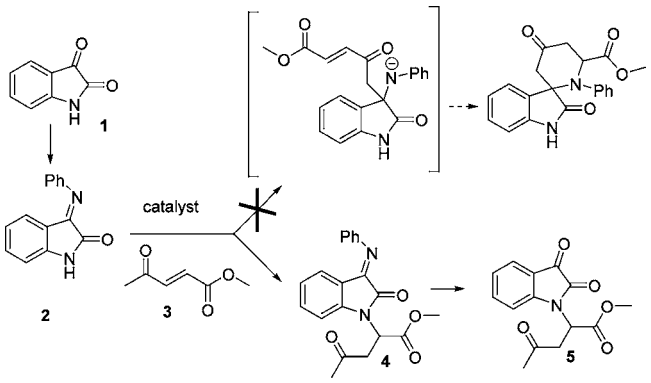
ABSTRACT: The concept of the remote activation of reactivity was first applied in asymmetric organocatalysis. An isatin 3-phenylimine derivative acts as a donor in the thiourea catalyzed asymmetric addition to unsaturated 1,4-ketoesters, affording aza-Michael adducts in high enantiomeric purity and yield.



Isatin **1** is a well-known natural compound.[1] Its derivatives have been widely used as synthetic intermediates for the synthesis of spirocyclic compounds[2] and in multicomponent reactions.[3] Its core structure can be found in various biologically active compounds possessing, among others, anti-HIV,[4] anticancer,[5] antibacterial,[6] and antimalarian properties.[7] The combination of a phenyl ring, a γ-lactam moiety, and a carbonyl group in the isatin molecule gives rise to a variety of chemical transformations. Electrophilic substitution in an aromatic ring,[8] dipolar cycloaddition,[9] and especially the nucleophilic addition to the C3 carbonyl function of isatin are well-described.[10] Much less attention has been paid to the reactivity of the nucleophilic center at nitrogen. So far, reactions at the nitrogen atom are scarce[11] and have mainly been limited to alkylation or acylation to prevent side reactions. To the best of our knowledge, there are only a few references, by the same authors, where this reactivity has been described in a Michael reaction.[12] However, the conditions of these reactions were unconventional, using either solvent-free microwave irradiation or ionic liquids as solvents. No asymmetric version of an aza-Michael reaction of isatin has been described.[13]

Herein, we describe a novel reactivity of isatin-derived imine **2** in a thiourea-catalyzed asymmetric organocatalytic aza-Michael reaction. The key feature of the reaction is the remote activation of the nucleophilicity of the nitrogen atom by a 3-phenylimine moiety. Exploiting the nucleophilicity of the nitrogen atom and using it in reactions with electrophiles considerably broadens the synthetic utility of isatin and makes it possible to use it for the synthesis of more complex cyclic structures. The resulting imine can be easily hydrolyzed with an aqueous workup affording *N*-substituted isatins in a one-pot procedure. In connection with our ongoing studies of 1,4-unsaturated dicarbonyl compounds[14] and organocatalytic cascade reactions[15] we envisioned that the organocatalytic reaction between an enolizable unsaturated 1,4-dicarbonyl compound **3** and imine **2** derived from isatin would give a cascade of Mannich−Michael reactions in the presence of a thiourea catalyst (Scheme 1). To our surprise, no Mannich reaction was observed even in the presence of Pihko catalysts **I** and **III** which are known to be very efficient in promoting Mannich reactions.[16] Instead, aza-Michael product **4** was formed in good yield and high enantioselectivity. During the acidic workup the imine was hydrolyzed and isatin derivative **5** was formed.

Scheme 1. Expected and Actual Reactivity of Imine 2 Derived from Isatin 1



Based on that result, we decided to investigate the aza-Michael reaction in detail. The thiourea catalysts used are presented in Figure 1, and the results of the optimization are in Table 1.

All four catalysts screened resulted exclusively in aza-Michael product **4** with excellent enantioselectivity; however, the reaction rate strongly depended on the catalyst structure. Both catalysts **I** and **IV** showed good results, affording the product in high yield and selectivity in a reasonable time. It is worth mentioning that catalyst **I**, being a dual-activated analogue of **II**, was more efficient, while the reaction with **IV** proceeded much more smoothly than with its dual-activated analogue **III**. Considering the multistep synthesis of catalyst **I** together with its lower reactivity, catalyst **IV** was chosen for

