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Chiral Phosphoric Acid-Catalyzed Direct Asymmetric Mannich Reaction of Cyclic *C*-Acylimines with Simple Ketones: Facile Access to C2-Quaternary Indolin-3-ones

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A chiral Brønsted acid-catalyzed direct asymmetric Mannich reaction of simple ketones with cyclic *C*-acylimines has been established for the synthesis of C2-quaternary indolin-3-ones. In the presence of 5-10 mol % chiral phosphoric acid, a series of 2-(2-oxo-2-phenylethyl)-2-arylindolin-3-ones were obtained in good to high yield with up to 99% ee. The adducts obtained could be readily converted into indolines, tricyclic indolin-3-ones, and tetracyclic tetrahydro-indolo[1,2-*a*]quinolines by simple modifications.

Indolin-3-one bearing a chiral quaternary carbon centre[1] at the C2 position is an important structure unit of many natural biologically active substances, such as (-)-isatisine A, (+)-austamide and brevianamide A (Figure 1).[2,3] Moreover, compounds with this skeleton have also found very interesting applications in the areas of fluorescence labelling and optoelectronic materials in recent years.[4] Thus, the development of catalytic methods for accessing functionalized indolin-3-one building blocks with structural complexity and skeleton diversity in an enantioselective fashion has always been the subject of intensive ongoing research.[5] As a subset, 2-(2-oxo-2-phenylethyl)-2-arylindolin-3-ones represent an attractive class of molecules that bear a quaternary carbon centre, and its multiple functionalities provide potential possibilities for the synthesis of biologically active compounds. In 2015, Ramana and co-workers reported a one-pot [3 + 2]-cycloaddition of nitrone with olefins followed by the Ru-catalyzed redox-neutral N–O bond cleavage of intermediate isoxazolidine to give the desired products with up to 74% yield (Scheme 1a).[6a] Subsequently, Miao's group disclosed a Cs_2CO_3-catalyzed reaction of 2-oxindoles with enones for the synthesis of 2,2-disubstituted indolin-3-ones through domino "Michael addition / oxidation / ring-cleavage / C–N coupling" process (Scheme 1b).[6b] More recently, the group of Rao and Zhang described a Pd-catalyzed one-pot transformation of 2-alkynyl arylazides and methyl ketones for the synthesis of 2-(2-oxo-2-phenylethyl)-2-arylindolin-3-ones (Scheme 1c).[6c] Encouraged by these important precedents, along with our interest in the Brønsted acid-catalyzed asymmetric construction of enantioenriched chiral compounds,[7] we envisioned that optically active 2-(2-oxo-2-phenylethyl)-2-arylindolin-3-ones could be constructed through the asymmetric Mannich reaction[8] of cyclic *C*-acylimines (2-substituted-3*H*-indol-3-ones)

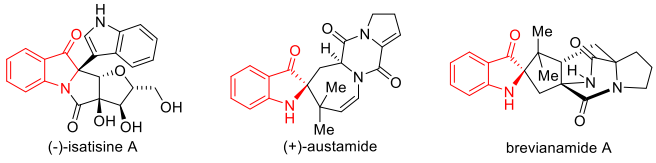
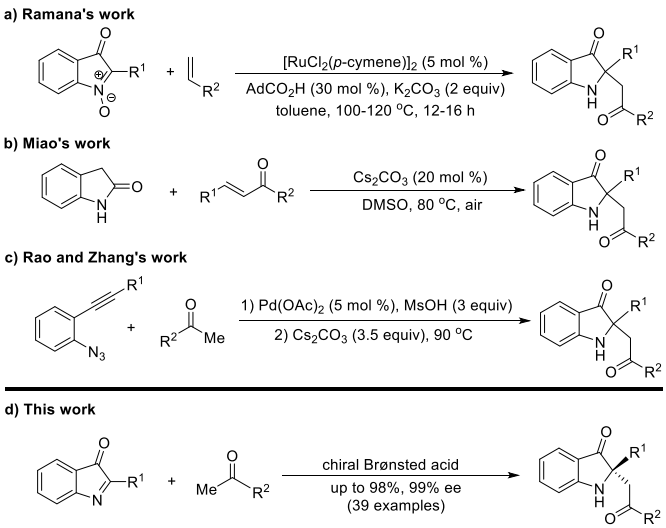


Figure 1 Selected natural products containing C2-quaternary indolin-3-ones.



