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An umpolung reaction of α -iminiothioesters possessing a cyclopropyl group†

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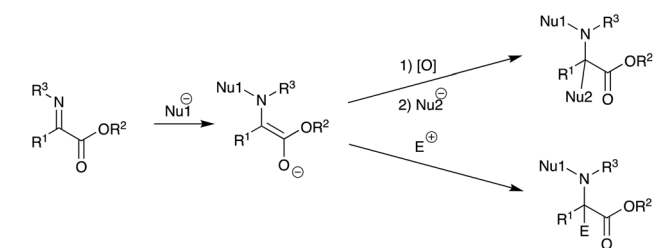
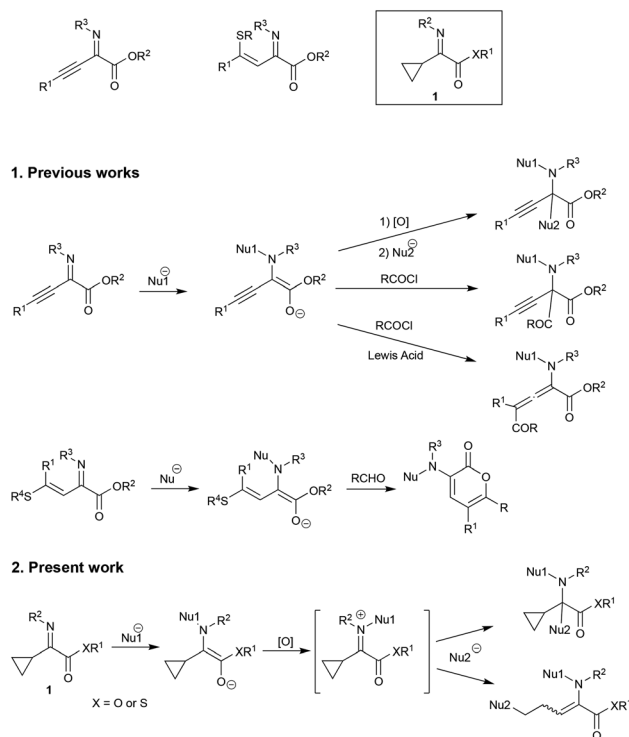
An umpolung *N*-alkylation reaction of α -cyclopropyl α -iminiothioesters with diethylaluminum chloride or ethylmagnesium bromide affords the corresponding *N*-ethylated α -aminiothioesters in good yields. Subsequent oxidation and reaction of the *N*-ethylated product with a thiolate or a chloride anion proceed effectively to give the ring-opened products in good yields. In contrast, relatively "hard" nucleophiles did not give the ring-opened products but gave the addition products to the iminium carbon.

1 Introduction

The unique properties of cyclopropyl moieties offer various useful reactions in many organic transformations.¹ Among them, cyclopropane ring-opening reactions have received considerable attention as a useful carbon chain elongation reaction, since strain-release ring opening of cyclopropanes gives rise to highly functionalized products.² On the other hand, we have been interested in the umpolung reactivity of α -iminioesters and have already disclosed several useful reactions (Scheme 1).³ Furthermore, upon the oxidation of an intermediary α -aminoester enolate derived from *N*-alkylation of α -iminioester, many nucleophiles can add to the resulting iminium salt, giving *N,C*-double addition products. When α,β -unsaturated α -iminioesters such as α -alkynyl or α -alkenyl derivatives were used as substrates, tandem *N*-alkylation– γ -acylation or

vinyllogous aldol reaction respectively proceeded in a regioselective manner.⁴ Along this line α -cyclopropyl α -imino(thio)esters **1** have intrigued us in particular regarding the cyclopropane ring-opening reaction of the α -cyclopropyl iminium ion intermediate (Scheme 2).

We have now found that α -cyclopropyl α -iminiothioesters **1** are reasonably reactive substrates for the umpolung *N*-alkylation and that the subsequent tandem reaction also proceeds well.


 Scheme 1 Tandem reaction of α -iminoesters.


Scheme 2 Previous and present works.

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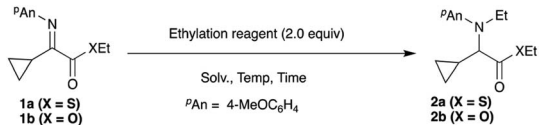
2 Results and discussion

The starting α -cyclopropyl α -iminoesters and their thioester counterparts **1** were readily prepared according to the reported procedures.⁵ First, the conditions for the ethylation reaction of α -cyclopropyl α -iminoester **1b** and its thioester counterpart **1a**, including the ethylation reagent, solvent, time, and temperature were examined. Table 1 summarizes the results.

Although ethyl Grignard reagent could be used for this reaction, diethylaluminum chloride recorded comparable results (entries 3 to 5). Regarding the ester moiety, normal ethyl ester gave a decreased yield of the desired *N*-ethylation product **2b** as compared with the thioester counterpart **2a** (entries 2 and 4).⁶ The best yield was obtained when the reaction was conducted in EtCN for 30 min, and the product **2a** was formed in 90% yield (entry 8). We next examined the oxidation reaction of an intermediary aluminum enolate species to the iminium salt that could accept the second nucleophile. Table 2 summarizes the results.

