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Highly efficient sequential N,N,C-trialkylation of α-*N*-acyloxyimino esters

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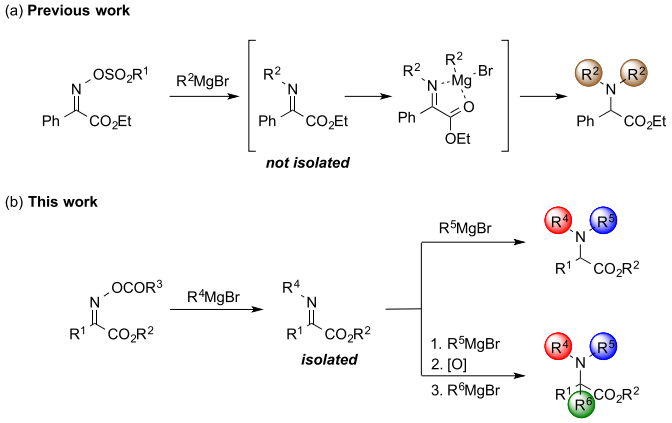
ABSTRACT

α-*N*-Acyloxyimino esters serve as highly efficient substrates for the N,N,C-trialkylation reaction that can introduce various patterns of nucleophiles at the imino nitrogen and carbon atoms to synthesize *N*,*N*-dialkylated and *N*,*N*,*C*-trialkylated α-amino esters in moderate to high yields.

1. Introduction

N,*N*-Dialkyl-α-amino acids and their α-alkylated derivatives along with amino alcohols formed from them are the core moieties in many important pharmaceuticals and catalyst scaffolds in organic synthesis.[1] In addition, they frequently serve as useful intermediates in the synthesis of bioactive materials such as antiarrhythmic agents.[2] Thus, the development of efficient methods that flexibly incorporate substituents in both the nitrogen and carbon atoms at the α-positions of amino acids is important and represents an attractive objective for synthetic studies. Although this topic has received considerable attention over the past decades, to the best of our knowledge, only a few methods that enable the construction of the *N*,*N*-dialkyl-α-amino acid framework with high efficiency are available.[3] Amination using α-imino esters allows electrophilic N-alkylation, an otherwise difficult process owing to the nucleophilicity of nitrogen.

An umpolung of an α-imino ester is a difficult amination because of the electronegativity of the imino group.[4] Our laboratory has developed umpolung reactions of α-imino esters along with various tandem C–C bond formation reactions using the metal enolate produced by N-alkylation.[5] We have previously reported N,N-di- and N,N,C-trialkylations of α-sulfoximino esters, featuring both α-imino esters and oximes based on tandem amination/N-alkylation/C-alkylation (Scheme 1(a)).[5j] However, there are some problems wherein the N,N-dialkylation is too rapid and cannot be controlled during N-monoalkylation. Moreover, these reactions have some limitation of scope of substrates and nucleophiles, and overall yields are not always satisfactory. In this study, we conducted further examinations to solve these problems, and report a new type of α-imino ester with an *N*-acyloxy group (an *N*-*p*-toluoyloxy group) that can introduce two types of nucleophiles freely on the imino nitrogen to give the *N*,*N*-dialkylated amino esters. A highly efficient N,N,C-trialkylation of *N*-*p*-toluoyloxyimino



Scheme 1. Previous and present works.

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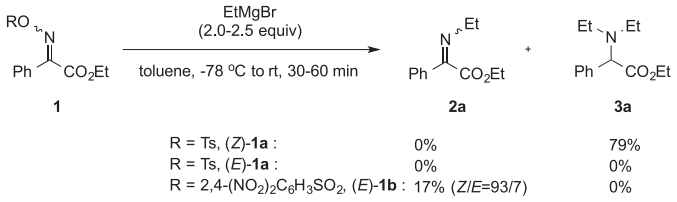
esters with three kinds of nucleophiles was also developed for construction of trialkylated amino esters in good yields (Scheme 1(b)).

As shown in Scheme 2, we have previously demonstrated that (*Z*)-α-sulfoximino ester such as ethyl (*Z*)-2-phenyl-2-[(tosyloxy)imino]acetate (*Z*)-**1a** is a suitable substrate for the N,N-dialkylation reaction to afford the diethylated product **3a**, while (*E*)-isomers such as ethyl (*E*)-2-[(2,4-dinitrophenyl)sulfonyloxy]imino-2-phenylacetate (*E*)-**1b** can provide the monoethylated product **2a** preferentially but in a low yield.[5j] Although it is not trivial to stop the reaction at the N-monoalkylation stage, these results provide a possible strategy for introducing two different alkyl substituents at the nitrogen atom.

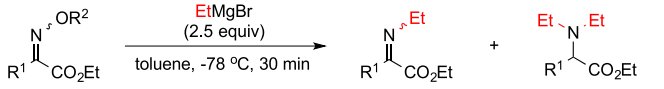


Scheme 2. N-Monoethylation and N,N-diethylation of α-sulfoximino esters.

2. Results and discussion

In this context, we examined monoethylation of various sulfonates; Table 1 summarizes the results. Although α-sulfoximino esters with various substituents such as 4-$ClC_6H_4SO_2$, 2,4-$Cl_2C_6H_3SO_2$, 4-$FC_6H_4SO_2$ and $C_6F_5SO_2$ were examined initially, the desired products were not obtained (entries 1–4). We found that monoethylated product **2** was obtained in 74% yield when ethyl (*Z*)-2-(benzoyloxy)imino-2-phenylacetate (*Z*)-**1g** was used (entry 6), whereas for the isomer (*E*)-**1g**, N,N-diethylation proceeded to give the *N*,*N*-diethylated product **3** in 37% yield (entry 5). The substrate with an acetoxy group at the nitrogen, (*Z*)-**1h** also gave the product in a good yield (entry 7), whereas that with a methoxy group, (*Z*)-**1i** gave no product (entry 8). Substrates having aromatic groups with electron-withdrawing and electron-donating *para*-substituents, heteroaromatic group, and ethoxycarbonyl group (*Z*)-**1j-l** and **1m** did not undergo the desired reaction to give the monoethylated products **2**; instead, the diethlyated product **3** was obtained in 53–84% yields (entries 9–12).

