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Sidearm Effect: Improvement of the Enantiomeric Excess in the Asymmetric Michael Addition‡ of Indoles to Alkylidene Malonates

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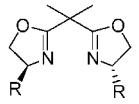
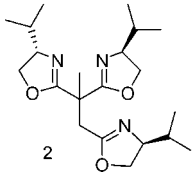
C_2-symmetric chiral bisoxazoline-metal complexes enjoy high prestige in asymmetric catalysis.[1] For example, bisoxazoline **1** derived Cu(II) complexes[2] have been well established as versatile catalysts for asymmetric C−C bond formations such as aldol,[3] cycloaddition,[4] ene,[5] Michael,[6] amination,[7] Friedel−Crafts,[8] Henry,[9] and Mannich[10] reactions. In most cases, excellent enantioselectivity could be achieved only when *tert*-leucinol-derived bisoxazoline **1b** was used. In sharp contrast to the great success of bisoxazolines, the development and application of trisoxazolines are rather limited.[11] In our efforts to develop superior catalysts which are cheap, easy to access, air-stable, and water-tolerant, we considered a sidearm approach, focusing on the improvement of bisoxazoline into pseudo-C_3-symmetric trisoxazoline **2,** for the following reasons: (1) compared with C_2-symmetric bisoxazolines **1**, coordination of three nitrogen atoms of trisoxazoline **2** to the metallic center induces a more tunable pseudo-C_3-symmetric chiral space, to shield distant reactive sites; (2) tridentate ligand **2** is expected to increase the stability of active intermediates with respect to ordinary bidentate bisoxazolines.[12] Thus, the metal complex may be tolerable to moisture, and it is possible to improve the catalytic activity. In this communication, we report our preliminary results on this subject.



1a R = Ph
1b R = t-Bu



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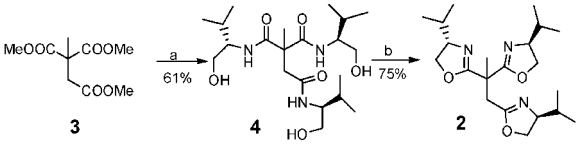
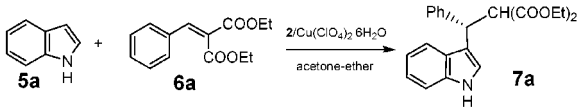
The trisoxazoline **2** can be easily synthesized from **3** and L-valinol by two steps. Compound **3** reacted with L-valinol without solvent[13] at 70 °C to afford white hydroscopic solid **4** in 61% yield. Treatment of compound **4** with PPh_3/CCl_4 [14] afforded desired trisoxazoline **2** as colorless oil in 75% yield.



3 4 2

Very recently, Jørgensen et al. pioneered asymmetric Michael addition of indoles to alkylidene malonates.[8c] They found that chiral Lewis acid **1b**/$Cu(OTf)_2$ could promote this reaction in moderate-to-good ee value (up to 69% ee). To examine if our design is operative, we tried the above reaction using the newly designed trisoxazoline **2**/$Cu(ClO_4)_2 \cdot 6H_2O$[12b,15] complex as the chiral Lewis acid. We are pleased to find that the catalytic activity was comparable to that of **1b**/$Cu(OTf)_2$ and the enantioselectivity of the reaction of indole with benzylidene malonate was enhanced greatly (entry 1, Table 1).

Table 1. Effect of Temperature and Additive on the Reaction between Indole **5a** and Benzylidene Malonate **6a**



entry	catalyst loading (%)	additive	temp (°C)	yield[a] (%)	ee[b,c] (%)
1	10	None	15	88	82
2	10	None	0	50	85
3	10	HFIP	0	99	85
4[d]	1	HFIP	0	90	78
5	10	HFIP	−20	84	89
6	10	HFIP	−25	56	93

[a] Isolated yield and performed on 0.25 mmol scale unless otherwise noted. [b] Determined by chiral HPLC. [c] Absolute configuration was assigned by chemical transformation. [d] Performed on 4 mmol scale. [e] All reactions were run in acetone−ether (1:3, v/v).

The alkylation of indole **5a** with malonate **6a** proceeded quite slowly at 0 °C, and the yield was only 50%; even the reaction time was prolonged to 72 h (entry 2 in Table 1) in the absence of hexafluoro-*i*-PrOH (HFIP). To our delight, we found that the addition of 2 equiv of HFIP[16] can greatly improve the reactivity without loss of ee (entry 3). The reaction was proved to be temperature-dependent. When the reaction temperature decreased from 0 to −25 °C, the ee value of compound **7a** increased from 85 to 93% (entries 3, 5, and 6 in Table 1).