Initially, we attempted to determine the amount of the hydrolyzed cyclopropyl ketoester **4**. However, this compound was transformed into other derivatives including a cyclopropane ring-opened product, a hydrate, a hydrolyzed acid, and so on under the present oxidation/hydrolysis conditions, and therefore, the yields of stable *N*-ethyl anisidine **3** are shown in Table 2. BPO that was effective for the tandem reaction of α -aryl α -iminoesters was unsuitable for the present substrate, giving *N*-ethyl anisidine **3** in moderate yields (entries 1 to 3). NBS and DBDMH did not efficiently oxidize the present aluminum enolate either (entries 4, 5, and 8), whereas with NCS *N*-ethyl anisidine **3** was obtained in good yield, indicating that NCS is the oxidation reagent of choice for the present substrate (entries 6 and 7). Using NCS as an oxidation reagent for the aluminum enolate, various nucleophiles known as good reagents for conjugate addition reactions were subjected to the present

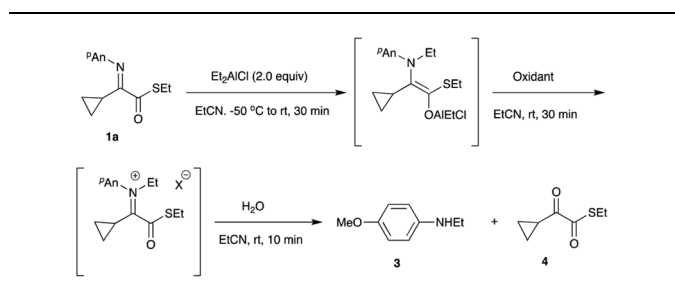
Table 1 *N*-Ethylation of α -cyclopropyl α -imino(thio)ester



Entry	X	Reagent	Solv.	Temp. (°C)	Time (min)	2: yield ^a (%)
1	O	Et ₂ AlCl	EtCN	-20 to rt	240	53
2	O	Et ₂ AlCl	EtCN	-50 to rt	120	41
3	S	EtMgBr	EtCN	-50 to rt	60	74
4	S	Et ₂ AlCl	EtCN	-50 to rt	120	75
5	S	Et ₂ AlCl	MeCN	-40 to rt	120	75
6	S	Et ₂ AlCl	CH ₂ Cl ₂	-50 to rt	120	61
7	S	Et ₂ AlCl ^b	EtCN	-50 to rt	120	68
8	S	Et ₂ AlCl	EtCN	-50 to rt	30	90
9	S	Et ₂ AlCl	EtCN	-50 to rt	10	86

^a Isolated yield. ^b Et₂AlCl (1.5 equiv.) was used.

Table 2 Oxidation of the intermediary aluminum enolate

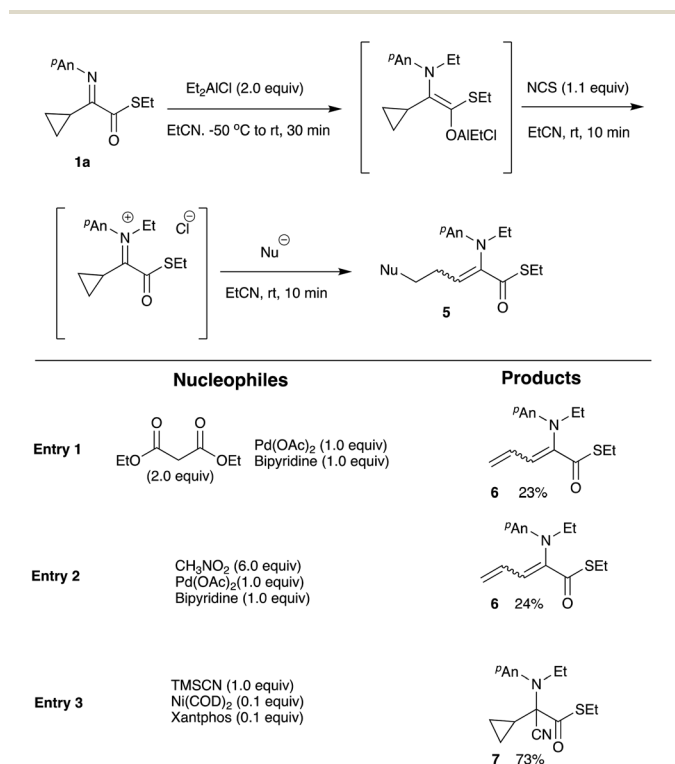


Entry	Oxidation reagent ^a	Equivalent	3: yield ^b (%)
1	BPO	1.1	40
2	BPO	1.5	34
3	BPO	2.0	13
4	NBS	1.1	27
5	NBS	2.0	26
6	NCS	1.1	63
7	NCS	2.0	69
8	DBDMH	1.1	27

^a Abbreviations, BPO: benzoyl peroxide, NBS: *N*-bromosuccinimide, NCS: *N*-chlorosuccinimide, DBDMH: 1,3-dibromo-5,5-dimethylhydantoin.
^b Isolated yield.

tandem cyclopropane ring-opening reaction, and Scheme 3 summarizes the results.

