Modification of Pseudo-C_3-Symmetric Trisoxazoline and Its Application to the Friedel–Crafts Alkylation of Indoles and Pyrrole with Alkylidene Malonates

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Received 4 December 2010

This paper is dedicated to Professor Xiyan Lu and Professor Li-Xin Dai on the occasion of the 60-year anniversaries of their research careers.

Abstract: New pseudo-C_3-symmetric hetero-trisoxazoline can be easily prepared on a gram scale in good yield. Its combination with copper(II) triflate exhibits high enantiomeric induction in the asymmetric Friedel–Crafts alkylation between indoles and alkylidene malonates, with up to 97% ee and good to excellent yields. The catalyst loading can be lowered to 0.5 mol% without loss of the enantiomeric excess.

Key words: asymmetric catalysis, alkylation, copper, enantioselectivity, indoles

Recently, we developed a synthesis of pseudo-C_3-symmetric trisoxazolines **1**[1–2] (TOX **1**; Figure 1) by a 'side-arm' approach.[3] The metal complexes of **1** were efficient catalysts for enantioselective Friedel–Crafts reaction of indole with alkylidene malonate,[4] 1,3-diploar cycloaddition reactions,[5] Diels–Alder reactions,[6] Kinugasa reactions,[7] and cyclopropanation reactions of alkenes with aryldiazoacetates.[8] Compared with the corresponding bisoxazoline, these TOX–metal complexes showed some promising properties, such as better enantioselectivity and stronger tolerance towards water and air in some cases.[4,5,7,8] However, the drawback of the TOX **1** ligands is that they are usually paste-like compounds, which complicates the purification and makes gram-scale synthesis difficult. Very recently, we designed pseudo-C_3-symmetric trisoxazoline **2**, which is an easily synthesized solid, on a gram scale. Trisoxazoline **2** proved to be very efficient in the asymmetric Friedel–Crafts alkylation[9] of indoles with alkylidene malonates. In addition, the enantiomeric excess was maintained even when the catalyst loading was reduced from 10 mol% to 0.5 mol%. Herein, we wish to report these results in detail.

Because trisoxazolines **1** are paste-like compounds, we envisioned that replacing the methyl group in TOX **1** with a large group might improve the crystallization properties of the trisoxazoline, which could simplify its purification. Thus, TOX **2** was designed in which a 3,5-di-*tert*-butylphenyl group was introduced instead of the methyl group in TOX **1**. The synthesis of **2** was very straightforward. As shown in Scheme 1, treatment of malononitrile **3** with amino alcohol **4** in refluxing toluene in the presence of one equivalent of $Zn(OTf)_2$ gave the desired bisoxazoline **5** in 69% yield.[10] The bisoxazoline, after deprotonation by *t*-BuLi, reacted with 2-chloromethyl oxazoline **6** to afford **2** in good yields as white solid. By this strategy, **2a** (2.64 g) was readily prepared.

Replacement of the methyl group with the 3,5-di-*tert*-butylphenyl group in **2** will change the conformation of the metal–**2** complex and affect the stereocontrol in the

