CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200600228

Enantioselective Synthesis of 3,4-Dihydropyran-2-ones by Domino Michael Addition and Lactonization with New Asymmetric Organocatalysts: Cinchona-Alkaloid-Derived Chiral Quaternary Ammonium Phenoxides

Takashi Tozawa,[a, b] Hitoshi Nagao,[a] Yoshinobu Yamane,[a] and Teruaki Mukaiyama*[a, c]

Abstract: Chiral quaternary ammonium phenoxides were readily prepared from commercially available cinchona alkaloids and proved to be useful new asymmetric organocatalysts. Among various chiral quaternary ammonium phenoxides, a cinchonidine-derived catalyst that bears both a sterically hindered *N*1-9-anthracenylmethyl group and a strongly electron withdrawing 9-*O*-3,5-bis(trifluoromethyl)benzyl group were found to be highly effective for the Michael addition of ketene silyl acetals (derived from phenyl carboxylates) and α,β-unsaturated ketones followed by lactonization. Optically active 3,4-dihydropyran-2-one derivatives were obtained in high yields with excellent control of enantio- and diastereoselectivity. This catalyst can be handled in air and stored at room temperature in a sealed bottle without decomposition for at least one month.

Keywords: alkaloids · dihydropyranones · domino reactions · Michael addition · organocatalysis

Introduction

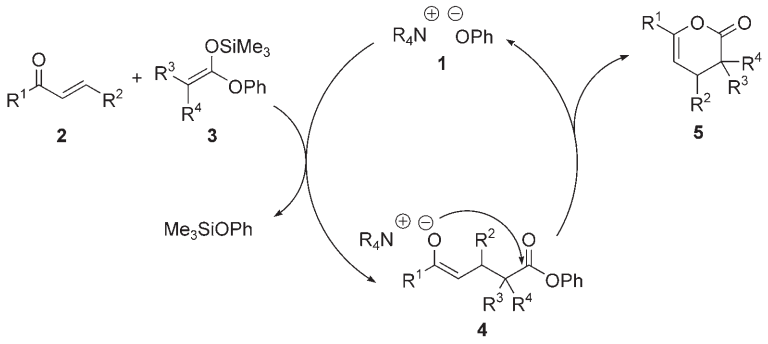
Six-membered oxygen-containing heterocycles such as dihydropyrans and dihydropyranones are widely recognized as useful building blocks for the synthesis of various biologically active compounds. 2,3-Dihydropyran-4-one derivatives are characteristic among them, for which hetero-Diels–Alder reactions of 1-alkoxy-3-trialkylsilyloxy-1,3-butadienes (Danishefsky dienes) with aldehydes are the best known method for the construction of the 2,3-dihydropyran-4-one skeleton. Effective chiral metal-based Lewis acids and hydrogen-bonding catalysts for these hetero-Diels–Alder reactions have been developed and applied to the total synthesis of various natural products.[1] On the other hand, 3,4-dihydropyran-2-one derivatives are useful synthetic intermediates for the preparation of 2-pyranones, γ-lactones, cyclic enamines, etc.,[2] although there are not many effective methods for the synthesis of 3,4-dihydropyran-2-ones. Among the few, an intramolecular cyclization through Michael addition is considered to be one of the most synthetically efficient and powerful strategies because it provides a wide variety of 3,4,6-trisubstituted-3,4-dihydropyran-2-ones in a one-pot preparation.[3] In 1997, Kobayashi et al. reported the first example of a facile one-pot synthesis of 3,4-dihydropyran-2-ones through a trityl salt catalyzed Michael reaction of silyl enol ethers derived from thioesters with α,β-unsaturated ketones and subsequent intramolecular cyclization of the resulting Michael adducts.[3b] Although this method provided the desired 3,4-dihydropyran-2-ones in excellent yields with high diastereoselectivity, excess toxic mercuric trifluoroacetate, $Hg(OCOCF_3)_2$, was required for the cyclization of the Michael adducts. In 2002, Katritzky et al. demonstrated that the reactions of lithium enolates of *N*-acylbenzotriazoles with α,β-unsaturated ketones afforded 3-alkyl 4,6-diaryl 3,4-dihydropyran-2-one derivatives in good yields.[3c] However, the scope of this method with regard to the preparation of substituted 3,4-dihydropyran-2-ones was limited to derivatives with unbranched alkyl substituents at the 3-position. Therefore, it is important to develop an efficient method for the synthesis of 3,4-dihydropyran-2-ones based on a broader concept. Recently, it was reported from our laboratory that a convenient one-pot preparation of 3,4-dihydropyran-2-ones was achieved by Michael addition and successive lactonization between various α,β-unsaturated ketones and

[a] Dr. T. Tozawa, H. Nagao, Y. Yamane, Prof. Dr. T. Mukaiyama
The Kitasato Institute, Center for Basic Research
6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003 (Japan)
Fax: (+81) 3-3911-3482
E-mail: mukaiyam@abeam.ocn.ne.jp

[b] Dr. T. Tozawa
Mitsubishi Pharma Corporation
1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033 (Japan)

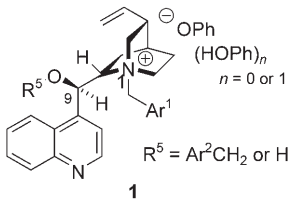
[c] Prof. Dr. T. Mukaiyama
Kitasato Institute for Life Science
Kitasato University
5-9-1 Shirokane, Minato-ku, Tokyo 108-8641 (Japan)

ketene silyl acetals derived from phenyl carboxylates in the presence of a catalytic amount of tetrabutylammonium phenoxide.[4] A catalytic cycle for the phenoxide-ion-catalyzed domino Michael addition and lactonization is illustrated in Scheme 1. In the presence of tetrabutylammonium phenoxide **1** (R = *n*Bu), ketene silyl acetals **3** are activated by nucleophilic attack of the phenoxide ion on the silicon center to react with α,β-unsaturated ketones **2** to afford Michael-adduct intermediates **4** and the trimethylsilyl ether of phenol. The ester carbonyl group in **4** undergoes intramolecular attack by the enolate intermediate formed in situ to form the corresponding 3,4-dihydropyran-2-ones **5** along with elimination of the phenoxide ion. In this catalytic system, the phenoxy group contained in the ketene silyl acetals works as an effective leaving group to facilitate intramolecular cyclization of the Michael-adduct intermediate.



Scheme 1. Phenoxide-ion-catalyzed domino Michael addition and lactonization.

To demonstrate further the synthetic utility and versatility of the phenoxide-ion-catalyzed domino Michael addition and lactonization, it was next planned to use chiral quaternary ammonium phenoxides in an asymmetric synthesis of 3,4-dihydropyran-2-one derivatives. Despite the fact that chiral quaternary ammonium halides have been widely employed as catalysts in synthetically useful stereoselective carbon–carbon bond-forming reactions, and many excellent catalytic asymmetric reactions have been developed in accordance with the advancement of newer effective catalysts,[5] there is no successful example of chiral quaternary ammonium phenoxides as asymmetric organocatalysts in synthetic reactions.[6] Herein we describe in detail our studies on the use of cinchona-alkaloid-derived chiral quaternary ammonium phenoxides **1** in catalytic domino Michael addition and lactonization reactions between ketene silyl acetals derived from phenyl carboxylates and α,β-unsaturated ketones to form optically active 3,4-dihydropyran-2-one derivatives.



Results and Discussion

Synthesis of Cinchona-Alkaloid-Derived Chiral Quaternary Ammonium Phenoxides

Cinchona alkaloids have often been employed in asymmetric reactions, and various catalysts derived from cinchonidine and cinchonine have been developed extensively in chiral phase-transfer catalysis because these alkaloids are in-

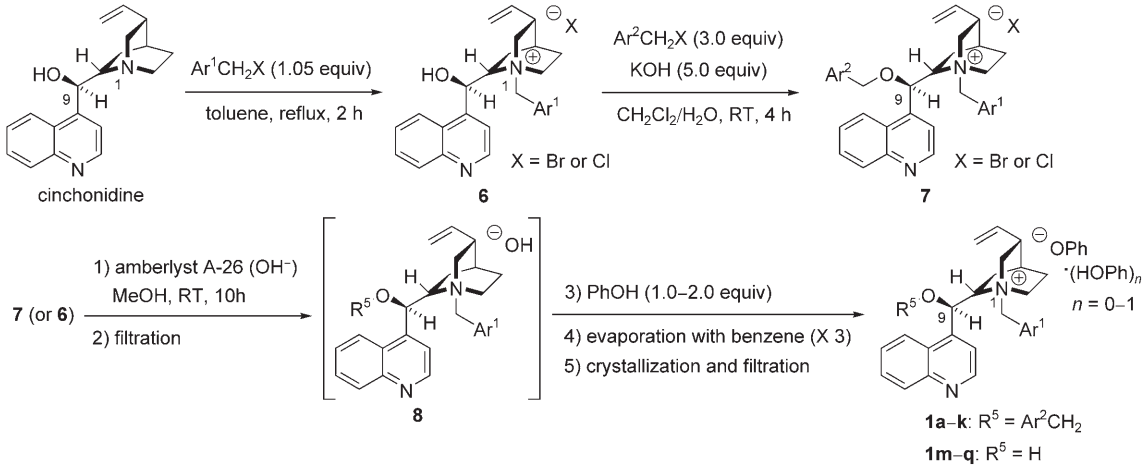
Abstract in Japanese:

入手容易なシンコナアルカロイドから導かれる４級アンモニウムフェノキシドは新しい有用な不斉有機分子触媒である。今回、シンコニジンのＮ１位に立体障害の大きい９－アントラセニル基を、また、Ｃ９位の酸素原子に電子吸引性の強い３，５－ビストリフルオロメチルベンジル基を導入した４級アンモニウムフェノキシドをルイス塩基触媒として用い、α，β－不飽和ケトンと各種ケイ素エノラートを反応させると、マイケル付加および連続するラクトン化反応が速やかに進行し、高いジアステレオかつエナンチオ選択性をもって、３，４－ジヒドロ－２－ピラノンが生成することを明らかにした。この触媒は空気中でも取り扱いができ、また１か月以上、室温において分解せずに保存することができる。

CHEMISTRY
AN ASIAN JOURNAL

expensive, readily available in both pseudoenantiomeric forms, and can easily be converted into effective phase-transfer catalysts.[5] Therefore, cinchonidine was chosen as a chiral source and cinchonidine-derived chiral quaternary ammonium phenoxides **1** were synthesized in three or four steps as shown in Scheme 2. Cinchonidine-derived chiral quaternary ammonium halides **6** and **7** were first prepared according to the procedure reported by Corey et al.[6] Once formed, **6** and **7** were transformed into the corresponding quaternary ammonium hydroxides in an anion-exchange reaction by using amberlyst A-26 (OH^-) in methanol.[7] The resulting ammonium hydroxide intermediates were then treated with phenol (1.0–2.0 equiv). The resultant mixture was co-evaporated with benzene three times, and crystallization of the residue from diethyl ether afforded pale-yellow solids, which were collected by filtration and dried under reduced pressure to give *N*,*O*-diarylmethylated cinchonidinium phenoxides **1a–k** and *N*-arylmethylated cinchonidinium phenoxides **1m–q**, which bear a free hydroxy group. It was also confirmed that cinchonine-derived chiral quaternary ammonium phenoxides were similarly prepared from cinchonine as a chiral starting material. Thus, a synthetic route to cinchona-alkaloid-derived chiral quaternary ammonium phenoxides, new asymmetric organocatalysts, was established. Notably, most of the compounds can be handled in air and stored at room temperature in a sealed bottle without decomposition for at least one month.

After detailed analysis of the cinchona-alkaloid-derived chiral quaternary ammonium phenoxides, some of these compounds with electron-withdrawing substituents were found to consist of quaternary ammonium phenoxide–phenol complexes $[R_4N^+\cdot C_6H_5O^-\cdot C_6H_5OH]$[8] by ^{1}H NMR spectroscopic and elemental analysis (see Experimental Section). For example, the ^{1}H NMR spectrum of cinchonidine-derived chiral quaternary ammonium salt **1k** (Ar^1 = 9-anthracenyl, R^5 = 3,5-bis(trifluoromethyl)benzyl) is shown in



Scheme 2. Synthesis of cinchonidine-derived chiral quaternary ammonium phenoxides.

