Sidearm Approach: A Promising Strategy for Construction of Bisoxazoline-Based Ligand Library

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Combinatorial chemistry offers the premise of increasing the efficiency to discover new catalysts for asymmetric transformations.[1] In this context, rapid construction of diverse chiral ligands with different activities and selectivities is one of the most important issues.[2] C_2-symmetrical bisoxazolines have been found to be very valuable for a wide range of metal-catalyzed reactions,[3] and thus, much effort has been devoted to the creation of superior bisoxazoline-based ligands by varying amino alcohols,[4] bridging linkers,[5] or backbones,[6] as demonstrated by the wide application of bisoxazoline (BOX) **1**,[7] DBPHOX[8] and PYBOX.[9] Although significant achievements have been obtained, the development of inexpensive, easily accessible and highly efficient bisoxazoline-based ligands is still of great interest. Very recently, we designed a pseduo-C_3-symmetric trisoxaozline (TOX) **2a** by a sidearm approach and found this trisoxazoline **2a** to be very useful in indole alkylation,[10a,c] the Kinugasa reaction,[10b] and the Diels−Alder reaction.[10d] In these reactions, the introduction of the sidearmed oxazoline improved the enantioselectivity and the activity greatly in some cases, as compared with the corresponding bisoxazoline, and trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ was found to be air- and water-stable so that the aforementioned reactions could even be carried out in air. These results suggested that the installation of the sidearmed oxazoline improved the properties of bisoxazolines in some aspects. To further understand the role of the pendant oxazoline in TOX and to develop new powerful ligands in asymmetric catalysis, we are interested in modifying bisoxazoline by installing another coordinating group as the sidearm. As described in Scheme 2, our strategy will mainly focus on the combination of the bisoxazoline frameworks with a diverse functionalized or unfunctionalized side chain and the systematical study of the sidearm effects on the enantioselectivity and activity in asymmetric catalysis. This strategy is attractive not only for its effectiveness in increasing the ligand diversity,[11] but also for the easy variation of the sidearm to tune the steric and electronic properties of the catalyst. By this approach, we synthesized a number of sidearmed bisoxazolines from inexpensive materials, preliminarily studied the sidearm effects in the indole alkylation with benzylidene malonate, and discovered some simple but powerful ligands in this reaction. In this paper, we report the preliminary results.

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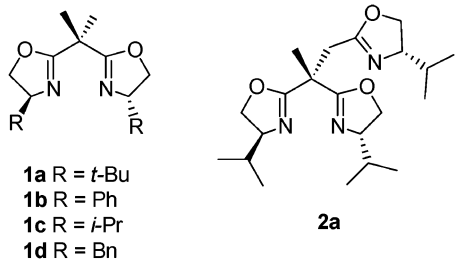
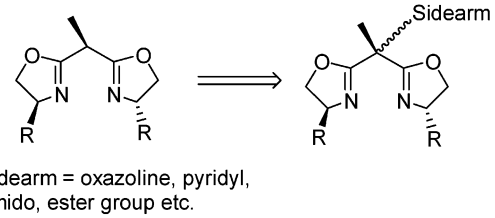
Scheme 1



Scheme 2



Synthesis of Sidearmed Bisoxazolines. There are two strategies for the preparation of the sidearmed bisoxazolines, which are shown in Scheme 3. The coupling of bisoxazoline with different halides, developed by Denmark,[5a] provides a facile and convenient way to access the sidearmed bisoxazolines from commercially inexpensive diethyl methylmalonate. First, we chose the inexpensive ^{i}Pr-BOX **10** to start our study. It was found that ^{i}Pr-BOX **10**, deprotonated by LDA, could react smoothly with a variety of halides with different structures to afford the desired bisoxazoline derivatives. Not only nonfunctionalized groups, such as cyclohexyl and phenyl, but also functionalized groups, such as ester, amido, and cyano groups, could be installed as a sidearm on the ^{i}Pr-BOX **10** to form bisoxazolines **3**−**7** in moderate to good yields, as is shown in Table 1**.** It is important to note that the bridging carbon atom in BOX ligands **3**−**7** is not stereogenic, since it bears two identical residues.[5c]

To further study the effect of the linker length of the third oxazoline on the activity and selectivity, we synthesized C_3-symmetric trisoxaozlines **2c** using the Gade's procedures.[12] Accordingly, trisoxazoline **2b** with two more carbons on the linker of the pendant oxazoline than **2c** was also synthesized, as is shown in Scheme 4. Thus, by these two strategies, a minilibrary including 15 bisoxazoline derivatives was developed, as shown in Chart 1.

