

# The Direct Asymmetric $\alpha$ Alkylation of Ketones by Brønsted Acid Catalysis\*\*

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The development of new catalytic asymmetric methodologies for organic transformations is an important area of research for organic chemists.<sup>[1]</sup> Among the numerous organic reactions,  $\alpha$  alkylation of carbonyl compounds is a highly valuable C–C bond-formation strategy.<sup>[2]</sup> In the last ten years, a number of organocatalytic methods, including asymmetric phase-transfer catalysis<sup>[3]</sup> and asymmetric amino catalysis,<sup>[4]</sup> have been developed for the  $\alpha$  alkylation of carbonyl compounds. Alcohols are ideal alkylation reagents for this reaction because water is the sole by-product.<sup>[5,4a–g]</sup> Theoretically, Brønsted acids are good catalysts for promoting the  $\alpha$  alkylation of carbonyl compounds, especially ketones and aldehydes, with alcohols. The reasons for this include the following: 1) Brønsted acids can promote enol formation with the ketones or aldehydes;<sup>[6]</sup> 2) Brønsted acids can activate alcohols by protonating the hydroxy group, and then promote formation of an active carbocation intermediate;<sup>[4a–i]</sup> and 3) whereas amino catalysts are potentially alkylated by the alkylation reagent and then deactivated,<sup>[4o]</sup> Brønsted acids are not. Despite their advantages, Brønsted acids have not been used for asymmetric catalysis in this important C–C bond-formation reaction,<sup>[7,8]</sup> and only a few direct alkylation reactions of carbonyl compounds with alcohols catalyzed by achiral Brønsted acids have been described.<sup>[6c,9]</sup> Our group reported an asymmetric Brønsted acid catalyzed  $\alpha$  alkylation reaction in 2009, but this involved enamides, preactivated ketones, as donors.<sup>[10]</sup> As a continuation of this research, we have attempted direct asymmetric  $\alpha$  alkylation of ketones with alcohols by Brønsted acid catalysis, and herein we report the first example of such an alkylation of unmodified ketones with alcohols in high yields (up to 98 %) with high diastereoselectivities (d.r., up to 99:1), and high enantioselectivities [up to 97 % enantiomeric excess (*ee*)].

Recently, 3-indolylmethanols were extensively used in the alkylation reaction of carbonyl compounds through organocatalysis.<sup>[4b,h–i,10]</sup> However, our initial attempt to introduce the 3-indolylmethanol **1a** (Figure 1) for the direct alkylation of unmodified ketones was unsuccessful. We found that **1a**

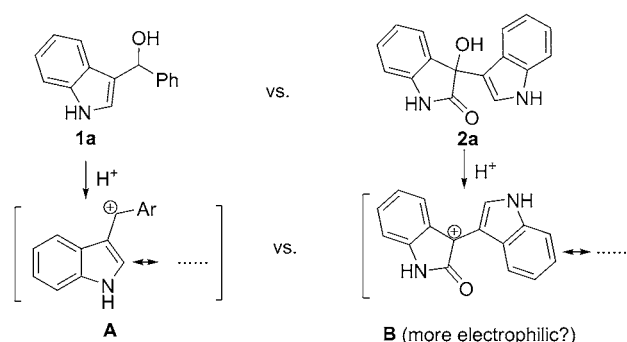


Figure 1. Selection of the alkylation reagent in this work.

decomposed quickly when it was mixed with cyclohexanone and a Brønsted acid catalyst in an organic solvent (see the Supporting Information). It is well known that **1a** can produce the stable carbocation or vinylogous imino intermediate **A** under acidic conditions (Figure 1),<sup>[4b,h–i,10]</sup> and we speculated that the weak electrophilicity of **A** could lead to the poor results in the direct alkylation of ketones. According to Mayr et al., ketones have lower nucleophilicity (*N*) than enamides. Consequently, the electrophilicity (*E*) of the corresponding electrophiles should be increased.<sup>[11]</sup> Because positive charge density has a large influence on electrophilicity, we chose to introduce an electron-withdrawing group on 3-indolylmethanol **1a** to increase the electrophilicity of intermediate **A**. The isatin-derived 3-hydroxy-3-indolyl-oxindole **2a** could serve as a good alkylation reagent for the direct alkylation reaction. Compound **2a** can lead to the intermediate **B**, which has similar stability to **A**, under acidic conditions. In addition, the amide group of intermediate **B** increases the positive charge density on C3, thus making it more electrophilic than intermediate **A**. Therefore, the reaction of **2a** with ketones could generate chiral 3-indolyl-oxindoles, a novel type of indole<sup>[12]</sup> and oxindole<sup>[13]</sup> that could be potentially used in indole alkaloid synthesis.<sup>[14]</sup> Thus, cyclohexanone (**3a**) and 3-hydroxy-3-indolyl-oxindole **2a** were chosen as reactants for the present study (see Table 1). 1,1'-Bi-2-naphthol-derived phosphoric acids **4** were chosen as catalysts because they are powerful Brønsted acid catalysts that have been used in many organic transformations.<sup>[15]</sup>