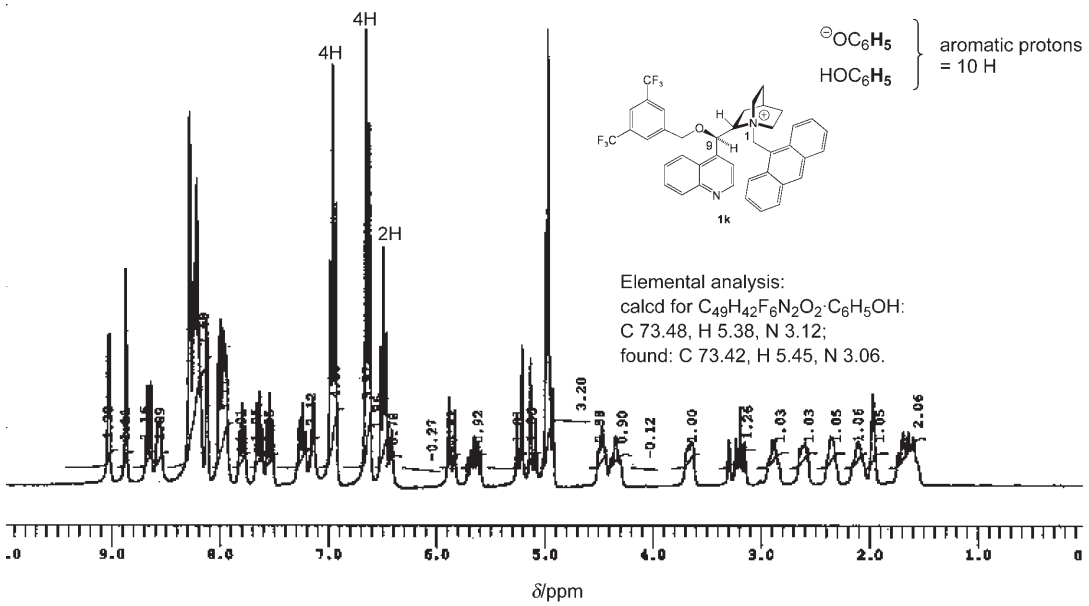


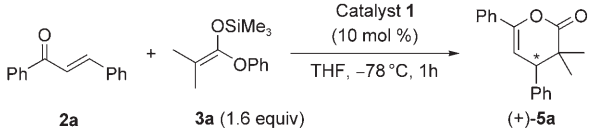
Figure 1. ^{1}H NMR spectrum of **1k** in CD_3OD.

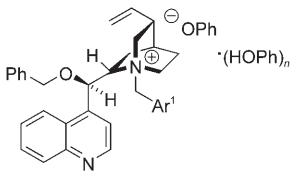
Figure 1, and the signals for the aromatic protons (10H) of both the phenoxide and phenol groups appear at approximately $\delta = 6.5$–7.0 ppm.

Asymmetric Synthesis of 3,4-Dihydropyran-2-ones by *N,O*-Diarylmethylated Cinchonidinium Phenoxide Catalyzed Domino Michael Addition and Lactonization[9]

For initial evaluation of the catalytic efficiency of cinchonidine-derived chiral quaternary ammonium phenoxides, reactions of chalcone **2a** with ketene silyl acetal **3a** derived from phenyl isobutyrate were tried in THF at −78 °C for 1 h in the presence of *N,O*-diarylmethylated cinchonidinium phenoxides **1a–f** (10 mol %), and the effects of the arylmethyl substituents at N1 (Ar^1) were examined (Table 1).

Table 1. Effects of *N*1-arylmethyl substituents (Ar^1) of *N,O*-diarylmethylated cinchonidinium phenoxides.





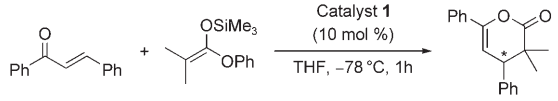
Entry	Catalyst **1** (Ar^1)	Yield [%][a]	*ee* [%][b]
1	**a** (Ph)	96	2
2	**b** (4-$CF_3C_6H_4$)	99	4
3	**c** (3,5-(tBu)$_2C_6H_3$)	96	12
4	**d** (1-naphthyl)	93	16
5	**e** (2-naphthyl)	96	27
6	**f** (9-anthracenyl)	94	78
7[c,d]	**f** (9-anthracenyl)	12	76

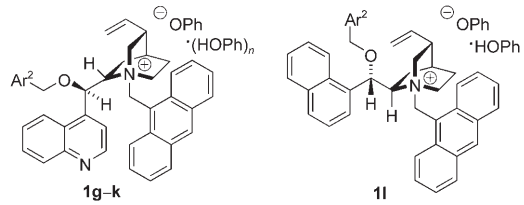
[a] Yield of isolated product. [b] The enantiomeric excess of (+)-**5a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as solvent. [c] Catalyst used: 5 mol %. [d] The reaction was carried out over 6 h.

When the catalyst **1a**, which bears a simple phenyl group, was used, Michael addition and successive lactonization proceeded smoothly to afford the desired 3,4-dihydropyran-2-one (+)-**5a** in 96 % yield, but the enantioselectivity of the product was very poor (only 2 % *ee*) (Table 1, entry 1). The introduction of bulky substituents such as a 3,5-di-*tert*-butylphenyl group (**1c**), a 1-naphthyl group (**1d**), or a 2-naphthyl group (**1e**) as Ar^1 enhanced the enantioselectivity slightly (Table 1, entries 3–5). When catalyst **1f**, which bears a sterically more-hindered 9-anthracenylmethyl group[6,10] at the quinuclidine nitrogen atom, was employed, the enantiomeric excess of (+)-**5a** increased dramatically to up to 78 % (Table 1, entry 6).

To improve the enantioselectivity of this asymmetric domino reaction further, the effects of the 9-*O*-arylmethyl substituents (Ar^2) of *N,O*-diarylmethylated catalysts were examined next (Table 2). The use of catalysts with electron-donating substituents such as a 4-methylphenyl group (**1g**) or a 4-methoxyphenyl group (**1h**) caused a slight decrease in the enantioselectivity of (+)-**5a** (Table 2, entries 1 and 2). On the other hand, catalysts with electron-withdrawing substituents such as a 4-chlorophenyl group (**1i**) or a 4-nitrophenyl group (**1j**) led to a slight increase in the enantioselectivity (Table 2, entries 3 and 4). Further structural modification of Ar^2 by introducing a strongly electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group (**1k**) improved not only the enantioselectivity but also the catalytic activity, and (+)-**5a** was obtained in 98 % yield with 90 % *ee*, even when the amount of the catalyst was decreased to 5 mol % (Table 2, entry 6). It was also found that the opposite enantiomer of the 3,4-dihydropyran-2-one (−)-**5a** was accessible if the pseudoenantiomeric cinchonine-derived catalyst **1l** was used (Table 2, entry 7).

Table 2. Effects of 9-*O*-arylmethyl substituents (Ar^2) of *N,O*-diarylmethylated catalysts.





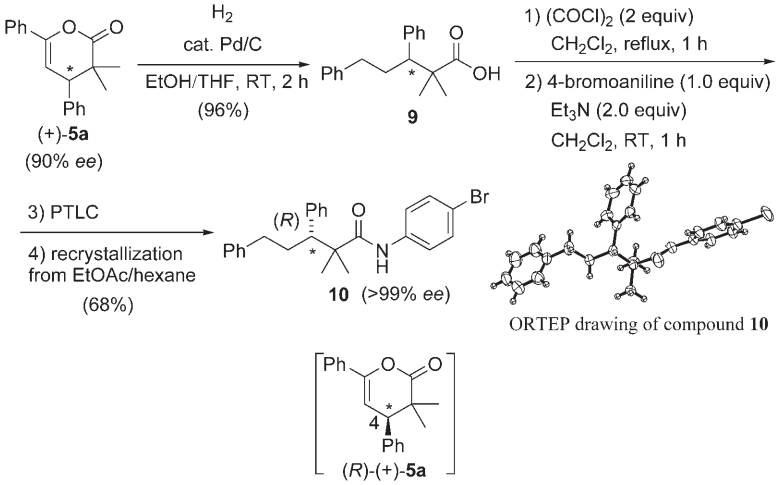
Entry	Catalyst **1** (Ar^2)	Yield [%][a]	*ee* [%][b]
1	**g** (4-MeC_6H_4)	89	77
2	**h** (4-$MeOC_6H_4$)	87	64
3	**i** (4-ClC_6H_4)	95	81
4	**j** (4-$NO_2C_6H_4$)	96	88
5	**k** (3,5-$(CF_3)_2C_6H_3$)	98	89
6[c]	**k** (3,5-$(CF_3)_2C_6H_3$	98	90
7	**l** (3,5-$(CF_3)_2C_6H_3$)	96	85[d]

[a] Yield of isolated product. [b] The enantiomeric excess of (+)-**5a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as solvent. [c] Catalyst used: 5 mol %. [d] The opposite enantiomer (−)-**5a** was obtained.

The absolute configuration of 3,4-dihydropyran-2-one (+)-**5a** was determined to be *R* by X-ray crystallographic analysis after conversion into the corresponding carboxamide **10** as shown in Scheme 3. The reductive ring-opening reaction of (+)-**5a** to carboxylic acid **9** was accomplished by catalytic hydrogenation with Pd/C under hydrogen, followed by amidation of **9** with 4-bromoaniline and recrystallization from EtOAc/hexane to afford carboxamide **10** as a crystalline compound, which was clearly identified by X-ray crystallographic analysis.[11]

The reactions of various α,β-unsaturated ketones **2** with ketene silyl acetal **3a** were tried in THF at −78 °C by using the most efficient cinchonidine-derived catalyst **1k**, which bears both the sterically hindered 9-anthracenylmethyl

CHEMISTRY
AN ASIAN JOURNAL



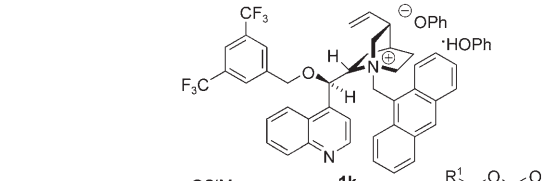
Scheme 3. Conversion of (+)-**5a** into carboxamide **10** and determination of the absolution configuration. ORTEP diagram drawn at the 50% probability level.

group and the strongly electron withdrawing *O*-3,5-bis(trifluoromethyl)benzyl group (Table 3). In most cases, the reactions proceeded smoothly to provide the corresponding 3,4-dihydropyran-2-ones **5** in high yields with high enantiomeric excesses. It was found that various types of α,β-unsaturated ketones with electron-withdrawing or -donating substituents on R^1 or R^2 were successfully employed in this procedure.

Asymmetric Domino Michael Addition and Lactonization by Using Cinchonidine-Derived Chiral Quaternary Ammonium Phenoxides That Bear a Hydroxy Group

To investigate further structural modification of the catalyst, *N*-arylmethylated cinchonidinium phenoxides with a hydroxy group instead of the above-mentioned *N*,*O*-diarylmethylated cinchonidinium phenoxides were also studied. The reactions of chalcone **2a** with ketene silyl acetal **3a** derived from phenyl isobutyrate were carried out in THF at −78 °C in the presence of *N*-arylmethylated cinchonidinium phenoxides **1m–q** (10 mol%), and the effects of the *N*1-arylmethyl substituents (Ar^1) were examined (Table 4). When the cinchonidine-derived catalyst **1m** with a simple benzyl substituent at the quinuclidine nitrogen atom was used, the reaction proceeded smoothly to afford the desired 3,4-dihydropyran-2-one **5a** in 97% yield with 24% *ee* (Table 4, entry 2). Interestingly, the absolute configuration of the product was proved to be *S*, which was the reversal of the case when using *N*,*O*-diarylmethylated cinchonidinium phenoxides such as catalyst **1k** under the same reaction conditions. Structural modification of Ar^1 by introducing bulky and/or electron-withdrawing substituents such as a 9-anthracenyl group (**1n**), a 3,5-bis(trifluoromethyl)phenyl group (**1o**), or a 3,5-di-*tert*-butylphenyl group (**1p**) as Ar^1 enhanced the enantioselectivity (Table 4, entries 3–5). Finally, cinchonidine-derived catalyst **1q**, which bears both a free hydroxy group and a 3,5-bis[3,5-bis(trifluoromethyl)phenyl]-benzyl group, was found to be the most effective, and (*S*)-(−)-**5a** was obtained in 97% yield with 87% *ee*, even when the amount of the catalyst was decreased to 5 mol% (Table 4, entry 7). These observations indicated that a hydroxy function contained in the cinchonidine-derived catalyst plays an important role in controlling the absolute stereochemistry of the newly created stereogenic carbon center in this asymmetric domino reaction. Although the detailed mechanism has not yet been clarified, it is conceivable that hydrogen-bonding interactions between the hydroxy group of the catalyst and the carbonyl group of the substrate is involved in controlling the addition of the nucleophile in the transition state.[12]

Table 3. Reactions of various α,β-unsaturated ketones **2** with ketene silyl acetal **3a** in the presence of cinchonidine-derived catalyst **1k**.



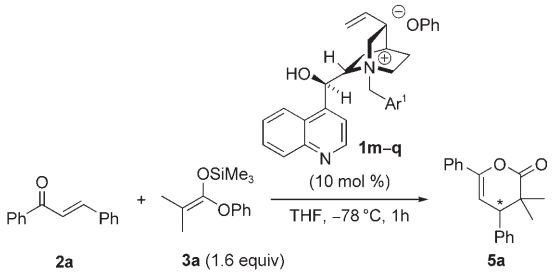
Entry	2	α,β-Unsaturated ketone R^1	R^2	Product	Yield [%][a]	*ee* [%][b]
1	**a**	Ph	Ph	(*R*)-**5a**	98	90
2	**b**	Ph	4-FC_6H_4	**5b**	98	84
3	**c**	4-FC_6H_4	Ph	**5c**	94	82
4	**d**	Ph	4-$MeOC_6H_4$	**5d**	98	96
5	**e**	4-$MeOC_6H_4$	Ph	**5e**	98	95
6	**f**	4-$MeOC_6H_4$	4-BrC_6H_4	**5f**	95	88
7	**g**	4-BrC_6H_4	4-$MeOC_6H_4$	**5g**	98	89
8	**h**	Ph	Me	**5h**	86	95
9	**i**	Ph	*i*Pr	**5i**	98	93

[a] Yield of isolated product. [b] The enantiomeric excess of (+)-**5** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H) with hexane/2-propanol as solvent.

