DOI: 10.1002/adsc.201200286

Organocatalytic Asymmetric Vinylogous Michael Addition of Dicyanoolefins to Imine Intermediates Generated *in situ* from Arenesulfonylalkylindoles

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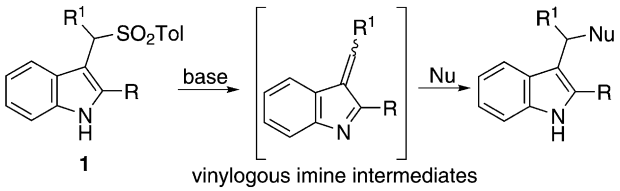
Received: May 5, 2012; Revised: August 9, 2012; Published online: October 30, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200286.

Abstract: An organocatalytic asymmetric vinylogous Michael addition of dicyanoolefins to vinylogous imine intermediates generated *in situ* from arenesulfonylalkylindoles has been developed. This protocol provides an easy and convenient approach to C-3 alkyl-substituted indole derivatives with high yields (up to 93%), diastereomeric ratios (up to 99:1 *dr*) and enantioselectivities (up to 99% *ee*). The resulting adducts can be also readily converted to pyrazolo derivatives or α-alkylation products of ketones without any decrease of the diastereoselectivities and enantioselectivities.

Keywords: arenesulfonylalkylindoles; asymmetric catalysis; dicyanoolefins; organic catalysis; vinylogous Michael addition

Optically active 3-substituted indole structural motifs have been widely found in a number of naturally occurring compounds and biologically active molecules.[1] Therefore, their asymmetric synthesis has been the subject of intensive investigation.[2] The most common strategy to access these compounds is *via* the enantioselective Friedel–Crafts reaction of indole at the 3-position.[3] However, some chiral 3-substituted indoles cannot be prepared by this approach due to the lack of the corresponding electrophiles. In 2006, an innovative solution to this structural skeleton using arenesulfonylalkyl-substituted indoles **1** was described by Petrini and co-workers.[4] Compounds **1**, generating *in situ* highly active vinylogous imine intermediates under basic conditions,[5] can react with various nucleophiles to afford the corresponding 3-substituted indole derivatives (Scheme 1).[6] Nevertheless, quite

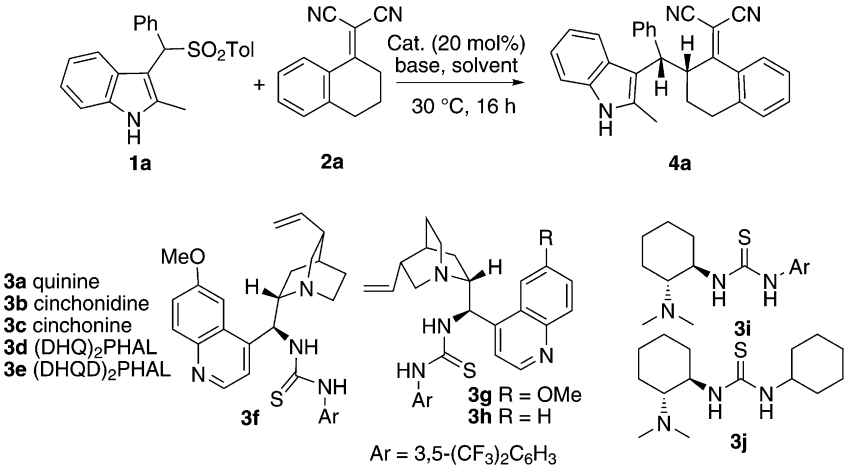


Scheme 1. Nucleophilic Michael addition to vinylogous imines generated *in situ* from arenesulfonylalkyl-substituted indoles **1**.

limited progress has been made in their asymmetric variants.[7] On the other hand, an asymmetric vinylogous-type reaction, which enables a facile access to chiral materials with structural diversity and complexity, has gained increasing attention.[8] Recently, α,α-dicyanoolefins,[9] which are readily prepared by the condensation of the corresponding carbonyl compounds and malononitrile, have been demonstrated as excellent vinylogous nucleophiles in some asymmetric vinylogous-type reactions by Jørgensen,[10] Deng or Chen,[11] Loh,[12] and Zhou groups.[13] Inspired by these elegant studies, and considering that the vinylogous Michael addition reaction is still in its infancy,[8i] herein we wish to demonstrate, to the best of our knowledge, the first highly stereoselective vinylogous Michael addition of dicyanoolefins to vinylogous imine intermediates generated *in situ* from arenesulfonylalkyl-substituted indoles under chiral organocatalysts.[14] The resulting Michael adducts can be further conveniently transformed to pyrazolo derivatives or the α-alkylation products of ketones without any decrease of the diastereoselectivities and enantioselectivities.

