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One-Pot Synthesis of α-Halo β-Amino Acid Derivatives via the Difunctional Coupling of Ethyl α-Diazoacetate with Silyl Halides and *N*,*O*-Acetals or Aromatic Tertiary Amines

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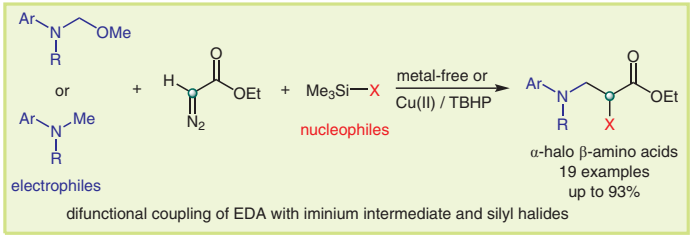

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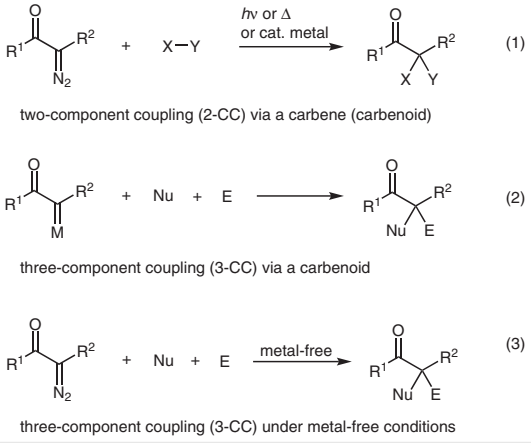
Abstract The difunctionalization of ethyl α-diazoacetate (EDA) using silyl halides as a nucleophile and *N*,*O*-acetals as an electrophile under metal-free conditions is described. This process undergoes a novel three-component coupling (3-CC) reaction using EDA, which leads to a one-pot preparation of α-halo β-amino acid esters. Also, this protocol could be adapted to accept an electrophile composed of aromatic tertiary amines. In both 3-CC reactions, the key reaction intermediate is an iminium intermediate that can be easily and effectively generated either from *N*,*O*-acetals or from aromatic tertiary amines.

Key words amino acids, *N*,*O*-acetals, iminium intermediates, multicomponent reactions, aromatic tertiary amines

α-Diazocarbonyl compounds continue to attract much attention in synthetic organic chemistry using various active carbon species, since the reactive intermediates, carbenes or carbenoids, which are generated via the photochemical, thermodynamic and catalytic elimination of nitrogen from α-diazocarbonyl compounds, have been effectively utilized in the preparations of a variety of naturally occurring compounds and highly valuable compounds as well as functional materials.[1] The central reaction manner of α-diazocarbonyl compounds is α,α-insertion, namely, difunctionalization through the formal insertion of carbenes (or carbenoids) between the X–Y bonds (Scheme 1, eq 1). For this type of reaction, several reaction substrates, such as halogens, hydrogen halides, alcohols, amines, and organoboron, organosilicon, organophosphorus, organosulfur and organoselenium compounds have been employed.[1a,d] Also, in another significant application using difunctionalization, an intermolecular or intramolecular C–H insertion of the in situ generated carbene (or carbenoid) intermediate has been developed. The intramolecular process has been widely applied particularly in the practical preparation of a variety of complicated natural compounds.[2] However, these useful methods are naturally limited to the two-component coupling (2-CC) of α-diazocarbonyl compounds and their counterparts.[3]



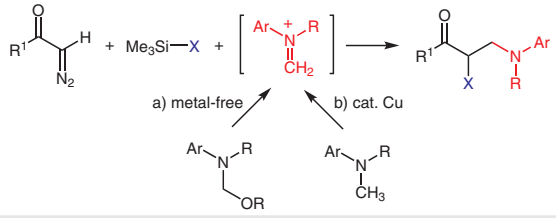
Scheme 1 Diverse coupling modes of difunctionalization of α-diazocarbonyl compounds

Also, three-component coupling (3-CC) reactions via difunctionalization of α-diazocarbonyl compounds with two electronically and structurally different reactants, electrophiles and nucleophiles in the presence of a transition metal catalyst, in which an ylide intermediate derives from a metal carbenoid and a nucleophile, such as an amine, an alcohol and a carboxylic acid, plays a central role, have recently gained attention (Scheme 1, eq 2).[4] Compared with eq 1 in Scheme 1, this type of difunctionalization simultaneously undergoes two sorts of bond formation on the carbon of carbenoid species, which would enable the practical construction of more complicated organic molecules. Recently, under transition-metal-free conditions, the same

type of 3-CC reactions of α-diazocarbonyl compounds, nucleophiles, and electrophiles have been developed, but these types of coupling are not investigated extensively (Scheme 1, eq 3).[5,6] In this context, it has been disclosed that transition-metal-free 3-CC reactions of α-diazocarbonyl compounds with aromatic tertiary amines and nucleophiles in the presence of an appropriate oxidizing agent proceed via a radical process.[7]

On the other hand, we previously reported that a catalytic system composed of a Lewis acid, $Hf(OTf)_4$ and a promoter, chlorotrimethylsilane (Me_3SiCl) effectively promotes aminomethylation of various carbon nucleophiles with an iminium intermediate generated in situ from an *N*,*O*-acetal.[8] During ongoing study on the utility of an iminium ion from an *N*,*O*-acetal and a common Lewis acid, we anticipated that an introduction of an α-diazocarbonyl compound, ethyl α-diazoacetate (EDA), into our reaction system involving carbon nucleophiles and iminium electrophiles would undertake a unique 3-CC reaction.

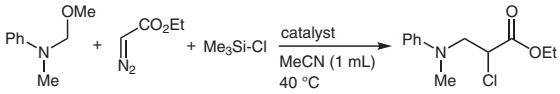
After several preliminary examinations, we found that a combination of EDA, silyl halides, and iminium intermediates derived from *N*,*O*-acetals could accomplish the novel type of 3-CC reaction, producing α-halo β-amino acid ester derivatives (Scheme 2, path a). Unlike related studies, a remarkable finding in this examination involves that a counter anion of silyl halides, which effectively activate an *N*,*O*-acetal, simultaneously functions as a novel nucleophile. Herein, we report the details on a novel type of 3-CC reaction using an α-diazocarbonyl compound. Also, in another application, we disclose a similar difunctionalization of EDA with silyl halides and tertiary aromatic amines under oxidizing conditions composed of a Cu(II)/TBHP (*tert*-butyl hydroperoxide) system (Scheme 2, path b).



Scheme 2 Difunctionalization of α-diazocarbonyl compounds with iminium compounds and silyl halides

Initially, to establish the optimal conditions, a model 3-CC reaction was conducted. An *N*,*O*-acetal (1 mmol) – which was prepared from *N*-methylaniline, formaldehyde, and methanol – ethyl diazoacetate (EDA: 1.1 equiv), and Me_3SiCl (1.5 equiv) were treated with CuCl (10 mol %) in a 1,2-dichloroethane (DCE) solution at 40 °C for 24 hours (Table 1). Consequently, the expected α-chloro β-amino acid ester, ethyl 2-chloro-3-(*N*-methyl-*N*-phenylamino)propanoate (**1**), was obtained in a 50% yield (Table 1, entry 1). The Me_3SiCl performed dual roles as the Lewis acidic activator of an *N*,*O*-acetal that would lead to an iminium intermediate and as a nucleophilic source of the coupling product. Also, a common C–H insertion into an *N*-methyl group by EDA was not observed during the coupling reaction. Among several copper catalysts, $CuSO_4$ demonstrated the most effective activity for the present reaction to give **1** in an 80% yield (entries 2, 3, and 5) and a strong Lewis acid, $Cu(OTf)_2$, resulted in a complicated mixture (entry 4). Moreover, a series of three-component couplings was completed within 1 hour and an equivalent of the copper catalyst was reduced to 5 mol% (entries 6 and 7). Surprisingly, the present coupling proceeded equally well without the copper catalyst (entry 8). Although the polarity of solvents is not critical to the improvement of the yield (entries 9–11), acetonitrile finally showed the best coupling effect, and **1** was isolated in a good yield (entry 12).