Table 1
Screening of the N-monoethylation of α-imino ester

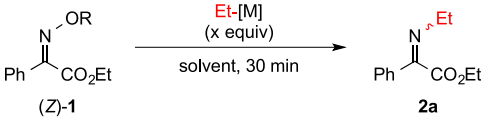


Entry	R^1	R^2	1	Product yield[a] (%)	
				2 (*Z*/*E*)	3
1	Ph	4-$ClC_6H_4SO_2$	(*E*)-**1c**	0	22
2	Ph	2,4-$Cl_2C_6H_3SO_2$	(*E*)-**1d**	0	0
3	Ph	4-$FC_6H_4SO_2$	(*E*)-**1e**	0	0
4	Ph	$C_6F_5SO_2$	(*E*)-**1f**	0	0
5	Ph	Bz	(*E*)-**1g**	0	37
6	Ph	Bz	(*Z*)-**1g**	74 (90/10)	0
7	Ph	Ac	(*Z*)-**1h**	69 (91/9)	0
8	Ph	Me	(*Z*)-**1i**	0	0
9[b]	4-ClC_6H_4	Ts	(*Z*)-**1j**	0	84
10[b]	4-$MeOC_6H_4$	Ts	(*Z*)-**1k**	0	59
11[b]	2-thienyl	Ts	(*E*)-**1l**	0	61
12[b]	CO_2Et	Ts	**1m**	0	53

[a] Yield of isolated product.
[b] EtMgBr (2.2 equiv), 30 °C, 15 min.

To find the optimum reaction conditions, we next screened several parameters for this reaction, and the results are summarized in Table 2. As shown in entries 1–5, 2.2 equiv of Grignard reagent were suitable for the reaction. Further optimization with respect to the reaction temperature and the solvent was carried out for this reaction (entries 6–13). Temperatures greater than −78 °C slightly decreased the product yields (entries 6–8). Regarding the solvent, toluene was found to be the best, and decreased product yields were observed in other examined solvents (entries 9–13). When other organometallic reagents such as Et_2AlCl, Et_2Zn were used, the desired products were not obtained at all (entries 15 and 16). Under the optimum reaction conditions (2.2 equiv of EtMgBr in toluene at −78 °C, entry 3), a further enhancement of the yield was observed using the *N*-*p*-toluoyloxyimino ester, and 78% yield was achieved (entry 18).

Table 2
Optimization of the reaction conditions



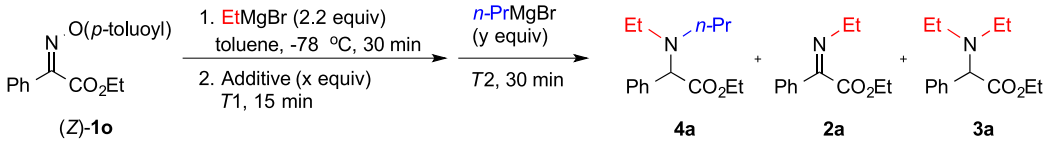
Entry	R (**1**)	Et-[M] (x equiv)	Solvent	*T* (°C)	Yield[a] (%) (*Z*/*E*)
1	Bz (**1g**)	EtMgBr (1.5)	toluene	−78	44 (88/12)
2	Bz (**1g**)	EtMgBr (2.0)	toluene	−78	64 (86/14)
3	Bz (**1g**)	EtMgBr (2.2)	toluene	−78	76 (96/4)
4	Bz (**1g**)	EtMgBr (2.5)	toluene	−78	74 (90/10)
5	Bz (**1g**)	EtMgBr (3.0)	toluene	−78	61 (90/10)
6	Bz (**1g**)	EtMgBr (2.2)	toluene	−78 to 30	55 (88/12)
7	Bz (**1g**)	EtMgBr (2.2)	toluene	0	66 (93/7)
8	Bz (**1g**)	EtMgBr (2.2)	toluene	30	51 (90/10)
9	Bz (**1g**)	EtMgBr (2.2)	CH_2Cl_2	−78	68 (90/10)
10	Bz (**1g**)	EtMgBr (2.2)	EtCN	−78	74 (91/9)
11	Bz (**1g**)	EtMgBr (2.2)	Et_2O	−78	60 (91/9)
12	Bz (**1g**)	EtMgBr (2.2)	THF	−78	65 (89/11)
13	Bz (**1g**)	EtMgBr (2.2)	DME	−78	69 (94/6)
14[b]	Bz (**1g**)	EtMgBr (2.2)	toluene	−78	72 (91/9)
15	Bz (**1g**)	Et_2AlCl (2.2)	toluene	−78	0
16	Bz (**1g**)	Et_2Zn (2.2)	toluene	−78	0
17	4-ClC_6H_4CO (**1n**)	EtMgBr (2.2)	toluene	−78	73 (95/5)
18	*p*-toluoyl[c] (**1o**)	EtMgBr (2.2)	toluene	−78	78 (91/9)

[a] Yield of the isolated product.
[b] EtMgBr in THF was used.
[c] *p*-toluoyl=4-MeC_6H_4CO.

Next, tandem N,N-dialkylations with two different nucleophiles were examined using ethyl and *n*-propyl Grignard reagents. As an initial reaction, ethyl (*Z*)-2-(4-methylbenzoyloxy)imino-2-phenylacetate (*Z*)-**1o** first reacted with 2.2 equiv of EtMgBr in toluene at −78 °C for 30 min followed by an umpolung reaction with 2.0 equiv of *n*-PrMgBr at −78 °C for 30 min. Unfortunately the monoethylated product **2** was obtained in 75% yield instead of the desired *N*-ethyl-*N*-*n*-propyl product **4a** (Table 3, entry 1). When the reaction was performed at −78 to 30 °C, the desired product **4a** was obtained in 33% (entry 2). To improve the yield of **4a**, the effects of additives as reaction promoters were next examined (entries 3–5). The use of additives such as TMSCl and BF_3OEt_2 gave the product **4a** in 69% and 17% yields, respectively (entries 3 and 4). Benzoic acid was the most effective additive in this reaction (entry 5). In the presence of 0.75 equiv of benzoic acid, the *N*,*N*-dialkylated product **4a** was isolated in 79% yield, whereas the use of 1.0 equiv of benzoic acid gave the product **4a** in 63% yield (entries 6 and 7). The role of benzoic acid is to quench an excess Grignard reagent after the first electrophilic amination.[6] The optimized reaction conditions were thus found to be using benzoic acid as an additive in toluene as solvent at −78 to 30 °C (entry 6).

