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Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with Aldehydes Using β-Amino Alcohol Organocatalyst

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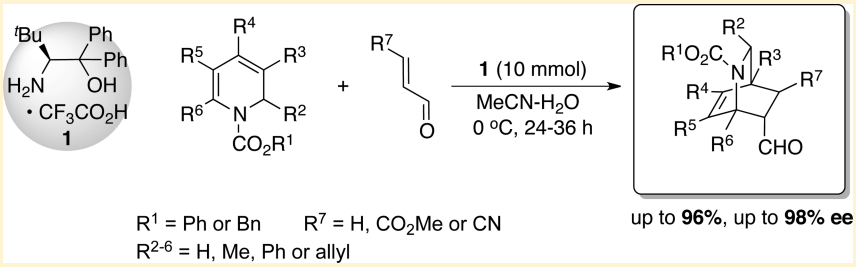
Supporting Information



ABSTRACT: The enantioselective Diels–Alder reaction of 1,2-dihydropyridines with aldehydes using an easily prepared optically active β-amino alcohol catalyst was found to provide optically active isoquinuclidines, an efficient synthetic intermediate of pharmaceutically important compounds such as oseltamivir phosphate, with a satisfactory chemical yield and enantioselectivity (up to 96%, up to 98% ee). In addition, the obtained highly optically pure isoquinuclidine was easily converted to an optically active piperidine having four successive carbon centers.

INTRODUCTION

The asymmetric Diels–Alder (DA) reaction using 1,2-dihydropyridines as a diene with acroleins is an important reaction for the construction of optically active isoquinuclidines (2-azabicyclo[2.2.2]octanes).[1] Isoquinuclidines are found widely in natural products such as iboga-type alkaloids, which have varied and interesting biological properties (Scheme 1).[2]

In particular, the anti-cancer drugs, vinblastine and vincristine, possess isoquinuclidines, with an aspidosperma portion[3] and ibogaine which reduces cravings for alcohol and other drugs by means of its ability to boost the levels of a growth factor known as the glial cell line-derived neurotrophic factor (GDNF).[4] Furthermore, isoquinuclidines can be used as synthetic intermediates for the synthesis of oseltamivir phosphate, an important anti-influenza drug.[5] It is, therefore, desirable to establish an effective catalytic asymmetric synthetic methodology for the production of optically active isoquinuclidines. A well-established route to the optically active ring system is through the asymmetric Diels–Alder reaction of 1,2-dihydropyridines with dienophiles. However, only a few examples using organometallic catalysts or organocatalysts have been reported by our group and others.[6]

Despite the obvious advantages of the catalytic enantioselective version using an organocatalyst, to the best of our knowledge, only two examples employing the MacMillan catalyst[7] and our developed oxazolidine catalyst[8] have been reported for the organocatalytic asymmetric version of this reaction. The reaction using the MacMillan catalyst affords a low chemical yield (26%), but excellent enantioselectivity (99% ee). Moreover, our oxazolidine is relatively unstable in air, although it affords a good chemical yield (71%) and excellent enantioselectivity (99% ee). Most recently, we proved that the enantioselective DA reaction of 1,2-dihydropyridines with acroleins using a simple β-amino alcohol that is the precursor of our developed oxazolidine catalyst is an efficient synthetic

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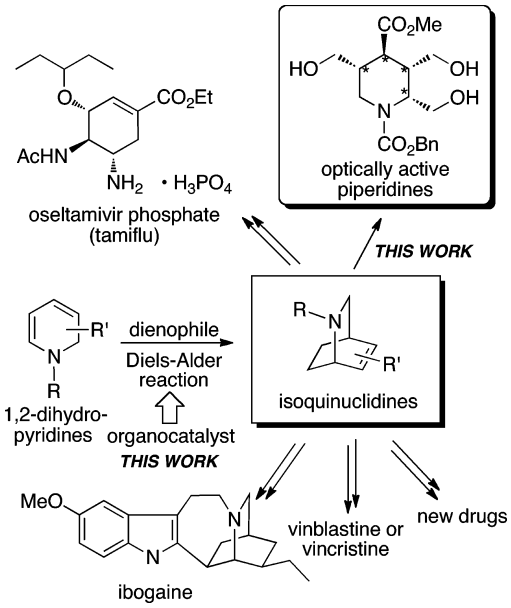
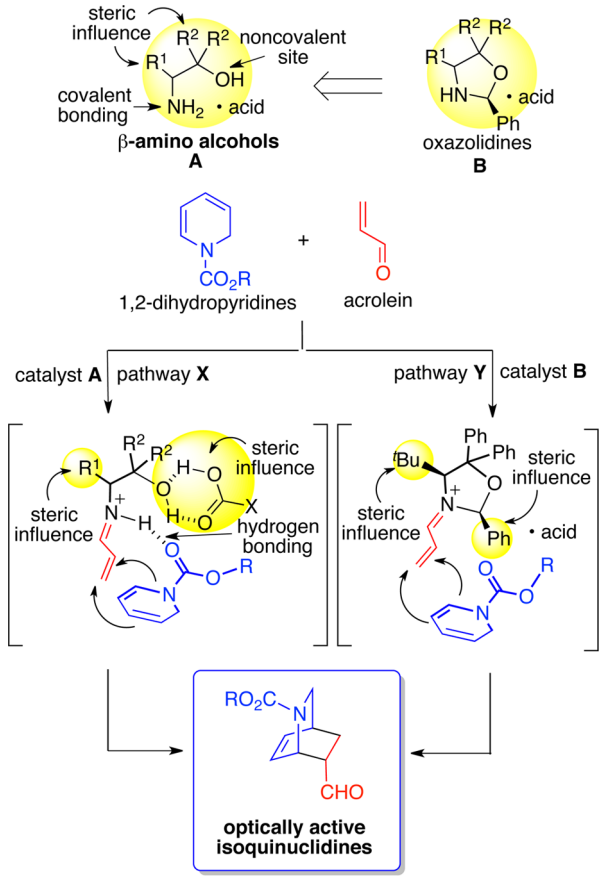
Scheme 1. Utility of Isoquinuclidines



Scheme 2. Function of β-Amino Alcohol Organocatalyst



methodology for obtaining optically active isquinuclidines at synthetically useful levels of chemical yield (96%) and enantiomeric excess (98% ee), and the preliminary results have been communicated.[9]

β-Amino alcohol salt **A** is stable in air and has the two advantageous features of easy preparation and desirable structural characteristics. Thus, it can be derived easily from the corresponding amino acid ester and contains both an amino covalent site and a hydroxyl noncovalent binding site in a single molecule (Scheme 2). Thus, the iminium ion intermediate was first formed from the condensation of **A** with acrolein. Here, the steric influences of both the α- and β-position substituents and an organic acid fixed with both a hydroxyl group at the α-position and an amino group at the β-position by hydrogen bonding might be able to control the approach of a diene that was fixed by hydrogen bonding interactions between the hydrogen on the iminium ion intermediate and the carbonyl group on 1,2-dihydropyridines, to afford high enantioselectivity in the reaction (pathway **X**), although the oxazolidine catalyst **B**[8] controls the approach of the diene only by the steric interactions of substituents at both sides of the amino covalent site (pathway **Y**).

In this paper, we describe the details of the practical enantioselective DA reaction of several 1,2-dihydropyridines with acroleins using β-amino alcohol organocatalysts, the determination of the absolute stereochemistry of the obtained optically active isoquinuclidines using X-ray and CD spectroscopy, and also the convenient transformation of the obtained optically active isoquinuclidines to optically active piperidines having four successive stereogenic centers.

RESULTS AND DISCUSSION

Primary β-amino alcohol salt catalysts **2a−p** having several substituent groups at the α-position or β-position were easily converted from the corresponding α-amino acid esters (Scheme 3).

Thus, catalysts **2a−j,m−p** having an aliphatic or aromatic moiety at the α- and/or β-positions, respectively, were easily prepared by the well-known Grignard reaction or reduction of the corresponding α-amino acid esters, followed by the treatment of the corresponding β-amino alcohols **1a−j,l** with acids (TFA: CF_3CO_2H; TCA: CCl_3CO_2H; TBA: CBr_3CO_2H; AcOH or HCl) in quantitative yields. The primary amine salt **2k** with no substitution for the hydroxyl group was prepared by the well-known method[10] via the oxazolidinones, followed by treatment with TFA. Furthermore, the bulkier β-amino alcohol salt catalyst **2q** having a super silyl [tris(trimethylsilyl)silyl: TTMSS] group[11] at the β-position was also easily prepared from the reaction of **1l** with TTMSSCl, followed by treatment of the corresponding TTMSS-amino alcohol **1q** with TFA. Furthermore, a secondary β-amino alcohol salt catalyst **3**, which was more effective for the formation of the iminium salt with acrolein **5**, was also easily synthesized by the *N*-methylation[12] of **1a** using MeI in the presence of K_2CO_3 in EtOH, followed by treatment of **1r** with TFA in quantitative yield (Scheme 3). The optical purities (>99% ee) of the obtained β-amino alcohols were checked by HPLC.

We first examined the DA reaction of the common 1-phenoxycarbonyl-1,2-dihydropyridine **4a** with acrolein **5** using the optically active catalysts **2a−q**, **3** under the same reaction conditions as those used for the oxazolidines organocatalyst.[8,9] The results are summarized in Table 1.

The reaction of **4a** with **5** barely proceeded in the absence of a catalyst. Initially, the catalytic activity of catalysts **2a−e** having an aromatic diphenyl group at the α-position was examined by the reaction of **4a** (1 equiv) with **5** (3 equiv) at 0 °C in MeCN−H_2O (19:1) in the presence of 10 mol % of catalysts **2a−e**, respectively, to give the DA adducts **6a,a′**, and their chemical and optical yields were determined by conversion to

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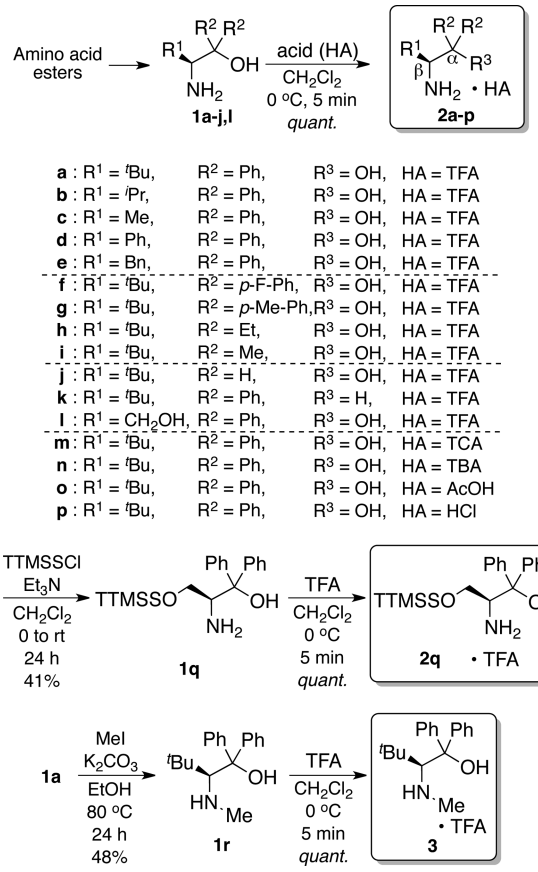
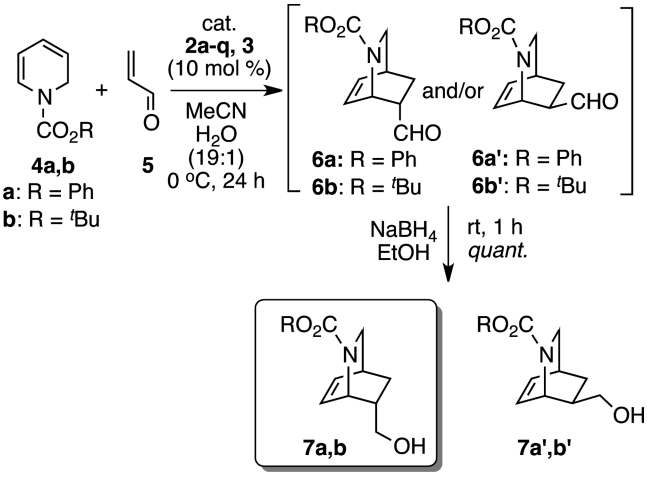
Scheme 3. Synthesis of β-Amino Alcohol Organocatalyst



