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Design of chiral tin(IV) aryloxide as a mild Lewis acid catalyst for enantioselective Diels–Alder reaction

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Abstract—A novel Sn(IV) aryloxide Lewis acid has been designed and prepared from $SnCl_4$ and (*S*)-3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-bi-2-naphthol. The chiral Sn(IV) Lewis acid has been successfully applied to the enantioselective Diels–Alder reaction.

The development of designer Lewis acids has become increasingly important for selective carbon–carbon bond formation, which is one of the most important transformations in modern organic synthesis.[1] Among them, chiral metal alkoxides $M(OR)_n$ including B,[2] Al,[3] Ti,[4] and Zr[5] have been developed in a number of enantioselective syntheses as asymmetric variants of ordinary Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$, and $ZrCl_4$, respectively. Although $SnCl_4$ has also been utilized extensively in organic synthesis for enhancing a variety of Lewis acid-promoted reactions,[6,7] the corresponding $Sn(OR)_4$ has so far received little attention due to its weak Lewis acidity[8] and hence the nature of such $Sn(OR)_4$ Lewis acid remains elusive. Herein, we wish to report the first example on the design of chiral tin(IV) aryloxides as a new class of mild Lewis acid catalysts for enantioselective Diels–Alder reaction.[9]

In order to develop a novel tin(IV) Lewis acid $Sn(OR)_4$, we chose to examine various phenols, which would be expected to be suitable ligands due to their ease of modification and the ready availability of chiral variants such as optically pure 1,1′-bi-2-naphthol (BINOL). The requisite tin(IV) aryloxides were prepared in situ from $SnCl_4$ and the corresponding lithium aryloxides, and their Lewis acidity was evaluated by carrying out the Diels–Alder reaction. Thus, in the presence of 10 mol % of the in situ generated catalysts **1**–**3**, the Diels–Alder reaction of cyclopentadiene and methacrolein was conducted at 0 °C. In the case of catalysts **1a**–**c**, however, the reactions gave poor results in reactivity regardless of the presence of electron-donating or electron-withdrawing groups on the phenoxy ligands (Fig. 1 and Table 1, entries 1–3).

Since catalyst **2** prepared from bidentate biphenol gave a slightly improved yield compared to tin(IV) aryloxides **1a**–**c** (entry 4), we prepared chiral tin(IV) aryloxides (*S*,*S*)-**3a**–**f** using various BINOL derivatives (*S*)-**4a**–**f** (Fig. 1 and Table 1, entries 5–11). The use of (*S*,*S*)-**3a** derived from (*S*)-BINOL (*S*)-**4a** exhibited some asymmetric induction without increasing the chemical yield (entry 5). On the other hand, (*S*,*S*)-**3b** possessing electron-deficient pentafluorophenyl groups at the 3,3′-position of (*S*)-BINOL significantly improved the chemical yield as well as the enantioselectivity (entry 6). Here toluene was found to be superior to CH_2Cl_2 as solvent to achieve higher ee values (entry 7). These results induced our investigation on the substituent effect at the 3,3′-position of (*S*)-BINOL. Replacing the pentafluorophenyl groups with phenyl or β-naphthyl groups in (*S*,*S*)-**3c** or **3d**, respectively, resulted in a significant decrease in both the yield and the enantioselectivity (entries 8 and 9). In contrast, use of (*S*,*S*)-**3e** or **3f** possessing electron-withdrawing 3,4,5-trifluorophenyl or 3,5-bis(trifluoromethyl)phenyl groups, respectively, afforded the Diels–Alder adduct with both higher chemical yields and higher levels of enantioselectivity (entries 10 and 11).

Using chiral tin(IV) Lewis acid (*S*,*S*)-**3f**, we optimized the reaction conditions. Lowering the reaction

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Keywords: Asymmetric catalysis; Lewis acids; Sn; Diels–Alder reaction.

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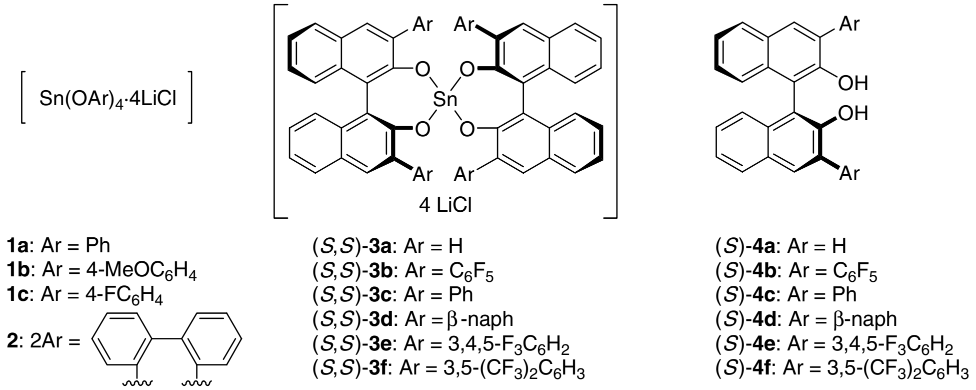
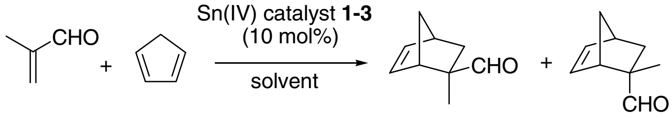


Figure 1. Possible structures of tin(IV) aryloxides and various BINOL derivatives.

