6,6′-Substituent effect of BINOL in bis-titanium chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of nitrones†

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By the accommodation of modified BINOLs as chiral ligands, enantioselectivities in the bis-titanium chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of *N*-diphenylmethyl nitrones and methacrolein could be improved.

In the field of asymmetric Lewis acid catalysis, 1,1′-binaphthyl-2,2′-diol (BINOL) is one of the best known privileged ligands having axial chirality, and has been successfully applied in a great number of enantioselective reactions.[1] It is also known that the introduction of an electron-withdrawing group at 6,6′-position of BINOL affects the reactivity and enantioselectivity by changing the Lewis acidity and the chiral environment of the catalyst.[2–4] In our recent study, the oxygen-bridged bis-titanium chiral Lewis acid (*S*,*S*)-**1a** (X = H, Fig. 1) containing BINOL ligands has been revealed to catalyze some asymmetric reactions, such as asymmetric allylation and 1,3-dipolar cycloaddition of nitrones.[5] We report herein a detailed study of the 6,6′-substituent effect of BINOL in our catalytic system, which led to the identification of a new highly efficient catalyst.

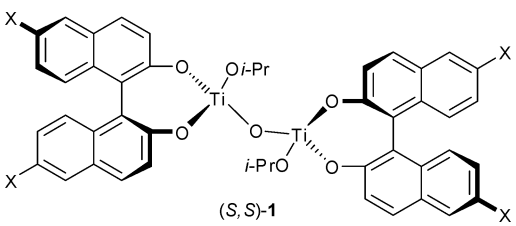

Fig. 1 Oxygen-bridged bis-titanium chiral Lewis acid (*S*,*S*)-**1**.

In our previous work, we have demonstrated that 1,3-dipolar cycloaddition of *C*-phenyl *N*-diphenylmethyl nitrone **2a** and methacrolein catalyzed by (*S*,*S*)-**1a** proceeded smoothly, giving the *endo*-cycloadduct as a single regioisomer with 90% ee (Table 1, entry 1). Furthermore, use of (*S*,*S*)-**1b** containing 6,6′-I_2-BINOL exhibited the enhanced reactivity and enantioselectivity compared to (*S*,*S*)-**1a** (entry 2).[5d,e] However, in the reaction of some other nitrones and methacrolein, (*S*,*S*)-**1b** catalyzed 1,3-dipolar cycloaddition was found to be still impractical, giving the products with less than 90% ee. In this context, we set out the investigation of other modified BINOLs having an electron-withdrawing group at 6,6′-positions to develop a more efficient catalyst.[6,7]

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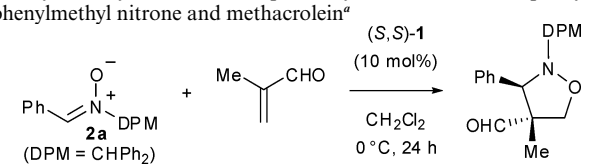
† Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday.

Table 1 Screening of 6,6′-substituent of the BINOL moiety in (*S*,*S*)-**1** catalyzed asymmetric 1,3-dipolar cycloaddition of *C*-phenyl *N*-diphenylmethyl nitrone and methacrolein[a]



Entry	X		Yield (%)[b]	Ee (%)[c]
1	H	(*S*,*S*)-**1a**	58	90
2	I	(*S*,*S*)-**1b**	80	93
3	Cl	(*S*,*S*)-**1c**	44	94
4	Br	(*S*,*S*)-**1d**	76	90
5	CF_3	(*S*,*S*)-**1e**	84	97

[a] The reaction with nitrone and methacrolein (3 equiv.) was carried out in the presence of 10 mol% of (*S*,*S*)-**1**. [b] Isolated yield. [c] Determined by HPLC analysis by chiral columns after reducing the aldehyde moiety.