We commenced our studies by using a series of catalysts **3** for the model reaction of arenesulfonylalkylindole **1a** and α,α-dicyanoolefin **2a** in toluene under

Table 1. Optimization of reaction conditions for reaction of arenesulfonylalkyl-substituted indole **1a** with α,α-dicyanoolefin **2a**.[a]

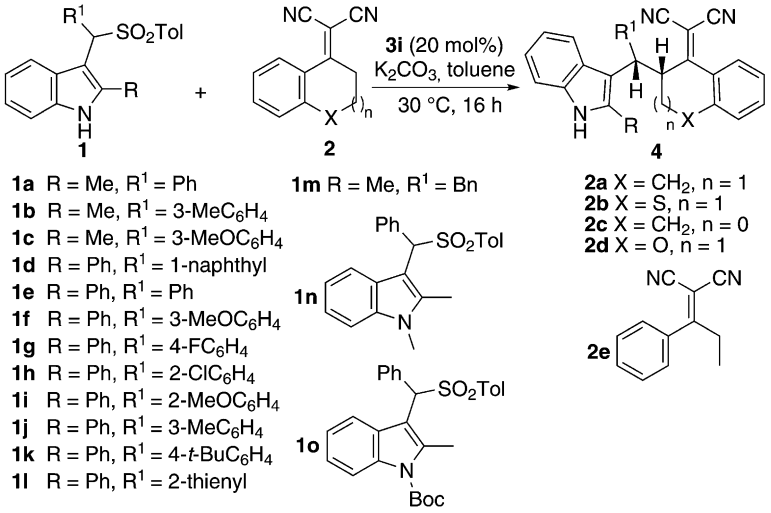


Entry	Cat.	Base	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**3a**	K_2CO_3	toluene	82	67:33	45
2	**3b**	K_2CO_3	toluene	85	63:37	26
3	**3c**	K_2CO_3	toluene	87	82:18	−36
4	**3d**	K_2CO_3	toluene	82	78:22	−23
5	**3e**	K_2CO_3	toluene	83	99:1	29
6	**3f**	K_2CO_3	toluene	92	99:1	−63
7	**3g**	K_2CO_3	toluene	88	99:1	46
8	**3h**	K_2CO_3	toluene	90	77:23	51
9	**3i**	K_2CO_3	toluene	93	99:1	80
10	**3j**	K_2CO_3	toluene	93	99:1	77
11	**3i**	K_3PO_4	toluene	92	99:1	57
12	**3i**	Na_3PO_4	toluene	82	99:1	46
13[e]	**3i**	Cs_2CO_3	toluene	90	99:1	42
14[f]	**3i**	Na_2CO_3	toluene	51	99:1	47
15	**3i**	LiOH	toluene	82	99:1	17
16[e]	**3i**	KOH	toluene	93	99:1	<5
17	**3i**	KF/Al_2O_3	toluene	98	50:50	51
18	**3i**	K_2CO_3	benzene	85	99:1	50
19	**3i**	K_2CO_3	mesitylene	90	87:13	65
20	**3i**	K_2CO_3	DCM	88	66:34	40
21	**3i**	K_2CO_3	chloroform	83	76:24	7
22	**3i**	K_2CO_3	dioxane	87	79:21	<5
23	**3i**	K_2CO_3	THF	89	75:25	<5

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.11 mmol), **2a** (0.1 mmol), catalyst (0.02 mmol) and base (0.11 mmol) in solvent (2.0 mL) at 30 °C for 16 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Reaction time 2 h.
[f] Reaction time 72 h.

K_2CO_3 conditions. As summarized in Table 1, all tested catalysts could smoothly afford the desired product **4a** in high yields with various *dr* and *ee*. Natural *Cinchona* alkaloids quinine **3a**, cinchonidine **3b** and cinchonine **3c** only gave poor diastereo- and enantioselectivities albeit with good yields (Table 1, entries 1–3). No enhancement in stereoselectivity was achieved when the reaction was carried out using $(DHQ)_2PHAL$ **3d** as catalyst (Table 1, entry 4). Surprisingly, excellent diastereoselectivity was observed when $(DHQD)_2PHAL$ **3e** was used as catalyst, although with no improvement in enantioselectivity (Table 1, entry 5). 9-Thiourea-*Cinchona* alkaloids **3f** and **3g** afforded the products with slightly increased *ee* and excellent *dr* values (Table 1, entries 6 and 7). However, catalyst **3h** gave poor results (Table 1,

Table 2. Asymmetric vinylogous Michael addition of dicyanoolefins to arenesulfonylalkyl-substituted indoles.[a]



