Asymmetric Cycloetherifications by Bifunctional Aminothiourea Catalysts: The Importance of Hydrogen Bonding

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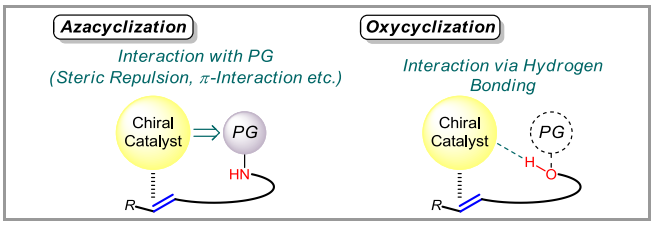
Abstract: Chiral oxacyclic frameworks are prevalent in many natural products and bioactive compounds. In addition, a number of them are important synthetic intermediates. Thus, the synthesis of such structures is a significant goal in the field of organic chemistry. However, the development of catalytic asymmetric cycloetherification for the straightforward synthesis of these compounds remains a challenge. In this study, we propose the use of aminothiourea catalysis as an effective way to accomplish such a challenge. The asymmetric synthesis of chiral oxygen heterocycles, including tetrahydrofurans, tetrahydropyrans, and 1,3-dioxolanes, is demonstrated herein using intramolecular oxy-Michael addition mediated by bifunctional aminothiourea catalysts.

Key words: oxycyclization, cycloetherification, hydrogen bonding, bifunctional aminothiourea catalyst, oxy-Michael addition

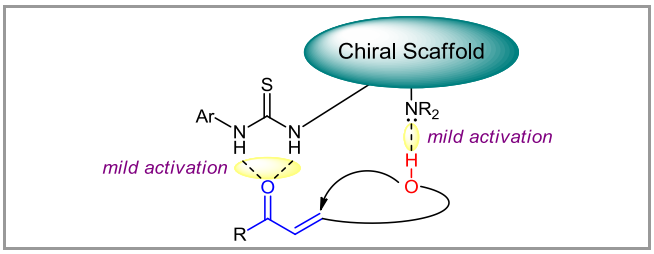
Cyclization from unsaturated substrates that bear a pendant nucleophilic oxygen atom is a straightforward way to synthesize chiral oxacyclic compounds. However, asymmetric oxycyclization reactions are highly challenging because of the difficulty in installing a suitable chiral environment during the rapid intramolecular process. On the other hand, several asymmetric azacyclizations have successfully been developed, including enantioselective intramolecular aza-Michael additions using a proline-derived catalyst[1] or a chiral phase-transfer-catalyst.[2] The enantioselection of these azacyclizations was largely controlled by the effects of the substituents on the nucleophilic nitrogen atom through steric repulsion or π-interactions. Meanwhile, because such a substituent is lacking in the oxycyclization substrates, those strategies can only be applied to starting materials that bear an appropriate substituent in the vicinity of the alcohol.[3,4] Therefore, a novel strategy is required to obtain an efficient asymmetric oxycyclization reaction. In this context, hydrogen bonding is an interaction with the potential to be able to control the behavior of a pendant OH group (Scheme 1). Thus, the use of organocatalysts that utilize hydrogen bonding[5] is a promising approach to realizing enantioselective oxycyclization. Moreover, multipoint recognition by an asymmetric catalyst would be favorable for the achievement of effective transfer of the chiral information during the cyclization process (Scheme 1).



Scheme 1 Strategies for asymmetric aza- and oxycyclizations. (PG: protecting group)

Evidence for the validity of this concept can be found in some recent reports on catalytic asymmetric halolactonizations using bifunctional organocatalysts. These allow multipoint interactions in the reaction transition states, one of which is hydrogen bonding with the pendant carboxyl group.[6] In addition, a number of other highly enantioselective oxycyclizations using organocatalysts have been developed, where hydrogen bonding is thought to have played a role in controlling the chirality.[7–10]

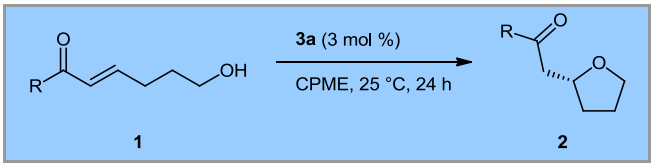
However, whereas an increasing number of methods for asymmetric cyclolactonizations have recently been reported,[6] examples of cycloetherifications are still limited.[3,7,9,10] In particular, catalytic enantioselective cycloetherifications are extremely challenging because of the higher nucleophilicity of hydroxyl groups compared to carboxyl groups. In fact, several of the previously reported cycloetherifications demonstrated only moderate enantioselectivity, resulting from background racemic reactions that occurred, even at low temperatures. They therefore required a stoichiometric or extremely high loading of chiral mediators in order to achieve acceptable selectivity.[11] To overcome such drawbacks, we developed an intramolecular oxy-Michael addition reaction[12] by employing bifunctional aminothiourea catalysts[13] that utilize hydrogen bonding at both catalytic sites. It was hypothesized that the mild character of hydrogen bonding would facilitate concerted catalysis through multipoint recognition, even with highly reactive substrates, for cycloetherification (Scheme 2).[7a,b]



Scheme 2 Asymmetric cycloetherification via intramolecular oxy-Michael addition reaction mediated by bifunctional organocatalyst.