Table 1 Examination of Reaction Conditions[a]



1

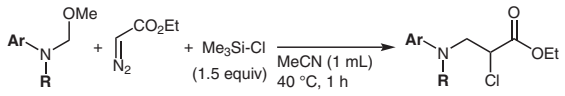
Entry	Catalyst	mol%	Solvent	Time (h)	Yield (%)[b]
1	CuCl	10	DCE	24	50
2	$Cu(OAc)_2$	10	DCE	24	32
3	$CuCl_2$	10	DCE	24	32
4	$Cu(OTf)_2$	10	DCE	24	–[c]
5	$CuSO_4$	10	DCE	24	80
6	$CuSO_4$	10	DCE	1	75
7	$CuSO_4$	5	DCE	1	85
8	–	–	DCE	1	72
9	–	–	$CHCl_3$	1	82
10	–	–	toluene	1	77
11	–	–	THF	1	86
12	–	–	MeCN	1	93 (89)

[a] Standard conditions: an *N*,*O*-acetal (0.5 mmol), EDA in 15 wt% toluene solution (1.1 equiv), Me_3SiCl (1.5 equiv), MeCN (1 mL), 40 °C, 24 h.
[b] NMR (isolated) yield.
[c] A complex mixture.

Then, to expand the substrate scope of the present coupling, *N*,*O*-acetals with various substituents were subjected to the optimal conditions involving EDA and Me_3SiCl, and the results are summarized in Table 2. Most *N*,*O*-acetals bonded to either an electron-donating group, such as a methyl and a methoxy group, or to an electron-withdrawing group, such as a fluoro group, on an aryl amine moiety gave the corresponding α-chloro β-amino acid esters **2**–**8** in good to excellent yields. The exception was product **6**, which had a *m*-methoxy group (Table 2, entries 1–7). In cases involving extensions of an *N*-alkyl chain to an ethyl group, the desired α-chloro β-amino acid esters **9** and **10** were obtained in good yields (entries 8 and 9). Also, the

extension to an *N*,*O*-acetal with a benzyl group afforded the expected α-chloro β-amino acid ester **11** in a low 31% yield (entry 10).

Table 2 Substrate Scope of *N*,*O*-Acetals



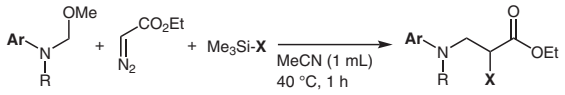
2–11

Entry	Ar	R	Product	Yield (%)[a]
1	*o*-MeC_6H_4	Me	**2**	63
2	*m*-MeC_6H_4	Me	**3**	87
3	*p*-MeC_6H_4	Me	**4**	91
4	*o*-$MeOC_6H_4$	Me	**5**	61
5	*m*-$MeOC_6H_4$	Me	**6**	13
6	*p*-$MeOC_6H_4$	Me	**7**	63
7	*p*-FC_6H_4	Me	**8**	88
8	Ph	Et	**9**	77
9	*m*-MeC_6H_4	Et	**10**	93
10	$PhCH_2$	Me	**11**	31

[a] Isolated yield.

The adaptation to other silyl halides, such as trimethylbromosilane (Me_3SiBr) and trimethyliodosilane (Me_3SiI), also was investigated under the optimal conditions, and the results are lined in Table 3. Consequently, the 3-CC reaction with Me_3SiBr gave the desired α-bromo β-amino acid derivatives **12**–**14** in relatively good yields, regardless of an electronic effect on the aryl group of *N*,*O*-acetals (Table 3, entries 1–3). In a similar manner, the 3-CC reaction involving an *N*,*O*-acetal, EDA and Me_3SiI, the latter of which was prepared from hexamethyldisilane and molecular iodine,[9] led to the preparation of α-iodo β-amino acid **15** in a 61% yield (entry 4). Although both silyl halides generally show stronger Lewis acidity and a high nucleophilicity of the counter anion than those of Me_3SiCl, neither the reactivity nor the yield showed remarkable improvement. On the other hand, the use of silyl halide analogues, such as Me_3SiN_3 and Me_3SiCN, resulted in the formation of a complicated mixture.

Table 3 Substrate Scope of Silyl Halides



12–15

Entry	Ar	Silane X	Product	Yield (%)[a]
1	Ph	Br	**12**	83
2	*p*-MeC_6H_4	Br	**13**	60
3	*p*-FC_6H_4	Br	**14**	81
4	Ph	I	**15**	25 (61)[b]

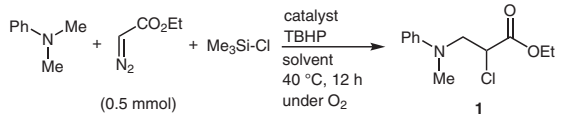
[a] Isolated yield.
[b] Use of Me_3SiI generated in situ from $(Me_3Si)_2$ and I_2.

At this stage, we expect an iminium intermediate to be a key electrophilic counterpart that would be generated in situ from an *N*,*O*-acetal and Me_3SiCl in a series of 3-CC reaction. In this context, we previously reported the cobalt(II)-catalyzed oxidative cyanation of aromatic tertiary amines with *tert*-butyl hydroperoxide (TBHP), in which an iminium species functions as a reaction intermediate.[5b] Based on that outcome, we recalled that an aromatic tertiary amine, instead of an *N*,*O*-acetal, would be adaptable as a new electrophilic partner.

As a preliminary examination, when the reaction mixture involving *N*,*N*-dimethylaniline (0.45 mmol), EDA (0.5 mmol), and Me_3SiCl (0.75 mmol) was treated with an acetonitrile solution (1 mL) containing $CuCl_2$ (10 mol%) and TBHP (1.5 equiv) at 40 °C for 12 hours, in contrast to our expectation, the expected α-chloro β-amino acid **1** was not obtained (Table 4, entry 1). Therefore, we started to explore the optimal conditions using several copper catalysts and solvents. Consequently, the most effective catalytic system for the coupling proved to be $Cu(acac)_2$ in a CH_2Cl_2 solution (entries 2–5). Strangely, unlike the previous work,[4c] $Cu(OTf)_2$ led to a complicated mixture. Typical solvents, such as toluene, THF, and chloroform, were ineffective for the 3-CC reaction. By contrast, an increase in the equivalent of dimethylaniline to 3.5 equivalents for EDA enhanced the yield of **1** to a practical level (entry 6). Moreover, running the same reaction under an ambient atmosphere resulted in equivalent behavior and **1** was isolated in a 62% yield after purification (entry 7). On the other hand, other metal catalysts, such as $Fe(acac)_3$ and $Co(acac)_2$, led to a decrease in the yield of **1** (entries 8 and 9). Throughout the examination with a copper catalyst, the formation of a small amount of by-product, such as a hydrolysate of the iminium intermediate, *N*-methylaniline, and a homo-coupling product of *N*,*N*-dimethylaniline was observed, but a dimerization product of EDA, which is derived from a carbene (a copper carbenoid) species, was not detected.

