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Organocatalytic asymmetric Michael addition of 2-naphthols to alkylideneindolenines generated in situ from arenesulfonylalkylindoles

Liangliang Yu, Xiaohua Xie, Song Wu, Rongming Wang, Wujun He, Dabin Qin, Quanzhong Liu, Linhai Jing *

Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province, China West Normal University, Nanchong 637002, PR China

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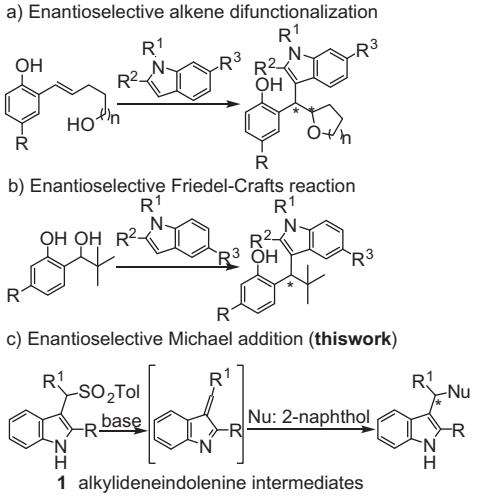
ABSTRACT

An efficient enantioselective Michael addition of 2-naphthols to alkylideneindolenines generated in situ from arenesulfonylalkylindoles has been described. The protocol provides an efficient and convenient access to C-3 alkyl-substituted indole derivatives containing phenolic hydroxyl groups with high yields (up to 96%) and enantioselectivities (up to 98% ee) under mild conditions.

The indole framework represents a privileged structure motif frequently found in pharmaceuticals, agrochemicals, and natural products.[1] Among various indole derivatives, optically active 3-substituted indole skeletons which contain phenolic hydroxyl groups in the substituents are important subunits in many synthetic and naturally occurring biologically active compounds.[2] However, efficient methods for their asymmetric synthesis are rare (Scheme 1).[2e,3] In 2010, Sigman and co-workers, developed the formation of 3-substituted indoles by a palladium-catalyzed enantioselective alkene difunctionalization reaction (Scheme 1a).[2e] Subsequently, Bach and co-workers, reported the construction of 3-substituted indole scaffolds through the enantioselective Friedel–Crafts reaction of indoles with secondary *ortho*-hydroxybenzylic alcohols in the presence of chiral phosphoric acids (Scheme 1b).[3] Inspired by Petrini group's innovative solution to indole skeletons,[4] herein we wish to describe a facile and efficient enantioselective strategy for accessing chiral 3-substituted indole derivatives including phenolic hydroxyl groups in the substituents by Michael addition of 2-naphthols to alkylideneindolenines, generated in situ from arenesulfonylalkylindoles **1** (Scheme 1c),[5–7] in the presence of chiral organocatalysts.[8]

At the outset of our study, arenesulfonylalkylindole **1a** and 2-naphthol **2a** were chosen as model substrates for surveying the reaction parameters, and the results are summarized in Table 1. Cinchona alkaloid-derived thiourea catalysts **3a–d** gave good yields and ee values (Table 1, entries 1–4).[9] Compared with other three catalysts, quinidine-derived catalyst **3b** provided slightly superior result (Table 1, entry 2).[10] A further study showed that diaminocyclohexane-derived Takemoto catalyst **3e** did not provide better result (Table 1, entry 5).[11] When $(DHQ)_2PHAL$ **3f** was used, almost racemic product was obtained (Table 1, entry 6). It perhaps



Scheme 1. Methods for the asymmetric synthesis of 3-substituted indole derivatives containing phenolic hydroxyl groups in the substituents.

* Corresponding author. Tel./fax: +86 817 2568081.
E-mail address: cwnujlh@yahoo.com.cn (L. Jing).

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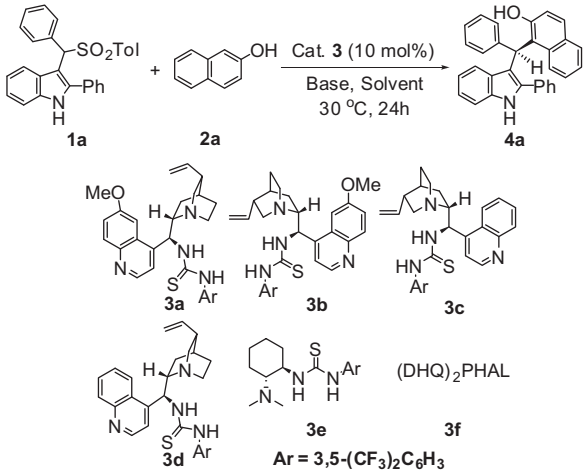
Table 1
Optimization of reaction conditions[a]