Herein, we describe a highly enantioselective catalytic cycloetherification for the synthesis of 2-substituted tetrahydrofurans (Table 1) and tetrahydropyrans (Table 2).[14] An intramolecular oxy-Michael addition reaction from ε- or ζ-hydroxy-α,β-unsaturated ketones could be performed in a highly enantioselective fashion by using cinchona-alkaloid-thiourea-based bifunctional organocatalyst **3a** (Figure 1). Screening of the catalysts shown in Figure 1 further demonstrated that **3c** is an efficient catalyst for obtaining the opposite enantiomer *ent*-**2a** in excellent yield with high enantioselectivity (Table 1, entry 2). Moreover, the catalytic loading could be decreased to as low as 1 mol % in the THF synthesis, while still giving excellent enantioselectivity (Table 1, entry 3). This catalytic process is a highly practical cycloetherification method that provides excellent enantioselectivities, even with low catalyst loadings at ambient temperature. Although the reactions were slower, a similar reaction condition also led to the highly enantioselective synthesis of 2-substituted tetrahydropyrans (Table 2).

Table 1. Asymmetric Synthesis of 2-Substituted Tetrahydrofurans via Cycloetherification Using Bifunctional Organocatalysts[a,b]



Entry	R	2	Yield (%)[c]	ee (%)
1	Ph	**2a**	99	95
2[d]	Ph	*ent*-**2a**	99	–96
3[e]	Ph	**2a**	95	96
4	4-$CH_3OC_6H_4$	**2b**	99	94
5[f]	4-$CF_3C_6H_4$	**2c**	93	85
6	2-naphthyl	**2d**	98	91
7	4-$CH_3C_6H_4$	**2e**	99	93
8	4-BrC_6H_4	**2f**	99	92
9[g]	$C_6H_5(CH_2)_2$	**2g**	97	90

[a] Reactions were run using **1** (0.25 mmol) and **3a** (0.0075 mmol) in CPME (0.5 mL).
[b] CPME = cyclopentyl methyl ether.
[c] Isolated yields.
[d] Reaction was run using **3c** instead of **3a**.
[e] Reaction was run using 1 mol % **3a** (0.0025 mmol).
[f] Reaction was run on a 0.125 mmol scale.
[g] Reaction was run for 120 h.

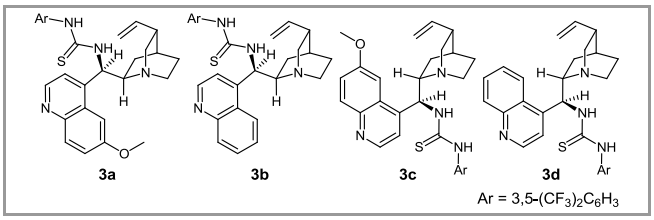
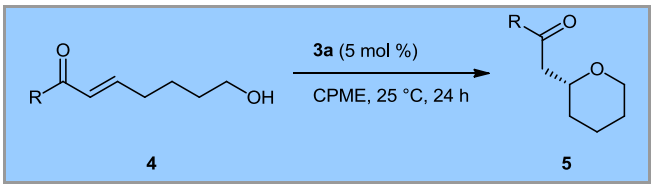


Figure 1 Cinchona-alkaloid-derived aminothiourea catalysts.

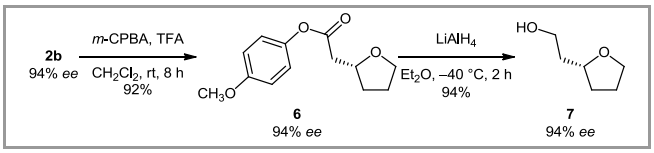
Table 2. Asymmetric Synthesis of 2-Substituted Tetrahydropyrans via Cycloetherification Using Bifunctional Organocatalysts[a,b]



Entry	R	5	Yield (%)[c]	ee (%)
1	Ph	**5a**	90	91
2	4-$CH_3OC_6H_4$	**5b**	56	94
3[d]	4-$CF_3C_6H_4$	**5c**	95	85
4	2-naphthyl	**5d**	80	94
5	4-$CH_3C_6H_4$	**5e**	76	94
6	4-BrC_6H_4	**5f**	99	94
7[e]	$C_6H_5(CH_2)_2$	**5g**	58	95

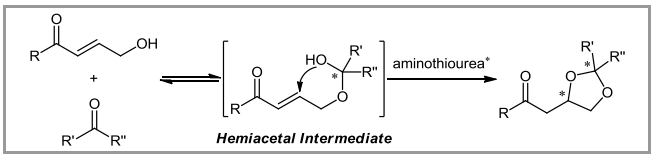
[a] Reactions were run using **1** (0.15 mmol) and **3a** (0.0075 mmol) in CPME (0.3 mL).
[b] CPME = cyclopentyl methyl ether.
[c] Isolated yields.
[d] Reaction was run on a 0.1 mmol scale.
[e] Reaction was run for 120 h.