Scheme 1 Synthesis of 2-(2-oxo-2-phenylethyl)-2-arylindolin-3-ones.

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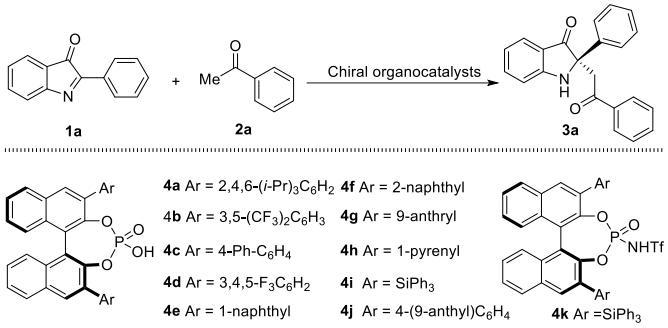
with simple ketones in the presence of chiral phosphoric acids (Scheme 1d). Herein, we describe the successful implementation of this process to provide C2-quaternary indolin-3-one derivatives and significant opportunities for structural diversification.

Initially, we embarked on this direct Mannich reaction between 2-phenyl-3*H*-indol-3-one **1a** and acetophenone **2a** with 5 mol % of chiral phosphoric acid (CPA)[9] **4a** in CH_2Cl_2. To our delight, the reaction proceeded smoothly to provide the desired product **3a** in 87% yield with 70% ee after being stirred at room temperature (Table 1, entry 1). This result encouraged us to further evaluate different CPAs for this transformation. As shown in Table 1, under these conditions, the Mannich product **3a** was obtained in high yield and with variable enantioselectivity (entries 2–10), with catalyst **4i** giving the best performance (entry 9). And chiral *N*-triflyl phosphoramide **4k**, a stronger Brønsted acid gave a similar result (entry 11). Unfortunately, no product was observed using the catalyst **4i** at 0 °C within 6 days (entry 12). Further investigations show that the solvent has no significant effect on both yields and ee values (entries 13–16). It is worth noting that the increasing reaction temperature could accelerate reaction largely without obviously affecting its enantioselectivity (entries 16–18). Thus, the Mannich reaction of 2-phenyl-3*H*-indol-3-one **1a** and acetophenone **2a** could be performed in dichloroethane at 25 °C to provide the desired product **3a** in 87% yield with 86% ee (entry 16).

Table 1. Catalyst screening and condition optimization.[a]



