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Double nucleophilic addition to iminomalonate, leading to the synthesis of quaternary α-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 α-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 α-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 α-amino acid moieties are also found as fundamental skeletons in medicines and agrochemicals such as Ecteinascidin 743, Salinosporamide A, and Neooxazolomycin (Fig. 1).[3–5]

However, it is not trivial to construct quaternary α-amino acid frameworks in a stereoselective manner.[6] For the synthesis of α-amino acids and their derivatives α-imino esters are useful substrates, since α-imino esters have a unique reactivity: either *N*- or *C*-alkylation is possible. Although an umpolung *N*-alkylation reaction of α-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 α-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 α-aryl α-iminoester **2**, and the subsequent oxidation and allylation were conducted with benzoyl peroxide and allyltributylstannane, respectively (eqn (1), Scheme 2).[9b] During investigations into amination ability of iminomalonate **1** to organometallics, we found that not only organoaluminum compounds but also Grignard reagents were readily aminated to give 2-aminomalonates in good to high yields (eqn (1), Scheme 1).[9a] 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 α-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.

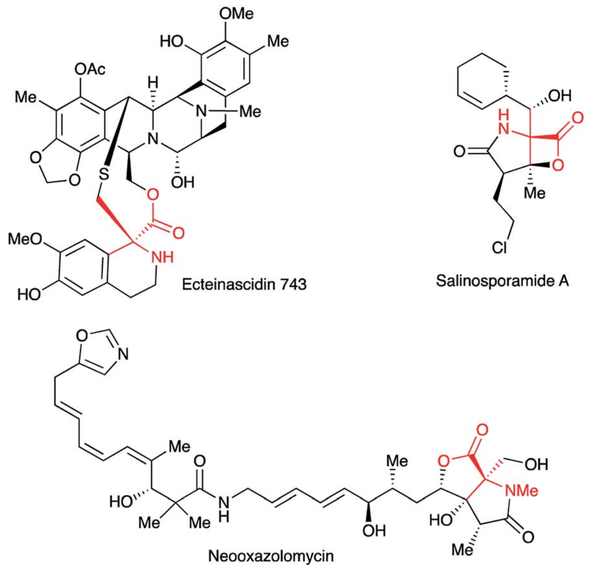

Fig. 1 Bioactive compounds possessing a quaternary α-amino acid structure.

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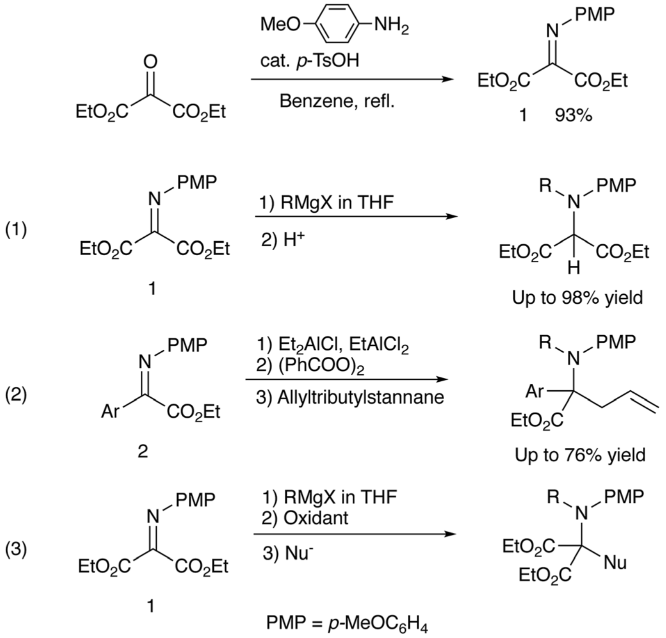


Scheme 1 Previous[9a,b] and present works.

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 α-amino diesters in good yields (eqn (3), Scheme 1).