Diethyl malonate/NaH, KH or DBU, ethyl acetoacetate/NaH, KH or DBU, acetylacetone/NaH, KH or DBU, MeNO₂/DBU, EtNO₂/DBU, allyltrimethylsilane/TiCl₄, silyl enol ether/TiCl₄,



Scheme 3 Attempted cyclopropane ring-opening reaction.



ketene silyl acetal/TiCl₄, indole, Bn₂NLi, Et₂AlCN, EtMgBr/CuI, EtMgBr/CuCN, Me₂CuLi, *n*Bu₂CuLi/BF₃·Et₂O, and Et₂CuLi/TMSCl did not give the desired addition/ring-opening product **5**, whereas trimethylsilyl cyanide underwent a 1,2-addition reaction to the iminium salt to give the nitrile **7** in 73% yield (entry 3). Noteworthy is the reaction in the presence of Pd(OAc)₂ and bipyridine, giving the ring-opened diene **6** in 23 and 24% yields, respectively (entries 1 and 2). This kind of diene formation is further examined, and details of this reaction are reported in the latter part of this article. One of the best nucleophiles for conjugate addition is thiolate,⁷ and therefore the use of thiolates was next examined. Table 3 summarizes the results.

The initial ring-opening reaction was carried out with lithium benzenethiolate, and the reaction actually gave the desired ring-opened product **8a** in 23% yield, indicating that thiolates could be used for the present ring-opening reaction (entry 1). Among the metal thiolates examined, sodium benzenethiolate effected the ring-opening to give the homoallylic sulfide **8a** in 38% yield (entry 2). Although the reaction with phenylthiotrimethylsilane⁸ for 2 h gave the homoallylic sulfide **8a** in low yield, prolonged reaction times increased the yield to 57% (entries 3 to 5). A better result was obtained when the reaction was carried out with phenylthiotri-*n*-butylstannane⁹ for 12 h, and the desired product **8a** was obtained in 60% yield (entry 6). Furthermore, the use of ethylthiotri-*n*-butylstannane⁹ recorded the best yield of 79% (entry 7).

We also examined the use of α -cyclopropyl α -iminoesters **1b** for this type of ring-opening reaction, and Scheme 4 summarizes the representative results.

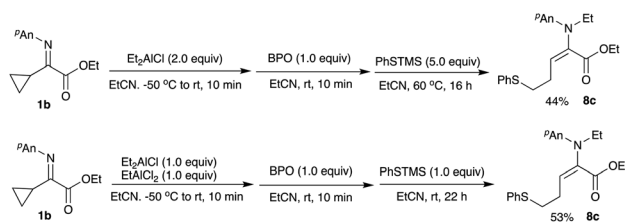
Although the yields of the desired ring-opened product **8c** were only moderate, the use of BPO together with TMSSPh was found to be crucial for this substrate. A combined use of Et₂AlCl and EtAlCl₂ (1 : 1), which was used for the prototype tandem reaction of α -phenyl α -iminoesters also resulted in a moderate success.^{3b}

In terms of the availability of various alkyl and aryl derivatives, the use of Grignard reagents as the first nucleophile was next examined, and Scheme 5 summarizes the results.

Table 3 Cyclopropane ring-opening reaction with thiolate

Entry	RSMet	Temp. (°C)	Time (h)	8 : yield ^a (%)	E/Z
1	PhSLi	-50 to rt	2	23	75/25
2	PhSNa	-50 to rt	2	38	86/14
3	PhSTMS	rt	2	16	100/0
4	PhSTMS	rt	12	56	100/0
5	PhSTMS	rt	64	57	100/0
6	PhSSnBu ₃	rt	12	60	100/0
7	EtSSnBu ₃	rt	13	79	98/2

^a Isolated yield.



Scheme 4 Ring-opening reaction of α -cyclopropyl α -iminoester **1b**.

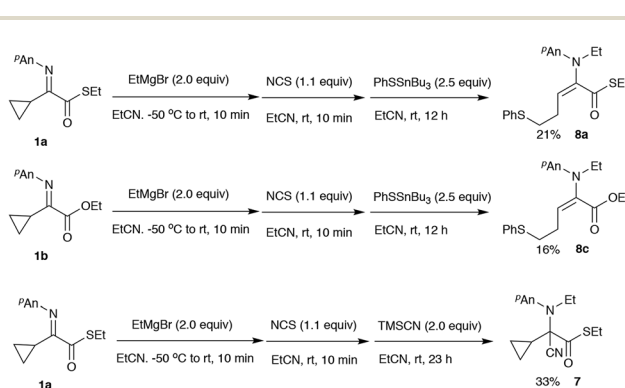
Although the first *N*-alkylation proceeded relatively well (see, Table 1, entry 3), the subsequent oxidation/second nucleophilic addition did not give the desired products in good yields. Therefore, aluminum reagents appear to be the reagent of choice for the present tandem reaction.