The scope of second nucleophiles was next examined under the optimized reaction conditions (Table 3, entry 6), and the results are

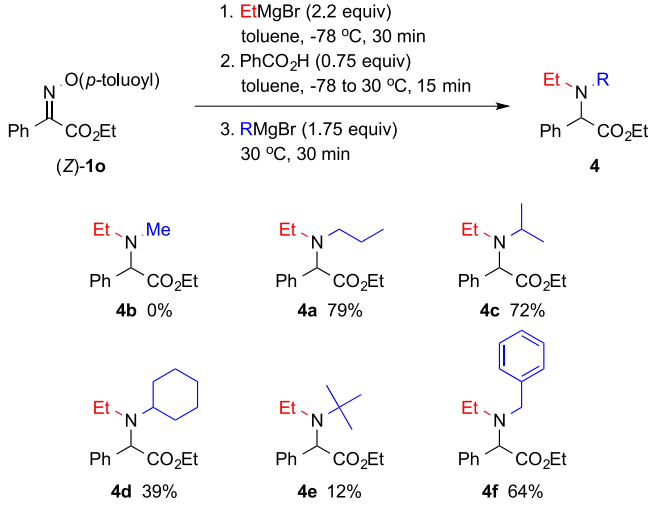
Table 3
Examination of additives for tandem N,N-dialkylation with different nucleophiles



Entry	Additive (x equiv)	T1 (°C)	y (equiv)	T2 (°C)	Yield[a] (%)		
					4a	**2a** (*Z*/*E*)	**3a**
1	—	—	2.0	−78	0	75 (91/9)	0
2	—	—	2.0	−78 to 30	33	13	27
3	TMSCl (2.0)	−78	2.0	30	69	0	6
4	$BF_3{\cdot}OEt_2$ (2.0)	−78 to 30	2.0	30	17	15 (86/14)	0
5	$PhCO_2H$ (0.5)	−78 to 30	2.0	30	78	0	0
6	$PhCO_2H$ (0.75)	−78 to 30	1.75	30	79	0	0
7	$PhCO_2H$ (1.0)	−78 to 30	2.5	30	63	0	0

[a] Yield of isolated product.

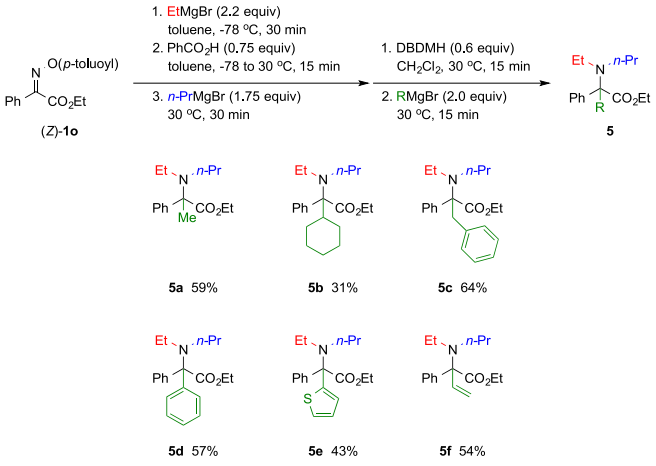
summarized in Scheme 3. Methyl Grignard reagent was not effective in this reaction. Primary and secondary alkyls such as *n*-Pr, *i*-Pr and Bn group were able to be introduced to the imino nitrogen to give the products **4a**,**c**,**f** in good to high yields, while in the case of an alicyclic substituent, Cy, the yield of the desired product **4d** decreased slightly. A bulky *tert*-butyl Grignard reagent gave the product **4e** in low yield.[7]



Scheme 3. Screening of the second nucleophiles for the tandem N,N-dialkylation to α-*p*-toluoyloxyimino ester.

Finally we also investigated a sequential N,N,C-trialkylation with three different nucleophiles under the optimized reaction conditions (Scheme 4). When a series of nucleophiles such as primary, secondary, aromatic, and vinyl Grignards were examined, the desired products **5a**–**f** were obtained in moderate to good overall yields. Notably, this one-pot sequential reaction is an effective method to synthesize the *N*,*N*,*C*-trialkylated amino acid derivatives, which are important pharmaceuticals, and building blocks in organic synthesis.

A proposed reaction mechanism is shown in Scheme 5. First, Grignard reagent coordinates with the two carbonyl oxygens of acyloxy and ester moiety of (*Z*)-acyloxyimino ester (*Z*)-**1** to activate an imino ester via an intermediate **A**. Amination proceeds to give a monoalkylated imino ester **2** through the formation of an eight-membered magnesium enolate intermediate **B**.[8] We assume that the second N-alkylation with Grignard reagent is unlikely owing to the stability of this eight-membered intermediate **B** (Scheme 5(a)); in the case of (*E*)-acyloxyimino ester, the magnesium enolate **D** is formed via a five-membered intermediate **C** after the N-monoalkylation to give



Scheme 4. Screening of the third nucleophiles for the tandem N,N,C-trialkylation to α-*p*-toluoyloxyimino ester.

the monoalkylated imino ester **2** in situ followed by the rapid second N-alkylation to give *N*,*N*-dialkylaion product (Scheme 5(b)). Regarding di- and trialkylations with different nucleophiles, the second Grignard reagent activates the imino ester **2** to form a five-membered intermediate **E**, and the second N-alkylation proceeds to give a magnesium enolate **F** followed by the oxidation with DBDMH to the iminium salt **G**. The final step is the reaction of the third Grignard reagent with the iminium salt **G** to afford the trialkylated product **5** (Scheme 5c).

