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Conjugate addition of aromatic amines to ethenetricarboxylates

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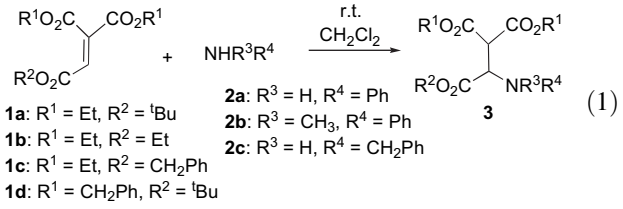
Abstract—The conjugate addition of amines is considered to be a useful reaction in synthetic organic chemistry. The reaction of reactive electrophilic olefins, ethenetricarboxylates, and aromatic amines with and without catalytic Lewis acids such as $ZnCl_2$ and $ZnBr_2$ at room temperature gave amine adducts in high yields. The products were converted to α-amino acid, DL-aspartic acid derivatives. Using Lewis acids such as $Sc(OTf)_3$ and $Zn(OTf)_2$ at higher temperature (40–80 °C), the reaction of ethenetricarboxylates and *N*-methylaniline gave an aromatic substitution product. A catalytic enantioselective conjugate addition using a chiral Lewis acid was also investigated. For example, the reaction of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate with *N*-methylaniline in the presence of chiral bisoxazoline-Cu(II) complex in THF at −20 °C for 17 h gave an amine adduct in 91% yield and 78% ee. On the other hand, the reaction with aniline and primary aniline derivatives gave adducts with almost no ee%.

1. Introduction

The conjugate addition of amines is considered to be a useful reaction in synthetic organic chemistry.[1] The reaction leads to formation of carbon–nitrogen bonds and β-amino acid derivatives.[2] The conjugate addition reaction sometimes involves reversibility arising from negative reaction entropy.[3] The exploration of both kinetically and thermodynamically favorable and synthetically useful systems is of high interest. We are interested in exploring reactivity and utility of highly electrophilic olefins, ethenetricarboxylates **1**.[4] The reaction of **1** and amines may lead to α-amino acid derivatives. Nucleophilic reaction of aromatic amines also involves a selectivity issue for nitrogen addition (C–N bond formation) or aromatic substitution (C–C bond formation). In this work, the reaction of ethenetricarboxylates with aromatic amines, transformation of the aza-Michael adducts to aspartic acid derivatives, and chiral Lewis acid-catalyzed reaction were investigated. Selective formation of a C–N or C–C bond in the presence of Lewis acid has been also found in the reaction of **1** and *N*-methylaniline.

2. Results and discussion

The reaction of reactive electrophilic olefins, ethenetricarboxylates **1**, and various amines with and without catalytic Lewis acids was investigated. The reaction of ethenetricarboxylates **1a–d** and aromatic amines **2a–c** in dichloromethane at room temperature overnight and subsequent work-up gave amine adducts **3** in high yields (Eq. 1, Table 1). The products from aniline **2a** and *N*-methylaniline **2b** are stable to silica gel column chromatography. The amine adducts from aliphatic amines such as benzylamine **2c**, pyrrolidine, and *N*-methyl benzylamine are obtained quantitatively as well, however, they are unstable to silica gel column chromatography and partially decomposed to starting materials.[5] The reaction of diethyl benzylidene malonate ($PhCH{=}C(CO_2Et)_2$) with *N*-methylaniline **2b** did not give an adduct in dichloromethane at room temperature with and without $ZnCl_2$.



(1)

Table 1. Reaction of **1** and **2** without Lewis acid in CH_2Cl_2

Entry	Substrate	R^1	R^2	Amine	R^3	R^4	**3** (Yield, %)[a]
1	**1a**	Et	^{t}Bu	**2a**	H	Ph	**3a** (98)
2	**1a**	Et	^{t}Bu	**2b**	CH_3	Ph	**3b** (91)
3	**1b**	Et	Et	**2a**	H	Ph	**3c** (88)
4	**1b**	Et	Et	**2b**	CH_3	Ph	**3d** (100)
5	**1c**	Et	CH_2Ph	**2b**	CH_3	Ph	**3e** (94[b])
6	**1d**	CH_2Ph	^{t}Bu	**2a**	H	Ph	**3f** (98)
7	**1d**	CH_2Ph	^{t}Bu	**2b**	CH_3	Ph	**3g** (61)
8	**1d**	CH_2Ph	^{t}Bu	**2c**	H	CH_2Ph	**3h** (100)

[a] Isolated yield.
[b] A small amount of unreacted **1c** could not be removed.

Keywords: Ethenetricarboxylate; Aromatic amine; Conjugate addition; Lewis acid.
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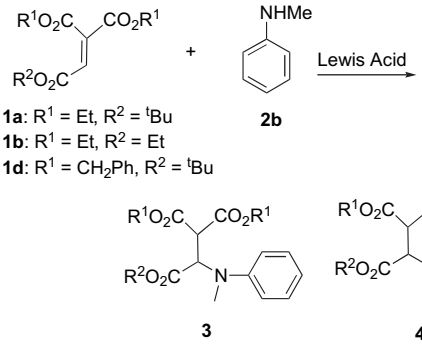
^{1}H NMR spectra of a mixture of **1a** and aniline **2a** in $CDCl_3$ showed the immediate formation of adducts **3a**. On the other hand, the reaction of **1a** and *N*-methylaniline **2b** proceeds slowly as shown in Figure 1. The reaction was not complete after 18 h. The reaction might complete by concentration of the solution, because the reaction without solvent proceeds faster. Equilibrium in solution is assumed. ΔG° differences of **1b+2b→3d** were calculated as positive values (less stable), +16.0 and +15.4 kcal/mol by B3LYP/6-31G* in the gas phase and SCRF=dipole (solvent CH_2Cl_2), respectively.[6,7] The compound **3d** was also calculated to have a large dipole moment, μ=9.39 D. The observation that the equilibrium is shifted to the right without solvent can be understood by stabilization of dipole–dipole interactions between molecules of the products **3**.[8]

The reaction of **1a** and **2b** in the presence of zinc chloride (0.2 equiv) in $CDCl_3$ at room temperature proceeded further faster than without solvent to give **3b**. The reaction of **1a** and **2b** in the presence of $ZnCl_2$, $ZnBr_2$, and $Sc(OTf)_3$ (0.2 equiv) at room temperature gave **3b** in high yields.[9] Using Lewis acids such as $ZnCl_2$, $Sc(OTf)_3$, and $Zn(OTf)_2$ at higher temperature (40–80 °C), the reaction of **1** and *N*-methylaniline **2b** gave an aromatic substitution product **4a** as the major product (Eq. 2, Table 2).[10] In addition, the reaction of isolated **3b** with $Sc(OTf)_3$ (0.2 equiv) in CH_2Cl_2 at 40 °C for 4 h gave **4b** in 75% yield.[11] The formation of a C–N bond must be reversible and amine adducts **3** are transformed to the stable C–C bond formation in the presence of the Lewis acid at higher temperature. A small amount of compound **5** was isolated from the reaction shown in entries 4 and 5. Compound **5** may be transiently formed during the formation of **4a** and it also shows the reversibility of C–N bond formation.