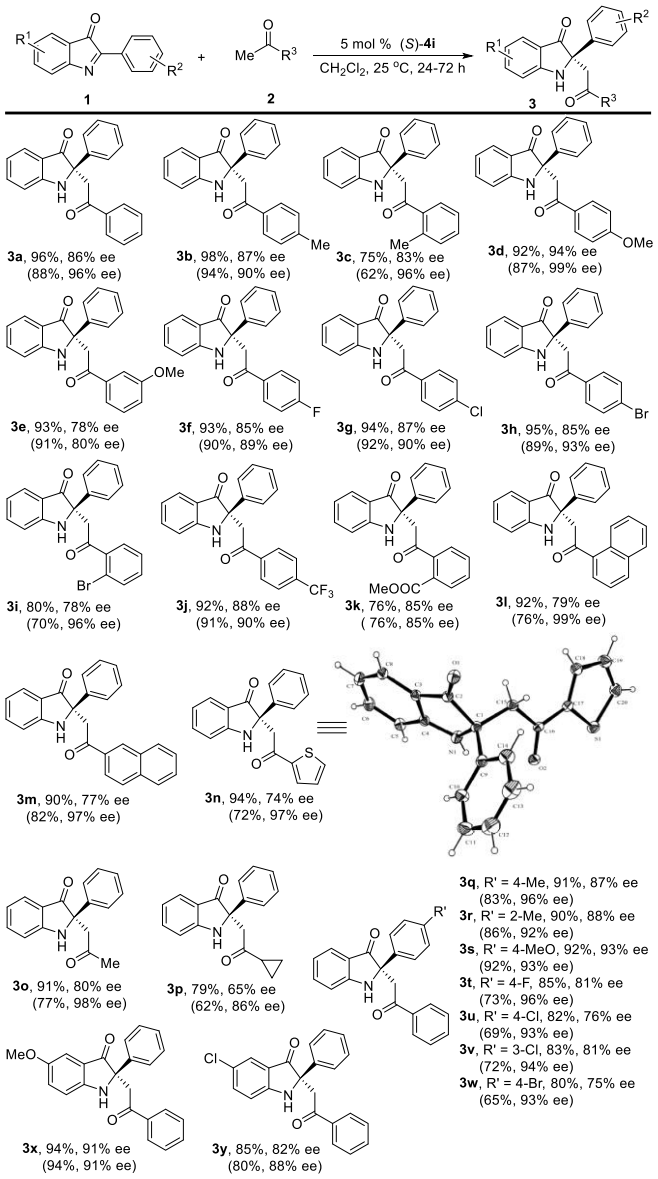
Entry	Catalyst	Solvent /Temp (°C) / Time (h)	Yield (%)[b]	Ee (%)[c]
1	**4a**	CH_2Cl_2 / 25/ 72	87	70
2	**4b**	CH_2Cl_2 / 25 / 24	84	40
3	**4c**	CH_2Cl_2 / 25 / 144	93	46
4	**4d**	CH_2Cl_2 / 25 / 96	81	43
5	**4e**	CH_2Cl_2 / 25/ 120	88	72
6	**4f**	CH_2Cl_2 /25 / 144	86	70
7	**4g**	CH_2Cl_2 /25 /144	76	79
8	**4h**	CH_2Cl_2 / 25 / 144	79	75
9	**4i**	CH_2Cl_2 /25/ 36	96	86
10	**4j**	CH_2Cl_2 /25 / 96	90	71
11	**4k**	CH_2Cl_2 / 25 / 48	91	83
12	**4i**	CH_2Cl_2 / 0 / 144	0	-
13	**4i**	THF / 25 / 96	88	80
14	**4i**	toluene / 25 / 12	80	83
15	**4i**	$CHCl_3$ / 25 / 34	91	85
16	**4i**	$ClCH_2CH_2Cl$/ 25 / 24	87	86
17	**4i**	$ClCH_2CH_2Cl$/ 40 / 15	83	86
18	**4i**	$ClCH_2CH_2Cl$/ 60 / 10	72	85

[a] General reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), and catalyst **4** (5 mol %) in solvent (1 mL) at the given temperature for the stated time. [b] Isolated yield. [c] Enantiomeric excess (ee) was determined by chiral HPLC analysis.

With the optimized reaction conditions in hand, a series of 2-aryl-substituted 3*H*-indol-3-one derivatives **1** was reacted with both aromatic and aliphatic ketones **2** to probe the generality of the reaction (Scheme 2). The corresponding Mannich products (**3b**, **3d**–**3h**, and **3j**) were obtained in good to high yields and enantioselectivities using several acetophenones bearing either electron-donating or electron-withdrawing substituents at the *meta* and *para* positions on the phenyl ring. The *ortho*-substituted phenyl methyl ketones (**2c**, **2i**, and **2k**) resulted in a relatively lower yields and enantioselectivities, probably owing to the steric effects (**3c**, **3i**, and **3k**). The fused-aryl and heteroaryl ketones and aliphatic ketones were also applicable to this Mannich reaction (**3l**–**3p**). X-ray crystallographic analysis of **3n** allowed the absolute configuration of the stereogenic center to be assigned as *R*. And similar results were obtained for 2-phenyl-3*H*-indol-3-ones **1** with both electron-donating and -withdrawing groups on the indolone ring (**3q**–**3y**). Notably, in most cases an improvement of the enantiopurity of the adducts could be achieved by simple recrystallization.

