Double nucleophilic addition to iminomalonate, leading to the synthesis of quaternary \( \alpha \)-amino diesters and desymmetrization of the products†

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Alkylation of iminomalonate with Grignard reagents followed by oxidation and allylation gave symmetrical quaternary \( \alpha \)-amino diesters in good yields. Subsequent desymmetrization of a diol derivative from these products was conducted via asymmetric carbamylation catalyzed by Cu-Bnbox to give chiral quaternary aminodiol mono-carbamates.

1 Introduction

Quaternary \( \alpha \)-amino acid or ester moieties are very important structural units in many biologically active compounds, since the incorporation of rigid amino acid surrogates concerns very useful information on the bioactive conformation and provides intriguing physiological effects. 1,2 Quaternary \( \alpha \)-amino acid moieties are also found as fundamental skeletons in medicines and agrochemicals such as Ecteinascidin 743, Salinosporamide A, and Neoxazolomycin (Fig. 1). 3–5

However, it is not trivial to construct quaternary \( \alpha \)-amino acid frameworks in a stereoselective manner. 6 For the synthesis of \( \alpha \)-amino acids and their derivatives \( \alpha \)-imino esters are useful substrates, since \( \alpha \)-imino esters have a unique reactivity: either \( N \)- or \( C \)-alkylation is possible. Although an umpolung \( N \)-alkylation reaction of \( \alpha \)-imino ester is difficult due to the electronegativity of the imino group, it can lead to a flexible introduction of substituents into the nitrogen atom of the amino acid frameworks. 7,8 We have already reported that umpolung \( N \)-alkylation reactions of \( \alpha \)-iminoesters 1 followed by \( C \)-electrophilic addition or oxidation followed by \( C \)-nucleophilic addition gives intriguing \( N,C \)-double addition products in good yields with high diastereoselectivities. 9 In our previous report, we found that a combined use of diethylaluminum chloride and ethylaluminium dichloride promoted most efficiently the \( N \)-alkylation of \( \alpha \)-aryl \( \alpha \)-iminoester 2, and the subsequent oxidation and allylation were conducted with benzoyl peroxide and allyltributylstannane, respectively (eqn (1), Scheme 2). 9

However, the resulting halomagnesium enolate that was an \( N \)-addition intermediate was not used for further \( C \)-\( C \) bond formations. Since the previous study shows that the oxidation of an intermediary \( \alpha \)-aminoester enolate readily gives an iminium species that is attacked by a nucleophile, the present intermediary halomagnesium enolate is expected to have a similar reactivity.

Fig. 1 Bioactive compounds possessing a quaternary \( \alpha \)-amino acid structure.
We have now found that oxidation of the halomagnesium enolate derived from N-alkylation of the iminomalonate 1 with an appropriate oxidation reagent followed by C-nucleophilic addition leads to the formation of N,C-double addition products, quaternary \(\alpha\)-amino diesters in good yields (eqn (3), Scheme 1).

### 2 Results and discussion

#### 2.1 N-Methylation/C-cyanation reactions

Our previous study leads to the N-ethylation/oxidation/C-cyanation reaction, which involves the formation of an intermediary iminium salt, responsible for the second nucleophilic addition. In the present examination, we carried out the double addition reaction as in the case with the previous one.\(^a\)\(^b\) Initially, methylation with methylmagnesium bromide, oxidation, and cyanation with TMSCN were examined regarding the oxidation reagent, and Table 1 summarizes the results.

As can be seen from Table 1, benzylic peroxide (BPO) that was effective in the previous cyanation of \(\alpha\)-iminoesters did not work,\(^a\)\(^b\) whereas with N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS) the desired double addition product 3 was obtained, albeit in low yields. The low yield is presumably due to the instability of the intermediary iminium salt, and therefore, the oxidation in the presence of TMSCN was next examined. Table 2 summarizes the results.