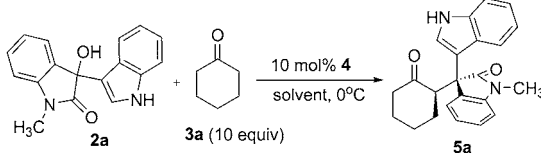
After the selection of the compounds for the model reaction, **2a** was reacted with **3a** in toluene with **4a** as the catalyst. As expected, the reaction proceeded smoothly and the desired alkylation product **5a** was obtained in good yield with high diastereoselectivity and enantioselectivity (Table 1, entry 1). These promising results encouraged evaluation of the catalytic ability of other phosphoric acids (Figure 2). All of the catalysts were acidified before use<sup>[16]</sup> (see the Support-

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**Table 1:** Screening of catalysts and optimization of reaction conditions.<sup>[a]</sup>



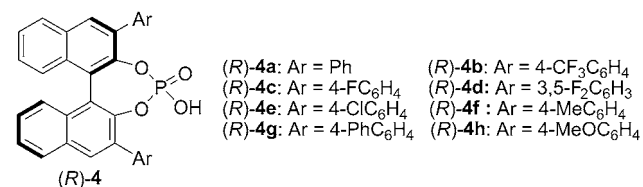
Entry	4	Solvent	t [h]	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	4a	toluene	18	71	93:7	88
2	4b	toluene	18	91	75:25	84
3	4c	toluene	18	97	83:17	85
4	4d	toluene	18	57	83:17	76
5	4e	toluene	18	98	86:14	83
6	4f	toluene	18	97	89:11	86
7	4g	toluene	18	89	86:14	80
8	4a	CH <sub>2</sub> Cl <sub>2</sub>	18	53	82:18	80
9	4a	CHCl <sub>3</sub>	48	trace	—	—
10	4a	Et <sub>2</sub> O	48	22	—	—
11	4a	MTBE	48	24	—	—
12	4a	m-xylene	18	84	92:8	86
13	4a	toluene	66	52	95:5	92 <sup>[e]</sup>
14	4h	toluene	48	80	95:5	91 <sup>[e]</sup>
15	4h	toluene	84	98	95:5	92 <sup>[f]</sup>

[a] The reaction was carried out with **2a** (0.1 mmol), **3a** (1.0 mmol), and **4** (0.01 mmol) in toluene (2 mL). [b] Yield of isolated product.

[c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The reaction was carried out at −10°C. [f] Using 0.5 mmol **3a** and 4 mL toluene at −15°C.

MTBE = methyl *tert*-butyl ether.

ing Information). As shown in Table 1, **4a** is the best catalyst in terms of diastereoselectivity and enantioselectivity (Table 1, entry 1). The introduction of *para*-substituted phenyl groups on the 3,3'-position of (*R*)-**4** increased the



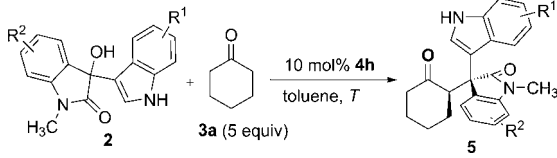
**Figure 2.** Catalysts used in this work.

yield greatly, but the diastereoselectivity and enantioselectivity decreased slightly (entries 2 and 3, and 5–7 versus entry 1). Evaluation of the solvent indicated that toluene was the best solvent for this reaction. Although the diastereoselectivity and enantioselectivity of **5a** increased slightly when the reaction was conducted at low temperature, the yield decreased dramatically (Table 1, entry 13). The catalyst **4h**, bearing electron-rich *para*-substituted phenyl groups on the 3,3'-position, had better catalytic activity than **4a** in this reaction (Table 1, entry 14 versus 13). Excellent outcomes (98% yield, 95:5 d.r., and 92% ee) were obtained when this reaction was carried out in toluene at −15°C with **4h** (Table 1, entry 15).