the alcohols **7a,a′**[9] (entries 1, 3−6). It has already been found that MeCN−H_2O (19:1) solvent is the best solvent for the same reaction using MacMillan organocatalyst by Fukuyama and co-workers.[5] The reaction catalyzed by 2-*tert*-butyl-**2a** with TFA gave the *endo*-DA adduct **6a** in excellent chemical yield (98%) and with excellent enantioselectivity (96% ee) (entry 1, Table 1). In contrast with the result of diene **4a**, the use of 1-*tert*-butoxycarbonyl-1,2-dihydropyridine **4b** afforded only a trace of the corresponding DA adduct **6b** (entry 2). The use of 2-isopropyl-**2b** with TFA gave a slight decrease in both chemical yield (90%) and enantioselectivity (94% ee) (entry 3). Furthermore, 2-methyl-**2c** with TFA afforded both the *endo*-**6a** and *exo*-**6a′** DA adducts as a mixture in only low chemical yield and enantioselectivity (31%, 64% ee) (entry 4). In addition, bulkier 2-phenyl-**2d** with TFA also produced a significant decrease in both chemical yield and enantioselectivity (27%, 13% ee) and afforded both the *endo*-**6a** and *exo*-**6a′** DA adducts as a mixture (entry 5). On the other hand, 2-benzyl-**2e** with TFA showed a high catalytic activity, to afford the *endo*-DA adduct **6a** (80%, 87% ee) (entry 6). To observe the electronic effect of the substituent group on the phenyl group at the α-position in the β-amino alcohol, the catalytic activities of β-amino alcohols **2f,g** with TFA having *p*-fluoro electron-withdrawing or *p*-methyl electron-donating groups on the phenyl groups at the α-position were also tested in the reaction (entries 7, 8). Although both catalysts afforded fairly good asymmetric inductions and good chemical yields (entry 7, **2f**: 73%, 93% ee; entry 8, **2g**: 75%, 95% ee), they did not give better results than those of catalyst **2a**. Furthermore, the catalytic activities of amino alcohols **2h** and **2i** containing aliphatic diethyl and dimethyl groups with TFA, respectively, at

Table 1. DA Reaction of 4 with 5 Using β-Amino Alcohol Catalyst



entry	cat.	diene	yield (%)[a]	*endo*/*exo*[b] (**6a**/**6a′**)	*endo*-**6a** ee (%)[c]
1	**2a**	**4a**	98	*endo* only	96
2	**2a**	**4b**	*trace*		
3	**2b**	**4a**	90	*endo* only	94
4	**2c**	**4a**	31	17:1	64
5	**2d**	**4a**	27	4:1	13
6	**2e**	**4a**	80	*endo* only	87
7	**2f**	**4a**	73	*endo* only	93
8	**2g**	**4a**	75	*endo* only	95
9	**2h**	**4a**	*trace*		
10	**2i**	**4a**	10	6:1	21
11	**2j**	**4a**	*trace*		
12	**2k**	**4a**	*trace*		
13	**1a**	**4a**	66	*endo* only	95
14	**2l**	**4a**	50	19:1	83
15	**2m**	**4a**	65	*endo* only	95
16	**2n**	**4a**	*trace*		
17	**2o**	**4a**	*trace*		
18	**2p**	**4a**	10	*endo* only	90
19	**2q**	**4a**	64	50:1	86
20	**3**	**4a**	*trace*		

[a]Isolated yield. [b]*endo*/*exo* ratio was determined by ^{1}H NMR. [c]Enantiomeric excess was determined by HPLC using a chiral column.

the α-position were also examined under the same reaction conditions of those of entries 1−8 (entries 9, 10). However, the reaction using **2h** barely proceeded (entry 9) under these reaction conditions, while the reaction using **2i** also afforded the DA adduct **6a** in only poor yield (10%, 21% ee) (entry 10). Similarly, amino alcohol **2j** with no substitution for a substituent at the α-position with TFA also barely showed any catalytic activity (entry 11). We also tested the reaction using catalyst **2k** with no substitution for the hydroxyl group at the α-position, but the catalyst no longer worked (entry 12). Furthermore, the same reaction using β-amino alcohol **1a** as a catalyst and TFA as a cocatalyst was also examined, but it did not give better results than the reaction using a catalyst with TFA salt **2a** for either chemical yield or enantioselectivity (66%, 95% ee) (entry 13). The catalytic activity of 2-hydroxylmethyl-**2l** with TFA having two hydrogen bonding sites at α- and β-positions was also examined, and the reaction afforded the *endo*-**6a** in moderate chemical yield (50%) and good enantioselectivity (83% ee) (entry 14). The above experiment showed that 2-*tert*-butyl-**2a** with TFA is the best catalyst in this

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DA reaction of 1,2-dihydropyridine **4a** with **5**. These results indicated that the influences of both the steric effect of the diphenyl group and the hydrogen bonding ability by hydroxyl groups at the α-position on the β-amino alcohol are important in order to proceed the reaction with a satisfactory enantioselectivity and a chemical yield.

The catalytic activity of 2-*tert*-butylated catalysts **2m**−**o** with other Brønsted acids (TCA, TBA, AcOH) was also tested (entries 15−17), respectively. Catalyst **2m** with TCA afforded the DA adduct **6a** in good chemical yield (65%) and with excellent enantioselectivity (95% ee) (entry 15). However, neither catalyst **2n** with TBA nor catalyst **2o** with AcOH yielded any DA adduct (entries 16, 17). It may be due to the bulky steric influence of TBA and for the weak acidity of AcOH, although the reasons are not clear. On the other hand, the reaction using catalyst **2p** with strong HCl as an acid barely proceeded at all, although high enantioselectivity was obtained (10%, 90% ee) (entry 18). Bulkier 2-TTMSSOCH$_2$-**2q** with TFA afforded the DA adduct **6a** in good chemical yield and enantioselectivity (64%, 86% ee), but it did not give better enantioselectivity than the reaction using a catalyst with TFA salt **2a** (96% ee) (entry 19). In addition, the catalytic activity of the more effective secondary β-amino alcohol salt catalyst **3** with TFA for formation of the iminium salt was examined under the same reaction conditions as used for catalyst **2a** (entry 20). However, the catalyst did not show any catalytic activity.

In order to optimize the reaction conditions using the superior catalyst **2a**, we next examined the effects of both reducing the molar ratio of catalyst **2a** and reducing the ratio of MeCN to H$_2$O in the MeCN−H$_2$O solvent in this reaction (Table 2).

Table 2. Optimization of 4a with 5 Using Catalyst 2a

entry[a]	cat. **2a**	solvent (MeCN/H$_2$O)	yield (%)[b]	**6a** ee (%)[c]
1	10	19:1	98	96
2	5	19:1	72	94
3	2.5	19:1	35	93
4	10	MeCN only	32	92
5	10	25:1	70	95
6	10	15:1	63	94
7	10	10:1	45	94
8	10	1:1	36	95
9	10	toluene only	trace	
10	10	CH$_2$Cl$_2$ only	trace	

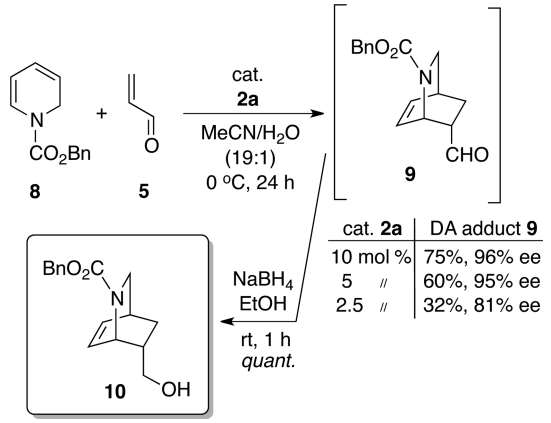
[a]The reaction was carried out at 0 °C for 24 h. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC using a chiral column.

First, the influence of the molar ratio of the catalyst **2a** was examined (entries 1−3, Table 2). The use of 5 mol % of **2a** afforded the DA adduct **6a** with enantioselectivity (94% ee) very similar to that of the reaction containing 10 mol % of **2a** (entry 1), but the chemical yield decreased to 72% (entry 2). At 2.5 mol %, the reaction was sluggish and the chemical yield was poor (35%), but the enantioselectivity (93% ee) was comparable to that obtained at higher levels of catalyst loading (entry 3). It may be due to the decrease of the rate of catalytic cycles, although the reasons are not clear. Next, the solvent effect on the catalytic activity of the superior catalyst **2a** was examined using **4a** and **5** in MeCN−H$_2$O solvent mixed in different ratios (entries 4−8). The enantioselectivity was highly dependent on the ratio of MeCN to H$_2$O solvent in this reaction. The reaction performed in only MeCN gave poor results for the chemical yield (32%, 92% ee) (entry 4). Furthermore, the reactions using MeCN−H$_2$O in the ratios of 25:1, 15:1, 10:1, and 1:1 also produced poor to moderate chemical yields (36−70%) (entries 5−8), although the enantioselectivity of these reactions (94−95% ee) was nearly equivalent to that of the reaction in MeCN−H$_2$O solvent with a 19:1 ratio. The decrease of chemical yield in entry 4 might be due to poor solubilities of the used catalyst and the iminium intermediate formed from the catalyst and acrolein. Furthermore, in both cases of entries 6−8, the hydrolysis of the iminium intermediate formed from the catalyst and dienophile was promoted by the increased amount of water. We also examined the reactions in toluene and CH$_2$Cl$_2$, respectively, as other solvents (entries 9, 10, Table 2). However, the reactions hardly proceeded in these solvents.

From the results shown in Tables 1 and 2, it appeared that the reaction using 10 mol % of catalyst **2a**, 2-*tert*-butyl-1-diphenyl amino alcohol with TFA, in MeCN−H$_2$O (19:1) was the most effective for producing the desired DA adduct **6a** in a satisfactory chemical and optical yield.

Synthetically useful 1-benzyloxycarbonyl-1,2-dihydropyridine **8** containing an easy deprotecting benzyloxycarbonyl group on the nitrogen atom was also examined using the superior catalyst **2a** and acrolein **5** (Scheme 4). The reaction of **8** with **5** was

Scheme 4. DA Reaction of 8 with 5 Using β-Amino Alcohol Catalyst



carried out at 0 °C for 24 h in the presence of 10 mol % of catalyst **2a**, to give the corresponding *endo*-DA adduct **9**. The chemical and optical yields of the DA adduct **9** were determined by converting to the alcohol **10**. As a result, catalyst **2a** showed fairly good catalytic activity, affording the desired DA adduct **9** in good chemical yield and excellent enantioselectivity (75%, 96% ee), which was similar to the results of the reaction using 1-phenoxycarbonyl-1,2-dihydropyridine **4a**. The effect of reducing the molar ratio of catalyst **2a** in the reaction using diene **8** was also examined.

At a low catalytic loading of 5 mol % of **2a**, the results (60%, 95% ee) were as satisfactory as those using 10 mol % of **2a**, but 2.5 mol % greatly decreased both the chemical yield and enantioselectivity (32%, 81% ee).