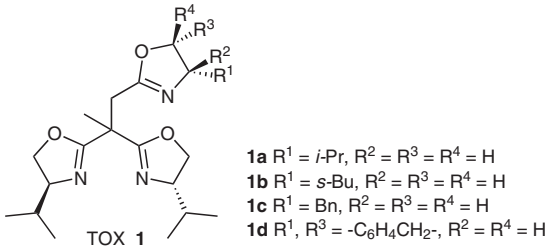
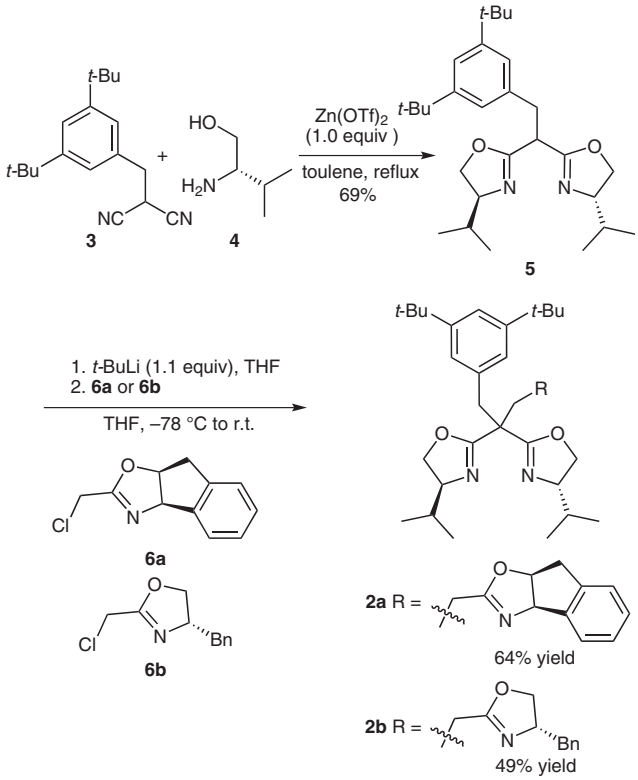


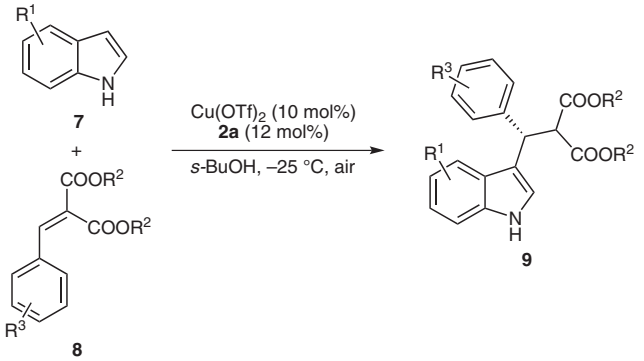
Figure 1 Pseudo-C_3-symmetric trisoxazolines



Scheme 1 Synthesis of modified trisoxazoline **2**

SYNLETT 2011, No. 7, pp 0935–0938
Advanced online publication: 10.03.2011
DOI: 10.1055/s-0030-1259721; Art ID: W33010ST

Table 1 Enantioselective Friedel–Crafts Reaction of Indoles with Alkylidene Malonates[a]



Entry	R^1	R^2	R^3	Yield (%)[b,c]	ee (%)[c,d]
1	H	Me	H	92 (93)	91 (91)
2	H	Et	H	99 (99)	94 (94)[4c]
3	H	*i*-Bu	H	95 (97)	97 (97)
4[e]	H	Et	4-Me	99	92
5	H	Et	4-Br	98 (85)	92 (93)
6[f]	H	Et	4-O_2N	86 (99)	92 (91)
7[f]	H	Et	3-O_2N	86 (99)	82 (83)
8	H	Et	3-Me	90	93
9	H	Et	3-Cl	91	92
10	H	Et	2-Cl	99 (93)	96 (97)
11[e]	H	Et	2-Br	70	95
12	2-Me	Et	H	98 (99)	81 (53)[g]
13	4-MeO	Et	H	98 (90)	97 (98)
14	5-MeO	Et	H	70 (79)	94 (94)
15	5-Me	Et	H	98 (89)	95 (95)

[a] Reaction conditions: **7** (0.30 mmol, 1.2 equiv), **8** (0.25 mmol, 1.0 equiv), $Cu(OTf)_2$ (0.025 mmol, 0.1 equiv), **2a** (0.030 mmol, 0.12 equiv), *s*-BuOH (1.25 mL).
[b] Isolated yield.
[c] Numbers in parentheses refer to the results obtained with **1a**/$Cu(OTf)_2$ in *i*-BuOH at –25 °C reported in reference 4b.
[d] Determined by chiral HPLC, the absolute configuration was determined by comparing the rotation with the known compound reported in reference 4c.
[e] Performed under an N_2 atmosphere.
[f] Performed at 0 °C.
[g] Opposite rotation was observed compared to the others.

