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Modular Synthesis of Chiral Homo- and Heterotrisoxazolines.† Improving the Enantioselectivity in the Asymmetric Michael Addition of Indole to Benzylidene Malonate

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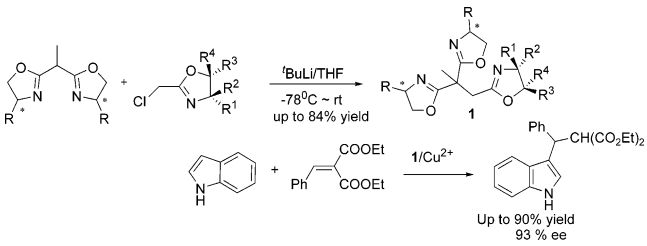
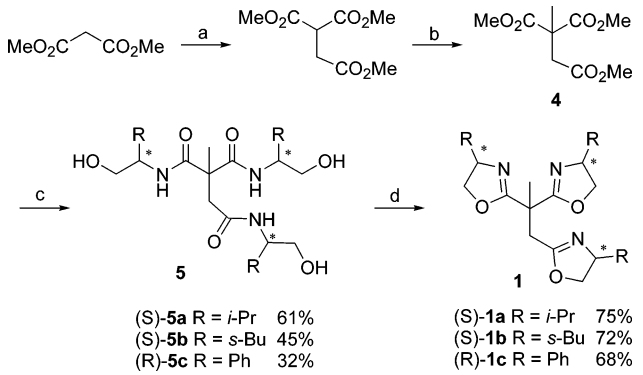


A simple approach to a diverse set of chiral trisoxazolines is described. Deprotonation of bisoxazolines **2**, followed by treatment of 2-chloromethyloxazolines **3**, affords chiral trisoxazolines, including chiral homo- and hetero-trisoxazolines in good to high yields. These trisoxazolines are successfully applied in the asymmetric reaction of indole with benzylidene malonate, and ee's up to 93% were obtained.

C_2-symmetrical bisoxazolines (BOX) have proven to be very powerful chiral ligands for a wide range of metal-catalyzed reactions.[1] Recently, several trisoxazolines have been developed and applied successfully in some asymmetric catalytic reactions[2] and molecular recognition.[3] In a previous study on asymmetric catalysis, we designed the pseudo-C_3-symmetric[4] trisoxazoline **1a** by a sidearm approach and found it very useful in the asymmetric Michael-type indole alkylation,[5] the Diels−Alder reaction,[6a] the 1,3-diploar cycloaddition reaction,[6b] and the Kinugasa reaction.[6c] The originally reported protocol for the synthesis of chiral trisoxazoline **1** started from triester **4** (Scheme 1).[5a] In this protocol, the condensation of triester **4** with amino alcohols is performed under a nitrogen atmosphere at 80 °C for 7−10 days. To achieve reasonable yields, the liberated methanol must be removed in a vacuum after the reaction mixture is to room temperature every 10 h. Thus, this method is very tedious and also limited to the preparation of homo-trisoxazolines. In this paper, we wish to report a conveniently modular approach for the synthesis of a diverse set of chiral trisoxazolines.

SCHEME 1. Previous Synthesis of Trisoxazolines[a]



[a] Reagents and conditions: (a) Na, MeOH, then $BrCH_2CO_2Me$, 0 °C to reflux, 46%; (b) Na, MeOH then CH_3I, 0−40 °C, 80%; (c) amino alcohol, 70 °C, solvent free; (d) PPh_3, CCl_4, Et_3N, CH_3CN, 25 °C.

In the literature, there are two strategies for the synthesis of trisoxazolines. One directly constructs the three oxazolines from the corresponding carboxylic acids or derivatives thereof. The advantage of this method is to enable the synthesis of such ligands in relatively few steps, and thus, this strategy is mostly adopted.[2e−i] However, the direct synthesis suffered from poor yields in the key step sometimes, and most of all, this method is limited to the preparation of chiral homo-trisoxazolines with identical oxazoline subunits, as in the case of the

† Chiral homo-trisoxazolines refer to trisoxazolines with three identical oxazoline subunits, while in chiral hetero-trisoxazolines, the oxazoline subunits are different from each other (or at least one oxazoline subunit is different from the other two).