(2)

The amine adducts **3** are considered as β- and α-amino acid equivalents.[12] Product elaboration was attempted. Thus, the amine adducts **3f** and **3h** were converted to DL-aspartic acid derivatives (Eq. 3). Dibenzyl esters **3f** and **3h** were transformed to acetyl products **6a** and **6b** in order to decrease the basicity of nitrogen and increase the stability toward β-elimination of amine. Hydrogenolysis of **6a** and **6b** and subsequent decarboxylation led to DL-aspartic acid derivatives **7a** and **7b** smoothly.

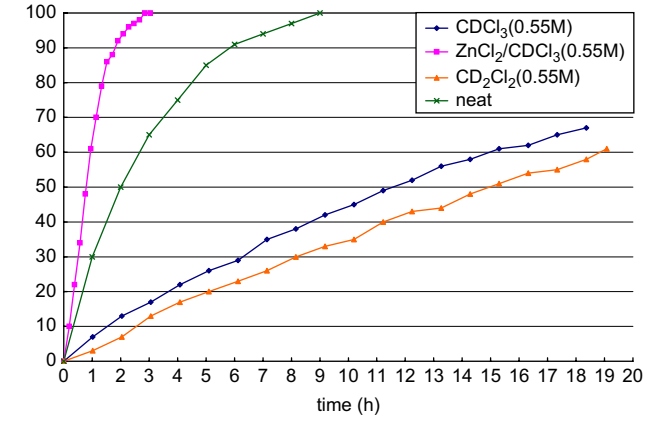
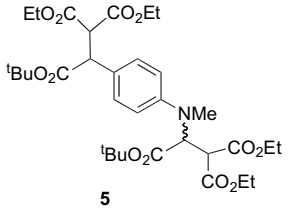


Figure 1. Reaction of **1a** and *N*-methylaniline **2b** (25 °C). Product percentage was estimated by NMR.

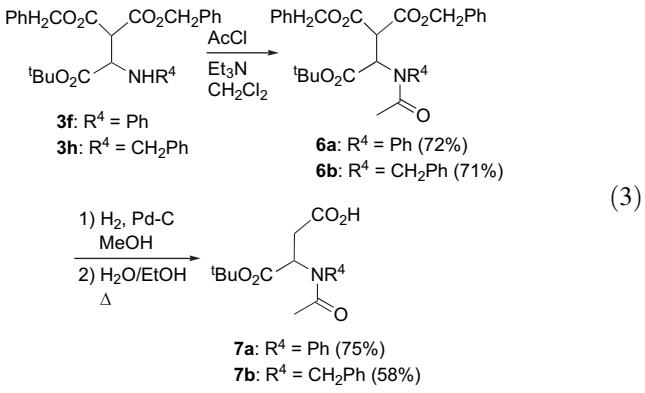
Table 2. Reaction of **1** and **2b** in the presence of Lewis acid

Entry	Substrate	Lewis acid (equiv)	Solvent	Condition	**3** (Yield, %)	**4** (Yield, %)
1	**1a**	$ZnCl_2$ (0.2)	CH_2Cl_2	rt,[a] 16 h	**3b** (89)	
2	**1a**	$ZnBr_2$ (0.2)	CH_2Cl_2	rt,[a] 16 h	**3b** (70)	
3	**1a**	$Sc(OTf)_3$ (0.2)	CH_2Cl_2	rt,[a] 16 h	**3b** (quant.)	
4	**1a**	$ZnCl_2$ (0.2)	CH_2Cl_2	40 °C, 16 h	**3b** (11)	**4a** (37)[b]
5	**1a**	$ZnCl_2$ (0.2)	$ClCH_2CH_2Cl$	80 °C, 2 h		**4a** (52)[c]
6	**1a**	$Zn(OTf)_2$ (0.2)	$ClCH_2CH_2Cl$	80 °C, 16 h		**4a** (42)
7	**1a**	$Sc(OTf)_3$ (0.2)	CH_2Cl_2	40 °C, 16 h		**4a** (58)
8	**1a**	$Sc(OTf)_3$ (0.2)	$ClCH_2CH_2Cl$	80 °C, 2 h		**4a** (75)
9	**1b**	$ZnCl_2$ (0.2)	CH_2Cl_2	rt,[a] 16 h	**3c** (77)	
10	**1b**	$Sc(OTf)_3$ (0.2)	CH_2Cl_2	40 °C, 18 h		**4b** (83)
11	**1b**	$Sc(OTf)_3$ (0.2)	$ClCH_2CH_2Cl$	80 °C, 17 h		**4b** (65)
12	**1d**	$ZnCl_2$ (0.2)	CH_2Cl_2	rt, 16 h	**3g** (77)	
13	**1d**	$Zn(OTf)_3$ (0.2)	$ClCH_2CH_2Cl$	40 °C, 16 h		**4c** (82)
14	**1d**	$Sc(OTf)_3$ (0.2)	$ClCH_2CH_2Cl$	40 °C, 16 h		**4c** (85)

[a] rt refers to ca. 20–25 °C.
[b] Compound **5** (as a diastereomixture) was isolated in 23% yield.
[c] Compound **5** was isolated in 8% yield.



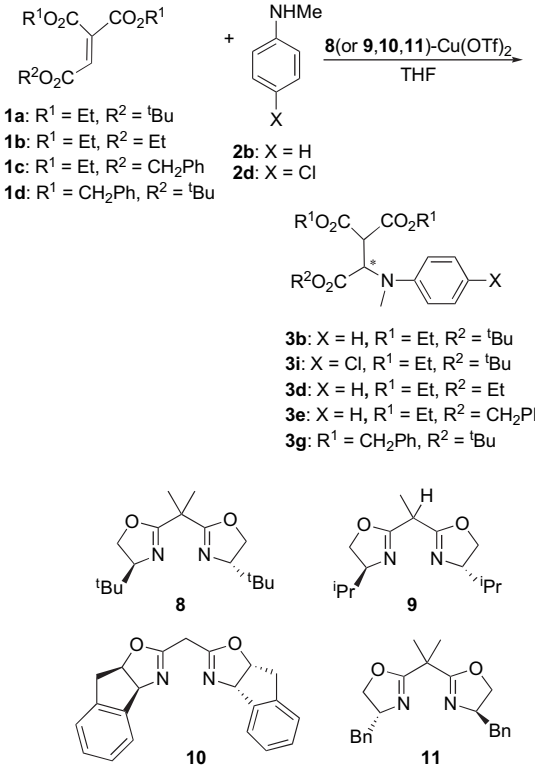
5



(3)