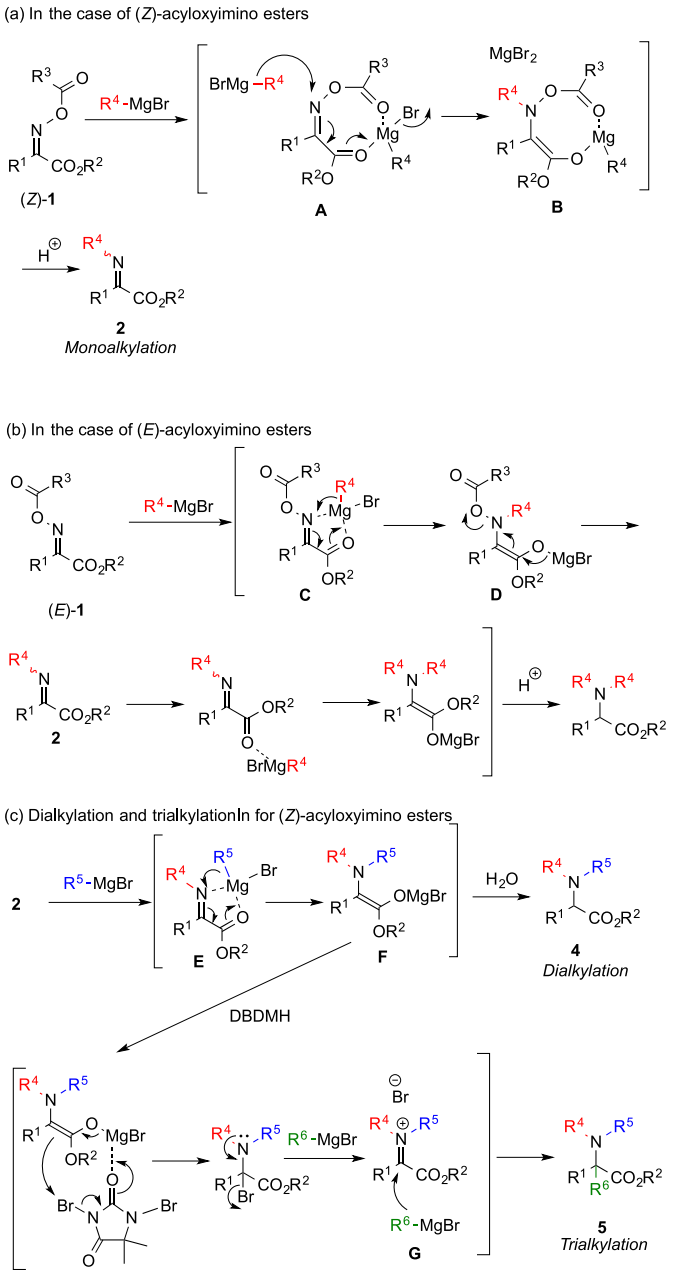
3. Conclusion

In conclusion, α-*N*-acyloxyimino ester is an excellent substrate for the sequential amination/umpolung N-alkylation/C-alkylation reaction, which can introduce various substituents freely on the imino nitrogen and carbon atoms. This unique method offers a new type of approach to *N*,*N*-dialkylated and *N*,*N*,*C*-trialkylated α-amino esters and an attractive method for the construction of tertiary and quaternary *N*,*N*-dialkylamino acids and alcohols. These products are used in bioactive materials such as antiarrhythmic drugs.

4. Experimental section

4.1. General aspects

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with



Scheme 5. Plausible mechanism.

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 and a SIMADZU GC–MS-QP2010 Ultra (CI) spectrometer. Toluene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4 Å. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride and stored over Molecular Sieves 4 Å. Propionitrile (EtCN) was distilled from phosphorus pentaoxide and then from calcium hydride and stored over Molecular Sieves 4 Å. Diethylether (Et_2O) and tetrahydrofuran (THF) were distilled from benzophenone ketyl immediately before use. Dimethoxyethane (DME) was distilled from calcium hydride and then cupper(I) chloride and stored over sodium. 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).

4.2. General procedure for the synthesis of α-sulfoximino esters 1a–f and 1j–m

Compounds (*Z*)-**1a**, (*E*)-**1a**, (*E*)-**1b** and (*E*)-**1d** were prepared according to the reported procedure.[5j]

In a 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed oxime ester (2.50 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C, and to it were added *i*-PrNEt (3.00 mmol) and sulfonyl chloride (2.80 mmol). The whole mixture was warmed to room temperature and stirred for 24 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (10 mL×3). The combined extracts were washed with satd NaCl aq (10 mL) and dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=4/1) to give the compound **1**.

*4.2.1. Ethyl (E)-2-[(4-chlorophenyl)sulfonyloxy]imino-2-phenylacetate ((E)-**1c**).* Yield 93%; Yellow solid; mp 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.1 Hz, 3H), 4.34 (q, *J*=7.1 Hz, 2H), 7.44–7.56 (m, 7H), 7.94–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 63.0, 126.9, 128.4, 129.2, 129.4, 130.6, 131.3, 133.2, 141.3, 156.8, 161.8; IR (neat) 3098, 2982, 1731, 1387, 1314, 1211, 1189, 1092, 1058, 891, 834, 685 cm^{-1}; HRMS (EI) Calcd for $C_{13}H_9ClNO_3S$ (M-$C_3H_5O_2$)$^+$ 293.9992, found 293.9994.

*4.2.2. Ethyl (E)-2-[(4-fluorophenyl)sulfonyloxy]imino-2-phenylacetate ((E)-**1e**).* Yield 95%; Yellow solid; mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.1 Hz, 3H), 4.34 (q, *J*=7.1 Hz, 2H), 7.23–7.27 (m, 2H), 7.42–7.50 (m, 5H), 8.03–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 63.0, 116.5 (d, *J*=23.0 Hz), 126.9, 128.4, 129.2, 130.7 (d, *J*=2.9 Hz), 131.3, 132.2 (d, *J*=9.6 Hz), 156.7, 161.9, 166.3 (d, *J*=257.8 Hz); IR (neat) 2985, 1738, 1592, 1494, 1387, 1231, 1194, 1094, 1051, 837, 778, 690 cm^{-1}; HRMS (EI) Calcd for $C_{16}H_{14}FNO_5S$ (M)$^+$ 351.0577, found 351.0563.

*4.2.3. Ethyl (E)-2-[(perfluorophenyl)sulfonyloxy]imino-2-phenylacetate ((E)-**1f**).* Yield 17%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.1 Hz, 3H), 4.39 (q, *J*=7.1 Hz, 2H), 7.44–7.66 (m, 3H), 8.05–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 63.4, 112.4, 118.8, 128.6, 129.1, 129.5, 132.1, 132.7, 133.3, 148.3, 158.7; IR (neat) 2983, 1738, 1657, 1450, 1305, 1256, 1208, 1179, 916, 769, 987 cm^{-1}; HRMS (EI) Calcd for $C_{10}H_{10}NO_3$ (M-$C_6F_5O_2S$)$^+$ 192.0661, found 192.0667.

*4.2.4. Ethyl (Z)-2-(4-chlorophenyl)-2-[(tosyloxy)imino]acetate ((Z)-**1j**).* Yield 90%; Yellow solid; mp 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.1 Hz, 3H), 2.44 (s, 3H), 4.47 (q, *J*=7.1 Hz, 2H), 7.35–7.38 (m, 4H), 7.47–7.51 (m, 2H), 7.88–7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.7, 63.0, 126.4, 128.6, 128.9, 129.3, 129.8, 131.9, 138.6, 145.6, 156.9, 160.6; IR (neat) 2984, 1741, 1593, 1383, 1223, 1196, 1093, 864, 772, 591 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{16}ClNO_5S$ (M)$^+$ 381.0438, found 381.0437.

*4.2.5. Ethyl (Z)-2-(4-methoxyphenyl)-2-[(tosyloxy)imino]acetate ((Z)-**1k**).* Yield 90%; Black oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J*=6.4 Hz, 3H), 2.43 (s, 3H), 3.81 (s, 3H), 4.46 (q, *J*=6.4 Hz, 2H), 6.87–6.89 (m, 2H), 7.33–7.49 (m, 4H), 7.88–7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.6, 55.4, 62.7, 114.4, 120.0, 128.9, 129.1, 129.7, 132.1, 145.3, 157.7, 161.2, 162.8; IR (neat) 2982, 2938, 2843, 1741, 1597, 1516, 1379, 1263, 1226, 1179, 1022, 815, 769, 661 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{19}NO_6S$ (M)$^+$ 377.0933, found 377.0916.