The 3-CC reactions were then conducted with a variety of tertiary aromatic amines under the optimal conditions (Table 5). Most dimethylanilines with an electron-donating and -withdrawing group gave the corresponding α-chloro β-amino acid derivatives in moderate to good yields equal to the above *N*,*O*-acetals (entries 1–7). However, the cases of an aromatic amine with a relatively strong electron-withdrawing group, such as a CF_3 group showed low reactivity, and afforded α-chloro β-amino acid **18** in a low yield (entry 8). Also, the introduction of a bromo group into the β-amino acid, via Me_3SiBr instead of Me_3SiCl, produced the desired α-bromo β-amino acid derivative **12** in a rather low

Table 4 Examination of Reaction Conditions for Dimethylaniline[a]

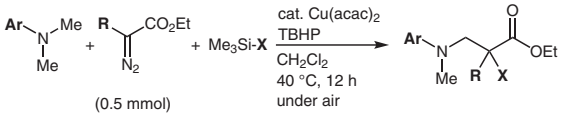


(0.5 mmol) **1**

Entry	Catalyst (10 mol%)	Amine (ratio)	Solvent	Yield (%)[b]
1	$CuCl_2$	0.9	MeCN	trace
2	$CuBr_2$	0.9	MeCN	29
3	$Cu(OTf)_2$	0.9	MeCN	–[c]
4	$Cu(acac)_2$	0.9	MeCN	35
5	$Cu(acac)_2$	0.9	CH_2Cl_2	36
6[d]	$Cu(acac)_2$	3.5	CH_2Cl_2	71
7[d,e]	$Cu(acac)_2$	3.5	CH_2Cl_2	73 (62)
8[d]	$Fe(acac)_3$	2	CH_2Cl_2	32
9[d]	$Co(acac)_2$	2	CH_2Cl_2	13

[a] Standard conditions: *N*,*N*-dimethylaniline (0.9–3.5 equiv for EDA), EDA in 15 wt% toluene solution (0.5 mmol), Me_3SiCl (1.5 equiv), solvent (1 mL), 40 °C, 12 h.
[b] NMR yield in entries 1–7 and GC (isolated) yield in entries 8–13.
[c] A complex mixture.
[d] EDA (neat).
[e] Under ambient atmosphere.

Table 5 Substrate Scope of Tertiary Aromatic Amines and α-Diazoacetates[a]



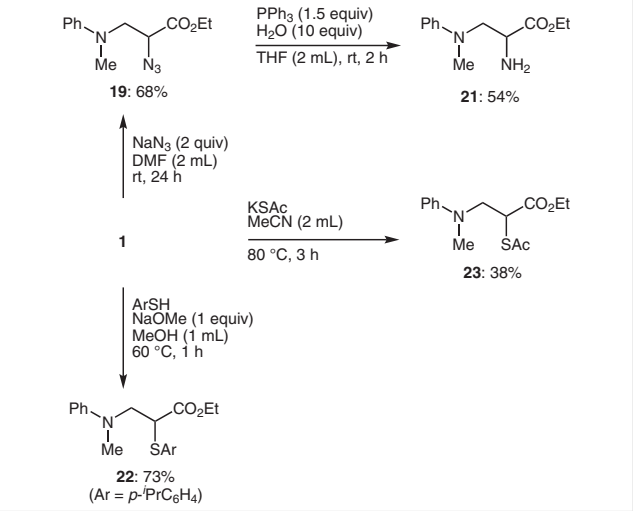
(0.5 mmol)

Entry	R	Silane X	Product Ar		Yield (%)[b]
1	H	Cl	*o*-MeC_6H_4	**2**	24 (68)
2	H	Cl	*m*-MeC_6H_4	**3**	36 (65)
3	H	Cl	*p*-MeC_6H_4	**4**	42 (63)
4	H	Cl	*p*-$MeOC_6H_4$	**7**	38 (58)
5	H	Cl	*p*-FC_6H_4	**8**	56 (79)
6	H	Cl	*p*-ClC_6H_4	**16**	44 (83)
7	H	Cl	*p*-BrC_6H_4	**17**	24 (61)
8	H	Cl	*p*-$CF_3C_6H_4$	**18**	18 (34)
9	H	Br	Ph	**12**	25
10[c]	H	N_3	Ph	**19**	60 (70)
11	Ph	Cl	Ph	**20**	–[d]

[a] Standard conditions: *N*,*N*-dimethylaniline (3.5 equiv for EDA), EDA (0.5 mmol), Me_3SiCl (1.5 equiv), CH_2Cl_2 (1 mL), 40 °C, 12 h.
[b] Isolated (NMR) yield.
[c] MeCN as a solvent.
[d] A complex mixture.

yield (entry 9). Moreover, during the experimental workup, unlike the above study using *N*,*O*-acetals, we encountered both the problematic isolation of α-halo β-amino acids from the residue containing the remaining aromatic tertiary amines and TBHP, and the decomposition of these β-amino acids, which, unfortunately, led to a remarkable decrease in the product yield. Although there are no clear reasons for the latter situation, presumably a remaining copper(II) catalyst would cause some kind of side reaction toward the obtained α-halo β-amino acid derivatives. Surprisingly, unlike the above case using an *N*,*O*-acetal under metal-free conditions, when the same coupling was carried out with Me_3SiN_3, the desired α-azido β-amino acid **19** was obtained in a relatively good yield (entry 10). On the other hand, instead of EDA, when the same coupling (Table 4, entry 7) was performed with a disubstituted α-diazoacetate, methyl α-diazo-α-phenylacetate, under the optimal conditions, the reaction led to a complicated mixture (entry 11).

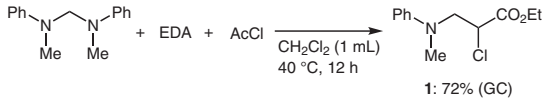
To demonstrate the utility of the prepared α-chloro β-amino acid derivative, the halogen moiety was then subjected to transformations of other usefully functional groups (Scheme 3). For instance, α-chloro β-amino acid ester **1** was initially treated with NaN_3, followed by a Staudinger reduction of formed azide **19** with a mixture of PPh_3 and H_2O to produce α-amino β-amino acid derivative **21** in a 54% yield.[10] When **1** was then treated with a benzenethiol derivative with a *para*-isopropyl group in the presence of a typical base, such as sodium methoxide, the expected α-mercapto-β-amino acid derivative **22** was obtained in a 73% yield. Also, when a similar reaction of **1** with potassium thioacetate was performed, the corresponding thioacetate derivative **23** was obtained, but the yield was lower than we expected, which was likely due to the low nucleophilicity of potassium thioacetate.[11]



Scheme 3 Transformations of α-chloro β-amino acid **1**

We assumed that an in situ generated iminium intermediate through both activation of an *N*,*O*-acetal or an aromatic tertiary amine would be a central and key compound of the 3-CC reaction. Thus, to enhance our outlook for the