To increase the effectiveness of this reaction, we examined the DA reactions of 1,2-dihydropyridines **4a** or **8** with the substituted acroleins **11a,b** (Scheme 5). Only few examples of the DA reactions of **4a** or **8** with highly functionalized dienophiles employing an organometallic catalyst or an

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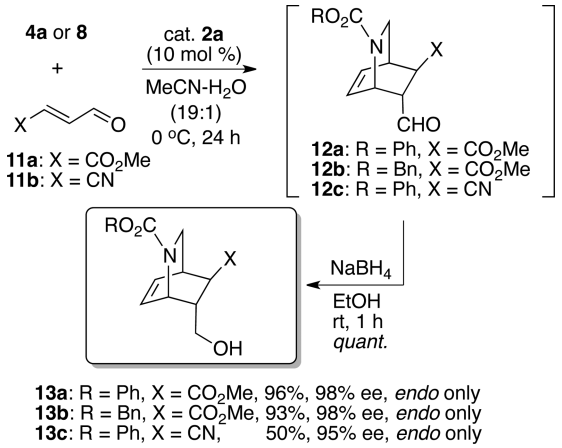
Scheme 5. DA Reactions of 4a, 8 with 11 Using Catalyst 2a



organocatalyst have been reported by our group[8] and others.[13] The DA adducts **12a−c** that are obtained by this reaction have four useful functional groups (amino, aldehyde, ester, and olefin) on the isoquinuclidine ring. Therefore, the adducts might have a high potential utility as a synthetic intermediate of pharmacologically important optically active compounds such as an antiviral drug.

The reactions of the dienes **4a** or **8** with dienophiles **11a,b**, respectively, were carried out at 0 °C for 24 h in the presence of 10 mol % of the superior catalyst **2a**, to give the single DA adducts **12a−c**, and the chemical and optical yields were determined by converting to the alcohols **13a−c**, respectively.

As a result, the desired synthetically useful DA adducts **12a−c** were obtained in the performed reactions. The reactions of **4a** or **8** with dienophile **11a**, respectively, afforded the corresponding DA adducts **13a,b**[9] in excellent chemical yields and almost complete enantioselectivity (**12a**: 96%, 98% ee, **12b**: 93%, 98%ee) in both reactions. On the other hand, the reaction using dienophile **11b**[14] with **4a** also afforded the DA adduct **12c** in excellent enantioselectivity (95% ee), although the chemical yield was moderate (50%). The absolute stereochemistries of the obtained optically active isoquinuclidines **12a** were determined by X-ray analysis of the Br-lactone derived from **12a**, and those of **12b** were determined by the conversion from **12a** to **12b** in our previous paper.[9]

Next, we examined the DA reactions of several different substituted 1,2-dihydropyridines inserting a methyl group in a different position on the pyridine ring. The enantioselective DA reaction using substituted 1,2-dihydropyridines as a diene has not been reported until now. The diene **14a**[15] was prepared from the reaction of pyridine with phenyl chloroformate, followed by Grignard reaction of the obtained pyridinium salts with MeMgBr in good yield (67%). Furthermore, the dienes **14b−d**[16] were obtained from *N*-carboxylation of the corresponding pyridines, followed by reduction using $NaBH_4$, respectively (**14b**: 58%, **14c**: 56%, **14d**: 42%). The reactions of 1-phenoxycarbonyl-1,2-dihydropyridines **14a−d** having a methyl group at positions 2−4 and 6 on the ring with acrolein **5**, respectively, were carried out at 0 °C for 36 h in the presence of 10 mol % of the superior catalyst **2a**, to afford the corresponding DA adducts **15** (Table 3).

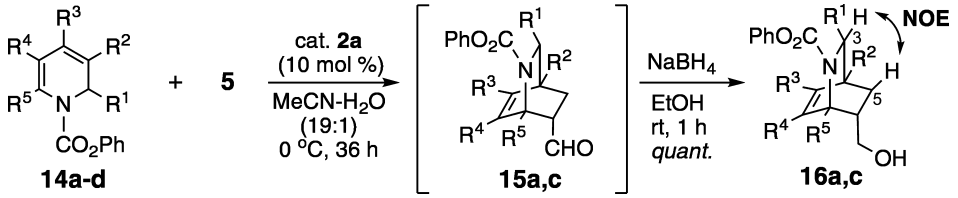
The chemical and optical yields of the obtained DA adduct **15** were determined by converting to the alcohol **16**. The results were different in the functional group of a position on the 1,2-dihydropyridines used. The reactions using 2-methyl-1,2-dihydropyridine **14a** afforded the corresponding DA adduct **15a** in moderate chemical yield and with good enantioselectivity (**15a**: 50%, 91% ee) (entry 1, Table 3). Furthermore, 4-methyl-1,2-dihydropyridine **14c** also afforded the DA adduct **15c** in 80% yield and with 80% ee (entry 3). Unfortunately, the reactions using other unstable dihydropyridines **14b,d** having the 3- or 6-positions at a methyl group, respectively, did not afford the corresponding DA adducts, but complex mixtures in the reaction conditions (entries 2, 4); however, the reasons for failure were not clear.

We next examined the DA reactions of 1,2-dihydropyridines **17** containing bulkier phenyl groups and those of **20** having synthetically useful allyl groups at the 2-position on the rings with acrolein **5** (Scheme 6).

Dienes **17** and **20**[14] were prepared from the reaction of pyridine with phenyl chloroformate, followed by Grignard reaction of the obtained pyridinium salts with PhMgBr or AllylMgBr, respectively, in good yields (**17**: 60%, **20**: 70%).

In consideration of the bulky structures **17** and **20**, the reactions were carried out at 0 °C for a longer reaction time of 48 h in the presence of 10 mol % of the superior catalyst **2a**, to give the corresponding *endo*-DA adducts **18** and **21**, respectively (Scheme 6). The chemical and optical yields of the obtained DA adducts **18** and **21** were determined by converting to the alcohols **19** and **22**, respectively. As a result, the reaction of **17** containing a phenyl group afforded the corresponding DA adduct **18** with moderate chemical yield and satisfactory enantioselectivity (50%, 92% ee). Furthermore, 1,2-dihydropyridines **20** also had fairly good enantioselectivity

Table 3. DA Reactions of 14 with 5 Using Catalyst 2a



entry	diene	R^1	R^2	R^3	R^4	R^5	DA adduct	yield (%)[a]	ee (%)[b]
1	**14a**	Me	H	H	H	H	**15a**	50	91
2	**14b**	H	Me	H	H	H	*cm*[c]		
3	**14c**	H	H	Me	H	H	**15c**	80	80
4	**14d**	H	H	H	H	Me	*cm*[c]		

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC. [c]*cm*: complex mixture.

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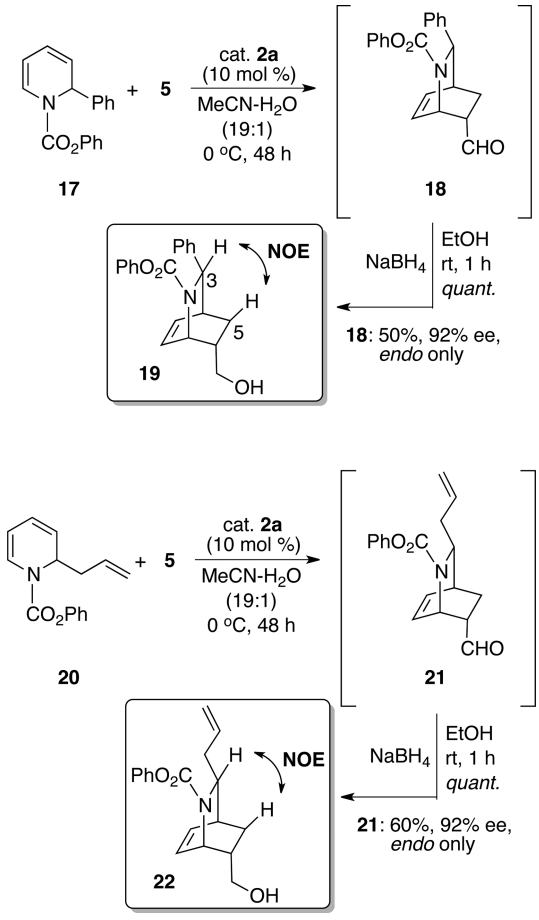
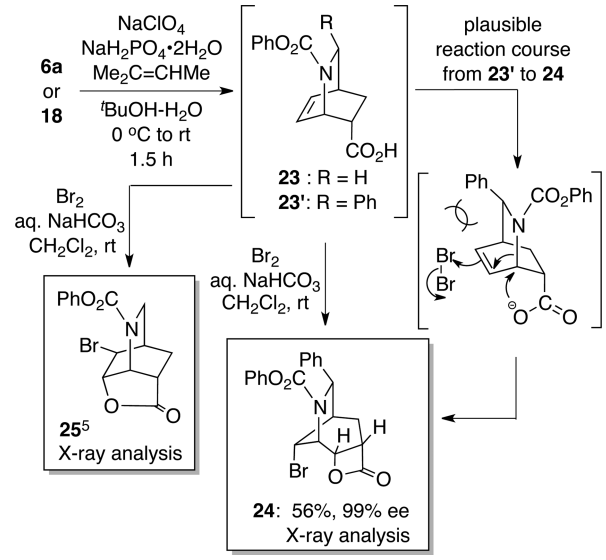
Scheme 6. DA Reactions of 17, 20 with 5 Using Catalyst 2a



Scheme 7. Br-Lactonizations of 6a, 18



(92% ee) and moderate yield (60%), respectively. The relative configurations of the stereogenic centers in 3- and 5-positions of the obtained isoquinuclidines **15a**, **18**, and **21** were determined from the NOE difference spectra (NOEDS) of the corresponding alcohols **16a**, **19**, and **22**. Thus, NOE enhancement was observed between the hydrogen at the 3-position and the hydrogen at the 5-position when the 3- and 5-positions were irradiated, respectively.[8,17]

The absolute configuration of the centers of the DA adducts 3-methyl-**15a**, 3-phenyl-**18**, and 3-allyl-**21** were determined as follows (Scheme 7).

The assignment of the DA adduct **18** was carried out by X-ray analysis of Br-lactone **24**, which was easily converted from the DA adduct **18** (Scheme 7). Interestingly, the 2-azabicyclo-[2.2.2]octane ring system forming isoquinuclidine **18** containing a phenyl group at the 3-position was transformed to a 2-azabicyclo[3.2.1]octane ring system forming the Br-lactone **24** by Br-lactonization of the carboxylic acid **23′** in moderate yield, which might be through the plausible reaction path of Scheme 7. Considering that the isoquinuclidine **6a** with no substitution for a substituent at the 3-position gave the corresponding the γ-Br-lactone **25**[5] retaining the 2-azabicyclo[2.2.2]octane ring system, this transformation from **18** to **24** might result from the steric influence of the bulky phenyl group at the 3-position on the DA adduct **18**. Br-lactone **24**, having a fused azabicyclo-[3.2.1]octane and the β-lactone ring system, might also be a useful synthetic intermediate for creating new biologically active compounds.