As mentioned earlier (Scheme 3, entries 1 and 2), an intriguing ring-opening reaction was observed after the oxidation of the intermediary aluminum enolate with NCS. Scheme 6 summarizes the results of ring opening–chlorination and/or diene formation.

After oxidation of the aluminum enolate with NCS the reaction mixture was allowed to stand with Ti(OEt)₄ at room temperature for 72 h to give the ring-opened/chlorinated product **9** in 55% yield, indicating that the chloride anion formed during the oxidation could attack the cyclopropane ring to open it. Regarding the diene formation, we screened several conditions and found that in the presence of triethylamine or triethylamine/silica gel the elimination of hydrogen chloride proceeded to give the diene **6** in 44% or 58%, respectively.

Moreover, we observed that the use of relatively “hard” nucleophiles such as metal cyanide led to the *C*-addition reaction of the iminium carbon instead of the ring-opening reaction (for example see, Scheme 3, entry 3 and Scheme 5). Other representative results of this type of 1,2-addition reaction are shown in Scheme 7.

As shown in Scheme 7 this iminium salt is a relatively reactive species for the nucleophiles. Both TMSCN and acetone cyanohydrin underwent a cyanation reaction to give the aminonitrile **7** in 89% and 88%, respectively. Regarding the α -cyclopropyl α -iminoester **1b**, *N*-ethylation/*C*-allylation reaction proceeded to give the double addition product **10** in 50% yield.

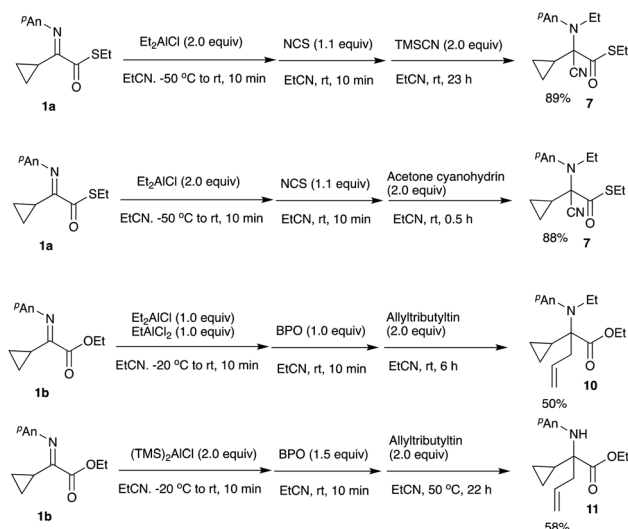


Scheme 5 Attempted use of Grignard reagent for the tandem reaction.

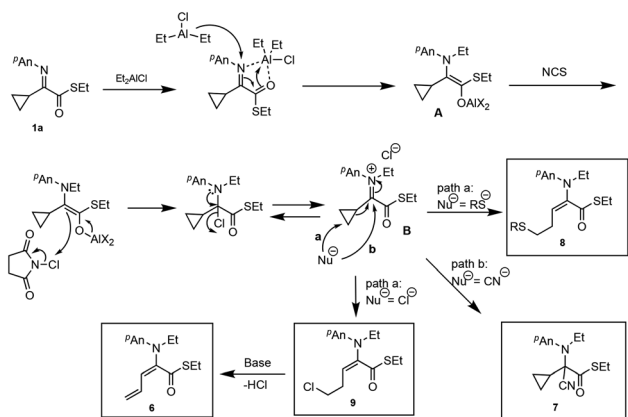




Scheme 6 Ring-opening/chlorination or diene formation.

Scheme 7 Tandem *N,C*-addition to α -cyclopropyl α -iminoesters **1a**, **1b**.

When $(\text{TMS})_2\text{AlCl}^{10}$ was used in place of ethylation reagents, the *C*-allylation product **11** was obtained in 58% yield after removal of the TMS moiety with aqueous KF. The following Scheme 8 shows the possible reaction pathways.



Scheme 8 Proposed reaction pathways.

First, ethylation at the imino nitrogen gives the aluminum enolate **A**, which in turn is oxidized with NCS to give the iminium salt **B**. This iminium salt **B** undergoes a ring-opening sulfenylation or chlorination reaction to give the homoallylic sulfide **8** or chloride **9**, respectively. Treatment of the homoallylic chloride **9** with a certain base induces the elimination of HCl to give the diene **6**.

3 Conclusions

In conclusion, α -cyclopropyl α -iminothioesters readily underwent the *N*-alkylation reaction with alkylaluminum reagents, giving the corresponding *N*-alkylated products in good yields. Subsequent oxidation/ring-opening of the *N*-alkylated products was conducted with NCS/*n*Bu₃SnSR to produce the homoallylic sulfides in moderate to good yields. Since homoallylic sulfides are useful compounds for further functional group interconversions including a selective C–C bond formation,¹¹ the present procedure offers a useful addition to the existing methodologies. We also found an intriguing homoallylic chloride formation induced by the formed chloride anion during the oxidation of the intermediate aluminum enolate with NCS. Tandem *N,C*-addition was also found using relatively “hard” second nucleophiles.