As expected the reaction proceeded relatively well and the desired product 3 was formed in 56% yield after 10 min (entry 1). Further optimization was carried out with respect to the reaction time; a prolonged reaction time of 4 h increased the product yield up to 64% (entry 2). We next examined the allylation reaction that would involve a stronger C–C bond formation, and Table 3 summarizes the results.

#### 2.2 N-Methylation/C-allylation reactions

Although we initially examined the use of allyltrimethylsilane, allylmagnesium chloride, and ketene silyl acetals, these nucleophiles gave the addition products in only low yields (less than 20%). Among the nucleophiles examined, tetrallylstannane effected the desired double addition reaction most efficiently. Treatment of the iminomalonate 1 with methylmagnesium bromide (1.5 equiv.) at \(-78^\circ\text{C}\) followed by oxidation with NBS (1.5 equiv.) and allylation with tetrallylstannane (1.0 equiv.) gave the desired product 3 with good yield.
double addition product 4a in 47% yield (entry 1). Further examination into the reactions led to the optimum conditions. Use of NBS (1.5 equiv.) and tetrallylstannane (1.5 equiv.) at room temperature afforded the desired product 4a in 74% yield (entry 3). Under the optimized conditions, various Grignard reagents underwent double addition reactions to give good to high yields of products 4, and Table 4 summarizes the results.

Table 3 Optimization of allylation reaction

| Entry | NBS (equiv.) | $T_1$ (°C) | Nu (equiv.) | $T_2$ (°C) | Time (h) | Yield$^a$ (%) |
|-------|-------------|------------|------------|------------|----------|--------------|
| 1     | 1.5         | −78        | 1.0        | −78 to rt  | 4        | 47           |
| 2     | 1.5         | −78        | 1.5        | −78 to rt  | 4        | 59           |
| 3     | 1.5         | rt         | 1.5        | rt         | 4        | 74           |
| 4     | 1.0         | rt         | 1.5        | rt         | 4        | 59           |
| 5     | 1.5         | rt         | 1.5        | rt         | 2        | 56           |

$^a$ Isolated yield.

double addition product 4a in 47% yield (entry 1). Further examination into the reactions led to the optimum conditions. Use of NBS (1.5 equiv.) and tetrallylstannane (1.5 equiv.) at room temperature afforded the desired product 4a in 74% yield (entry 3). Under the optimized conditions, various Grignard reagents underwent double addition reactions to give good to high yields of products 4, and Table 4 summarizes the results.

Table 4 Use of various Grignard reagents

| Entry | RMgX     | $T$ (°C) | 4: Yield$^a$ (%) |
|-------|----------|----------|-----------------|
| 1     | MeMgBr   | −78      | 4a: 74          |
| 2     | EtMgBr   | −78      | 4b: 68          |
| 3     | $n$PrMgBr| −78      | 4c: 79          |
| 4     | $n$BuMgBr| −78      | 4d: 72          |
| 5     | iPrMgBr  | −90      | 4e: 40          |
| 6     | tBuMgBr  | −90      | 4f: Trace       |
| 7     | PhMgBr   | −90      | 4g: 0           |

$^a$ Isolated yield.

Scheme 2 Reactions in the presence of a radical scavenger or quencher.

Scheme 3 Proposed reaction mechanism.
2.3 N-Alkylation/C-allylation reactions

As shown in Table 4, methyl, ethyl, npropyl, and nbutyl Grignard reagents underwent N-addition reaction rapidly and cleanly, and the subsequent oxidation and alkylation also proceeded well to give N-alkylation C-allylation products 4a–d in good yields (entries 1 to 4), whereas sterically bulky iso-propyl and tert-butyl counterparts effected the first addition reaction sluggishly to give the desired products 4e–f in moderate to low yields (entries 5 and 6). The present double addition reaction has a limitation; aromatic Grignard reagents did not effect the overall tandem addition, although the first umpolung addition to the nitrogen actually gave the single addition product in 59% yield (entry 7). To examine the reaction pathways, these control experiments were carried out (Scheme 2).

