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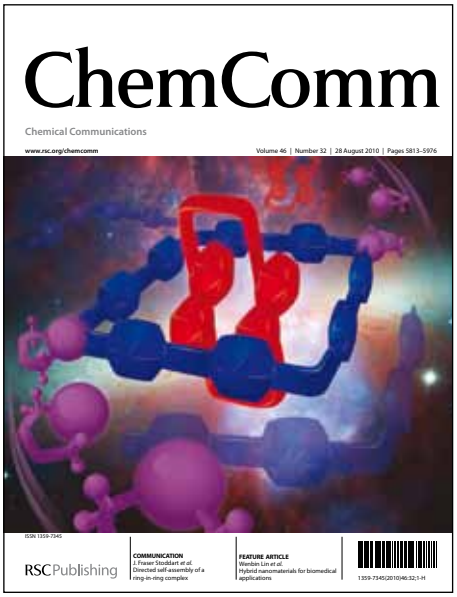

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ARTICLE TYPE

Asymmetric direct α-alkylation of 2-oxindoles with Michlers Hydrol catalyzed by bis-cinchona alkaloid/Brønsted acid via S_N1-type pathway†

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An enantioselective direct α-alkylation of 2-oxindoles with Michlers Hydrol via S_N1-type pathway in the non-covalent activation mode using the bis-cinchona alkaloid and Brønsted acid as the co-catalyst was developed in good to high yields and enantioselectivities.

Inspired by the works of Enders[1], Rueping[2] and Melchiorre[3], Cozzi and co-workers introduced carbocations to asymmetric organocatalysis in 2008,[4] when the promising S_N1-type reaction had seldom been used for stereoselective tranformations. Only a few years passed, it has been becoming a powerful and attractive tool in organic synthesis. Enamine-catalyzed asymmetric reaction of carbocations have accomplished the α-alkylation of aldehydes and ketones. However, there is no successful example of the enantioselective direct α-alkylation of amides involving carbocation. Among all the reported catalytic asymmetric reactions involving carbocation, the majority is charactered by the combination of a chiral enamine and a carbocation via the covalent activation mode.[4-5] In contrast, there is only one successful example[6] reported through non-covalent mechanism,[7] which was promoted by the chiral phosphoric acid.[8] Although the chiral tertiary amine bearing the thiourea moiety was used as a catalyst in the alkylation of oxazolones under the non-covalent catalysis, the attempts for efficient asymmetric induction failed and only 13% ee was obtained.[9] The poor enantioselectivity might be attributed to the flexibility of non-covalent catalysis for stereocontrol and the poor stability of the generated carbocation.

In general, if the alcohol was used as an electrophile to undergo alkylation reaction, the hydroxy group of the alcohol must be converted to the fuctional group with stronger leaving ability[3, 5f] However, the direct alkylation reaction with the alcohol is a significant and attractive chemical transformation owing to its green, atom-economical and environmentally benign properties.[10] Therefore, the asymmetric alkylation reaction utilizing carbocations directly generated from alcohols is of great significance. On the other hand, the oxindoles bearing a quaternary carbon stereocenter at 3-position of the indole ring constitute a ubiquitous structural motif in a variety of natural products and biologically active drug candidates.[11]

Herein, we would like to report our preliminary results of an enantioselective α-alkylation of 2-oxindoles with Michlers Hydrol promoted by a proper combination of bis-tertiary amine and Brønsted acid (1:1) in the non-covalent mode.

Bis(4-dimethylamino-phenyl)methanol **2** (Michlers Hydrol), which can generate a stabilized carbocation under acidic conditions,[12] was employed in the model reaction with N-Boc-3-benzyl-2-oxindole **1a**. Initially, cinchona alkaloids, **3a** (QD) or **3b** (DHQD) was used as the catalyst with benzoic acid as co-catalyst at room temperature to give the product **5a** in 55~58% yield. Unfortunatly, in both cases, the product was a racemic mixture (Table 1, entries 1 and 2).