*4.2.6. Ethyl (E)-2-(thiophen-2-yl)-2-[(tosyloxy)imino]acetate ((E)-**1l**).* Yield 47%; Yellow solid; 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.1 Hz, 3H), 2.44 (s, 3H), 4.47 (q, *J*=7.1 Hz, 2H), 7.04–7.06 (m, 1H), 7.25–7.26 (m, 1H), 7.34–7.36 (m, 2H), 7.48–7.49 (m, 1H),

7.88–7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.7, 63.1, 127.8, 129.0, 129.7, 130.6, 131.4, 131.8, 132.3, 145.5, 153.2, 160.0; IR (neat) 3112, 2984, 1743, 1595, 1426, 1382, 1322, 1221, 1194, 912, 864, 815, 771 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{15}NO_5S_2$ $(M)^+$ 353.0392, found 353.0407.

*4.2.7. Diethyl 2-[(tosyloxy)imino]malonate (**1m**).* Yield 84%; White solid; mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 1.36 (t, J=7.1 Hz, 3H), 2.46 (s, 3H), 4.33 (q, J=7.1 Hz, 2H), 4.40 (q, J=7.1 Hz, 2H), 7.36–7.38 (m, 2H), 7.87–7.89 (m. 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 21.7, 63.3, 63.4, 129.2, 129.9, 131.1, 146.2, 149.7, 157.9, 158.0; IR (neat) 2986, 2941, 1752, 1392, 1324, 1259, 1197, 1182, 1100, 828, 752, 661 cm^{-1}; HRMS (EI) HRMS (EI) Calcd for $C_{14}H_{17}NO_7S$ $(M)^+$ 343.0726, found 343.0733.

4.3. General procedure for the synthesis of α-acyloxyimino esters 1g–i, 1n, 1o

In a 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed ethyl 2-hydroxyimino-2-phenylacetate **A** (5.00 mmol) in DMF (5.0 mL) and DMAP (1.00 mmol) at 0 °C, and to it were added *i*-PrNEt (10.5 mmol) and benzoyl chloride (10.0 mmol). The whole mixture was warmed to room temperature and stirred for 21 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with ethyl acetate (10 mL×3). The combined extracts were washed with satd NaCl aq (10 mL) and dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=4/1) and recrystallization from CH_2Cl_2 to give the compound **1**.

*4.3.1. Ethyl (E)-2-(benzoyloxy)imino-2-phenylacetate ((E)-**1g**).* Yield 67%; White solid; mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J=7.3 Hz, 3H), 4.44 (q, J=7.3 Hz, 2H), 7.38–7.59 (m, 8H), 7.86–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 63.0, 127.8, 128.3, 128.6, 128.7, 128.9, 129.8, 130.7, 133.7, 156.9, 162.8, 162.9; IR (neat) 2983, 1766, 1725, 1447, 1314, 1209, 1064, 1000, 930, 854, 704 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{10}NO_2$ $(M\text{-}C_3H_5O_2)^+$ 224.0712, found 224.0707.

*4.3.2. Ethyl (Z)-2-(benzoyloxy)imino-2-phenylacetate ((Z)-**1g**).* Yield 83%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J=7.1 Hz, 3H), 4.53 (q, J=7.1 Hz, 2H), 7.44–7.63 (m, 6H), 7.79–7.81 (m, 2H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 62.4, 127.5, 128.1, 128.4, 128.6, 128.9, 129.7, 132.1, 133.7, 158.0, 162.2, 162.8; IR (neat) 2982, 1742, 1450, 1243, 1060, 1012, 774, 706, 616, 605, 586 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{10}NO_2$ $(M\text{-}C_3H_5O_2)^+$ 224.0712, found 224.0707.

*4.3.3. Ethyl (Z)-2-acetoxyimino-2-phenylacetate ((Z)-**1h**).* Yield 86%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J=7.1 Hz, 3H), 2.22 (s, 3H), 4.49 (q, J=7.1 Hz, 2H), 7.41–7.53 (m, 3H), 7.70–7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.3, 62.3, 127.3, 128.4, 128.9, 132.0, 157.1, 162.1, 167.3; IR (neat) 2985, 2939, 1782, 1741, 1447, 1372, 1334, 1227, 1023, 934, 694 cm^{-1}; HRMS (EI) Calcd for $C_{10}H_{10}NO_3$ $(M\text{-}C_2H_3O)^+$ 192.0661, found 192.0667.

*4.3.4. Ethyl (Z)-2-methoxyimino-2-phenylacetate ((Z)-**1i**).* Yield 67%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J=6.9 Hz, 3H), 4.02 (s, 3H), 4.42 (q, J=6.9 Hz, 2H), 7.36–7.42 (m, 3H), 7.56–7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 61.8, 62.9, 126.2, 128.7, 130.2, 130.3, 150.6, 163.6; IR (neat) 2982, 2940, 1738, 1447, 1370, 1331, 1222, 1060, 1035, 893, 772, 687 cm^{-1}; HRMS (EI) Calcd for $C_{11}H_{13}NO_3$ $(M)^+$ 207.0895, found 207.0892.

*4.3.5. Ethyl (Z)-2-(4-chlorobenzoyloxy)imino-2-phenylacetate ((Z)-**1n**).* Yield 86%; White solid; mp 70–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J=7.1 Hz, 3H), 4.52 (q, J=7.1 Hz, 2H), 7.45–7.56 (m, 5H), 7.77–7.80 (m, 2H), 7.96–8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 62.5, 126.6, 127.6, 128.3, 129.0, 129.0, 131.0, 132.2, 140.2, 158.2, 162.0, 162.1; IR (neat) 2984, 1745, 1595, 1488, 1248, 1090, 1068, 1008, 909, 845, 749, 687 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_9ClNO_2$ $(M\text{-}C_3H_5O_2)^+$ 258.0322, found 258.0317.

*4.3.6. Ethyl (Z)-2-(4-methylbenzoyloxy)imino-2-phenylacetate ((Z)-**1o**).* Yield 88%; White solid; mp 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J=7.1 Hz, 3H), 2.43 (s, 3H), 4.52 (q, J=7.1 Hz, 2H), 7.26–7.29 (m, 2H), 7.44–7.55 (m, 3H), 7.78–7.81 (m, 2H), 7.93–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.7, 62.4, 125.3, 127.6, 128.6, 129.0, 129.3, 129.8, 132.0, 144.6, 157.8, 162.4, 162.9; IR (neat) 2982, 1747, 1611, 1250, 1179, 1065, 1010, 743, 687, 580 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{17}NO_4$ $(M)^+$ 311.1158, found 311.1162.