4 Experimental

General aspects

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ¹H NMR and ¹³C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Acetonitrile (MeCN) and propionitrile (EtCN) were distilled from phosphorus pentoxide and then from calcium hydride, and stored over Molecular Sieves 4A. Diethylether (Et₂O) was purified with a Glass Contour Organic Solvent Purification System of Nikko Hansen & Co., Ltd. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride and stored over molecular sieves 4Å. *S*-Ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a**^{3e,5} and ethyl 2-cyclopropyl[(4-methoxyphenyl)imino]acetate **1b**^{3b} were synthesized by the reported procedures. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wako Gel B-5F).

Synthesis of *S*-ethyl 2-cyclopropyl-2-[ethyl(4-methoxyphenyl)amino]ethanethioate **2a**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at $-50\text{ }^\circ\text{C}$. To it was added Et₂AlCl (0.27 mL, 0.286 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 30 min at room temperature, the reaction was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with



ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **2a**.

Yield 90% (39.6 mg); yellow oil; *R*_f = 0.6 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 0.22–0.29 (m 1H), 0.45–0.57 (m 2H), 0.69–0.76 (m 1H), 1.14–1.25 (m 1H), 1.17 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.21 (dd, *J* = 7.3, 7.3 Hz, 3H), 2.75–2.88 (m 2H), 3.22 (d, *J* = 9.6 Hz, 1H), 3.32–3.51 (m 2H), 3.75 (s, 3H), 6.80–6.81 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 4.2, 5.2, 12.1, 14.6, 23.0, 42.8, 55.5, 114.4, 118.2, 142.1, 153.1, 203.4; IR (neat) 2970, 2931, 2833, 1684, 1511, 1244, 1040, 830, 814, 728, 514 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₃NO₂S (M)⁺ 293.1450, found 293.1459.

Synthesis of ethyl 2-cyclopropyl-2-[ethyl(4-methoxyphenyl)amino]acetate **2b**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]acetate **1b** (37.1 mg, 0.150 mmol) in propionitrile (1.5 mL) at –20 °C. To it was added Et₂AlCl (0.15 mL, 0.165 mmol, 1.07 M in *n*hexane). After the mixture was stirred for 4 h at room temperature, the reaction was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **2b**.

Yield 53% (22.0 mg); yellow oil; *R*_f = 0.5 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 0.32–0.38 (m, 1H), 0.44–0.50 (m, 1H), 0.58–0.71 (m, 2H), 1.14 (dd, 3H, *J* = 7.1, 7.1 Hz), 1.21 (t, 3H, *J* = 7.1 Hz), 1.23–1.30 (m, 1H), 3.21 (d, *J* = 9.6 Hz, 1H), 3.38–3.57 (m, 2H), 3.74 (s, 3H), 4.13 (q, 2H, *J* = 7.1 Hz), 6.76–6.81 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 4.6, 4.8, 12.4, 14.1, 14.2, 42.6, 55.6, 60.4, 68.9, 114.4, 117.6, 142.7, 152.8, 173.1; IR (neat) 2979, 1732, 1512, 1464, 1370, 1244, 1180, 1038, 815, 535 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₃NO₂S (M)⁺ 293.1449, found 293.1450.

Oxidation of the intermediary aluminum enolate to produce *N*-ethylanisidine **3**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at –50 °C. To it was added Et₂AlCl (0.27 mL, 0.286 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 30 min at room temperature, a solution of NCS (39.9 mg, 0.30 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 30 min at room temperature and then quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica

gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give *N*-ethylanisidine **3**.

Yield 69% (15.6 mg); yellow oil; *R*_f = 0.3 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 1.24 (t, *J* = 7.3 Hz, 3H), 3.11 (q, *J* = 7.3 Hz, 2H), 3.74 (s, 3H), 6.59 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H). The N–H proton could not be detected; ¹³C NMR (100 MHz, CDCl₃) δ 15.0, 39.5, 55.8, 114.1, 114.9, 142.7, 152.1; IR (neat) 2880, 1530, 1260, 1050, 830 cm⁻¹; HRMS (EI) calcd for C₉H₁₃NO (M)⁺ 151.0997, found: 151.0981.

Synthesis of *S*-ethyl (*E*)-2-(ethyl(4-methoxyphenyl)amino) penta-2,4-dienethioate **6**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (26.8 mg, 0.10 mmol) in propionitrile (0.5 mL) at –50 °C. To it was added Et₂AlCl (0.19 mL, 0.20 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 14 h at room temperature and then quenched with sat. aq. NaHCO₃ (10 mL). The whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1 + 10% Et₃N) to give the title compound **9**.

Yield 58% (25.3 mg); reddish oil; *R*_f = 0.45 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 1.21 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 2.88 (q, *J* = 7.3 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 5.43 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.64 (dd, *J* = 17.2, 1.0 Hz, 1H), 6.35 (ddd, *J* = 17.0, 11.0, 10.0 Hz, 1H), 6.63–6.67 (m, 2H), 6.78–6.82 (m, 2H) 7.13 (d, *J* = 11.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.0, 14.4, 23.4, 46.0, 55.6, 114.2, 114.7, 126.6, 131.5, 133.8, 140.1, 141.2, 152.2, 194.4; HRMS (EI) calcd for C₁₆H₂₁NO₂S (M)⁺ 291.1293, found 291.1299.