The obtained THF product **2b** could be further transformed into the corresponding ester **6** by means of Baeyer–Villiger oxidation with *m*-CPBA in the presence of TFA in 92% yield without any loss of optical purity (Scheme 3). Subsequent reduction of **6** with lithium aluminum hydride afforded (*R*)-2-(tetrahydrofuran-2-yl)ethanol (**7**), which is a valuable synthetic intermediate (Scheme 3).[15]



Scheme 3 Transformation of **2b**.

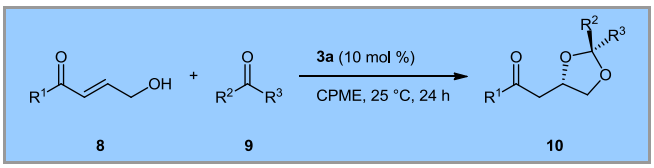
These results subsequently motivated us to exploit this efficient oxycyclization protocol for the development of a catalytic formal [3+2] cycloaddition reaction starting from γ-hydroxy-α,β-unsaturated carbonyls[16] with aldehydes or ketones (Scheme 4). This method led to the successful divergent synthesis of chiral 1,3-dioxolanes.[17] In this reaction, the hemiacetal intermediate generated in situ was the *substrate* for the cycloetherification mediated by chiral aminothiourea.[18,19]



Scheme 4 Chiral 1,3-dioxolane synthesis via asymmetric cycloetherification using a bifunctional aminothiourea catalyst.

Employing the conditions described in Table 3, various 1,3-dioxolanes were stereoselectively obtained by the formal cycloaddition reaction using **3a** as a catalyst.[20] In addition, catalyst screening identified **3c** as an efficient catalyst for obtaining the opposite enantiomer *ent*-**10aa** in good yield with high enantioselectivity (Table 3, entry 2).

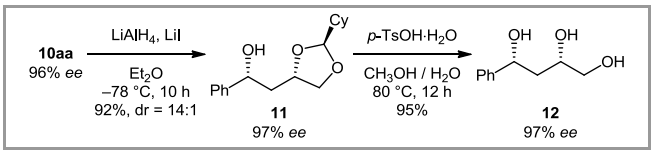
Table 3. Asymmetric Synthesis of 1,3-Dioxolanes by organocatalytic formal [3+2] cycloaddition[a,b]



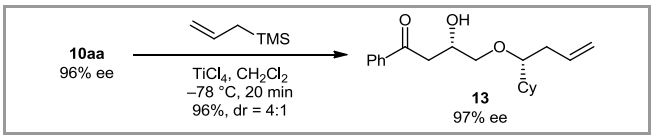
Entry	R^1, R^2, R^3	10	Yield (%)[c]	dr[d]	ee (%)[e]
1	Ph, Cy, H	**10aa**	95	3.0:1	96
2[f]	Ph, Cy, H	*ent*-**10aa**	91	4.0:1	–93
3[g]	4-$CH_3OC_6H_4$, Cy, H	**10ba**	93	3.4:1	96
4	4-$CF_3C_6H_4$, Cy, H	**10ca**	83	2.5:1	95
5	4-BrC_6H_4, Cy, H	**10da**	88	4.7:1	96
6	2-$CH_3C_6H_4$, Cy, H	**10ea**	71	3.3:1	91
7	1-naphthyl, Cy, H	**10fa**	82	2.9:1	90
8	2-thienyl, Cy, H	**10ga**	84	3.3:1	98
9[h]	$C_6H_5(CH_2)_2$, Cy, H	**10ha**	82	3.3:1	96
10	Ph, Et, H	**10ab**	94	3.0:1	94
11	Ph, *i*-Pr, H	**10ac**	92	2.7:1	93
12[i]	Ph, *t*-Bu, H	**10ad**	84	2.6:1	94
13	Ph, CF_3, Ph	**10ae**	99	1.2:1	70

[a] Reactions were run using **8** (0.25 mmol), **9** (0.3 mmol), and **3a** (0.025 mmol) in CPME (0.5 mL).
[b] CPME = cyclopentyl methyl ether.
[c] Isolated yields.
[d] Diastereomeric ratios were determined by ^{1}H NMR.
[e] Values are for the major diastereomers of **10**. See ref 20 for minor diastereomers.
[f] Reaction was run using **3c** instead of **3a**.
[g] Reaction was run for 48 h.
[h] Reaction was run for 96 h.
[i] Reaction was run for 120 h.

The utility of the products as synthetic intermediates was demonstrated by performing the transformation of **10aa**. Reduction with lithium aluminum hydride in the presence of lithium iodide afforded the corresponding alcohol **11** with high diastereoselectivity, and subsequent de-acetalization gave optically active triol **12** (Scheme 5). In addition, treatment of **10aa** with allyltrimethylsilane in the presence of titanium tetrachloride led to allylative ring cleavage to provide **13** in a regio- and diastereoselective fashion while maintaining the optical purity (Scheme 6).

