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Silyloxy Amino Alcohol Organocatalyst for Enantioselective 1,3-Dipolar Cycloaddition of Nitrones to α,β-Unsaturated Aldehydes

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The catalytic activity of a simple amino alcohol that contains a bulky super silyl group [i.e., tris(trimethylsilyl)silyl (TTMSS)] bonded to the oxygen atom at the γ-position along with a primary amine moiety was examined in the enantioselective 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated aldehydes. The organocatalyst successfully provided optically active isoxazolidines in good chemical yields (up to 86 %) with excellent diastereoselectivities (*endo*/*exo*, up to 96:4) and enantioselectivities (up to 97 % *ee*). Furthermore, the obtained isoxazolidines were easily converted into γ-amino diols that contain three contiguous stereogenic centers.

Introduction

The development of new optically active organocatalysts for use in asymmetric synthesis has attracted considerable interest in the scientific community over the past 10 years.[1] Excellent covalent and noncovalent organocatalysts have been developed for use in a wide range of reactions. Recently, we reported that an amino alcohol that contains a primary amino group can act as an efficient organocatalyst in the enantioselective Diels–Alder reaction of 1,2-dihydropyridines with dienophiles.[2] Amino alcohol **A** is stable when exposed to air and has the advantages of being easy to prepare and having the desirable structural characteristics. It is easily derived from the corresponding amino acid ester and contains both an amino covalent site and a hydroxy noncovalent binding site in a single molecule (Scheme 1).

The enantioselective 1,3-dipolar cycloaddition (1,3-DC) of nitrones to α,β-unsaturated aldehydes is an efficient reaction for the construction of optically active isoxazolidines.[3,4] Isoxazolidines are valuable chiral building blocks that are readily converted into γ-amino alcohols, β-amino acids, and β-lactams, which can be used in the synthesis of various biological compounds.[5] Although several groups have reported enantioselective organocatalytic versions of this cycloaddition, few examples have employed a primary amine[4f] in a 1,3-DC, and the catalytic effectiveness of an amino alcohol as an organocatalyst in a 1,3-DC has not yet been revealed.

To further expand the usefulness of an amino alcohol with a primary amino group as an organocatalyst in asymmetric reactions, we focused on investigating simple amino alcohol **A**, which contains a primary amine moiety and a bulky substituent (Scheme 1). In the pathway for the 1,3-DC reaction, an iminium ion intermediate is first formed from the condensation of amino alcohol **A** with an α,β-unsaturated aldehyde in the presence of a proton from an acid additive. The steric influence between the α-, β-, or γ-substituents in this intermediate and the counter anion of the acid might control the approach of the nitrone substrate.

Thus, we report herein that TTMSS-amino alcohol **1** [TTMSS = tris(trimethylsilyl)silyl], which contains a pri-

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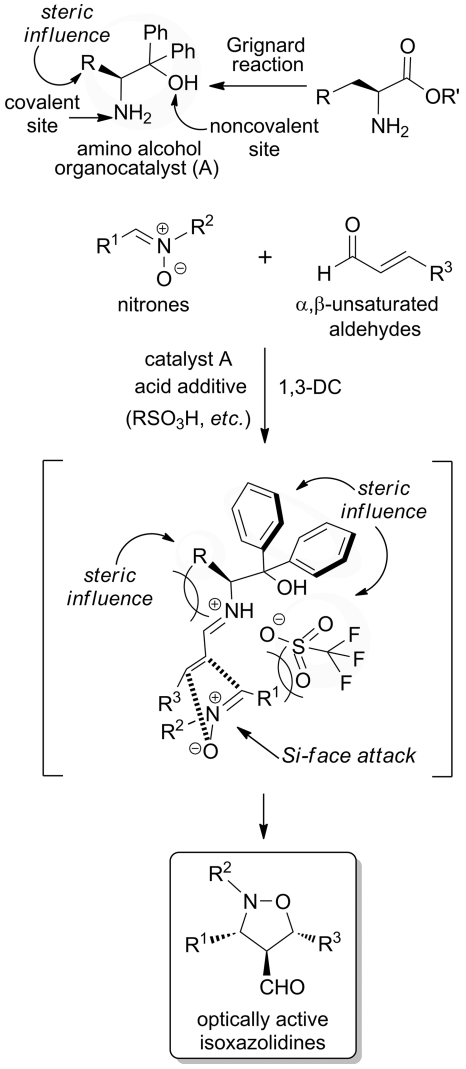
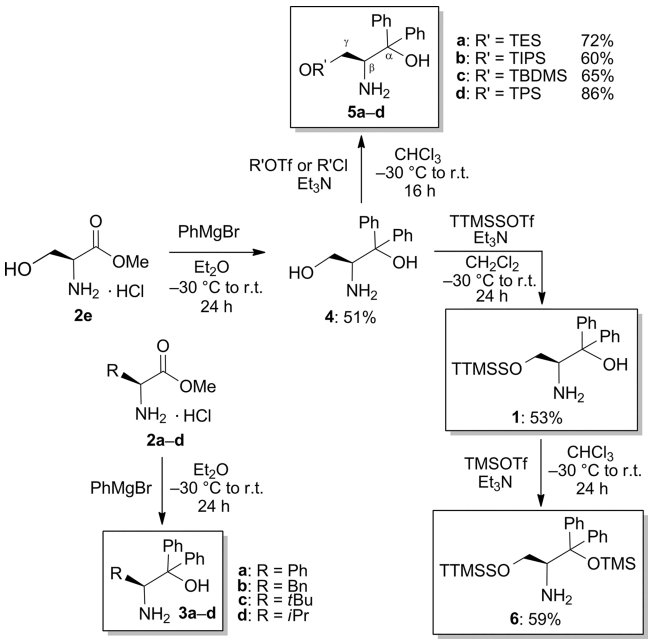


Scheme 1. Function of amino alcohol organocatalyst.

mary amine and a super silyl group (i.e., TTMSS) is an efficient organocatalyst in the enantioselective 1,3-DC of nitrones with α,β-unsaturated aldehydes to afford optically active isoxazolidines in good chemical yields (up to 86%) and with excellent enantioselectivities (up to 97%*ee*). We also report the convenient transformation of the obtained optically active isoxazolidines into γ-amino alcohols that contain three contiguous stereogenic centers.

