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Syntheses of (*R*)-(+)-cibenzoline and analogues via catalytic enantioselective cyclopropanation using (*S*)-phenylalanine-derived disulfonamide

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Abstract—Cyclopropanation of 3,3-diaryl-2-propen-1-ols **1** with Et_2Zn and CH_2I_2 proceeded in the presence of a catalytic amount of (*S*)-2-(methanesulfonyl)amino-1-(*p*-toluenesulfonyl)amino-3-phenylpropane **2** to afford the corresponding cyclopropylmethanols with 20–76% ee. (+)-2,2-Diphenylcyclopropylmethanol **3a** (76% ee) was oxidized with IBX in DMSO, followed by $NaClO_2$, H_2O_2, and NaH_2PO_4 in MeCN–H_2O to give the corresponding acid **5a**, which was converted with ethylenediamine, in the presence of PyBOP and Et_3N in CH_2Cl_2, to the amide **6a** in quantitative overall yield from **3a**. Amide **6a** was cyclized at 160 °C under reduced pressure (2 mmHg) to afford (*R*)-(+)-cibenzoline in 55% yield.

1. Introduction

Cibenzoline is a commercially available medicine as a class I antiarrhythmic agent[1] and consists of four rings, such as a cyclopropane skeleton which has a stereogenic carbon, two benzene ones, and an imidazoline one. Since Kobayashi reported the first and unique enantioselective Simmons–Smith cyclopropanation catalyzed by a C_2-symmetrical disulfonamide–zinc or aluminum complex,[2e,h–j] Denmark has optimized conditions for Kobayashi's method.[2d,f,g] Recently, Charette has developed another enantioselective catalytic cyclopropanation using 25 mol % of C_2-symmetrical titanium complex of (4*R*,5*R*)-2,2-diethyl-α,α,α′,α′-tetraphenyl-1,3-dioxane-4,5-dimethanol (Ti-TADDOLate), which is a large and complex molecule.[2c] We have developed a catalytic enantioselective Simmons–Smith reaction[2a,b] and alkylation[3a] using the simple disulfonamides derived from α-amino acids. Herein, we report a catalytic enantioselective cyclopropanation of 3,3-diaryl-2-propen-1-ols **1**[4] with Et_2Zn and CH_2I_2 using 10 mol % of (*S*)-2-(methanesulfonyl)amino-1-(*p*-toluenesulfonyl)amino-3-phenylpropane **2** and synthesis of optically active cibenzoline and some analogues.

2. Results and discussion

In a preliminary investigation, the reaction of 3,3-diphenyl-2-propen-1-ol **1a** with Et_2Zn and CH_2I_2 in the presence of 10 mol % of **2** afforded the corresponding cyclopropane product **3a**[5] with 76% ee, as indicated in entry 1 of Table 1. The cyclopropanation of 3,3-diaryl-2-propen-1-ols substituted on the aromatic ring by electron-donating or electron-withdrawing groups was then examined: the results from the cyclopropanation of various 3,3-diaryl-2-propen-1-ols **1b**–**1f** with Et_2Zn and CH_2I_2 in the presence of 10 mol % of **2** are collected in Table 1. We selected methoxy and methyl substituents as representative electron-donating groups (see entries 2 and 3), trifluoromethyl and chloro substituents as electron-withdrawing groups (see entries 4 and 5), and a fluorenyl substituent for making the spiro-ring (see entry 6). Fortunately, cyclopropanation of un-substituted allylic alcohol **1a**, which can be converted to cibenzoline gave the highest ee among these 3,3-diaryl-2-propen-1-ols **1a**–**1f**. The reactions of the allylic alcohols

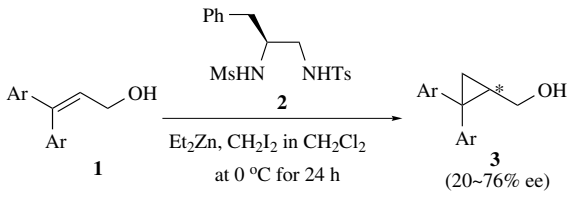

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Table 1. Cyclopropanation of 3,3-diaryl-2-propen-1-ols **1a**–**f** in the presence of **2**[a]