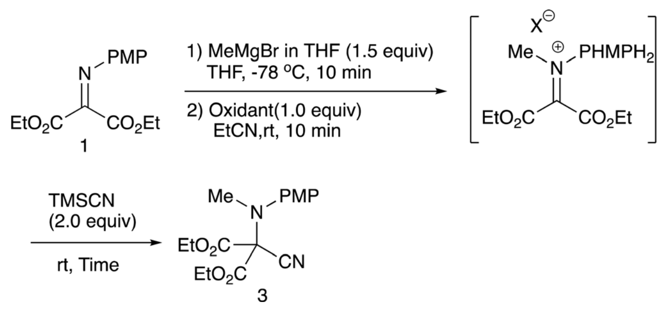
2 Results and discussion

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.[9b] 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, benzoyl peroxide (BPO) that was effective in the previous cyanation of α-iminoesters did not work,[9b] 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.

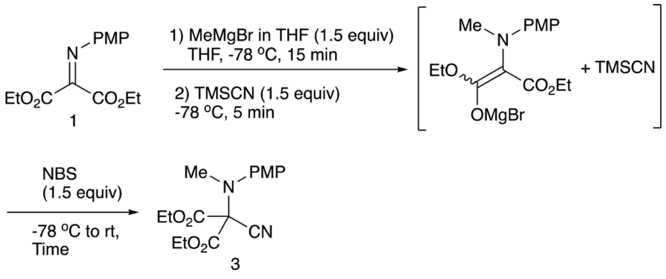
Table 1 Comparison of the oxidation reagents



Entry	Oxidant	Time (min)	Yield of **3**[a] (%)
1	BPO	15	0
2	NCS	15	8
3	NBS	15	18
4	NBS	30	23

[a] Isolated yield.

Table 2 Optimization of the reaction time



Entry	Time (min)	Yield of **3**[a] (%)
1	10	56
2	240	64
3	10	56

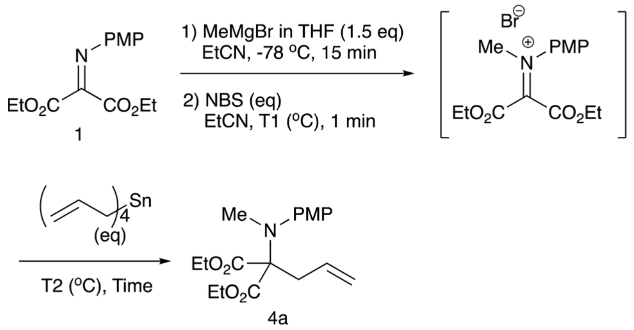
[a] Isolated yield.

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, teteraallylstannane effected the desired double addition reaction most efficiently. Treatment of the iminomalonate **1** with methylmagnesium bromide (1.5 equiv.) at −78 °C followed by oxidation with NBS (1.5 equiv.) and allylation with tetrallylstannane (1.0 equiv.) gave the desired

Table 3 Optimization of allylation reaction

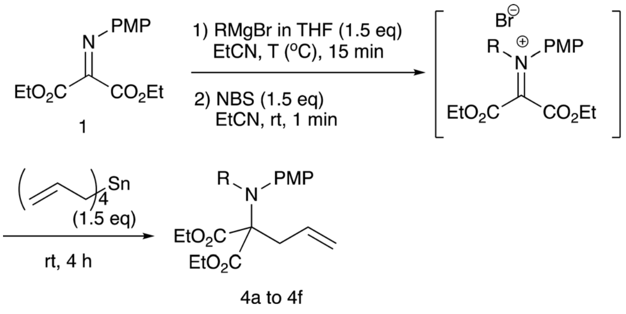


Entry	NBS (equiv.)	T_1 (°C)	Nu (equiv.)	T_2 (°C)	Time (h)	Yield[a] (%)
1	1.5	−78	1.0	−78 to rt	4	47
2	1.5	−78	1.5	−78 to rt	4	59
3	1.5	rt	1.5	rt	4	74
4	1.0	rt	1.5	rt	4	59
5	1.5	rt	1.5	rt	2	56

[a] Isolated yield.