(1) Reviews: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Pfaltz, A. *J. Heterocycl. Chem.* **1999**, *36*, 1437. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (e) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (f) Reiser, O. *Nachr. Chem. Technol. Lab.* **1996**, *44*, 744. (g) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (h) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (i) Bolm, C. *Angew. Chem.* **1991**, *103*, 556.

(2) For chiral trisoxazolines, see: (a) Kim, S.-G.; Seong, H. R.; Kim, J.; Ahn, K. H. *Tetrahedron Lett.* **2004**, *45*, 6835. (b) Rocchetti, M. T.; Fino, V.; Capriati, V.; Florio, S.; Luisi, R. *J. Org. Chem.* **2003**, *68*, 1394. (c) Bellemin-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3473. (d) Kim, S.-G.; Ahn, K. H. *Tetrahedron Lett.* **2001**, *42*, 4175. (e) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941. (f) Chuang, T.-H.; Fang, J.-M. Bolm, C. *Synth. Commun.* **2000**, *30*, 1627. (g) Chan, T. H. Zheng, G. Z. *Can. J. Chem.* **1997**, *75*, 629. (h) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337. (i) Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* **1995**, 1245. For achiral trisoxazolines, see: (j) Capriati, V.; Florio, S.; Luisi, R.; Rocchetti, M. T. *J. Org. Chem.* **2002**, *67*, 759. (k) Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Commun.* **2002**, 1286. (l) Sorrell, T. N.; Pigge, F. C.; White, P. S. *Inorg. Chim. Acta* **1993**, *210*, 87.

(3) (a) Kim, S.-G.; Kim, K.-H.; Kim, Y. K.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2003**, *125*, 13819. (b) Ahn, K. H.; Ku, H.-y.; Kim, Y.; Kim, S.-G.; Kim, Y. K.; Son, H. S.; Ku, J. K. *Org. Lett.* **2003**, *5*, 1419. (c) Kim, S.-G.; Kim, K.-H.; Jung, J.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2002**, *124*, 591. (d) Kim, S.-G.; Ahn, K. H. *Chem. Eur. J.* **2000**, *6*, 3399. (e) Ahn, K. H.; Kim, S.-G.; Jung, J.; Kim, K.-H.; Kim, J.; Chin, J.; Kim, K. *Chem. Lett.* **2000**, 170.

(4) For a review on C_3-symmetric chiral ligands in asymmetric catalysis, see: Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248.

(5) (a) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (b). Zhou, J.; Ye, M.-C.; Huang, Z.-Z. Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309. (c) Zhou, J.; Ye, M.-C.; Tang, Y. *J. Comb. Chem.* **2004**, *6*, 301. (d) Zhou, J.; Tang, Y. *Chem. Commn.* **2004**, 432.

(6) (a) Zhou, J.; Tang, Y. *Org. Biomol. Chem.* **2004**, *2*, 429. (b) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677. (c) Ye, M.-C.; Zhou, J.; Huang, Z.-Z. Tang, Y. *Chem. Commu*n. **2003**, 2554.