Enantio- and Diastereoselective Synthesis of 3,4-Dihydropyran-2-ones by *N*,*O*-Diarylmethylated Cinchonidinium Phenoxide Catalyzed Domino Michael Addition and Lactonization[13]

The diastereoselectivity of the two newly created adjacent carbon centers was studied in detail to explore the potential of this asymmetric domino reaction further. In the presence of 5 mol% of cinchonidine-derived catalyst **1k**, which bears

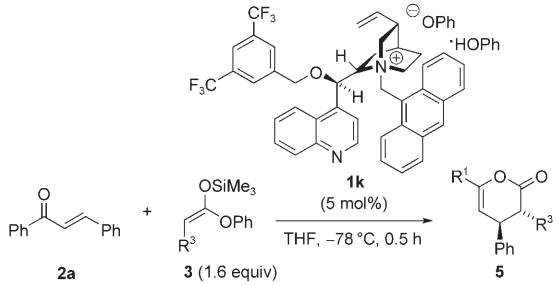
Table 4. Asymmetric domino Michael addition and lactonization by using cinchonidine-derived chiral quaternary ammonium phenoxides that bear a hydroxy group.



Entry	Catalyst **1** (Ar^1)	Yield [%][a]	*ee* [%][b] (config.)
1	**k**	98	90 (*R*)[c]
2	**m** (Ph)	97	24 (*S*)
3	**n** (9-anthracenyl)	32	43 (*S*)
4	**o** (3,5-$(CF_3)_2C_6H_3$)	96	60 (*S*)
5	**p** (3,5-$(t\mathrm{Bu})_2C_6H_3$)	92	83 (*S*)
6	**q** (3,5-(3,5-$(CF_3)_2C_6H_3)_2C_6H_3$)	96	87 (*S*)
7	**q** (3,5-(3,5-$(CF_3)_2C_6H_3)_2C_6H_3$)	97	87 (*S*)[c]

[a] Yield of isolated product. [b] The enantiomeric excess of **5a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as a solvent. [c] Catalyst used: 5 mol%.

Table 5. Reactions of chalcone **2a** with various ketene silyl acetals **3** in the presence of cinchonidine-derived catalyst **1k**.



Entry	**3** (R^3)[a]	Product	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	**b** (Me)	**5j**	91	92:8	25 (75[e])
2	**c** (Et)	**5k**	99	99:1	67
3	**d** (*i*Bu)	**5l**	96	99:1	76
4	**e** (*i*Pr)	**5m**	99	>99:1	96
5[f,g]	**f** (*t*Bu)	**5n**	96	>99:1	96

[a] *E*/*Z* > 95:5. [b] Yield of isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. [d] The enantiomeric excess of the major *trans*-**5** isomer was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol (50:1 *v*/*v*) as solvent. [e] Enantiomeric excess of the minor *cis*-**5j** isomer. [f] Catalyst used: 10 mol%. [g] The reaction was carried out at −78 °C for 0.5 h, and the reaction mixture was then gradually warmed to room temperature.

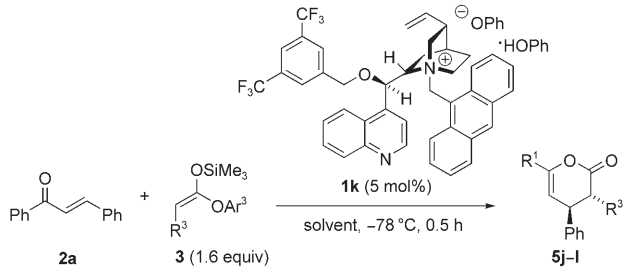
both the *N*1-9-anthracenylmethyl and the 9-*O*-3,5-bis(trifluoromethyl)benzyl groups, reactions of chalcone **2a** with various (*E*)-ketene silyl acetals **3b–f** derived from phenyl carboxylates were tried in THF at −78 °C, and the stereochemical behavior of the alkyl substituents R^3 of the ketene silyl acetals **3** was examined (Table 5). When ketene silyl acetal **3b** (R^3 = Me) derived from phenyl propionate was used, the domino reaction proceeded smoothly to afford the corresponding 3,4-dihydropyran-2-one **5j** in 91% yield with high *trans* selectivity (*trans*/*cis* = 92:8), although the enantioselectivity of the major *trans* isomer turned out to be poor (25% *ee*) (Table 5, entry 1). Structural assignment of the diastereomeric 3,4-dihydropyran-2-ones was based on the ^{1}H NMR chemical shift of the characteristic vinyl proton, which resonated at a lower magnetic field in the *cis* isomer than in the *trans* isomer.[4b] Next, it was observed that the use of ketene silyl acetal **3c** (R^3 = Et) derived from phenyl *n*-butyrate enhanced both diastereo- and enantioselectivity, and the desired product **5k** was obtained quantitatively with excellent *trans* selectivity (*trans*/*cis* = 99:1) and 67% *ee* (*trans* isomer) (Table 5, entry 2). Significantly, the reactions that used sterically more-hindered ketene silyl acetals **3e** (R^3 = *i*Pr) and **3f** (R^3 = *t*Bu) produced the corresponding 3,4-dihydropyran-2-ones **5m** and **5n** in excellent yields with almost complete stereochemical control (*trans*/*cis* > 99:1, 96% *ee*) (Table 5, entries 4 and 5). It was consequently revealed that the alkyl substituents R^3 in the ketene silyl acetals play an important role in controlling both the diastereo- and enantioselectivity of this asymmetric reaction, and therefore stereoselectivity improved as the bulk of R^3 increased.

To improve the stereoselectivity of the above-mentioned reactions further, particularly in the case of ketene silyl acetals with relatively small alkyl substituents R^3, the effects of the aryl substituents Ar^3 in the ketene silyl acetals were also examined (Table 6). Introduction of sterically hindered aryl substituents such as a 1-naphthyl group (**3h**) and a 2-isopropylphenyl group (**3i**) instead of a simple phenyl group (**3c**) enhanced the enantioselectivity, and *trans*-**5k** was obtained in 95% yield with 76% *ee* when ketene silyl acetal **3i** (R^3 = Et, Ar^3 = 2-*i*PrC_6H_4) was used (Table 6, entry 4). Next, the effect of other solvents was examined by taking the reaction of **2a** with ketene silyl acetal **3i**. When the reaction was tried in toluene, the desired product was not obtained owing to the poor solubility of the catalyst (Table 6, entry 5). Among the solvents examined, a mixture of toluene and CH_2Cl_2 (1:1 *v*/*v*) gave the best result, and the enantiomeric excess of *trans*-**5k** increased to up to 84% (Table 6, entry 7). Taking the above results into consideration, it was also noted that the use of ketene silyl acetals **3b** (R^3 = Me, Ar^3 = 2-*i*PrC_6H_4) and **3d** (R^3 = *i*Bu, Ar^3 = 2-*i*PrC_6H_4) improved the stereoselectivity to give the corresponding 3,4-dihydropyran-2-ones **5j** and **5l** with excellent *trans* selectivity and appreciable enantioselectivity (Table 6, entries 9 and 11).

The reactions of ketene silyl acetals **3e** (R^3 = *i*Pr, Ar^3 = Ph) and **3i** (R^3 = Et, Ar^3 = 2-*i*PrC_6H_4) with various α,β-unsaturated ketones **2** were then tried in the presence of cinchonidine-derived catalyst **1k** (5 mol%) in THF or in toluene/CH_2Cl_2 (1:1 *v*/*v*) at −78 °C (Table 7). In most cases, the reactions proceeded smoothly to provide the corresponding 3,4-dihydropyran-2-ones **5** in high yields with almost complete *trans* selectivity and high to excellent enantioselectivity. The relative and absolute configurations at the two newly created adjacent carbon centers of compound **5s** were clearly identified by X-ray crystallographic analysis (Figure 2).[14]

CHEMISTRY
AN ASIAN JOURNAL

Table 6. Effects of aryl substituents Ar^3 in ketene silyl acetals **3**.



Entry	3[a] Ar³	R³	Solvent	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	**c** (Ph)	Et	THF	99	99:1	67
2	**g** (2-naphthyl)		THF	93	98:2	55
3	**h** (1-naphthyl)		THF	84	>99:1	70
4	**i** (2-*i*PrC$_6$H$_4$)		THF	95	>99:1	76
5	**i** (2-*i*PrC$_6$H$_4$)		toluene	trace	–	–
6	**i** (2-*i*PrC$_6$H$_4$)		CH_2Cl_2	95	98:2	77
7	**i** (2-*i*PrC$_6$H$_4$)		toluene/CH_2Cl_2[e]	99	>99:1	84
8	**b** (Ph)	Me	THF	91	92:8	25
9	**j** (2-*i*PrC$_6$H$_4$)		toluene/CH_2Cl_2[e]	93	98:2	57
10	**d** (Ph)	*i*Bu	THF	96	99:1	76
11	**k** (2-*i*PrC$_6$H$_4$)		toluene/CH_2Cl_2[e]	99	>99:1	88

[a] *E*/*Z* > 95:5. [b] Yield of isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. [d] The enantiomeric excess of the major *trans*-**5** isomer was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane/2-propanol (50:1 *v*/*v*) as solvent. [e] 1:1 *v*/*v*.

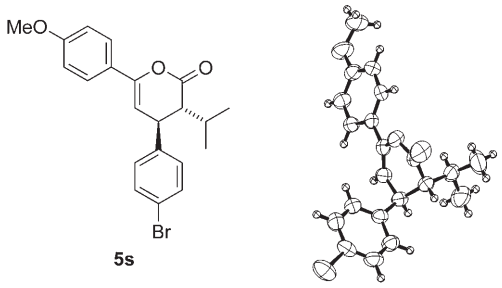
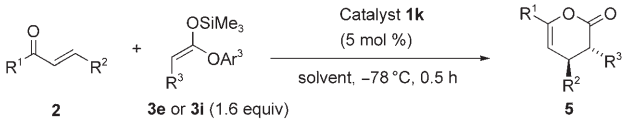


Figure 2. ORTER drawing of compound **5s** (ellipsoids drawn at the 50% probability level).

Table 7. Enantio- and diastereoselective synthesis of 3,4-dihydropyran-2-ones by using cinchonidine-derived catalyst **1k**.



Entry	R^1	R^2	R^3	Solvent	Product	Yield [%][a] (*trans*/*cis*)[b]	*ee* [%][c]
1	Ph	4-FC$_6$H$_4$	*i*Pr (**3e**)	THF	**5o**	98 (>99:1)	95
2	4-FC$_6$H$_4$	Ph			**5p**	92 (>99:1)	94
3	Ph	4-MeOC$_6$H$_4$			**5q**	93 (>99:1)	94
4	4-MeOC$_6$H$_4$	Ph			**5r**	94 (>99:1)	97
5	4-MeOC$_6$H$_4$	4-BrC6H4			**5s**	98 (>99:1)	95
6	4-BrC$_6$H$_4$	4-MeOC$_6$H$_4$			**5t**	94 (>99:1)	92
7	Ph	4-MeOC$_6$H$_4$	Et (**3i**)	toluene/CH_2Cl_2[d]	**5u**	95 (>99:1)	85
8	4-MeOC$_6$H$_4$	Ph			**5v**	97 (>99:1)	87
9	PhCH=CH$_2$	Ph			**5w**	87 (97:3)	86

[a] Yield of isolated product. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. [c] The enantiomeric excess of the major *trans*-**5** isomer was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H or Chiralcel OD-H) with hexane/2-propanol as solvent. [d] 1:1 *v*/*v*.

