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Highly Enantioselective Alkylation Reaction of Enamides by Brønsted-Acid Catalysis

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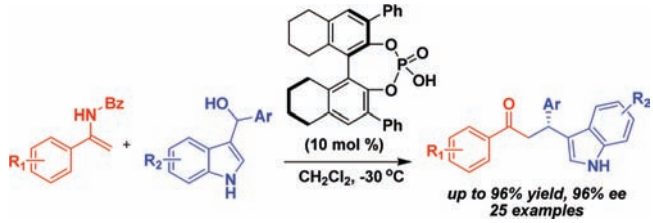
ABSTRACT



The H_8−BINOL-derived, phosphoric acid catalyzed, highly enatioselective alkylation reaction of enamides with indolyl alcohols has been described. A phosphoric acid derived from H8-BINOL enabled an asymmetric α-alkylation of enamides with indolyl alcohols to give *β*-aryl 3-(3-indolyl)propanones in high yields (up to 96%) and with excellent enantioselectivity (up to 96% ee).

The catalytic enantioselective intermolecular α-alkylation of carbonyl derivatives is a highly challenging and valuable C−C bond-forming strategy in organic synthesis.[1] This enormously important methodology has remained a long-standing problem in asymmetric catalysis in general until very recently.[2] In the past decades, extensive efforts have been devoted to the development of general enantioselective α-alkylation of carbonyl compounds.[3] Most recently, Petrini and Melchiorre and Cozzi reported their enamine-catalyzed asymmetric alkylation of aldehydes on the basis of stable carbocations.[4] MacMillan and co-workers have introduced a new enamine catalytic activation concept termed singly occupied molecular orbital (SOMO) catalysis, enabling highly enanantioselective catalytic direct α-alkylation of aldehydes.[5] Despite these elegant methods, a Brønsted acid

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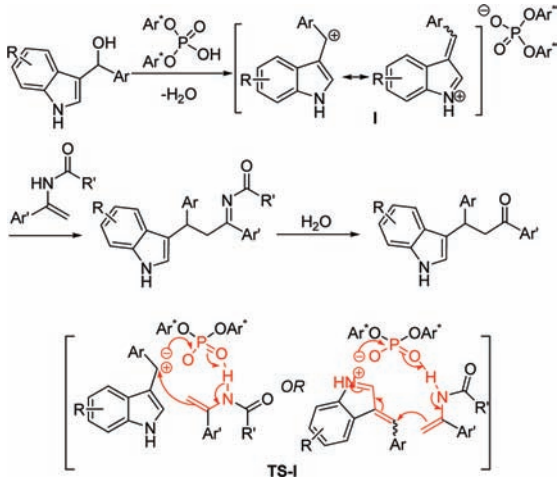
catalyzed asymmetric alkylation of carbonyl compounds has not yet been reported.

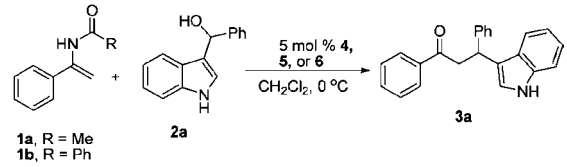
The chiral counterion strategy has successfully been used in the fields of phase-transfer catalysis, transition-metal catalysis, and organocatalysis.[3a,6] Chiral Brønsted acids, in particular, chiral phosphoric acids, are powerful organocatalysts in asymmetric organic synthesis.[7,8] The chiral ion pairs between phosphate anions and cations, including iminiums,[9] metal ions,[6b] and carbocations,[4a] are well-known in the fields of chiral phosphoric acid catalyzed organic synthesis. On the basis of the chiral phosphate anion−iminium interaction model, List and co-workers developed a powerful concept of asymmetric counteranion-directed catalysis (ACDC) and have successfully applied this strategy to several highly enantioselective transformations.[9a−c] Inspired by these findings, we proposed that the ACDC concept might principally be applicable to the organocatalytic alkylation reaction, as long as the cation generated in situ from alcohols under acidic conditions forms a tight chiral ion pair with the phosphate anion. (1*H*-Indol-3-yl)(aryl)methanols can form stable cations in the presence of a Brønsted acid,[10] thereby allowing the formation of a chiral ion pair **I** with chiral phosphate.[11] Enamides are important nucleophiles participating in many C−C and C−N bond-forming reactions.[12] In principle, the Lewis basic phosphoryl oxygen in the tight ion pair **I** will be able to activate the enamide by a hydrogen-bonding interaction with the proton of the enamide,[13] leading to possible **TS-I** that results in an intramolecular alkylation or a conjugated addition reaction[14] in an enantioselective manner (Scheme 1). Herein, we report a highly enantioselective alkylation of enamides using chiral ion pairs to control stereochemistry.