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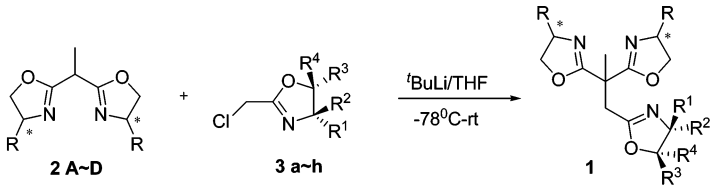
TABLE 1. Modular Synthesis of Trisoxazolines[a]



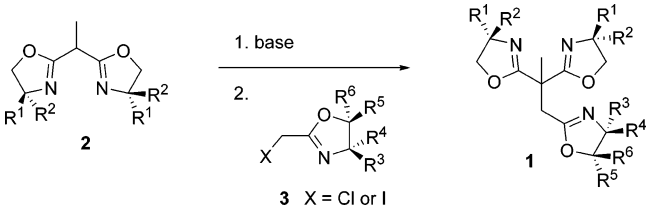
2A: R = (4S)-^{i}Pr **3a**: R^1 = ^{i}Pr, R^2 = R^3 = R^4 = H; **3e**: R^2 = Ph, R^1 = R^3 = R^4 = H;
2B: R = (4S)-Ph **3b**: R^1 = ^{s}Bu,R^2 = R^3 = R^4 = H; **3f**: R^1 = Bn, R^2 = R^3 = R^4 = H;
2C: R = (4R)-Ph **3c**: R^1 = ^{t}Bu, R^2 = R^3 = R^4 = H; **3g**: R^1 = ^{i}Pr, R^2 = H, R^3 = R^4 = Me;
2D: R = (4S)-^{t}Bu **3d**: R^1 = Ph, R^2 = R^3 = R^4 = H; **3h**: R^1, R^3 = -$C_6H_4CH_2$-, R^2 = R^4 = H;

entry	trisoxazoline	yield(%) [b]	entry	trisoxazoline	yield(%) [b]
1	**1a**	74	7	**1Ag**	36
2	**1Ab**	67	8	**1Ah**	74
3	**1Ac**	84	9	**1Ba**	52
4	**1Ad**	77	10	**1Ca**	82
5	**1Ae**	55	11	**1Dc**	42
6	**1Af**	50	12	**1a**	78

[a] All reactions were performed in THF at −78 °C to room temperature under nitrogen. Scale: 1.1 equiv of *tert*-butyllithium, 1.0 equiv of bisoxazoline, and 1.4 equiv of 2-chloromethyloxazoline. [b] Isolated yield. [c] On a 4.16 mmol scale.

synthesis of pseudo-C_3-symmetric trisoxazoline **1a**.[5a] Another way is by modular synthesis, developed by Florio and Gade. Florio et al. developed a novel tris(oxazolinyl)-cyclopropane via "trimerization" of metalated 2-chloroalkyl-2-oxazolines.[2b,i] Almost at the same time, Gade and co-workers reported the preparation of C_3-symmetric trisoxazolines from bisoxazoline by addition−elimination reaction.[2c,k] Very recently, to synthesize a chiral benzene-based hetero-trisoxazoline, Ahn et al. described an oxazoline exchange reaction with amino alcohols.[2a] The most promising character of these modular methods is to enable the synthesis of trisoxazolines with different oxazoline subunits, so that both chiral homo- and hetero-trisoxazolines can be synthesized at will. For this reason, we tried the strategy shown in Scheme 2, by alkylation of bisoxazoline[7] with 2-chloromethyl oxazoline,[8] to arrive at a modified synthesis of chiral trisoxazolines **1a**. In previous studies, Denmark reported that bisoxazoline could be easily deprotonated by LDA/TMEDA and then