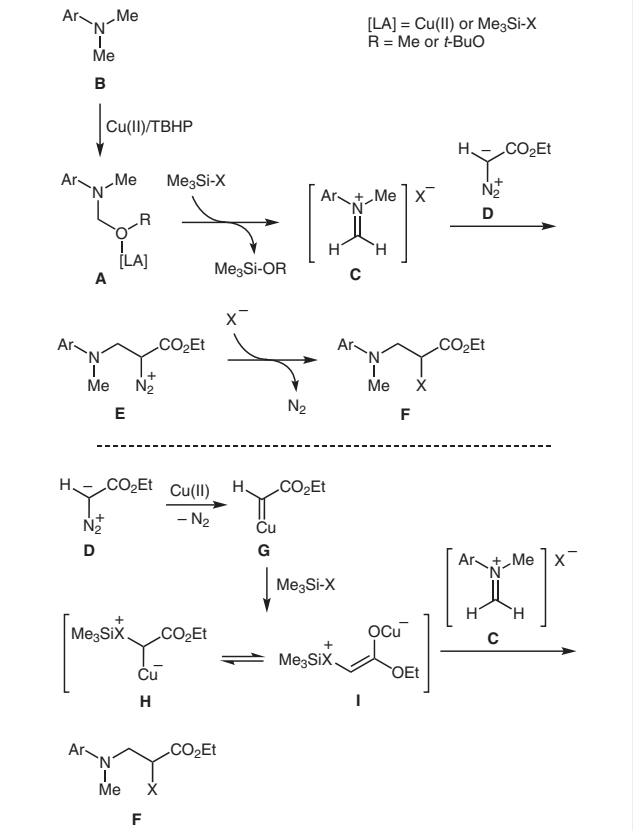
former reaction system using an *N*,*O*-acetal, a control experiment was examined (Scheme 4). When attempting difunctionalization of an *N*,*N*-aminal as another iminium precursor,[12] with EDA and acetyl chloride both as a promoter and a nucleophile, the formation of the expected α-chloro β-amino acid ester **1** was confirmed in a good yield.



Scheme 4 A plausible reaction path for the three-component coupling reaction

On the basis of these results, two plausible reaction paths are shown in Scheme 5. As a main route (upper path in Scheme 5), initially, the reaction of either the starting *N*,*O*-acetal **A** (R= Me) or the *N*,*O*-acetal analogue **A** (R = *t*-BuO), which is generated from tertiary aromatic amine **B** using a Cu(II)/TBHP oxidizing system with a silyl halide occurs to form iminium intermediate **C**.[12–14] Then, intermediate **C** underwent nucleophilic attack from EDA (**D**) to form diazonium salt **E**.[15] Finally, as a nucleophile, the releasing halide ion reacted with **E** to produce α-halo β-amino acid ester **F** along with the liberation of N_2. It seems that because the liberated alkoxide ion from the acetal is smoothly trapped with the silyl halide, a releasing halide ion (X^-) is relatively free to behave as a nucleophilic source. On the other hand, as another route proposed by Li, Tu and Jiang's group (bottom path in Scheme 5),[4c] it is anticipated that the reaction of copper carbenoid **G** with a silyl halide (or a silyl azide) generates ylide intermediates **H** or **I**, followed by nucleophilic addition to iminium **C** to produce final product **F**.

In conclusion, we have described a 3-CC reaction of *N*,*O*-acetals, ethyl α-diazoacetate (EDA), and silyl halides under metal-free and neutral conditions along with a copper-catalyzed oxidative coupling reaction of aromatic tertiary amines, ethyl diazoacetate (EDA), and silyl halides. This reaction is a novel approach to the preparation of a variety of α-halo β-amino acid esters with a framework that is easily converted to useful compounds. One of the key step in a series of the 3-CC coupling involves a nucleophilic addition of EDA to an iminium intermediate, which is derived from an *N*,*O*-acetal activated by a silyl halide. Another key is the subsequent S_N2 reaction of the diazonium compound with a liberated halide anion. Our group is currently developing a new combination of electrophiles and nucleophiles that could be applied to the 3-CC reaction.



Scheme 5 Two plausible reaction paths for the three-component coupling reaction

MeOH was dried over Mg and I_2 and then distilled. THF was fleshly distilled over Na-benzophenone prior to use. MeCN, DMF, and Me_3SiCl were dried over CaH_2 and distilled. CH_2Cl_2 was dried over P_2O_5 and distilled. Chemicals, such as $Cu(acac)_2$, Na_2SO_4, K_2CO_3, NaN_3, NaOMe, KSAc, PPh_3, *tert*-butyl hydroperoxide (TBHP), ethyl diazoacetate (EDA), 4-bromo-*N*,*N*-dimethylaniline, Me_3SiBr, and Me_3SiN_3 were commercially available and used without further purification, unless otherwise noted. *N*,*N*-Dimethylaniline, 4-methyl-*N*,*N*-dimethylaniline, and 4-isopropylbenzenethiol were commercially available, and purified by distillation under reduced pressure prior to use. Column chromatography was performed using silica gel. ^1H NMR spectra were recorded at 500 MHz using TMS as an internal standard (0.00 ppm). The ^{13}C NMR spectra were recorded at 125 MHz using the center peak of $CHCl_3$ (77.0 ppm) as standard. High-resolution mass spectra (HRMS) were recorded using NBA (3-nitrobenzyl alcohol) as a matrix. The starting *N*,*O*-acetals are known compounds, and were prepared according to the literature procedure,[16] and each structure was characterized by ^1H and ^{13}C NMR spectra. Also, Me_3SiI and methyl α-diazo-α-phenylacetate were prepared via the procedure described in the literature, respectively.[9,17]

Difunctionalization of EDA with an *N*,*O*-Acetal and a Silyl Halide Leading to an α-Halo β-Amino Acid Ester Derivative; General Procedure A

An *N*,*O*-acetal (1 mmol) and ethyl α-diazoacetate (1.1 mmol in 15 wt% toluene solution) were added to freshly distilled MeCN (1 mL) in a screw-capped test tube at rt. The tube was sealed with a cap that contained a PTFE septum, followed by replacement with N_2. The tube was cooled to 0 °C with an ice bath, and the distilled or in situ prepared silyl halide (1.5 mmol) was added via a syringe. The reaction mixture was stirred at 40 °C for 1 h. After cooling, to remove volatile

compounds, the resultant mixture was passed through a silica gel pad (3 cm) with an eluent (EtOAc containing 1 wt% of Et_3N). The filtrate was evaporated, and the crude residue was purified by silica gel column chromatography (eluent: hexane/EtOAc (9:1 to 19:1) containing 1 wt% of Et_3N) to obtain the corresponding α-halo β-amino acid ester.

Difunctionalization of EDA with a Tertiary Aromatic Amine and a Silyl Halide Leading to an α-Halo β-Amino Acid Ester Derivative; General Procedure B

To a screw-capped test tube in a glovebox was added $Cu(acac)_2$ (0.05 mmol). The test tube was sealed with a cap that contained a PTFE septum, and then removed from the glovebox. CH_2Cl_2 (1 mL), a tertiary amine (1.75 mmol), and ethyl diazoacetate (0.5 mmol) were added to the test tube in that order. Then, the tube was cooled to 0 °C, and a silyl halide (0.75 mmol) and TBHP (0.750 mmol, 0.136 mL, 5.5 M solution in decane) were successively added. The mixture was heated at 40 °C for 1 h. To quench the reaction, the resultant mixture was directly subjected to a short pad filled with wet silica gel (eluent: EtOAc containing 1 wt% of Et_3N), and the collected filtrate was evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (eluent: hexane/EtOAc (20:1 to 5:1) containing **1** wt% of Et_3N) to give the corresponding α-halo β-amino acid ester.

Ethyl 2-Chloro-3-[methyl(phenyl)amino]propanoate (1)[18]

General procedure A was followed with *N*-(methoxymethyl)-*N*-methylaniline (150 mg, 0.992 mmol) and Me_3SiCl (158 mg, 1.45 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **1**; yield: 214 g (89%); pale yellow oil.