Conclusions

An efficient method for the synthesis of optically active 3,4-dihydropyran-2-one derivatives was established through asymmetric domino Michael addition and lactonization between various ketene silyl acetals derived from phenyl carboxylates and α,β-unsaturated ketones in the presence of a catalytic amount of cinchona-alkaloid-derived chiral quaternary ammonium phenoxides, novel types of air-stable and storable organocatalysts. Furthermore, unique relationships between the structure of the catalyst and the absolute stereochemistry in this asymmetric domino reaction were described. Further studies on the use of chiral quaternary ammonium phenoxides in other catalytic asymmetric reactions, particularly by using various organosilicon reagents, are now in progress.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and were not corrected. IR spectra were recorded on a SensIR Technologies Travel*IR*™ Portable FTIR spectrometer (attenuated total reflection). ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 L (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard. The optical rotations were measured with a JASCO P-1020 polarimeter. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer. Elemental analysis was performed on a Yanagimoto CHN CORDER MT-6. X-ray crystallographic analysis was undertaken on a Rigaku AFC7R diffractometer with graphite monochromated $Cu_{K\alpha}$ radiation. Analytical high-performance liquid

chromatography (HPLC) was performed on a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. The enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H, $\phi = 4.6 \times 250$ mm) with hexane/2-propanol as solvent. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Column chromatography was conducted on Merck silica gel 60 and preparative thin-layer chromatography (PTLC) was carried out on Wakogel B-5F. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise noted. Dehydrated solvents were purchased from Kanto Chemical. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Kokusan Chemical, Wako Pure Chemical Industries, or Aldrich. Amberlyst A-26 (OH^-) was purchased from Aldrich and used without further purification. Cinchonidine and cinchonine were purchased from Tokyo Kasei Kogyo or Wako Pure Chemical Industries and used after purification by silica-gel column chromatography with MeOH/EtOAc (1:1 *v*/*v*) as solvent to remove impurities, 10,11-dihydro-derivatives. α,β-Unsaturated ketones (**2f**,**g**, and **i**) were prepared according to reported procedures.[15] All ketene silyl acetals **3** were prepared from the corresponding phenyl carboxylates by known methods.[16]

Typical procedure for the preparation of cinchonidine-derived chiral quaternary ammonium phenoxide **1** (Scheme 2 and Table 2, entry 6): Ion-exchange resin Amberlyst A-26 (OH^-) (1.0 g) was added to a stirred solution of *N*-(9-anthracenylmethyl)-*O*-[3,5-bis(trifluoromethyl)benzyl]cinchonidinium bromide[17] (1.0 g, 1.26 mmol) in methanol (10 mL) at room temperature. The mixture was stirred for 10 h at the same temperature, filtered, and washed with methanol. Phenol (119 mg, 1.26 mmol) was added to the filtrate, and the resulting mixture was co-evaporated three times with benzene. Crystallization of the residue from diethyl ether afforded a pale-yellow solid, which was collected by filtration and dried under reduced pressure to form cinchonidine-derived chiral quaternary ammonium salt **1k** (Ar^1 = 9-anthracenyl, R^5 = 3,5-bis(trifluoromethyl)benzyl) as a quaternary ammonium phenoxide–phenol complex[8] (0.49 g, 43% yield). The yield of **1k** increased to 89% when phenol (237 mg, 2.52 mmol, 2 equiv) was used in the above-mentioned procedure. This reagent can be handled in air and stored in a sealed bottle without decomposition for at least one month at room temperature. Pale-yellow powder; $[\alpha]_D^{29} = -97.2°$ ($c = 1.00$ in $CHCl_3$); m.p. 117 °C (decomp.); IR (ATR): $\tilde{\nu} = 1592$, 1491, 1476, 1347, 1276, 1170, 1132 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.02$ (d, $J = 4.3$ Hz, 1H), 8.88 (s, 1H), 8.64 (d, $J = 9.2$ Hz, 1H), 8.56–8.51 (m, 1H), 8.31–7.89 (m, 10H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.24 (t, $J = 7.6$ Hz, 1H), 7.15 (br s, 1H), 7.00 (t, $J = 7.3$ Hz, 4H), 6.65 (d, $J = 7.3$ Hz, 4H), 6.54 (t, $J = 7.3$ Hz, 2H), 6.45 (d, $J = 13.8$ Hz, 1H), 5.85 (d, $J = 13.8$ Hz, 1H), 5.73–5.59 (m, 1H), 5.24 (d, $J = 12.4$ Hz, 1H), 5.12 (d, $J = 12.4$ Hz, 1H), 5.01–4.90 (m, 2H), 4.50–4.29 (m, 2H), 3.71–3.60 (m, 1H), 3.21 (t, $J = 11.6$ Hz, 1H), 2.98–2.84 (m, 1H), 2.70–2.59 (m, 1H), 2.44–2.36 (m, 1H), 2.20–2.08 (m, 1H), 2.00–1.97 (m, 1H), 1.79–1.58 ppm (m, 2H); ^{13}C NMR (CD_3OD): $\delta = 162.8$, 151.0, 149.2, 142.2, 141.5, 138.1, 134.6, 134.3, 134.0, 133.4, 132.9, 132.9, 132.5, 131.5, 131.3, 131.1, 130.6, 130.0, 129.4, 129.4, 129.2, 129.1, 128.7, 126.8, 126.6, 126.6, 126.2, 126.0, 124.9, 124.3, 123.9, 123.2, 123.2, 123.1, 122.6, 121.8, 118.6, 118.5, 117.9, 117.8, 117.6, 116.6 (135–115: multiple peaks), 71.1, 70.4, 63.4, 57.6, 53.8, 39.4, 27.3, 26.2, 23.1 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{43}H_{37}F_6N_2O]^+$: 711.2810; found: 711.2802; elemental analysis: calcd for $C_{49}H_{42}F_6N_2O_2 \cdot C_6H_5OH$: C 73.48, H 5.38, N 3.12; found: C 73.42, H 5.45, N 3.06.

1a (Ar^1 = Ph, Ar^2 = Ph): Pale-yellow powder; $[\alpha]_D^{20} = -109°$ ($c = 1.00$ in $CHCl_3$); m.p. 144 °C (decomp.); IR (ATR): $\tilde{\nu} = 1592$, 1492, 1476, 1457, 1309, 1214, 1067 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.01$ (d, $J = 4.3$ Hz, 1H), 8.27–8.16 (m, 2H), 7.96–7.79 (m, 3H), 7.61–7.37 (m, 10H), 7.02 (t, $J = 7.3$ Hz, 2H), 6.67 (d, $J = 7.3$ Hz, 2H), 6.57 (t, $J = 7.3$ Hz, 1H), 6.43 (s, 1H), 5.70–5.57 (m, 1H), 5.11–4.92 (m, 2H), 4.84 (d, $J = 11.3$ Hz, 1H), 4.74 (d, $J = 12.4$ Hz, 1H), 4.62 (d, $J = 12.4$ Hz, 1H), 4.60 (d, $J = 11.3$ Hz, 1H), 4.16–4.03 (m, 1H), 3.97–3.88 (m, 1H), 3.55–3.21 (m, 3H), 2.69–2.56 (m, 1H), 2.47–2.37 (m, 1H), 2.22–2.09 (m, 1H), 2.08–2.00 (m, 1H), 1.88–1.74 (m, 1H), 1.60–1.48 ppm (m, 1H); ^{13}C NMR (CD_3OD): $\delta = 162.7$, 150.9, 149.1, 142.8, 138.3, 137.5, 134.6, 131.7, 131.3, 130.5, 130.2, 130.1, 130.0, 129.9, 129.3, 129.2, 128.1, 126.8, 123.7, 121.6, 117.8, 117.7, 117.5, 73.0, 72.3, 69.5, 65.3, 62.0, 52.6, 38.9, 28.0, 25.8, 22.8 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{33}H_{35}N_2O]^+$: 475.2749; found: 475.2760.

1b (Ar^1 = 4-$CF_3C_6H_4$, Ar^2 = Ph): Catalyst **1b** was obtained as a quaternary ammonium phenoxide-phenol complex. Pale-yellow powder; $[\alpha]_D^{20} = -103°$ ($c = 1.00$ in $CHCl_3$); m.p. 129 °C (decomp.); IR (ATR): $\tilde{\nu} = 1587$, 1465, 1325, 1233, 1167, 1131, 1116, 1067 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.01$ (d, $J = 4.6$ Hz, 1H), 8.26–8.15 (m, 2H), 8.01–7.79 (m, 5H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.60–7.37 (m, 5H), 7.04 (t, $J = 7.3$ Hz, 4H), 6.68 (d, $J = 7.3$ Hz, 4H), 6.60 (t, $J = 7.3$ Hz, 2H), 6.42 (s, 1H), 5.70–5.57 (m, 1H), 5.11–4.92 (m, 2H), 4.85 (d, $J = 11.3$ Hz, 1H), 4.81 (d, $J = 12.2$ Hz, 1H), 4.66 (d, $J = 12.2$ Hz, 1H), 4.62 (d, $J = 11.3$ Hz, 1H), 4.20–4.04 (m, 1H), 3.99–3.88 (m, 1H), 3.57–3.20 (m, 3H), 2.70–2.57 (m, 1H), 2.51–2.38 (m, 1H), 2.22–2.09 (m, 1H), 2.08–2.01 (m, 1H), 1.89–1.74 (m, 1H), 1.61–1.48 ppm (m, 1H); ^{13}C NMR (CD_3OD): $\delta = 162.2$, 151.0, 149.1, 142.6, 138.2, 137.5, 135.5, 134.1, 133.7, 133.2, 132.7, 132.4, 132.4, 131.4, 131.1, 130.6, 130.2, 130.1, 130.0, 129.9, 129.3, 129.2, 127.1, 126.8, 123.6, 123.1, 118.0, 117.7 (135–115: multiple peaks), 73.0, 72.3, 69.8, 64.3, 62.1, 52.9, 38.8, 27.8, 25.7, 22.8 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{34}H_{34}F_3N_2O]^+$: 543.2623; found: 543.2641.

1c (Ar^1 = 3,5-(tBu)$_2C_6H_3$, Ar^2 = Ph): Pale-yellow powder; $[\alpha]_D^{21} = -80.1°$ ($c = 1.00$ in $CHCl_3$); m.p. 89 °C (decomp.); IR (ATR): $\tilde{\nu} = 2955$, 1739, 1587, 1464, 1365, 1230, 1216 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.01$ (d, $J = 4.3$ Hz, 1H), 8.24–8.16 (m, 2H), 7.98–7.82 (m, 3H), 7.65–7.28 (m, 8H), 7.02 (t, $J = 7.3$ Hz, 2H), 6.67 (d, $J = 7.3$ Hz, 2H), 6.56 (t, $J = 7.3$ Hz, 1H), 6.42 (s, 1H), 5.71–5.53 (m, 1H), 5.10–4.84 (m, 3H), 5.10–4.84 (m, 3H), 4.72–4.49 (m, 3H), 4.18–3.99 (m, 1H), 3.97–3.79 (m, 1H), 3.50–3.21 (m, 3H), 2.72–2.57 (m, 1H), 2.50–2.36 (m, 1H), 2.24–1.99 (m, 2H), 1.91–1.74 (m, 1H), 1.61–1.47 (m, 1H), 1.38 ppm (s, 18H); ^{13}C NMR (CD_3OD): $\delta = 161.6$, 153.2, 151.0, 149.1, 142.7, 138.4, 137.5, 131.4, 130.6, 130.3, 130.1, 130.0, 129.3, 128.9, 127.3, 126.8, 125.8, 123.6, 121.6, 118.3, 117.5, 117.4, 73.1, 72.4, 69.6, 66.0, 61.9, 52.5, 38.9, 35.9, 31.8, 27.9, 25.8, 22.9 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{41}H_{51}N_2O]^+$: 587.4001; found: 587.4001.

1d: (Ar^1 = 1-naphthyl, Ar^2 = Ph): Pale-yellow powder; $[\alpha]_D^{21} = -156°$ ($c = 1.00$ in $CHCl_3$); m.p. 114 °C (decomp.); IR (ATR): $\tilde{\nu} = 1590$, 1467, 1234, 1067, 1024 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.03$ (d, $J = 4.6$ Hz, 1H), 8.46–8.37 (m, 1H), 8.21–8.17 (m, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.06–7.97 (m, 3H), 7.96–7.31 (m, 3H), 7.69–7.42 (m, 8H), 7.03 (t, $J = 7.3$ Hz, 2H), 6.73 (s, 1H), 6.68 (d, $J = 7.3$ Hz, 2H), 6.59 (t, $J = 7.3$ Hz, 1H), 5.72–5.59 (m, 1H), 5.48 (d, $J = 13.0$ Hz, 1H), 5.28 (d, $J = 13.0$ Hz, 1H), 5.10–4.89 (m, 3H), 4.77 (d, $J = 11.1$ Hz, 1H), 4.30–4.17 (m, 2H), 3.77–3.65 (m, 1H), 3.41 (t, $J = 12.4$ Hz, 1H), 3.18–3.05 (m, 1H), 2.60–2.41 (m, 2H), 2.20–2.09 (m, 1H), 2.08–1.97 (m, 1H), 1.75–1.49 ppm (m, 2H); ^{13}C NMR (CD_3OD): $\delta = 161.9$, 150.9, 149.1, 142.7, 138.3, 137.8, 135.6, 134.4, 133.1, 131.4, 130.5, 130.1, 130.0, 129.8, 129.7, 129.4, 129.2, 128.8, 127.4, 126.8, 126.2, 124.2, 124.0, 121.6, 118.2, 117.6, 117.5, 74.1, 72.5, 69.7, 62.5, 61.8, 53.4, 39.1, 27.6, 25.9, 23.1 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{37}H_{37}N_2O]^+$: 525.2906; found: 525.2907.

1e (Ar^1 = 2-naphthyl, Ar^2 = Ph): Pale-yellow powder; $[\alpha]_D^{22} = -113°$ ($c = 1.00$ in $CHCl_3$); m.p. 115 °C (decomp.); IR (ATR): $\tilde{\nu} = 1590$, 1456, 1067, 1023 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.02$ (d, $J = 4.6$ Hz, 1H), 8.25–8.17 (m, 2H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.06–7.77 (m, 7H), 7.68–7.40 (m, 8H), 7.03 (t, $J = 7.3$ Hz, 2H), 6.67 (d, $J = 7.3$ Hz, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.49 (s, 1H), 5.73–5.59 (m, 1H), 5.08 (d, $J = 17.0$ Hz, 1H), 4.99 (d, $J = 10.5$ Hz, 1H), 4.93–4.85 (m, 2H), 4.77 (d, $J = 12.4$ Hz, 1H), 4.64 (d, $J = 11.3$ Hz, 1H), 4.24–4.12 (m, 1H), 4.04–3.92 (m, 1H), 3.61–3.27 (m, 3H), 2.69–2.57 (m, 1H), 2.52–2.39 (m, 1H), 2.25–2.12 (m, 1H), 2.10–2.02 (m, 1H), 1.86–1.74 (m, 1H), 1.63–1.51 ppm (m, 1H); ^{13}C NMR (CD_3OD): $\delta = 162.4$, 151.0, 149.1, 142.9, 138.4, 137.6, 135.2, 135.2, 134.3, 131.3, 130.6, 130.4, 130.3, 130.2, 130.0, 129.3, 129.2, 128.9, 128.7, 128.2, 126.8, 125.3, 123.6, 121.6, 117.9, 117.7, 117.5, 72.4, 69.5, 65.5, 62.2, 52.8, 38.9, 28.0, 25.8, 22.8 ppm; HRMS (ESI^+): *m*/*z* calcd for $[C_{37}H_{37}N_2O]^+$: 525.2906; found: 525.2910.