CD spectroscopy can also be used to determine the absolute stereochemistry of the DA adducts **15a**, **18**, and **21**. The absorption and CD spectra of alcohols **7a**, **16a**, **19**, and **22** are shown in Figure 1. The difference between these compounds is

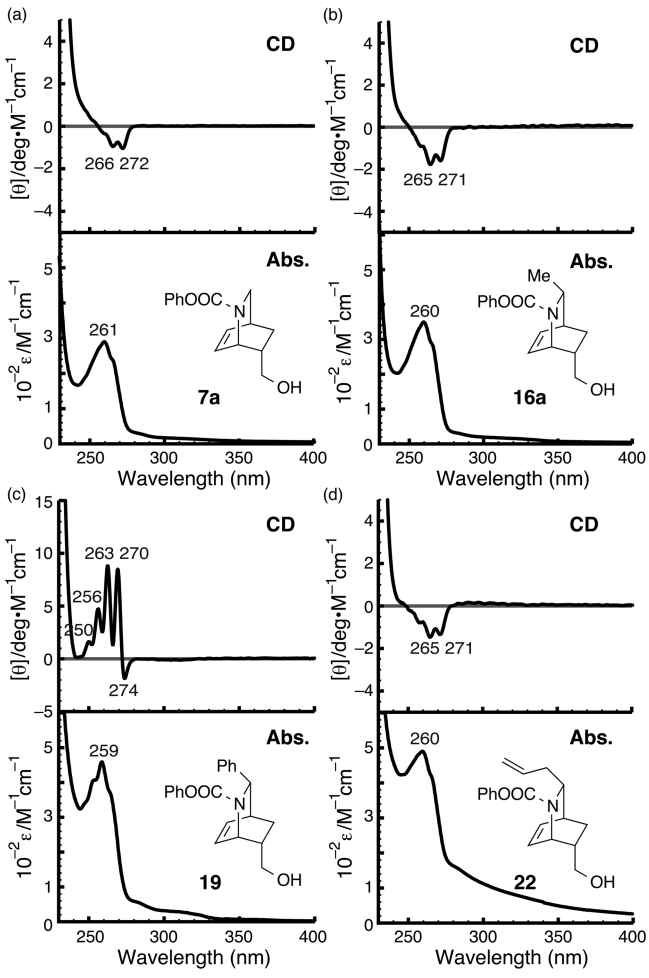


Figure 1. UV–vis absorption and CD spectra of **7a** (a), **16a** (b), **19**(c), and **22** (d) in methanol.

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only one substituent at the 3-position. All of the compounds have intense absorption bands at around 260 nm, which originate from the benzoate group at the nitrogen. Only the CD spectra of **19** shows intense negative first and positive second Cotton effects due to coupling of the two excitons originating from the *N*-benzoate group and the phenyl group at the 3-position. On the basis of exciton coupling theory,[18] the negative-to-positive CD signal in ascending energy is consistent with an anticlockwise screw arrangement of two chromophores (Figure 2).

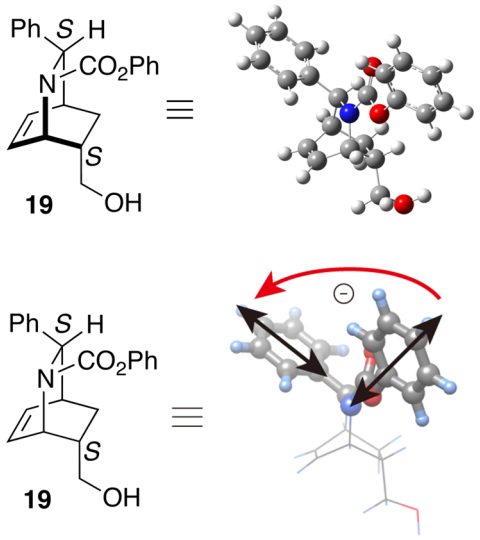
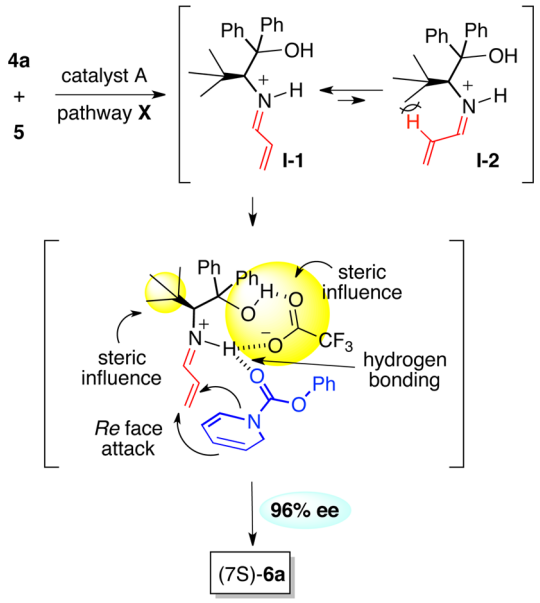


Figure 2. Optimized structure of (3*S*, 7*S*)-**19**. The molecular geometry was optimized at the DFT level using the B3LYP/6-311++G(d,p).

Furthermore, the absolute stereochemistry of **19** was already determined to be the same as that of **24**, whose structure was analyzed by X-ray diffraction. Thus, from this standpoint also, the arrangement of the two chromophores in **19** is anticlockwise. In the case of **7a** (H), **16a** (Me), and **22** (allyl), there is no chromophore that can interact effectively with the benzoate group, so that the CD intensities are relatively weak, which, in turn, suggests that we can neglect the difference of the substituent group at the third position. Although it is not always entirely safe to determine the absolute stereochemistry of these compounds from only the CD spectra, we can use the CD spectra of **7a** as a standard, since the absolute stereochemistry of **7a** (*S* configuration) was determined by X-ray diffraction of **25**[5] (Scheme 7). As seen in this figure, **7a**, **16a**, and **22** show commonly negative CD peaks at around 270 nm, while the shape of the overall CD envelope is similar to that of **7a**, suggesting strongly that the configuration of these compounds is the same. Thus, the stereochemistry of **16a** and **22** also appears to be in an *S* configuration at the 7-position.

On the basis of both the high enantiopurity (96% ee) of the optically active DA adduct (7*S*)-**6a** that was obtained from the reaction of diene **4a** with dienophile **5** and Isihara, Seebach, Melchiorre, and co-workers' detailed studies[19] for an amino organocatalyzed DA reaction mechanism, a model of the enantioselective reaction is proposed as follows (Scheme 8). Thus, the reaction might be through the intermediate **I-1** that has a less steric interaction between the *tert*-butyl substituent in the *β*-position in the catalyst and the olefin part of the dienophile.[9] Then, the iminium ion intermediate generated by

Scheme 8. Plausible Reaction Mechanism for DA Reaction of 4a with 5 Using 2a

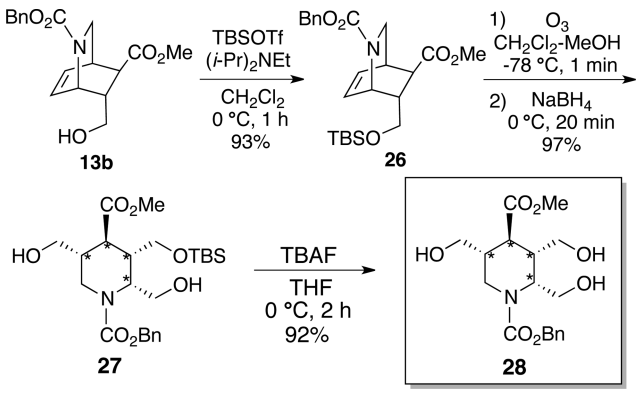


2a with **4a** and **5** was fixed by hydrogen bonding interactions between the hydrogen on the iminium ion intermediate and the carbonyl group on the diene **4a** and $CF_3CO_2^-$ counteranion. Subsequently, **4a** was prevented from approaching the sterically hindered *Si*-face of the iminium ion intermediate by the steric influences of the bulky *tert*-butyl, diphenyl group, and the hydrogen bonding of the hydroxyl group with a TFA moiety. Thus, **4a** attacks from the sterically less hindered *Re*-face. The conformational predominancy of the iminium ion intermadiate **I-1** was indicated by our calculation study.[9]

Many medicines and biologically active compounds include a piperidine skeleton[20] in their structure. Therefore, it is important to develop an effective and convenient synthetic methodology for optically active piperidines containing two or more stereogenic centers in the structure. In order to develop this kind of methodology, we attempted to obtain an optically active piperidine derivative containing four continuous carbon centers by means of the ozonolysis of DA adduct **28** converted from **13b** (Scheme 9).

Ozonolysis of the TBSO-compound **26**, followed by reduction using $NaBH_4$, afforded the desired optically active

Scheme 9. Conversion from Isoquinuclidines 13b to Piperidines 28



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[2*R*,3*S*,4*R*,5*R*]-piperidine derivative **27** having four successive stereogenic centers at the 2,3,4,5-positions in excellent yield (97%). Furthermore, the TBS group on **27** was easily deprotected by TBAF, to afford a piperidine alcohol **28** in 92% yield. The obtained polyfunctional piperidine alcohol **28** is expected to function as a useful synthetic intermediate for several pharmacologically important compounds, such as azasugars.[21]

CONCLUSION

In conclusion, new optically active β-amino alcohol salt organocatalysts **2a**–**p** were prepared easily in two steps and showed dramatic reactivity for affording optically active isoquinuclidines with satisfactory chemical yields and enantioselectivities (up to 98% yield, up to 96% ee) in the DA reactions of 1,2-dihydropyridines **4a**,**b**, **8**, **14**, **17**, and **20** with acroleins **5** or **11a**,**b**. In particular, the reactions catalyzed by **2a** containing a 2-*tert*-butyl moiety with TFA afforded the corresponding *endo*-DA adducts **6a**,**b**, **9**, **12a**–**c**, **15a**,**c**, **18**, and **21** in good to excellent chemical yields and with excellent enantioselectivities, when 10 mol % of catalyst was used. The developed β-amino alcohol catalyst might be superior for practical use. One advantage is that the catalyst is very stable in air and is prepared easily in two steps. In addition, the highly optically pure isoquinuclidine **13b** obtained here was easily converted to the optically active piperidine **28** having four successive carbon centers, which may be useful as a synthetic intermediate for the creation of new drugs. Studies aimed at examining the scope and limitations of this β-amino alcohol organocatalyst for the catalytic asymmetric version of the DA reactions of other 1,2-dihydropyridines with other acroleins are now in progress.

EXPERIMENTAL SECTION

General Methods. All commercial reagents were purchased and used without further purification. All reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254}, and analytes were detected 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 using a micromelting point apparatus. Infrared (IR) spectra were measured with an FT/IR spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured in $CDCl_3$ or DMSO-d_6. ^{1}H NMR data were reported as follows: chemical shifts in ppm (parts per million) from tetramethylsilane or the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double–doublet, m = multiplet and br = broad), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-performance liquid chromatography (HPLC) was performed using the chiral columns AD-H, AS-H and OD-H 4.6 mm × 25 cm column. Optical rotations were measured with a digital polarimeter. HRMS spectra were performed by EI or FAB using sector instruments. Circular dichroism (CD) spectra were measured using a spectropolarimeter.

General Procedure for the Synthesis of 1f, 1h, and 1i. To a dry Et_2O (20.0 mL) solution of corresponding aryl or alkylmagnesium bromide (10.0 mmol), *L*-*tert*-butyl-leucine methyl ester hydrochloride (0.36 g, 2.0 mmol) in dry Et_2O (5.0 mL) solution was added at 0 °C for 30 min under argon. The resulting mixture was stirred at room temperature for 24 h and then quenched with saturated NH_4Cl at 0 °C. The organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 5:1) to give the corresponding β-amino alcohols **1f** (0.24 g, 40%), **1h** (79.7 mg, 23%), and **1i** (61.0 mg, 21%).

*(S)-2-Amino-1,1-bis(4-fluorophenyl)-3,3-dimethylbutan-1-ol (**1f**).* Colorless crystal. mp 196–198 °C; $[\alpha]_D^{22}$ = −146.34 (*c* 0.41, $CHCl_3$); IR (neat) cm^{-1}: 3244, 2971, 1686, 1507; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (2H, dd, *J* = 8.7, 5.2 Hz), 7.48 (2H, dd, *J* = 8.6, 5.5 Hz), 7.00 (2H, t, *J* = 8.6 Hz), 6.91 (2H, t, *J* = 8.6 Hz), 4.54 (0.7H, br), 3.75 (1H, s), 1.45 (2H, br), 0.78 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 162.5, 160.6, 160.5, 145.6, 145.5, 141.0, 141.0, 127.8, 127.7, 127.3, 127.2, 115.5, 115.3, 114.7, 114.6, 79.4, 63.8, 35.6, 29.1; FAB-MS *m*/*z*: 306 (M + H)$^+$; HRMS (FAB): calcd for $C_{18}H_{22}F_2NO$ (M + H)$^+$ 306.1669, found: 306.1656.