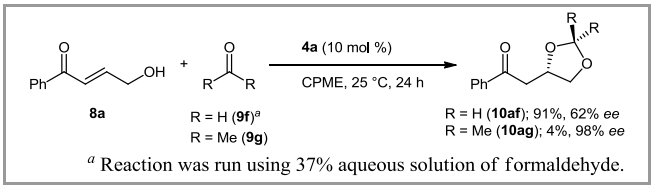


Scheme 5 Synthesis of chiral triol **12**.

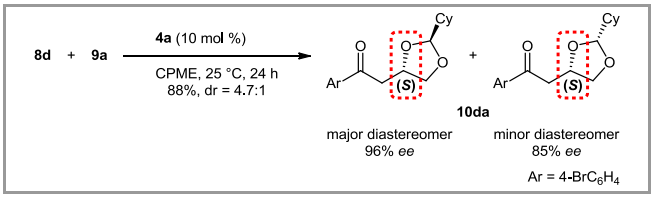


Scheme 6 Stereospecific ring cleavage of **10aa**.

To gain further insight into the enantio-determining step, formal [3+2] cycloaddition reactions were investigated using formaldehyde (**9f**) and acetone (**9g**) with **8a** (Scheme 7). It was found that products **10af** and **10ag** were obtained enantioselectively, regardless of the achirality of the forming acetal carbon. These results strongly suggest that the intramolecular oxy-Michael addition from the hemiacetal intermediates proceeded with high enantioselectivity according to our original hypothesis. This is also in agreement with the consistent absolute configuration (the same (*S*)-configuration) at the β-position of the carbonyl group in both diastereomers of **10da** (Scheme 8).



Scheme 7 Formal [3+2] cycloaddition with formaldehyde (**9f**) and acetone (**9g**).



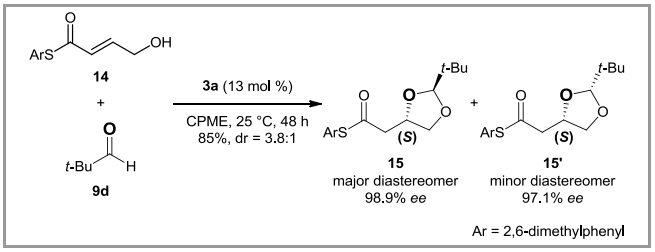
Scheme 8 The absolute configurations of **10da**, as determined by X-ray analysis for both diastereomers.[21]

Considering these stereochemical outcomes, although the diastereoselectivity was only moderate, these reactions can be recognized as a way to achieve highly enantioselective oxygen atom introduction at the β-position of the carbonyl group. This cyclization protocol was therefore applied to reactions using carboxylic acid derivatives as substrates. There have been very few demonstrations of asymmetric oxy-Michael additions to high oxidation state substrates, such as α,β-unsaturated carboxylic acid derivatives,[22] despite their great synthetic importance.[23]

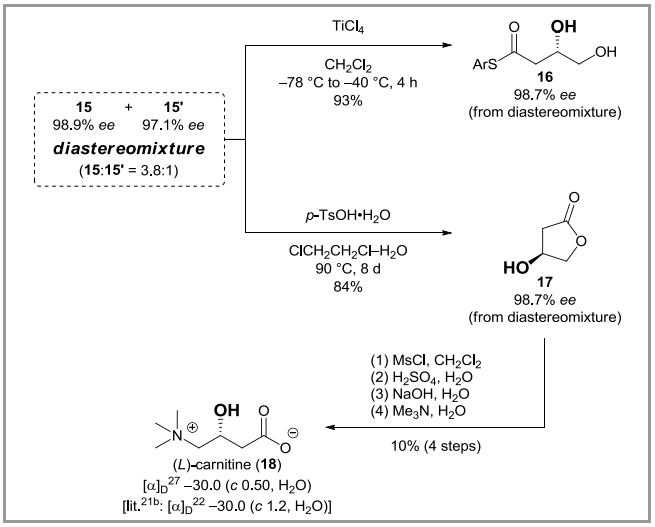
By employing studies involving the optimization of substrates and reaction conditions, 2,6-

dimethylbenzenethiol ester **14** was identified as the best substrate, and pivalaldehyde (**9d**) proved to be a good counterpart. The reaction between these components, using **3a** as a catalyst, gave a diastereomer mixture of the desired products (**15** and **15′**) in high yield, with excellent enantioselectivity for both diastereomers (Scheme 9).[24] Stereochemical analysis of the products revealed that these diastereomers had the same (*S*)-configuration at the β-position of the carbonyl group as was expected.[25]

The easily removable acetal functionality enables this oxy-Michael addition method to be useful as an enantioselective formal hydration.[26] In order to demonstrate this, the obtained products were further extended to the asymmetric syntheses of some β-hydroxy carboxyl compounds (Scheme 10). Treatment of the diastereomer mixture of **15** and **15′** with titanium tetrachloride led to the generation of free β,γ-dihydroxy compound **16** with high optical purity, while keeping the thioester group intact. Alternatively, treatment of the diastereomer mixture with *p*-toluenesulfonic acid in an aqueous medium gave β-hydroxy-γ-butyrolactone **17**, a versatile chiral synthetic intermediate,[27] which could be transformed into (*L*)-carnitine (**18**), an important bioactive agent, using a previously reported procedure.[28]