1f (Ar^1 = 9-anthracenyl, Ar^2 = Ph): Pale-yellow powder; $[\alpha]_D^{22} = -136°$ ($c = 1.00$ in $CHCl_3$); m.p. 94 °C (decomp.); IR (ATR): $\tilde{\nu} = 1591$, 1477, 1453, 1143, 1067, 1025 cm^{-1}; ^1H NMR (CD_3OD): $\delta = 9.06$ (d, $J = 4.6$ Hz, 1H), 8.85 (s, 1H), 8.67 (d, $J = 8.9$ Hz, 1H), 8.63–8.55 (m, 1H), 8.26–8.17 (m, 3H), 8.10–8.03 (m, 2H), 8.00–7.89 (m, 2H), 7.81–7.47 (m, 8H), 7.38–7.31 (m, 1H), 7.05–6.98 (m, 3H), 6.66 (d, $J = 7.3$ Hz, 2H), 6.56 (t, $J =$

7.3 Hz, 1H), 6.25 (d, J=13.8 Hz, 1H), 5.84 (d, J=13.8 Hz, 1H), 5.71–5.58 (m, 1H), 5.03–4.90 (m, 4H), 4.51–4.31 (m, 2H), 3.73–3.62 (m, 1H), 3.13 (t, J=10.8 Hz, 1H), 2.89–2.77 (m, 1H), 2.59–2.47 (m, 1H), 2.41–2.31 (m, 1H), 2.18–2.03 (m, 1H), 1.96–1.90 (m, 1H), 1.69–1.46 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=162.6, 150.9, 149.2, 142.7, 138.3, 138.0, 134.6, 134.3, 133.8, 132.9, 132.8, 131.5, 131.1, 131.1, 130.6, 130.2, 130.0, 129.7, 129.3, 129.2, 129.1, 127.0, 126.5, 126.3, 125.0, 124.6, 121.8, 118.6, 117.8, 117.8, 117.7, 72.6, 70.3, 63.3, 57.5, 53.8, 39.5, 27.3, 26.2, 23.3 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{41}H_{39}N_2O]^+$: 575.3062; found: 575.3062.

1g (Ar^1=9-anthracenyl, Ar^2=4-MeC_6H_4): Pale-yellow powder; $[\alpha]_D^{22}$=−121° (c=1.00 in $CHCl_3$); m.p. 97°C (decomp.); IR (ATR): $\tilde{\nu}$=1589, 1476, 1452, 1138, 1067 cm^{-1}; ^{1}H NMR (CD_3OD): δ=9.06 (d, J=4.6 Hz, 1H), 8.85 (s, 1H), 8.66 (d, J=8.9 Hz, 1H), 8.62–8.54 (m, 1H), 8.25–8.17 (m, 3H), 8.07–8.02 (m, 2H), 7.99–7.89 (m, 2H), 7.82–7.74 (m, 1H), 7.68–7.54 (m, 4H), 7.45–7.36 (m, 3H), 7.04–6.97 (m, 3H), 6.65 (d, J=7.3 Hz, 2H), 6.54 (t, J=7.3 Hz, 1H), 6.19 (d, J=13.8 Hz, 1H), 5.83 (d, J=13.8 Hz, 1H), 5.70–5.57 (m, 1H), 4.99–4.90 (m, 3H), 4.84 (d, J=11.3 Hz, 1H), 4.49–4.29 (m, 2H), 3.70–3.59 (m, 1H), 3.09 (t, J=10.8 Hz, 1H), 2.89–2.76 (m, 1H), 2.57–2.44 (m, 1H), 2.42 (s, 3H), 2.40–2.25 (m, 1H), 2.17–2.02 (m, 1H), 1.95–1.88 (m, 1H), 1.65–1.43 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=162.8, 150.9, 149.2, 142.8, 139.8, 138.3, 134.9, 134.6, 134.2, 133.8, 132.9, 132.8, 131.4, 131.1, 131.1, 130.8, 130.6, 130.0, 129.5, 129.3, 129.3, 129.0, 127.0, 126.5, 126.4, 125.0, 124.6, 124.1, 121.8, 118.6, 117.9, 117.7, 117.6, 72.4, 70.4, 63.2, 57.6, 53.9, 39.4, 27.3, 26.2, 23.2, 21.4 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{42}H_{41}N_2O]^+$: 589.3219; found: 589.3230.

1h (Ar^1=9-anthracenyl, Ar^2=4-MeOC_6H_4): Pale-yellow powder; $[\alpha]_D^{22}$=−134° (c=1.00 in $CHCl_3$); m.p. 92°C (decomp.); IR (ATR): $\tilde{\nu}$=1611, 1586, 1512, 1464, 1302, 1249, 1066, 1028 cm^{-1}; ^{1}H NMR (CD_3OD): δ=9.06 (d, J=4.9 Hz, 1H), 8.86 (s, 1H), 8.63 (d, J=8.9 Hz, 1H), 8.62–8.53 (m, 1H), 8.27–8.18 (m, 3H), 8.08–8.01 (m, 2H), 8.00–7.89 (m, 2H), 7.82–7.74 (m, 1H), 7.66–7.48 (m, 5H), 7.11 (d, J=8.4 Hz, 1H), 7.04–6.96 (m, 3H), 6.65 (d, J=7.3 Hz, 2H), 6.52 (t, J=7.3 Hz, 1H), 6.17 (d, J=13.8 Hz, 1H), 5.82 (d, J=13.8 Hz, 1H), 5.69–5.56 (m, 1H), 4.98–4.86 (m, 3H), 4.78 (d, J=11.3 Hz, 1H), 4.47–4.26 (m, 2H), 3.83 (s, 3H), 3.66–3.55 (m, 1H), 3.07 (t, J=10.8 Hz, 1H), 2.90–2.78 (m, 1H), 2.59–2.45 (m, 1H), 2.39–2.25 (m, 1H), 2.17–2.04 (m, 1H), 1.94–1.87 (m, 1H), 1.68–1.46 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=163.1, 161.4, 150.9, 149.2, 142.9, 142.5, 138.2, 134.6, 134.2, 133.8, 132.8, 131.4, 131.1, 131.1, 130.7, 130.6, 129.9, 129.8, 129.3, 129.1, 127.0, 126.5, 126.4, 125.0, 124.6, 124.0, 121.9, 118.6, 118.0, 117.7, 117.4, 115.5, 114.7, 72.2, 70.5, 63.0, 57.6, 55.8, 54.0, 39.4, 27.3, 26.1, 23.1 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{42}H_{41}N_2O_2]^+$: 605.3168; found: 605.3176.

1i (Ar^1=9-anthracenyl, Ar^2=4-ClC_6H_4): Pale-yellow powder; $[\alpha]_D^{22}$=−108° (c=1.00 in $CHCl_3$); m.p. 103°C (decomp.); IR (ATR): $\tilde{\nu}$=1590, 1492, 1478, 1452, 1065 cm^{-1}; ^{1}H NMR (CD_3OD): δ=9.06 (d, J=4.1 Hz, 1H), 8.86 (s, 1H), 8.68 (d, J=8.9 Hz, 1H), 8.62–8.54 (m, 1H), 8.26–8.18 (m, 3H), 8.09 (d, J=8.9 Hz, 1H), 8.03 (d, J=4.6 Hz, 1H), 8.00–7.89 (m, 2H), 7.82–7.54 (m, 7H), 7.43–7.37 (m, 1H), 7.07–6.95 (m, 3H), 6.65 (d, J=7.3 Hz, 2H), 6.53 (t, J=7.3 Hz, 1H), 6.29 (d, J=13.8 Hz, 1H), 5.85 (d, J=13.8 Hz, 1H), 5.71–5.57 (m, 1H), 4.99–4.89 (m, 4H), 4.51–4.26 (m, 2H), 3.72–3.62 (m, 1H), 3.13 (t, J=11.9 Hz, 1H), 2.90–2.77 (m, 1H), 2.59–2.47 (m, 1H), 2.41–2.29 (m, 1H), 2.18–2.02 (m, 1H), 1.95–1.89 (m, 1H), 1.68–1.45 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=162.9, 150.9, 149.2, 142.6, 138.2, 136.8, 135.4, 134.6, 134.3, 133.8, 132.9, 132.8, 131.5, 131.2, 131.1, 130.8, 130.6, 130.2, 130.0, 129.4, 129.0, 127.0, 126.5, 126.4, 125.0, 124.4, 124.1, 121.7, 118.6, 117.9, 117.7, 117.6, 71.8, 70.3, 63.3, 57.5, 53.8, 39.4, 27.3, 26.2, 23.2 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{41}H_{38}ClN_2O]^+$: 609.2673; found: 609.2679.

1j (Ar^1=9-anthracenyl, Ar^2=4-$NO_2C_6H_4$): Catalyst **1j** was obtained as a quaternary ammonium phenoxide-phenol complex. Pale-yellow powder; $[\alpha]_D^{19}$=−99.2° (c=1.00 in $CHCl_3$); m.p. 99°C (decomp.); IR (ATR): $\tilde{\nu}$=1591, 1520, 1473, 1344, 1257, 1067 cm^{-1}; ^{1}H NMR (CD_3OD): δ=9.05 (d, J=4.6 Hz, 1H), 8.86 (s, 1H), 8.67 (d, J=8.9 Hz, 1H), 8.61–8.54 (m, 1H), 8.43 (d, J=8.6 Hz, 2H), 8.28–8.13 (m, 4H), 8.09–7.90 (m, 5H), 7.83–7.76 (m, 1H), 7.66–7.59 (m, 1H), 7.58–7.51 (m, 1H), 7.34–7.26 (m, 1H), 7.12 (br s, 1H), 7.00 (t, J=7.3 Hz, 4H), 6.65 (d, J=7.3 Hz, 4H), 6.54 (t, J=7.3 Hz, 2H), 6.38 (d, J=14.0 Hz, 1H), 5.85 (d, J=14.0 Hz, 1H), 5.73–5.59 (m, 1H), 5.18 (d, J=12.7 Hz, 1H), 5.04 (d, J=12.7 Hz, 1H), 5.02–4.95 (m, 2H), 4.53–4.41 (m, 1H), 4.40–4.29 (m, 1H), 3.76–3.63 (m, 1H), 3.20 (t, J=10.8 Hz, 1H), 2.93–2.78 (m, 1H), 2.64–2.54 (m, 1H), 2.43–2.34 (m, 1H), 2.21–2.04 (m, 1H), 2.01–1.95 (m, 1H), 1.73–1.52 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=162.6, 151.0, 149.3, 149.2, 145.4, 142.3, 138.2, 134.6, 134.3, 133.9, 132.9, 132.8, 131.5, 131.2, 131.1, 131.0, 130.7, 130.0, 129.5, 129.4, 129.2, 128.9, 126.9, 126.6, 126.5, 126.4, 125.1, 124.9, 124.3, 124.0, 121.5, 118.6, 117.8, 117.8, 71.3, 70.3, 63.5, 57.5, 53.8, 39.4, 27.3, 26.3, 23.2 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{41}H_{38}N_3O_3]^+$: 620.2913; found: 620.2920.

1l (Ar^1=9-anthracenyl, Ar^2=3,5-$(CF_3)_2C_6H_3$): Catalyst **1l** was obtained as a quaternary ammonium phenoxide-phenol complex. Pale-yellow powder; $[\alpha]_D^{20}$=+85.2° (c=1.00 in $CHCl_3$); m.p. 103°C (decomp.); IR (ATR): $\tilde{\nu}$=1592, 1466, 1363, 1277, 1175, 1130 cm^{-1}; ^{1}H NMR (CD_3OD): δ=9.05 (d, J=4.9 Hz, 1H), 8.87 (s, 1H), 8.78 (d, J=8.9 Hz, 1H), 8.66–8.56 (m, 1H), 8.33 (s, 2H), 8.28–8.17 (m, 4H), 8.07 (d, J=4.6 Hz, 1H), 7.99 (dd, J=6.5, 3.2 Hz, 2H), 7.89–7.81 (m, 2H), 7.65 (t, J=6.8 Hz, 1H), 7.47 (t, J=6.8 Hz, 1H), 7.10 (br s, 1H), 7.01 (t, J=7.3 Hz, 4H), 6.83 (t, J=7.6 Hz, 1H), 6.66 (d, J=7.3 Hz, 4H), 6.56 (t, J=7.3 Hz, 2H), 6.16–5.94 (m, 3H), 5.21–4.92 (m, 4H), 4.53–4.41 (m, 1H), 4.25–4.10 (m, 2H), 3.19 (t, J=11.3 Hz, 1H), 2.86–2.69 (m, 2H), 2.34–2.21 (m, 1H), 1.95–1.73 (m, 2H), 1.71–1.58 (m, 1H), 1.42–1.29 ppm (m, 1H); ^{13}C NMR (CD_3OD): δ=162.8, 151.0, 149.3, 141.6, 141.4, 137.0, 134.5, 134.3, 134.1, 133.9, 133.6, 133.1, 133.0, 132.8, 132.6, 131.5, 131.4, 131.0, 130.5, 130.0, 129.4, 129.3, 129.2, 128.9, 128.4, 126.8, 126.6, 126.1, 125.1, 124.2, 124.0, 123.3, 122.7, 121.5, 118.5, 118.0, 117.9, 117.6 (135–115: multiple peaks), 76.2, 70.8, 69.0, 59.1, 57.5, 56.6, 38.8, 27.2, 24.7, 23.4 ppm; HRMS (ESI$^+$): m/z calcd for $[C_{43}H_{37}F_6N_2O]^+$: 711.2810; found: 711.2807.