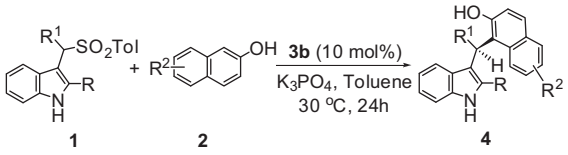
Entry	Cat	Base	Solvent	Yield[b] (%)	ee[c] (%)
1	**3a**	K_3PO_4	Toluene	87	−84
2	**3b**	K_3PO_4	Toluene	90	89
3	**3c**	K_3PO_4	Toluene	87	74
4	**3d**	K_3PO_4	Toluene	84	−84
5	**3e**	K_3PO_4	Toluene	89	77
6	**3f**	K_3PO_4	Toluene	78	−5
7	**3b**	KF/Al_2O_3	Toluene	93	83
8	**3b**	NaOH	Toluene	90	77
9	**3b**	KOH	Toluene	94	77
10	**3b**	K_2CO_3	Toluene	87	79
11	**3b**	Cs_2CO_3	Toluene	90	67
12	**3b**	K_3PO_4	Benzene	92	85
13	**3b**	K_3PO_4	Xylene	70	84
14	**3b**	K_3PO_4	^{t}Bu-benzene	89	89
15	**3b**	K_3PO_4	Ethylbenzene	92	84
16	**3b**	K_3PO_4	Mesitylene	88	86
17	**3b**	K_3PO_4	DCM	84	73
18	**3b**	K_3PO_4	*o*-Dichlorobenzene	82	73

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst **3** (0.01 mmol), and base (0.3 mmol) in solvent (1.0 mL) at 30 °C for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

implies the importance of the N–H of thiourea for the control of the enantioselectivity of the reaction. To improve the enantioselectivity of the reaction, further optimization of the reaction conditions, including bases and solvents, was carried out. However, to our disappointment, no better enantioselectivities were observed (Table 1, entries 7–18).

With the optimized reaction conditions in hand, we then screened a series of arenesulfonylalkylindoles **1** and 2-naphthols **2** to establish the general utility of this asymmetric transformation. As listed in Table 2, both electron-withdrawing and electron-donating substituents on the aryl ring of R^1 groups could be well tolerated (Table 2, entries 2–7, 11–15, and 18–23). The positions of substituents on the phenyl ring of R^1 groups seem to show important influence on the enantioselectivity of the reaction. A *meta* substituent seemed to be more beneficial than *para* substituent. For example, 3-F-substituted **1d** gave 84% ee, whereas 77% ee was obtained in the case of 4-F-substituted **1b** (Table 2, entries 2 vs 4). Similar phenomena were also observed in the reactions of **1e** compared with **1j** (Table 2, entries 13 vs 15 and 20 vs 22). Heterocycle-substituted arenesulfonylalkylindole was also a suitable substrate. For example, 2-pyridyl substituted **1m** gave 91% yield and 95% ee (Table 2, entry 24). Unfortunately, when alkyl substituted

Table 2
Asymmetric Michael addition of 2-naphthols **2** to arenesulfonylalkylindoles **1**[a]



Entry	**1**	R	R^1	**2**	R^2	**4**	Yield[b] (%)	ee[c] (%)
1	**1a**	Ph	Ph	**2a**	H	**4a**	90	89
2	**1b**	Ph	4-F-Ph	**2a**	H	**4b**	95	77
3	**1c**	Ph	4-Br-Ph	**2a**	H	**4c**	73	80
4	**1d**	Ph	3-F-Ph	**2a**	H	**4d**	93	84
5	**1e**	Ph	3-Cl-Ph	**2a**	H	**4e**	86	84
6	**1f**	Ph	3-Me-Ph	**2a**	H	**4f**	90	80
7	**1g**	Ph	3-OMe-Ph	**2a**	H	**4g**	88	82
8	**1h**	Ph	^{t}Bu	**2a**	H	**4h**	72	0
9	**1i**	H	Ph	**2a**	H	**4i**	96	26
10	**1a**	Ph	Ph	**2b**	7-OMe	**4j**	94	97
11	**1c**	Ph	4-Br-Ph	**2b**	7-OMe	**4k**	80	81
12	**1d**	Ph	3-F-Ph	**2b**	7-OMe	**4l**	92	89
13	**1e**	Ph	3-Cl-Ph	**2b**	7-OMe	**4m**	82	88
14	**1g**	Ph	3-OMe-Ph	**2b**	7-OMe	**4n**	81	88
15	**1j**	Ph	4-Cl-Ph	**2b**	7-OMe	**4o**	90	81
16	**1k**	Ph	^{i}Bu	**2b**	7-OMe	**4p**	64	13
17	**1a**	Ph	Ph	**2c**	7-Br	**4q**	95	98
18	**1c**	Ph	4-Br-Ph	**2c**	7-Br	**4r**	67	73
19	**1d**	Ph	3-F-Ph	**2c**	7-Br	**4s**	92	84
20	**1e**	Ph	3-Cl-Ph	**2c**	7-Br	**4t**	74	80
21	**1g**	Ph	3-OMe-Ph	**2c**	7-Br	**4u**	85	84
22	**1j**	Ph	4-Cl-Ph	**2c**	7-Br	**4v**	80	73
23	**1l**	Ph	3,4-diCl-Ph	**2c**	7-Br	**4w**	88	81
24	**1m**	Ph	2-Pyridyl	**2c**	7-Br	**4x**	91	95
25	**1a**	Ph	Ph	**2d**	6-Br	**4y**	85	65