General procedure B was followed with *N*,*N*-dimethylaniline (213 mg, 1.75 mmol), Me_3SiCl (80.5 mg, 0.741 mmol), and ethyl diazoacetate (58.8 mg, 0.515 mmol) for 12 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **1**; yield: 77.2 mg (62%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (dt, *J* = 7.5, 2.0 Hz, 2 H, ArH), 6.78–6.72 (m, 3 H, ArH), 4.49 (dd, *J* = 8.0, 6.5 Hz, 1 H, CH), 4.24–4.13 (m, 2 H, CH_2), 4.02 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH), 3.74 (dd, *J* = 15.0, 6.0 Hz, 1 H, CH), 3.02 (s, 3 H, CH_3), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.0, 148.0, 129.4, 117.4, 112.2, 62.3, 56.7, 53.3, 39.4, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{16}ClNO_2$: 241.0870; found: 241.0872.

Ethyl 2-Chloro-3-[(2-methylphenyl)(methyl)amino]propanoate (2)

General procedure A was followed with 2-methyl-*N*-(methoxymethyl)-*N*-methylaniline (159 mg, 0.963 mmol) and Me_3SiCl (178 mg, 1.64 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **2**; yield: 154 mg (63%); colorless oil.

General procedure B was followed with $Cu(acac)_2$ (19.8 mg, 0.0756 mmol), *N*,*N*-dimethyl-*o*-toluidine (179 mg, 1.32 mmol), Me_3SiCl (61.0 mg, 0.561 mmol), ethyl diazoacetate (47.9 mg, 0.420 mmol), and TBHP (1.26 mmol, 0.228 mL, 5.5 M solution in decane) for 14 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **2**; yield: 25.7 mg (24%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.16 (t, *J* = 7.5 Hz, 2 H, ArH), 7.10 (d, *J* = 8.0 Hz, 1 H, ArH), 7.01 (t, *J* = 7.5 Hz, 1 H, ArH), 4.25 (dd, *J* = 9.0, 6.0 Hz, 1 H, CH), 4.18–4.14 (m, 2 H, CH_2), 3.62 (dd, *J* = 13.5, 9.0 Hz, 1 H, CH), 3.44 (dd, *J* = 13.5, 6.0 Hz, 1 H, CH), 2.72 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 1.24 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.2, 150.4, 134.1, 131.2, 126.6, 124.2 121.2, 61.9, 59.2, 53.8, 43.5, 17.9, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}ClNO_2$: 255.1026; found: 255.1026.

Ethyl 2-Chloro-3-[(3-methylphenyl)(methyl)amino]propanoate (3)

General procedure A was followed with 3-methyl-*N*-(methoxymethyl)-*N*-methylaniline (171 mg, 1.03 mmol) and Me_3SiCl (189 mg, 1.74 mmol) for 1 h. Column chromatography (hexane/EtOAc 29:1 containing 1 wt% of Et_3N) afforded **3**; yield: 231 mg (87%); colorless oil.

General procedure B was followed with *N*,*N*-dimethyl-*m*-toluidine (239 mg, 1.76 mmol), Me_3SiCl (87.4 mg, 0.804 mmol), and ethyl diazoacetate (61.3 mg, 0.537 mmol) for 12 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **3**; yield: 49.4 mg (36%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.15 (dt, *J* = 7.5, 3.0 Hz, 1 H, ArH), 6.60 (d, *J* = 7.0 Hz, 1 H, ArH), 6.53 (d, *J* = 6.5 Hz, 1 H, ArH), 4.49 (dd, *J* = 8.0, 6.5 Hz, 1 H, CH), 4.25–4.14 (m, 2 H, CH_2), 4.01 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH), 3.72 (dd, *J* = 15.0, 6.5 Hz, 1 H, CH), 3.00 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.1, 148.0, 139.1, 129.2, 118.3, 112.9, 109.4, 62.3, 56.8, 53.3, 39.5, 21.9, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ Calcd for $C_{13}H_{18}ClNO_2$: 255.1026; found: 255.1033.

Ethyl 2-Chloro-3-[(4-methylphenyl)(methyl)amino]propanoate (4)

General procedure A was followed with 4-methyl-*N*-(methoxymethyl)-*N*-methylaniline (167 mg, 1.01 mmol) and Me_3SiCl (176 mg, 1.62 mmol) for 1 h. Column chromatography (hexane/EtOAc 29:1 containing Et_3N) afforded **4**; yield: 236 mg (91%); colorless oil.

General procedure B was followed with *N*,*N*-dimethyl-*p*-toluidine (239 mg, 1.77 mmol), Me_3SiCl (83.5 mg, 0.769 mmol), and ethyl diazoacetate (61.7 mg, 0.541 mmol) for 14 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **4**; yield: 58.1 mg (42%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ =7.07 (d, *J* = 8.0 Hz, 2 H, ArH), 6.66 (d, *J* = 8.5 Hz, 2 H, ArH), 4.47 (dd, *J* = 8.0, 6.0 Hz, 1 H, CH), 4.24–4.13 (m, 2 H, CH_2), 3.98 (dd, *J* = 14.5, 8.0 Hz, 1 H, CH), 3.70 (dd, *J* = 15.0, 6.0 Hz, 1 H, CH), 2.98 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.1, 145.9, 129.9, 126.7, 112.5, 62.3, 57.0, 53.3, 39.5, 20.2, 13.9.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}ClNO_2$: 256.1104; found: 256.1108.

Ethyl 2-Chloro-3-[(2-methoxyphenyl)(methyl)amino]propanoate (5)

General procedure A was followed with 2-methoxy-*N*-(methoxymethyl)-*N*-methylaniline (137 mg, 0.772 mmol) and Me_3SiCl (175 mg, 1.61 mmol) for 1 h. Column chromatography (hexane/EtOAc 9:1 containing 1 wt% of Et_3N) afforded **5**; yield: 129 mg (61%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.99–6.94 (m, 2 H, ArH), 6.90 (dd, *J* = 8.0, 1.5 Hz, 1 H, ArH), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 4.45 (dd, *J* = 7.5, 6.0 Hz, 1 H, CH), 4.10 (q, *J* = 7.0 Hz, 2 H, CH_2), 3.91 (dd, *J* = 14.0, 8.0 Hz, 1 H, CH), 3.86 (s, 3 H, CH_3), 3.54 (dd, *J* = 14.0, 6.0 Hz, 1 H, CH), 2.93 (s, 3 H, CH_3), 1.23 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.5, 152.4, 139.5, 122.9, 120.8, 120.2, 111.5, 61.9, 58.4, 55.3, 54.5, 41.1, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}ClNO_3$: 271.0975; found: 271.0975.

Ethyl 2-Chloro-3-[(3-methoxyphenyl)(methyl)amino]propanoate (6)

General procedure A was followed with 3-methoxy-*N*-(methoxymethyl)-*N*-methylaniline (139 mg, 0.767 mmol) and Me_3SiCl (174 mg, 1.60 mmol) for 1 h. Column chromatography (hexane/EtOAc 9:1 containing 1 wt% of Et_3N) afforded **6**; yield: 26.1 mg (13%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.17 (t, *J* = 8.0 Hz, 1 H, ArH), 6.35–6.33 (m, 2 H, ArH), 6.27 (t, *J* = 2.5 Hz, 1 H, ArH), 4.50 (dd, *J* = 8.0, 6.0 Hz, 1 H, CH), 4.25–4.14 (m, 2 H, CH_2), 4.01 (dd, *J* = 15.0, 8.5 Hz, 1 H, CH), 3.80 (s, 3 H, CH_3), 3.72 (dd, *J* = 15.5, 6.0 Hz, 1 H, CH), 3.01 (s, 3 H, CH_3), 1.27 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.0, 160.8, 149.3, 130.1, 105.1, 102.0, 98.9, 62.3, 56.7, 55.1, 53.2, 39.6, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}ClNO_3$: 271.0975; found: 271.0969.