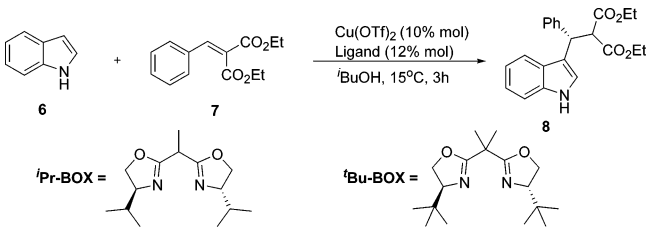
SCHEME 2



reacted with different halides to give bisoxazoline derivatives.[7] Very recently, we found that *i*-Pr-bisoxazoline, after deprotonation by LDA/TMEDA, could couple readily with functionalized bromide to give bisoxazoline with a pendant functional group.[5c] However, we failed to extend this methodology to synthesis of chiral trisoxazoline **1**. It was found that reaction of ^{i}Pr-bisoxazoline, deprotonated by LDA/TMEDA, with 2-chloromethyl-2-oxazoline gave unexpected products. The reason, we proposed, is probably the "trimerization" of the chloride by[2b] and the replacement of diisopropylamine with the 2-chloromethyloxazoline. Thus, we tried to use *t*-BuLi instead of LDA, and it was found that the coupling reaction worked well under these conditions (Table 1, entries 1−11). ^{i}Pr-BOX **2A**, deprotonated by *t*-BuLi, could react with 2-chloro-

(7) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, *5875*.
(8) (a) Musser, J. H.; Kubrak, D. M.; Chang, J.; Dizio, S. M.; Hite, M.; Hand, J. M.; Lewis, A. J. *J. Med. Chem.* **1987**, *30*, 400. (b) Breton, P.; André-Barrés, C.; Langlois, Y. *Synth. Commun.* **1992**, *22*, 2543. (c) Sudo, A.; Hashimoto, Y.; Kimoto, H.; Hayashi, K.; Saigo, K. *Tetrahadron: Asymmetry* **1994**, *5*, 1333.

TABLE 2. Substituent Effects of Trisoxazolines[a]



entry	ligand	yield[b] (%)	ee[c] (%)
1	**^{i}Pr-BOX**	85	79
2	**^{t}Bu-BOX**	63[d]	48
3	**1a**	90	93 (90)[e]
4	**1Ab**	83	90
5	**1Ac**	75	89
6	**1Ad**	85	85
7	**1Ae**	80	86
8	**1Af**	89	90
9	**1Ag**	90	85
10	**1Ah**	92	91
11	**1Ba**	79	73
12	**1Ca**	65	−61
13	**1Dc**	50[f]	26

[a] Reactions are performed on a 0.25 mmol scale in ^{i}BuOH (5 mL). [b] Isolated yield after 3 h. [c] Determined by HPLC analysis (Chiracel OD-H, 10% ^{i}PrOH/hexane, 0.9 mL/min, 254 nm). [d] Isolated yield after 24 h. [e] Number in parentheses is the ee using ^{i}Pr-TOX prepared by the previous procedure. [f] Isolated yield after 96 h.

methyl-2-oxazoline with different substituents such as isopropyl, phenyl, *sec*-butyl, benzyl, *tert*-butyl, indenyl, etc. and afforded the chiral homo- or hetero-trisoxazolines in moderate to good yields (Table 1, entries 1−8).[9] In addition, the lithiated **2A** could also couple with both enantiomers **3d** and **3e** smoothly to give desired diastereomeric products. Not only ^{i}Pr-BOX **2A** but also phenyl- and ^{t}Bu-BOX are good substrates for this reaction. Noticeably, ^{t}Bu-BOX **2D** allowed the incorporation of *tert*-butyl-2-methyleneoxazoline to construct the bulky *tert*-butyltrisoxazolines **1Dc**, which could not be obtained by the previously used direct synthesis, demonstrating the superiority of the modular synthesis. This reaction was performed on a gram scale in good yield for ^{i}Pr-trisoxazoline **1a** (Table 1, entry 12).