Results and Discussion

Amino alcohol catalysts **1**, **3a**–**3d**, and **5a**–**5d** that contain several substituents at the β- or γ-position were prepared as shown in Scheme 2. Amino alcohols **3a**–**3d**, which have an aliphatic or aromatic substituent at the β-position, were easily obtained by using a Grignard reaction to obtain the corresponding α-amino acid esters, and the bulkier β-amino alcohols **5a**–**5d**, which have several different silyl groups bonded to the oxygen atom at the γ-position, were also easily prepared[2d] by treating amino diol **4** with R′OTf [R′ = TES (triethylsilyl), TIPS (triisopropylsilyl), TBDMS (*tert*-butyldimethylsilyl), TPS (triphenylsilyl), and OTf = trifluoromethanesulfonate]. In addition, the bulkiest β-amino alcohol catalyst **1**, which contained a super silyl group[6] on the oxygen atom at the γ-position was also easily obtained in 53% yield by the reaction between **4** and TTMSSOTf.[2a] Catalyst **6**, which has a trimethylsilyl-protected (TMS = trimethylsilyl) hydroxy group was obtained in moderate yield from the reaction of **1** with TMSOTf.

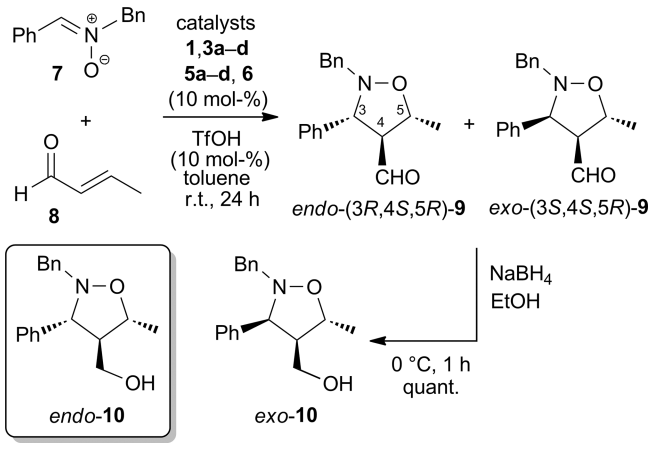


Scheme 2. Synthesis of amino alcohol organocatalysts.

We first examined the 1,3-DC of common *N*-benzylidenebenzylamine *N*-oxide (**7**) with (*E*)-crotonaldehyde (**8**,[4] Table 1). The reaction of **7** and **8** was carried out in toluene at room temperature in the presence of 10 mol-% of catalysts **3a**–**3d** and HOTf (10 mol-%) as an acid additive to afford optically active DC adducts **9** [i.e., *endo*-(3*R*,4*S*,5*R*)-**9** and *exo*-(3*S*,4*S*,5*R*)-**9**]. The enantiomeric excess value of the major *endo* adduct was determined by converting the mixture into the corresponding alcohols **10**.[4n] The relative and absolute configurations of the obtained DC adducts and the *endo*/*exo* stereochemistry were determined by analyzing the relationship of the ^{1}H NMR signals for the phenyl group at the 3-position and the aldehyde at the 4-position of the corresponding DC adduct and by comparing the experimental and literature data.[4n] The results are summarized in Table 1. In the absence of the amine catalyst or an acid additive, the reaction barely occurred. When catalyzed by β-Ph-substituted **3a**, the reaction afforded *endo*-DC adduct **9** in a moderate chemical yield (57%) with good diastereoselectivity (*endo*/*exo*, 78:22) but low enantioselectivity (46%*ee*; Table 1, Entry 1). Similarly, the use of β-Bn-substituted catalyst **3b** produced almost the same enantioselectivity (42%*ee*), although the chemical yield and the diastereoselectivity increased (71% yield, *endo*/*exo*,

87:13; Table 1, Entry 2). Catalyst **3c** with a β-*tert*-butyl substituent resulted in a greatly increased enantioselectivity of 76%*ee* with a moderate chemical yield (53%) and very good diastereoselectivity (*endo*/*exo*, 92:8; Table 1, Entry 3). The β-*i*Pr-substituted catalyst **3d** also had sufficient catalytic activity and provided *endo*-DC adduct **9** in good chemical yield (72%), diastereoselectivity (*endo*/*exo* = 89:11), and enantioselectivity (73%*ee*; Table 1, Entry 4). Taking these results into consideration, we concluded that the substituent at the β-position of the amino alcohol may have a significant role in the strategy to increase the enantioselectivity.

Table 1. 1,3-DC of **7** and **8** by using amino alcohol catalysts.



Entry	Catalyst	Yield [%][a]	*endo*/*exo*[b]	% *ee* of *endo*[c]
1	**3a**	57	78:22	46
2	**3b**	71	87:13	42
3	**3c**	53	92:8	76
4	**3d**	72	89:11	73
5	**5a**	58	87:13	73
6	**5b**	76	86:14	66
7	**5c**	86	81:19	65
8	**5d**	79	83:17	75
9	**1**	83	94:6	91
10	**6**	64	80:20	43

[a] Isolated combined yield of *endo* and *exo* products. [b] Determined by ^{1}H NMR spectroscopic analysis of 1,3-DC adducts **9**.[4] [c] Determined by HPLC analysis of the *endo* isomer using a chiral column.

Next, we examined the same reaction by using β-amino alcohol organocatalysts **5a**–**5d**, which have the bulkier silyl groups (i.e., TES, TIPS, TBDMS, and TPS) on the oxygen atom at the γ-position (Table 1, Entries 5–9). All of the reactions afforded the desired *endo*-DC adduct **9** in moderate to good chemical yields (58–86%) with good diastereoselectivities (*endo*/*exo*, 81:19–87:13) and moderate to good enantioselectivities (65–75%*ee*). These results show that a β-amino alcohol with the bulkier substituent at the γ-position may more effectively provide the desired DC adduct **9** in satisfactory chemical yield and enantioselectivity. The reaction with β-amino alcohol catalyst **1**, which may effectively provide DC adduct **9** in satisfactory chemical yield and enantioselectivity, was then examined under the same reaction conditions as those used for catalysts **5a**–**5d** (Table 1, Entry 9). Catalyst **1** afforded the best results with high catalytic activity to give a good chemical yield (83%) along with good diastereoselectivity (*endo*/*exo*, 94:6) and enantioselectivity (91%*ee*). However, when the same reaction was catalyzed by γ-TTMSSO-α-TMSO-amino silyl ether **6**, in which the α-hydroxy group was protected by a trimethylsilyl group, the enantioselectivity (43%*ee*) was significantly less that that afforded by TTMSS-amino alcohol **1** with a free hydroxy group (91%*ee*; Table 1, Entry 10). The difference in the data may result from weaker electric interactions with the counter anions or from the steric influence of the bulkier trimethylsilyl group, although the reasons are not clear. Nevertheless, this result indicates that the presence of the free hydroxy group at the α-position in the catalyst may be necessary to realize satisfactory results.