Synthesis of *S*-ethyl 2-cyano-2-cyclopropyl-2-[ethyl(4-methoxyphenyl)amino]ethanethioate **7**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at –50 °C. To it was added Et₂AlCl (0.27 mL, 0.286 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and TMSCN (0.04 mL 0.30 mmol) was added. After the mixture was stirred for 23 h at room temperature, it was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **7**.



Yield 89% (42.5 mg); yellow oil; $R_f = 0.5$ (*n*hexane : ethyl acetate = 6 : 1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.06–0.13 (m, 1H), 0.26–0.33 (m, 1H), 0.39–0.46 (m, 1H), 0.52–0.59 (m, 1H), 0.94 (t, $J = 7.1$ Hz, 3H), 1.04–1.11 (m, 1H), 1.28 (t, $J = 7.6$ Hz, 3H), 2.77–2.98 (m, 3H), 3.19–3.27 (m, 1H), 3.80 (s, 3H), 6.83–6.87 (m, 2H), 7.24–7.28 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 1.7, 5.6, 13.0, 14.4, 18.7, 23.5, 48.3, 55.4, 79.42, 113.9, 129.8, 136.5, 158.4, 198.8; IR (neat) 2973, 2364, 2332, 1690, 1510, 1244, 1167, 1082, 1038, 879, 835, 547, 502 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (M^+) 318.1402, found 318.1402.

Synthesis of *S*-ethyl (*E*)-2-[ethyl(4-methoxyphenyl)amino]-5-(phenylthio)pent-2-enethioate **8a**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50°C . To it was added Et_2AlCl (0.27 mL, 0.286 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and a solution of *n*Bu₃SnSPh (119.7 mg, 0.30 mmol) in propionitrile (1.0 mL) was added. After the mixture was stirred for 64 h at room temperature, it was quenched with sat. aq. NaHCO_3 (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL \times 3). The combined extracts were washed with brine (5 mL \times 2), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **8a**.

Yield 60% (36.3 mg); yellow oil; $R_f = 0.4$ (*n*hexane : ethyl acetate = 6 : 1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.1$ Hz, 3H), 1.21 (t, $J = 7.5$ Hz, 3H), 2.32 (dt, $J = 7.3, 7.3$ Hz, 2H), 2.83 (q, $J = 7.5$ Hz, 2H), 2.91 (t, $J = 7.3$ Hz, 2H), 3.41 (q, $J = 7.1$ Hz, 2H), 3.75 (s, 3H), 6.59–6.63 (m, 2H), 6.74–6.81 (m, 3H), 7.13–7.24 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 12.9, 14.3, 23.4, 27.9, 31.8, 45.5, 55.6, 114.2, 114.7, 126.1, 128.9, 129.4, 134.6, 135.5, 140.8, 142.1, 152.2, 193.9; IR (neat) 2932, 1715, 1649, 1510, 1247, 1029, 834, 740, 692, 530, 516 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_2\text{S}$ (M^+) 401.1483, found 401.1502.

Synthesis of *S*-ethyl (*E*)-2-[ethyl(4-methoxyphenyl)amino]-5-(ethylthio)pent-2-enethioate **8b**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50°C . To it was added Et_2AlCl (0.27 mL, 0.286 mmol, 1.05 M in *n*hexane). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and a solution of *n*Bu₃SnSEt (131.7 mg, 0.38 mmol) in propionitrile (1.0 mL) was added. After the mixture was stirred for 13 h at room temperature, it was quenched with sat. aq. NaHCO_3 (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL \times 3). The combined

extracts were washed with brine (5 mL \times 2), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **8b**.

Yield 79% (41.7 mg); yellow oil; $R_f = 0.4$ (*n*hexane : ethyl acetate = 6 : 1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.5$ Hz, 3H), 1.20 (t, $J = 7.3$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 2.27 (q, $J = 7.3$ Hz, 2H), 2.40 (dt, $J = 7.5, 7.5$ Hz, 2H), 2.53 (t, $J = 7.5$ Hz, 2H), 2.82 (q, $J = 7.5$ Hz, 2H), 3.48 (q, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 6.62–6.67 (m, 2H), 6.73 (t, $J = 7.5$ Hz, 1H), 6.77–6.81 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 11.7, 14.3, 14.7, 24.0, 26.5, 28.0, 31.4, 46.8, 55.5, 114.4, 118.6, 129.5, 142.1, 145.6, 153.5, 194.2; IR (neat) 2930, 1712, 1645, 1510, 1247, 1029, 833, 741, 691, 536 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_2\text{S}_2$ (M^+) 353.1483, found 353.1479.