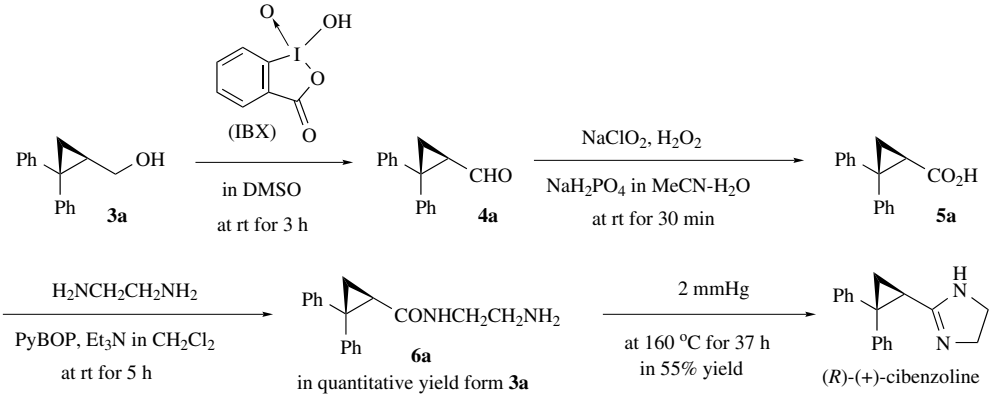
Entry	1	Ar	Yield (%)	ee[b] (%)	Eluent[c] (%)	$[\alpha]_D^{25}$
1	**1a**	Ph	82	76	5	+115.9 (*c* 1.07, $CHCl_3$)
2	**1b**	4-$MeOC_6H_4$	40	48	5	+60.4 (*c* 1.41, $CHCl_3$)
3	**1c**	4-MeC_6H_4	71	67	5	+95.4 (*c* 1.33, $CHCl_3$)
4	**1d**	4-$CF_3C_6H_4$	84	20	5	+13.4 (*c* 1.29, $CHCl_3$)
5	**1e**	4-ClC_6H_4	32	29	5	+30.6 (*c* 1.58, $CHCl_3$)
6	**1f**	Fluorenyl	54	51	5	+9.4 (*c* 1.41, $CHCl_3$)

[a] All reactions were carried out with 1 equiv of 3,3-diaryl-2-propen-1-ol **1**, 0.1 equiv of **2**, 2 equiv of Et_2Zn, and 3 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined by HPLC analysis using Chiralcel OD.
[c] The number indicates concentration of *i*-PrOH in hexane as an eluent on HPLC analysis for determination of enantiomeric excess of the product.

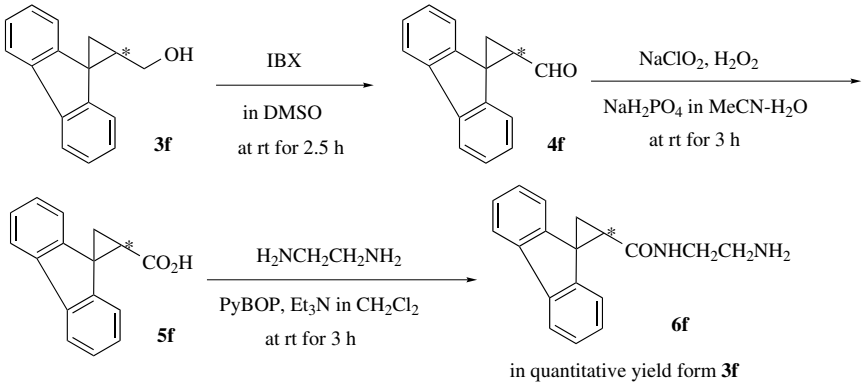
1b and **1c** (entries 2 and 3, respectively) substituted with an electron-donating group afforded higher enantioselectivities than those of the allylic alcohols **1d** and **1e** (entries 4 and 5, respectively) substituted with an electron-withdrawing group.

(*R*)-(+)-Cibenzoline was synthesized from (+)-2,2-diphenylcyclopropylmethanol **3a** as follows. Alcohol **3a** was oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) at rt for 3 h to afford the corresponding aldehyde **4a**, which was treated with $NaClO_2$, H_2O_2, and NaH_2PO_4 in MeCN–H_2O at rt for 30 min to give acid **5a**. Acid **5a** was condensed with ethylenediamine in the presence of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and Et_3N in CH_2Cl_2 at rt for 5 h to obtain the corresponding amide **6a**[6] in quantitative overall yield from **3a**. Then, amide **6a** was converted under reduced pressure (2 mmHg) at 160 °C for 37 h to (*R*)-(+)-cibenzoline[7] in 55% yield, as shown in Scheme 1. These results suggest that the absolute configurations of compounds **3a**–**6a** are (*R*). The fluorenyl alcohol **3f**, which is connected at the *ortho*-position of each benzene ring in **3a**, was converted to the corresponding amide **6f** in quantitative overall yield in a similar manner to that described for the preparation of **6a**, Scheme 2. The amide **6f** was not cyclized and recovered in 52% yield under reduced pressure (2 mmHg) at 160 °C for 26 h. It was found that the fluorenyl group of the amide **6f** stereochemically hinders the formation of the imidazoline ring because the two benzene rings of **6f** are fixed in the same plane.