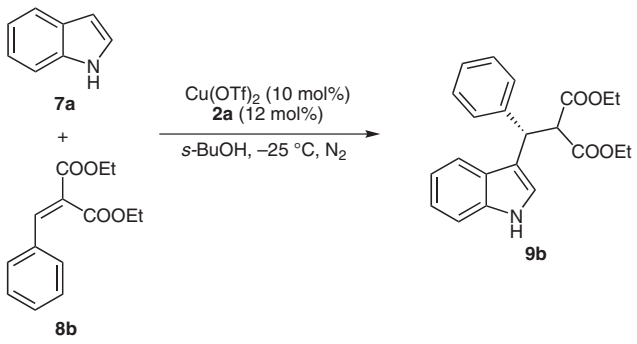
asymmetric catalysis. Thus, **2a** was initially employed in the asymmetric Friedel–Crafts reaction of indoles with alkylidene malonates. Under the optimal conditions, the reaction proceeded well in *s*-BuOH under air atmosphere in the presence of TOX **2a**/$Cu(OTf)_2$, giving the desired products with good to excellent enantioselectivities (91–97% ee) and high yields (up to 99%). The ester group influenced the enantioselectivities and the ee values increased in the order of methyl < ethyl < isobutyl group (Table 1, entries 1–3). Alkylidene malonates with different steric and electronic properties were also examined in the reaction with indole (entries 2–11). All malonates provided the desired products with ee values in the range of 91–97%, except for nitro-substituted substrates, which also give high ee values at 0 °C (entries 6 and 7).

To further investigate the generality of the reaction, the substituent effects of indole were also examined. Substituents at the 4- or 5-position had little effect on either the enantioselectivity or yield (entries 13–15). When 2-methylindole was employed, TOX **2a** gave 81% ee, which was much higher than that obtained with TOX **1a** (entry 12).[4c] These results demonstrated that TOX **2a** is comparable to TOX **1a** in the asymmetric Friedel–Crafts reaction of indoles with alkylidene malonates.[4b]

Further studies showed that the catalyst loading could be reduced sharply without loss of enantioselectivity. For example, when indole **7a** was reacted with **8b** (0.5 M) in *s*-BuOH at –25 °C using 1.0 mol% of $Cu(OTf)_2$/**2a** as a catalyst, 93% ee and 81% yield was obtained (Table 2, entry 2). The ee value was maintained even with 0.5 mol% catalyst loading. Thus, the reaction between **8b** (5.0 mmol, 2.0 M) and **7a** in the presence of 0.5 mol% $Cu(OTf)_2$/**2a** gave **9b** in 82% yield with 94% ee at –25 °C (Table 2, entry 3).

In our previous work, the asymmetric Friedel–Crafts reaction between pyrroles and alkylidene malonates was investigated with $Cu(OTf)_2$/trisoxazoline, and the highest ee value reported to date in literature was achieved (66%).[11] We were pleased to find that TOX **2** exhibited even better

Table 2 Effect of Catalyst Loading and Substrate Concentration[a]

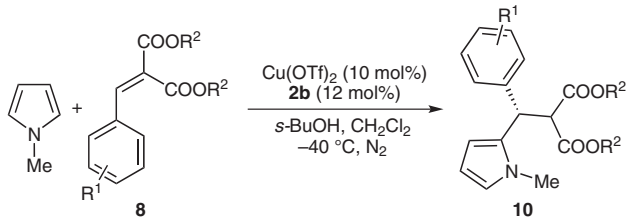


Entry	Cat. (mol%)	Concn of **8b** (M)	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	10	0.2	19.5	99	94
2	1	0.5	74	81	93
3[e]	0.5	2.0	67	82 (91)	94

[a] Reaction conditions: **7a** (1.2 mmol, 1.2 equiv), **8b** (1.0 mmol, 1.0 equiv), $Cu(OTf)_2$ (0.025 mmol, 0.1 equiv), **2a** (0.030 mmol, 0.12 equiv), *s*-BuOH (1.25 mL).
[b] Isolated yield; data in parenthesis is yield based on the conversion of **8b**.
[c] Determined by chiral HPLC.
[d] Conducted with **8b** on 0.20 mmol scale, under air atmosphere.
[e] Conducted with **8b** on 5.0 mmol scale.

behavior than that disclosed previously in the reactions between pyrroles and alkylidene malonates and, generally, the enantioselectivity of **10** was further improved by more than 10% ee. As shown in Table 3, for example, upon treatment of **8b** with *N*-methyl pyrrole under the optimized conditions, **10a** was generated in 82% yield with 75% ee in the presence of $Cu(OTf)_2$/**2b**.