2.5 Desymmetrization of the products

For further use of products 4, we carried out desymmetrization reactions of the aminodiesters 4. The initial examination was carried out using biocatalysts such as lipases for the asymmetric hydrolysis of the ester moiety. However, none of the satisfactory results was obtained. We next examined chemical transformations via asymmetric acylation of the diol 6a derived from the diester 4a catalyzed by Cu-Bnbox system, which finally worked well to give chiral products 7 with good enantio-purities. The reduction of the diester 4a was carried out using LiAlH₄ to give the diol 6a in 81% yield (Scheme 4). Table 5 summarizes the results of the subsequent desymmetrization.

The desymmetrization reaction was carried out with aryl isocyanate in the presence of a catalytic amount of copper(II) triflate and a ligand in THF. Among the ligands examined, the use of Bnbox recorded the best result of 64% ee (entry 1), while tridentate ligands, pybox derivatives, did not work well in the present system (entries 5 and 6). An increase in the amount of both the ligand and Cu(II) to 50 mol% gave a slight increase in the enantiopurity of 66% (entry 2). Further increase in the ees would be possible by changing ArNCO derivatives, and the results will be reported elsewhere.

2.4 Control experiments and a proposed reaction mechanism

The reaction was carried out in the presence of a radical scavenger or a quencher. The yields of the desired product 4a did not noticeably decrease. These results indicate that no radical pathway would be involved in the present reaction. On the basis of these results and our previous investigations, the following pathways are proposed (Scheme 3).

First, Grignard reagent attacks at the nitrogen atom to form the halomagnesium enolate, which is oxidized with NBS to form the iminium salt. The reduction of the diester 4a with LiAlH₄ gave the diol 6a derived from the diester 4a catalyzed by Cu-Bnbox system, which finally worked well to give chiral products 7 with good enantio-purities. The reduction of the diester 4a was carried out using LiAlH₄ to give the diol 6a in 81% yield (Scheme 4). Table 5 summarizes the results of the subsequent desymmetrization.

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Table 5 Comparison of the chiral ligands

| Entry | Ligand   | Yielda (%) | Eeb (%) |
|-------|----------|------------|---------|
| 1     | Bnbox    | 60         | 64      |
| 2     | Bnbox'   | 57         | 66      |
| 3     | Phbox    | 82         | 42      |
| 4     | iPrbox   | 92         | 58      |
| 5     | Ph-pybox | 67         | 3       |
| 6     | iPr-pybox| 81         | 1       |

a Isolated yield. b Determined by chiral HPLC analysis. c Cu(OTf)₂ (0.5 equiv.) and Bnbox (0.5 equiv.) were used.

3 Conclusions

A double nucleophilic addition to iminomalonate was developed using the tandem N-alkylation/oxidation/allylation reaction of diethyl 2-[N-(p-methoxyphenyl)iminom]malonate with Grignard reagent/NBS/tetraallylstannane in good to high yields. We also found that the desymmetrization of a diol derivative of the above products with ArNCO/Cu(at)-Bnbox gave a monocarbobate in good enantiomeric excess.

4 Experimental

4.1 General aspects

1H NMR and 13C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-
chloride, distilled, and stored over Molecular Sieves 4A. Purification was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wako Gel B-5F).