Synthesis of ethyl (*E*)-2-[ethyl(4-methoxyphenyl)amino]-5-(phenylthio)pent-2-enethioate **8c**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed ethyl 2-cyclopropyl[(4-methoxyphenyl)imino]acetate **1b** (37.1 mg, 0.150 mmol) and BPO (0.150 mmol, 36.3 mg) in propionitrile (5.0 mL) at -50°C . To it was added EtAlCl_2 (0.14 mL, 0.150 mmol, 1.07 M in *n*hexane), Et_2AlCl (0.14 mL, 0.150 mmol, 1.07 M in *n*hexane), and TMSSPh (0.029 mL, 0.15 mmol). After the mixture was stirred for 22 h at room temperature, it was quenched with sat. aq. NaHCO_3 (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL \times 3). The combined extracts were washed with brine (5 mL \times 2), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **8c**.

Yield 53% (30.8 mg); yellow oil; $R_f = 0.4$ (*n*hexane : ethyl acetate = 6 : 1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.13 (t, 3H, $J = 7.3$ Hz), 1.17 (t, 3H, $J = 7.1$ Hz), 2.51 (q, 2H, $J = 7.3$ Hz), 2.96 (t, 2H, $J = 7.3$ Hz), 3.38 (dt, 2H, $J = 7.1, 7.3$ Hz), 3.73 (s, 3H), 4.12 (q, 2H, $J = 7.1$ Hz), 6.56–6.60 (m, 2H), 6.74–6.79 (m, 2H), 6.87 (t, 1H, $J = 7.1$ Hz), 7.13–7.18 (m, 1H), 7.21–7.29 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 13.2, 14.1, 27.8, 32.1, 45.3, 55.6, 60.8, 114.3, 114.6, 126.1, 128.9, 129.0, 129.3, 136.2, 139.0, 141.7, 152.0, 165.8; IR (neat) 2975, 2360, 1715, 1509, 1241, 1180, 1040, 818, 739, 690, 535, 510 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_3\text{S}$ (M^+) 385.1712, found 385.1719.

Synthesis of *S*-ethyl (*E*)-2-[ethyl(4-methoxyphenyl)amino]-5-(phenylthio)pent-2-enethioate **8a** using ethyl Grignard reagent

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50°C . To it was added EtMgBr (0.27 mL, 0.300 mmol, 1.10 M in THF). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and a solution of *n*Bu₃SnSPh (119.7 mg, 0.30 mmol) in propionitrile (1.0 mL) was added. After



the mixture was stirred for 12 h at room temperature, it was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **8a** (12.7 mg, 21% yield).

Synthesis of ethyl (*E*)-2-[ethyl(4-methoxyphenyl)amino]-5-(phenylthio)pent-2-enethioate **8c** using ethyl Grignard reagent

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed ethyl 2-cyclopropyl-[(4-methoxyphenyl)imino]acetate **1b** (37.1 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50 °C. To it was added EtMgBr (0.27 mL, 0.300 mmol, 1.10 M in THF). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and a solution of *n*Bu₃SnSPh (119.7 mg, 0.30 mmol) in propionitrile (1.0 mL) was added. After the mixture was stirred for 12 h at room temperature, it was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **8c** (9.3 mg, 16% yield).

Synthesis of *S*-ethyl 2-cyano-2-cyclopropyl-2-[ethyl(4-methoxyphenyl)amino]ethanethioate **7** using ethyl Grignard reagent

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50 °C. To it was added EtMgBr (0.27 mL, 0.300 mmol, 1.10 M in THF). After the mixture was stirred for 10 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) was added. The mixture was stirred for 10 min at room temperature, and TMSCN (0.04 mL, 0.30 mmol) was added. After the mixture was stirred for 23 h at room temperature, it was quenched with sat. aq. NaHCO₃ (10 mL), and the whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **7** (15.8 mg, 33% yield).

Synthesis of *S*-ethyl (*E*)-5-chloro-2-[ethyl(4-methoxyphenyl)amino]pent-2-enethioate **9**

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed *S*-ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]ethanethioate **1a** (39.5 mg, 0.150 mmol) in propionitrile (0.5 mL) at -50 °C. To it was added Et₂AlCl (0.27 mL, 0.286 mmol,

1.05 M in *n*hexane). After the mixture was stirred for 30 min at room temperature, a solution of NCS (22.0 mg, 0.15 mmol) in propionitrile (0.75 mL) and Ti(OEt)₄ (0.063 mL, 0.30 mmol) were added successively. The mixture was stirred for 72 h at room temperature and then quenched with sat. aq. NaHCO₃ (10 mL). The whole mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine (5 mL × 2), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 6 : 1) to give the title compound **9**.

Yield 55% (27.0 mg); yellow oil; *R*_f = 0.4 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 1.22 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 2.46 (dt, *J* = 6.9, 6.9 Hz, 2H), 2.84 (q, *J* = 7.3 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 3.75 (s, 3H), 6.63–6.67 (m, 2H), 6.72 (t, *J* = 6.9 Hz, 1H), 6.78–6.82 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 13.0, 14.3, 23.8, 31.1, 42.4, 45.5, 55.6, 114.3, 114.8, 132.4, 140.6, 143.0, 152.3, 193.8; IR (neat) 2967, 2932, 2470, 1673, 1512, 1456, 1250, 1031, 835, 753, 560, 513 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₂ClNO₂S (M)⁺ 327.1060, found 327.1056.