Cyclopropanemethanols **3c**, **3d**, **3e** which are substituted with methyl, trifluoromethyl, chloro groups at the *para*-po-

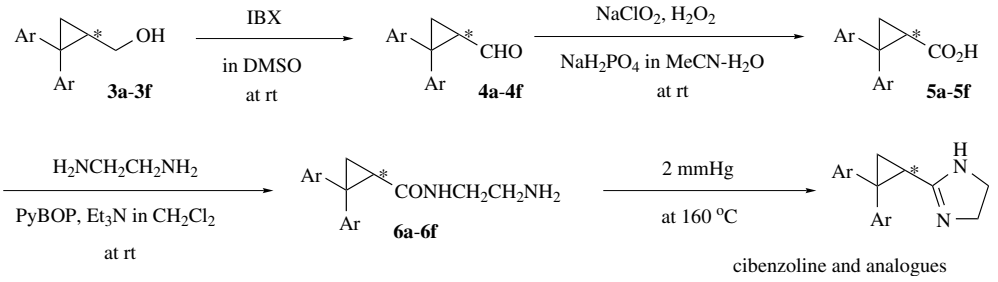


Scheme 1. Synthesis of (*R*)-(+)-cibenzoline from (+)-2,2-diphenylcyclopropylmethanol **3a**.



Scheme 2. Trial for the preparation of a cibenzoline analogue from (+)-cyclopropylmethanol **3f**.

Table 2. Synthesis of (*R*)-(+)-cibenzoline and the analogues from (+)-2,2-diarylcyclopropylmethanols **3a**–**3f**



Entry	3	Ar	6		Cibenzoline and the analogues	
			Yield[a] (%)	$[\alpha]_D^{25}$	Yield (%)	$[\alpha]_D^{25}$
1	**3a**	Ph	Quant.	+102.8 (*c* 1.03, MeOH)	55	+30.1 (*c* 1.12, MeOH)
2	**3b**	4-$MeOC_6H_4$	0	—	—	—
3	**3c**	4-MeC_6H_4	Quant.	+23.9 (*c* 1.38, MeOH)	43	+25.6 (*c* 0.64, MeOH)
4	**3d**	4-$CF_3C_6H_4$	89	+19.2 (*c* 1.27, MeOH)	46	+21.6 (*c* 0.75, MeOH)
5	**3e**	4-ClC_6H_4	55	+38.7 (*c* 1.39, MeOH)	50	+3.3 (*c* 0.67, MeOH)
6	**3f**	Fluorenyl	Quant.	+97.4 (*c* 1.63, MeOH)	0	—

[a] Overall yields from the cyclopropylmethanols **3a**–**3f**.

sition on the benzene rings were converted to the corresponding cibenzoline analogues in similar methods to the preparation of cibenzoline. All specific rotations of amide **6a**–**6f**, cibenzoline, and cibenzoline analogues are summarized in Table 2.

3. Conclusion

In summary, (*S*)-2-(methanesulfonyl)amino-1-(*p*-toluenesulfonyl)amino-3-phenylpropane **2** works efficiently as a catalyst in the Simmons–Smith cyclopropanation of sterically hindered allylic alcohols such as 3,3-diaryl-2-propen-1-ols **1a**–**1f**. In our procedure, it is possible to prepare various chiral 2,2-disubstituted cyclopropylmethanols conveniently and to synthesize the corresponding chiral cibenzoline analogues. We are still working on the optimization of α-amino acid-derived chiral disulfonamides for the catalytic enantioselective cyclopropanation of 3,3-diphenyl-2-propen-1-ol **1a**.

Acknowledgements

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6. Compound **6a**: ^{1}H NMR (CD_3OD) δ 1.50 (1H, dd, $J = 5.0$, 8.2 Hz), 2.16 (1H, dd, $J = 5.0$, 5.9 Hz), 2.53 (1H, dd, $J = 5.9$, 8.2 Hz), 2.73 (2H, m), 3.23 (2H, t, $J = 6.2$ Hz), 7.12–7.36 (10H, m); ^{13}C NMR (CD_3OD) δ 19.4, 31.0, 38.6, 40.2, 41.1, 127.5, 127.9, 128.7, 129.3, 129.4, 130.9, 142.0, 146.6, 173.6; HRMS (ESI-TOF): Calcd for $C_{18}H_{21}N_2O$ ($M+H^+$): 281.1648. Found: 281.1654.
7. (*R*)-(+)-Cibenzoline:[1] ^{1}H NMR (CD_3OD) δ 1.58 (1H, dd, $J = 5.4$, 8.6 Hz), 2.09 (1H, dd, $J = 5.4$, 6.3 Hz), 2.43 (1H, dd, $J = 6.3$, 8.6 Hz), 3.20 (2H, m), 3.37 (2H, m), 7.11–7.38 (10H, m); ^{13}C NMR (CD_3OD) δ 19.5, 25.2, 30.8, 39.9, 48.9, 127.6, 128.1, 128.8, 129.3, 129.5, 131.0, 141.4, 146.4, 168.9; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}N_2$ ($M+H^+$): 263.1543. Found: 263.1540.