Scheme 1. Genaral Strategy for the Alkylation Reaction of Enamides



To validate our hypothesis, a reaction of *N*-(1-phenylvinyl)acetamide **1a** with (1*H*-indol-3-yl)(phenyl)methanol **2a** was conducted in the presence of a BINOL-based phosphoric acid **4a** in CH_2Cl_2 at 0 °C. As expected, the reaction successfully proceeded to afford *β*-indolyl ketone **3a** in 84% yield and with 51% ee (Table 1, entry 1). The preliminary results encouraged us to evaluate BINOL- and H_8−BINOL-based phosphoric acids **4** and **5** as well the *O*-linked bisphosphoric acid **6** (Table 1). The catalyst **5a** (Figure 1) turned out to be the catalyst of choice in terms of yield and enantioselectivity (entry 8). A survey of solvents revealed that dichloromethane enabled the reaction to give the best results (Table S1, Supporting Information). The N-protecting group of enamide has great influence on the enantioselectivity. Thus, a high enantioselectivity was obtained by the replacement of Ac (acetyl) with Bz (benzoyl) as the

Table 1. Screening Catalysts and Optimization of Reaction Conditions[a]



entry	1	catalyst	time (h)	yield[b] (%)	ee[c] (%)
1	**1a**	**4a**	12	84	51
2	**1a**	**4b**	12	84	27
3	**1a**	**4c**	12	74	33
4	**1a**	**4d**	12	92	16
5	**1a**	**4e**	12	78	53
6	**1a**	**4f**	12	58	41
7	**1a**	**4g**	4	51	48[d]
8	**1a**	**5a**	12	78	56
9	**1a**	**5b**	20	81	38[d]
10	**1a**	**6**	4	86	14[d]
11	**1b**	**4a**	5	26	79[d]
12	**1b**	**4a**	34	90	91[e]
13	**1b**	**5a**[f]	51	73	92[g]

[a] The reaction was carried out with **1** (0.2 mmol), **2** (0.1 mmol), and 5 mol % of catalyst in CH_2Cl_2 (2 mL) at 0 °C. [b] Isolated yield. [c] The ee value was determined by HPLC on an AS-H column. [d] Using 0.12 mmol of **1**. [e] Using 10 mol % of **4a** in CH_2Cl_2 (3 mL) at −20 °C. [f] The **5a** was acidified by 2 M HCl before use (see the Supporting Information). [g] Using 10 mol % of **5a** in CH_2Cl_2 (3 mL) at −30 °C.

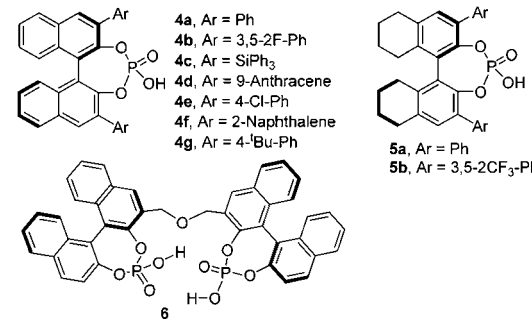
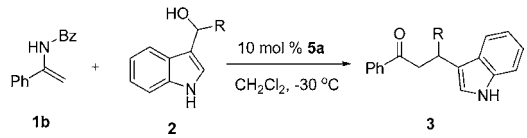


Figure 1. Catalysts used in this work.

protecting group (entry 11). When the reaction was conducted with 10 mol % of **4a** at −20 °C, the product **3a** was isolated in 90% yield with excellent enatioselectivity of 91% ee (entry 12). Upon conducting the reaction at an even lower temperature, the catalyst **5a** offered 92% ee although the reaction comparably slowed (entry 13).

Having established the optimal reaction conditions, we explored the substrate scope, first emphasizing the generality for the aryl substituent of (1*H*-indol-3-yl)(aryl)methanols (Table 2, entries 1−11). Both electron-rich and electron-deficient aryl groups were tolerable and provided high yields and excellent enantioselectivities. Both of the (1*H*-indol-3-yl)(aryl)methanols bearing a phenyl group with a para substituent, a meta substituent, or 3,4-disubstituents were suitable reaction partners able to participate in smooth alkylation reactions with excellent stereochemical outcomes.

Table 2. Scope of (1*H*-Indol-3-yl)(aryl)methanols **2**[a]



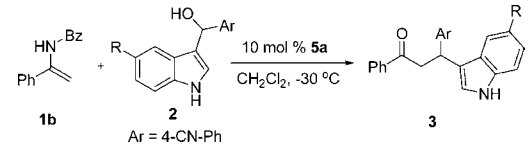
entry	3	R	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**	Ph	34	90	91[d]
2	**3b**	4-MePh	57	80	92
3	**3c**	4-ClPh	64	74	91
4	**3d**	4-BrPh	51	72	92
5	**3e**	4-CNPh	57	80	94
6	**3f**	4-CF_3Ph	56	96	90[d]
7	**3g**	3-FPh	48	78	90
8	**3h**	3-NO_2Ph	57	85	90
9	**3i**	3-CNPh	51	74	91
10	**3j**	3,4-2FPh	57	89	94
11	**3k**	3-Cl-4-FPh	48	90	90
12	**3l**	2-naphthal	48	90	90
13		Bn	48	0	-[e]

[a] The reaction was carried out with **1b** (0.2 mmol), **2** (0.1 mmol), and 10 mol % of **5a** in CH_2Cl_2 (3 mL) at −30 °C. [b] Isolated yield. [c] The ee value was determined by HPLC on an AS-H, AD-H, or Chromasil CHI-TBB column. [d] Using 10 mol % **4a** as catalyst. [e] No desired reaction occurred.