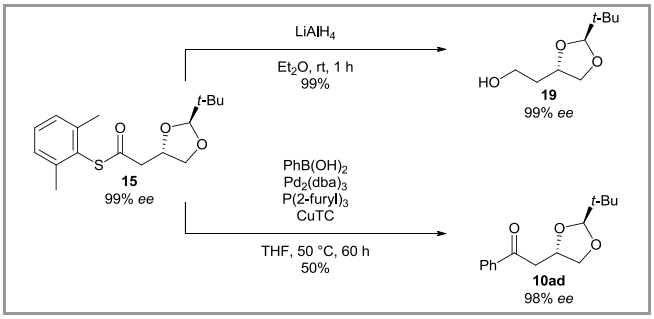


Scheme 9 Asymmetric oxy-Michael addition to γ-hydroxy-α,β-unsaturated thioester **14**.



Scheme 10 Syntheses of chiral β-hydroxy carboxyl compounds.

Taking advantage of the thioester functionality, we also carried out functional group transformations of **15**, and it was found that the chiral acetal moiety was unchanged after the transformations (Scheme 11). Reduction of **15** with lithium aluminium hydride afforded the corresponding primary alcohol **19** quantitatively, without any erosion of optical purity. In addition, Liebeskind–Srogl cross coupling enabled the replacement of the arylthio group of **15** to give ketone **10ad**,[29] indicating that these thioester products can be easily transformed into a wide variety of chiral compounds.



Scheme 11 Transformations of the thioester group of **15**.

In summary, we have demonstrated asymmetric intramolecular oxy-Michael addition reactions using cinchona-alkaloid-thiourea-based bifunctional organocatalysts. The developed methods afforded several important oxacyclic compounds, including tetrahydrofurans, tetrahydropyrans, and 1,3-dioxolanes. A number of the resulting products were demonstrated to be useful synthetic intermediates that could be further transformed into valuable bioactive compounds. This study indicates that the approach based on the use of hydrogen bonding is an effective way to achieve enantioselective cycloetherification. Further studies on the application of this methodology to the synthesis of other chiral oxygen heterocycles are currently underway in our laboratory and will be reported in due course.

^{1}H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane as an internal standard for ^{1}H NMR (δ = 0 ppm) and $CDCl_3$ as an internal standard for ^{13}C NMR (δ = 77.0 ppm). When a ^{13}C NMR spectrum was measured using C_6D_6 as a solvent, C_6D_6 was used as an internal standard (δ = 128.06 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). GC-MS analyses and High-resolution mass spectra were obtained with

a JEOL JMS-700 spectrometer by electron ionization at 70 eV. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on a Bruker Smart APEX X-Ray diffractometer equipped with a large area CCD detector. The structures were solved with the program system SHELXS-97 and refined with SHELXL-97 package from Bruker. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating.

Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification.

General procedure for preparation of bifunctional aminothiourea catalysts 3

Bifunctional organocatalysts **3** were prepared by the literature procedure.[13c] A cinchona alkaloid (5 mmol) and triphenylphosphine (1.6 g, 6 mmol) were dissolved in THF (25 mL), and the solution was cooled to 0 °C. Diethyl azodicarboxylate (1.0 g, 6 mmol) was subsequently added. To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (1.3 mL, 6 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to ambient temperature. After being stirred for 24 h, it was heated to 50 °C and stirred for 10 h. Triphenylphosphine (1.7 g, 6.5 mmol) was added again, and the mixture was stirred at 50 °C for additional 15 h. After the solution was cooled to ambient temperature, H_2O (0.5 mL) was added, and the solution was stirred for 24 h. The solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2/10% aqueous hydrochloric acid (25 mL/25 mL). The aqueous phase was separated and washed with CH_2Cl_2 (25 mL × 4). It was subsequently made alkaline with aqueous ammonia, and the aqueous phase was extracted with CH_2Cl_2 (25 mL × 4). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 9/1) then $CHCl_3$/CH_3OH (v/v = 8/2) as an eluent gave the corresponding 9-amino(9-deoxy)cinchona alkaloids. Next, to the solution of the obtained 9-amino(9-deoxy)cinchona alkaloid in THF (6 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1 equiv) in THF (4 mL) at ambient temperature. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 95/5–97.5/2.5) or EtOAc as an eluent gave the corresponding bifunctional organocatalyst **3**.