1m (R^5=H, Ar^1=Ph): Pale-yellow powder; $[\alpha]_D^{20}$=−92.1° (c=1.00 in $CHCl_3$); m.p. 118°C (decomp.); IR (ATR): $\tilde{\nu}$=3047, 1585, 1469, 1257, 1161 cm^{-1}; ^{1}H NMR (CD_3OD): δ=8.79 (d, J=4.6 Hz, 1H), 8.11 (d, J=7.8 Hz, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.84 (d, J=4.6 Hz, 1H), 7.78–7.61 (m, 2H), 7.60–7.50 (m, 2H), 7.49–7.38 (m, 3H), 6.87 (t, J=7.3 Hz, 2H), 6.60–6.46 (m, 3H), 6.41 (t, J=7.3 Hz, 1H), 5.62–5.41 (m, 1H), 5.12–4.71 (m, 5H), 4.43–4.23 (m, 1H), 3.92–3.74 (m, 1H), 3.58–3.42 (m, 1H), 3.41–3.11 (m, 2H), 2.62–2.45 (m, 1H), 2.21–1.99 (m, 2H), 1.96–1.83 (m, 1H), 1.78–1.59 (m, 1H), 1.32–1.15 ppm (m, 1H); ^{13}C NMR (CD_3OD): δ=163.3, 150.8, 148.5, 147.7, 138.5, 134.7, 131.5, 130.9, 130.2, 130.0, 129.1, 128.8, 128.5, 125.9, 123.9, 121.3, 118.2, 117.3, 117.3, 69.7, 66.1, 65.1, 61.9, 52.5, 39.0, 28.0, 25.9, 22.5; HRMS (FAB$^+$): m/z calcd for $[C_{26}H_{29}N_2O]^+$: 385.2280; found: 385.2272.

1n (R^5=H, Ar^1=9-anthracenyl): Pale-yellow powder; $[\alpha]_D^{20}$=−324° (c=1.00 in $CHCl_3$); m.p. 120°C (decomp.); IR (ATR): $\tilde{\nu}$=3047, 1584, 1492, 1467, 1253, 1159 cm^{-1}; ^{1}H NMR (CD_3OD): δ=8.90 (d, J=4.9 Hz, 1H), 8.78–8.66 (m, 2H), 8.62–8.48 (m, 2H), 8.20–8.05 (m, 3H), 8.03 (d, J=4.9 Hz, 1H), 7.92–7.64 (m, 4H), 7.63–7.50 (m, 2H), 7.01 (br s, 1H), 6.88 (t, J=8.1 Hz, 2H), 6.62 (d, J=8.1 Hz, 2H), 6.46–6.30 (m, 2H), 5.78 (d, J=13.8 Hz, 1H), 5.66–5.53 (m, 1H), 5.00–4.83 (m, 3H), 4.78–4.61 (m, 1H), 4.42–4.32 (m, 1H), 3.80–3.68 (m, 1H), 3.08 (t, J=11.6 Hz, 1H), 2.78–2.62 (m, 1H), 2.34–2.12 (m, 2H), 2.09–1.94 (m, 1H), 1.79 (br s, 1H), 1.43–1.23 ppm (m, 2H); ^{13}C NMR (CD_3OD): δ=163.9, 150.8, 148.5, 147.9, 138.5, 134.5, 134.4, 133.4, 132.7, 132.7, 130.9, 130.9, 130.1, 129.9, 129.1, 129.1, 128.9, 126.4, 126.1, 125.3, 125.1, 124.2, 121.5, 119.1, 118.4, 117.4, 116.9, 70.0, 67.2, 63.5, 56.6, 53.2, 39.5, 27.1, 26.2, 23.1 ppm; HRMS (FAB$^+$): m/z calcd for $[C_{34}H_{33}N_2O]^+$: 485.2593; found: 485.2610.

1o (R^5=H, Ar^1=3,5-$(CF_3)_2C_6H_3$): Pale-yellow powder; $[\alpha]_D^{23}$=−105° (c=1.00 in $CHCl_3$); m.p. 107°C (decomp.); IR (ATR): $\tilde{\nu}$=1588, 1471, 1373, 1278, 1174, 1129 cm^{-1}; ^{1}H NMR (CD_3OD): δ=8.79 (d, J=4.6 Hz, 1H), 8.28 (s, 2H), 8.18–8.08 (m, 2H), 8.03–7.95 (m, 1H), 7.85 (d, J=4.6 Hz, 1H), 7.76–7.63 (m, 2H), 6.79 (t, J=7.3 Hz, 2H), 6.52–6.42 (m, 3H), 6.27 (t, J=7.3 Hz, 1H), 5.60–5.46 (m, 1H), 5.22 (d, J=12.4 Hz, 1H), 5.07–4.80 (m, 4H), 4.58–4.41 (m, 1H), 3.91–3.79 (m, 1H), 3.62–3.51 (m, 1H), 3.39–3.16 (m, 2H), 2.57 (br s, 1H), 2.21–2.02 (m, 2H), 1.93 (br s, 1H), 1.80–1.65 (m, 1H), 1.30–1.16 ppm (m, 1H); ^{13}C NMR (CD_3OD): δ=165.6, 150.9, 148.5, 148.0, 135.3, 135.2, 134.2, 133.7, 133.2, 132.7, 132.0, 131.9, 130.9, 130.4, 130.2, 129.9, 128.8, 126.4, 126.0, 125.5, 125.4, 125.3, 123.8, 122.4, 121.4, 119.1, 118.4, 117.4, 116.1 (135–115: multiple peaks), 70.5, 66.4, 63.3, 61.9, 52.8, 39.1, 27.9, 25.9, 22.6 ppm; HRMS (FAB$^+$): m/z calcd for $[C_{28}H_{27}F_6N_2O]^+$: 521.2028; found: 521.2008.

1p (R^5 = H, Ar^1 = 3,5-(tBu)$_2$C$_6$H$_3$): Pale-yellow powder; $[\alpha]_D^{22} = -55.3°$ (c = 1.00 in $CHCl_3$); m.p. 116 °C (decomp.); IR (ATR): $\tilde{\nu}$ = 2954, 1587, 1469, 1363, 1249, 1205, 1161 cm^{-1}; ^{1}H NMR (CD_3OD): δ = 8.90 (d, J = 4.6 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 4.6 Hz, 1H), 7.88–7.73 (m, 3H), 7.65 (br s, 1H), 7.54–7.44 (m, 2H), 6.97 (t, J = 7.3 Hz, 2H), 6.67–6.56 (m, 3H), 6.49 (t, J = 7.3 Hz, 1H), 5.74–5.60 (m, 1H), 5.15–4.85 (m, 6H), 4.58–4.38 (m, 1H), 3.99–3.85 (m, 1H), 3.64–3.25 (m, 3H), 2.70 (br s, 1H), 2.36–2.13 (m, 2H), 2.03 (br s, 1H), 1.95–1.76 (m, 1H), 1.36 ppm (s, 18H); ^{13}C NMR (CD_3OD): δ = 164.0, 160.6, 153.1, 150.9, 148.6, 147.8, 138.7, 131.0, 130.2, 129.9, 128.9, 128.8, 127.8, 126.1, 125.6, 123.9, 121.2, 118.4, 117.3, 117.0, 69.5, 66.2, 65.9, 62.1, 52.8, 39.2, 35.9, 31.8, 28.1, 26.0, 22.5 ppm; HRMS (FAB$^+$): m/z calcd for $[C_{34}H_{45}N_2O]^+$: 497.3532; found: 497.3549.

1q (R^5 = H, Ar^1 = 3,5-[3,5-(CF_3)$_2$C$_6$H$_3$]$_2$C$_6$H$_3$): Pale-yellow powder; $[\alpha]_D^{23} = -83.4°$ (c = 1.00 in $CHCl_3$); m.p. 154 °C (decomp.); IR (ATR): $\tilde{\nu}$ = 1586, 1473, 1371, 1281, 1239, 1168, 1128 cm^{-1}; ^{1}H NMR (CD_3OD): δ = 8.84 (d, J = 4.6 Hz, 1H), 8.37 (s, 4H), 8.26 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.09–7.96 (m, 5H), 7.89 (d, J = 4.6 Hz, 1H), 7.83–7.68 (m, 2H), 6.85 (t, J = 7.3 Hz, 2H), 6.63–6.45 (m, 3H), 6.33 (t, J = 7.3 Hz, 1H), 5.64–5.51 (m, 1H), 5.26 (d, J = 12.4 Hz, 1H), 5.08–4.82 (m, 4H), 4.62–4.45 (m, 1H), 3.92–3.79 (m, 1H), 3.63–3.37 (m, 2H), 3.28–3.19 (m, 1H), 2.68–2.56 (m, 1H), 2.30–2.08 (m, 2H), 1.99 (br s, 1H), 1.89–1.71 (m, 1H), 1.40–1.21 ppm (m, 1H); ^{13}C NMR (CD_3OD): δ = 165.0, 150.9, 148.5, 148.1, 143.3, 141.5, 138.6, 134.1, 133.9, 133.6, 133.1, 132.6, 131.0, 130.9, 130.7, 130.3, 129.9, 129.6, 129.1, 128.8, 126.7, 126.0, 123.6, 122.7, 122.7, 122.6, 121.4, 118.8, 117.3, 116.4 (135–115: multiple peaks), 70.4, 66.5, 64.6, 62.4, 52.8, 39.3, 28.0, 26.0, 22.6 ppm; HRMS (FAB$^+$): m/z calcd for $[C_{42}H_{33}F_{12}N_2O]^+$: 809.2402; found: 809.2396.

Typical procedure for the synthesis of optically active 3,4-dihydropyran-2-ones 5 by using cinchonidine-derived catalyst **1k** (Table 3, entry 1): A solution of chalcone **2a** (62.5 mg, 0.3 mmol) in THF (1.4 mL) and a solution of ketene silyl acetal **3a** (113 mg, 0.48 mmol) in THF (0.6 mL) were added successively to a stirred solution of cinchonidine-derived catalyst **1k** (13.5 mg, 0.015 mmol) in THF (1.0 mL) at −78 °C. After the mixture was stirred for 0.5–1 h at the same temperature, the reaction was quenched with aqueous HCl (1 M), and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by PTLC to give the corresponding **5a** (82.0 mg, 98% yield). The enantiomeric excess of the product was determined by HPLC analysis (90% *ee*).

5a: Colorless crystals; $[\alpha]_D^{25} = +182°$ (c = 1.00 in $CHCl_3$, 90% *ee*); m.p. 129–130 °C; IR (ATR): $\tilde{\nu}$ = 1762, 1493, 1449, 1386, 1321, 1276, 1187, 1078, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.70–7.66 (m, 2H), 7.39–7.23 (m, 6H), 7.19–7.14 (m, 2H), 5.93 (d, J = 5.4 Hz, 1H), 3.49 (d, J = 5.4 Hz, 1H), 1.43 (s, 3H), 1.04 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.4, 148.9, 138.7, 132.0, 128.9, 128.5, 128.4, 127.4, 124.4, 103.7, 50.1, 41.1, 26.0, 21.7 ppm; elemental analysis: calcd for $C_{19}H_{18}O_2$: C 81.99, H 6.52; found: C 82.03, H 6.59; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 9.6 min (4*S*) and 11.2 min (4*R*).

5b: Colorless crystals; $[\alpha]_D^{27} = +150°$ (c = 1.00 in $CHCl_3$, 84% *ee*); m.p. 143–144 °C; IR (ATR): $\tilde{\nu}$ = 1756, 1504, 1224, 1095, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.70–7.66 (m, 2H), 7.45–7.35 (m, 3H), 7.16–7.10 (m, 2H), 7.02–6.95 (m, 2H), 5.91 (d, J = 5.4 Hz, 1H), 3.49 (d, J = 5.4 Hz, 1H), 1.43 (s, 3H), 1.03 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.2, 162.0 (d, J = 245.6 Hz), 149.0, 134.5 (d, J = 2.9 Hz), 131.8, 130.0 (d, J = 7.8 Hz), 129.0, 128.4, 124.4, 115.4 (d, J = 21.3 Hz), 103.5, 49.3, 41.2, 25.9, 21.7 ppm; elemental analysis: calcd for $C_{19}H_{17}FO_2$: C 77.01, H 5.78; found: C 76.69, H 5.86; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 11.7 min (major) and 14.0 min (minor).

5c: Colorless crystals; $[\alpha]_D^{30} = +149°$ (c = 1.00 in $CHCl_3$, 82% *ee*); m.p. 115–117 °C; IR (ATR): $\tilde{\nu}$ = 1765, 1508, 1232, 1090, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.68–7.62 (m, 2H), 7.32–7.24 (m, 3H), 7.17–7.02 (m, 4H), 5.86 (d, J = 5.4 Hz, 1H), 3.49 (d, J = 5.4 Hz, 1H), 1.43 (s, 3H), 1.04 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.3, 163.0 (d, J = 248.4 Hz), 148.1, 138.7, 128.5, 128.4, 128.2 (d, J = 2.8 Hz), 127.5, 126.4 (d, J = 8.4 Hz), 115.4 (d, J = 21.8 Hz), 103.4, 50.1, 41.1, 26.0, 21.7; elemental analysis: calcd for $C_{19}H_{17}FO_2$: C 77.01, H 5.78; found: C 76.88, H 5.82; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 13.3 min (major) and 15.0 min (minor).