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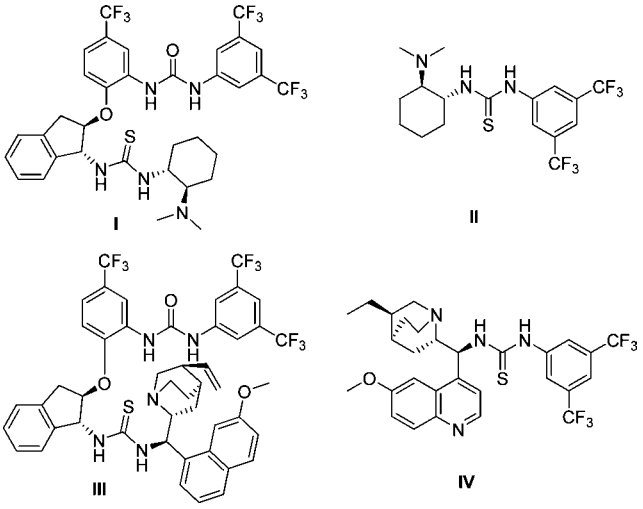
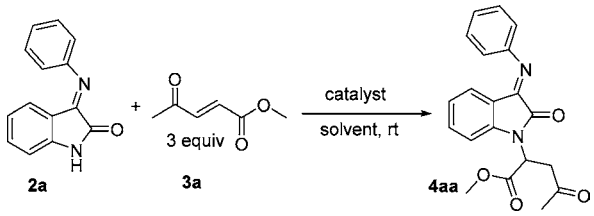


Figure 1. Screened chiral catalysts.

Table 1. Optimization of Reaction Conditions



entry	catalyst (mol %)	solvent	time (h)	yield[a] (%)	ee (%)[b]
1	**I** (20)	toluene	48	99	95
2	**I** (10)	toluene	96	95	98
3	**I** (5)	toluene	216	51	99
4	**II** (10)	toluene	72	46	97
5	**III** (10)	toluene	72	29	97
6	**IV** (10)	toluene	72	95	96[c]
7	**IV** (10)	DCM	72	77	96[c]
8	**IV** (10)	THF	72	51	95[c]

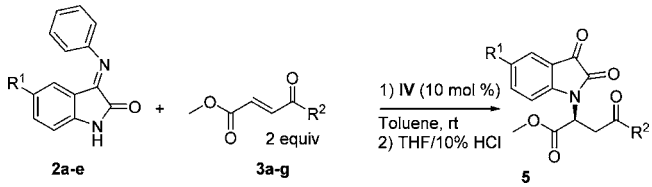
[a]Isolated yield. [b]Determined by chiral HPLC. [c]Opposite enantiomer was in excess.

further investigations. The solvent screening revealed that toluene was the best solvent for the reaction.

With the optimal conditions in hand (10% of catalyst **IV**, toluene, room temperature), the reaction scope was investigated by using aliphatic or aromatic *para*-substituted unsaturated ketoesters **3a**–**g** (2 equiv) and 5-substituted isatin derivatives **2a**–**e** (Table 2).

In all cases, high or excellent enantioselectivities were obtained. Aliphatic ketoester **3a** was less reactive than aromatic ones (Table 2, entries 1 and 2–6). Compounds with electron-withdrawing substituents in the indolinone ring (**2d**, **2e**) increased the acidity of the N–H proton making deprotonation easier and the obtained conjugate base a better nucleophile, or alternatively, shifted the lactam–lactim equilibrium toward a more nucleophilic lactim. A shorter reaction time was needed to obtain a high yield for these compounds (Table 2, entries 10, 11). In contrast, isatin derivatives with electron-donating substituents (**2b**, **2c**) required a longer reaction time (Table 2, entries 8, 9). Michael acceptor **3** was, as expected, activated by electron-withdrawing groups at the aromatic ring of the phenyl-substituted ketoester (Table 2, entries 5, 7).

Table 2. Scope of the Reaction[a]



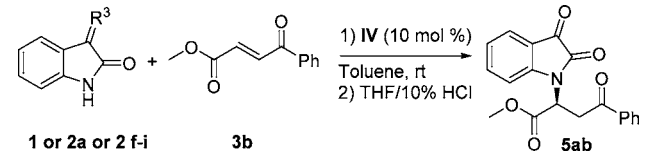
entry	2 R^1	3 R^2	5	time (h)	yield (%)[b]	ee (%)[c,d]
1	**2a**, H	**3a**, Me	**5aa**	72	80	97
2	**2a**, H	**3b**, Ph	**5ab**	18	95	94
3	**2a**, H	**3c**, *p*MePh	**5ac**	16	97	95
4	**2a**, H	**3d**, *p*MeOPh	**5ad**	16	95	96
5	**2a**, H	**3e**, *p*ClPh	**5ae**	5	95	93
6	**2a**, H	**3f**, *p*BrPh	**5af**	24	82	96
7[e]	**2a**, H	**3g**, *p*NO_2Ph	**5ag**	4	73	88
8	**2b**, Me	**3b**, Ph	**5bb**	20	83	90
9	**2c**, MeO	**3b**, Ph	**5cb**	96	75	95
10	**2d**, Br	**3b**, Ph	**5db**	3.5	91	91
11	**2e**, NO_2	**3b**, Ph	**5eb**	2.5	96	95

[a]For experimental conditions, see: Supporting Information. [b]Isolated yield. [c]Determined by HPLC with chiral stationary phase. [d]Absolute configuration (*S*) was determined by X-ray structure analysis[17] of **5ae** and presumed to be the same with the other substrates. [e]Ethyl ester was used.