To optimize the reaction conditions by using the superior TTMSS-amino alcohol **1**, we next examined the effect of reducing the molar ratio of catalyst **1** in the reaction system

Table 2. Opimization of 1,3-DC of **7** and **8** by using catalyst **1**.

Entry	Catalyst **1** [mol-%]	Temp. [°C]	HX	Solvent	Yield [%][a]	*endo*/*exo*[b]	% *ee* of *endo*[c]
1	20	r.t.	TfOH	toluene	82	94:6	92
2	5	r.t.	TfOH	toluene	73	94:6	90
3	2.5	r.t.	TfOH	toluene	63	91:9	71
4	10	0	TfOH	toluene	79	94:6	92
5	10	–25	TfOH	toluene	30	95:5	92
6	10	–50	TfOH	toluene	trace	–	–
7	10	0	HCl	toluene	trace	–	–
8	10	0	TFA[d]	toluene	9	84:16	76
9	10	0	TBA[d]	toluene	6	85:15	76
10	10	0	PFA[d]	toluene	4	93:7	76
11	10	0	TfOH	benzene	71	93:7	91
12	10	0	TfOH	MeCN	63	95:5	92
13	10	0	TfOH	$CHCl_3$	65	93:7	92
14	10	0	TfOH	CH_2Cl_2	54	91:9	89
15	10	0	TfOH	Et_2O	73	96:4	95

[a] Isolated combined yield of *endo* and *exo* products. [b] Determined by ^{1}H NMR spectroscopic analysis of 1,3-DC adducts **9**.[4] [c] Determined by HPLC analysis of the *endo* isomer using a chiral column. [d] TFA = trifluoroacetic acid, TBA = tribromoacetic acid, PFA = $CF_3(CF_2)_5CO_2H$.

(Table 2, Entries 1–3). The use of 20 mol-% of **1** provided DC adduct **9** in good chemical yield (82%), excellent diastereoselectivity (*endo*/*exo*, 94:6), and fairly good enantioselectivity (92%*ee*), which is very similar to that of the earlier reaction that employed 10 mol-% of **1** (Table 2, Entry 1). When 5 mol-% of **1** was employed, the reaction also gave the DC adduct **9** with good enantioselectivity (90%*ee*) but with a lower chemical yield (73%; Table 2, Entry 2). Employing a catalytic loading of 2.5 mol-% also resulted in a lower chemical yield (63%) and enantioselectivity (71%*ee*; Table 2, Entry 3).

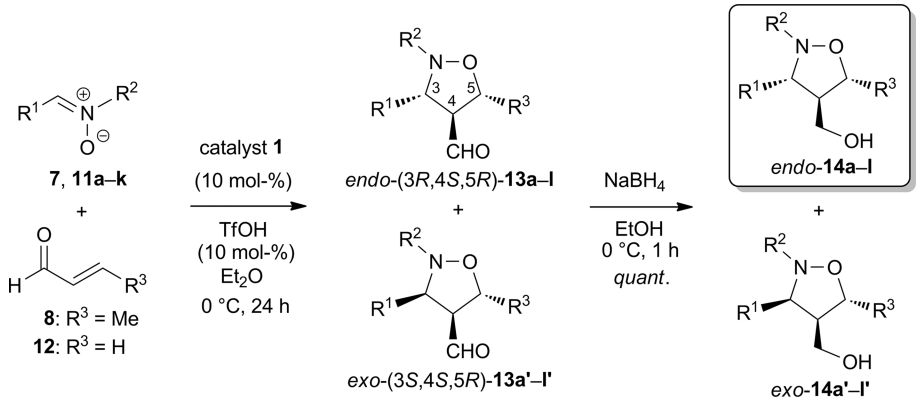
To further optimize the reaction conditions for TTMSS-amino alcohol **1**, the reactions were carried out at lower temperatures, that is, from 0 to –50 °C (Table 2, Entries 4–6). At 0 °C, a good chemical yield (79%), diastereoselectivity (*endo*/*exo*, 94:6), and enantioselectivity (92%*ee*) were obtained at similar levels to those achieved at room temperature (Table 2, Entry 4). At –25 °C, the reaction resulted in a significantly decreased chemical yield (30%), although the enantioselectivity remained high at 92%*ee* (Table 2, Entry 5). The reaction virtually ceased when carried out at –50 °C (Table 2, Entry 6).

The effect of acid additives (10 mol-%) such as HCl, CF_3CO_2H, CBr_3CO_2H, and $CF_3(CF_2)_5CO_2H$ in the reaction were also investigated (Table 2, Entries 7–10). Unfortunately, these additives did not perform more effectively than TfOH, and the chemical yields were significantly lower under these reaction conditions.

We also examined the effects of solvent on the reaction. Commonly used solvents (i.e., benzene, MeCN, $CHCl_3$, CH_2Cl_2, and Et_2O) were screened in the 1,3-DC (Table 2, Entries 11–15) and showed good results in each case with regard to chemical yield, diastereoselectivity, and enantioselectivity. The best enantioselectivity (95%*ee*) was obtained by using Et_2O as the solvent. In diethyl ether, a good chemical yield (73%) and excellent diastereoselectivity also resulted (*endo*/*exo*, 96:4; Table 2, Entry 15).

Under the optimized conditions, a wide range of 1,3-DC reactions were investigated. Nitrones **7** and **11a**–**11k** with α,β-unsaturated aldehydes **8** and **12** were submitted to the reaction with catalyst **1** and TfOH in Et_2O at 0 °C, and the enantioselectivities were determined by converting the resulting DC *endo* adduct into the corresponding alcohols **14a**–**14l**.[4,7] The absolute configuration of the DC adduct and the *endo*/*exo* stereochemistry were determined by analyzing the relationship of the ^{1}H NMR signals for the aromatic hydrocarbon at the 3-position and the aldehyde at the 4-position of the corresponding DC adduct and by comparing this data with that in the literature.[4c,4f,4i,4n] The results are summarized in Table 3. The reaction of 4-MeC_6H_4-substituted nitrone **11a**, 4-*i*PrC_6H_4-substituted **11b**, and 4-$OMeC_6H_4$-substituted **11c**, which have electron-donating groups on the benzene ring afforded the desired *endo*-DC adducts **13a**–**13c** in excellent enantioselectivities (90–94%*ee*) with good chemical yields and diastereoselectivities (67–76% yield, *endo*/*exo*, 95:5–96:4; Table 3, Entries 1–3).

Table 3. 1,3-DC of **7** and **11a**–**11k** with **8** and **12** using β-amino alcohol catalyst **1**.