Ethyl 2-Chloro-3-[(4-methoxyphenyl)(methyl)amino]propanoate (7)

General procedure A was followed with 4-methoxy-*N*-(methoxymethyl)-*N*-methylaniline (185 mg, 1.02 mmol) and Me_3SiCl (167 mg, 1.54 mmol) for 1 h. Column chromatography (hexane/EtOAc 9:1 containing 1 wt% of Et_3N) afforded **7**; yield: 186 mg (63%); yellow oil.

General procedure B was followed with $Cu(acac)_2$ (25.3 mg, 0.0967 mmol), 4-methoxy-*N*,*N*-dimethylaniline (264 mg, 1.75 mmol), Me_3SiCl (83.2 mg, 0.766 mmol), ethyl diazoacetate (58.4 mg, 0.512 mmol), and TBHP (1.54 mmol, 0.279 mL, 5.5 M solution in decane) for 14 h. Column chromatography (hexane/EtOAc 5:1 containing 1 wt% of Et_3N) afforded **7**; yield: 52.9 mg (38%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.84 (d, *J* = 9.0 Hz, 2 H, ArH), 6.71 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 4.45 (dd, *J* = 8.5, 6.5 Hz, 1 H, CH), 4.24–4.13 (m, 2 H, CH_2), 3.94 (dd, *J* = 15.0, 8.5 Hz, 1 H, CH), 3.76 (s, 3 H, CH_3), 3.64 (dd, *J* = 15.0, 6.0 Hz, 1 H, CH), 2.95 (s, 3 H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.1, 152.3, 142.9, 114.9, 114.4, 62.2, 57.9, 55.8, 53.4, 39.8, 14.0.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}ClNO_3$: 271.0975; found: 271.0970.

Ethyl 2-Chloro-3-[(4-fluorophenyl)(methyl)amino]propanoate (8)

General procedure A was followed with 4-fluoro-*N*-(methoxymethyl)-*N*-methylaniline (173 mg, 1.02 mmol) and Me_3SiCl (170 mg, 1.56 mmol) for 1 h. Column chromatography (hexane/EtOAc 9:1 containing Et_3N) afforded **8**; yield: 233 mg (88%); pale yellow oil.

General procedure B was followed with $Cu(acac)_2$ (25.7 mg, 0.0981 mmol), 4-fluoro-*N*,*N*-dimethylaniline (246 mg, 1.77 mmol), Me_3SiCl (88.0 mg, 0.810 mmol), ethyl diazoacetate (58.2 mg, 0.510 mmol), and TBHP (1.53 mmol, 0.277 mL, 5.5 M solution in decane) for 14 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **8**; yield: 74.2 mg (56%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.96 (t, *J* = 9.0 Hz, 2 H, ArH), 6.69–6.66 (m, 2 H, ArH), 4.45 (dd, *J* = 8.0, 6.0 Hz, 1 H, CH), 4.24–4.13 (m, 2 H, CH_2), 3.97 (dd, *J* = 15.0, 8.5 Hz, 1 H, CH), 3.67 (dd, *J* = 15.0, 6.5 Hz, 1 H, CH), 2.97 (s, 3 H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.0, 156.8 (d, *J* = 236.4 Hz), 144.7, 115.8 (d, *J* = 21.4 Hz), 113.5 (d, *J* = 7.5 Hz), 62.3, 57.4, 53.2, 39.7, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}ClFNO_2$: 259.0775; found: 259.0778.

Ethyl 2-Chloro-3-[ethyl(phenyl)amino]propanoate (9)

General procedure A was followed with *N*-(methoxymethyl)-*N*-ethylaniline (175 mg, 1.06 mmol) and Me_3SiCl (173 mg, 1.59 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **9**; yield: 211 mg (77%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.27–7.23 (m, 2 H, ArH), 6.76–6.71 (m, 3 H, ArH), 4.45 (dd, *J* = 8.0, 5.5 Hz, 1 H, CH), 4.24–4.16 (m, 2 H, CH_2), 3.96 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH), 3.69 (dd, *J* = 15.5, 6.0 Hz, 1 H, CH), 3.51–3.38 (m, 2 H, CH_2), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.13 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.2, 146.7, 129.4, 117.2, 112.6, 62.2, 54.8, 53.2, 45.9, 13.9, 11.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}ClNO_2$: 255.1026; found: 255.1032.

Ethyl 2-Chloro-3-[ethyl(3-methylphenyl)amino]propionate (10)

General procedure A was followed with 3-methyl-*N*-(methoxymethyl)-*N*-ethylaniline (177 mg, 0.987 mmol) and Me_3SiCl (177 mg, 1.63 mmol) for 1 h. Column chromatography (hexane/EtOAc 9:1 containing 1 wt% of Et_3N) afforded **10**; yield: 248.1 mg (93%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.14 (dd, *J* = 9.0, 7.5 Hz, 1 H, ArH), 6.59–6.52 (m, 3 H, ArH), 4.45 (dd, *J* = 8.5, 6.0 Hz, 1 H, CH), 4.24–4.16 (m, 2 H, CH_2), 3.94 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH), 3.67 (dd, *J* = 14.5, 5.5 Hz, 1 H, CH), 3.50–3.36 (m, 2 H, CH_2), 2.32 (s, 3 H, CH_3), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.12 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.2, 146.8, 139.1, 129.3, 118.1, 113.3, 109.7, 62.2, 54.8, 53.3, 45.9, 22.0, 13.9, 12.0.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{14}H_{20}ClNO_2$: 269.1183; found: 269.1183.

Ethyl 3-[Benzyl(methyl)amino]-2-chloropropanoate (11)

General procedure A was followed with *N*-(methoxymethyl)-*N*-methylbenzylamine (165 mg, 0.999 mmol) and Me_3SiCl (161 mg, 1.48 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **11**; yield: 80.0 mg (31%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.32–7.23 (m, 5 H, ArH), 4.43–4.21 (m, 3 H, CH_2, CH), 3.63–3.56 (m, 2 H, CH_2), 3.12 (dd, *J* = 13.0, 9.0 Hz, 1 H, CH), 2.83 (dd, *J* = 13.0, 6.0 Hz, 1 H, CH), 2.26 (s, 3 H, CH_3), 1.30 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.3, 138.4, 128.8, 128.2, 127.2, 62.4, 61.9, 60.9, 53.9, 42.4, 14.0.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}ClNO_2$: 256.1104; found: 256.1105.

Ethyl 2-Bromo-3-[methyl(phenyl)amino]propanoate (12)[19]

General procedure A was followed with *N*-(methoxymethyl)-*N*-methylaniline (150 mg, 0.992 mmol) and Me_3SiBr (277 mg, 1.81 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing Et_3N) afforded **12**; yield: 235 mg (83%); pale yellow oil.