Catalytic enantioselective conjugate addition using a chiral Lewis acid was also investigated. Chiral bisoxazolines were first examined as chiral ligands of Lewis acid because the Friedel–Crafts reaction of substrates **1** using the catalysts has been proven to be effective.[4d] The reaction of 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate **1a** with aniline **2a** in the presence of a catalytic amount of chiral bisoxazoline ((*S*,*S*)-2,2′-isopropylidene bis-(4-*tert*-butyl-2-oxazoline) **8**) copper(II) complex, **8**-Cu(OTf)$_2$[13] (10%) in THF was first examined, however, the reaction gave an adduct with almost no ee%. The reaction of **1a** with *N*-methylaniline **2b** in the presence of **8**-Cu(OTf)$_2$ (10%) in THF at room temperature overnight gave an amine adduct **3b** in 79% yield and 40% ee (Eq. 4, Table 3). When the reaction temperature was decreased to −20 °C, the reaction gave an amine adduct **3b** in 91% yield and 78% ee. The reaction did not proceed at −40 °C. Reactions of substrates **1a–d** and *N*-methylanilines **2b** and **2d** under various reaction conditions such as use of chiral ligands **9**[14] and **10** and other metal triflates were also examined. Use of **8**-Zn(OTf)$_2$ also gave similar ee% at room temperature and −20 °C compared to use of **8**-Cu(OTf)$_2$ (entries 6 and 7). By use of **8**-Mg(OTf)$_2$ or **8**-Sc(OTf)$_3$ the reaction proceeded with almost no ee%. Chiral ligands **9** gave similar ee% at room temperature compared to **8** (entries 8 and 17), whereas ligands **10** and **11** gave lower ee% (entries 9, 10, 18, and 19). Reactions in dichloromethane have also been examined (entries 4, 5, 20, and 21). Use of CH_2Cl_2 gave similar or lower yields and ee% compared to THF in the most cases. The detailed solvent effects are under investigation. Aniline **2a** as described above and primary aniline derivatives **2e–g** bearing *para* and *ortho*-substituents (4-CF_3, 2-OCH_3, and 2-Cl) gave almost no ee% (Eq. 5).

The obtained amine adducts in enantiomerically enriched form did not give suitable crystals for X-ray analysis and the absolute stereochemistry has not been determined yet.

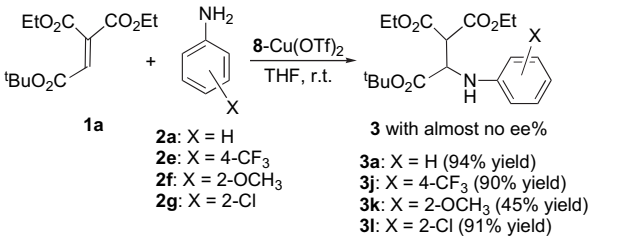


(4)

Table 3. Reaction of **1** with **2** in the presence of chiral Lewis acid

Entry	Substrate	Amine	Lewis acid	Condition	**3** (Yield, %)	ee (%)	$[\alpha]_D$ (°)
1	**1a**	**2b**	**8**-Cu(OTf)$_2$	rt/THF	**3b** (79)	40	−84
2	**1a**	**2b**	**8**-Cu(OTf)$_2$	−20 °C/THF	**3b** (91)	78	−163
3	**1a**	**2b**	**8**-Cu(OTf)$_2$	−40 °C/THF	No reaction		
4	**1a**	**2b**	**8**-Cu(OTf)$_2$	rt/CH_2Cl_2	**3b** (53)[b]	69	−126
5	**1a**	**2b**	**8**-Cu(OTf)$_2$	−20 °C/CH_2Cl_2	**3b** (86)[b]	77	−146
6	**1a**	**2b**	**8**-Zn(OTf)$_2$	rt/THF	**3b** (56)	49	−110
7	**1a**	**2b**	**8**-Zn(OTf)$_2$	−20 °C/THF	**3b** (54)	61	−115
8	**1a**	**2b**	**9**-Cu(OTf)$_2$	rt/THF	**3b** (83)	49	−100
9	**1a**	**2b**	**10**-Cu(OTf)$_2$	rt/THF	**3b** (56)	39	−64
10	**1a**	**2b**	**11**-Cu(OTf)$_2$	rt/THF	**3b** (75)	0.9	−5.5
11	**1a**	**2d**	**8**-Cu(OTf)$_2$	rt/THF	**3i** (74)	75	−110
12	**1a**	**2d**	**8**-Cu(OTf)$_2$	−20 °C/THF	**3i** (87)	87	−159
13	**1b**	**2b**	**8**-Cu(OTf)$_2$	rt[a]/THF	**3d** (78)	41	−103
14	**1c**	**2b**	**8**-Cu(OTf)$_2$	rt[a]/THF	**3e** (75)	43	−61
15	**1d**	**2b**	**8**-Cu(OTf)$_2$	rt/THF	**3g** (58)	71	−80
16	**1d**	**2b**	**8**-Cu(OTf)$_2$	−20 °C/THF	**3g** (79)	41	−62
17	**1d**	**2b**	**9**-Cu(OTf)$_2$	rt/THF	**3g** (68)	58	−81
18	**1d**	**2b**	**10**-Cu(OTf)$_2$	rt/THF	**3g** (61)	22	−28
19	**1d**	**2b**	**11**-Cu(OTf)$_2$	rt/THF	**3g** (78)	18	+25
20	**1d**	**2b**	**8**-Cu(OTf)$_2$	rt/CH_2Cl_2	**3g** (48)	23	−23
21	**1d**	**2b**	**8**-Cu(OTf)$_2$	−20 °C/CH_2Cl_2	**3g** (69)	24	−29

[a] The reaction at −20 °C gave inferior yields and ee% to rt.
[b] A small amount of unreacted **1a** could not be removed.



(5)

Amine conjugate addition mechanisms in neutral conditions have been studied.[15,16] The studies suggest that the reaction proceeds with trimeric or dimeric amines. In Lewis acid-promoted amine conjugate addition, it may be also necessary to take into account the trimeric or dimeric forms of amine nucleophiles. Evans and co-workers have proposed a mechanism for the catalytic asymmetric Mukaiyama–Michael reaction of arylidene malonate.[17] However, the proposed facial selectivity is opposite to the Friedel–Crafts/Michael reaction of arylidene malonate and ethenetricarboxylates **1** with indoles because the two faces of the complex may not be simply differentiated.[4d] We have explained the observed enantioselectivity by the secondary orbital interaction on approach of indole to the less hindered side of bisoxazoline-Cu(II)-coordinated complex of **1**.[4d] The facial selectivity in conjugate addition of amines with bisoxazoline-Cu(II)-coordinated complex of **1** by steric interaction is not straightforward. The diastereomeric interaction of the two faces with amine nucleophile will be further investigated as well as the absolute stereochemistry determination.

One feature of the aromatic amine addition of **1** is that the products are relatively stable at room temperature and to silica gel column chromatography. In the reaction mechanism of β-elimination of amine in neutral and acidic conditions similar to the amine addition process, more molecules of **3** or eliminated amine may participate in the proton transfer step.[15,16] The acidity of malonate hydrogen and basicity of the amino group facilitate the elimination process. The introduction of an ester group at the 2-position of methylene malonates for a decrease in basicity of the amino group by electron-withdrawing effects and use of aromatic amines seem to increase the stability of the amine adducts toward silica gel column chromatography and room temperature conditions to some degree.