Ethyl 2-cyclopropyl-2-[ethyl(4-methoxyphenyl)amino]-4-pentenoate **10**

Under an argon atmosphere, to a propionitrile (0.5 mL) solution of ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)imino]acetate **1b** (41.6 mg, 0.150 mmol) and benzoyl peroxide (36.3 mg, 0.150 mmol) were added diethylaluminum chloride (0.158 mL, 0.150 mmol, 0.95 M in *n*hexane), ethylaluminum dichloride (0.167 mL, 0.150 mmol, 0.90 M in *n*hexane) and allyltributyltin (0.094 mL, 0.300 mmol) at -20 °C. The reaction mixture was allowed to warm to ambient temperature with stirring for 8 h. After the addition of 10% aq. Na₂SO₃ (5 mL) and subsequently sat. aq. KF (5 mL), the whole mixture was extracted with ethyl acetate (10 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by preparative TLC on silica gel to give the title compound **10**.

Yield 50% (15.9 mg); yellow oil; *R*_f = 0.3 (*n*hexane : ethyl acetate = 6 : 1); ¹H NMR (400 MHz, CDCl₃) δ 0.27–0.40 (m, 3H), 0.43–0.49 (m, 1H), 0.85 (t, 3H, *J* = 7.0 Hz), 1.07–1.13 (m, 1H), 1.31 (t, 3H, *J* = 7.3 Hz), 2.35 (dd, 1H, *J* = 7.9, 14.0 Hz), 2.43 (dd, 1H, *J* = 6.1, 14.0 Hz), 3.04 (dq, 1H, *J* = 7.0, 13.8 Hz), 3.20 (dq, 1H, *J* = 7.0, 13.8 Hz), 3.78 (s, 3H), 4.18 (q, 2H, *J* = 7.3 Hz), 5.02–5.05 (m, 2H), 5.91–5.99 (m, 1H), 6.76–6.79 (m, 2H), 7.14–7.17 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 2.8, 3.3, 14.4, 14.8, 17.1, 41.6, 45.0, 55.3, 60.3, 69.8, 113.1, 117.2, 130.4, 134.9, 140.0, 156.6, 174.1; IR (neat) 2950, 1735, 1515, 1220, 1045, 920, 840 cm⁻¹; HRMS (EI) calcd for C₁₉H₂₇NO₃ (M)⁺ 317.1991, found 317.1999.

Ethyl 2-cyclopropyl-2-[(4-methoxyphenyl)amino]-4-pentenoate **11**

Bis(trimethylsilyl)aluminum chloride was prepared by mixing aluminum chloride (13.4 mg, 0.100 mmol) and tris(trimethylsilyl)aluminum (0.385 mL, 0.200 mmol) from 0 °C to ambient temperature under an argon atmosphere. Under an argon atmosphere, to a propionitrile (0.5 mL) solution of ethyl



2-cyclopropyl-2-[(4-methoxyphenyl)imino]acetate **1b** (39.5 mg, 0.150 mmol) and benzoyl peroxide (54.5 mg, 0.225 mmol) were added bis(trimethylsilyl)aluminum chloride (0.300 mmol) prepared as above and allyltributyltin (0.094 mL, 0.300 mmol) at $-20\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm to ambient temperature and heated at $50\text{ }^{\circ}\text{C}$ with stirring for 23 h. After the addition of 10% aq. Na_2SO_3 (5 mL) and subsequently sat. aq. KF (5 mL), the whole mixture was extracted with ethyl acetate (10 mL \times 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC on silica gel to give the title compound **11**.

Yield 58% (25.2 mg); yellow oil; $R_f = 0.25$ (*n*hexane : ethyl acetate = 6 : 1); ^1H NMR (400 MHz, CDCl_3) δ 0.36–0.60 (m, 4H), 1.20 (t, 3H, $J = 7.3$ Hz), 1.24–1.34 (m, 1H), 2.69 (dd, 1H, $J = 7.3$, 14.2 Hz), 2.82 (dd, 1H, $J = 7.6$, 14.0 Hz), 3.73 (s, 3H), 4.08 (br, 1H), 4.15 (q, 2H, $J = 7.3$ Hz), 5.00–5.07 (m, 2H), 5.65–5.80 (m, 1H), 6.64–6.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 2.9, 3.1, 14.2, 18.0, 40.2, 55.6, 61.2, 64.1, 114.2, 117.9, 118.6, 133.1, 139.4, 152.7, 174.2; IR (neat) 3380, 2980, 1740, 1520, 1245, 1190, 1050, 925, 830 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ (M^+) 289.1678, found 289.1691.

Conflicts of interest

There are no conflicts to declare.

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- To clarify the exact origin of the reactivity of thioesters, computational study was carried out using the Gaussian 03 program. After the structural optimization, we found that the LUMO energy of the thioester was lower than that of the normal ester. We also found that the frontier electron density of the thioester was higher than that of the normal ester, leading to the increased reactivity of the nitrogen atom of the thioester. These computational analyses support the experimental results. Details of these studies have already been communicated.^{3e}



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