It was noteworthy that the biscinchona alkaloids could provide a stronger interaction with substrates than monocinchona alkaloids.[13] Therefore, the subsequent catalyst screening focused on biscinchona alkaloids (**3c**~**3g**, Figure 1) under the same reaction conditions. Compared with pseudoenantiomer $(DHQ)_2PHAL$ (**3c**), $(DHQD)_2PHAL$ (**3d**) showed better stereocontrol, with opposite configuration of newly formed chiral center (entry 3 vs 4). When the linker was changed to 2,5-diphenylpyrimidine (**3e**), the reaction provided lower yield and the enantioselectivity sharply decreased to 24% (entry 5). The stereoselectivity was even reversed with the use of anthracene-9,10-dione unit as a linker (**3f**) (entry 6). Athough the reaction could proceed smoothly in the presence of catalyst **3g** with the phthalate linker, poor asymmetric induction was observed (entry 7).

Subsequently, various acids were employed as co-catalyst in the **3d**-catalyzed reaction of **1a** with **2** (Table 2). Among the achiral organic and inorganic acids (entries 1 to 6), MsOH displayed the best catalytic efficiency (85% yield and 76% ee) (entry 4). For chiral Brønsted acid, in comparison with **(*S*)-4b**, chiral phosphoric acid **(*S*)-4a** relatively matched with the catalyst bis-cinchona alkaloid **3d** (entries 7 and 9). However, in the absence of **3d**, single catalyst **(*S*)-4a** could offer very poor result (entry 8, 7% ee). To our surprise, the same enantioselectivity and value were deduced for both

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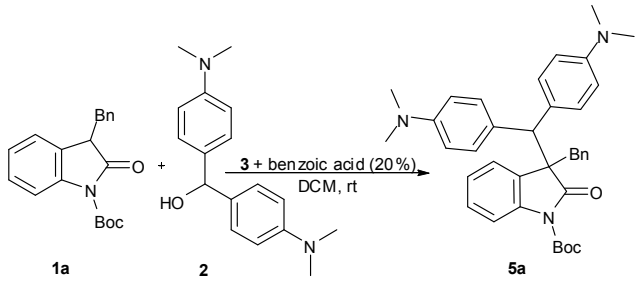
enantiomers of camphorsulfonic acid **4c** (entries 10 and 11), which seemed that the chirality of anion of acid did not determine the transfer of stereochemistry during the catalysis.

Table 1. Catalyst Screening for the reaction of **1a** with **2**[a]



1a **2** **5a**

Entry	Catalyst	Yield (%)[b]	Ee (%)[c]
1	**3a**	58	rac
2	**3b**	55	rac
3	**3c**	69	-26[d]
4	**3d**	79	66
5	**3e**	57	24
6	**3f**	69	-5[d]
7	**3g**	83	40

[a] Reaction conditions: **1a** (0.11 mmol), **2** (0.1 mmol), 20 mol % of **3**, 20 mol % of benzoic acid, 0.5 mL DCM. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The opposite enantiomer was obtained.

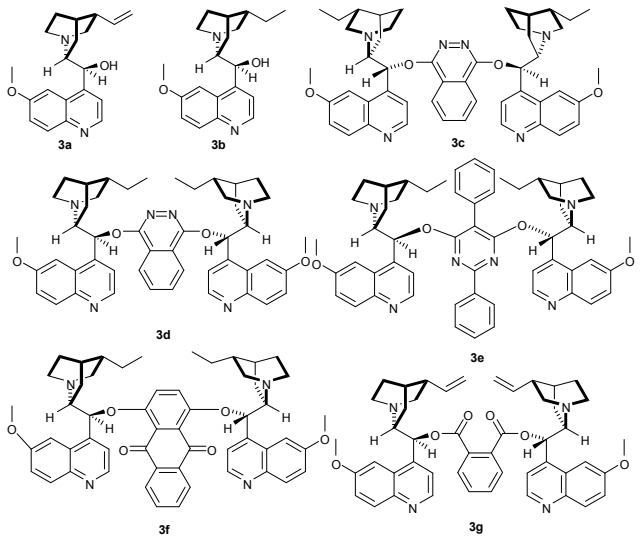
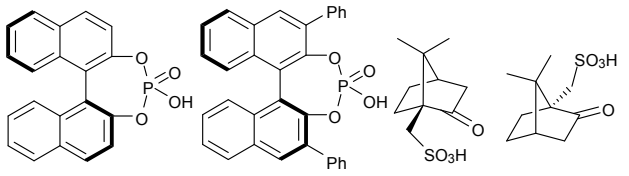