4.4. General procedure for the N-monoalkylation of α-imino esters

Under an argon atmosphere, a suspension of α-imino esters **1** (0.20 mmol) in toluene (5.0 mL) was stirred at −78 °C for 5 min, and to it was added EtMgBr (0.50 mmol, 0.98 *N* in Et_2O) slowly. After the mixture was stirred for 30 min, it was quenched with satd NH_4Cl aq (5.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel on TLC (*n*-hexane/ethyl acetate/Et_3N=10/1/1) to give the monoalkylated and/or dialkylated products.

*4.4.1. Ethyl 2-ethylimino-2-phenylacetate (**2a**).*[5j] Yield 74%, *Z*/*E*=90:10; Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.3 Hz, 0.3H), 1.33 (t, J=7.3 Hz, 2.7H), 1.39 (t, J=7.3 Hz, 3H), 3.49 (q, J=7.3 Hz, 0.2H), 3.58 (q, J=7.3 Hz, 1.8H), 4.33 (q, J=7.3 Hz, 0.2H), 4.42 (q, J=7.3 Hz, 1.8H), 7.37–7.45 (m, 3H), 7.70–7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 15.8, 49.5, 61.3, 127.1, 128.5, 130.8, 134.4, 159.8, 165.6; IR (neat) 2978, 2935, 2871, 1734, 1633, 1299, 1206, 1095, 1037, 1017, 691 cm^{-1}; MS (CI) Calcd for $C_{12}H_{15}NO_2$ $(M+H)^+$ 206, found 206.

*4.4.2. Ethyl 2-(diethylamino)-2-phenylacetate (**3a**).*[5j] Yield 37%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 6H), 1.23 (t, J=7.1 Hz, 3H), 2.56–2.69 (m, 4H), 4.15 (dq, J=7.1, 10.5 Hz, 1H), 4.21 (dq, J=7.1, 10.5 Hz, 1H), 4.47 (s, 1H), 7.26–7.34 (m, 3H), 7.43–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 14.1, 43.6, 60.5, 69.3, 127.8, 128.2, 128.4, 128.7, 137.2, 172.4; IR (neat) 1738, 1454, 1369, 1196, 1155, 1061, 1026, 732, 698 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_21NO_2$ $(M)^+$ 235.1572, found 235.1565.

*4.4.3. Ethyl 2-(4-chlorophenyl)-2-(diethylamino)acetate (**3b**).* Yield 84%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (dd, J=7.1, 7.1 Hz, 6H), 1.23 (dd, J=7.1, 7.1 Hz, 3H), 2.55–2.67 (m, 4H), 4.15 (dq, J=7.1, 11.0 Hz, 1H), 4.21 (dq, J=7.1, 11.0 Hz, 1H), 4.43 (s, 1H), 7.29–7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.2, 43.6, 60.7, 68.6, 128.5, 130.0, 133.6, 136.0, 171.9; IR (neat) 2973, 2871, 1737, 1490, 1198, 1156, 1091, 1017, 835, 631 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{20}ClNO_2$ $(M)^+$ 269.1183, found 269.1170.

*4.4.4. Ethyl 2-diethylamino-2-(4-methoxyphenyl)acetate (**3c**).* Yield 59%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (dd, J=7.1, 7.1 Hz, 6H), 1.23 (dd, J=7.1, 7.1 Hz, 3H), 2.55–2.68 (m, 4H), 3.80 (s, 3H), 4.13 (dq, J=7.1, 10.8 Hz, 1H), 4.20 (dq, J=7.1, 10.8 Hz, 1H), 4.39 (s, 1H), 6.85–6.87 (m, 2H), 7.35–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 14.2, 43.4, 55.2, 60.5, 68.9, 113.7, 129.2, 129.9, 159.2, 172.6; IR (neat) 2971, 2837, 1736, 1510, 1250, 1176, 1155, 1033, 836,

793 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{23}NO_3$ $(M)^+$ 265.1678, found 265.1682.

*4.4.5. Ethyl 2-diethylamino-2-(thiophen-2-yl)acetate (**3d**).* Yield 61%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (dd, J=7.1, 7.1 Hz, 6H), 1.29 (dd, J=7.1, 7.1 Hz, 3H), 2.62–2.71 (m, 4H), 4.22 (dq, J=7.1, 10.9 Hz, 1H), 4.27 (dq, J=7.1, 10.9 Hz, 1H), 4.76 (s, 1H), 6.94–7.01 (m, 2H), 7.26–7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 14.3, 44.1, 60.9, 63.9, 125.7, 126.3, 126.4, 141.0, 171.2; IR (neat) 2972, 1738, 1465, 1372, 1238, 1179, 1025, 808, 698, 569 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{19}NO_2S$ $(M)^+$ 241.1137, found 241.1142.

*4.4.6. Diethyl 2-(diethylamino)malonate (**3e**).* Yield 53%; Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J=7.1 Hz, 6H), 1.29 (t, J=7.1 Hz, 6H), 2.75 (q, J=7.1 Hz, 4H), 4.24 (q, J=7.1 Hz, 4H), 4.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.1, 45.8, 61.1, 67.2, 168.4; IR (neat) 2976, 2936, 2872, 1734, 1467, 1372, 1302, 1210, 1154, 1093, 1031, 865 cm^{-1}; HRMS (EI) Calcd for $C_{11}H_{21}NO_4$ $(M)^+$ 231.1471, found 231.1478.

4.5. General procedure for the tandem N,N-dialkylation to α-*p*-toluoyloxyimino esters

Under an argon atmosphere, a suspension of ethyl (*Z*)-2-(4-methylbenzoyloxy)imino-2-phenylacetate (*Z*)-**1o** (0.20 mmol) in toluene (5.0 mL) was stirred at −78 °C for 5 min, and to it was added EtMgBr (0.44 mmol, 1.02 *N* in Et_2O) slowly. After the mixture was stirred for 30 min, benzoic acid (0.15 mmol) in toluene (1.0 mL) was added to the reaction mixture at −78 °C for 10 min and then warmed up to 30 °C, and stirred for 5 min. Then RMgBr (0.35 mmol) was added to the mixture and stirred for 30 min. The reaction was quenched with satd $NaHCO_3$ aq (5.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified on silica gel TLC (*n*-hexane/ethyl acetate/Et_3N=10/1/1) to give the compound **4**.