In summary, we have shown the reaction of ethenetricarboxylates with aromatic amines with and without catalytic Lewis acids such as $ZnCl_2$ and $ZnBr_2$ gave amine adducts in high yields. Transformation of the aza-Michael adducts to aspartic acid derivatives was demonstrated. The reaction of **1** and *N*-methylaniline **2b** with Lewis acids such as $Sc(OTf)_3$ and $Zn(OTf)_2$ at higher temperature (40–80 °C) gave an aromatic substitution product preferentially. Chiral Lewis acid-catalyzed reaction of **1** and *N*-methylaniline **2b** gave an amine adduct enantioselectively. A new utility of ethenetricarboxylates in organic synthesis has been demonstrated in this study. Further elaboration of the products as well as determination of the absolute stereochemistry of the chiral products and elucidation of the origin of enantioselectivity is under investigation.

3. Experimental section

3.1. General methods

Melting points are uncorrected. IR spectra were recorded in the FT-mode. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. ^{1}H chemical shifts are reported in parts per million relative to Me_4Si. ^{13}C chemical shifts are reported in parts per million relative to $CDCl_3$ (77.1 ppm). ^{19}F chemical shifts are reported in parts per million relative to $CFCl_3$. ^{13}C multiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. HPLC analysis was performed with a UV detector (detection, 254 nm light) and flow rate of 1.0 mL/min using a CHIRALPAK AS-H (0.46 cm×250 mm) column at 30 °C. Optical rotations were measured with a 1 cm i.d.×10 cm cell. All reactions were carried out under a nitrogen atmosphere.

3.2. Typical experimental procedure (Table 2, entry 1)

To a solution of **1a** (272 mg, 1.0 mmol) in dichloromethane (1.8 mL) were added *N*-methylaniline **2b** (107 mg, 0.11 mL, 1.0 mmol) and $ZnCl_2$ (27 mg, 0.2 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight (16 h). The reaction mixture was quenched by water and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give **3b** (338 mg, 89%).

3.2.1. Compound 3b. R_f=0.7 (hexane–ether=1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.07 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.35 (s, 9H), 2.79 (s, 3H), 3.94–4.09 (m, 2H), 4.16–4.27 (m, 2H), 4.17 (d, J=11.4 Hz, 1H), 5.06 (d, J=11.4 Hz, 1H), 6.80 (tt, J=7.2, 1.0 Hz, 1H), 6.93 (dd, J=8.8, 0.9 Hz, 2H), 7.20–7.25 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91 (q), 14.08 (q), 27.99 (q), 33.64 (q), 52.56 (d), 61.76 (t), 61.83 (t), 63.76 (d), 82.18 (s), 115.28 (d), 119.02 (d), 128.91 (d), 150.03 (s), 167.06 (s), 167.36 (s), 168.67 (s); IR (neat) 2982, 1752, 1721, 1602, 1502, 1369, 1291, 1255, 1147, 1032 cm^{-1}; MS (EI) m/z 379 (M^+, 18), 278 (100), 160 (54%); HRMS M^+ 379.1996 (calcd for $C_{20}H_{29}NO_6$ 379.1995).

3.2.2. 1-*tert*-Butyl 2,2-diethyl 1-(phenylamino)ethane-1,2,2-tricarboxylate (3a). R_f=0.6 (hexane–ether=1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J=7.1 Hz, 3H), 1.31 (t, J=7.1 Hz, 3H), 1.42 (s, 9H), 4.02 (d, J=5.2 Hz, 1H), 4.12–4.28 (m, 4H), 4.64 (d, J=5.2 Hz, 1H), 6.69–6.72 (m, 2H), 6.76 (tt, J=7.3, 1.0 Hz, 1H), 7.16–7.21 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.07 (q), 14.14 (q), 27.89 (q), 54.24 (d), 57.00 (d), 61.79 (t), 61.87 (t), 82.78 (s), 113.99 (d), 118.82 (d), 129.34 (d), 146.65 (s), 167.23 (s), 167.76 (s), 169.83 (s); IR (neat) 3386, 2980, 1735, 1604, 1509, 1370, 1255, 1155 cm^{-1}; MS (EI) m/z 365 (M^+, 23), 264 (100%); HRMS M^+ 365.1839 (calcd for $C_{19}H_{27}NO_6$ 365.1838).

3.2.3. Triethyl 1-(phenylamino)ethane-1,2,2-tricarboxylate (3c). R_f=0.5 (hexane–ether=1:1); colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.22 (t, J=7.1 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 4.05 (d, J=5.3 Hz, 1H), 4.11–4.28 (m, 6H), 4.74 (d, J=5.3 Hz, 1H), 6.70–6.73 (m, 2H), 6.77 (tt, J=7.4, 1.0 Hz, 1H), 7.16–7.21 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.02 (q), 14.08 (q), 54.22 (d), 56.56 (d), 61.91 (t), 61.96 (t), 114.01 (d), 119.01 (d), 129.37 (d), 146.36 (s), 167.16 (s), 167.66 (s), 171.04 (s); IR (neat) 3387, 2983, 1734, 1604, 1510, 1371, 1255, 1178, 1030 cm^{-1}; MS (FAB) m/z 338 (M+H)$^+$; HRMS (M+H)$^+$ 338.1600 (calcd for $C_{17}H_{24}NO_6$ 338.1604).

3.2.4. Triethyl 1-(*N*-methyl-*N*-phenylamino)ethane-1,2,2-tricarboxylate (3d). R_f=0.6 (hexane–ether=1:1); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (t, J=7.1 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 2.78 (s, 3H), 3.92–4.26 (m, 4H), 4.22 (d, J=11.2 Hz, 1H), 5.17 (d, J=11.2 Hz, 1H), 6.81 (tt, J=7.3, 1.0 Hz, 1H), 6.92–6.94 (m, 2H), 7.21–7.26 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.80 (q), 13.99 (q), 14.22 (q), 33.50 (q), 52.47 (d), 61.37 (t), 61.75 (t), 61.83 (t), 62.63 (d), 114.93 (d), 119.04 (d), 128.96 (d), 149.59 (s), 166.76 (s), 167.26 (s), 169.68 (s); IR (neat) 2983, 1734, 1600, 1505, 1369, 1261, 1175, 1028 cm^{-1}; MS (EI) m/z 351 (M$^+$, 42), 278 (100%); HRMS M$^+$ 351.1689 (calcd for $C_{18}H_{25}NO_6$ 351.1682).