*(S)-4-Amino-3-ethyl-5,5-dimethylhexan-3-ol (**1h**).* Colorless oil. $[\alpha]_D^{25}$ = −24.46 (*c* 0.49, $CHCl_3$); IR (neat) cm^{-1}: 2961, 2881, 1229; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (1H, s), 1.82–1.75 (1H, m), 1.54–1.38 (3H, m), 1.04 (9H, s), 0.96–0.90 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.4, 62.7, 35.3, 29.6, 29.4, 28.9, 8.3, 8.0; FAB-MS *m*/*z*: 174 (M + H)$^+$; HRMS (FAB) calcd for $C_{10}H_{24}NO$ (M + H)$^+$: 174.1858, found: 174.1866.

*(S)-3-Amino-2,4,4-trimethylpentan-2-ol (**1i**).* Colorless oil. $[\alpha]_D^{25}$ = −18.15 (*c* 0.21, $CHCl_3$); IR (neat) cm^{-1}: 2980, 2856, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (1H, s), 1.32 (3H, m), 1.15 (3H, m), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.3, 68.4, 35.1, 30.0, 28.9, 25.8; FAB-MS *m*/*z*: 146 (M+H)$^+$; HRMS (FAB) calcd for $C_8H_{20}NO$ (M + H)$^+$: 146.1545, found: 146.1542.

Supersilylation of 1l. To a solution of **2l** (0.46 g, 1.9 mmol) in dry CH_2Cl_2 (20 mL) and chlorotris(trimethylsilyl)silane (0.80 mg, 2.8 mmol), Et_3N (0.32 mL, 2.3 mmol) was added at 0 °C for 10 min under argon. The solution was stirred at 45 °C for 24 h and then quenched with H_2O. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, *n*-hexane:EtOAc = 5:1) to give **1q** (0.38 mg, 41%).

*(S)-2-Amino-1,1-diphenyl-3-(tris(trimethylsilyl)silyloxypropan-1-ol (**1q**).* Light yellow oil. $[\alpha]_D^{25}$ = −41.33 (*c* 0.75, EtOH); IR (neat) cm^{-1}: 2948, 2892, 1448, 1244; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.13 (10H, m), 3.83 (1H, dd, *J* = 6.0, 2.9 Hz), 3.52 (1H, dd, *J* = 9.7, 6.0 Hz), 3.32 (1H, dd, *J* = 9.5, 2.9 Hz), 0.11 (27H, s); ^{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; EI-MS *m*/*z*: 489 (M)$^+$; HRMS (EI) calcd for $C_{24}H_{43}NO_2Si_4$: 489.2371 (M)$^+$, found: 489.2367.

Methylation of 1a. To a solution of **1a** (0.27 g, 1.0 mmol) in EtOH (10.0 mL), K_2CO_3 (0.41 g, 3.0 mmol) and MeI (0.12 mL, 2.0 mmol) were added at 0 °C. The resulting mixture was refluxed for 24 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, *n*-hexane:EtOAc = 5:1) to give the corresponding secondary β-amino alcohol **1r** (0.14 g, 48%).

*(S)-3,3-Dimethyl-2-methylamino-1,1-diphenylbutan-1-ol (**1r**).* Colorless crystal. mp 104–107 °C; $[\alpha]_D^{24}$ = −149.99 (*c* 0.28, $CHCl_3$); IR (neat) cm^{-1}: 3282, 2951; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (2H, dd, *J* = 8.6, 1.1 Hz), 7.63 (2H, dd, *J* = 8.6, 1.1 Hz), 7.32–7.29 (2H, m), 7.22–7.15 (3H, m), 7.17–7.09 (1H, m), 3.29 (1H, s), 2.16 (3H, s), 0.77 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 145.1, 127.8, 127.6, 127.0, 126.5, 126.2, 79.7, 74.4, 38.6, 37.6, 29.2; FAB-MS *m*/*z*: 284 (M + H)$^+$; HRMS (FAB) calcd for $C_{19}H_{26}NO$ (M + H)$^+$: 284.2014, found: 284.2012.

General Procedure for the Synthesis of Catalyst 2a–q and 3. To a solution of the corresponding β-amino alcohol **1a**–**l** and **1q**,**r** (0.03 mmol) in CH_2Cl_2 (0.7 mL), acids (CF_3CO_2H, CBr_3CO_2H, CCl_3CO_2H, CH_3CO_2H, HCl) (0.036 mmol) were added at 0 °C. The resulting mixture was stirred at that temperature for 5 min. Solvent was removed under a reduced pressure to afford the corresponding catalysts **2a**–**q**, **3**.

*(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Trifluoroacetate (**2a**).*[8] Colorless crystal (EtOAc). mp 160–164 °C;

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$[\alpha]_D^{24}$ = −63.49 (*c* 0.38, EtOH); IR (neat) cm^{-1}: 3301, 1686, 1134; ^1H NMR (500 MHz, DMSO-d_6) δ 7.64 (2H, d, *J* = 7.4 Hz), 7.54 (2H, d, *J* = 7.4 Hz), 7.40 (br, 2H), 7.32 (t, 2H, *J* = 7.4 Hz), 7.24−7.19 (3H, m), 7.11 (1H, t, *J* = 7.2 Hz), 6.28 (1H, s), 4.34 (1H, s), 0.79 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.8, 145.9, 129.1, 128.3, 127.6, 127.2, 126.3, 126.2, 80.6, 63.3, 35.7, 29.1; FAB-MS *m*/*z*: 270 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) (M + H − CF_3CO_2H)$^+$ calcd for $C_{18}H_{24}NO$: 270.1858, found: 270.1859.

(S)-1-Hydroxy-3-methyl-1,1-diphenylbutan-2-aminium Trifluoroacetate ***(2b)***. Colorless crystal (EtOAc). mp 196−198 °C; $[\alpha]_D^{23}$ = +16.32 (*c* 0.49, EtOH); IR (neat) cm^{-1}: 1688, 1665, 1523, 1134; ^1H NMR (500 MHz, DMSO-d_6) δ 7.60 (2H, d, *J* = 7.3 Hz), 7.53 (2H, d, *J* = 7.3 Hz), 7.48 (2H, br), 7.33−7.28 (4H, m), 7.23−7.16 (2H, m), 6.37 (1H, s), 4.19 (1H, s), 1.83 (1H, q, *J* = 7.1 Hz), 0.97 (3H, d, *J* = 7.1 Hz), 0.91 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.3, 144.9, 129.0, 128.7, 127.7, 127.4, 126.3, 126.0, 80.2, 61.0, 27.5, 22.3, 17.2; FAB-MS *m*/*z*: 256 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{17}H_{22}NO$: 256.1701 (M + H − CF_3CO_2H)$^+$, found: 256.1704.

(S)-1-Hydroxy-1,1-diphenylpropan-2-aminium Trifluoroacetate ***(2c)***. Colorless crystal (EtOAc). mp 197−200 °C; $[\alpha]_D^{23}$ = +23.34 (*c* 0.51, EtOH); IR (neat) cm^{-1}: 3060, 1694, 1572, 1182, 1150; ^1H NMR (500 MHz, DMSO-d_6) δ 7.56−7.50 (6H, m), 7.33−7.28 (4H, m), 7.22−7.18 (2H, m), 6.41 (1H, s), 4.52 (1H, d, *J* = 6.5 Hz), 1.10 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.9, 144.4, 129.0, 128.7, 127.7, 127.5, 126.2, 78.3, 52.9, 14.7; FAB-MS *m*/*z*: 228 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{15}H_{18}NO$: 228.1388 (M + H − CF_3CO_2H)$^+$, found: 228.1388.

(S)-2-Hydroxy-1,2,2-triphenylethanaminium Trifluoroacetate ***(2d)***. Colorless crystal (EtOAc). mp 178−180 °C; $[\alpha]_D^{23}$ = −115.19 (*c* 0.41, EtOH); IR (neat) cm^{-1}: 3459, 1687, 1537, 1139; ^1H NMR (500 MHz, DMSO-d_6) δ 8.14 (3H, br), 7.81 (2H, d, *J* = 8.0 Hz), 7.42−7.39 (4H, m), 7.30−7.27 (3H, m), 7.18−7.16 (3H, m), 7.07−7.04 (2H, m), 7.00−6.97 (1H, m), 6.73 (1H, s), 5.51 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.4, 144.2, 135.4, 130.3, 129.1, 128.7, 128.0, 127.9, 127.1, 126.8, 126.5, 79.6, 60.3; FAB-MS *m*/*z*: 290 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{20}H_{20}NO$: 290.1545 (M + H − CF_3CO_2H)$^+$, found: 290.1543.

(S)-1-Hydroxy-1,1,3-triphenylpropan-2-aminium Trifluoroacetate ***(2e)***. Colorless crystal (EtOAc). mp 161−163 °C; $[\alpha]_D^{22}$ = −36.47 (*c* 0.85, EtOH); IR (neat) cm^{-1}: 1669, 1525, 1206, 1179, 1141; ^1H NMR (500 MHz, DMSO-d_6) δ 7.68−7.60 (7H, m), 7.35−7.18 (12H, m), 6.58 (1H, s), 4.63 (1H, s), 2.81−2.73 (2H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.8, 144.2, 137.2, 129.8, 129.1, 129.0, 128.8, 127.9, 127.6, 127.3, 126.5, 126.2, 79.1, 58.6, 35.2; FAB-MS *m*/*z*: 304 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{21}H_{22}NO$: 304.1701 (M + H − CF_3CO_2H)$^+$, found: 304.1701.

(S)-1,1-Bis(4-fluorophenyl)-1-hydroxy-3,3-dimethylbutan-2-aminium Trifluoroacetate ***(2f)***. Colorless crystal (EtOAc). mp 179−182 °C; $[\alpha]_D^{22}$ = −53.43 (*c* 0.52, EtOH); IR (neat) cm^{-1}: 1686, 1507, 1211, 1182, 1136; ^1H NMR (500 MHz, DMSO-d_6) δ 7.66 (2H, dd, *J* = 8.9, 5.4 Hz), 7.57 (2H, dd, *J* = 8.9, 5.4 Hz), 7.48 (2H, br), 7.14 (2H, t, *J* = 8.9 Hz), 7.07 (2H, t, *J* = 8.9 Hz), 6.50 (1H, s), 4.34 (1H, s), 0.80 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.7, 162.4, 160.8, 160.5, 158.7, 158.4, 142.7, 142.1, 128.5, 128.4, 115.9, 115.7, 115.2, 115.0, 80.1, 63.3, 35.7, 29.1; FAB-MS *m*/*z*: 306 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{18}H_{22}F_2NO$: 306.1669 (M + H − CF_3CO_2H)$^+$, found: 306.1667.

(S)-1-Hydroxy-3,3-dimethyl-1,1-di-p-tolylbutan-2-aminium Trifluoroacetate ***(2g)***. Colorless crystal (EtOAc). mp 186−188 °C; $[\alpha]_D^{22}$ = −137.14 (*c* 0.35, EtOH); IR (neat) cm^{-1}: 3436, 1676, 1519, 1183, 1132; ^1H NMR (500 MHz, DMSO-d_6) δ 7.49 (2H, d, *J* = 8.1 Hz), 7.38 (2H, d, *J* = 8.1 Hz), 7.35 (2H, br), 7.11 (2H, d, *J* = 8.1 Hz), 7.01 (2H, d, *J* = 8.1 Hz), 6.13 (1H, s), 4.26 (1H, s), 2.22 (3H, s), 2.17 (3H, s), 0.79 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ; 144.1, 143.2, 136.6, 136.2, 129.6, 128.8, 126.2, 126.1, 80.4, 63.3, 35.6, 29.1, 21.0; FAB-MS *m*/*z*: 298 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{20}H_{28}NO$: 298.2171 (M + H − CF_3CO_2H)$^+$, found: 298.2176.