*4.5.1. Ethyl 2-(N-ethyl-N-propylamino)-2-phenylacetate (**4a**).*[5j] Yield 79%, Yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J=7.3 Hz, 3H), 0.98 (t, J=7.3 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H), 1.35–1.52 (m, 2H), 2.44–2.55 (m, 2H), 2.63 (q, J=7.3 Hz, 2H), 4.13–4.25 (m, 2H), 4.51 (s, 1H), 7.25–7.34 (m, 3H), 7.40–7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 12.3, 14.2, 20.4, 44.3, 52.0, 60.4, 69.1, 127.7, 128.2, 128.7, 137.4, 172.4; IR (neat): 1737, 1453, 1372, 1154, 1067, 1029, 728, 696 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{18}N$ $(M\text{-}C_3H_5O_2)^+$ 176.1434, found 176.1434.

*4.5.2. Ethyl 2-(N-ethyl-N-isopropylamino)-2-phenylacetate (**4c**).*[5j] Yield 72%, Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H), 1.04 (d, J=6.9 Hz, 3H), 1.05 (d, J=6.9 Hz, 3H), 1.25 (t, J=7.3 Hz, 3H), 2.67 (dq, J=7.3, 14.2 Hz, 1H), 2.73 (dq, J=7.3, 14.2 Hz, 1H), 3.12 (sept, J=6.9 Hz, 1H), 4.16 (dq, J=7.3, 10.6 Hz, 1H), 4.21 (dq, J=7.3, 10.6 Hz, 1H), 4.62 (s, 1H), 7.24–7.33 (m, 3H), 7.37–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 15.9, 19.0, 20.5, 40.4, 49.2, 60.4, 66.0, 127.5, 128.1, 128.5, 138.6, 173.8; IR (neat) 3062, 2969, 2872, 1739, 1453, 1385, 1157, 1030, 726, 696 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{18}N$ $(M\text{-}C_3H_5O_2)^+$ 176.1434, found 176.1434.

*4.5.3. Ethyl 2-(N-cyclohexyl-N-ethylamino)-2-phenylacetate (**4d**).*[5j] Yield 39%; Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J=7.3 Hz, 3H), 1.05–1.22 (m, 4H), 1.26 (t, J=7.3 Hz, 3H), 1.34–1.42 (m, 1H), 1.57–1.60 (m, 1H), 1.68–1.77 (m, 3H), 1.92–1.93 (m, 1H), 2.63–2.83 (m, 3H), 4.17 (qd, J=7.3, 11.0 Hz, 1H), 4.22 (qd, J=7.3, 11.0 Hz, 1H), 4.69 (s, 1H), 7.24–7.32 (m, 3H), 7.37–7.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 15.9, 26.2, 26.3, 26.4, 29.9, 31.7, 40.9, 58.7, 60.3, 65.7, 127.4, 128.1, 128.5, 138.8, 174.0; IR (neat) 3061, 3029, 2982, 2930, 2854, 1739, 1450, 1150, 1028, 742, 696 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{27}NO_2$ $(M)^+$ 289.2042, found 289.2041.

*4.5.4. Ethyl 2-(N-tert-butyl-N-ethylamino)-2-phenylacetate (**4e**).*[5j] Yield 12%; Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.49 (t, J=7.0 Hz, 3H), 1.20 (s, 9H), 1.28 (t, J=7.0 Hz, 3H), 2.75–2.82 (m, 1H), 3.09–3.17 (m, 1H), 4.15–4.26 (m, 2H), 4.91 (s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.016, 14.2, 19.2, 28.8, 38.4, 55.7, 60.1, 63.2, 127.1, 128.0, 128.8, 139.6, 175.3; IR (neat) 2974, 2928, 1738, 1369, 1212, 1163, 1120, 1029, 756, 700 cm^{-1}; HRMS (EI) Calcd for $C_{13}H_{20}N$ $(M\text{-}C_3H_5O_2)^+$ 190.1590, found 190.1582.

*4.5.5. Ethyl 2-(N-benzyl-N-ethylamino)-2-phenylacetate (**4f**).*[5j] Yield 64%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.3 Hz, 3H), 1.28 (t, J=7.3 Hz, 3H), 2.61–2.67 (m, 2H), 3.69 (d, J=14.2 Hz, 1H), 3.77 (d, J=14.2 Hz, 1H), 4.21 (dq, J=7.3, 11.0 Hz, 1H), 4.26 (dq, J=7.3, 11.0 Hz, 1H), 4.62 (s, 1H), 7.21–7.36 (m, 8H), 7.41–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.3, 44.2, 54.2, 60.4, 67.5, 126.7, 127.7, 128.1, 128.3, 128.5, 128.6, 137.2, 140.1, 172.3; IR (neat) 2971, 2933, 2850, 1734, 1452, 1370, 1167, 1026, 731, 696 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{23}NO_2$ $(M)^+$ 297.1729, found 297.1739.

4.6. General procedure for the tandem N,N,C-trialkylation to α-*p*-toluoyloxyimino esters

Under an argon atmosphere, a suspension of ethyl (*Z*)-2-(4-methylbenzoyloxy)imino-2-phenylacetate (*Z*)-**1o** (0.20 mmol) in toluene (5.0 mL) was stirred at −78 °C for 5 min, and to it was added EtMgBr (0.44 mmol, 1.09 *N* in Et_2O) slowly. After the mixture was stirred for 30 min, benzoic acid (0.15 mmol) in toluene (1.0 mL) was added to the reaction mixture at −78 °C for 10 min and then warmed up to 30 °C, and stirred for 5 min. Then *n*-PrMgCl (0.35 mmol, 0.93 *N* in Et_2O) was added to the mixture and stirred for 30 min. Then DBDMH (0.12 mmol) in CH_2Cl_2 (2.0 mL) was added and the mixture was stirred for 15 min followed by the addition of RMgBr (0.40 mmol) with stirring for 15 min. The reaction was quenched with satd $NaHCO_3$ aq (5.0 mL), and the whole mixture was extracted with ethyl acetate (5.0 mL×3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified on silica gel TLC (*n*-hexane/ethyl acetate/Et_3N=10/1/1) to give the trialkylayed compound **5**.