[a] Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2** (0.1 mmol), **3b** (0.01 mmol), and K_3PO_4 (0.3 mmol) in toluene (1.0 mL) at 30 °C for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

1h and **1k** were employed, only racemate and 13% ee were obtained, respectively (Table 2, entries 8 and 16). It is noteworthy that the substituent R at the 2-position of the indole ring has a significant influence on the enantioselectivity of the reaction. When **1a** was treated with **2a**, 89% ee could be obtained (Table 2, entry 1), whereas only 26% ee was observed when **1i** was used (Table 2, entry 9). Finally, the survey of several 2-naphthols reveals that the position of R^2 substituent plays an important role in the enantioselectivity of the reaction. When **2c** was reacted with **1a**, up to 98% ee was obtained; however, only 65% ee could be observed when **2d** was employed (Table 2, entries 17 vs 25).

The absolute configuration of stereocenter of the Michael addition product **4j** was unambiguously assigned as *R* by X-ray diffraction analysis (Fig. 1).[12] The absolute configurations of other products were assigned by analogy.

Based on these experimental results, a plausible bifunctional transition state was proposed. The tertiary amine of the catalyst interacts with hydrogen atom of phenolic hydroxyl group through hydrogen bonding. Meanwhile, the thiourea moiety of the catalyst serves as a Brønsted acid to activate the prochiral *E*-alkylideneindolenine intermediate by double hydrogen bonds,[7d] as shown in Scheme 2.

In summary, we have developed the first enantioselective Michael addition reaction of 2-naphthols to alkylideneindolenine intermediates generated in situ from arenesulfonylalkylindoles under chiral thiourea catalysts. A series of optically active C-3 alkyl-substituted indole derivatives containing phenolic hydroxyl groups have been obtained. The organocatalytic protocol provides a more

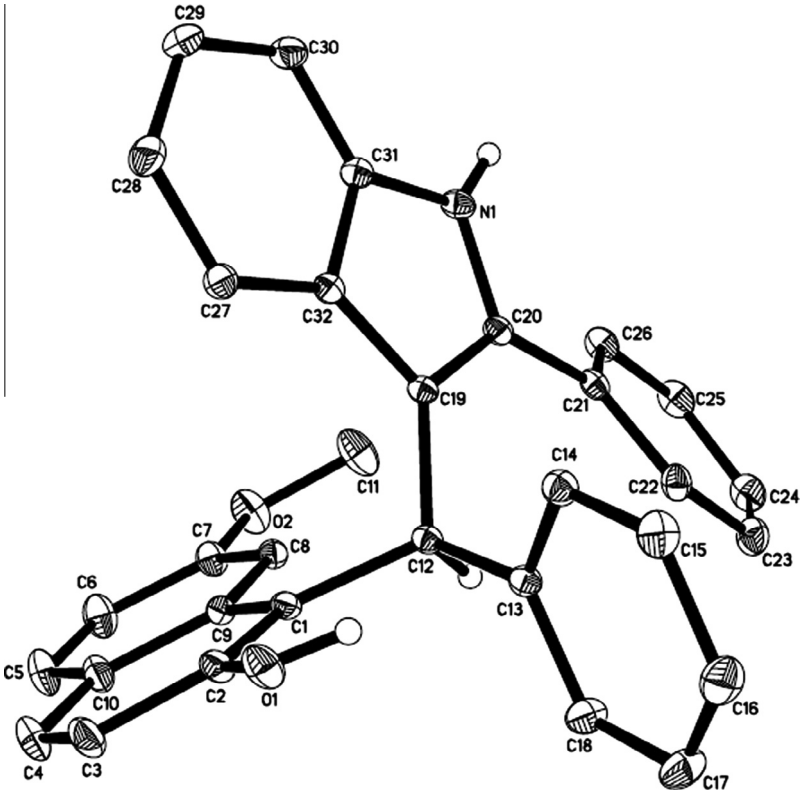
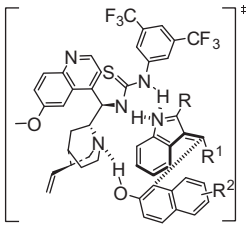


Figure 1. X-ray crystal structure of adduct **4j**. H atoms, except H1-N, H1-O ,and H-12, have been omitted for clarity.



Scheme 2. Proposed transition state.

efficient and convenient access to valuable chiral 3-indolyl derivatives containing phenolic hydroxyl groups in high yields and enantioselectivities. A plausible bifunctional transition state has been proposed. Further investigations to broaden the scope of this type of transformation and find evidence for the mechanism are currently underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterisation data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.011.

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12. CCDC-896164 (**4j**) 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.