(S)-4-Ethyl-4-hydroxy-2,2-dimethylhexan-3-aminium Trifluoroacetate ***(2h)***. Colorless crystal (EtOAc). mp 173−176 °C; $[\alpha]_D^{23}$ = +21.73 (*c* 0.14, EtOH); IR (neat) cm^{-1}: 3430, 3144, 2977, 1672, 1173, 1137; ^1H NMR (500 MHz, DMSO-d_6) δ 2,47 (brs), 1.64−1.45 (m, 4H), 1.02 (s, 9H), 0.85−0.81 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 75.5, 63.6, 34.1, 29.4, 28.7, 28.4, 8.3, 8.1; FAB-MS *m*/*z*: 174 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{10}H_{24}NO$: 174.1858 (M + H − CF_3CO_2H)$^+$, found: 174.1858.

(S)-2-Hydroxy-2,4,4-trimethylpentan-3-aminium Trifluoroacetate ***(2i)***. Colorless crystal (EtOAc). mp 160−164 °C; $[\alpha]_D^{24}$ = −76.40 (*c* 1.00, EtOH); IR (neat) cm^{-1}: 696, 799, 1604, 1689, 3393 ; ^1H NMR (500 MHz, DMSO-d_6) δ 2.74 (m, 1H), 1.29 (s, 3H), 1.17 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 71.7, 68.1, 33.7, 30.3, 28.7, 26.0; FAB-MS *m*/*z*: 146 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_8H_{20}NO$: 146.1545 (M + H − CF_3CO_2H)$^+$, found: 146.1544.

(S)-1-Hydroxy-3,3-dimethylbutan-2-aminium Trifluoroacetate ***(2j)***. Colorless crystal (EtOAc). mp 110−113 °C; $[\alpha]_D^{22}$ = +23.8 (*c* 0.13, EtOH); IR (neat) cm^{-1}: 3104, 2969, 1682, 1179, 1134; ^1H NMR (500 MHz, DMSO-d_6) δ 7.67 (3H, br), 5.31 (1H, br), 3.68 (1H, td, *J* = 11.4, 3.6 Hz), 2.79 (1H, dd, *J* = 8.9, 3.6 Hz), 0.91 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 61.7, 59.1, 32.3, 26.7; FAB-MS *m*/*z*: 118 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_6H_{16}NO$: 118.1232 (M + H − CF_3CO_2H)$^+$, found: 118.1233.

(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Trichloroacetate ***(2k)***. Colorless crystal (EtOAc). mp 160−164 °C; $[\alpha]_D^{24}$ = −76.40 (*c* 0.13, EtOH); IR (neat) cm^{-1}: 696, 799, 1604, 1689, 3393; ^1H NMR (500 MHz, DMSO-d_6) δ 7.49−7.46 (m, 4H), 7.40 (br, 2H), 7.31−7.28 (m, 2H), 7.23−7.18 (m, 3H), 7.13−7.10 (m, 1H), 4.21 (d, *J* = 10.5 Hz, 1H), 4.14 (d, *J* = 10.5 Hz, 1H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ143.9, 141.7, 129.6, 129.2, 129.1, 128.7, 127.7, 127.1, 61.1, 52.8, 35.2, 27.8 ; FAB-MS *m*/*z*: 254 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{18}H_{24}N$: 254.1909 (M + H − CF_3CO_2H)$^+$, found: 254.1908.

(S)-1,3-Dihydroxy-1,1-diphenylpropan-2-aminium Trifluoroacetate ***(2l)***. Colorless crystal (EtOAc). mp 62−64 °C; $[\alpha]_D^{22}$ = −14.28 (*c* 0.56, EtOH); IR (neat) cm^{-1}: 3087, 1669, 1182, 1133; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58−7.15 (m, 10H), 6.04 (br), 4.22 (2H, t, *J* = 4.5 Hz), 3.66 (1H, d, *J* = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 142.7, 129.2, 128.8, 128.1, 127.7, 125.2, 125.0, 79.7, 60.0, 57.7; EI-MS *m*/*z*: 244 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) [M + H − CF_3CO_2H]$^+$ calcd for $C_{15}H_{18}NO_2$: 244.1338, found: 244.1339.

(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Trichloroacetate ***(2m)***. Colorless crystal (EtOAc). mp 170−173 °C; $[\alpha]_D^{25}$ = −63.18 (*c* 0.36, EtOH); IR (neat) cm^{-1}: 3394, 3284, 1660, 1341; ^1H NMR (500 MHz, DMSO-d_6) δ 8.32 (br), 7.64 (2H, d, *J* = 7.1 Hz), 7.58 (2H, d, *J* = 7.2 Hz), 7.28 (2H, m), 7.19 (2H, m), 7.13 (1H, m), 7.06 (1H, m), 5.32 (br), 3.79 (br), 0.76 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.3, 145.4, 128.6, 127.8, 127.1, 126.7, 125.8, 125.7, 80.1, 62.7, 32.2, 28.6; FAB-MS *m*/*z*: 270 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{18}H_{24}NO$: 270.1858 (M + H − CCl_3CO_2H)$^+$, found: 270.1859.

(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Tribromoacetate ***(2n)***. Colorless crystal (EtOAc). mp 132−136 °C; $[\alpha]_D^{24}$ = −46.51 (*c* 0.34, EtOH); IR (neat) cm^{-1}: 3379, 3283, 1650, 1334; ^1H NMR (500 MHz, DMSO-d_6) δ 7.70−6.45 (m, 11H), 6.35 (s, 1H), 4.30 (s, 1H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.0, 145.2, 128.4, 127.9, 127.9, 126.2, 126.0, 125.8, 80.0, 62.3, 32.5, 28.6; FAB-MS *m*/*z*: 270 (M + H − CF_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{18}H_{24}NO$: 270.1858 (M + H − CBr_3CO_2H)$^+$, found: 270.1857.

(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Acetate ***(2o)***. Colorless crystal (EtOAc). mp 139−142 °C; $[\alpha]_D^{25}$ = −90.47 (*c* 0.42, EtOH); IR (neat) cm^{-1}: 3321, 2962, 1530; ^1H NMR (500 MHz, DMSO-d_6) δ 7.60 (2H, dd, *J* = 8.6, 1.2 Hz), 7.54 (2H, dd, *J* = 8.6, 1.2 Hz), 7.23 (2H, t, *J* = 7.8 Hz), 7.14 (2H, t, *J* = 7.8 Hz), 7.08 (1H, t, *J* = 7.4 Hz), 7.01 (1H, t, *J* = 7.4 Hz), 3.71 (1H, s), 3.53 (br), 1.86 (3H, s), 0.71 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.7, 150.7, 148.1, 128.6, 127.9, 126.3, 126.2, 126.1, 126.1, 81.8, 63.2, 36.4, 30.1, 21.7; FAB-MS *m*/*z*: 270 (M + H − CH_3CO_2H)$^+$; HRMS (FAB) calcd for $C_{18}H_{24}NO$: 270.1858 (M + H − CH_3CO_2H)$^+$, found: 270.1856.

(S)-1-Hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-amininium Chloride ***(2p)***. Colorless crystal (EtOAc). mp 230−240 °C; $[\alpha]_D^{24}$ =

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−34.40 (*c* 0.12, EtOH); IR (neat) cm^{-1}: 3263, 2948; ^1H NMR (500 MHz, DMSO-d_6) δ 7.66 (2H, d, J = 7.5 Hz), 7.62 (1H, br), 7.56 (2H, d, J = 7.5 Hz), 7.29 (2H, t, J = 7.7 Hz), 7.22−7.16 (3H, m), 7.09 (2H, t, J = 7.4 Hz), 6.38 (1H, s), 4.40 (1H, s), 0.82 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.8, 146.4, 129.1, 128.3, 127.5, 127.0, 126.3, 126.1, 80.5, 63.5, 35.8, 29.3; FAB-MS m/z: 270 $(M + H - HCl)^+$; HRMS (FAB) calcd for $C_{18}H_{24}NO$: 270.1858 $(M + H - HCl)^+$, found: 270.1859.

*(S)-1-Hydroxy-1,1-diphenyl-3-(tris(trimethylsilyl)silyloxypropan-2-aminium Trifluoroacetate (**2q**).* Light yellow oil. $[\alpha]_D^{25}$ = −19.99 (*c* 0.45, EtOH); IR (neat) cm^{-1}: 3387, 2950, 2893, 1675, 1246; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, dd, J = 7.2, 1.2 Hz), 7.47 (2H, dd, J = 7.2, 1.2 Hz), 7.32−7.29 (4H, m), 7.22−7.19 (1H, m), 7.15−7.12 (1H, m), 4.21 (1H, dd, J = 5.7, 3.2 Hz), 3.79 ((1/2)2H, dd, J = 10.6, 5.4 Hz), 3.52 ((1/2)2H, dd, J = 10.6, 2.9 Hz), 0.09 (27H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 143.0, 129.1, 128.8, 127.9, 127.6, 125.5, 124.9, 77.8, 65.6, 58.2, 0.06; EI-MS m/z: 489 $(M)^+$; HRMS (EI) $(M - CF_3CO_2H)^+$ calcd for $C_{24}H_{43}NO_2Si_4$: 489.2371, found: 489.2359.

*(S)-1-Hydroxy-N,3,3-trimethyl-1,1-diphenylbutan-2-aminium Trifluoroacetate (**3**).* Colorless crystal (EtOAc). mp 160−164 °C; $[\alpha]_D^{24}$ = −76.40 (*c* 1.00, EtOH); IR (neat) cm^{-1}: 696, 799, 1604, 1689, 3393 ; ^1H NMR (500 MHz, DMSO-*d6*) δ 7.84−6.15 (m, 10H), 5.72 (s, 1H), 2.47 (s, 3H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ 159.1, 145.9, 145.0, 137.5, 133.2, 130.2, 129.1, 128.7, 128.2, 128.0, 127.5, 126.9, 81.2, 73.5, 29.0; FAB-MS m/z: 284 $(M + H - CF_3CO_2H)^+$; HRMS (FAB) calcd for $C_{19}H_{26}NO$: 284.2014 $(M + H - CF_3CO_2H)^+$, found: 284.2012.

Synthesis of 2-Methyl-, Phenyl-, or Allyl-1-Phenoxycarbonyl-1,2-dihydropyridines (14a, 17, or 20). To a solution of 3.0 M methylmagnesium bromide, 3.0 M phenylmagnesium bromide, or 0.7 M allylmagnesium bromide in ether (10 mmol) was added a solution of pyridine (0.97 mL, 12 mmol) in dry Et_2O (30 mL) at −78 °C over 30 min under argon, and a solution of phenyl chloroformate (1.26 mL, 10 mmol) in dry Et_2O (25 mL) was added to the solution over 30 min. The reaction mixture was stirred for 2 h at the same temperature. The mixture was a quenched with water and extracted with ether, washed with brine, and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc = 30:1) to give **14a** (1.44 g, 67%), **17** (1.66 g, 60%), and **20** (1.68 g, 70%).

*2-Methyl-1-phenoxycarbonyl-1,2-dihydropyridine (**14a**).* Colorless crystal. mp 49−52 °C; IR (neat) cm^{-1}: 1736; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.14 (m, 5H), 6.82 (d, J = 7.7 Hz, (3/5)1H), 6.76 (d, J = 7.7 Hz, (2/5)1H), 5.95−5.89 (m, 1H), 5.65−5.59 (m, 1H), 5.40−5.36 (m, (2/5)1H), 5.34−5.31 (m, (3/5)1H), 5.01−4.90 (m, 1H), 1.30 (d, J = 6.5 Hz, (2/5)3H), 1.23 (d, J = 6.5 Hz, (3/5)3H); ^{13}C NMR (125 Mz, $CDCl_3$): δ 151.7, 151.1, 129.5, 129.5, 125.9, 125.7, 124.8, 124.7, 124.3, 124.0, 121.7, 121.7, 121.0, 120.4, 106.5, 106.2, 49.3, 48.9, 19.8, 18.8; EI-MS m/z: 215 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0941.