3a. White solid; 41% yield (1.2 g) (for 2steps from quinidine). $[\alpha]_D^{23}$+122.6 (*c* 1.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.65 (br s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.86 (s, 2H), 7.67 (s, 1H), 7.59 (br s, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.23 (br s, 1H), 5.86 (br s, 2H), 5.19 (br s, 1H), 5.15 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 3.22 (br s, 1H), 3.10 (br s, 1H), 3.03 (m, 2H), 2.94 (m, 1H), 2.38 (m, 1H), 1.70 (s, 1H), 1.61 (m, 2H), 1.27 (br s, 1H), 1.02 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 158.1, 147.3, 144.7, 144.5, 140.1, 139.6, 132.5 (q, *J* = 33.6 Hz), 131.6, 128.0, 123.5, 122.9 (q, *J* = 273.0 Hz), 122.3, 118.7, 115.3, 101.7, 61.4, 55.6, 48.5, 47.1, 38.7, 27.1, 26.1, 25.0. Mp. 125.0–125.2 °C. IR (KBr): 3221, 2944, 2361, 1735, 1623, 1511, 1475, 1384, 1278, 1177, 1134, 1034, 959, 916, 884, 850, 826, 682 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4OS$: $[M+H]^+$, 595.1966. Found: *m*/*z* 595.1961.

3b. White solid; 36% yield (1.0 g) (for 2steps from cinchonine). $[\alpha]_D^{23}$+163.3 (*c* 1.23, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.83 (br s, 1H), 8.28 (br s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.85 (br s, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.68 (s, 1H), 7.64 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (br s, 1H), 5.81 (br s, 2H), 5.14 (m, 2H), 3.21 (br s, 1H), 3.00 (m, 3H), 2.92 (br s, 1H), 2.36 (m, 1H), 1.66 (s, 1H), 1.59 (m, 2H), 1.22 (br s, 1H), 0.95 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.3, 150.0, 148.6, 145.8, 140.2, 139.3, 132.5 (q, *J* = 33.6 Hz), 130.5, 129.5, 127.1, 126.7, 123.4, 122.9 (q, *J* = 273.1 Hz), 122.8, 119.0, 118.7, 115.5, 61.8, 55.7, 48.5, 47.0, 38.9, 27.3, 26.0, 24.9. Mp. 189.9–190.3 °C. IR (KBr): 3428, 3246, 2944, 2360, 1622, 1588, 1512, 1474, 1386, 1281, 1183, 1126, 960, 882, 848, 752, 682 cm^{-1}. HRMS Calcd for $C_{28}H_{27}F_6N_4S$: $[M+H]^+$, 565.1861. Found: *m*/*z* 565.1855.

3c. White solid; 27% yield (0.80 g) (for 2steps from quinine). $[\alpha]_D^{23}$ –99.0 (*c* 1.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.82 (br s, 2H), 7.68 (s, 1H), 7.62 (br s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.18 (br s, 1H), 5.84 (br s, 1H), 5.70 (m, 1H), 5.01 (m, 2H), 3.96 (s, 3H), 3.37 (br s, 1H), 3.30 (br s, 1H), 3.18 (m, 1H), 2.79 (br s, 2H), 2.35 (br s, 1H), 1.72 (s, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 0.92 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 158.2, 147.4, 144.8, 144.0, 140.6, 140.0, 132.6 (q, *J* = 33.6 Hz), 131.8, 127.9, 123.6, 122.9 (q, *J* = 273.0 Hz), 122.0, 118.8, 115.1, 102.1, 61.2, 55.7, 54.9, 41.3, 39.0, 27.5, 27.1, 25.7. Mp. 121.0–121.5 °C. IR (neat): 3220, 2946, 2360, 1623, 1510, 1475, 1384, 1279, 1180, 1134, 1032, 959, 917, 885, 850, 683 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4OS$: $[M+H]^+$, 595.1966. Found: *m*/*z* 595.1961.

3d. White solid; 44% yield (1.2 g) (for 2steps from cinchonidine). $[\alpha]_D^{23}$ –101.0 (*c* 1.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.80 (br s, 1H), 8.35 (br s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 2H), 7.74 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.69 (s, 1H), 7.63 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.27 (br s, 1H), 5.78 (br s, 1H), 5.67 (m, 1H), 4.98 (m, 2H), 3.26 (m, 1H), 3.20 (br s, 1H), 3.17 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.78 (m, 2H), 2.33 (br s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H), 0.93 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 180.9, 149.9, 148.5, 145.9, 140.7, 139.9, 132.6 (q, *J* = 33.6 Hz), 130.4, 129.5, 127.0, 123.6, 122.9 (q, *J* = 273.0 Hz), 119.1, 118.9, 115.0, 61.5, 56.5, 54.9, 41.1, 39.2, 27.5, 27.1, 25.7. Mp. 122.8–123.1 °C. IR (neat): 3240, 3081, 2946, 2366, 1510, 1473, 1384, 1281, 1181, 1135, 990, 958, 884, 849, 755, 683 cm^{-1}. HRMS Calcd for $C_{28}H_{27}F_6N_4S$: $[M+H]^+$, 565.1861. Found: *m*/*z* 565.1855.

General procedure for asymmetric synthesis of 2-substituted tetrahydrofurans 2

In a 5-mL vial, we sequentially added ε-hydroxy-α,β-unsaturated ketone **1** (0.25 mmol), cyclopentyl methyl ether (CPME, 0.5 mL), and quinidine-derived bifunctional catalyst **3a** (0.0075 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding 2-substituted tetrahydrofuran **2**.