General procedure B was followed with *N*,*N*-dimethylaniline (214 mg, 1.77 mmol), Me_3SiBr (114 mg, 0.754 mmol), and ethyl diazoacetate (61.3 mg, 0.537 mmol) for 12 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **12**; yield: 38.3 mg (25%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (t, *J* = 7.5 Hz, 2 H, ArH), 6.77 (t, *J* = 7.0 Hz, 1 H, ArH), 6.71 (d, *J* = 8.0 Hz, 2 H, ArH), 4.41 (dd, *J* = 9.5, 5.0 Hz, 1 H, CH), 4.24–4.14 (m, 2 H, CH_2), 4.03 (dd, *J* = 15.0, 9.5 Hz, 1 H, CH), 3.81 (dd, *J* = 15.0, 5.0 Hz, 1 H, CH), 3.00 (s, 3 H, CH_3), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.3, 147.9, 129.4, 117.5, 112.2, 62.2, 56.5, 41.3, 39.3, 13.9.

MS (FAB): *m*/*z* = 286 $(M + H)^+$.

Ethyl 2-Bromo-3-[(4-methylphenyl)(methyl)amino]propanoate (13)

General procedure A was followed with 4-methyl-*N*-(methoxymethyl)-*N*-methylaniline (160 mg, 0.969 mmol) and Me_3SiBr (236 mg, 1.54 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **13**; yield: 175 mg (60%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.08 (d, *J* = 9.0 Hz, 2 H, ArH), 6.65 (d, *J* = 8.5 Hz, 2 H, ArH), 4.39 (dd, *J* = 10.0, 5.5 Hz, 1 H, CH), 4.24–4.14 (m, 2 H, CH_2), 3.99 (dd, *J* = 14.5, 5.0 Hz, 1 H, CH), 3.77 (dd, *J* = 15.0, 5.0 Hz, 1 H, CH), 2.96 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.4, 145.9, 129.9, 126.8, 112.4, 62.2, 56.8, 41.4, 39.4, 20.2, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}BrNO_2$: 299.0521; found: 299.0525.

Ethyl 2-Bromo-3-[(4-fluorophenyl)(methyl)amino]propanoate (14)

General procedure A was followed with 4-fluoro-*N*-(methoxymethyl)-*N*-methylaniline (151 mg, 0.892 mmol) and Me_3SiBr (230 mg, 1.50 mmol) for 1 h. Column chromatography (hexane/EtOAc 19:1 containing 1 wt% of Et_3N) afforded **14**; yield: 219 mg (81%); yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.96 (t, *J* = 9.0 Hz, 2 H, ArH), 6.68–6.65 (m, 2 H, ArH), 4.37 (dd, *J* = 9.5, 5.0 Hz, 1 H, CH), 4.24–4.14 (m, 2 H, CH_2), 3.99 (dd, *J* = 15.0, 9.5 Hz, 1 H, CH), 3.73 (dd, *J* = 15.0, 5.0 Hz, 1 H, CH), 2.95 (s, 3 H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.3, 155.0 (d, $J_{C,F}$ = 236.5 Hz), 144.7, 115.6 (d, $J_{C,F}$ = 22.6 Hz), 113.6 (d, $J_{C,F}$ = 7.5 Hz), 62.3, 57.2, 41.2, 39.6, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}BrFNO_2$: 303.0270; found: 303.0268.

Ethyl 2-Iodo-3-[methyl(phenyl)amino]propanoate (15)

General procedure A was followed with *N*-(methoxymethyl)-*N*-methylaniline (159 mg, 1.05 mmol) and Me_3SiI (320 mg, 1.60 mmol) for 1 h. Column chromatography (hexane containing 1 wt% of Et_3N) afforded **15**; yield: 83.3 mg (25%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (t, *J* = 8.0 Hz, 2 H, ArH), 6.77 (t, *J* = 9.0 Hz, 1 H, ArH), 6.68 (d, *J* = 8.0 Hz, 2 H, ArH), 4.50 (dd, *J* = 10.5, 4.0 Hz, 1 H, CH), 4.22–4.12 (m, 2 H, CH_2), 3.99 (dd, *J* = 15.0, 10.5 Hz, 1 H, CH), 3.85 (dd, *J* = 15.0, 4.0 Hz, 1 H, CH), 2.99 (s, 3 H, CH_3), 1.24 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.0, 147.8, 129.4, 117.4, 112.1, 62.0, 57.8, 39.3, 18.1, 13.7.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{16}INO_2$: 333.0226; found: 333.0221.

Ethyl 2-Chloro-3-[(4-chlorophenyl)(methyl)amino]propanoate (16)

General procedure B was followed with $Cu(acac)_2$ (25.7 mg, 0.0981 mmol), 4-chloro-*N*,*N*-dimethylaniline (273 mg, 1.75 mmol), Me_3SiCl (83.6 mg, 0.770 mmol), ethyl diazoacetate (60.4 mg, 0.529 mmol), and TBHP (1.59 mmol, 0.288 mL, 5.5 M solution in decane) for 12 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **16**; yield: 64.3 mg (44%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.18 (d, *J* = 9.0 Hz, 2 H, ArH), 6.63 (d, *J* = 9.0 Hz, 2 H, ArH), 4.46 (dd, *J* = 8.0, 6.0 Hz, 1 H, CH), 4.25–4.14 (m, 2 H, CH_2), 3.99 (dd, *J* = 15.5, 8.0 Hz, 1 H, CH), 3.71 (dd, *J* = 15.5, 6.5 Hz, 1 H, CH), 2.99 (s, 3 H, CH_3), 1.27 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.8, 146.6, 129.1, 122.4, 113.4, 62.4, 56.7, 53.1, 39.5, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}Cl_2NO_2$: 275.0480; found: 275.0480.

Ethyl 2-Chloro-3-[(4-bromophenyl)(methyl)amino]propanoate (17)

General procedure B was followed with $Cu(acac)_2$ (26.7 mg, 0.102 mmol), 4-bromo-*N*,*N*-dimethylaniline (350 mg, 1.75 mmol), Me_3SiCl (82.4 mg, 0.758 mmol), ethyl diazoacetate (56.5 mg, 0.495 mmol), and TBHP (1.49 mmol, 0.269 mL, 5.5 M solution in decane) for 12 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **17**; yield: 38.1 mg (24%); brown oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32 (d, *J* = 9.0 Hz, 2 H, ArH), 6.59 (d, *J* = 9.0 Hz, 2 H, ArH), 4.45 (dd, *J* = 8.0, 6.5 Hz, 1 H, CH), 4.25–4.14 (m, 2 H, CH_2), 3.98 (dd, *J* = 15.5, 8.0 Hz, 1 H, CH), 3.71 (dd, *J* = 15.5, 6.0 Hz, 1 H, CH), 2.99 (s, 3 H, CH_3), 1.27 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.8, 147.0, 132.0, 113.8, 109.5, 62.4, 56.6, 53.1, 39.5, 14.0.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}BrClNO_2$: 318.9975; found: 318.9978.