Table 3 Enantioselective Friedel–Crafts Reaction of Pyrroles with Alkylidene Malonates[a]



Entry	R^1	R^2	Time (h)	Yield (%)[b]	ee (%)[c,d]
1	H	Et	62	82 (**10a**)	75 (66)
2[e]	2-Cl	Et	93	29 (**10b**)	56 (40)
3	3-O_2N	Et	98.5	69 (**10c**)	78 (58)
4	4-Br	Et	62	78 (**10d**)	78 (66)
5	4-O_2N	Et	98.5	56 (**10e**)	77
6[e]	4-MeO	Et	65.5	68 (**10f**)	67 (64)

[a] Reaction conditions: *N*-methyl pyrrole (1.80 mmol, 6.0 equiv), **8b** (0.3 mmol, 1.0 equiv), $Cu(OTf)_2$ (0.030 mmol, 0.1 equiv), **2b** (0.036 mmol, 0.12 equiv), *s*-BuOH (1.60 mL), CH_2Cl_2 (0.4 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Data in parentheses are the best results reported in the literature, see reference 11.
[e] Conducted with *s*-BuOH (1.80 mL) and CH_2Cl_2 (0.2 mL) at –20 °C.

In summary, solid TOX **2** was readily synthesized in good yields on a gram scale. TOX **2** has been successfully applied to $Cu(OTf)_2$-catalyzed asymmetric Friedel–Crafts alkylation of both indoles and pyrrole with alkylidene malonates.[12] Up to 99% yield and 97% ee were achieved, offering better results than those obtained with TOX **1**. In addition, the catalyst loading can be reduced to 0.5 mol% without loss of enantioselectivity. The application of TOX **2** in other asymmetric catalytic reactions is now in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful for financial support from the Natural Sciences Foundation of China (No. 20821002 and 21072207) and the Major State Basic Research Development Program (Grant No. 2009CB25300), the Science and Technology Commission of Shanghai Municipality.

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(12) **Procedure for the preparation of *i*-Pr-bisoxazoline**: 2-(3,5-Di-*tert*-butylbenzyl)malononitrile (5.36 g, 20 mmol) and $Zn(OTf)_2$ (7.27 g, 20 mmol) in anhydrous toluene (150 mL) was stirred for 5 min under a nitrogen atmosphere. To the mixture was added a solution of (*S*)-2-amino-3-methylbutan-1-ol (4.16 g, 40 mmol) in anhydrous toluene (50 mL) and the resulting reaction mixture was heated at reflux for 72 h. After cooling to r.t., the mixture was washed with brine (3 × 100 mL) and $NaHCO_3$ (3 × 100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give pure *i*-Pr-BOX as a buff-colored oil. Yield: 6.07 g (69%). $[\alpha]_D^{20}$ –34.1 (*c* 0.50, $CHCl_3$); IR (neat): 2959, 2872, 1665, 1599, 1468, 1362, 1249, 1201, 991, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (t, *J* = 1.8 Hz, 1 H), 7.08 (d, *J* = 1.8 Hz, 2 H), 4.17–4.26 (m, 2 H), 4.00 (t, *J* = 7.8 Hz, 1 H), 3.80–3.97 (m, 4 H), 3.15–3.31 (m, 2 H), 1.69–1.80 (m, 1 H), 1.52–1.62 (m, 1 H), 1.30 (s, 18 H), 0.72–0.90 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.63, 163.60, 149.9, 136.7, 122.78, 120.0, 71.4, 71.4, 69.7, 69.6, 41.0, 35.9, 34.3, 31.9, 31.1, 18.1, 18.0, 17.4; MS (EI): *m*/*z* = 440 [M^+]; HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{28}H_{44}O_2N_2$ 440.3403. Found: 440.3402.