After the optimal reaction conditions were established, the substrate scope of the substituted 3-hydroxy-3-indolyllox-

indoles **2** in this alkylation reaction was investigated (Table 2). First, substitution of the indole ring was investigated (Table 2, entries 1–8). The enantioselectivities greatly depended upon the substituents on the indole ring. For

**Table 2:** The substrate scope of 3-hydroxy-3-indolylloxindoles.<sup>[a]</sup>



Entry	R <sup>1</sup> , R <sup>2</sup> , ( <b>2</b> )	T [°C]	5	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	H, H ( <b>2a</b> )	−15	<b>5a</b>	98	95:5	92
2	5-MeO, H ( <b>2b</b> )	−15	<b>5b</b>	65	95:5	91
3	5-Me, H ( <b>2c</b> )	−15	<b>5c</b>	84	95:5	91
4	6-Me, H ( <b>2d</b> )	−15	<b>5d</b>	86	94:6	93
5	7-Me, H ( <b>2e</b> )	−15	<b>5e</b>	91	86:14	93
6	5-Cl, H ( <b>2f</b> )	−10	<b>5f</b>	95	88:12	84
7	5-Br, H ( <b>2g</b> )	−10	<b>5g</b>	90	87:13	80
8	6-F, H ( <b>2h</b> )	−10	<b>5h</b>	69	99:1	85
9	H, 5-Me ( <b>2i</b> )	−5	<b>5i</b>	94	90:10	92
10	H, 7-Cl ( <b>2j</b> )	0	<b>5j</b>	82	93:7	89
11	5-MeO, 7-Cl ( <b>2k</b> )	−15	<b>5k</b>	90	94:6	92
12	5-MeO, 5-Cl ( <b>2l</b> )	0	<b>5l</b>	94	90:10	91
13	5-MeO, 5-Br ( <b>2m</b> )	0	<b>5m</b>	74	89:11	90
14	6-Me, 5-F ( <b>2n</b> )	−5	<b>5n</b>	66	92:8	91
15	6-Me, 6-Cl ( <b>2o</b> )	−15	<b>5o</b>	71	93:7	92

[a] The reaction was carried out with **2** (0.1 mmol), **3a** (0.5 mmol), and **4h** (0.01 mmol) in toluene (4 mL) for 48–159 h (see the Supporting Information). [b] Yield of two isolated diastereomers. [c] Diastereomeric ratio determined by <sup>1</sup>H NMR spectroscopy on the crude reaction mixture. [d] The enantioselectivity of the major component determined by HPLC analysis using a chiral stationary phase.

example, high enantioselectivities were obtained when compound **2** had an electron-rich indole ring (Table 2, entries 2–5), whereas the enantioselectivities decreased slightly when the indole ring was electron deficient (Table 2, entries 6–8). Substitution on the oxindole ring was then investigated (Table 2, entries 9–15). The desired products **5i–5o** were obtained in high yields with high diastereoselectivities and enantioselectivities with both electron-rich and electron-deficient oxindole rings (Table 2, entries 9–15).

The substrate scope of various cyclic ketones and acyclic ketones in this reaction was also investigated (Table 3). Six-membered cyclic ketones, such as tetrahydropyran-4-one (**3b**), tetrahydrothiopyran-4-one (**3c**), the N-protected piperidin-4-one **3d**, and 1,4-dioxaspiro[4.5]decan-8-one (**3e**), produced the desired products **5p–5t** in high yields with high diastereoselectivities and enantioselectivities (Table 3, entries 1–5). The best enantioselectivity in this work (97% ee) was obtained when ketone **3c** reacted with **2e** in toluene with **4h** as the catalyst (Table 3, entry 3). The yields and enantioselectivities decreased when a five- or seven-membered cyclic ketone was used as the donor (Table 3, entries 6 and 7). Notably, acyclic ketones were also suitable for this alkylation reaction. For example, butanone reacted with **2a** smoothly and produced the desired product **5w** in moderate

**Table 3:** The substrate scope of the ketones.<sup>[a]</sup>

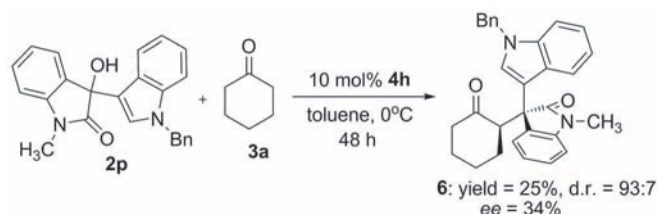
Entry	<b>3</b>	<i>T</i> [°C]	<i>t</i> [h]	<b>5</b>	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	<i>ee</i> [%] <sup>[d]</sup>
1	<b>3b</b>	−5	91	<b>5p</b>	77	78:22	92
2	<b>3c</b>	−5	88	<b>5q</b>	91	85:15	92
3	<b>3c</b>	−5	60	<b>5r</b>	94	83:17	97 <sup>[e]</sup>
4	<b>3d</b>	0	71	<b>5s</b>	84	89:11	86
5	<b>3e</b>	−5	66	<b>5t</b>	87	86:14	88 <sup>[e]</sup>
6	<b>3f</b>	0	44	<b>5u</b>	49	98:2	81
7	<b>3g</b>	0	93	<b>5v</b>	53	93:7	74
8	<b>3h</b>	0	93	<b>5w</b>	53	97:3	81
9	<b>3i</b>	0	91	<b>5x</b>	37	95:5	97 <sup>[e]</sup>
10	<b>3j</b>	0	88	<b>5y</b>	27	95:5	89