With these trisoxazolines at hand, we examined the effects of the pendant oxazolines on the enantioselectivity of the indole alkylation with benzylidene malonates.[5] The results are summarized in Table 2. Trisoxazolines **1a**−**1Ah,** derived from ^{i}Pr-BOX **2A**, gave higher enantioselectivities (85%−93%) than the parent ^{i}Pr-BOX under the same conditions (entries 1, 3−10). Using the currently prepared ^{i}Pr-TOX **1a** instead of the previous one, interestingly, the enantiomeric excess was slightly improved, and up to 93% ee was obtained at 15 °C. Compared with the ^{i}Pr-BOX-derived trisoxazolines, Ph-BOX-derived trisoxzaolines gave lower ee's (entries 11 and 12). Opposite enantioselectivities were observed using **1Ca** and **1Ba**, indicating that the stereochemical course of this reaction depends on the stereochemistry of the bisoxazoline backbone. Unlike ^{i}Pr-BOX **2A**, the installation of a pendant oxazoline on ^{t}Bu-BOX **2D** resulted in decreasing the enantiomeric excess and the reaction rate (entries 2 and 13), probably due to the steric effects of *tert*-butyl group.

In summary, we have developed an efficient method for the synthesis of various chiral trisoxazolines. Compared with the previous report, this method provides an easy and simplified access to a diverse set of homo- and especially hetero-trisoxazolines in gram scale. By this strategy, we found that the enantioselectivity of the Cu(II)-catalyzed Michael addition of indole to benzylidene malonate could be improved up to 93% ee under mild conditions. The application of these newly developed ligands in other reactions is now in progress in our laboratory.

Experimental Section

General Procedure for the Synthesis of Chiral Homo- and Hetero-trisoxazolines. To a solution of bisoxazoline (**2A**−**D**) (2 mmol) in dried THF (30 mL) was added dropwise *t*-BuLi (1.3 mL, 1.7 M in hexanes, 2.2 mmol) within 15−20 min at −78 °C. The resulting yellow solution was stirred for an additional 1 h at this temperature. Then a solution of 2-chloromethyl oxazoline (2.8 mmol) in THF (10 mL) was added dropwise at −78 °C over 10 min. The solution was slowly warmed to room temperature and was stirred for a further 10 h. The mixture was diluted with CH_2Cl_2 (20 mL) and was washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/acetone = 1/10).

1,2,2-Tris[2-[(4*S*)-4-isopropyl-1,3-oxazolinyl]]propane 1a: [6a] colorless oil (74%); $[\alpha]^{20}_D$ −47.2 (*c* 3.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22−4.07 (m, 3H), 4.00−3.77 (m, 6H), 3.05 (ABd, J = 14.7 Hz, 1H), 2.91 (ABd, J = 14.4 Hz, 1H), 1.79−1.61 (m, 3H), 1.56 (s, 3H), 0.90 (d, J = 6.6 Hz, 6H), 0.86 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 7.2 Hz, 6H), 0.81 (d, J = 7.2 Hz, 3H).

General Procedures for Trisoxazoline/Cu(OTf)$_2$-Catalyzed Asymmetric Michael Addition Reaction. To a Schlenk tube was added Cu(OTf)$_2$ (0.10 equiv) followed trisoxazoline **1** (0.12 equiv) under air atomosphere. Then ^{i}BuOH (2.5 mL) was added, and the resulting blue-green solution was stirred at room temperature (10−25 °C) for 1 h before alkylidene malonate (1.0 equiv in ^{i}BuOH, 2.5 mL) was added. The mixture was allowed to stir at room temperature for 15 min, and then the indole (1.2 equiv) was added. After the reaction was complete (by TLC), the mixture was concentrated under reduced pressure at room temperature, and the residue was purified by flash column chromatography on silica gel [eluted with CH_2Cl_2/petroleum ether (1/1, v/v) then pure CH_2Cl_2] to afford the desired product.

Ethyl (3*S*)-2-ethoxycarbonyl-3-(3-indolyl)-3-phenylpropanoate 8: [5b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (brs, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 6.9 Hz, 2H), 7.10−7.30 (m, 6H), 7.03−7.06 (m, 1H), 5.08 (d, J = 11.7 Hz, 1H), 4.29 (d, J = 11.4 Hz, 1H), 3.99 (m, 4H), 1.00 (m, 6H).

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

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(9) No desired product was isolated when 2-chloromethyl-2-oxazoline without substitute was used.