The high yield and excellent enantioselectivity encouraged us to study the generality of this reaction by investigating a variety of structurally different indole derivatives and alkylidene malonates (Table 2). Arylidene malonates with indole worked well to afford the desired products in excellent yields with high ee. Unlike the ee that were different between dimethyl and diethyl malonates in the case of **1b**/$Cu(OTf)_2$, both methyl ester and ethyl ester maintained excellent face selectivity when trisoxazoline was used (entries 1−4). Enantiomeric excesses ranging from 90 to 92% were obtained in high yields for various substituted arylidene malonates (entry 4−8). Diethyl ethylidene malonate could also react with indole smoothly, but it was less enantioselective (entry 9). The reaction of benzylidene malonate with 4-methoxyindole, 5-methoxyindole, and 5-methylindole resulted in the alkylation products in high-to-excellent yields with excellent ee value (entries 10, 11, 12), indicating that the substituents on indole ring had almost no effect on the enantioselectivity.

It is noteworthy that trisoxazoline **2**/$Cu(ClO_4)_2 \cdot 6H_2O$ complex is an air- and water-stable compound. *It maintained the same*

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‡ This reaction is also regarded as Friedel−Crafts reaction in ref 8c.

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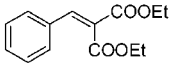
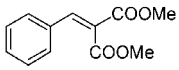
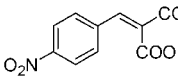
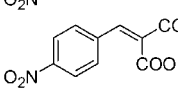
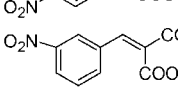
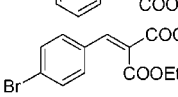
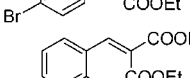
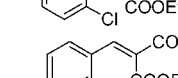
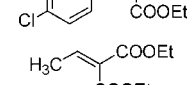
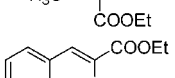
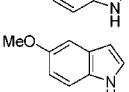
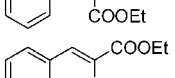
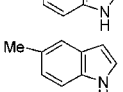
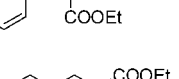
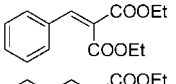
Table 2. Asymmetric alkylation of indoles **5** with various alkylidene malonates **6**

entry	malonate **6**	indole **5**	yield %[b]	ee%[c]
1			84	89
2			98	88 (50)[d]
3			99	91 (56)[d]
4			99	91
5			99	91
6			95	90 (50)[d]
7			99	92 (69)[d]
8			84	90
9[e]			84	60
10			73	91 (60)[d]
11			92	93
12			97	91
13			95	91[f]

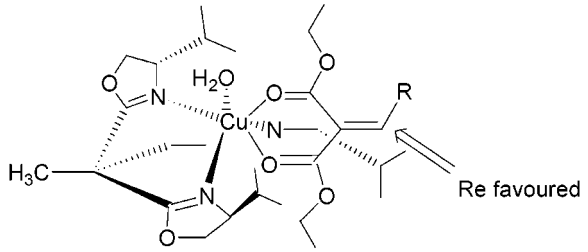
[a] Reactions were run in acetone−ether (1:3 v/v) with 10 mol % chiral catalyst at −20 °C. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Number in parentheses refers to the best result in the literature. [e] Run at −35 °C. [f] Performed under air atmosphere.

catalytic reactivity almost without loss of enantioselectivity even when the reaction was carried out under air atmosphere (entry 13 in Table 2).

Optical purity of the products could be enhanced by recrystallization. For example, 99.6% ee was obtained in 71% yield after compound **7a** (86% ee) was recrystallized from a mixed solvent of petroleum ether, CH_2Cl_2, and acetone. These indole derivatives prepared by the current method are potentially synthetically useful because they can undergo many chemical transformations, in particular for the preparation of β-substituted tryptophans[17] and some bioactive indole derivatives.[18]

The high ee values obtained with L-valinol-derived trisoxazoline **2** are rather intriguing. The proposed transition-state model shown below supports all the experimental observation and is consistent with the absolute configuration of some selected products. The indoles could only approach the *re* face of the alkylidene malonates due to steric hindrance.

In conclusion, we have demonstrated that pseudo-C_3-symmetric trisoxazoline **2** has the encouraging ability to achieve high face selectivity in asymmetric Michael reaction of indoles to alkylidene malonates. The cheap and easy synthesis of trisoxazoline−Cu (II) complexes, the high selectivity, and the mild reaction conditions including water- and air-tolerance make our method potentially



useful. In particular, our ligand design strategy may also provide a basis for further optimization of the sidearmed bisoxazoline to enhance both enantioselectivity and catalytic efficiency.

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Supporting Information Available: Characterization data for all compounds, absolute configuration, and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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