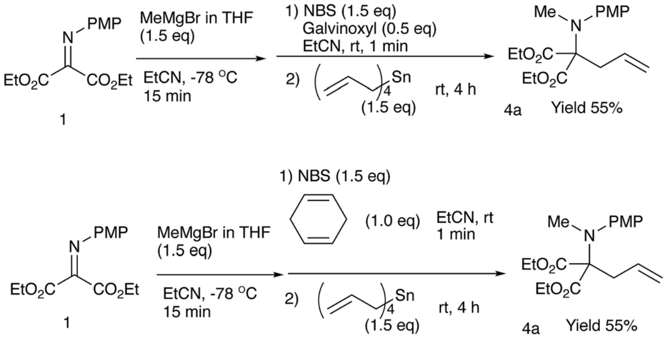
double addition product **4a** in 47% yield (entry 1). Further examination into the reactions led to the optimum conditions. Use of NBS (1.5 equiv.) and tetrallylstannane (1.5 equiv.) at room temperature afforded the desired product **4a** in 74% yield (entry 3). Under the optimized conditions, various 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

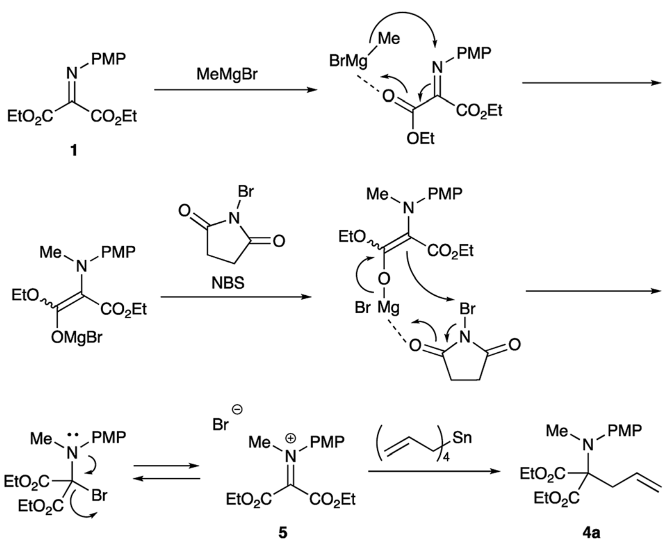


Entry	RMgX	T (°C)	**4**: Yield[a] (%)
1	MeMgBr	−78	**4a**: 74
2	EtMgBr	−78	**4b**: 68
3	*n*PrMgBr	−78	**4c**: 79
4	*n*BuMgBr	−78	**4d**: 72
5	iPrMgBr	−90	**4e**: 40
6	*t*BuMgBr	−90	**4f**: Trace
7	PhMgBr	−90	**4g**: 0

[a] Isolated yield.



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



Scheme 3 Proposed reaction mechanism.

2.3 *N*-Alkylation/*C*-allylation reactions

As shown in Table 4, methyl, ethyl, *n*propyl, and *n*butyl Grignard reagents underwent *N*-addition reaction rapidly and cleanly, and the subsequent oxidation and allylation 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).[9a] To examine the reaction pathways, these control experiments were carried out (Scheme 2).

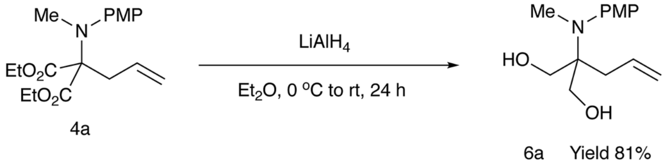
2.4 Control experiments and a proposed reaction mechanism

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,[9b] 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 **5**. This iminium salt **5** is attacked by tetraallylstannane to give the desired double addition product **4a**.

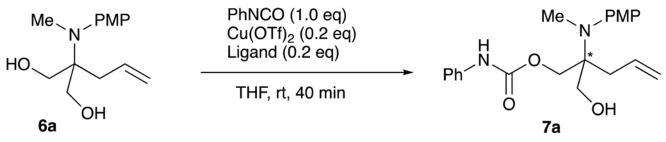
2.5 Desymmetrization of the products

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.[10] 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.[11] The reduction of the diester **4a** was carried out using $LiAlH_4$ to give the diol **6a** in 81% yield (Scheme 4). Table 5 summarizes the results of the subsequent desymmetrization.