4.2 Synthesis of diethyl 2-[N(4-methoxyphenyl)imino]-malonate (1)

This compound 1 was prepared according to the published procedure.9,12–14

4.3 Synthesis of diethyl 2-[N(4-methoxyphenyl)-N-methylamino]-2-cyanomalonate (3)

Method A. In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N(p-methoxyphenyl)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at –78 °C. To it was added MeMgBr (0.21 mL, 0.23 mmol, 1.12 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (40.0 mg, 0.23 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO3 (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/nhexane = 1/4) to give the title compound 4a (35.4 mg, 74%) as a colorless oil. Rf = 0.5 (ethyl acetate/nhexane = 1/4); 1H NMR (400 MHz, CDCl3) δ: 1.29 (t, J = 7.1 Hz, 6H), 2.60 (d, J = 6.9, 2H), 2.95 (s, 3H), 3.77 (s, 3H), 4.26 (q, J = 7.0), 4.93–5.01 (m, 2H), 5.79–5.89 (m, 1H), 6.77–6.81 (m, 2H), 7.08–7.12 (m, 2H); 13C NMR (100 MHz, CDCl3) δ: 14.2, 40.1, 41.9, 55.3, 61.2, 74.6, 113.9, 118.0, 128.2, 133.0, 141.8, 156.9, 169.8; HRMS (EI) calc’d for C14H15NO2 (M – C3H5O2)+ 335.1733, found 335.1723.

Method B. In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N(p-methoxyphenyl)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at –78 °C. To it was added MeMgBr (0.20 mL, 0.23 mmol, 1.12 M THF). After the mixture was stirred for 15 min at room temperature, to it was added NBS (36.3 mg, 0.15 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 15 min at room temperature. Then, TMSCN (0.037 mL, 0.30 mmol) was added and the mixture was stirred for 15 min at room temperature. The reaction was quenched with sat aq NaHCO3 (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/nhexane = 1/4) to give the title compound 3 (10.9 mg, 23%) as a yellow oil. Rf = 0.5 (ethyl acetate/nhexane = 1/4); 1H NMR (400 MHz, CDCl3) δ: 1.21 (t, J = 7.1 Hz, 6H), 2.94 (s, 3H), 3.78 (s, 3H), 4.19–4.27 (m, 4H), 6.80–6.84 (m, 2H), 7.30–7.34 (m, 2H); 13C NMR (100 MHz, CDCl3) δ: 13.7, 41.5, 55.4, 64.1, 74.9, 113.5, 114.2, 127.1, 140.5, 158.1, 161.9; HRMS (EI) calc’d for C14H16N2O2 (M – C3H5O2)+ 320.1372, found 320.1363.

4.4 Synthesis of diethyl 2-[N(4-methoxyphenyl)-N-methylamino]-2-allylmalonate (4a)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N(p-methoxyphenyl)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at –78 °C. To it was added MeMgBr (0.20 mL, 0.23 mmol, 0.99 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (40.0 mg, 0.23 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO3 (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/nhexane = 1/4) to give the title compound 4a (35.4 mg, 74%) as a colorless oil. Rf = 0.5 (ethyl acetate/nhexane = 1/4); 1H NMR (400 MHz, CDCl3) δ: 1.29 (t, J = 7.1 Hz, 6H), 2.60 (d, J = 6.9, 2H), 2.95 (s, 3H), 3.77 (s, 3H), 4.26 (q, J = 7.0), 4.93–5.01 (m, 2H), 5.79–5.89 (m, 1H), 6.77–6.81 (m, 2H), 7.08–7.12 (m, 2H); 13C NMR (100 MHz, CDCl3) δ: 14.2, 40.1, 41.9, 55.3, 61.2, 74.6, 113.9, 118.0, 128.2, 133.0, 141.8, 156.9, 169.8; HRMS (EI) calc’d for C14H15NO2 (M – C3H5O2)+ 335.1733, found 335.1723.

4.5 Synthesis of diethyl 2-[N(4-methoxyphenyl)-N-ethylamino]-2-allylmalonate (4b)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N(p-methoxyphenyl)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at –78 °C. To it was added EtMgBr (0.25 mL, 0.23 mmol, 0.91 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (26.7 mg, 0.15 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO3 (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/nhexane = 1/4) to give the title compound 4b (35.6 mg, 68%) as a colorless oil. Rf = 0.5 (ethyl acetate/nhexane = 1/6, developed twice); 1H NMR (400 MHz, CDCl3) δ: 0.90 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 6H), 2.44–2.46 (m, 2H), 3.17 (q, J = 6.9 Hz, 2H), 3.78 (s, 3H), 4.25 (q, J = 7.2 Hz, 4H), 4.91–4.99 (m, 2H), 5.78–5.89 (m, 1H), 6.78–6.82 (m, 2H), 7.08–7.12 (m, 2H); 13C NMR (100 MHz, CDCl3) δ: 14.2, 14.9, 40.4, 48.4, 55.3, 61.1, 75.6, 113.8, 117.7, 131.2, 133.4, 138.4, 157.8, 170.3; HRMS (EI) calc’d for C14H17N2O2 (M – C3H5O2)+ 349.1892, found 349.1892.