Typical procedure for the synthesis of chiral heterotrisoxazoline 2: To a solution of bisoxazoline **5** (2.97 g, 7.0 mmol) in dried THF (90 mL) was added dropwise *t*-BuLi (5.0 mL, 1.6 M in hexanes, 8.0 mmol) within 15–20 min at –78 °C. The resulting yellow solution was stirred for 1 h at the same temperature, then a solution of 2-chloromethyl oxazoline **6a** (1.99 g, 9.8 mmol) in THF (50 mL) was added dropwise at –78 °C over 20 min. The mixture was slowly warmed to room temperature and kept stirring for a further 36 h. The solvent was removed and the residue was diluted with CH_2Cl_2 (100 mL), then washed with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Petroleum ether was added to precipitate 2-chloromethyl oxazoline, the filtrate was collected, and the solvent was removed in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 10:1→1:2) to give pure product as a white solid. Yield: 2.64 g (64%); $[\alpha]_D^{20}$ –8.2 (*c* 1.00, $CHCl_3$); IR (KBr): 2958, 2926, 2870, 1659, 1599, 1478, 1459, 1362, 1247, 1177, 1001, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 6.0 Hz, 1 H), 7.22–7.26 (m, 4 H), 7.08 (s, 2 H), 5.54 (d, *J* = 8.0 Hz, 1 H), 5.37 (t, *J* = 6.8 Hz, 1 H), 4.28 (t, *J* = 8.8 Hz, 1 H), 3.98 (t, *J* = 7.6 Hz, 1 H), 3.70–3.83 (m, 3 H), 3.35–3.55 (m, 4 H), 3.06–3.13 (m, 2 H), 2.68 (d, *J* = 14.8 Hz, 1 H), 1.67–1.76 (m, 1 H), 1.54–1.62 (m, 1 H), 1.26 (s, 18 H), 0.70–0.87 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 165.3, 164.7, 150.0, 142.4, 140.1, 135.3, 128.2, 127.2, 125.4, 125.4, 124.9, 120.5, 82.9, 76.4, 71.7, 71.0, 70.0, 69.4, 46.0, 40.1, 38.3, 34.6, 32.4, 31.8, 31.5, 30.4, 18.8, 18.4, 17.6, 17.0; MS (EI): *m*/*z* = 611 [M^+]; HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{39}H_{53}O_3N_3$: 611.4087. Found: 611.4088.

Typical procedure for 2/Cu(OTf)$_2$-catalyzed asymmetric Friedel–Crafts reaction (9b as an example): To a Schlenk tube was added **2** (18.4 mg, 0.030 mmol), $Cu(OTf)_2$ (9.1 mg, 0.025 mmol), and *s*-BuOH (1.25 mL) under an N_2 atmosphere, and the resulting blue-green solution was stirred at room temperature for 2–3 h. The solution of catalyst was transferred to **8b** (62.5 mg, 0.25 mmol) under an air atmosphere and the mixture was allowed to stir at –25 °C for 15 min, then indole (36.0 mg, 0.30 mmol) was added. The reaction was held at –25 °C until complete (reaction monitored by TLC), then the mixture was concentrated under reduced pressure, and the residue was submitted to flash column chromatography on silica gel (CH_2Cl_2–PE, 1:1 then pure CH_2Cl_2) to afford the desired product **9b** as a white solid. Yield: 91.6 mg (99%); 94% ee [Chiralcel OD-H, *i*-PrOH–hexane, 10:90, 0.90 mL/min, 254 nm: t_R (minor) = 20.35 min, t_R (major) = 24.73 min.]; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br s, 1 H), 7.55 (d, *J* = 8.1 Hz, 1 H), 7.19–7.38 (m, 6 H), 7.11–7.16 (m, 2 H), 7.01–7.06 (m, 1 H), 5.08 (d, *J* = 12 Hz, 1 H), 4.29 (d, *J* = 12 Hz, 1 H), 3.99 (m, 4 H), 1.00 (m, 6 H).