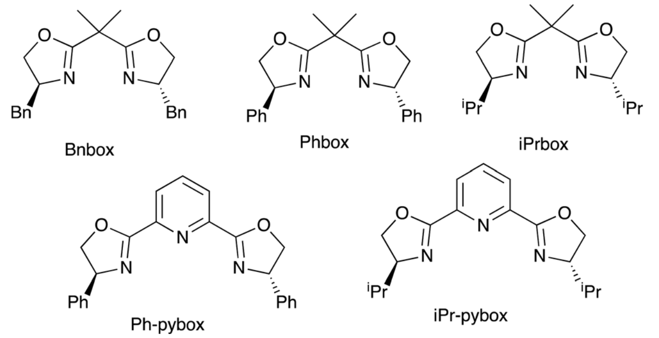
Scheme 4 Reduction of the diester **4a**.

Table 5 Comparison of the chiral ligands



Entry	Ligand	Yield[a] (%)	Ee[b] (%)
1	Bnbox	60	64
2	Bnbox[c]	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.



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.

3 Conclusions

A double nucleophilic addition to iminomalonate was developed using the tandem *N*-alkylation/oxidation/allylation reaction of diethyl 2-[*N*-(*p*-methoxyphenyl)imino]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(II)-Bnbox gave a monocarbamate in good enantiomeric excess.

4 Experimental

4.1 General aspects

^1H NMR and ^{13}C 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-

700D spectrometer. High performance liquid chromatography was carried out using these apparatuses; HITACHI Pump L-2130, Column Oven L-2300, and UV Detector L-2400. Propionitrile (EtCN) was distilled from phosphorus pentaoxide and then from calcium hydride, and stored over Molecular Sieves 4A. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified with a Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. Benzene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4A. Purification of products 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.[9a,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 10 min at room temperature, to it were 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 at room temperature for 30 min. The reaction was quenched with sat aq $NaHCO_3$ (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/4) to give the title compound **3** (10.9 mg, 23%) as a yellow oil. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/4); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) calcd for $C_{16}H_{20}N_2O_5$ $(M - C_3H_5O_2)^+$ 320.1372, found 320.1363.

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 −78 °C, TMSCN (28.0 μL, 0.23 mmol) was added at that temperature and the mixture was stirred for 5 min. Then, NBS (40.0 mg, 0.23 mmol) and EtCN (1.0 mL) were added, and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched with sat aq $NaHCO_3$ (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/4) to give the title compound **3** (30.6 mg, 64%) as a yellow oil.

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 $NaHCO_3$ (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 Na_2SO_4, 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** (35.4 mg, 74%) as a colorless oil. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/4); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) calcd for $C_{18}H_{25}NO_5$ $(M - C_3H_5O_2)^+$ 355.1733, found 355.1723.

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 $NaHCO_3$ (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/4) to give the title compound **4b** (35.6 mg, 68%) as a colorless oil. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/6, developed twice); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) calcd for $C_{19}H_{27}NO_5$ $(M - C_3H_5O_2)^+$ 349.1889, 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)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at −78 °C. To it was added *n*PrMgBr (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 $NaHCO_3$ (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/4) to give the title compound **4c** (43.3 mg, 79%) as a yellow oil. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (t, $J = 18.3$ Hz, 3H), 1.28 (m, 8H), 2.44 (d, $J = 6.9$ Hz, 2H), 3.08 (t, $J = 7.4$ Hz, 2H), 3.78 (s, 2H), 4.25 (q, $J = 6.9$ Hz, 4H), 4.92–4.98 (m, 2H), 5.77–5.88 (m, 1H), 6.78–6.82 (m, 2H), 7.09–7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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) calcd for $C_{20}H_{29}NO_5$ $(M - C_3H_5O_2)^+$ 363.2046, found 363.2038.

4.7 Synthesis of diethyl 2-[*N*-(4-methoxyphenyl)-*N*-butylamino]-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)imino]malonate (41.9 mg, 0.15 mmol) in THF (1.0 mL) at −78 °C. To it was added *n*BuMgBr (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 $NaHCO_3$ (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 Na_2SO_4, 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. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, $J = 6.8$ Hz, 3H), 1.24–1.32 (m, 10H), 2.44 (d, $J = 6.9$ Hz, 2H), 3.10 (t, $J = 6.8$ Hz, 2H), 3.79 (s, 3H), 4.25 (q, $J = 7.1$ Hz, 4H), 4.92–4.98 (m, 2H), 5.78–5.88 (m, 1H), 6.79–6.82 (m, 2H), 7.08–7.12 (m, 2H): ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2, 20.0, 31.5, 40.5, 53.8, 55.3, 61.0, 75.6, 113.7, 117.8, 130.9, 133.3, 138.7, 157.7, 170.2; HRMS (EI) calcd for $C_{21}H_{31}NO_5$ $(M - C_3H_5O_2)^+$ 377.2202, found 377.2201.