With these sidearmed bisoxazolines at hand, we first examined the sidearm effects in the indole alkylation with benzylidene malonates.[13] Considering that the stereochemistry of this reaction is solvent-dependent,[10c] we carefully evaluated all of these new sidearmed bisoxazolines in several representative solvents. The results are summarized in Table 2. When the reaction was carried out in THF at 15 °C, the ^{i}Pr-BOX **1c** and **10** gave only moderate enantioselectivity (46 and 53%, respectively), similar to that obtained by the corresponding bisoxazolines **3a** and **3b** with noncoordinating sidearms (entries 2, 6, 7, and 18). Compared with ^{i}Pr-BOX

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Scheme 3

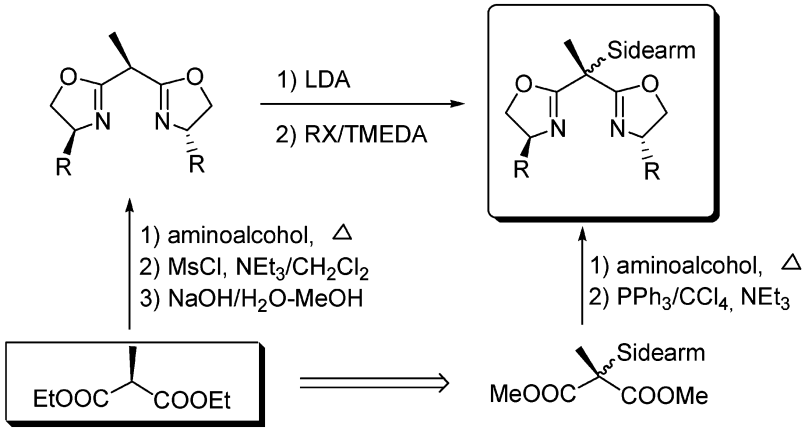
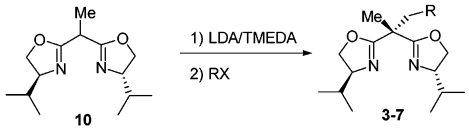
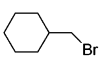
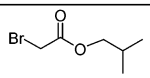
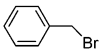
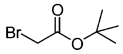
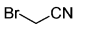
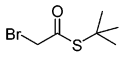
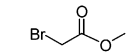
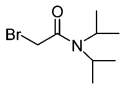
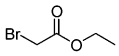
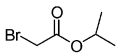
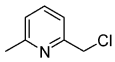


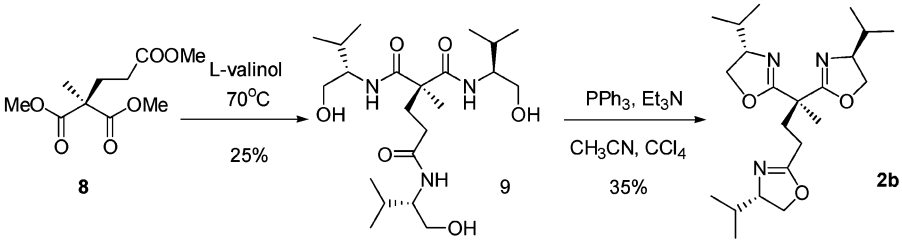
Table 1. Synthesis of the Sidearmed Bisoxazolines[a]



Entry	RX	L	Yield[b] (%)	Entry	RX	L	Yield[b] (%)
1		**3a**	78	7		**4d**	70
2		**3b**	38	8		**4e**	84
3		**3c**	50	9		**5**	49
4		**4a**	77	10		**6**	69
5		**4b**	62	11		**7a**	63
6		**4c**	79	12		**7b**	20

[a] For detailed reaction conditions, please see the Supporting Information. [b] Isolated yield.