Entry	1	2	4	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1a**	**2a**	**4a**	93	99:1	80
2	**1b**	**2a**	**4b**	82	89:11	91
3	**1c**	**2a**	**4c**	86	87:13	90
4	**1d**	**2a**	**4d**	69	69:31	95
5	**1e**	**2a**	**4e**	78	92:8	96
6	**1f**	**2a**	**4f**	61	93:7	>99
7[e]	**1g**	**2a**	**4g**	65	90:10	86
8	**1h**	**2b**	**4h**	68	99:1	76
9	**1i**	**2b**	**4i**	93	80:20	98
10[f]	**1j**	**2b**	**4j**	60	99:1	−90
11	**1k**	**2b**	**4k**	67	80:20	95
12	**1l**	**2b**	**4l**	91	86:14	97
13	**1m**	**2b**	**4m**	62	99:1	71
14[g]	**1n**	**2b**	–	–	–	–
15[g]	**1o**	**2b**	–	–	–	–
16	**1d**	**2c**	**4n**	77	95:5	94
17	**1e**	**2c**	**4o**	74	58:42	93
18	**1f**	**2c**	**4p**	61	60:40	86
19	**1l**	**2c**	**4q**	82	52:48	94
20	**1d**	**2d**	**4r**	67	58:42	81
21[f]	**1e**	**2d**	**4s**	65	81:19	−82
22	**1f**	**2d**	**4t**	67	93:7	71
23	**1l**	**2e**	**4u**	74	80:20	96

[a] Unless otherwise noted, all reactions were carried out with **1** (0.11 mmol), **2** (0.1 mmol), **3i** (0.02 mmol) and K_2CO_3 (0.11 mmol) in toluene (2.0 mL) at 30 °C for 16 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the crude mixture.
[d] Enantiomeric ratios were measured using chiral stationary phase HPLC.
[e] Reaction time 72 h.
[f] Catalyst **3f** was used instead of **3i** and gave the opposite enantiomer.
[g] Reaction time 48 h.

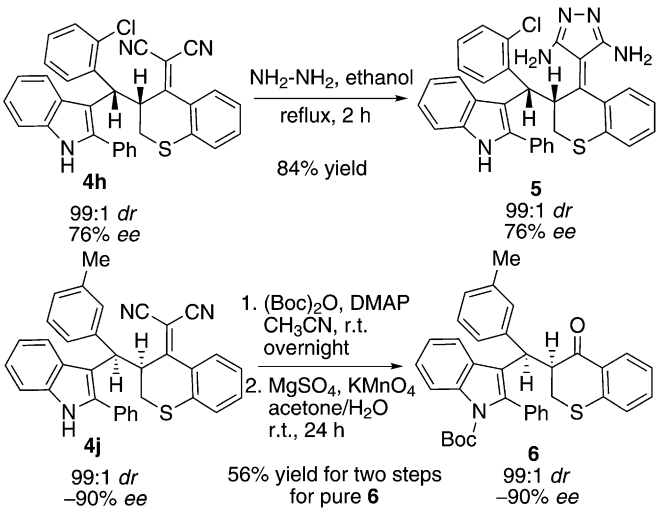
entry 8). Then our attention turned to another type of thiourea catalyst bearing a chiral diaminocyclohexane skeleton. To our delight, Takemoto's catalyst **3i** provided the highest *ee* value and excellent diastereoselectivity (Table 1, entry 9).[15] Subsequently, a variety of bases was investigated. Moderate enantioselectivities were observed with the use of K_3PO_4, Na_3PO_4, Cs_2CO_3 and Na_2CO_3 (Table 1, entries 11–14). LiOH and KOH gave much more inferior results and even racemates, respectively (Table 1, entries 15 and 16). Only a 1:1 *dr* was obtained when KF/Al_2O_3 was applied (Table 1, entry 17). The influence of other sol-

vents was also examined and much more inferior stereoselectivities were observed compared with toluene (Table 1, entries 18–23).