3.2.5. 1-Benzyl 2,2-diethyl 1-(*N*-methyl-*N*-phenylamino)-ethane-1,2,2-tricarboxylate (3e). R_f=0.4 (hexane–ether=2:1); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06 (t, J=7.1 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 2.69 (s, 3H), 3.93–4.09 (m, 2H), 4.13–4.25 (m, 2H), 4.23 (d, J=11.4 Hz, 1H), 5.05 (d, J=12.5 Hz, 1H), 5.19 (d, J=12.5 Hz, 1H), 5.24 (d, J=11.4 Hz, 1H), 6.82 (tt, J=7.3, 0.9 Hz, 1H), 6.91 (d, J=8.1 Hz, 2H), 7.15–7.17 (m, 2H), 7.20–7.29 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.86 (q), 13.99 (q), 33.48 (q), 52.48 (d), 61.82 (t), 61.91 (t), 62.84 (d), 66.87 (t), 115.22 (d), 119.26 (d), 128.02 (d), 128.20 (d), 128.44 (d), 129.03 (d), 135.47 (s), 149.63 (s), 166.71 (s), 167.20 (s), 169.50 (s); IR (neat) 2982, 1734, 1600, 1505, 1455, 1370, 1260, 1227, 1166, 1114, 1032 cm^{-1}; MS (EI) m/z 413 (M$^+$, 1.6), 351 (49), 278 (100%); HRMS M$^+$ 413.1842 (calcd for $C_{23}H_{27}NO_6$ 413.1838).

3.2.6. 1-*tert*-Butyl 2,2-dibenzyl 1-(phenylamino)ethane-1,2,2-tricarboxylate (3f). R_f=0.6 (hexane–ether=1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.36 (s, 9H), 4.15 (d, J=5.1 Hz, 1H), 4.67 (d, J=5.1 Hz, 1H), 5.10 (d, J=12.3 Hz, 1H), 5.16 (d, J=12.3 Hz, 2H), 5.23 (d, J=12.4 Hz, 1H), 6.66 (d-like, J=7.5 Hz, 2H), 6.76 (t-like, J=7.3 Hz, 1H), 7.14–7.18 (m, 2H), 7.23–7.34 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 27.85 (q), 54.28 (d), 57.06 (d), 67.53 (t), 67.62 (t), 82.91 (s), 114.07 (d), 118.93 (d), 128.28 (d), 128.39 (d), 128.45 (d), 128.52 (d), 128.59 (d), 128.68 (d), 129.34 (d), 135.04 (s), 135.16 (s), 146.49 (s), 166.99 (s), 167.47 (s), 169.65 (s); IR (neat) 3388, 3033, 2988, 1739, 1603, 1506, 1456, 1370, 1256, 1152 cm^{-1}; MS (FAB) m/z 490 (M+H)$^+$; HRMS (M+H)$^+$ 490.2237 (calcd for $C_{29}H_{32}NO_6$ 490.2230).

3.2.7. 1-*tert*-Butyl 2,2-dibenzyl 1-(*N*-methyl-*N*-phenylamino)ethane-1,2,2-tricarboxylate (3g). R_f=0.6 (hexane–ether=2:1); pale yellow crystals; mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 9H), 2.73 (s, 3H), 4.31 (d, J=11.4 Hz, 1H), 4.87 (d, J=12.2 Hz, 1H), 5.00 (d, J=12.2 Hz, 1H), 5.07 (d, J=11.4 Hz, 1H), 5.14 (d, J=12.4 Hz, 1H), 5.22 (d, J=12.4 Hz, 1H), 6.81 (tt, J=7.1, 0.9 Hz, 1H), 6.87 (dd, J=8.8, 0.9 Hz, 2H), 7.07–7.09 (m, 2H), 7.17–7.34 (m, 10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 27.96 (q), 33.84 (q), 52.59 (d), 63.88 (d), 67.45 (t), 67.50 (t), 82.30 (s), 115.42 (d), 119.15 (d), 128.24 (d), 128.33 (d), 128.39 (d), 128.49 (d), 128.61 (d), 128.94 (d), 135.02 (s), 135.29 (s), 149.90 (s), 166.80 (s), 167.10 (s), 168.48 (s); IR (KBr) 2979, 1747, 1727, 1599, 1503, 1455, 1367, 1304, 1261, 1235, 1154 cm^{-1}; MS (EI) m/z 503 (M$^+$, 1.4), 405 (51), 187 (63), 159 (76), 141 (89), 59 (100%); HRMS M$^+$ 503.2309 (calcd for $C_{30}H_{33}NO_6$ 503.2308); Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.25; H, 6.67; N, 2.80.

3.2.8. 1-*tert*-Butyl 2,2-dibenzyl 1-(benzylamino)ethane-1,2,2-tricarboxylate (3h). R_f=0.4 (hexane–ether=1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.41 (s, 9H), 3.70 (d, J=13.0 Hz, 1H), 3.84 (d, J=7.1 Hz, 1H), 3.96 (d, J=13.0 Hz, 1H), 3.97 (d, J=7.1 Hz, 1H), 5.09–5.30 (m, 2H), 7.20–7.35 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 27.97 (q), 52.28 (t), 55.45 (d), 60.26 (d), 67.25 (t), 67.30 (t), 82.20 (s), 127.11 (d), 128.27 (d), 128.33 (d), 128.35 (d), 128.57 (d), 135.28 (s), 135.34 (s), 139.72 (s), 167.26 (s), 167.45 (s), 171.19 (s); IR (neat) 3344, 3032, 2977, 1738, 1497, 1456, 1369, 1259, 1152 cm^{-1}; MS (EI) m/z 398 (M$^+$−NH_2Ph, 16), 107 (H_2NCH_2Ph, 45), 91 (CH_2Ph, 100%).

3.2.9. 1-*tert*-Butyl 2,2-diethyl 1-(*N*-(4-chlorophenyl)-*N*-methylamino)ethane-1,2,2-tricarboxylate (3i). R_f=0.4 (hexane–ether=2:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.36 (s, 9H), 2.76 (s, 3H), 3.97–4.11 (m, 2H), 4.15 (d, J=11.4 Hz, 1H), 4.17–4.29 (m, 2H), 4.99 (d, J=11.4 Hz, 1H), 6.83–6.87 (m, 2H), 7.16–7.20 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.98 (q), 14.07 (q), 28.01 (q), 33.79 (q), 52.47 (d), 61.84 (t), 61.93 (t), 63.72 (d), 82.47 (s), 116.32 (d), 123.87 (s), 128.78 (d), 148.62 (s), 166.95 (s), 167.20 (s), 168.34 (s); IR (neat) 2981, 1732, 1597, 1498, 1369, 1258, 1154, 1034 cm^{-1}; MS (EI) m/z 415 (M$^+$, 12), 413 (M$^+$, 34), 314 (83), 312 (100), 194 (78%); HRMS M$^+$ 413.1602 (calcd for $C_{20}H_{28}{}^{35}ClNO_6$ 413.1605), 415.1598 (calcd for $C_{20}H_{28}{}^{37}ClNO_6$ 415.1576).