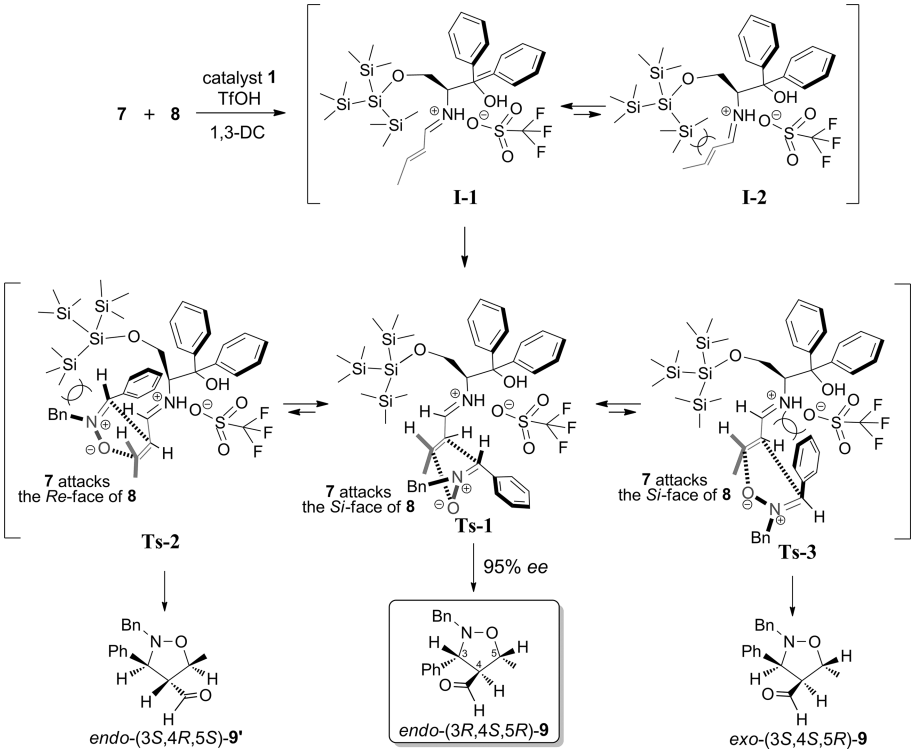
Entry	Nitrone	R^1	R^2	Aldehyde	DC adduct **13**	Yield [%][a]	*endo*/*exo*[b]	% *ee* of *endo*[c]
1	**11a**	4-MeC_6H_4	Bn	**8**	**13a**	67	95:5	94
2	**11b**	4-*i*PrC_6H_4	Bn	**8**	**13b**	75	96:4	90
3	**11c**	4-$OMeC_6H_4$	Bn	**8**	**13c**	76	96:4	92
4	**11d**	4-ClC_6H_4	Bn	**8**	**13d**	59	89:11	89
5	**11e**	4-BrC_6H_4	Bn	**8**	**13e**	44	90:10	90
6	**11f**	2-ClC_6H_4	Bn	**8**	**13f**	49	93:7	93
7	**11g**	4-$CF_3C_6H_4$	Bn	**8**	**13g**	58	92:8	62
8	**11h**	1-naphthyl	Bn	**8**	**13h**	59	92:8	71
9	**11i**	2-naphthyl	Bn	**8**	**13i**	63	92:8	92
10	**11j**	Ph	Me	**8**	**13j**	65	96:4	97
11	**11k**	4-ClC_6H_4	Me	**8**	**13k**	37	90:10	96
12	**7**	Ph	Bn	**12**	**13l**	79	61:39	70

[a] Isolated combined yield of *endo* and *exo* products. [b] Determined by ^{1}H NMR spectroscopic analysis of 1,3-DC adducts **13**.[4] [c] Determined by HPLC analysis of *endo* isomer using a chiral column.

The use of ClC_6H_4- and BrC_6H_4-substituted nitrones **11d**–**11f**, which contain electron-withdrawing groups on the benzene ring, provided *endo*-DC adducts **13d**–**13f** in fairly good to excellent enantioselectivities (89–93%*ee*) and diastereoselectivities (*endo*/*exo*, 89:11–93:7), but the chemical yields were poor to moderate (44–59%; Table 3, Entries 4–6). The reaction with $CF_3C_6H_4$-substituted nitrone **7g** led to a substantial decrease in the enantioselectivity to 62%*ee* (Table 3, Entry 7). These results indicate that substrates that have an electron-withdrawing group on the benzene ring lead to a sharp decrease in chemical yield, whereas bulkier substituents may induce more satisfactory enantioselectivities. The 1,3-DC reactions that employed bulkier 1-naphthyl nitrone **11h** or 2-naphthyl nitrone **11i** were also examined under the same reaction conditions as used for of **11a**–**11g** (Table 3, Entries 8 and 9). Substrate **11h** provided *endo*-DC adduct **13h** in good chemical yield (59%), diastereoselectivity (*endo*/*exo*, 92:8), and enantioselectivity (71%*ee*; (Table 3, Entry 8). The reaction of **11i** also proceeded with fairly good enantioselectivity (92%*ee*), diastereoselectivity (*endo*/*exo*, 92:8), and chemical yield (63%) to provide the *endo*-DC adduct **13i** (Table 3, Entry 9). In addition, the reaction of nitrone **11j** (R^1 = Ph, R^2 = Me) with aldehyde **8** was examined under the same reaction conditions, and the highest enantioselectivity (97%*ee*) and a good chemical yield (65%) were obtained along with excellent diastereoselectivity (*endo*/*exo*, 96:4; Table 3, Entry 10). On the other hand, the use of nitrone **11k** (R^1 = 4-ClC_6H_4, R^2 = Me) led to a significant decrease in the chemical yield (37%), but the enantioselectivity was almost the same as that for nitrone **11j** (Table 3, Entry 11).

The reaction of nitrone **7** (R^1 = Ph, R^2 = Bn) with simple acrolein (**12**) as the α,β-unsaturated aldehyde provided *endo*-DC adduct **13l** in good chemical yield (79%) and good enantioselectivity (70%*ee*) but with a significantly lower diastereoselectivity (61:39; Table 3, Entry 12).