Scheme 4. Synthesis of Trisoxazoline **2b**



1c and **10**, ᵗBu-BOX **1a** afforded higher enantioselectivity (entries 1, 2, and 18). Encouragingly, the introduction of a coordinating group (−CN) improved the enantioselctivity to 61% (entry 8). By installing a pendant oxazoline on BOX **10**, enantioselectivity was obviously improved (entries 3−5). The best results were achieved when ester groups were introduced as the sidearm (entries 9−13), of which both bisoxazoline **4e** with bulky *tert*-butyl ester (entry 13) and **5** with *tert*-butyl thioester (entry 14) gave the best activity and enantioselectivity (79 and 80% ee, respectively). Bisoxazoline **6** with an amido group as the sidearm also improved the enantioselectivity above 70% ee (entry 15), as compared with the nonsidearmed bisoxazoline **1c** and **10**. The pyridyl as the sidearm obviously slowed the reaction, and the enantioselectivity is also unsatisfactory (entries 16 and 17).

Thus, in THF, the installation of the sidearm with a suitable coordination group on the corresponding bisoxazoline **10** can significantly influence the enantioselectivity and reactivity in the reaction of indole alkylation with benzylidene malonate. Interestingly, when the reaction was

Chart 1

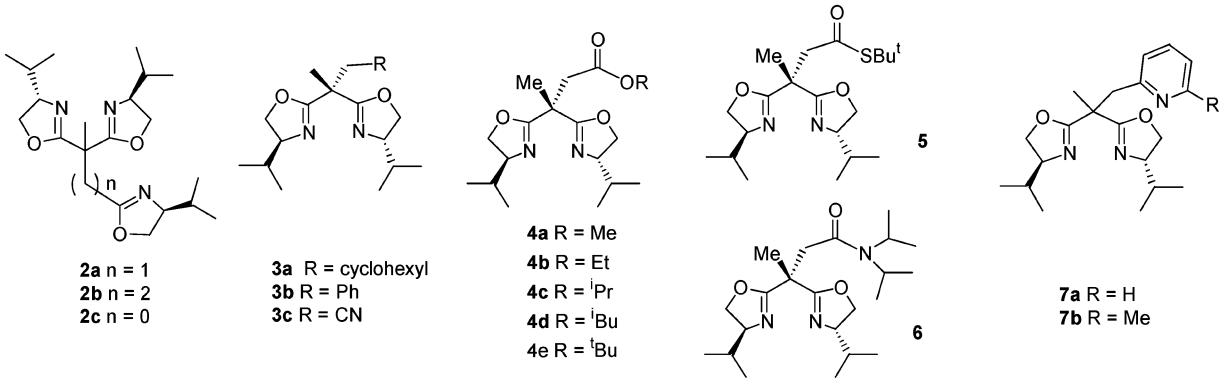
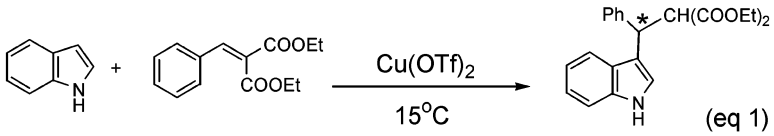


Table 2. Screening of the Sidearmed Bisoxazolines[a]