3.2.10. 1-*tert*-Butyl 2,2-diethyl 1-(4-(trifluoromethyl)-phenylamino)ethane-1,2,2-tricarboxylate (3j). R_f=0.4 (hexane–ether=1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.22 (t, J=7.1 Hz, 3H), 1.31 (t, J=7.1 Hz, 3H), 1.42 (s, 9H), 4.04 (d, J=4.9 Hz, 1H), 4.12–4.24 (m, 2H), 4.26 (q, J=7.1 Hz, 2H), 4.68 (d, J=4.9 Hz, 1H), 6.72 (d, J=8.4 Hz, 2H), 7.42 (dq, J=8.4, 0.6 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.05 (CH_3), 14.12 (CH_3), 27.88 (CH_3), 53.80 (CH), 56.24 (CH), 61.99 (CH_2), 62.07 (CH_2), 83.25 (C), 113.02 (CH), 120.39 (q, J_{CF}=33 Hz, C), 124.84 (q, J_{CF}=270 Hz, C), 126.73 (q, J_{CF}=3.8 Hz, CH), 149.31 (C), 167.00 (C), 167.74 (C), 169.24 (C); ^{19}F NMR (376 MHz, $CDCl_3$) −61.71; IR (neat) 3383, 2983, 1739, 1618, 1535, 1371, 1330, 1156, 1113, 1067 cm^{-1}; MS (EI) m/z 433 (M$^+$, 12), 332 (100%); HRMS M$^+$ 433.1720 (calcd for $C_{20}H_{26}F_3NO_6$ 433.1712).

3.2.11. 1-*tert*-Butyl 2,2-diethyl 1-(2-methoxyphenylamino)ethane-1,2,2-tricarboxylate (3k). R_f=0.5 (hexane–ether=1:1); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (t, J=7.4 Hz, 3H), 1.30 (t, J=7.1 Hz, 3H), 1.41 (s, 9H), 3.83 (s, 3H), 4.03 (d, J=5.7 Hz, 1H), 4.12–4.28 (m, 4H), 4.65 (d, J=5.7 Hz, 1H), 6.69–6.73 (m, 2H), 6.78 (dd, J=6.8, 1.6 Hz, 1H), 6.83–6.88 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.07 (q), 14.11 (q), 27.87 (q), 54.38 (d), 55.59 (q), 56.69 (d), 61.75 (t), 61.78 (t), 82.57 (s), 110.01 (d), 110.74 (d), 117.94 (d), 121.10 (d), 136.49 (s), 147.47 (s), 167.19 (s), 167.59 (s), 169.74 (s); IR (neat) 3392, 2980, 1739, 1603, 1516, 1459, 1370, 1253, 1155, 1030 cm^{-1}; MS (EI) m/z 395 (M^+, 54), 339 (36), 294 (100%); HRMS M^+ 395.1944 (calcd for $C_{20}H_{29}NO_7$ 395.1944).

3.2.12. 1-*tert*-Butyl 2,2-diethyl 1-(2-chlorophenylamino)ethane-1,2,2-tricarboxylate (3l). R_f=0.5 (hexane–ether=2:1); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J=7.1 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.42 (s, 9H), 4.05 (d, J=5.3 Hz, 1H), 4.13–4.31 (m, 4H), 4.69 (br d, J=5.3 Hz, 1H), 5.42 (br s, 1H), 6.67–6.71 (m, 1H), 6.78 (d-like, J=8.1 Hz, 1H), 7.12–7.16 (m, 1H), 7.26 (dd, J=7.8, 1.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.02 (q), 14.10 (q), 27.81 (q), 54.02 (d), 56.68 (d), 61.91 (t), 61.96 (t), 82.92 (s), 112.23 (d), 118.71 (d), 120.40 (s), 127.42 (d), 129.47 (d), 142.77 (s), 166.95 (s), 167.54 (s), 169.25 (s); IR (neat) 3388, 2981, 1739, 1598, 1514, 1370, 1257, 1156, 1035 cm^{-1}; MS (EI) m/z 401 (M^+, 3.0) 399 (M^+, 8.4), 298 (45), 100 (30), 57 (100%); HRMS M^+ 399.1453 (calcd for $C_{19}H_{26}{}^{35}ClNO_6$ 399.1449), 401.1446 (calcd for $C_{19}H_{26}{}^{37}ClNO_6$ 401.1419).

3.2.13. 1-*tert*-Butyl 2,2-diethyl 1-(*N*-benzyl-*N*-phenylamino)ethane-1,2,2-tricarboxylate (3m). R_f=0.7 (hexane–ether=1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.02 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.35 (s, 9H), 3.89–3.96 (m, 2H), 4.16–4.25 (m, 2H), 4.20 (d, J=11.2 Hz, 1H), 4.46 (d, J=16.7 Hz, 1H), 4.53 (d, J=16.7 Hz, 1H), 5.21 (d, J=11.2 Hz, 1H), 6.76 (t-like, J=7.1 Hz, 1H), 6.90 (d-like, J=8.1 Hz, 2H), 7.11–7.16 (m, 3H), 7.20–7.22 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.71 (q), 14.05 (q), 27.93 (q), 51.02 (t), 52.85 (d), 61.83 (t), 61.88 (t), 64.51 (d), 82.50 (s), 117.01 (d), 119.60 (d), 126.73 (d), 127.06 (d), 128.27 (d), 128.79 (d), 138.13 (s), 147.86 (s), 167.21 (s), 167.32 (s), 169.05 (s); IR (neat) 2980, 1758, 1733, 1600, 1505, 1369, 1301, 1244, 1152 cm^{-1}; MS (EI) m/z 455 (M^+, 14) 354 (100%); HRMS M^+ 455.2300 (calcd for $C_{26}H_{33}NO_6$ 455.2308).

3.3. Typical experimental procedure (Table 2, entry 8)

To a solution of **1a** (136 mg, 0.5 mmol) in 1,2-dichloroethane (0.9 mL) were added *N*-methylaniline **2b** (54 mg, 54 μL, 0.5 mmol) and $Sc(OTf)_3$ (49 mg, 0.1 mmol). The mixture was heated to 80 °C for 2 h. The reaction mixture was cooled to room temperature and quenched by water and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified as above to give **4a** (143 mg, 75%).

3.3.1. Compound 4a. R_f=0.3 (hexane–ether=2:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.01 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.37 (s, 9H), 2.80 (s, 3H), 3.94 (q, J=7.1 Hz, 2H), 4.07 (s, 2H), 4.19–4.24 (m, 2H), 6.52 (d-like, J=8.7 Hz, 2H), 7.08 (d-like, J=8.7 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.89 (q), 14.09 (q), 27.86 (q), 30.74 (q), 50.96 (d), 55.71 (d), 61.31 (t), 61.73 (t), 81.11 (s), 112.53 (d), 123.75 (s), 129.12 (d), 148.83 (s), 167.57 (s), 168.23 (s), 171.46 (s); IR (neat) 3419, 2980, 1732, 1616, 1524, 1369, 1300, 1149 cm^{-1}; MS (EI) m/z 379 (M^+, 77), 305 (53), 278 (100%); HRMS M^+ 379.1997 (calcd for $C_{20}H_{29}NO_6$ 379.1995).