On the basis of the high enantiopurity (95%*ee*) of optically active *endo*-DC adduct **9**, which was obtained from the reaction of nitrone **7** with α,β-unsaturated aldehyde **8**, and studies of the mechanism of amino organocatalyzed cycloadditions by Ishihara, Seebach, Melchiorre, and our group,[2a,8] a plausible model for the mechanism of this enantioselective reaction is proposed (Scheme 3). The combination of catalyst **1**, α,β-unsaturated aldehyde **8**, and TfOH is thought to form intermediate **I-1**, in which there is less steric interaction between the TTMSS substituent on the oxygen atom at the γ-position of the catalyst and the olefin portion of the dienophile.[9] The reaction then proceeds through transition state **Ts-1**, in which there is less steric interaction between the intermediate **I-1** and nitrone **7** moieties than found in **Ts-2** or **Ts-3**, in which there is greater repulsive interactions between these units. Thus, the steric effects from the bulky TTMSS, diphenyl, and TfO^- units in **I-1** prevent nitrone **7** from approaching the sterically hindered *re* face of iminium ion intermediate **I-1** in **Ts-2**. Thus, **7** attacks the sterically less-hindered *si* face as shown in **Ts-1**. In **Ts-1** and **Ts-3**, the *endo*/*exo* diastereoselectivity (*endo*-**9**/*endo*-**9′**, 96:4) of the reaction could depend on the steric interactions of the diphenyl and TfO^- moieties of **I-1** with nitrone **7**. Hence, the reaction may occur through **Ts-1**, which has less steric interactions between **I-1** and **7**, rather than through **Ts-3**, which has greater steric



Scheme 3. Plausible reaction mechanism for 1,3-DC reaction of **7** with **8** using **1**.

interactions between **I-1** and **7**. Our calculations show a conformational predominancy of iminium ion intermediate **I-1** .[9]

Theoretical calculations were performed to elucidate the diastereoselectivity of **Ts-1**.[9] As shown in Figure 1, the orbital interactions between the LUMO of the iminium ion and the HOMO of nitrone in **Ts-1** are phase matched, and the cycloaddition reaction was allowed. However, a phase mismatch between the molecular orbitals was determined for **Ts-3**. Because the steric hindrance of the super silyl group of the iminium ion does not allow easy access to the dienophile moiety of the nitrone, only a small amount of the *endo*-**9′** product was obtained through transition state **Ts-2**.[9] Similar 1,3-DC of other nitrones with α,β-unsaturated aldehydes may also proceed according to this plausible reaction mechanism.

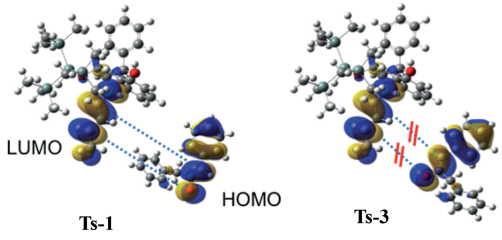
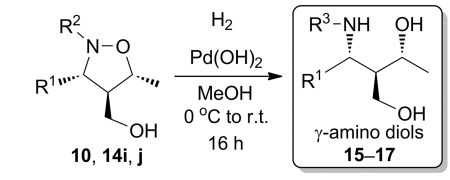


Figure 1. Depiction of the frontier orbitals of the iminium ion and nitrone calculated at the B3LYP/6-311++g(d,2p) level of theory.

We then examined the conversion of optically active isoxazolidines **10**, **14i**, and **14j** into γ-amino diols **15**–**17** (Scheme 4). Optically active amino alcohols, including amino diols, are useful chiral building blocks[10] for introducing one or more asymmetric centers of many biologically active compounds. Moreover, they can be employed not only as a chiral building block for the synthesis of biologically active compounds but also as a chiral ligand,[11] catalyst,[12] and auxiliary[13] for asymmetric synthesis. Therefore, the exploration of an efficient synthetic method for the preparation of optically active amino alcohols that have a set of one or more asymmetric centers is quite important to the field of synthetic organic chemistry. For this purpose, the conversion of the obtained optically active isoxazolidines **10**, **14i**, **14j** into γ-amino diols **15**–**17** by catalytic hydrogenation [H_2, $Pd(OH)_2$][10a] was examined



10: R^1 = Ph, R^2 = Bn
95% *ee*
endo/*exo* = 96:4

14i: R^1 = 2-Naph, R^2 = Bn
92% *ee*
endo/*exo* = 92:8

14j: R^1 = Ph, R^2 = Me
97% *ee*
endo/*exo* = 96:4

15: R^1 = Ph, R^3 = H
66%, 95% *ee*
(>99% *ee* after a recryst.)

16: R^1 = 2-Naph, R^3 = H
50%, 92% *ee*
(>99% *ee* after a recryst.)

17: R^1 = Ph, R^3 = Me
71%, 97% *ee*

Scheme 4. Conversion of isoxazolidines to γ-amino alcohols.

(Scheme 4). The conversions of **10** and **14j** were smoothly carried out, and optically active γ-amino diols **15** and **17** were obtained in good chemical yields (66 and 71%, respectively) and excellent enantioselectivities (95 and 97% *ee*, respectively). Similarly, isoxazolidine **14i** was also converted into γ-amino diol **16** in moderate chemical yield (50%) with 92% *ee*. Subsequently, γ-amino diols **15** and **16** were purified by recrystallization to >99% *ee*.

Conclusions

In summary, new catalytically active amino alcohol organocatalysts **1** and **5a**–**5d**, which contain a primary amine, were easily prepared in two steps, and their use in the asymmetric 1,3-dipolar cycloaddition of nitrones **7** and **11a**–**11k** with α,β-unsaturated aldehydes **8** and **12** was investigated. These amino alcohols worked effectively as organocatalysts, and, in particular, TTMSS-β-amino alcohol **1**, which has a TTMSS group on the oxygen atom at the γ-position, exhibited dramatic catalytic activity. When 10 mol-% of catalyst **1** and TfOH as a acid additive were used, the corresponding optically active *endo*-DC adducts **9** and **13a**–**13l** were afforded in good to excellent chemical yields (up to 86% yield), diastereoselectivities (*endo*/*exo*, up to 96:4), and enantioselectivities (up to 97% *ee*). The advantages of this catalyst are that it is very stable when exposed to air and is easily prepared in two steps. The obtained optically pure nitrones **10**, **14i**, and **14j** were easily converted into optically active γ-amino diols **15**–**17**, which contain three contiguous stereogenic centers. These compounds may be useful synthetic intermediates for the preparation of new biologically active compounds with potential applications in pharmaceutical chemistry. Studies aimed at examining the scope and limitations of this β-amino alcohol organocatalyst in asymmetric 1,3-DC reactions of other nitrones with other α,β-unsaturated aldehydes are now in progress.