Figure 1 Catalysts for the reaction of **1a** with **2**[a]

Various solvents were examined in the reaction of **1a** with **2** in the presence of bis-cinchona alkaloid/Brønsted acid catalyst (detailed results listed in supporting information). It was found that in all cases the reaction could proceed smoothly in good yields with resonable enantioselectivities. Even if the reaction was proceeded in water, 37% ee of the product **5a** could be observed. The optimum conditions were selected as the combination of **3d** + MsOH (20 mol %, **3d**/MsOH=1:1) in DCM (0.2M) at room tempreture.

Under the optimum conditions various N-Boc-2-oxindoles with 3-alkyl substituents (Table 3, **1a-j**), including *n*-propyl (**1j**) and benzyl (**1a**) groups, were employed in the asymmetric direct α-alkylation of 2-oxindoles with Michlers Hydrol (**2**), affording the corresponding products (**5a-j**) in up to 85% yield and 82% ee (Table 3). For 3-benzyl-2-oxindoles bearing the functional group either at meta- or para-position on the aromatic ring of the benzyl group gave the corresponding products (**5b-i**) in good to high yields and enantioselectivities (entries 2-9). With *N*-unprotected 3-benzyl-2-oxindole, the reaction provided racemic product with 65% yield.

Table 2. Acid Screening for the reaction of **1a** with **2**[a]

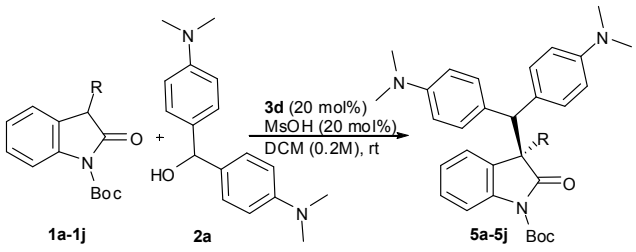


(S)-4a **(S)-4b** **(S)-4c** **(R)-4c**

Entry	Brönsted acid	Yield of **5a** (%)[b]	Ee (%)[c]
1	HOAc	59	48
2	TFA	79	70
3	TsOH	78	72
4	MsOH	85	76
5	CF_3SO_3H	87	14
6	HNO_3	66	74
7	(*S*)-**4a**	87	72
8[d]	(*S*)-**4a**	46	7
9	(*S*)-**4b**	66	rac
10	(*S*)-**4c**	69	74
11	(*R*)-**4c**	78	74

[a] Reaction performed at a 0.11 mmol scale **1a** with 0.1 mmol of **2**, 20 mol % of (**3d** + acid) in DCM (0.5mL). [b] Isolated yield after FC. [c] Determined by chiral HPLC analysis. [d] in absence of **3d**.

Table 3 Organocatalytic α-alkylation of 2-oxindoles with alcohol



1a-1j **2a** **5a-5j**

Entry[a]	R	Products	Yield (%)[b]	Ee (%)[c]
1	**1a**, Bn	**5a**	85	76
2	**1b,** 3-MeO-$C_6H_4CH_2$	**5b**	63	82
3	**1c,** 3-Me-$C_6H_4CH_2$	**5c**	71	76
4	**1d,** 3-Cl-$C_6H_4CH_2$	**5d**	62	76
5	**1e,** 3-F-$C_6H_4CH_2$	**5e**	64	80
6	**1f,** 4-MeO-$C_6H_4CH_2$	**5f**	71	73
7	**1g,** 4-Me-$C_6H_4CH_2$	**5g**	64	70
8	**1h,** 4-Br-$C_6H_4CH_2$	**5h**	63	72
9	**1i,** 3,4-OCH_2O-$C_6H_4CH_2$	**5i**	73	70
10	**1j**, *n*-Pr	**5j**	58	76