With the optimized reaction conditions in hand, we then screened a series of arenesulfonylalkyl-substituted indoles **1** and α,α-dicyanoolefins **2** to establish the general utility of this asymmetric transformation. As outlined in Table 2, most arenesulfonylalkyl-substituted indoles and α,α-dicyanoolefins underwent the reaction smoothly to afford the corresponding products with good to excellent results. The substituent R at the 2-position of the indole ring had a significant influence on the enantioselectivity of the reaction.[16] For example, 2-phenyl-substituted **1e** gave 96% *ee*, whereas only 80% *ee* was obtained in the case of 2-methyl-substituted **1a** (Table 2, entry 1 *vs.* entry 5). A similar phenomenon was also observed in the reaction of **1f** compared with **1c** (Table 2, entry 3 *vs.* entry 6). Surprisingly, for arenesulfonylalkylindoles bearing a phenyl group with an *ortho* substituent, the nature of the substituent shows an important influence on the outcome of the reaction (Table 2, entries 8 and 9). Sulfonylalkylindole **1m** with an aliphatic substituent could be also tolerated albeit with moderate enantioselectivity (Table 2, entry 13). In addition, 2-thienyl-substituted sulfonylalkylindole **1l** could be also employed and excellent enantioselectivities were attained (Table 2, entries 12, 19 and 23). Notably, *N*-methyl substituted **1n** and *N*-Boc substituted **1o** gave no desired products (Table 2, entries 14 and 15). This seems to imply the importance of a nitrogen-bound hydrogen atom for the formation of the vinylogous imine intermediate under basic conditions.[5a] When catalyst **3f** was used instead of **3i**, an opposite enantiomer was obtained (Table 2, entries 10 and 21). Finally, the non-cyclic dicyanoolefin **2e** could also furnish the vinylogous Michael addition product with excellent *ee* value (Table 2, entry 23).

The synthetic versatility of this methodology is illustrated in Scheme 2. The adduct **4h** was readily converted to pyrazolo derivative **5** through the reaction with hydrazine hydrate in ethanol at reflux temperature.[17] On the other hand, the product **4j** was also conveniently transformed to the α-alkylation product of a ketone, **6**, in 56% yield by a known oxidative cleavage procedure,[10b,c,d,11h] and in both cases without any loss of the stereoselectivities. The absolute configuration of the two contiguous stereocenters of the vinylogous Michael addition product **4a** was unambiguously assigned as (2*R*,3*S*) by X-ray diffraction analysis (Figure 1),[18] and based on this information, the absolute configurations of other products were assigned by analogy.

In conclusion, we have developed the first highly stereoselective vinylogous Michael addition reaction of dicyanoolefins to vinylogous imine intermediates generated *in situ* from 3-arensulfonylalkylindoles under chiral thiourea catalysis. The organocatalytic protocol provides convenient access to valuable chiral 3-indolyl derivatives in high yields and stereoselectivities, and the resulting adducts can be readily converted to pyrazolo derivatives or α-alkylation products of ketones without any decrease of the diastereoselectivity and enantioselectivity. Further investigations to broaden the scope of this type of transformation are currently underway.



Scheme 2. Synthetic transformation of Michael adducts.

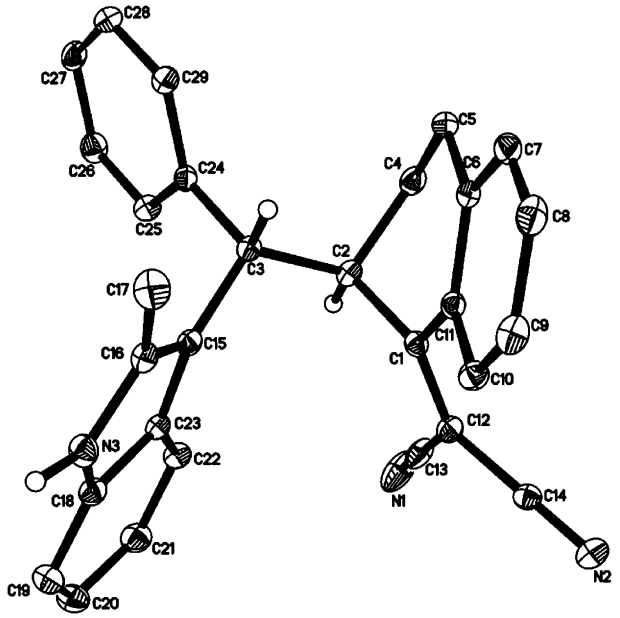


Figure 1. X-ray structure of **4a**. Thermal ellipsoids are set at 30% probability. Solvent molecule and H atoms, except H-3-N, H-2 and H-3, have been omitted for clarity.

Experimental Section

General Experimental Procedure

To a solution of arenesulfonylalkyl-substituted indole **1** (0.11 mmol), α,α-dicyanoolefin **2** (0.1 mmol), and Takemoto's catalyst **3i** (0.02 mmol) in toluene (2 mL) was added K_2CO_3 (0.11 mmol). After being stirred at 30 °C for 16 h, the reaction mixture was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:20–1:10) to afford the corresponding product **4**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude material and the enantiomeric excess was determined by chiral-phase HPLC analysis. Further experimental details can be found in the Supporting Information.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21102117), the Education Department of Sichuan Province (10A026), Chemical Synthesis and Pollution Control Key Laboratory of Sichuan Province (11CSPC-1-1), and China West Normal University (10B005).

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