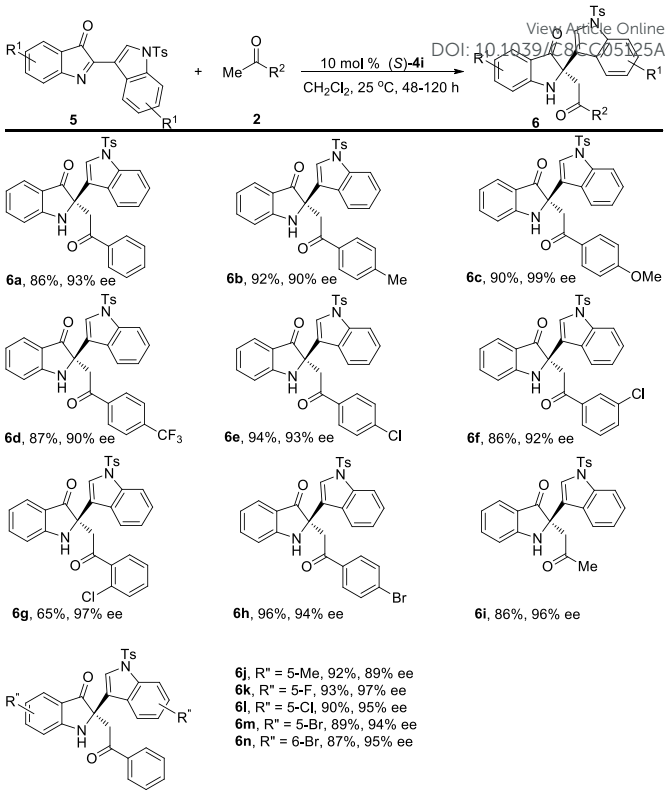
Next, various 1'*H*,3*H*-[2,3'-biindol]-3-ones[7h] were tested to further broaden the substrate scope for this Mannich reaction. To our surprise, no products could be obtained by increasing catalyst loading to 20 mol % within 10 days. Considering the previous results, we thought that the free NH moiety of indole might be the key factor to prevent this transformation. Thus *N*-tosylated 1'*H*,3*H*-[2,3'-biindol]-3-ones **5**[10] were used as new substrates. Gratifyingly, the Mannich reaction proceeded very well in the presence of 10 mol % (*S*)-**4i** to give the desired product **6a** in 86% yield and 93% ee at room temperature. Encouraged by this result, we turned our attention to expand the substrate scope. In general, both aromatic and aliphatic ketones **2** reacted with a series of *N*-tosylated 1'*H*,3*H*-[2,3'-biindol]-3-ones to give the corresponding products **6a**–**n** in good yields with excellent enantioselectivities. And the absolute configuration of **6i** could also be assigned by comparison with the chromatographic and optical rotation data reported in the literature.[5a]

To demonstrate the synthetic utility of this protocol, we conducted further manipulation by using the obtained products. As shown in Scheme 4, **3d** was efficiently converted into 2,2-disubstituted indoline **7** with good enantiomeric excess (84%) by using $LiAlH_4$ and $AlCl_3$. The resulting *gem*-disubstituted indolines are particularly interesting skeleton because of their strong bioactivity profiles, as seen in representative examples such as kopsinine, strempeliopine, and vallesamidine.[11] And as part of our continuing interest in constructing multisubstituted fused aziridines,[12] a new fused