[a] Reaction conditions: 0.11 mmol **1** with 0.1mmol **2**, 20 mol % catalyst (**3d** +MsOH) in DCM (0.5 mL) at room temperature for 2d. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

It was proposed that the catalyst system of biscinchona alkaloid with two tertiary amine moieties and an additional acid (1:1) simultaneously activates oxindoles both **1** and alcohol **2** (Figure 2).[14] One tertiary amine moiety

deprotonates the C3 methine proton of the 2-oxindole leading to the generation of the enolate-anion intermediate, and the other tertiary amine moiety combined with acid interacts with activated alcohol (**2**) to produce diarylmethine carbocation by dehydration.

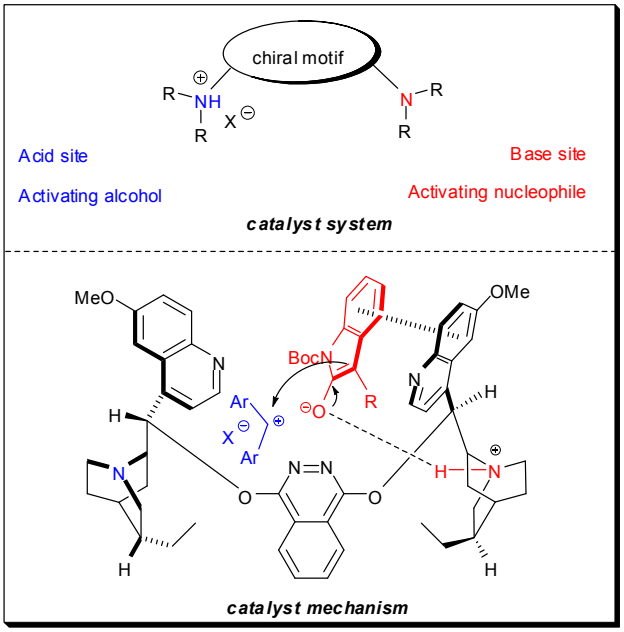


Figure 2 Proposed catalytic system and activated mechanism

The absolute configuration of the main enantiomer of **5a** was deduced as (*R*) by Vibrational Circular Dichroism (VCD) spectroscopy analysis (see supporting information).[15] As suggested by Corey and Noe,[13a, 16] the biscinchona alkaloid catalyst could construct a chiral pocket, which was favorable to firmly fix both of the formed carbocation and enolated 2-oxindole, resulting in highly efficent stereocontrol in S_N1-type alkylation reaction. The approach of carbocation to the enolate anion from *Re* face results in the formation of *R*-stereoselective product **5a** (Figure 2).

In summary, we have firstly developed a novel organocatalytic asymmetric α-alkylation of 2-oxindoles with Michlers alcohol via S_N1-type reaction pathway, which was catalyzed by the combination of chiral bis-cinchona alkaloid and Brønsted acid (1:1). Good to high yields and enantioselectivities were obtained. The investigation of organocatalytic asymmetric α-alkylation of carbonyl compounds with other alcohols is underway in our lab.

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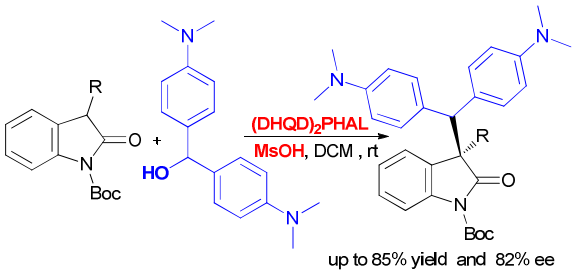

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