The (1*H*-indol-3-yl)(2-naphthal)methanol reacted with **1b** to afford the product **3k** in 90% yield with 90% ee (entry 12). Unfortunately, no reaction occurred when we replaced the diaryl methanol by 1-(1*H*-indol-3-yl)-2-phenylethanol (Table 2, entry 13).

The next exploration of the scope with respect to the substituent on indole ring was performed (Table 3). The

Table 3. Scope of 5-Substituted Indolyl Alcohols **2**[a]



entry	3	R	time (h)	yield[b] (%)	ee[c] (%)
1	**3m**	Cl	68	80	88
2	**3n**	Br	68	79	85
3	**3o**	Me	68	70	95
4	**3p**	MeO	68	69	94

[a] The reaction was carried out with **1b** (0.2 mmol), **2** (0.1 mmol), 10 mol % of **5a** in CH_2Cl_2 (3 mL) at −30 °C. [b] Isolated yield. [c] The ee value was determined by HPLC on an AS-H, AD-H, or Chromasil CHI-TBB column.

electron-donating substituent on the 5-position of the indole ring had a positive influence on the enantioselectivity. Thus, the alcohols derived from 5-methylindole and 5-methoxyindole underwent the alkylation with **1b** to afford **3o** and **3p** with 95% ee and 94% ee, respectively (entries 3 and 4). On the contrary, the introduction of electronically withdrawing substituents to the 5-position of the indole ring resulted in a slight decrease in the enantioselectivity (entries 1 and 2).

The generality for the enamide component was also examined (Table 4). The enamides bearing either an electronically poor or rich phenyl substituent were able to smoothly undergo the alkylation reaction with various indole-derived alcohols, giving rise to the desired products in high yields with excellent enantioselectivities. In particular, the 4-chlorophenyl enamide offered the highest enantioselectivity (96% ee, Table 4, entries 1−3). A much cleaner reaction with no sacrifice of the enantioselectivity was realized by introducing an electronically rich phenyl group to the enamides (Table 4, entries 6−8). The enamide **1e** could not undergo this alkylation reaction with indolyl alcohol **2a** under the optimal conditions (Table 4, entry 10). It is noteworthy that asymmetric organocatalytic Michael additions of indoles to chalcones afforded chiral β-aryl ketones of type **3** with only moderate enantioselectivity;[15] therefore, this method

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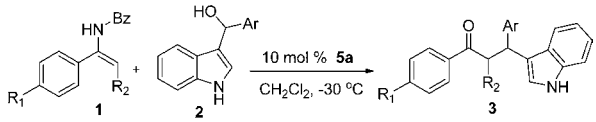
(14) In the conjugated addition manner, there may exist another interaction model, in which the phosphoric acid activate the vinyloguos imino intermediates and enamides by hydrogen bonding, respectively.

Table 4. Scope of Enamides and Several Indolyl Alcohols[a]



1c: R_1 = Cl, R_2 = H
1d: R_1 = Me, R_2 = H
1e: R_1 = H, R_2 = Me

entry	3	1	Ar	time (h)	yield[b] (%)	ee[c] (%)
1	**3q**	**1c**	4-CNPh	66	78	96
2	**3r**	**1c**	3-Cl-4-FPh	66	83	96
3	**3s**	**1c**	3,4-2FPh	66	85	96
4	**3t**	**1c**	2-naphthal	66	75	93
5	**3u**	**1c**	4-MePh	60	84	92
6	**3v**	**1d**	4-CNPh	66	91	93
7	**3w**	**1d**	3,4-2FPh	66	90	94
8	**3x**	**1d**	3-Cl-4-FPh	66	87	92
9	**3y**	**1d**	4-MePh	60	85	90
10		**1e**	Ph	48	0	–[d]

[a] The reaction was carried out with **1** (0.2 mmol), **2** (0.1 mmol), and 10 mol % of **5a** in CH_2Cl_2 (3 mL) at −30 °C. [b] Isolated yield. [c] The ee value was determined by HPLC on an AS-H, AD-H, or Chromasil CHI-TBB column. [d] No desired reaction occurred.

provides a unique access to highly enantiomerically enriched β-indolyl ketones which contain the indole framework, a type of privileged structural motif present in a large number of natural products and therapeutic agents.[16]

In summary, we have disclosed the first Brønsted acid catalyzed highly enatioselective alkylation reaction of enamides with indolyl alcohols. The phosphoric acid **5a** enabled the α-alkylation of enamides with indolyl alcohols to give β-aryl 3-(3-indolyl) propanones in high yields (up to 96%) and with excellent enantioselectivities (up to 96% ee). This work not only represents an unprecedented protocol for the organocatalytic α-alkylation of carbonyl compounds complementary to the protocols using aminocatalysis but is also the first case to apply the chiral counteranion-direct catalysis to highly enantioselective organocatalytic alkylation reactions. In addition, this method provides a new access to β-indolyl ketone compounds with high enantiomeric purity.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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