4.6 Synthesis of diethyl 2-[N(4-methoxyphenyl)-N-propylamino]-2-allylmalonate (4c)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was
placed diethyl 2-[N-(p-methoxyphenyl)limino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at −78 °C. To it was added nPrMgBr (0.24 mL, 0.23 mmol, 0.93 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (26.7 mg, 0.15 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO₃ (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/n-hexane = 1/4) to give the title compound 4d (40.7 mg, 72%) as a yellow oil. 

\[ R_1 = 0.5 \text{ (ethyl acetate/n-hexane = 1/4)}; \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta = 0.82 \left( t, J = 18.3 \text{ Hz}, 3H \right), 1.28 \left( m, 8H \right), 2.44 \left( d, J = 6.9 \text{ Hz}, 2H \right), 3.08 \left( t, J = 7.4 \text{ Hz}, 2H \right), 3.78 \left( s, 2H \right), 4.25 \left( q, J = 6.9 \text{ Hz}, 4H \right), 4.92–4.98 \left( m, 2H \right), 5.77–5.88 \left( m, 1H \right), 6.78–6.82 \left( m, 2H \right), 7.09–7.13 \left( m, 2H \right); \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta = 11.2, 14.2, 22.3, 40.5, 55.3, 55.7, 61.0, 75.6, 113.7, 117.7, 130.9, 133.4, 138.7, 157.7, 170.2; \]

HRMS (EI) calced for C₂₀H₂₉NO₅ (M + C₃H₅O₂)⁺, found 363.2046.

4.7 Synthesis of diethyl 2-[N-(4-methoxyphenyl)-N-butylimino]-2-allylmalonate (4d)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N-(p-methoxyphenyl)limino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at −78 °C. To it was added nBuMgBr (0.20 mL, 0.23 mmol, 1.1 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (26.7 mg, 0.15 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO₃ (20.0 mL), and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/n-hexane = 1/4) to give the title compound 4d (40.7 mg, 72%) as a yellow oil.

\[ R_1 = 0.5 \text{ (ethyl acetate/n-hexane = 1/4)}; \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta = 0.82 \left( t, J = 18.3 \text{ Hz}, 3H \right), 1.24–1.32 \left( m, 10H \right), 2.44 \left( d, J = 6.9 \text{ Hz}, 2H \right), 3.10 \left( t, J = 6.8 \text{ Hz}, 2H \right), 3.79 \left( s, 3H \right), 4.25 \left( q, J = 7.1 \text{ Hz}, 4H \right), 4.92–4.98 \left( m, 2H \right), 5.78–5.88 \left( m, 1H \right), 6.79–6.82 \left( m, 2H \right), 7.08–7.12 \left( m, 2H \right); \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta = 11.5, 14.1, 22.6, 40.0, 51.5, 55.2, 61.14, 74.65, 113.0, 133.1, 139.7, 157.5, 171.57; \]

HRMS (EI) calced for C₂₀H₂₉NO₅ (M + C₃H₅O₂)⁺, found 363.2046.

4.8 Synthesis of diethyl 2-[N-(4-methoxyphenyl)-N-(2-propylamino)]-2-allylmalonate (4e)

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed diethyl 2-[N-(p-methoxyphenyl)limino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at −90 °C. To it was added iPrMgBr (0.27 mL, 0.23 mmol, 0.85 M THF). After the mixture was stirred for 15 min at room temperature, to it were added NBS (26.7 mg, 0.15 mmol) and EtCN (1.0 mL), and the reaction mixture was stirred for 1 min at room temperature. Then, tetraallylstannane (0.054 mL, 0.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with sat aq NaHCO₃ (20.0 mL), and the whole mixture was extracted with...
ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/n-hexane = 1/4) to give the title compound 4a (26.3 mg, 55%) as a colorless oil.