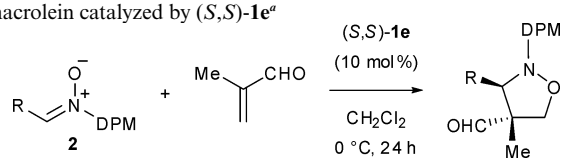
Attachment of chlorine as 6,6′-substituent resulted in diminished yield and slightly higher enantioselectivity (entry 3). Use of catalyst (*S*,*S*)-**1d** composed of the 6,6′-Br_2-BINOL ligand led to the deterioration of both yield and enantioselectivity (entry 4). Upon further investigation, the introduction of the trifluoromethyl group at 6,6′-position of BINOL was found to be optimal, giving the cycloadduct in 84% yield and 97% ee (entry 5).

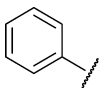
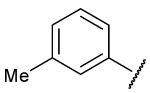
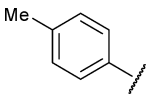
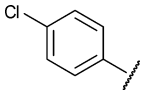
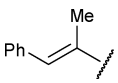
With the promising catalyst (*S*,*S*)-**1e** in hand, we then examined the scope of 1,3-dipolar cycloaddition of various *N*-diphenylmethyl nitrones and methacrolein as shown in Table 2. The reaction with nitrones bearing a 3- or 4-tolyl group gave the corresponding cycloadducts with 97% ee and 94% ee, respectively (entries 2 and 3), which were better than the results obtained by the use of (*S*,*S*)-**1b** (Table 2, in parentheses). In the case of nitrone **2d** bearing the electron-withdrawing group, an increase in enantiomeric excess was also observed (entry 4). The use of *C*-cyclopentenyl nitrone **2e** provided the cycloadduct with the excellent level of enantioselectivity (entry 5). The remarkable increase of the enantioselectivity was observed in the reaction of nitrone **2f** containing a substituted styryl moiety, although the ee still remained at a moderate level (entry 6).

We then moved our attention to the accommodation of this successful system to the reaction using crotonaldehyde as dipolarophile. Compared to the previous report using (*S*,*S*)-**1a** or (*S*,*S*)-**1b**, the clear superiority of (*S*,*S*)-**1e** was observed. Thus, the cycloadduct with three consecutive stereocenters could be isolated in 81% with 96% ee (Scheme 1).

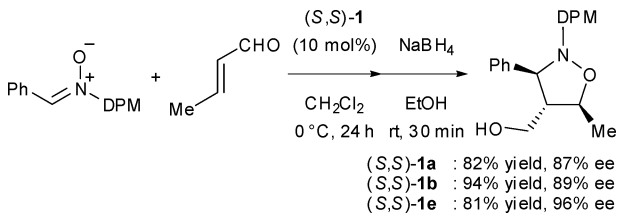
To demonstrate the synthetic utility, the facile transformation of the so-obtained oxazolidine into the β-amino acid ester having a quaternary center at the α-position was implemented. First, the

Table 2 Asymmetric 1,3-dipolar cycloaddition of various nitrones and methacrolein catalyzed by (*S*,*S*)-**1e**[a]



Entry	R		Yield (%)[b]	Ee (%)[c,d]
1		**2a**	84	97 (93)
2		**2b**	75	97 (96)
3		**2c**	76	94 (88)
4[e]		**2d**	42	91 (88)
5		**2e**	41	93 (88)
6		**2f**	70	83 (70)

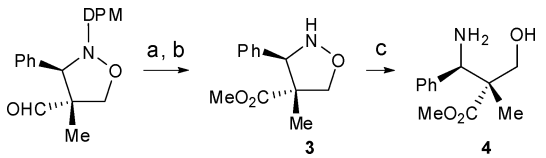
[a] The reaction with nitrone and methacrolein (3 equiv.) was carried out in the presence of 10 mol% (*S*,*S*)-**1e**. [b] Isolated yield. [c] Determined by HPLC analysis by chiral columns after reducing the aldehyde moiety. [d] Ee in parentheses indicates the result obtained by the use of (*S*,*S*)-**1b**. [e] Performed with 20 mol% (*S*,*S*)-**1e**.