*2-Phenyl-1-phenoxycarbonyl-1,2-dihydropyridine (**17**).* Colorless solid. mp: 49−50 °C; IR (neat) cm^{-1}: 1730; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51−7.27 (m, 7H), 7.21−7.10 (m, 2H), 6.97−6.92 (m, 2H), 6.14−6.02 (m, 1H), 5.95 (d, J = 5.7 Hz, 1H), 5.77−5.71 (m, 1H), 5.41−5.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 152.3, 151.0, 150.8, 142.0, 140.4, 129.5, 128.8, 128.7, 128.3, 127.7, 126.7, 125.9, 125.8, 125.0, 123.2, 123.0, 121.7, 121.0, 120.6, 106.2, 105.8, 57.4, 56.0; EI-MS m/z: 277 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{18}H_{15}NO_2$ 277.1103, found 277.1111.

*2-Allyl-1-phenoxycarbonyl-1,2-dihydropyridine (**20**).* Light yellow oil; IR (neat) cm^{-1}: 1742; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44−7.36 (m, 2H), 7.29−7.21 (m, 1H), 7.15−7.12 (m, 2H), 6.86 (d, J = 7.7 Hz, (3/5)1H), 6.82 (d, J = 7.7 Hz, (2/5)1H), 6.03−5.97 (m, 1H), 5.92−5.83 (m, 1H), 5.67 (dd, J = 9.4, 5.8 Hz, 1H), 5.44 (m, (2/5)1H), 5.36−5.34 (m, (3/5)1H), 5.14−5.08 (m, 2H), 4.99 (dd, J = 12.2, 6.1 Hz, (2/5)1H), 4.93 (dd, J = 12.2, 6.1 Hz, (3/5)1H), 2.45−2.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 152.0, 151.1, 150.9, 133.6, 133.3, 129.7, 129.5, 129.5, 126.4, 125.9, 125.8, 125.3, 124.6, 123.1, 122.7, 122.1, 121.7, 121.6, 121.5, 121.0, 118.5, 118.0, 107.3, 106.8, 52.6, 52.2, 39.0, 38.4; EI-MS m/z: 241 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1099.

Synthesis of Methylated 1,2-Dihydropyridines 14b−d. To a solution of $NaBH_4$ (0.38 g, 10 mmol) and methylpyridine (10.0 mmol) in dry methanol (7.5 mL) was added slowly phenyl or benzyl chloroformate (10.0 mmol) at −78 °C for 30 min under argon. The reaction mixture was stirred at that temperature for 2 h. After 2 h, the reaction temperature was allowed to rise slowly to 0 °C, and the mixture was poured into a flask with ice and extracted with Et_2O. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, *n*-hexane:EtOAc = 30:1) to give **14b** (1.25 g, 58%), **14c** (1.21 g, 56%), and **14d** (0.90 g, 42%).

*3-Methyl-1-phenoxycarbonyl-1,2-dihydropyridine (**14b**).* Light yellow oil. IR (neat) cm^{-1}: 1730; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.14 (m, 5H), 6.80 (d, J = 7.7 Hz, (3/5)1H), 6.73 (d, J = 7.7 Hz, (2/5)1H), 5.64 (br, 1H), 5.26−5.21 (m, 1H), 4.45 (s, (7/20)2H), 4.30 (s, (13/20)2H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7,151.8,151.1,151.0, 130.0, 129.3, 128.6,125.8, 125.8, 123.1, 122.5, 121.7, 117.0, 116.6, 106.1, 48.6, 48.1, 20.9; EI-MS m/z: 215 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0942.

*4-Methyl-1-phenoxycarbonyl-1,2-dihydropyridine (**14c**).* Light yellow oil. IR (neat) cm^{-1}: 1738; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.14 (m, 5H), 6.88 (d, (3/5)1H, J = 7.8 Hz), 6.82 (d, J = 7.8 Hz, (2/5)1H), 5.30 (br, (3/5)1H), 5.26 (br, (2/5)1H), 5.17 (d, J = 8.1 Hz, (2/5)1H), 5.13 (d, J = 8.1 Hz, (3/5)1H), 4.53 (s, (2/5)2H), 4.40 (s, (3/5)2H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7, 151.6, 151.1, 151.0, 130.3, 130.0, 129.5, 125.8, 125.8, 125.7, 125.0, 121.7, 114.3, 113.7, 109.7, 109.6, 109.5, 44.6, 44.1, 20.7; EI-MS m/z: 215 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0939.

*6-Methyl-1-phenoxycarbonyl-1,2-dihydropyridine (**14d**).* Light yellow oil. IR (neat) cm^{-1}: 1739; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39−7.11 (m, 5H), 5.98−5.95 (m, 1H), 5.72−5.69 (m, 1H), 5.54−5.53 (m, 1H), 4.34 (d, J = 3.2 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 151.2, 151.0, 129.6, 129.5, 126.2, 125.7, 124.2, 121.7, 121.1, 119.8, 113.7, 55.5, 44.1, 21.2; EI-MS m/z: 215 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{13}H_{13}NO_2$: 215.0946, found: 215.0933.

Genaral Procedure for the DA Reaction of 1,2-Dihydropyridines 4, 8, 14, 17, 20 with Acroleins 5, 11 Using Catalyst 3a. To a solution of catalyst **2a** (3.8 mg, 10 mol %) and 1,2-dihydropyridines **4**, **8**, **14**, **17**, and **20** (0.1 mmol) in MeCN−H_2O (19:1), distilled acroleins **5** or **11** (0.3 mmol) were added at −25 °C, and the solution was stirred at 0 °C for 24−36 h. The reaction was quenched with water and extracted with Et_2O. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure to give a crude DA adduct, which was used in the next reaction without purification. To a solution of the crude DA adduct in EtOH (2.0 mL), $NaBH_4$ (4.0 mg, 0.10 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. Solvent was removed under a reduced pressure. The reaction mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, *n*-hexane:EtOAc = 1:1) to give the corresponding alcohols **7a** (25.4 mg, 98%), **10** (20.5 mg, 75%), **13a** (30.5 mg, 96%), **13b** (30.8 mg, 93%), **13c** (14.2 mg, 50%), **16a** (13.7 mg, 50%), **16b** (21.9 mg, 80%), **19** (16.8 mg, 50%), and **22**(18.0 mg, 60%).

*8-Cyano-7-(hydroxymethyl)-2-phenoxycarbonyl-2-azabicyclo-[2.2.2]oct-5-ene (**13c**).* Light yellow oil. $[\alpha]_D^{24}$ = −17.64 (*c* 0.34, $CHCl_3$); IR (neat) cm^{-1}: 3461, 2927, 2884, 2238, 1697, 1400, 1201; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.35 (m, 2H), 7.23−7.20 (m, 1H), 7.14−7.12 (m, 2H), 6.53−6.49 (m, 2H), 5.03 (brs, (3/10)1H), 4.96 (brs, (7/10)1H), 3.98 (m, (7/10)1H), 3.80 (m, (3/10)1H), 3.45−3.36 (m, 2H), 3.29 (m, (7/10)1H), 3.20 (m, (3/10)1H), 3.13 (brs, 1H), 2.74 (brs, 1H), 2.32 (brs, (7/10)1H), 2.23 (brs, (3/10)1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.74, 132.52, 129.42, 125.58, 121.80, 64.22, 47.52, 46.28, 43.20, 34.01, 28.44; EI-MS m/z: 284

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(M)$^+$; HRMS (EI) [M]$^+$ calcd for $C_{16}H_{16}N_2O_3$: 284.1161, found: 284.1166. The enantiomeric excess (ee) was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.2 mL/min, *n*-hexane:2-propanol = 87:13, *tr* (minor) = 18.9 min, *tr* (major) = 25.1 min for DA adduct **13c** (95% ee)].

*(1S,3R,4S,7S)-7-Hydroxymethyl-3-methyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (**16a**).* Colorless oil; $[\alpha]_D^{22}$ = +17.6 (*c* 0.34, $CHCl_3$); IR (neat) cm^{-1}: 3420, 1689, 1202; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.10 (m, 5H), 6.43−6.34 (m, 2H), 4.95 (brs, (2/5)1H), 4.87 (brs, (3/5)1H), 3.83 (brs, (3/5) 1H), 3.77 (brs, (2/5)1H), 3.34−3.16 (m, 2H), 2.64 (brs, 1H), 2.37 (brs, 1H), 1.88−1.83 (m, 2H), 1.21 (d, (3/5)3H, *J* = 5.9 Hz), 1.15 (d, (2/5)3H, *J* = 5.9 Hz), 0.94−0.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 153.0, 151.5, 151.4, 134.9, 134.4, 129.7, 129.4, 129.3, 129.3, 125.2, 125.2, 122.0, 121.7, 77.4, 77.1, 76.9, 65.8, 57.2, 54.9, 54.4, 48.7, 48.3, 41.7, 41.1, 37.6, 37.2, 26.3, 26.2, 20.5, 19.0. EI-MS *m*/*z*: 273 (M$^+$) ; HRMS (EI) (M)$^+$ calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1369. The enantiomeric excess (ee) was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.2 mL/min, *n*-hexane:2-propanol = 87:13, *tr* (major) = 33.4 min, *tr* (minor) = 49.3 min for DA adduct **16a** (91% ee).]

*(1S,4S,7S)-7-Hydroxymethyl-5-methyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (**16c**).* Colorless oil. $[\alpha]_D^{24}$ = +13.0 (*c* 1.00, $CHCl_3$); IR (neat) cm^{-1}: 3477, 1686, 1401; ^{1}H NMR (500 MHz, $CDCl_3$): 7.36−7.10 (m, 5H), 6.03 (d, *J* = 6.0 Hz, 1H), 4.89 (dd, *J* = 6.1, 2.9 Hz, (2/5)1H), 4.81 (dd, *J* = 6.1, 2.9 Hz, (3/5)1H), 3.47−3.09 (m, 4H), 2.60 (br, 1H), 2.43 (br, 1H), 1.89 (m, 3H), 1.87−1.81 (m, 1H), 0.95−0.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6, 153.2, 151.5, 144.8, 144.4, 129.3, 125.2, 123.1, 122.7, 121.9, 121.9, 65.8, 65.7, 48.8, 48.0, 47.2, 47.1, 42.4, 42.3, 36.5, 36.2, 26.1, 26.0, 19.7. EI-MS *m*/*z*: 273 (M$^+$) ; HRMS (EI) (M)$^+$ calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1364. The ee was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.2 mL/min, *n*-hexane:2-propanol = 93:7, *tr* (major) = 64.4 min, *tr* (minor) = 84.4 min for DA adduct **16c** (76% ee).]

*(1S,3S,4S,7S)-7-Hydroxymethyl-3-phenyl-2-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (**19**).* Colorless solid. $[\alpha]_D^{25}$ = −30.0 (*c* 0.40, $CHCl_3$); mp: 100.2−101.0 °C; IR (neat) cm^{-1}: 3459, 1680, 1396; ^{1}H NMR (500 Mz, $CDCl_3$): δ 7.33−6.71 (m, 10H), 6.72−6.70 (m, 1H), 6.13−6.07 (m, 1H), 5.21 (brs, (3/10)1H), 5.15 (br, (7/10)1H), 4.86 (d, (7/10)1H, *J* = 2.0 Hz), 4.80 (d, (3/10)1H, *J* = 2.0 Hz), 3.41−3.22 (m, 2H), 2.93 (brs, 1H), 2.54 (brs, 1H), 2.04−2.10 (m, 1H), 2.00 (br, 1H), 1.04−0.93 (m, 1H); ^{13}C NMR (125 Mz, $CDCl_3$): δ 153.9, 153.0, 151.4, 151.2, 142.7, 141.7, 134.2, 133.6, 130.5, 130.1, 129.2, 129.1, 128.0, 128.0, 126.9, 126.2, 126.2, 125.2, 121.9, 121.7, 65.7, 61.7, 61.3, 49.2, 48.4, 42.1, 41.7, 39.5, 39.1, 26.9, 26.7. EI-MS *m*/*z*: 335 (M$^+$) ; HRMS (EI) (M)$^+$ calcd for $C_{21}H_{21}NO_3$ 335.1521, found 335.1522. The ee was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.2 mL/min, *n*-hexane:2-propanol = 87:13, *tr* (major) = 40.7 min, *tr* (minor) = 58.3 min for DA adduct **19** (92% ee).]