Table 1. Diels–Alder reaction catalyzed by Tin(IV) catalysts[a]



Entry	Catalyst	Conditions (°C, h)	Yield (%)[b] [*exo*:*endo*][c]	ee (%)[d] [config]
1	**1a**	0, 2	7 [7.2:1]	
2	**1b**	0, 2	6 [12:1]	
3	**1c**	0, 2	7 [8.5:1]	
4	**2**	0, 2	17 [8.1:1]	
5	(*S*,*S*)-**3a**	0, 2	19 [8.6:1]	25 [*R*]
6	(*S*,*S*)-**3b**	0, 2	68 [9.0:1]	43 [*R*]
7	(*S*,*S*)-**3b**	−78, 2; 0, 9	79 [5.1:1]	57 [*R*]
8	(*S*,*S*)-**3c**	−78, 1; 0, 2	11 [7.2:1]	10 [*R*]
9	(*S*,*S*)-**3d**	−78, 1; 0, 2	49 [6.3:1]	29 [*R*]
10	(*S*,*S*)-**3e**	−78, 1; 0, 2	78 [6.8:1]	68 [*R*]
11	(*S*,*S*)-**3f**	−78, 1; 0, 2	77 [12:1]	77 [*R*]
12	(*S*,*S*)-**3f**	−78, 0.5; −40, 4	68 [20:1]	80 [*R*]
13	(*S*,*S*)-**3f**	−40, 4	94 [34:1]	92 [*R*]

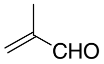
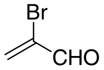
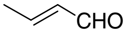
[a] The asymmetric Diels–Alder reaction was carried out as described in Ref. 11 except generating a lithium aryloxide at −78 °C in CH_2Cl_2 (entries 1–6) or toluene (entries 7–12).

[b] Isolated yield by column chromatography for the *exo*/*endo* mixture.

[c] The *exo*/*endo* ratio was determined by ^1H NMR analysis of Diels–Alder adducts.

[d] The ee of the major *exo* isomer and the absolute configuration of its carbonyl α-carbon are indicated. The ee of the product was determined by capillary GC after conversion of Diels–Alder adducts into a diastereomeric mixture of acetals with (2*R*,4*R*)-(−)-2,4-pentanediol. The absolute configuration was assigned by comparison with data in the literature.[2b]

Table 2. Asymmetric Diels–Alder reaction catalyzed by chiral tin(IV) catalyst (*S*,*S*)-**3f**[a]

Entry	Dienophile	Conditions (°C, h)	Yield (%)[b] [*exo*:*endo*][c]	ee (%)[d] [config]
1	 CHO	−40, 4	94 [34:1]	92 [*R*][e]
2	 Br CHO	−78, 2	89 [>99:1]	92 [*S*]
3	 CHO	0, 6	50 [1:8.0]	81 [*S*]

[a] The reaction was carried out as described in Ref. 11.

[b] Isolated yield by column chromatography for the *exo*/*endo* mixture.

[c] The *exo*/*endo* ratio was determined by ^1H NMR analysis of Diels–Alder adducts.

[d] The ee of the major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration was assigned by comparison with data in the literature.[2b] Unless otherwise specified, the ee of the product was determined by GC analysis using chiral capillary column (ASTEC CHIRALDEX G-TA).

[e] The ee of the product was determined by capillary GC after conversion of Diels–Alder adducts into a diastereomeric mixture of acetals with (2*R*,4*R*)-(−)-2,4-pentanediol.

temperature from 0 to −40 °C did not affect the enantioselectivity (entry 12). However, when the deprotonation of ligand (*S*)-**4f** with BuLi was carried out at room temperature in the preparation of the tin catalyst (*S*,*S*)-**3f**,[10] the Diels–Alder reaction proceeded in a high yield and with a high level of enantioselectivity (entry 13).

With the catalyst (*S*,*S*)-**3f** in hand, some selected examples using other aldehydes are summarized in Table 2. Similar high levels of enantioselectivity and *exo* selectivity were obtained when α-bromoacrolein was used as a dienophile (entry 2). In the case of less reactive crotonaldehyde, good enantioselectivity was also observed (entry 3).

In summary, we have shown that chiral tin(IV) aryloxides (*S*,*S*)-**3** prepared from $SnCl_4$ and chiral (*S*)-BINOL derivatives (*S*)-**4** can be utilized as mild chiral Lewis acids in catalytic asymmetric Diels–Alder reactions. Further investigations to clarify the precise structure of the catalyst and efforts toward development of other enantioselective reactions using this catalyst are in progress.

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10. ^1H NMR showed that a single species with C_2 symmetry was formed. Compound (*S*,*S*)-**3f**: ^1H NMR (400 MHz, toluene-d_8) δ 8.44 (2H, s), 8.22 (2H, s), 7.94 (1H, s), 7.64 (1H, s), 7.57 (1H, d, $J = 8$ Hz), 7.55 (1H, s), 7.46 (1H, s), 7.39 (1H, d, $J = 8$ Hz), 6.93–6.98 (2H, m), 6.89 (1H, app t), 6.78 (1H, app t), 6.67–6.72 (2H, m).
11. General procedure: To a solution of (*S*)-**4f** (78 mg, 0.11 mmol) in toluene (1.5 mL) was added a 1.54 M hexane solution of *n*-BuLi (143 μL, 0.22 mmol) at −78 °C. After 1 h of stirring at room temperature, a 1 M hexane solution of $SnCl_4$ (50 μL, 0.05 mmol) was added at −78 °C and the mixture was stirred at the same temperature for 0.5 h and at room temperature for 1 h. Then α,β-unsaturated aldehyde (0.5 mmol) and cyclopentadiene (124 μL, 1.5 mmol) were added at −78 °C. The mixture was then stirred under the conditions as described in Table 2. The reaction mixture was directly purified by flash column chromatography on silica gel (ether/pentane = 1:18 as eluent) to give the corresponding cycloadduct. The enantioselectivity of the product was determined by the reported method.[2]