3.3.2. Triethyl 1-(4-(methylamino)phenyl)ethane-1,2,2-tricarboxylate (4b). R_f=0.5 (hexane–ether=1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.01 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 2.79 (s, 3H), 3.95 (q, J=7.1 Hz, 2H), 4.00–4.08 (m, 1H), 4.13–4.25 (m, 3H), 4.16 (br s, 2H), 6.52 (d-like, J=8.7 Hz, 2H), 7.09 (d-like, J=8.7 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.81 (q), 13.98 (q), 30.57 (q), 49.92 (d), 55.55 (d), 61.14 (t), 61.33 (t), 61.77 (t), 112.41 (d), 122.82 (s), 129.16 (d), 149.05 (s), 167.32 (s), 168.14 (s), 172.47 (s); IR (neat) 3419, 2982, 1733, 1616, 1525, 1369, 1300, 1158, 1030 cm^{-1}; MS (EI) m/z 351 (M^+, 58), 305 (48), 277 (100%); HRMS M^+ 351.1699 (calcd for $C_{18}H_{25}NO_6$ 351.1682); Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.37; H, 7.26; N, 3.96.

3.3.3. 1-*tert*-Butyl 2,2-dibenzyl 1-(4-(methylamino)phenyl)ethane-1,2,2-tricarboxylate (4c). R_f=0.4 (hexane–ether=1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (s, 9H), 2.80 (s, 3H), 4.09 (d, J=11.9 Hz, 1H), 4.22 (d, J=11.9 Hz, 1H), 4.87 (s, 2H), 5.17 (s, 2H), 6.47 (d-like, J=8.6 Hz, 2H), 6.98–7.04 (m, 2H), 7.04 (d-like, J=8.6 Hz, 2H), 7.20–7.37 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 27.79 (q), 30.65 (q), 50.94 (d), 55.72 (d), 67.03 (t), 67.31 (t), 81.22 (s), 112.55 (d), 123.40 (s), 128.07 (d), 128.08 (d), 128.12 (d), 128.27 (d), 128.38 (d), 128.54 (d), 129.08 (d), 135.13 (s), 135.38 (s), 148.84 (s), 167.30 (s), 167.92 (s), 171.26 (s); IR (neat) 3422, 2979, 1733, 1615, 1524, 1456, 1369, 1294, 1147 cm^{-1}; MS (EI) m/z 503 (M^+, 38), 402 (19), 338 (25), 91 (100%); HRMS M^+ 503.2309 (calcd for $C_{30}H_{33}NO_6$ 503.2308).

3.3.4. Compound 5 (assumed to be ca. 1:1 diastereomixture). R_f=0.4 (hexane–ether=1:2); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.01 (m, 6H), 1.28 (t, J=7.1 Hz, 6H), 1.33 (s, 9H), 1.36 (s, 9H), 2.75 (s, 3H), 3.91–4.27 (m, 11H), 5.02 (d, J=11.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 2H), 7.13 (dd, J=8.4, 1.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.89 (q), 14.04 (q), 14.08 (q), 27.81 (q), 27.95 (q), 33.69 (q), 50.85 (d), 52.45 (d), 52.48 (d), 55.56 (d), 61.27 (t), 61.68 (t), 61.76 (t), 61.82 (t), 63.47 (d), 63.59 (d), 81.11 (s), 82.16 (s), 115.07 (d), 115.13 (d), 125.47 (s), 128.78 (d), 149.45 (s), 149.49 (s), 166.92 (s), 166.96 (s), 167.26 (s), 167.36 (s), 168.14 (s), 168.48 (s), 171.26 (s); IR (neat) 2980, 1732, 1612, 1519, 1369, 1301, 1152, 1035 cm^{-1}; MS (EI) m/z 651 (M^+, 30), 550 (100%); HRMS M^+ 651.3257 (calcd for $C_{33}H_{49}NO_{12}$ 651.3255).

3.3.5. 1-*tert*-Butyl 2,2-dibenzyl 1-(*N*-phenylacetamido)ethane-1,2,2-tricarboxylate (6a). To a solution of **3f** (490 mg, 1.0 mmol) in dichloromethane (0.8 mL) were

added triethylamine (202 mg, 0.28 mL, 2.0 mmol) and acetyl chloride (157 mg, 0.14 mL, 2.0 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight (16 h). The reaction mixture was cooled to 0 °C and water was added to the mixture. The mixture was extracted with dichloromethane and the organic phase was washed with 1 N HCl and saturated NaCl solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give **6a** (385 mg, 72%).

R_f=0.4 (hexane–ether=1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.42 (s, 9H), 1.69 (s, 3H), 4.64 (d, J=10.6 Hz, 1H), 5.01 (d, J=10.6 Hz, 1H), 5.01 (d, J=12.3 Hz, 1H), 5.07 (d, J=12.3 Hz, 1H), 5.16 (d, J=12.3 Hz, 1H), 5.23 (d, J=12.3 Hz, 1H), 7.18–7.34 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 22.67 (q), 27.90 (q), 52.47 (d), 62.81 (d), 67.42 (t), 83.00 (s), 128.15 (d), 128.25 (d), 128.27 (d), 128.30 (d), 128.33 (d), 128.44 (d), 128.55 (d), 128.61 (d), 129.54 (d), 135.23 (s), 135.28 (s), 143.18 (s), 166.98 (s), 167.10 (s), 167.69 (s), 171.37 (s); IR (neat) 2978, 1737, 1673, 1596, 1495, 1370, 1260, 1154 cm^{-1}; MS (EI) m/z 531 (M^+, 5.4), 489 (17), 430 (23), 388 (44), 91 (100%); HRMS M^+ 531.2258 (calcd for $C_{31}H_{33}NO_7$ 531.2257).

3.3.6. 1-*tert*-Butyl 2,2-dibenzyl 1-(*N*-benzylacetamido)-ethane-1,2,2-tricarboxylate (6b). R_f=0.3 (hexane–ether=1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (s, 9H), 1.79 (s, 3H), 4.18 (d, J=17.0 Hz, 1H), 4.21 (d, J=17.0 Hz, 1H), 4.60 (br s, 2H), 5.03 (d, J=12.1 Hz, 1H), 5.10 (d, J=12.0 Hz, 1H), 5.20 (d, J=12.3 Hz, 1H), 5.23 (d, J=12.1 Hz, 1H), 7.10–7.34 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 21.57 (q), 27.82 (q), 51.84 (d), 54.42 (t), 60.93 (d), 67.40 (t), 67.53 (t), 82.67 (s), 127.43 (d), 127.69 (d), 128.22 (d), 128.30 (d), 128.43 (d), 128.53 (d), 128.62 (d), 128.72 (d), 128.94 (d), 135.28 (s), 135.38 (s), 136.26 (s), 167.27 (s), 171.66 (s); IR (neat) 2978, 1733, 1661, 1497, 1456, 1369, 1278, 1154 cm^{-1}; MS (EI) m/z 545 (M^+, 7.2), 489 (26), 446 (72), 91 (100%); HRMS M^+ 545.2433 (calcd for $C_{32}H_{35}NO_7$ 545.2414).