[a] The reaction was carried out with **2a** (0.1 mmol), **3** (0.5 mmol), and **4h** (0.01 mmol) in toluene (4 mL). [b] Yield of two isolates diastereomers. [c] Diastereomeric ratio determined by <sup>1</sup>H NMR spectroscopy. [d] Enantioselectivity determined by HPLC analysis using a chiral stationary phase. [e] Using **2e** as an acceptor.

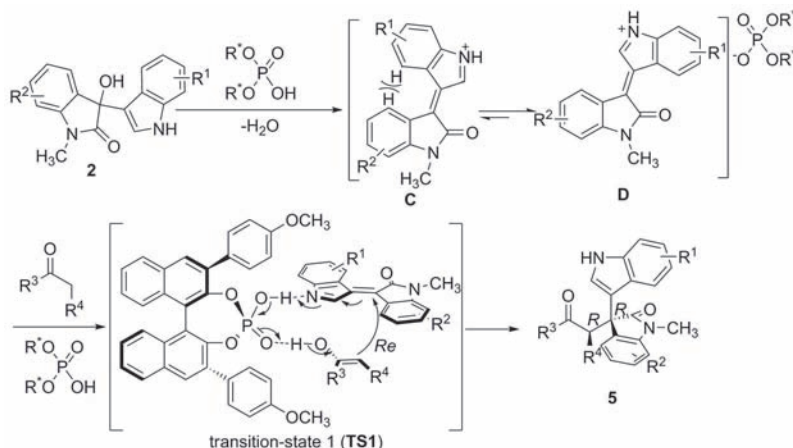
yield with high diastereoselectivity and good enantioselectivity (Table 3, entry 8). Ketones with large steric bulk, such as 2-pentanone (**3i**) and 3-pentanone (**3j**), did participate in this reaction and the desired products were obtained with high diastereoselectivities and good enantioselectivities but in low yields (Table 3, entries 9 and 10). These are successful examples of highly enantioselective Brønsted acid catalyzed organic reactions of aliphatic ketones having large steric bulk.<sup>[6]</sup>

The relative and absolute configurations of **5q** (*R,R*) were determined by X-ray crystallography of recrystallized **5q** (see the Supporting Information).<sup>[17]</sup> The stereochemistry of other alkylation products were assigned by comparison to **5q**.

The 3-hydroxy-3-indolyloxindoles **2** can form two possible active intermediates under acidic conditions.<sup>[10]</sup> One is the carbocation intermediate, and the other is the vinylogous imino intermediate. To clarify what intermediate was involved in this alkylation reaction, the *N*-benzyl-indole-derived 3-hydroxy-3-indolyloxindole **2p** was synthesized and used in this transformation. As shown in Scheme 1, the yield and enantioselectivity of **6** decreased greatly, thus indicating that the 3-hydroxy-3-indolyloxindole underwent this reaction via a vinylogous imino intermediate. Thus, the 3-hydroxy-3-indolyloxindole formed the corresponding vinylogous imino intermediates **C** and **D** under acidic conditions (Scheme 2). We believe the intermediate **D** is dominant because of the unfavorable steric interactions between the two hydrogen atoms on the isatin ring and indole ring in **C**. The catalyst complexes with **D** and the enol form of the ketone reacts through the transition-state **TS1**. The enol attacks the vinylogous imino **D** at the *Re* face, thus giving the alkylation adduct **5**.


**Scheme 1.** The alkylation reaction of cyclohexanone with **2p**. Bn = benzyl.

In conclusion, this is the first example of a Brønsted acid catalyzed direct alkylation of unmodified ketones with an activated alcohol. Phosphoric acid promoted this transformation to afford 3-indolyloxindoles in high yields (up to 98 %) with high diastereoselectivities (up to 99:1) and high enantioselectivities (up to 97% *ee*). This reaction has broad substrate scope for the substituted 3-hydroxy-3-indolyloxin-


**Scheme 2.** A possible transition state (**TS1**) in this reaction.

doles and ketones. Both cyclic and acyclic ketones afforded the corresponding products with good outcomes.

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- [17] CCDC 842355 (**5q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).