Ethyl 2-Chloro-3-{4-[(trifluoromethyl)phenyl](methyl)amino}-propanoate (18)

General procedure B was followed with $Cu(acac)_2$ (26.2 mg, 0.100 mmol), 4-trifluoromethyl-*N*,*N*-dimethylaniline (325 mg, 1.72 mmol), Me_3SiCl (85.4 mg, 0.786 mmol), ethyl diazoacetate (56.0 mg, 0.491 mmol), and TBHP (1.47 mmol, 0.267 mL, 5.5 M solution in decane) for 14 h. Column chromatography (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) afforded **18**; yield: 27.3 mg (18%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48 (d, *J* = 8.5 Hz, 2 H, ArH), 6.73 (d, *J* = 9.0 Hz, 2 H, ArH), 4.48 (dd, *J* = 7.5, 6.5 Hz, 1 H, CH), 4.26–4.15 (m, 2 H, CH_2), 4.08 (dd, *J* = 15.5, 8.0 Hz, 1 H, CH), 3.79 (dd, *J* = 15.5, 6.5 Hz, 1 H, CH), 3.07 (s, 3 H, CH_3), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 168.7, 150.1, 126.6 (q, $J_{C,F}$ = 3.8 Hz), 125.9 (t, $J_{C,F}$ = 270.4 Hz), 119.0 (q, $J_{C,F}$ = 32.7 Hz), 62.5, 56.2, 53.0, 39.5, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{13}H_{15}ClF_3NO_2$: 309.0743; found: 309.0733.

Ethyl 2-Azido-3-[methyl(phenyl)amino]propanoate (19)[20]

General procedure B was followed with $Cu(acac)_2$ (26.2 mg, 0.100 mmol), *N*,*N*-dimethylaniline (214 mg, 1.77 mmol), trimethylsilyl azide (88.7 mg, 0.770 mmol), ethyl diazoacetate (67.0 mg, 0.586 mmol), TBHP (1.54 mmol, 0.279 mL, 5.5 M solution in decane), and MeCN (1 mL) instead of CH_2Cl_2 for 14 h. Column chromatography (hexane/EtOAc 10:1 containing 1 wt% of Et_3N) afforded **19**; yield: 87.4 mg (60%); colorless oil.

According to another approach shown in Scheme 3, to a screw-capped vial were added NaN_3 (65.0 mg, 1.00 mmol), DMF (2 mL), and **1** (120.9 mg, 0.500 mmol) in that order. The tube was sealed with a cap that contained a PTFE septum, following replacement of the atmosphere with N_2. The mixture was stirred at rt for 40 h. After completion of the reaction, the mixture was poured into H_2O (2 mL) and extracted with hexane/EtOAc (10: 1; 3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc 10:1 containing 1 wt% of Et_3N) to give the desired product **19**; yield: 84.4 mg (68%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28–7.25 (m, 2 H, ArH), 6.78–6.76 (m, 3 H, ArH), 4.29–4.19 (m, 3 H, CH_2, CH), 3.95 (dd, *J* = 15.0, 4.5 Hz, 1 H, CH), 3.54 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH), 3.04 (s, 3 H, CH_3), 1.31 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.3, 148.0, 129.4, 117.4, 112.3, 62.1, 60.4, 54.4, 39.4, 14.1.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{12}H_{16}N_4O_2$: 248.1273; found: 248.1273.

Ethyl 2-Amino-3-[methyl(phenyl)amino]propanoate (21)

To a screw-capped vial were added NaN_3 (65.0 mg, 1.00 mmol), DMF (2 mL), and **1** (120.9 mg, 0.5000 mmol) in that order. The tube was sealed with a cap that contained a PTFE septum, followed by replacement of the atmosphere with N_2. The mixture was stirred at rt for 40 h. After completion of the reaction, the mixture was poured into H_2O (2 mL) and extracted with hexane/EtOAc (10: 1; 3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was dissolved in THF (2 mL), to which was added PPh_3 (196.7 mg, 0.750 mmol) and H_2O (90.1 mg, 5.00 mmol) for 2 h at rt under N_2. After completion, the mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 70:1 to 9:1) to give the desired product **21**; yield: 60.0 mg (54%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.24 (t, *J* = 7.5 Hz, 2 H, ArH), 6.79 (d, *J* = 9.0, 2 H, ArH), 6.73 (t, *J* = 7.5 Hz, 1 H, ArH), 4.20–4.08 (m, 2 H, CH_2), 3.81 (t, *J* = 6.5 Hz, 1 H, CH), 3.75–3.69 (m, 1 H, CH), 3.45 (dd, *J* = 15.0, 7.5 Hz, 1 H, CH), 2.99 (s, 3 H, CH_3), 1.63 (s, 2 H, NH_2), 1.25 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 174.7, 149.1, 129.2, 116.9, 112.4, 61.2, 57.5, 53.4, 39.3, 14.1.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}N_2O_2$: 223.1447; found: 223.1451.

Ethyl 2-[(4-Isopropylphenyl)thio]-3-[methyl(phenyl)amino]propanoate (22)[21]

To a screw-capped vial, NaOMe (27.0 mg, 0.500 mmol), MeOH (1 mL), and 4-isopropylbenzenethiol (76.1 mg, 0.500 mmol) were added in that order. The tube was sealed with a cap that contained a PTFE septum, following replacement of the atmosphere with N_2. Then, the reaction mixture was heated at 60 °C for 1 h. After cooling to rt, **1** (120.9 mg, 0.500 mmol) was added. Then the mixture was heated at 60 °C for another 24 h under N_2 atmosphere. After cooling to rt, the mixture was poured into H_2O (2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (hexane/EtOAc 20:1 containing 1 wt% of Et_3N) to give the desired product **22**; yield: 130 mg (73%); colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.42 (d, *J* = 8.0 Hz, 2 H, ArH), 7.20–7.17 (m, 4 H, ArH), 6.71 (t, *J* = 7.0 Hz, 1 H, ArH), 6.58 (d, *J* = 8.0 Hz, 2 H, ArH), 4.12–4.02 (m, 2 H, CH_2), 3.89 (dd, *J* = 9.5, 4.5 Hz, 1 H, CH), 3.82 (dd, *J* = 14.5, 9.5 Hz, 1 H, CH), 3.71 (dd, *J* = 15.0, 4.5 Hz, 1 H, CH), 2.94–2.88 (m, 4 H, CH_3, CH), 1.23 (d, *J* = 7.0 Hz, 6 H, 2 × CH_3), 1.14 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.5, 149.6, 148.2, 134.1, 129.2, 129.1, 127.2, 116.8, 112.2, 61.4, 54.8, 48.7, 39.1, 33.8, 23.88, 23.85, 13.9.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{21}H_{27}NO_2S$: 357.1762; found: 357.1761.

Ethyl 2-(Acetylthio)-3-[methyl(phenyl)amino]propanoate (23)

To a screw-capped vial were added KSAc (114.2 mg, 1.000 mmol), MeCN (2 mL), and **1** (120.9 mg, 0.500 mmol) in that order. The tube was sealed with a cap that contained a PTFE septum, followed by replacement of the atmosphere with N_2. Then, the reaction mixture was heated at 80 °C for 3 h. After cooling to rt, the mixture was poured into H_2O (2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc 10:1 to 2:1 containing 1 wt% of Et_3N) to give the desired product **23**; yield: 53.4 mg (38%); pale yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ =7.25 (t, *J* = 8.0 Hz, 2 H, ArH), 6.80 (d, *J* = 8.5 Hz, 2 H, ArH), 6.75 (t, *J* = 7.5 Hz, 1 H, ArH), 4.51 (dd, *J* = 9.0, 5.5 Hz, 1 H, CH), 4.15–4.05 (m, 2 H, CH_2), 3.88 (dd, *J* = 15.0, 9.5 Hz, 1 H, CH), 3.60 (dd, *J* = 15.0, 5.5 Hz, 1 H, CH), 2.97 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 193.6, 170.6, 148.5, 129.2, 117.2, 112.5, 61.9, 54.9, 44.3, 38.8, 30.3, 13.9.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_3S$: 282.1164; found: 282.1169.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690864.

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