Experimental Section

General Methods: All commercial reagents were purchased and used without further purification. All reactions were carried out under argon in flame-dried glassware with magnetic stirring. Thin layer chromatography was performed on silica gel 60 F_{254}, and the analytes were detected by using UV light (254 nm) and iodine vapor. Column chromatography was carried out on silica gel 60N (40–100 μm), and preparative TLC was carried out on silica gel 60 F_{254}. Melting points were measured with a micromelting point apparatus. Infrared spectra were measured with an FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a 500 and 125 MHz spectrometer, respectively. The samples were dissolved in $CDCl_3$, $(CD_3)_2SO$, or CD_3OD. The ^{1}H NMR data are reported as follows: chemical shifts in ppm from tetramethylsilane (δ = 0.0 ppm) or the residual protio solvent [for $(CD_3)(CD_2H)SO$, δ = 2.50 ppm; for CD_2HOD, δ = 3.31 ppm] as an internal standard, integration, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublets), m (multiplet). and br. (broad)], coupling constants in Hz, number of protons, and assignment. The ^{13}C NMR spectra were measured with complete proton decoupling. Chemical shifts were reported in ppm from the

residual solvent as the internal standard (for $CDCl_3$, δ = 77.16 ppm; for CD_3OD, δ = 49.0 ppm). High performance liquid chromatography was performed with AD-H, AS-H, and OD-H (4.6 mm × 25 cm) chiral columns. Optical rotations were measured with a digital polarimeter. HRMS spectra were performed by EI using sector instruments.

General Procedure for the 1,3-DC of Nitrones 7 and 11a–11k with α,β-Unsaturated Aldehydes 8 and 12: The catalyst (0.01 mmol) and TfOH (0.01 mmol) were dissolved in diethyl ether (1.00 mL) at 0 °C, and the resulting solution was stirred for 5 min. To the solution was added the corresponding nitrone (0.10 mmol) followed by the corresponding α,β-unsaturated aldehyde (0.40 mmol). The reaction mixture was stirred at room temperature (or as indicated in Table 2) for 24 h and then passed through a silica gel column (EtOAc). The filtrate was concentrated under reduced pressure. The crude mixture was subjected to ^1H NMR analysis to determine the diastereoselectivity. The residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:2) to afford DC adducts **9** (20.6 mg, 73%) or DC adducts **13a**–**13l** (**13a**: 19.7 mg, 67%; **13b**: 24.2 mg, 75%; **13c**: 23.6 mg, 76%; **13d**: 18.7 mg, 59%; **13e**: 15.9 mg, 44%; **13f**: 15.4 mg, 49%; **13g**: 20.3 mg, 58%; **13h**: 19.5 mg, 59%; **13i**: 21.0 mg, 63%; **13j**: 13.4 mg, 65%; **13k**: 8.9 mg, 37%; **13l**: 21.1 mg, 79%) as a colorless oil. To a solution of DC adduct **9** or **13a**–**13l** in EtOH (2.00 mL) was added $NaBH_4$ (0.10 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h and then quenched with H_2O. EtOH was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:2) to give the corresponding alcohol **10** or **14a**–**14l**. The *ee* values were determined by HPLC [DAICEL chiral OD-H column; hexane/2-propanol, 98:2; flow rate: 0.70 mL min^{-1}]: **10**: t_R = 46.9 (major) and 44.1 min (minor, 95%*ee*); **14a**: t_R = 57.6 (major) and 36.3 min (minor, 94%*ee*); **14c**: t_R = 108.5 (major) and 69.3 min (minor, 92%*ee*); **14d**: t_R = 58.9 (major) and 47.3 min (minor, 89%*ee*); **14e**: t_R = 75.5 (major) and 54.2 min (minor, 90%*ee*); **14f**: t_R = 31.9 (major) and 30.4 min (minor, 93%*ee*); **14h**: t_R = 91.4 (major) and 85.6 min (minor, 71%*ee*); **14j**: t_R = 46.7 (major) and 39.0 min (minor, 97%*ee*); **14k**: t_R = 32.0 (major) and 26.7 min (minor, 96%*ee*); **14l**: t_R = 22.9 (major) and 18.6 min (minor, 70%*ee*). HPLC [DAICEL chiral AD-H column; hexane/EtOH, 97:3; flow rate: 1.0 mL min^{-1}]: **14i**: t_R = 238.3 (major) and 77.3 min (minor, 92%*ee*). HPLC [DAICEL chiral AS-H column; hexane/2-propanol, 98:2; flow rate: 0.70 mL min^{-1}]: **14b**: t_R = 28.3 (major) and 18.9 min (minor, 90%*ee*); **14g**: t_R = 26.5 (major) and 31.9 min (minor, 62%*ee*).

(*S*)-2-Amino-1,1-diphenyl-3-[tris(trimethylsilyl)silyloxy]propan-1-ol (1): Triflic acid (177.8 μL, 2.0 mmol) was added to dry CH_2Cl_2 (3.0 mL), and the solution was cooled to 0 °C. Tris(trimethylsilyl)-silane (617.8 μL) was added slowly, and the resulting solution was stirred at room temperature for 1 h. To a solution of **4** (122 mg, 0.50 mmol) in dry CH_2Cl_2 (7.0 mL) were added the solution of tris(trimethylsilyl)silyl triflate and Et_3N (278.8 μL, 2.00 mmol) at –30 °C over 10 min under argon. The reaction mixture was stirred at room temperature for 24 h and then quenched with H_2O. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:6) to give **1** (130.3 mg, 53%) as a yellow oil. $[\alpha]_D^{25}$ = –41.33 (*c* = 0.75, EtOH). IR (neat): $\tilde{\nu}$ = 2948, 2892, 1448, 1244 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.13 (m, 10 H, C_6H_5), 3.83 (dd, *J* = 6.0, 2.9 Hz, 1 H, NCH), 3.52 (dd, *J* = 9.7, 6.0 Hz, 1 H, CCH_2), 3.32 (dd, *J* = 9.5, 2.9 Hz, 1 H, CCH_2), 0.11 [s, 27 H, $Si(TMS)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.0, 145.4, 128.6, 128.3, 126.8, 126.6, 125.8, 125.2, 79.5, 69.5, 57.2, 0.26 ppm. MS (EI): *m*/*z* = 489 $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{43}NO_2Si_4$ $[M]^+$ 489.2371; found 489.2367.

(*S*)-2-Amino-1,1-diphenyl-3-(triethylsilyloxy)propanol (5a): To a solution of **4** (122 mg, 0.50 mmol) in dry $CHCl_3$ (10.0 mL) were added triethylsilyl triflate (135.6 μL, 0.60 mmol) and Et_3N (83.6 μL, 0.60 mmol) at –30 °C over 10 min under argon. The solution was stirred at room temperature for 16 h and then quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3 × 30mL), and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:4) to give **5a** (128.6 mg, 72%) as a yellow oil. $[\alpha]_D^{24}$ = –63.38 (*c* = 0.55, EtOH). IR (neat): $\tilde{\nu}$ = 2911, 2876, 1449, 1269 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 2 H, C_6H_5), 7.50–7.49 (m, 2 H, C_6H_5), 7.34–7.15 (m, 6 H, C_6H_5), 3.94–3.93 (t, *J* = 4.3 Hz, 1 H, NCH), 3.60–3.59 (m, 2 H, CCH_2), 1.81 (br. signal, 2 H, NH_2), 0.91–0.88 (t, *J* = 8.0 Hz, 9 H, CCH_3), 0.56–0.51 (q, *J* = 8.0 Hz, 6 H, $SiCH_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.1, 145.0, 128.5, 128.2, 126.7, 126.5, 125.5, 125.1, 79.1, 64.1, 57.2, 6.64, 4.12 ppm. MS (EI): *m*/*z* = 358 $[M + H]^+$. HRMS (EI): calcd. for $C_{21}H_{32}NO_2Si$ $[M + H]^+$ 358.2202; found 358.2202.