General procedure for asymmetric synthesis of 2-substituted tetrahydropyrans 5

In a 5-mL vial, we sequentially added ζ-hydroxy-α,β-unsaturated ketone **4** (0.15 mmol), cyclopentyl methyl ether (CPME, 0.3 mL), and quinidine-derived bifunctional catalyst **3a** (0.0075 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding tetrahydropyran **5**.

1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5a).

Yield: 90% (27.1 mg), 91% *ee*, colorless oil. $[\alpha]_D^{26}$ +16.8 (*c* 2.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.96 (m, 2H), 3.48 (m, 1H), 3.29 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.92 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.84 (m, 1H), 1.75 (m, 1H), 1.57 (m, 2H), 1.52 (m, 1H), 1.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 198.4, 137.4, 133.0, 128.5, 128.3, 74.4, 68.7, 45.4, 32.0, 25.9, 23.4. TLC: R_f 0.45 (hexane/EtOAc = 3:1). IR (neat): 3060, 2936, 2849, 1686, 1597, 1581, 1449, 1379, 1357, 1325, 1292, 1273, 1208, 1194, 1175, 1088, 1045, 1003, 971, 904, 810, 777, 751, 692, 661, 471 cm^{-1}. HRMS Calcd for $C_{13}H_{17}O_2$: $[M+H]^+$, 205.1229. Found: *m*/*z* 205.1227. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 6.1 min, t_{major} = 8.0 min.

1-(4-Methoxyphenyl)-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5b).

Yield: 56% (19.7 mg), 94% *ee*, colorless oil. $[\alpha]_D^{25}$ +20.8 (*c* 1.97, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 6.91 (m, 2H), 3.95 (m, 1H), 3.93 (m, 1H), 3.86 (s, 3H), 3.47 (m, 1H), 3.23 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.86 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.59–1.49 (m, 3H), 1.34 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 196.9, 163.4, 130.5, 130.1, 113.6, 74.4, 68.6, 55.4, 45.0, 32.0, 25.8, 23.3. TLC: R_f 0.29 (hexane/EtOAc = 3:1). IR (neat): 2934, 2844, 1672, 1600, 1577, 1510, 1309, 1261, 1170, 1087, 1045, 1031, 843, 450 cm^{-1}. HRMS Calcd for $C_{14}H_{19}O_3$: $[M+H]^+$, 235.1329. Found: *m*/*z* 235.1377. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 34.6 min, t_{major} = 44.6 min.

1-(4-Trifluoromethylphenyl)-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5c).

Reaction wasrun on 0.1 mmolscale.

Yield: 95% (25.9 mg), 85% *ee*, white solid. $[\alpha]_D^{25}$ +3.86 (*c* 2.59, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.06 (m, 2H), 7.72 (m, 2H), 3.95 (m, 1H), 3.93 (m, 1H), 3.50 (m, 1H), 3.30 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.90 (dd, *J* = 16.0, 5.0 Hz, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.59 (m, 1H), 1.55 (m, 1H), 1.52 (m, 1H), 1.39 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.6, 139.9, 134.2 (q, *J* = 32.7 Hz), 128.6, 125.6 (q, *J* = 3.9), 123.5 (q, *J* = 272.6 Hz), 74.2, 68.6, 45.6, 31.9, 25.7, 23.3. ^{19}F NMR ($CDCl_3$) δ 98.7. Mp. 51.5–52.5 °C. TLC: R_f 0.49 (hexane/EtOAc = 3:1). IR (KBr): 2946, 2936, 2925, 2857, 1681, 1412, 1334, 1323, 1213, 1170, 1158, 1134, 1124, 1113, 1107, 1084, 1070, 1006, 848, 829 cm^{-1}. HRMS Calcd for $C_{14}H_{16}F_3O_2$: $[M+H]^+$, 273.1097. Found: *m*/*z* 273.1106. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 15.8 min, t_{major} = 18.9 min.

1-(Naphthalen-2-yl)-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5d).

Yield: 80% (30.5 mg), 94% *ee*, colorless oil. $[\alpha]_D^{25}$ +26.7 (*c* 3.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.49 (m, 1H), 8.04 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.88 (m, 2H), 7.58 (m, 1H), 7.55 (m, 1H), 4.02 (m, 1H), 3.96 (m, 1H), 3.51 (m, 1H), 3.45 (dd, *J* = 16.0, 6.5 Hz, 1H), 3.05 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.86 (m, 1H), 1.78 (m,

1H), 1.62–1.55 (m, 2H), 1.51 (m, 1H), 1.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 198.3, 135.5, 134.5, 132.4, 130.1, 129.6, 128.43, 128.36, 127.7, 126.7, 123.9, 74.4, 68.6, 45.4, 32.0, 25.8, 23.4. TLC: R_f 0.36 (hexane/EtOAc = 3:1). IR (neat): 3508, 2935, 2848, 2739, 2667, 2314, 1680, 1636, 1469, 1387, 1355, 1295, 1209, 1087, 863, 821, 747, 677, 450 cm^{-1}. HRMS Calcd for $C_{17}H_{19}O_2$: $[M+H]^+$, 255.1380. Found: *m*/*z* 255.1388. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 35.1 min, t_{major} = 47.8 min.