Scheme 1 Asymmetric 1,3-dipolar cycloaddition of *C*-phenyl *N*-diphenylmethyl nitrone and crotonaldehyde catalyzed by (*S*,*S*)-**1**.

aldehyde moiety of the cycloadduct was oxidized to the carboxylic acid. Subsequent acidic treatment of this material led to the concomitant esterification and removal of the *N*-diphenylmethyl moiety, giving the ester **3** in moderate yield. The reductive cleavage of the N–O bond provided the β-amino acid methyl ester **4** in high yield (Scheme 2).[8,9]

In summary, we have developed a newly modified bis-titanium chiral Lewis acid containing 6,6′-bis(trifluoromethyl)-BINOL ligands.[10] With this methodology, only one isomer of the cycloadduct could be obtained exclusively, out of the possible 8 isomers (regioisomer, *endo*/*exo* isomer and enantiomer).



Scheme 2 *Reagents and conditions*: a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, 87%; b) conc. HCl, MeOH, 59%; c) Raney-Ni, H_2 (balloon), MeOH, 93%.

Acknowledgements

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8 Data for compound **3**: ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (5H, m, ArH), 6.24 (1H, br, NH), 4.84 (1H, s, ONCH), 4.39 (1H, d, J = 7.2 Hz, NOCHH), 3.81 (3H, s, CO_2CH_3), 3.77 (1H, d, NOCHH, J = 8.0 Hz), 0.98 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 137.3, 128.3, 127.5, 79.5, 69.5, 58.2, 52.7, 19.2; IR (neat) 3224, 3030, 2980, 2953, 2875, 2343, 1728, 1456, 1435, 1288, 1269, 1226, 1122, 1033 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{15}NO_3$: m/z 222.1125 ([M + H]$^+$), found: m/z 222.1124 ([M + H]$^+$); $[a]_D^{24}$ = +59.3 (c = 1.0, $CHCl_3$).

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9 Data for compound **4**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.24–7.14 (5H, m, ArH), 4.22 (1H, s, $CHNH_2$), 3.63 (2H, m, CH_2OH), 3.54 (3H, s, CO_2CH_3), 0.96 (1H, s, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 177.0, 142.3, 129.1, 129.0, 128.6, 67.7, 61.5, 54.1, 52.3, 16.6; IR (neat) 3377, 3308, 2949, 2928, 2856, 2380, 2320, 1718, 1454, 1435, 1362, 1280, 1232, 1126, 1049 cm^{-1}; HRMS (ESI) exact mass calcd. for $C_{12}H_{17}NO_3$: *m/z* 224.1281 ([M + H]$^+$), found: *m/z* 224.1273 ([M + H]$^+$); $[a]_D^{25} = -1.5$ ($c = 1.0$, CH_3OH).

10 General procedure for 1,3-dipolar cycloaddition of *N*-diphenylmethyl nitrones and methacrolein: To a stirred mixture of Ag_2O (0.05 mmol, 11.6 mg) in CH_2Cl_2 (1.0 mL) was added 1.0 M hexanes solution of $ClTi(OiPr)_3$ (0.10 mmol, 100 μL) at room temperature under Ar. After stirring for 12 h at room temperature, a solution of the corresponding BINOL derivative (0.10 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture, which was then stirred for 2 h at room temperature to afford the dark colored solution of bis-titanium chiral Lewis acid (*S*,*S*)-**1**. To the catalyst solution prepared as described above were added freshly distilled methacrolein (1.5 mmol, 124 μL) and a solution of nitrone (0.50 mmol) in CH_2Cl_2 (1.0 mL) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 24 h. The mixture was quenched with aqueous $NaHCO_3$, filtered to remove insoluble materials and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with hexane–ethyl acetate = 20 : 1) to give the cycloadduct.