(*S*)-2-Amino-1,1-diphenyl-3-(triisopropylsilyloxy)propanol (5b): To a solution of **4** (122 mg, 0.50 mmol) in dry $CHCl_3$ (10.0 mL) were added triisopropylsilyl triflate (161 μL, 0.60 mmol) and Et_3N (83.6 μL, 0.60 mmol) at –30 °C over 10 min under argon. The solution was stirred at room temperature for 16 h and then quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3 × 30mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:4) to give **5b** (118.9 mg, 60%) as a yellow oil. $[\alpha]_D^{24}$ = –57.14 (*c* = 0.63, EtOH). IR (neat): $\tilde{\nu}$ = 2942, 2889, 1449, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.59 (m, 2 H, C_6H_5), 7.51–7.47 (m, 2 H, C_6H_5), 7.34–7.14 (m, 6 H, C_6H_5), 3.95–3.93 (dd, *J* = 5.8 Hz, *J* = 3.8 Hz, 1 H, NCH), 3.71–3.65 (m, 2 H, CCH_2), 1.67 (br. signal, 2 H, NH_2), 1.00–0.98 {m, 21 H, $Si[CH(CH_3)_2]_3$} ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.1, 145.0, 128.5, 128.2, 126.7, 126.6, 125.6, 125.1, 79.1, 64.8, 57.4, 17.9, 11.7 ppm. MS (EI): *m*/*z* = 399 $[M]^+$. HRMS (EI): calcd. for $C_{24}H_{37}NO_2Si$ $[M]^+$ 399.2594; found 399.2589.

(*S*)-2-Amino-3-(*tert*-butyldimethylsilyloxy)-1,1-diphenylpropanol (5c): To a solution of **4** (73.0 mg, 0.30 mmol) in dry $CHCl_3$ (6.00 mL) were added *tert*-butyldimethylsilyl chloride (54.3 mg, 0.36 mmol), and Et_3N (65.2 μL, 0.36 mmol) at 0 °C over 10 min under argon. The solution was stirred at room temperature for 16 h and then quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3 × 30mL), and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:4) to give **5c** (69.7 mg, 65%) as a white solid; m.p. 49–51 °C (Et_2O/hexane). $[\alpha]_D^{22}$ = –51.11 (*c* = 0.45, EtOH). IR (neat): $\tilde{\nu}$ = 2951, 2882, 1468, 1307 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H, C_6H_5), 7.50–7.48 (m, 2 H, C_6H_5), 7.34–7.15 (m, 6 H, C_6H_5), 3.92–3.90 (t, *J* = 4.6 Hz, 1 H, NCH), 3.59–3.58 (d, *J* = 4.6 Hz, 2 H, CCH_2), 0.86 [s, 9 H, $C(CH_3)_3$], –0.02 (s, 3 H, $SiCH_3$), –0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.0, 145.1,

128.5, 128.2, 126.7, 126.6, 125.5, 125.3, 125.1, 79.3, 64.6, 57.1, 25.8, 18.1, –5.60, –5.71 ppm. MS (EI): *m*/*z* = 358 [M + H]$^+$. HRMS (EI): calcd. for $C_{21}H_{31}NO_2Si$ [M + H]$^+$ 358.2202; found 358.2202.

(*S*)-2-Amino-1,1-diphenyl-3-(triphenylsilyloxy)propanol (5d): To a solution of **4** (48.7 mg, 0.20 mmol) in dry $CHCl_3$ (4.00 mL) were added triphenylsilyl chloride (70.8 mg, 0.24 mmol) and Et_3N (27.9 μL, 0.24 mmol) at 0 °C for 10 min under argon. The solution was stirred at room temperature for 16 h and then quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3× 30mL), and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:4) to give **5d** (86.4 mg, 86%) as a white solid; m.p. 91–92 °C (Et_2O/pentane). $[\alpha]_D^{22}$ = –55.76 (*c* = 0.52, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2951, 2882, 1468, 1307 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 8 H, C_6H_5), 7.46–7.43 (m, 3 H, C_6H_5), 7.37–7.35 (m, 6 H, C_6H_5), 7.30–7.27 (m, 4 H, C_6H_5), 7.18–7.14 (m, 3 H, C_6H_5), 7.11–7.08 (m, 1 H, C_6H_5), 4.68 (s, 1 H, OH), 4.02–3.98 (dd, *J* = 6.5 Hz, *J* = 3.5 Hz, 1 H, NCH), 3.80–3.75 (m, 2 H, CCH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.3, 144.1, 135.3, 133.5, 130.2, 128.4, 128.1, 128.0, 126.7, 126.5, 125.5, 125.0, 78.2, 65.0, 57.7 ppm. MS (EI): *m*/*z* = 501 [M]$^+$. HRMS (EI): calcd. for $C_{33}H_{31}NO_2Si$ [M]$^+$ 501.2124; found 501.2123.

(*S*)-1,1-Diphenyl-1-(trimethylsilyloxy)-3-[tris(trimethylsilyl)silyloxy]propane-2-amine (6): To a solution of **1** (147 mg, 0.30 mmol) in dry $CHCl_3$ (10.0 mL) were added trimethylsilyl triflate (109 μL, 0.60 mmol), and Et_3N (50.2 μL, 0.36 mmol) at –30 °C for 10 min under argon. The solution was stirred at room temperature for 24 h and then quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3× 30mL), and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; EtOAc/hexane, 1:20) to give **6** (99.5 mg, 59%) as a yellow oil. $[\alpha]_D^{22}$ = –47.23 (*c* = 0.55, EtOH). IR (neat): $\tilde{\nu}$ = 2950, 2893, 1492, 1311 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.21 (m, 10 H, C_6H_5), 3.83–3.81 (dd, *J* = 9.8 Hz, *J* = 3.1 Hz, 1 H, CCH_2), 3.47–3.44 (dd, *J* = 9.2 Hz, *J* = 3.2 Hz, 1 H, CCH_2), 2.84–2.80 (t, *J* = 9.5 Hz, 1 H, NCH), 1.64 (br. signal, 2 H, NH_2), 0.09 [s, 27 H, $Si(TMS)_3$], –0.13 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.6, 143.9, 128.2, 128.0, 127.8, 127.4, 127.2, 126.9, 82.4, 69.8, 58.9, 2.07, 0.18 ppm. MS (EI): *m*/*z* = 562 [M + H]$^+$. HRMS (EI): calcd. for $C_{27}H_{51}NO_2Si_5$ [M + H]$^+$ 562.2844; found 562.2858.