entry	L	THF[d] yield (%)[b], ee (%)[c]	^{i}BuOH[d] yield (%)[b], ee (%)[c]	CH_2Cl_2[e] yield (%)[b], ee (%)[c]	TTCE[e] yield (%)[b], ee (%)[c]
1	**1a**	77, 60 (*S*)	95, 40 (*S*)	71, 57 (*S*)	20, 27 (*S*)
2	**1c**	99, 46 (*S*)	99, 83 (*S*)	88, 67 (*R*)	89, 71 (*R*)
3	**2a**	10, 82 (*S*)	99, 90 (*S*)	60, 51 (*R*)	76, 65 (*R*)
4	**2b**	31, 60 (*S*)	99, 91 (*S*)	94, 75 (*R*)	72, 73 (*R*)
5	**2c**	99, 67 (*S*)	99, 87 (*S*)	87, 75 (*R*)	73, 69 (*R*)
6	**3a**	99, 37 (*S*)	99, 83 (*S*)	39, 68 (*R*)	94, 74 (*R*)
7	**3b**	99, 48 (*S*)	99, 88 (*S*)	12, 78 (*R*)	45, 75 (*R*)
8	**3c**	99, 61 (*S*)	99, 86 (*S*)	75, 59 (*R*)	58, 48 (*R*)
9	**4a**	99, 73 (*S*)	99, 82 (*S*)	40, 70 (*R*)	72, 71 (*R*)
10	**4b**	99, 72 (*S*)	99, 87 (*S*)	70, 69 (*R*)	61, 77 (*R*)
11	**4c**	99, 73 (*S*)	99, 88 (*S*)	68, 74 (*R*)	76, 65 (*R*)
12	**4d**	99, 74 (*S*)	99, 92 (*S*)	70, 78 (*R*)	84, 60 (*R*)
13	**4e**	99, 79 (*S*)	99, 88 (*S*)	80, 82 (*R*)	81, 79 (*R*)
14	**5**	95, 80 (*S*)	96, 89 (*S*)	80, 82 (*R*)	80, 84 (*R*)
15	**6**	99, 72 (*S*)	99, 83 (*S*)	99, 48 (*R*)	82, 67 (*R*)
16	**7a**	82, 49 (*S*)	99, 86 (*S*)	20, 60 (*R*)	75, 75 (*R*)
17	**7b**	10, 47 (*S*)	99, 82 (*S*)	27, 57 (*R*)	15, 65 (*R*)
18	**10**	99, 53 (*S*)	99, 82 (*S*)	90, 78 (*R*)	30, 74 (*R*)

[a] Reactions were run under N_2 at 15 °C with 11−12 mol % of ligand and 10 mol % of $Cu(OTf)_2$. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/hexanes, 0.80 mL/min, 254 nm. [d] 15 °C. [e] 0 °C.

carried out in ^{i}BuOH at 15 °C, all ligands except *tert*-butyl bisoxaozline **1a** gave good to high enantioselectivity. In contrast to bisoxazoline **10**, the sidearmed bisoxalines with a coordinating group afforded better selectivity (enties 3−16), and bisoxazolines **4d** could achieve 92% ee in excellent yield, even at 15 °C.

As was found, the enantioselectivity of this reaction is solvent-dependent.[10c] After finishing the evaluation of bisoxazoline ligands **1**−**7** and **10** in isobutyl alcohol, we evaluated all of these ligands in weak the coordinating solvent CH_2Cl_2 and TTCE at 0 °C. Again, all the isopropyl-derived ligands reversed the enantioselectivity in halogenated solvents. In our screened conditions, it was found that bisoxazoline **5** with bulky *tert*-butyl thioester could deliver enantioselectivity best; a value as high as 84% for the *R* enantiomer was obtained. This is also the highest enantioselectivity found for the synthesis of the *R* enantiomer of this substrate, just by changing the solvent (entry 14).[14] It should also be noted that the amido group as the sidearm accelerates the reaction in weak coordinating solvents. Ligand **6** could promote the reaction to completion in just 10 h when the reaction was carried out in CH_2Cl_2, obviously faster than other ligands.

In summary, we demonstrated that the sidearm approach, combining a bisoxazoline scaffold with diverse functional groups, was very useful in rapid construction of a bisoxazoline-based ligand library. By this strategy, we found that inexpensive and readily available bisoxazoline sidearmed with a *tert*-butyl ester or thioester group is much better than the commonly used and expensive *tert*-butyl bisoxazoline **1a** in the Friedel−Crafts reaction of indole with benzylidene malonate. It is noted that the enantioselectivity of the reaction between indole and benzylidene malonate could be reversed from +92 to −84% ee by the choice of ligands and solvents using mild conditions. This is also the best result achieved for this reaction. The extension of this approach to develop more bisoxazoline-based chiral ligands and the application of these newly developed ligands in other reactions is now in progress in our laboratory.

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

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(14) For rationalization of the influence of the solvent on indole alkylation, please see the Supporting Information.

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