5d: Colorless crystals; $[\alpha]_D^{30} = +153°$ (c = 1.00 in $CHCl_3$, 96% *ee*); m.p. 118–119 °C; IR (ATR): $\tilde{\nu}$ = 1758, 1509, 1248, 1178, 1092, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.69–7.65 (m, 2H), 7.45–7.35 (m, 3H), 7.07 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.91 (d, J = 5.4 Hz, 1H), 3.77 (s, 3H), 3.44 (d, J = 5.4 Hz, 1H), 1.41 (s, 3H), 1.03 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.5, 158.7, 148.7, 132.0, 130.6, 129.5, 128.9, 128.4, 124.4, 113.8, 104.0, 55.2, 49.2, 41.3, 25.9, 21.7 ppm; elemental analysis: calcd for $C_{20}H_{20}O_3$: C 77.90, H 6.54; found: C 77.86, H 6.54; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 9.5 min (minor) and 11.1 min (major).

5e: Colorless crystals; $[\alpha]_D^{30} = +157°$ (c = 1.00 in $CHCl_3$, 95% *ee*); m.p. 105–107 °C; IR (ATR): $\tilde{\nu}$ = 1765, 1512, 1284, 1246, 1178, 1091, 1065, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.61 (d, J = 8.9 Hz, 2H), 7.32–7.22 (m, 3H), 7.17–7.14 (m, 2H), 6.90 (d, J = 8.9 Hz, 2H), 5.79 (d, J = 5.4 Hz, 1H), 3.81 (s, 3H), 3.46 (d, J = 5.4 Hz, 1H), 1.42 (s, 3H), 1.03 ppm (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 173.6, 160.1, 148.7, 139.0, 128.5, 128.4, 127.3, 125.8, 124.6, 113.8, 101.8, 55.3, 50.0, 41.1, 26.0, 21.7 ppm; elemental analysis: calcd for $C_{20}H_{20}O_3$: C 77.90, H 6.54; found: C 77.82, H 6.73; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 9:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 14.0 min (major) and 15.4 min (minor).

5f: Colorless crystals; $[\alpha]_D^{30} = +107°$ (c = 1.00 in $CHCl_3$, 88% *ee*); m.p. 115–117 °C; IR (ATR): $\tilde{\nu}$ = 1754, 1511, 1251, 1178, 1105, 1073, 1021, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.60 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 5.74 (d, J = 5.4 Hz, 1H), 3.82 (s, 3H), 3.44 (d, J = 5.4 Hz, 1H), 1.42 (s, 3H), 1.02 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.2, 160.2, 149.1, 138.1, 131.5, 130.1, 125.9, 124.3, 121.2, 113.8, 101.1, 55.3, 49.5, 41.0, 25.9, 21.7 ppm; elemental analysis: calcd for $C_{20}H_{19}BrO_3$: C 62.03, H 4.95; found: C 61.73, H 5.14; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 14.7 min (major) and 16.1 min (minor).

5g: Colorless oil; $[\alpha]_D^{29} = +109°$ (c = 1.00 in $CHCl_3$, 89% *ee*); IR (ATR): ν = 1758, 1511, 1247, 1178, 1094, 1072, 1029, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.59–7.48 (m, 4H), 7.06 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 5.92 (d, J = 5.4 Hz, 1H), 3.78 (s, 3H), 3.44 (d, J = 5.4 Hz, 1H), 1.41 (s, 3H), 1.03 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.2, 158.8, 147.8, 131.5, 130.9, 130.3, 129.4, 125.9, 123.0, 113.9, 104.6, 55.2, 49.2, 41.3, 25.9, 21.7 ppm; HRMS (DEI$^+$): m/z calcd for $C_{20}H_{19}BrO_3$ $[M]^+$: 386.0518; found: 386.0517; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 12.5 min (major) and 26.1 min (minor).

5h: Colorless oil; $[\alpha]_D^{24} = +64.3°$ (c = 1.00 in $CHCl_3$, 95% *ee*); IR (ATR): $\tilde{\nu}$ = 1758, 1448, 1332, 1279, 1240, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.64–7.59 (m, 2H), 7.40–7.32 (m, 3H), 5.67 (d, J = 4.6 Hz, 1H), 2.50–2.41 (m, 1H), 1.34 (s, 3H), 1.22 (s, 3H), 1.10 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 174.3, 147.9, 132.1, 128.6, 128.3, 124.2, 105.8, 40.4, 36.9, 24.3, 20.0, 15.4 ppm; HRMS (DEI$^+$): m/z calcd for $C_{14}H_{16}O_2$ $[M]^+$: 216.1150; found: 216.1150; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 6.1 min (major) and 6.6 min (minor).

5i: Colorless crystals; $[\alpha]_D^{28} = +138°$ (c = 1.00 in $CHCl_3$, 93% *ee*); m.p. 38–39 °C; IR (ATR): $\tilde{\nu}$ = 2961, 1753, 1388, 1350, 1276, 1206, 1105, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.67–7.63 (m, 2H), 7.39–7.34 (m, 3H), 5.73 (d, J = 6.5 Hz, 1H), 2.20 (dd, J = 6.5, 3.8 Hz, 1H), 2.18–2.03 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.76 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 174.9, 149.4, 132.3, 128.7, 128.3, 124.4, 99.8, 49.5, 39.3, 28.8, 27.8, 21.6, 21.2, 15.6 ppm; elemental analysis: calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.97, H 8.36; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 1000:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 15.2 min (minor) and 16.2 min (major).

5j: Colorless crystals; $[\alpha]_D^{17} = +27.4°$ ($c = 0.50$ in $CHCl_3$, 57% *ee*); m.p. 72–74 °C; IR (ATR): $\tilde{\nu} = 1759$, 1494, 1449, 1317, 1279, 1141, 1083, 1043 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.67–7.63$ (m, 2H), 7.42–7.23 (m, 8H), 5.83 (d, $J = 3.0$ Hz, 1H), 3.58 (dd, $J = 11.1$, 3.0 Hz, 1H), 2.79 (dq, $J = 11.1$, 6.8 Hz, 1H), 1.22 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 170.9$, 149.4, 141.5, 132.0, 129.0, 128.9, 128.4, 127.6, 127.4, 124.5, 105.0, 44.9, 41.0, 14.1 ppm; elemental analysis: calcd for $C_{18}H_{16}O_2$: C 81.79, H 6.10; found: C 81.77, H 6.24; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol = 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 17.1 min (major) and 17.7 min (minor).

5k:[3c] Colorless oil; $[\alpha]_D^{19} = +123°$ ($c = 0.33$ in $CHCl_3$, 84% *ee*); IR (ATR): $\tilde{\nu} = 1759$, 1494, 1450, 1279, 1143, 1073 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.68–7.64$ (m, 2H), 7.41–7.21 (m, 8H), 5.84 (d, $J = 4.6$ Hz, 1H), 3.71 (dd, $J = 7.3$, 4.6 Hz, 1H), 2.73 (q, $J = 7.3$ Hz, 1H), 1.81–1.64 (m, 2H), 1.04 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 169.8$, 149.3, 141.3, 132.0, 129.0, 128.9, 128.4, 127.3, 127.3, 124.5, 103.5, 48.0, 42.4, 22.8, 11.4 ppm; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol = 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 16.5 min (major) and 17.7 min (minor).

5l: Colorless crystals; $[\alpha]_D^{22} = +158°$ ($c = 0.50$ in $CHCl_3$, 88% *ee*); m.p. 108–109 °C; IR (ATR): $\tilde{\nu} = 2962$, 1760, 1493, 1276, 1235, 1177, 1086, 1070 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.70–7.66$ (m, 2H), 7.42–7.19 (m, 8H), 5.86 (d, $J = 5.1$ Hz, 1H), 3.61 (t, $J = 5.1$ Hz, 1H), 2.89–2.81 (m, 1H), 1.82–1.72 (m, 2H), 1.46–1.33 (m, 1H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.86 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 170.1$, 149.5, 141.2, 132.0, 129.0, 128.9, 128.4, 127.3, 127.2, 124.5, 102.5, 44.9, 43.6, 39.6, 26.0, 22.7, 22.0 ppm; elemental analysis: calcd for $C_{21}H_{22}O_2$: C 82.32, H 7.24; found: C 82.00, H 7.21; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 12.2 min (major) and 14.3 min (minor).

5m: Colorless crystals; $[\alpha]_D^{21} = +188°$ ($c = 1.00$ $CHCl_3$, 96% *ee*); m.p. 73–75 °C; IR (ATR): $\tilde{\nu} = 2962$, 1756, 1494, 1450, 1279, 1180, 1123, 1071 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.70–7.66$ (m, 2H), 7.42–7.16 (m, 8H), 5.86 (d, $J = 5.9$ Hz, 1H), 3.81 (dd, $J = 5.9$, 3.2 Hz, 1H), 2.55 (dd, $J = 7.6$, 3.2 Hz, 1H), 2.08–1.96 (m, 1H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.05 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 168.9$, 149.8, 141.3, 132.0, 129.0, 128.9, 128.4, 127.2, 127.0, 124.5, 101.9, 54.3, 41.2, 29.1, 21.1, 20.1 ppm; elemental analysis: calcd for $C_{20}H_{20}O_2$: C 82.16, H 6.89; found: C 82.25, H 6.98; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 15.0 min (major) and 16.7 min (minor).

5n: Colorless crystals; $[\alpha]_D^{22} = +250°$ ($c = 0.50$ in $CHCl_3$, 96% *ee*); m.p. 90–92 °C; IR (ATR): $\tilde{\nu} = 2962$, 1758, 1745, 1494, 1221, 1195, 1068, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.70–7.65$ (m, 2H), 7.41–7.15 (m, 8H), 5.87 (d, $J = 6.5$ Hz, 1H), 3.88 (d, $J = 6.5$ Hz, 1H), 2.60 (s, 1H), 1.13 ppm (s, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 168.1$, 149.9, 142.5, 132.1, 129.0, 129.0, 128.4, 127.1, 126.8, 124.5, 101.9, 57.8, 39.5, 34.8, 28.6 ppm; elemental analysis: calcd for $C_{21}H_{22}O_2$: C 82.32, H 7.24; found: C 82.20, H 7.20; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 14.0 min (major) and 20.2 min (minor).

5o: Colorless oil; $[\alpha]_D^{14} = +141°$ ($c = 0.33$ in $CHCl_3$, 95% *ee*); IR (ATR): $\tilde{\nu} = 1758$, 1507, 1224, 1177, 1071 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.76–7.66$ (m, 2H), 7.47–7.35 (m, 3H), 7.20–7.09 (m, 2H), 7.03–6.95 (m, 2H), 5.85 (d, $J = 5.9$ Hz, 1H), 3.81 (dd, $J = 5.9$, 3.0 Hz, 1H), 2.55–2.46 (m, 1H), 2.08–1.94 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.05 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 168.7$, 161.8 (d, $J = 246.2$ Hz), 150.0, 137.0 (d, $J = 3.4$ Hz), 131.8, 129.1, 128.6 (d, $J = 7.8$ Hz), 128.4, 124.5, 115.8 (d, $J = 21.3$ Hz), 101.5, 54.6, 40.4, 29.0, 21.1, 20.2 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{20}H_{19}FO_2$ $[M]^+$: 310.1369; found: 310.1370; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 16.3 min (major) and 18.1 min (minor).

5p: Colorless oil; $[\alpha]_D^{16} = +170°$ ($c = 0.33$ in $CHCl_3$, 94% *ee*); IR (ATR): $\tilde{\nu} = 1760$, 1508, 1232, 1159, 1067 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.68–7.62$ (m, 2H), 7.41–7.16 (m, 5H), 7.11–7.02 (m, 2H), 5.79 (d, $J = 5.9$ Hz, 1H), 3.85–3.78 (m, 1H), 2.60–2.53 (m, 1H), 2.08–1.94 (m, 1H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.05 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 168.7$, 163.0 (d, $J = 248.9$ Hz), 149.0, 141.3, 129.0, 128.2 (d, $J = 3.3$ Hz), 127.3, 127.0, 126.4 (d, $J = 7.9$ Hz), 115.4 (d, $J = 21.8$ Hz), 101.6, 54.2, 41.2, 29.1, 21.1, 20.1 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{20}H_{19}FO_2$ $[M]^+$: 310.1369; found: 310.1373; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 8.8 min (major) and 12.2 min (minor).

5q: Colorless oil; $[\alpha]_D^{17} = +160°$ ($c = 0.50$ in $CHCl_3$, 94% *ee*); IR (ATR): $\tilde{\nu} = 1758$, 1510, 1248, 1176, 1071, 1033, 1018 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.69–7.65$ (m, 2H), 7.44–7.36 (m, 3H), 7.11 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.85 (d, $J = 5.9$ Hz, 1H), 3.79–3.73 (m, 4H), 2.51 (dd, $J = 7.8$, 3.2 Hz, 1H), 2.08–1.96 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 169.0$, 158.6, 149.6, 133.3, 132.0, 128.9, 128.4, 128.1, 124.4, 114.3, 102.2, 55.3, 54.6, 40.3, 28.9, 21.1, 20.2 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{21}H_{22}O_3$ $[M]^+$: 322.1569; found: 322.1567; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 10.6 min (minor) and 11.8 min (major).