1-(4-Methylphenyl)-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5e).

Yield: 76% (24.9 mg), 94% *ee*, colorless oil. $[\alpha]_D^{25}$ +14.9 (*c* 2.49, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.26 (m, 2H), 3.95 (m, 1H), 3.93 (m, 1H), 3.47 (m, 1H), 3.23 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.90 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.40 (s, 3H), 1.83 (m, 1H), 1.74 (m, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.49 (m, 1H), 1.35 (m, 1H). ^{13}C NMR ($CDCl_3$) 198.0, 143.8, 134.7, 129.2, 128.4, 74.4, 68.6, 45.2, 32.0, 25.8, 23.4, 21.6. TLC: R_f 0.44 (hexane/EtOAc = 3:1). IR (neat): 2933, 2853, 2360, 2331, 1686, 1607, 1087, 1045, 971, 475, 448 cm^{-1}. HRMS Calcd for $C_{14}H_{19}O_2$: $[M+H]^+$, 219.1380. Found: *m*/*z* 219.1389. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 24.0 min, t_{major} = 30.7 min.

1-(4-Bromophenyl)-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5f).

Yield: 99% (42.1 mg), 94% *ee*, white solid. $[\alpha]_D^{25}$ +10.9 (*c* 4.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.56 (m, 2H), 3.92 (m, 1H), 3.90 (m, 1H), 3.41 (m, 1H), 3.22 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.83 (dd, *J* = 16.0, 5.5 Hz, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.59–1.52 (m, 2H), 1.48 (m, 1H), 1.35 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.4, 135.8, 131.7, 129.7, 128.2, 74.2, 68.5, 45.2, 31.9, 25.7, 23.3. Mp. 55.3–55.5 °C. TLC: R_f 0.49 (hexane/EtOAc = 3:1). IR (KBr): 2960, 2937, 2924, 2845, 1684, 1584, 1400, 1207, 1087, 1072, 999, 973, 835, 807 cm^{-1}. HRMS Calcd for $C_{13}H_{16}BrO_2$: $[M+H]^+$, 283.0328. Found: *m*/*z* 283.0339. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 21.7 min, t_{major} = 25.4 min.

4-Phenyl-1-(tetrahydro-2H-pyran-2-yl)butan-2-one (5g).

Yield: 58% (20.0 mg), 95% *ee*, colorless oil. $[\alpha]_D^{25}$ +3.50 (*c* 2.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 2H), 7.20–7.17 (m, 3H), 3.92 (m, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 2.89 (m, 2H), 2.79 (m, 2H), 2.65 (dd, *J* = 15.5, 6.0 Hz, 1H), 2.38 (dd, *J* = 15.5, 4.5 Hz, 1H), 1.81 (m, 1H), 1.58 (m, 1H), 1.53–1.46 (m, 3H), 1.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 208.5, 141.1, 130.4, 128.3, 126.0, 74.1, 68.5, 49.6, 45.2, 31.7, 29.4, 25.7, 23.3. TLC: R_f 0.38 (hexane/EtOAc = 3:1). IR (neat): 2935, 2854, 1718, 1684, 1653, 1636, 1559, 1539, 1457, 1088, 1044, 747, 699, 456 cm^{-1}. HRMS Calcd for $C_{15}H_{21}O_2$: $[M+H]^+$, 233.1536. Found: *m*/*z* 233.1545. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98.5/1.5, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 14.5 min, t_{major} = 15.6 min.

General procedure for asymmetric synthesis of 1,3-dioxolanes 10

In a 5-mL vial, we sequentially added γ-hydroxy-α,β-unsaturated ketone **8** (0.25 mmol), cyclopentyl methyl ether (CPME, 0.5 mL), aldehyde or ketone **9** (0.3 mmol), and quinidine-derived bifunctional catalyst **3a** (0.025 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent afforded the corresponding 1,3-dioxolane **3** as a mixture of the diastereomers. In most cases, the diastereomers were further separated by flash silica gel column chromatography (see ref 20 for details).

Pocedure for asymmetric oxy-Michael addition reaction to γ-hydroxy-α,β-unsaturated thioester 14

In a 5-mL vial, we sequentially added γ-hydroxy-α,β-unsaturated thioester **14** (2.0 mmol), cyclopentyl methyl ether (CPME, 2.0 mL), pivalaldehyde (**9d**, 4.0 mmol), and quinidine-derived bifunctional catalyst **3a** (0.26 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 48 h. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/Et_2O (v/v = 10/1) as an eluent afforded the corresponding oxy-Michael adducts **15** and **15′** as a mixture of the diastereomers.

See ref 14, 20, and 24 for further details on the experimental procedures and the characterization data of compounds.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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