Next, the role of the imine functional group was studied. Isatin **1** was much less effective in terms of yield, enantioselectivity, and reaction time than its imine derivative **2**. According to *ab initio* quantum chemistry calculations there is no significant difference in the charges of the amide N and H atoms of compounds **1** and **2a** (see Supporting Information). Therefore, we assumed that the interaction of imine derivative **2** with the catalyst was dependent on the substitution at the N-atom, and that plays a crucial role in the outcome of the reaction.

To check this assumption, various Schiff bases with different substituents (**2a**, **2f**–**i**) were prepared and tested in the reaction (Table 3). The results clearly illustrated that the difference in imine reactivity was based on its substituent. While using *N*-phenyl substituted imine **2a** resulted in nearly quantitative yield or product **5** within a reasonable reaction time (Table 3, entry 2), the other substituted imines **2f**–**i** were considerably less active.

Table 3. Effect of the Imine Substituent



entry	R^3	time (h)	yield (%)[a]	ee (%)[b]
1[c]	(isatin **1**), O	48	59	62
2	**2a**, *N*-Ph	18	97	94
3	**2f**, *N*-H	144	12	75
4	**2g**, *N*-iPr	128	30	88
5	**2h**, *N*-*p*-MeOPh	72	62	98
6	**2i**, *N*-*p*-NO_2Ph	72	21	90

[a]Isolated yield. [b]Determined by HPLC with chiral stationary phase. [c]3 equiv of ketoester **3b** used.

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Unsubstituted imine **2f** afforded the product in the lowest yield; however, the enantioselectivity of the reaction was higher than with isatin **1** (Table 3, entries 1, 3). Because **2f** was even less reactive than isatin, we concluded that replacing the carbonyl group with an unsubstituted imino group did not activate isatin. *N*-Alkyl substitution at the N atom (compound **2g**) exhibited slightly enhanced reactivity if compared with **2f**; however, the yield was still much lower than that for **2a** (Table 3, entries 2 and 4). The substitution at the *para* position of the aromatic ring of phenylimines (compounds **2h** and **2i**) also had a deleterious effect on the reactivity. Surprisingly, both the electron-donating methoxy group (compound **2h**) and electron-withdrawing nitro group (compound **2i**) had negative impacts on the reaction (Table 3, entries 5, 6). The low reactivity of nitro-substituted compound **2i** was probably caused by its poorer solubility if compared with the other investigated imines.

These experiments revealed the essential role of *N*-phenyl substitution at imine in making isatin derivative **2a** an active aza-Michael donor. An extra aromatic ring of imine **2a** (comparing with isatin **1**) let us assume that, in addition to the H-bonding interaction between the catalyst and oxindole derivative, $\pi-\pi$ interactions between aromatic rings could play some role. We assumed that the remote activation of isatin via complexation between imine **2** and catalyst **IV** by $\pi-\pi$ interactions of a quinoline fragment of the catalyst and imine's aromatic ring took place, increasing the nucleophilicity of the heterocyclic nitrogen. Simultaneously, the tertiary amino group from the quinuclidine fragment of **IV** could assist the deprotonation of the N−H proton of lactam and ketoester **3** could be activated by the hydrogen bonds from a thiourea moiety of the catalyst.

In order to obtain more evidence of the possible $\pi-\pi$ stacking between the catalyst **IV** and imines, the mixtures of these compounds were studied by NMR. A comparison of NMR spectra of imine **2a** (E/Z = 95:5) and the mixture of imine and catalyst **IV** showed differences in their chemical shifts (see Supporting Information). In the presence of the catalyst, the most significant differences occurred in the five-membered ring of isatin. The difference was biggest for the α-carbon to the nitrogen (0.5 ppm for ^{13}C). All signals of the protons of the six-membered ring of **2a** were shifted to a higher field pointing to the association with the aromatic ring(s) of the catalyst. The same can be concluded from the broadening of doublets of phenyl ring protons of imine. In the presence of catalyst **IV**, the NH signal of phenylimine **2a** at 135.0 ppm in ^{15}N NMR spectra ($CDCl_3$ solution at 296 K) was shifted 2.2 ppm to lower field. Imine nitrogen of **2a** which gave a signal at 356.7 ppm could not be detected on the addition of the catalyst due to the exchange broadening of *ortho* protons of the phenyl ring used for the detection of the ^{15}N resonance via the HMBC spectrum. In the case of imine **2g** (E/Z = 3:1) methyls of the isopropyl group became diastereotopic. It is only possible then that imine is in anisotropic environment, most likely due to binding to an enantiomerically pure catalyst.

In conclusion, the first highly enantioselective aza-Michael addition of isatin is reported. The reaction efficiency was greatly enhanced by derivatizing the isatin to a Schiff base that can be easily converted back by hydrolysis with no loss of yield and enantiomeric excess. This is the first example of remote activation of nucleophilicity in an organocatalytic reaction. The described reaction is efficient affording *N*-substituted isatins in high enantiomeric purity and high yield.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, copies of NMR spectra, HPLC chromatograms, X-ray structure, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) The .cif file of **5ae** structure is available free of charge as a part of the Supporting Information.

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