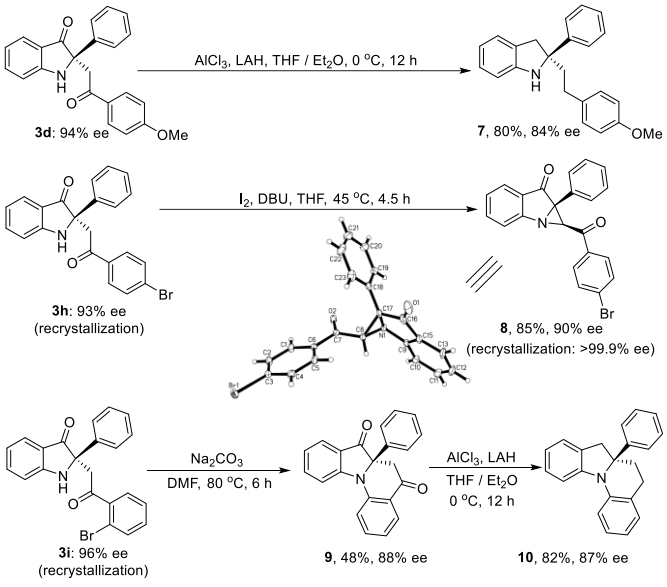


Scheme 2 Scope of the direct asymmetric Mannich reaction. Values in parentheses are for mother liquor after recrystallization.

aziridine derivative **8** was obtained as a single diastereomer in 85% yield with 90% ee without obvious racemization according to a modified procedure.[6b] The absolute configuration of **8** was unambiguously established by single-crystal X-ray structural analysis.[13] The aziridine motif is also widely present in many biologically active natural products.[14] Of particular interest, product **3i** underwent an intramolecular S_NAr reaction[15] to afford an uncommon and intriguing polycyclic indolin-3-one compound **9**, which could be further transformed into a etracyclic tetrahydroindolo[1,2-*a*]quinoline molecule **10**. The tetracyclic molecule represents an important class of structural unit that is frequently found in a large family of natural products and biologically active molecules such as leuconoxine, and secoleuconoxine.[16] It should be noted that the conventional transition metal-catalysed amination or Ullmann coupling approach proved to be ineffective.[17] And the addition



Scheme 3 Direct asymmetric Mannich reaction of 1'*H*,3*H*-[2,3'-biindol]-3-ones.



Scheme 4 Further synthetic transformations.

of strong base may cause significant racemization in these transformations (see the ESI).

On the basis of the experimental results and previous reports,[7] a potential transition state was proposed. As shown in Figure 2, BINOL-derived phosphoric acid could

simultaneously activate cyclic *C*-acylimine and enolized ketone through the hydrogen bonding interaction, therefore creating a chiral environment wherein the enol attacks the *Si* face of the C=N group preferentially. Further studies are required to fully elucidate the detailed mechanism of this direct Mannich reaction.

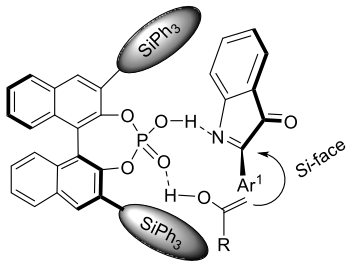


Figure 2 Proposed transition state for the reaction.

In summary, we have developed a chiral Brønsted acid-catalyzed direct asymmetric Mannich reaction of cyclic *C*-acylimines with unmodified methyl ketones. This method tolerates a series of 2-aryl-substituted 3*H*-indol-3-ones, affording the C2-quaternary indolin-3-ones in good to high yields (up to 98%) and enantioselectivities (up to 99% ee). Moreover, the adducts obtained can be readily converted into various interesting compounds such as *gem*-disubstituted indolines, tricyclic indolin-3-one fused aziridines, and tetracyclic tetrahydro-indolo[1,2-*a*]quinolines by simple modifications. Further applications of this strategy to other substrate classes are ongoing in our laboratory.

Notes and references

‡ This work was supported by the National Natural Science Foundation of China (No. 21472137, 21532008, and 21772142), the National Basic Research Program of China (973 Program, 2014CB745100).

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