5r: Colorless oil; $[\alpha]_D^{19} = +142°$ ($c = 1.00$ in $CHCl_3$, 97% *ee*); IR (ATR): $\tilde{\nu} = 1757$, 1608, 1511, 1250, 1172, 1067, 1023 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.61$ (d, $J = 8.6$ Hz, 2H), 7.41–7.12 (m, 5H), 6.91 (d, $J = 8.6$ Hz, 2H), 5.71 (d, $J = 5.7$ Hz, 1H), 3.88–3.80 (m, 4H), 2.55–2.50 (m, 1H), 2.07–1.96 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 169.1$, 160.1, 149.6, 141.6, 128.9, 127.1, 127.0, 125.9, 124.6, 113.8, 99.9, 55.3, 54.4, 41.1, 29.0, 21.1, 20.1 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{21}H_{22}O_3$ $[M]^+$: 322.1569; found: 322.1564; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 13.7 min (major) and 18.1 min (minor).

5s:[14] Colorless crystals; $[\alpha]_D^{19} = +110°$ ($c = 1.00$ in $CHCl_3$, 95% *ee*); m.p. 135–136 °C; IR (ATR): $\tilde{\nu} = 1757$, 1608, 1511, 1250, 1172, 1070, 1009 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.61$ (d, $J = 8.9$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.07 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.9$ Hz, 2H), 5.68 (d, $J = 5.7$ Hz, 1H), 3.82 (s, 3H), 3.80–3.71 (m, 1H), 2.51–2.44 (m, 1H), 2.07–1.94 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 168.7$, 160.2, 150.0, 140.6, 132.0, 128.8, 126.0, 124.3, 121.0, 113.8, 99.1, 55.3, 54.4, 40.5, 29.0, 21.1, 20.2 ppm; elemental analysis: calcd for $C_{21}H_{21}BrO_3$: C 62.85, H 5.27; found: C 62.83, H 5.34; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 42.4 min (3*S*,4*R*) and 47.7 min (3*R*,4*S*).

5t: Colorless oil; $[\alpha]_D^{20} = +104°$ ($c = 0.50$ in $CHCl_3$, 92% *ee*); IR (ATR): $\tilde{\nu} = 1761$, 1510, 1248, 1175, 1069, 1028, 1006 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.59–7.48$ (m, 4H), 7.11 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.85 (d, $J = 5.7$ Hz, 1H), 3.81–3.70 (m, 4H), 2.56–2.49 (m, 1H), 2.06–1.91 (m, 1H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 168.7$, 158.7, 148.7, 133.0, 131.5, 130.9, 128.0, 126.0, 123.1, 114.3, 102.9, 55.3, 54.4, 40.4, 29.0, 21.1, 20.1 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{21}H_{21}BrO_3$ $[M]^+$: 400.0674; found: 400.0674; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 11.5 min (major) and 14.1 min (minor).

5u: Colorless oil; $[\alpha]_D^{12} = +119°$ ($c = 0.67$ in $CHCl_3$, 85% *ee*); IR (ATR): $\tilde{\nu} = 1758$, 1511, 1248, 1177, 1143, 1076, 1031 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.67–7.63$ (m, 2H), 7.43–7.33 (m, 3H), 7.14 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.82 (d, $J = 4.9$ Hz, 1H), 3.78 (s, 3H), 3.66 (dd, $J = 7.3$, 4.9 Hz, 1H), 2.70 (q, $J = 7.3$ Hz, 1H), 1.78–1.65 (m, 2H), 1.03 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 169.9$, 158.6, 149.0, 133.3, 132.0, 128.9, 128.4, 128.3, 124.4, 114.3, 103.8, 55.3, 48.2, 41.6, 22.7, 11.4 ppm; HRMS (DEI$^+$): *m/z* calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1412; found: 308.1411; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol = 50:1, $\lambda = 254$ nm, flow rate = 1.0 mL min^{-1}, retention time = 16.2 min (minor) and 18.6 min (major).

5v: Colorless oil; $[\alpha]_D^{14} = +97.3°$ ($c = 0.50$ in $CHCl_3$, 87% *ee*); IR (ATR): $\tilde{\nu} = 1761$, 1608, 1511, 1249, 1174, 1144, 1073, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.59$ (d, $J = 8.6$ Hz, 2H), 7.36–7.20 (m, 5H), 6.89 (d, $J = 8.6$ Hz, 2H), 5.69 (d, $J = 4.3$ Hz, 1H), 3.81 (s, 3H), 3.68 (dd, $J = 7.3$, 4.3 Hz, 1H), 2.71 (q, $J = 7.3$ Hz, 1H), 1.79–1.65 (m, 2H), 1.03 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 169.9$, 160.1, 149.0, 141.6, 128.8,

127.2, 127.2, 125.9, 124.5, 113.7, 101.6, 55.3, 48.0, 42.3, 22.7, 11.4 ppm; HRMS (DEI$^+$): m/z calcd for $C_{20}H_{20}O_3$ $[M]^+$: 308.1412; found 308.1415; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 18.7 min (major) and 24.5 min (minor).

5w: Colorless crystals; $[\alpha]_D^{17} = +155°$ (c = 0.50 in $CHCl_3$, 86% *ee*); m.p. 96–97 °C; IR (ATR): $\tilde{\nu}$ = 1760, 1450, 1145, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.45–7.17 (m, 10H), 7.09 (d, J = 15.9 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H), 5.37 (d, J = 4.6 Hz, 1H), 3.66 (dd, J = 7.0, 4.6 Hz, 1H), 2.70 (q, J = 7.0 Hz, 1H), 1.80–1.64 (m, 2H), 1.03 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 169.5, 148.7, 141.3, 136.0, 129.8, 128.9, 128.6, 128.1, 127.3, 127.2, 126.7, 119.6, 108.2, 48.1, 42.6, 22.8, 11.4 ppm; elemental analysis: calcd for $C_{21}H_{20}O_2$: C 82.86, H 6.62; found: C 82.69, H 6.70; HPLC analysis: DAICEL Chiralcel OD-H, hexane/2-propanol 50:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 32.2 min (minor) and 38.5 min (major).

9: Pd/C (10%; 40.0 mg) was added to a solution of (+)-**5a** (400 mg, 1.44 mmol, 90% *ee*) in EtOH/THF (5:1; 12 mL), and the mixture was stirred under hydrogen at ambient temperature for 1 h. The reaction mixture was then filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to give carboxylic acid **9** (390 mg, 96% yield) as a colorless oil. $[\alpha]_D^{20} = +23.0°$ (c = 1.00 in $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 3027, 2977, 2942, 1693, 1453, 1287 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.36–7.12 (m, 8H), 7.08–7.04 (m, 2H), 3.02 (dd, J = 11.9, 2.7 Hz, 1H), 2.49–2.25 (m, 2H), 2.23–2.07 (m, 1H), 1.98–1.86 (m, 1H), 1.15 (s, 3H), 1.04 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 184.4, 141.9, 139.4, 129.8, 128.2, 128.2, 127.9, 126.8, 125.7, 52.1, 46.6, 34.2, 32.1, 24.8, 20.4 ppm; HRMS (FAB$^+$): m/z calcd for $C_{19}H_{22}O_2Li$ $[M+Li]^+$: 289.1780; found: 289.1779.

10:[11] A solution of oxalyl chloride (113 mg, 0.80 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of **9** (113 mg, 0.40 mmol) in CH_2Cl_2 (10 mL). The mixture was heated at reflux for 1 h, and the solvent and oxalyl chloride were removed under reduced pressure. CH_2Cl_2 (10 mL), 4-bromoaniline (68.8 mg, 0.40 mmol), and a solution of triethylamine (80.9 mg, 0.80 mmol) in CH_2Cl_2 (2 mL) were added successively to the residue at room temperature. The mixture was stirred for 1 h at the same temperature, quenched with aqueous HCl (1 M), and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by PTLC and recrystallized from EtOAc/hexane to afford the corresponding carboxamide **10** (119 mg, 68% yield) as colorless crystals. $[\alpha]_D^{18} = +26.4°$ (c = 0.73 in $CHCl_3$, >99% *ee*); m.p. 153–154 °C; IR (ATR): $\tilde{\nu}$ = 3410, 3026, 2951, 1653, 1587, 1511, 1487, 1453, 1390, 1304, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.42–7.12 (m, 12H), 7.05–6.99 (m, 2H), 6.95 (br s, 1H), 2.96 (dd, J = 11.9, 3.0 Hz, 1H), 2.51–2.37 (m, 1H), 2.34–1.92 (m, 3H), 1.24 (s, 3H), 1.13 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 175.2, 141.8, 139.5, 136.5, 131.6, 129.7, 128.3, 128.2, 128.0, 126.9, 125.7, 121.7, 116.7, 52.9, 47.1, 34.1, 31.4, 24.6, 21.8 ppm; elemental analysis: calcd for $C_{25}H_{26}BrNO$: C 68.81, H 6.01, N 3.21; found: C 69.04, H 6.07, N 3.18; HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 4:1, λ = 254 nm, flow rate = 1.0 mL min^{-1}, retention time = 7.2 min (3*S*) and 19.1 min (3*R*).

Acknowledgements

This study was supported in part by a Grant of the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan. The authors thank Mr. Nobuhiro Marubayashi (Mitsubishi Pharma Corporation) for his support in X-ray crystallographic analysis.

[1] a) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; b) X. Zhang, H. Du, Z. Wang, Y-D. Wu, K. Ding, *J. Org. Chem.* **2006**, *71*, 2862–2869 and references cited therein.

[2] a) D. Rosenthal, P. Grabowich, E. F. Sabo, J. Fried, *J. Am. Chem. Soc.* **1963**, *85*, 3971–3979; b) T. Kume, H. Iwasaki, Y. Yamamoto, K. Akiba, *Tetrahedron Lett.* **1988**, *29*, 3825–3828; c) A. K. Mandal, D. G. Jawalker, *Tetrahedron Lett.* **1986**, *27*, 99–100; d) A. K. Mandal, D. G. Jawalker, *J. Org. Chem.* **1989**, *54*, 2364–2369; e) S. H. Thang, D. J. Rigg, *Synth. Commun.* **1993**, *23*, 2355–2361; f) J. R. Heys, S. G. Senderoff, *J. Org. Chem.* **1989**, *54*, 4702–4706; g) D. C. Harrowven, J. C. Hannam, *Tetrahedron* **1999**, *55*, 9333–9340; h) J. A. Robl, *Tetrahedron Lett.* **1990**, *31*, 3421–3424; i) Y. D. Gong, H. Tanaka, N. Iwasawa, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2181–2185; j) F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097–1100.

[3] a) D. A. Oare, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 157–172; b) S. Kobayashi, M. Moriwaki, *Synlett* **1997**, *5*, 551–552; c) A. R. Katritzky, O. V. Denisko, *J. Org. Chem.* **2002**, *67*, 3104–3108.

[4] a) T. Tozawa, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 1454–1455; b) T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 514–515.

[5] For recent reviews, see: a) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; b) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518–525; c) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526–533; d) K. Maruoka and T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028.

[6] For the preparation and X-ray crystallographic analysis of quaternary ammonium *p*-nitrophenoxide, see: E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

[7] A. Ando, T. Miura, T. Tatematsu, T. Shioiri, *Tetrahedron Lett.* **1993**, *34*, 1507–1510.

[8] a) R. Goddard, H. M. Herzog, M. T. Reetz, *Tetrahedron* **2002**, *58*, 7847–7850; b) A. W. Hanson, A. W. McCulloch, A. G. McInnes, *Tetrahedron Lett.* **1982**, *23*, 607–610.

[9] T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 56–57.

[10] B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595–8598.

[11] CCDC-612957 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambrige Crystallographic Data Centre, 12 Union Road, Cambrige CB21EZ, UK; fax: (+44) 1223–336–033; or deposit@ccdc.cam.ac.uk).

[12] For some recent reports of hydrogen-bond-promoted asymmetric catalysis, see: a) S. Rajaram, M. S. Sigman, *Org. Lett.* **2005**, *7*, 5473–5475; b) T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 3195–3197; c) A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 1336–1337; d) T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845; e) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; see also reference [1b].

[13] T. Tozawa, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 360–361.

[14] CCDC-612956 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambrige Crystallographic Data Centre, 12 Union Road, Cambrige CB21EZ, UK; fax: (+44) 1223–336–033; or deposit@ccdc.cam.ac.uk).

[15] J. M. Chong, L. Shen, N. J. Taylor, *J. Am. Chem. Soc.* **2000**, *122*, 1822–1823.

[16] S. Kobayashi, K. Manabe, H. Ishitani, J. Matsuo in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, *Vol. 4* (Eds.: D. Bellus, S. V. Ley, R. Noyori, M. Regitz, E. Schaumann, I. Shinkai, E. J. Thomas, B. M. Trost), Thieme, Stuttgart, **2002**, pp. 317–369.

[17] *N*-(9-Anthracenylmethyl)-*O*-[3,5-bis(trifluoromethyl)benzyl]cinchonidinium bromide was prepared according to the procedure reported by Corey et al.[6]

Received: July 20, 2006
Revised: October 10, 2006
Published online: December 12, 2006