*(1S,3R,4S,7S)-3-Allyl-7-hydroxymethyl-2-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (**22**).* Yellow oil. $[\alpha]_D^{26}$ = +4.9 (*c* 1.22, $CHCl_3$); IR (neat) cm^{-1}: 3431, 1691, 1392; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.10 (m, 5H), 6.41 (m, 2H), 5.79−5.71 (m, 1H), 5.07−5.02 (m, 2H), 4.97 (brs, (1/2)1H), 4.88 (brs, (1/2)1H), 3.72 (td, (1/2)1H, *J* = 10.0, 2.8 Hz), 3.65 (td, (1/2)1H, *J* = 10.0, 2.8 Hz), 3.34−3.14 (m, 2H), 2.58 (brs, 1H), 2.73−2.65 (m, 1H), 2.38 (brs, 1H), 2.07−1.76 (m, 2H), 0.95−0.89 (m, 1H); ^{13}C NMR (125 Mz, $CDCl_3$): δ 154.2, 153.3, 151.4, 151.4, 135.1, 134.8, 134.6, 134.1, 129.9, 129.7, 129.4, 129.3, 125.3, 125.3, 122.0, 121.7, 117.5, 117.2, 65.7, 59.2, 58.6, 48.9, 48.5, 42.1, 41.5, 38.6, 37.1, 33.7, 33.3, 25.9, 25.8. EI-MS *m*/*z*: 300 (M+H)$^+$; HRMS (EI) (M+H)$^+$ calcd for $C_{18}H_{22}NO_3$ 300.1600, found 300.1595. The ee was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.2 mL/min, *n*-hexane:2-propanol = 87:13, *tr* (major) = 29.7 min, *tr* (minor) = 43.7 min for DA adduct **22** (91% ee).]

Bromolactonization Reaction of DA Adduct 18a. To a solution of the DA adduct **18a** in *tert*-butyl alcohol (0.66 mL, 7.0 mmol) and water (0.22 mL) were added sodium dihydrogen phosphate dihydrate (95.2 mg, 0.6 mmol) and 2-methyl-2-butene (0.22 mL, 2.0 mmol). To the mixture was added sodium chlorite (110 mg, 1.2 mmol) potionwise at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 90 min. The reaction was quenched with sodium sulfite, and the reaction mixture was partitioned between EtOAc and 3 N HCl. The aqueous layer was extracted with EtOAc. The extracts were washed with water and brine and concentrated under reduced pressure. The concentrated solution was diluted with EtOAc and extracted with a saturated aqueous sodium bicarbonate solution. To a vigorously stirred mixture of the combined aqueous extracts and CH_2Cl_2 was added bromine until the reddish color of bromine persisted. The reaction was quenched with sodium sulfite, and the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was treated with MeOH to promote crystallization. The crystals were filtered to afford Br-lactone **24** (24.0 mg, 56%).

*(1R,2S,5S,7R,8S,10R)-10-Bromo-8-phenyl-9-phenoxycarbonyl-3-oxa-9-azatricyclo[5.2.1.0^{2,5}]decan-4-one (**24**).* Colorless solid. $[\alpha]_D^{27}$ = −25.0 (*c* 0.24, $CHCl_3$); mp: 181.4−182.6 °C; IR (neat) cm^{-1}: 1830, 1722; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.13 (m, 9H), 6.77 (d, 1H, *J* = 8.0 Hz), 5.03 (brs, (2/5)1H), 4.96 (brs, (3/5)1H), 4.91 (s, (3/5)1H), 4.88−4.85 (m, 1H), 4.84 (s, (2/5)1H), 4.62−4.56 (m, 1H), 3.96−3.88 (m, 1H), 2.75−2.67 (m, 1H), 2.60−2.55 (m, 1H), 2.30−2.22 (m, 1H); ^{13}C NMR (125 Mz, $CDCl_3$): δ 170.8, 170.5, 152.1, 151.4, 150.5, 150.4, 140.8, 139.7, 129.6, 129.4, 129.0, 128.1, 128.1, 126.0, 125.9, 125.0, 121.3, 121.3, 68.7, 67.8, 66.1, 65.8, 56.0, 55.5, 46.9, 45.9, 42.9, 42.7, 39.5, 39.0, 24.1, 24.0. EI-MS *m*/*z*: 427 (M$^+$) ; HRMS (EI) (M)$^+$ calcd for $C_{21}H_{18}BrNO_4$ 427.0419, found 427.0400. The ee was determined by HPLC [DAICEL CHIRALPAK OD-H, 0.8 mL/min, *n*-hexane:2-propanol = 70:30, *tr* (major) = 35.0 min, *tr* (minor) = 58.6 min for Br-lactone **24** (>99% ee).]

***tert*-Butyldimethylsilylation of 12b.** To a CH_2Cl_2 (2.0 mL) solution of DA adduct **12b** (36.1 mg, 0.11 mmol), diisopropylethylamine (38.3 μL, 0.22 mmol) and TBSOTf (37.9 μL, 0.17 mmol) were added at 0 °C, and the solution was stirred at 0 °C for 1 h. The reaction was quenched with sat. Na_2CO_3. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, *n*-hexane:EtOAc = 1:1) to afford **26** (45.6 mg, 93%).

*(1S,4R,7S,8R)-2-benzyloxycarbonyl-7-(tert-butyldimethylsilyloxymethyl)-8-methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (**26**).* Colorless oil; $[\alpha]_D^{22}$ = +40.4 (*c* 0.37, $CHCl_3$); IR (neat) cm^{-1}: 1734, 1698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.26 (m, 5H), 6.46−6.31 (m, 2H), 5.14−5.05 (m, 2H), 4.89 (brs, (1/2)1H), 4.86 (brs, (1/2)1H), 3.70 (s, (1/2)3H), 3.70 (s, (1/2)3H), 3.48−3.01 (m, 4H), 2.95 (t, *J* = 1.5 Hz, 1H), 2.75−2.68 (m, 1H), 1.95 (d, *J* = 1.0 Hz, (1/2)1H), 1.83 (d, *J* = 1.0 Hz, (1/2)1H), 0.87 (s, (1/2)9H), 0.83 (s, (1/2)9H), 0.02 (s, (1/2)6H), −0.01 (s, (1/2)6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 173.4, 155.1, 154.7, 137.0, 136.9, 134.0, 133.5, 132.1, 131.5, 128.5, 128.5, 127.9, 127.9, 127.9, 127.8, 67.0, 66.8, 65.3, 65.2, 52.2, 52.1, 47.3, 47.0, 44.8, 44.6, 43.3, 42.8, 42.7, 42.5, 33.7, 33.4, 25.9, 25.8, 18.3, 18.2, −5.3, −5.4, −5.5; EI-MS *m*/*z*: 445 (M$^+$) ; HRMS (EI) [M]$^+$ calcd for $C_{24}H_{35}NO_5Si$ 445.2285, found 445.2274.

Ozonolysis of 26. A CH_2Cl_2−MeOH (5:1) (6.0 mL) solution of **26** (32.3 mg, 0.072 mmol) was cooled at −78 °C under argon, and ozone was bubbled through the solution for 10 min at the same temperature. Argon was passed through the solution for 10 min, and then $NaBH_4$ (13.7 mg, 0.36 mmol) was added to the solution. The mixture was stirred at 0 °C for 20 min. The reaction was quenched with H_2O. The resulting mixure was extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, *n*-hexane:EtOAc = 2:1) to afford **27** (33.6 mg, 97%).

*(2R,3S,4R,5R)-1-benzyloxycarbonyl-3-(tert-butyldimethylsilyloxymethyl)-2,5-bis(hydroxymethyl)-4-methoxycarbonylpiperidine (**27**).* Colorless oil; $[\alpha]_D^{24}$ = +10.7 (*c* 0.47, $CHCl_3$); IR (neat) cm^{-1}: 3427, 1733, 1676; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.31 (m, 5H),

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5.16−5.09 (m, 2H), 4.52 (dd, J = 11.8, 5.5 Hz, (1/2)1H), 4.46 (dd, J = 11.8, 5.5 Hz, (1/2)1H), 4.22 (dd, J = 13.6, 4.2 Hz, (1/2)1H), 4.14 (dd, J = 13.6, 4.2 Hz, (1/2)1H), 3.85−3.70 (m, 2H), 3.66 (s, 3H), 3.62−3.48 (m, 4H), 2.95 (t, J = 13.0 Hz, (1/2)1H), 2.85 (t, J = 13.0 Hz, (1/2)1H), 2.74−2.66 (m, 1H), 2.22 (brs, 1H), 1.93 (brs, 1H), 0.87 (s, (1/2)9H), 0.84 (s, (1/2)9H), 0.06−0.03 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 174.9, 156.2, 155.8, 136.6, 136.5, 128.6, 128.1, 128.0, 127.9, 67.6, 67.5, 63.4, 63.3, 62.3, 62.2, 61.2, 60.4, 54.4, 54.2, 51.9, 42.5, 42.3, 42.1, 41.9, 41.8, 41.7, 41.6, 41.3, 25.9, 25.8, 18.3, 18.2, −5.7, −5.8; EI-MS m/z: 481 (M^+) ; HRMS (EI) $[M]^+$ calcd for $C_{24}H_{39}NO_7Si$ 481.2496, found 481.2484.

Deprotection of 27. To a THF (2.0 mL) solution of piperidine **27** (26.0 mg, 0.054 mmol), 1.0 M TBAF in THF (54 μL, 0.054 mmol) was added at 0 °C, and the solution was stirred at 0 °C for 2 h. The resultant solution was extracted with $CHCl_3$. The combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was evaporated under a reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, n-hexane:EtOAc = 1:1) to afford **28** (18.3 mg, 92%).

*(2R,3S,4R,5R)-1-benzyloxycarbonyl-2,3,5-tris(hydroxymethyl)-4-methoxycarbonylpiperidine (**28**).* Colorless oil; $[\alpha]_D^{24}$ = 13.4 (c 0.22, $CHCl_3$); IR (neat) cm^{-1}: 3394, 2927, 1729, 1671; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 5.19−5.11 (m, 2H), 4.54 (dd, J = 11.4, 5.6 Hz, (1/2)1H), 4.46 (dd, J = 11.4, 5.6 Hz, (1/2)1H), 4.23 (dd, J = 13.7, 4.0 Hz, (1/2)1H), 4.15 (dd, J = 13.7, 4.0 Hz, (1/2)1H), 3.91 (brs, 1H), 3.72 (s, 3H), 3.69−3.53 (m, 4H), 3.10 (brs, 1H), 3.89−2.70 (m, 2H), 2.21 (brs, 1H), 2.03 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 156.0, 155.6, 136.6, 136.5, 128.7, 128.2, 128.0, 67.7, 67.6, 63.2, 62.0, 62.0, 60.5, 60.4, 60.3, 54.4, 53.9, 52.2, 42.6, 42.4, 42.3, 42.2, 41.6, 41.3, 41.2, 40.9; EI-MS m/z: 367 (M^+) ; HRMS (EI) $[M]^+$ calcd for $C_{18}H_{25}NO_7$ 367.1631, found 367.1613.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, and ^{13}C NMR spectra of **1f**, **1h,i**, **1q,r**, **2a−l**, **2o−q**, **13c**, **14a−d**, **16a,c**, **17**, **19**, **20**, **22**, **24**, **26**, **27**, and **28**; X-ray data and CIF for compounds **24** and **25**; and theoretical calculation of **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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