(1*R*,2*R*,3*R*)-1-(Amino)-2-(hydroxymethyl)-1-phenylbutan-3-ol (15): Isoxazolidine **10** (57.9 mg, 0.20 mmol) was dissolved in MeOH (5.00 mL), and 20 wt.-% $Pd(OH)_2$/C (69.2 mg, 0.13 mmol) was added to the solution at room temperature. The resulting mixture was stirred at room temperature for 16 h under H_2 (1 atm) and then passed through Celite (MeOH). The filtrate was concentrated under a reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; MeOH/$CHCl_3$, 1:4) to give **15** (25.8 mg, 66%) as a white solid. After crystallization (MeOH/ether), the desired compound was obtained in >99%*ee*. The *ee* value was determined by HPLC [DAICEL chiral OD-H column; hexane/2-propanol, 80:20; flow rate: 0.50 mL min^{-1}]: t_R = 37.3 (major) and = 23.7 min (minor). $[\alpha]_D^{20}$ = 12.69 (*c* = 0.63, EtOH). IR (neat): $\tilde{\nu}$ = 3425, 3286, 2923, 1321, 1028 cm^{-1}, m.p. 219–220 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.53–7.41 (m, 5 H, C_6H_5), 4.73–4.71 (d, *J* = 7.0 Hz, 1 H, NCH), 3.79–3.75 (m, 1 H, CCH), 3.44–3.40 (dd, *J* = 6.5 Hz, *J* = 10.9 Hz, 1 H, CCH_2), 3.39–3.36 (dd, *J* = 3.7 Hz, *J* = 10.9 Hz, 1 H, CCH_2), 2.06–2.02 (m, 1 H, CCH), 1.27–1.26 (d, *J* = 6.2 Hz, 3 H, CCH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 136.6, 130.1, 130.0, 129.2, 67.8, 60.5, 58.3, 51.1, 22.8 ppm. MS (EI): *m*/*z* = 195 [M]$^+$. HRMS (EI): calcd. for $C_{11}H_{17}NO_2$ [M]$^+$ 195.1259; found 195.1262.

(1*R*,2*R*,3*R*)-1-(Amino)-2-(hydroxymethyl)-1-(2-naphthyl)butan-3-ol (16): Isoxazolidine **14i** (66.3 mg, 0.20 mmol) was dissolved in MeOH (5.00 mL), and 20 wt.-% $Pd(OH)_2$/C (69.2 mg, 0.13 mmol) was added to the solution at room temperature. The resulting mixture was stirred at room temperature for 16 h under H_2 (1 atm) and then passed through Celite (MeOH). The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; MeOH/$CHCl_3$ = 1:4) to give **16** (24.4 mg, 50%) as a white solid. After crystallization (MeOH/ether), the desired compound was obtained in >99%*ee*. The *ee* value was determined by HPLC [DAICEL chiral AS-H column; hexane/2-propanol, 80:20; flow rate: 0.50 mL min^{-1}]: t_R = 66.7 (major) and 125.8 min (minor). $[\alpha]_D^{20}$ = 9.47 (*c* = 0.95, EtOH). IR (neat): $\tilde{\nu}$ = 3282, 2967, 2926, 1495, 846 cm^{-1}, m.p. 225–227 °C. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.02–7.90 (m, 4 H, $C_{10}H_7$), 7.67–7.54 (m, 3 H, $C_{10}H_7$), 4.74–4.73 (d, *J* = 6.5 Hz, 1 H, NCH), 3.69–3.63 (m, 1 H, CCH), 3.27–3.16 (m, 2 H, CCH_2), 2.09–2.06 (m, 1 H, CCH), 1.16–1.15 (d, *J* = 6.0 Hz, 3 H, CCH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 134.9, 134.6, 133.9, 129.9, 129.2, 129.0, 128.8, 128.0, 127.8, 126.1, 68.0, 60.6, 58.5, 51.2, 22.9 ppm. MS (EI): *m*/*z* = 245 [M]$^+$. HRMS (EI): calcd. for $C_{15}H_{19}NO_2$ [M]$^+$ 245.1416; found 245.1418.

(1*R*,2*R*,3*R*)-2-(Hydroxymethyl)-1-(methylamino)-1-phenylbutan-3-ol (17): Isoxazolidine **14j** (41.5 mg, 0.20 mmol) was dissolved in MeOH (5.00 mL), and 20 wt.-% $Pd(OH)_2$/C (69.2 mg, 0.13 mmol) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 16 h under H_2 (1 atm) and then passed through Celite (MeOH). The filtrate was concentrated under reduced pressure to give a residue, which was purified by flash chromatography (SiO_2; MeOH/$CHCl_3$, 1:4) to give **17** (29.8 mg, 71%) as a yellow oil. The *ee* value were determined by HPLC [DAICEL chiral AD-H column; hexane/2-propanol, 80:20; flow rate: 0.50 mL min^{-1}]: t_R = 32.3 (major) and 30.5 min (minor, 97%*ee*). $[\alpha]_D^{22}$ = –19.69 (*c* = 0.66, EtOH). IR (neat): $\tilde{\nu}$ = 3316, 2964, 1305, 1202, 865 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.38–7.26 (m, 5 H, C_6H_5), 4.04–4.00 (m, 1 H, CCH), 3.83–3.81 (d, *J* = 9.0 Hz, 1 H, NCH), 3.46–3.44 (dd, *J* = 4.0 Hz, *J* = 11.0 Hz, 1 H, CCH_2), 3.16–3.14 (dd, *J* = 3.5 Hz, *J* = 11.0 Hz, 1 H, CCH_2), 2.18 (s, 3 H, NCH_3), 1.76–1.70 (m, 1 H, CCH), 1.26–1.25 (d, *J* = 6.0 Hz, 3 H, CCH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 142.0, 129.5, 129.3, 129.1, 128.4, 70.3, 68.0, 61.1, 52.4, 33.8, 22.2 ppm. MS (EI): *m*/*z* = 209 [M]$^+$. HRMS (EI): calcd. for $C_{12}H_{19}NO_2$ [M]$^+$ 209.1416; found 209.1425.

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