3.3.7. 3-(*tert*-Butoxycarbonyl)-3-(*N*-phenylacetamido)-propanoic acid (7a). A mixture of **6a** (320 mg, 0.602 mmol) and 10% Pd–C (64 mg, 10 mol%) in methanol (6.0 mL) was stirred in a hydrogen atmosphere for 17 h at room temperature. The catalyst was removed by filtration (Celite) and washed with methanol. The filtrate was concentrated to give a crude residue. To the residue was added water–ethanol (1:1, 0.6 mL) and the mixture was refluxed for 3 h. The reaction mixture was concentrated in vacuo and extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give **7a** (139 mg, 75%).

R_f=0.1 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 9H), 1.85 (s, 3H), 2.79 (dd, J=16.8, 7.1 Hz, 1H), 3.26 (dd, J=16.8, 7.1 Hz, 1H), 4.82 (t, J=7.1 Hz, 1H), 7.28–7.44 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 22.70 (q), 27.95 (q), 35.01 (t), 59.88 (d), 82.51 (s), 128.37 (d), 128.62 (d), 129.81 (d), 142.38 (s), 168.63 (s), 171.39 (s), 175.84 (s); IR (neat) 2979, 1738, 1626, 1594, 1495, 1394, 1370, 1258, 1156 cm^{-1}; MS (EI) m/z 307 (M^+, 5.4), 206 (32), 164 (100%); HRMS M^+ 307.1419 (calcd for $C_{16}H_{21}NO_5$ 307.1420).

3.3.8. 3-(*tert*-Butoxycarbonyl)-3-(*N*-benzylacetamido)-propanoic acid (7b). R_f=0.3 (ether); pale yellow crystals; mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.40 (s, 9H), 2.15 (s, 3H), 2.62 (dd, J=16.9, 6.0 Hz, 1H), 3.29 (dd, J=16.9, 7.4 Hz, 1H), 4.35 (dd, J=7.4, 6.0 Hz, 1H), 4.59 (d, J=16.8 Hz, 1H), 4.64 (d, J=16.8 Hz, 1H), 7.19–7.38 (m, 5H), 9.22 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 21.74 (q), 27.85 (q), 34.89 (t), 53.88 (t), 58.03 (d), 82.28 (s), 127.32 (d), 127.96 (d), 128.85 (d), 136.03 (s), 168.41 (s), 171.81 (s), 175.88 (s); IR (KBr) 2980, 1735, 1701, 1607, 1487, 1449, 1420, 1365, 1290, 1180, 1159 cm^{-1}; MS (EI) m/z 321 (M^+, 1.4), 265 (54), 222 (49), 178 (100%); HRMS M^+ 321.1576 (calcd for $C_{17}H_{23}NO_5$ 321.1576); Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.32; H, 7.21; N, 4.32.

3.4. Typical procedure for Table 3 (entry 2)

A powdered mixture of $Cu(OTf)_2$ (18 mg, 0.05 mmol) and **8** (16 mg, 0.054 mmol) was dried under vacuum for 1 h. THF (1 mL) was added under N_2 and the solution stirred for 1 h. The mixture was cooled to −20 °C and compound **1a** (0.136 g, 0.5 mmol) in THF (0.4 mL) was added to the mixture and stirred for 15 min, followed by addition of **2b** (54 mg, 0.05 mL, 0.5 mmol). After 17 h the reaction mixture was filtered through a plug of silica gel, washed with Et_2O, dried ($MgSO_4$), and the solvent removed. The residue was purified by column chromatography over silica gel eluting with hexane–ether to give **3b** (173 mg, 91%). **3b**; HPLC (hexane–^{i}PrOH=49:1) minor peak t_{R1}=4.7 min, major peak t_{R2}=6.6 min, 78% ee; $[\alpha]_D^{27}$ −163 (c 1.06, $CHCl_3$).

Compound **3i** (Table 3, entry 12); HPLC (hexane–^{i}PrOH=49:1) minor peak t_{R1}=4.7 min, major peak t_{R2}=6.5 min, 87% ee; $[\alpha]_D^{27}$ −159 (c 1.63, $CHCl_3$).

Compound **3d** (Table 3, entry 13); HPLC (hexane–^{i}PrOH=49:1) minor peak t_{R1}=6.1 min, major peak t_{R2}=8.2 min, 41% ee; $[\alpha]_D^{24}$ −103 (c 1.30, $CHCl_3$).

Compound **3e** (Table 3, entry 14); HPLC (hexane–^{i}PrOH=49:1) minor peak t_{R1}=7.6 min, major peak t_{R2}=12.1 min, 43% ee; $[\alpha]_D^{23}$ −61 (c 1.57, $CHCl_3$).

Compound **3g** (Table 3, entry 15); HPLC (hexane–^{i}PrOH=49:1) minor peak t_{R1}=6.5 min, major peak t_{R2}=8.1 min, 71% ee; $[\alpha]_D^{26}$ −80 (c 0.69, $CHCl_3$).

3.5. ^{1}H NMR measurements for reactions shown in Figure 1

(a) $CDCl_3$ or CD_2Cl_2 solution: a NMR sample was prepared by addition of *N*-methylaniline **2b** (36 mg, 37 μL, 0.33 mmol) (and $ZnCl_2$ (9 mg, 0.067 mmol)) to a solution of **1a** (90 mg, 0.33 mmol) in $CDCl_3$ or CD_2Cl_2 (0.6 mL) in a NMR tube. The tube was set into an NMR probe and periodically measured at 25 °C. (b) Neat reaction: *N*-methylaniline **2b** (107 mg, 0.11 mL, 1.0 mmol) was added to **1a**

(272 mg, 1.0 mmol) in a flask and stirred at 25 °C. A portion was periodically taken from the mixture and diluted with $CDCl_3$. The ^1H NMR spectrum was measured immediately. The product percentage was calculated by peak area ratios.

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Supplementary data

Computational data (the Cartesian coordinate of the optimized geometry of **3d**). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.058.

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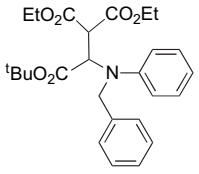
9. The reaction of **1a** with benzylphenylamine gave C–N adduct **3m** only in 39% yield along with starting materials. This is probably because of the steric hindrance of the amine nucleophile.



3m

10. Using various Lewis acid such as $ZnCl_2$, $AlCl_3$, and $SnCl_4$ at higher temperature and longer reaction time, the product yields decreased or the reaction mixture decomposed.
11. The reaction of the isolated **3b** with $ZnCl_2$ (0.2 equiv) in CH_2Cl_2 at room temperature for 17 h and work-up gave the mixture of **3b**, **1a**, and **2b** (ca. 6:1:1). This result also shows the reversibility of C–N bond.
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