4.11 Synthesis of 2-[(4-methoxyphenyl)-N,N-methylamino]-2-allylpropan-1,3-diol (6a)

In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon, were placed LiAlH₄ (0.33 g, 8.7 mmol). To it was added a solution of diethyl 2-[(4-methoxyphenyl)-N,N-methylamino]-2-allylmalonate (1.0 g, 3.1 mmol) in Et₂O (30 mL) at 0 °C, and the mixture was stirred for 40 min under argon. The reaction was quenched with sat aq Na₂SO₄, and the whole mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the crude product was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to give the title compound 6a (0.64 g, 81%) as a colorless oil. Rf = 0.1 (ethyl acetate/n-hexane = 1/2); 1H NMR (400 MHz, CDCl₃): δ: 2.25 (d, J = 7.3 Hz, 2H), 2.55 (s, 2H), 2.82 (s, 3H), 3.60 (q, J = 11.5, 8.4 Hz, 2H), 1.80 (s, 3H), 5.05–5.12 (m, 2H), 5.78–5.83 (m, 1H), 6.82–6.86 (m, 2H), 7.21–7.25 (m, 2H); 13C NMR (100 MHz, CDCl₃): δ: 34.7, 37.3, 55.4, 63.8, 64.7, 113.8, 118.3, 129.0, 133.8, 141.9, 157.1; HRMS (EI) calecd for C₁₄H₂₁NO₃ (M+): 251.1521, found 251.1524.

4.12 Desymmetrization of 2-[(4-methoxyphenyl)-N,N-methylamino]-2-allylpropan-1,3-diol

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed Cu(OtBu)₂ (10.9 mg, 0.03 mmol) and Bnbox (10.9 mg, 0.03 mmol). To it were added a solution of 2-[(4-methoxyphenyl)-N,N-methylamino]-2-allylpropan-1,3-diol (37.7 mg, 0.15 mmol) in THF (1.5 mL) and PhNCO/16.0 μL, 0.15 mmol). After the mixture was stirred for 40 min at room temperature, it was quenched with H₂O (20.0 mL) and the whole mixture was extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude product was purified on silica gel TLC (ethyl acetate/n-hexane = 1/2) to give 2-[(4-methoxyphenyl)-N,N-methylamino]-2-allyl-3-hydroxypropylphenylcarbamate 7a (33.4 mg, 60%, 64% ee) as a colorless oil. Rf = 0.3 (ethyl acetate/n-hexane = 1/2); 1H NMR (400 MHz, CDCl₃): δ: 2.25–2.35 (m, 2H), 2.83 (s, 3H), 2.92 (s, 1H), 3.54 (s, 2H), 3.75 (s, 3H), 4.12 (d, J = 11.7, 1H), 4.29 (d, J = 11.7, 1H), 5.10–5.14 (m, 2H), 5.78–5.88 (m, 1H), 6.57 (s, 1H), 6.80 (d, J = 8.8, 2H), 7.06–7.10 (m, 1H), 7.17 (d, J = 8.8, 2H), 7.29–7.35 (m, 4H); 13C NMR (100 MHz, CDCl₃): δ: 35.4, 37.5, 55.3, 62.0, 63.0, 65.2, 113.6, 118.7, 123.7, 129.1, 129.2, 133.4, 137.5, 141.8, 157.1; HRMS (EI) calecd for C₁₉H₁₄N₂O₄ (M+ - C₂H₄O₂)⁺: 370.1893, found 370.1905; HPLC (Daicel Chiralpak AD, flow rate = 1.0 mL min⁻¹, n-hexane/iPrOH = 30/1, detection at 254 nm, set temperature 35 °C).

Conflicts of interest
There are no conflicts to declare.

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