4.8 Synthesis of diethyl 2-[*N*-(4-methoxyphenyl)-*N*-(2-propyl)amino]-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)imino]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 $NaHCO_3$ (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/4) to give the title compound **4e** (22.1 mg, 40%) as a yellow oil. $R_f = 0.5$ (ethyl acetate/*n*hexane = 1/4); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (d, $J = 6.6$ Hz, 6H), 1.31 (t, $J = 7.1$ Hz, 6H), 2.50 (d, $J = 7.1$ Hz, 2H), 3.60–3.67 (m, 1H), 3.79 (s, 3H), 4.19–4.32 (m, 4H), 4.76–4.92 (m, 2H), 5.61–5.71 (m.1H), 6.77–6.81 (m, 2H), 7.06–7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.5, 14.1, 22.6, 40.0, 51.5, 55.2, 61.14, 74.65, 113.0, 117.7, 133.1, 133.9, 157.5, 171.57; HRMS (EI) Calculated for $C_{20}H_{29}NO_5$ $(M - C_3H_5O_2)^+$ 363.2046, found 363.2043.

4.9 Synthesis of diethyl 2-[*N*-(4-methoxyphenyl)-*N*-methylamino]-2-allylmalonate (4a) in the presence of galvioxiyl

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), galvioxyl (7.2 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 $NaHCO_3$ (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 Na_2SO_4, 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.

4.10 Synthesis of diethyl 2-[*N*-(4-methoxyphenyl)-*N*-methylamino]-2-allylmalonate (4a) in the presence of 1,4-cyclohexadiene

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), 1,4-cyclohexadiene (80.13 mg, 0.075 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 $NaHCO_3$ (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 Na_2SO_4, 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-[*N*-(4-methoxyphenyl)-*N*-methylamino]-2-allylpropan-1,3-diol (6a)

In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, an argon balloon, and a rubber septum was placed $LiAlH_4$ (0.33 g, 8.7 mmol). To it was added a solution of diethyl 2-[*N*-(4-methoxyphenyl)-*N*-methylamino]-2-allylmalonate (1.0 g, 3.1 mmol) in Et_2O (30 mL) at 0 °C, and the whole mixture was stirred at room temperature for 16 h. The reaction was quenched with sat aq Na_2SO_4, and the whole mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give a crude oil, which 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. R_f = 0.1 (ethyl acetate/*n*hexane = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (d, J = 7.3 Hz, 2H), 2.55 (s, 2H), 2.82 (s, 3H), 3.63 (q, J = 11.5, 8.4 Hz, 4H), 3.80 (s, 3H), 5.05–5.12 (m, 2H), 5.73–5.83 (m, 1H), 6.82–6.86 (m, 2H), 7.21–7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 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) calcd for $C_{14}H_{21}NO_3$ $(M - C_3H_5O_2)^+$ 251.1521, found 251.1524.

4.12 Desymmetrization of 2-[*N*-(4-methoxyphenyl)-*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 $Cu(OTf)_2$ (10.9 mg, 0.03 mmol) and Bnbox (10.9 mg, 0.03 mmol). To it were added a solution of 2-[*N*-(4-methoxyphenyl)-*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 H_2O (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 Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (ethyl acetate/*n*hexane = 1/2) to give 2-[*N*-(4-methoxyphenyl)-*N*-methylamino]-2-allyl-3-hydroxypropylphenylcarbamate **7a** (33.4 mg, 60%, 64% ee) as a colorless oil. R_f = 0.3 (ethyl acetate/*n*hexane = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) calcd for $C_{21}H_{26}N_2O_4$ $(M - C_3H_5O_2)^+$ 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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