*4.6.1. Ethyl 2-ethyl(propyl)amino-2-phenylpropanoate (**5a**).* Yield 59%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (dd, J=7.1, 7.1 Hz, 3H), 1.02 (t, J=7.1 Hz, 3H), 1.27 (dd, J=7.1, 7.1 Hz, 3H), 1.41–1.60 (m, 5H, including singlet at 1.60 ppm, 3H), 2.37–2.44 (m, 1H), 2.50–2.66 (m, 3H), 4.15–4.27 (m, 2H), 7.20–7.31 (m, 3H), 7.45–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 14.3, 16.4, 24.2, 24.3, 46.5, 54.2, 60.5, 72.0, 126.9, 127.9, 144.5, 174.7; IR (neat) 2965, 2872, 1725, 1447, 1373, 1229, 1176, 1098, 1070, 699 cm^{-1}; HRMS (EI) Calcd for $C_{13}H_{20}N$ $(M\text{-}C_3H_5O_2)^+$ 190.1596, found 190.1581.

*4.6.2. Ethyl 2-cyclohexyl-2-ethyl(propyl)amino-2-phenylacetate (**5b**).* Yield 31%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.27–0.36 (m, 1H), 0.42–0.52 (m, 1H), 0.74–0.94 (m, 4H, including dd at 0.82 ppm, J=7.3, 7.3 Hz, 3H), 1.05 (dd, J=7.3, 7.3 Hz, 3H), 1.17–1.36 (m, 6H, including dd at 1.30 ppm, J=7.3, 7.3 Hz, 3H), 1.50–1.68 (m, 6H), 1.94–1.97 (m, 1H), 2.23–2.30 (m, 1H), 2.36–2.44 (m, 1H), 2.59–2.60 (m, 2H), 4.20–4.28 (m, 2H), 7.21–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 14.6, 15.3, 23.4, 26.6, 26.8, 27.0, 27.2, 30.9, 42.3, 59.9, 77.9, 126.3, 126.5, 129.5, 138.9, 171.4; IR (neat) 2931, 2852, 1719, 1492, 1446, 1377, 1207, 1170, 1026, 711 cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{28}N$ $(M\text{-}C_3H_5O_2)^+$ 258.2222, found 258.2232.

*4.6.3. Ethyl 2-ethyl(propyl)amino-2,3-diphenylpropanoate (**5c**).* Yield 64%; Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86

(t, J=7.1 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H), 1.32 (t, J=7.1 Hz, 3H), 1.56–1.66 (m, 2H), 2.46–2.54 (m, 1H), 2.63–2.84 (m, 4H), 3.75 (d, J=7.1 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 6.61–6.62 (m, 2H), 6.94–7.12 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 14.6, 16.4, 24.7, 45.6, 46.3, 53.7, 60.2, 76.3, 125.8, 126.6, 127.0, 127.1, 128.5, 131.0, 137.2, 141.2, 171.1; IR (neat) 3030, 2966, 2872, 1720, 1495, 1451, 1256, 1182, 1029, 700, 618 cm^{-1}; HRMS (EI) Calcd for $C_{22}H_{29}NO_2$ (M)$^+$ 339.2198, found 339.2196.

*4.6.4. Ethyl 2-ethyl(propyl)amino-2,2-diphenylacetate (**5d**).* Yield 57%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, J=7.1 Hz, 3H), 1.13 (t, J=7.1 Hz, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.60–1.69 (m, 2H), 2.39–2.43 (m, 2H), 2.55 (q, J=7.1 Hz, 2H), 4.27 (q, J=7.1 Hz, 2H), 7.13–7.25 (m, 6H), 7.46–7.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.3, 16.4, 24.4, 47.9, 55.8, 60.7, 80.5, 126.5, 127.5, 128.5, 142.2, 171.8; IR (neat) 3060, 2966, 2933, 2871, 1726, 1598, 1492, 1177, 1026, 916, 742, 705 cm^{-1}; HRMS (EI) Calcd for $C_{21}H_{27}NO_2$ (M)$^+$ 325.2042, found 325.2053.

*4.6.5. Ethyl 2-ethyl(propyl)amino-2-phenyl-2-(thiophen-2-yl)acetate (**5e**).* Yield 43%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, J=7.3 Hz, 3H), 1.08 (dd, J=7.3, 7.3 Hz, 3H), 1.28 (t, J=7.3 Hz, 3H), 1.50–1.60 (m, 2H), 2.47–2.51 (m, 2H), 2.63 (q, J=7.3 Hz, 2H), 4.30 (q, J=7.3 Hz, 2H), 6.89–6.91 (m, 1H), 7.10–7.11 (m, 1H), 7.19–7.29 (m, 4H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.2, 16.3, 24.3, 48.1, 55.8, 61.1, 78.1, 125.1, 125.8, 127.2, 127.2, 127.7, 128.1, 142.4, 146.4, 171.9; IR (neat) 2965, 2871, 1730, 1447, 1212, 1166, 1025, 802, 749, 699 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{25}NO_2S$ (M)$^+$ 331.1606, found 331.1615.

*4.6.6. Ethyl 2-ethyl(propyl)amino-2-phenylbut-3-enoate (**5f**).* Yield 54%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (dd, J=7.3, 7.3 Hz, 3H), 1.05 (dd, J=7.3, 7.3 Hz, 3H), 1.28 (t, J=7.3 Hz, 3H), 1.52 (ddq, J=7.3, 7.3, 7.3 Hz, 2H), 2.41–2.69 (m, 4H), 4.26 (q, J=7.3 Hz, 2H), 5.21–5.27 (m, 2H), 6.24 (dd, J=10.8, 17.5 Hz, 1H), 7.20–7.31 (m, 3H), 7.43–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 14.3, 16.6, 24.6, 47.4, 55.1, 60.6, 77.6, 115.5, 127.1, 127.7, 128.4, 139.5, 141.2, 172.7; IR (neat) 2964, 2933, 2872, 1728, 1447, 1222, 1130, 1032, 926, 760, 701 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{25}NO_2$ (M)$^+$ 275.1885, found 275.1890.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.04.111.

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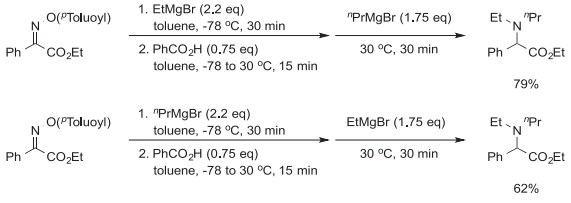
6. Although we have not fully examined the effects of the added benzoic acid on α-sulfoximino esters, the second alkylation was too rapid with (*Z*)-α-sulfoximino derivatives regardless of the addition of benzoic acid.
7. The order of addition is very important as shown in the following examples. Less bulky nucleophiles should be added first.



8. We assume that one of the important factors to stop the addition reaction at the mono-N-alkylation stage is the formation of the eight-membered intermediate **B** for the (*Z*)-acyloxyimino ester as proposed in Scheme 5. Isomerization of the imine geometry of the mono-N-alkylation product may be also involved.