RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 13097

Received 13th March 2021
Accepted 31st March 2021

DOI: 10.1039/d1ra02000e

rsc.li/rsc-advances

N-Alkylation/aldol reaction of α-aldimino thioesters: a facile three-component coupling reaction†

Makoto Shimizu, *[ab] Asako Higashino,[b] Isao Mizota [b] and Yusong Zhu [a]

Theoretical calculation of the reactivity of α-imino thioesters indicates that they are very reactive substrates for Umpolung *N*-alkylation. In fact, treatment of α-aldimino thioesters with dialkylzinc reagents in the presence of aldehydes or imines gives three-component coupling products in good yields.

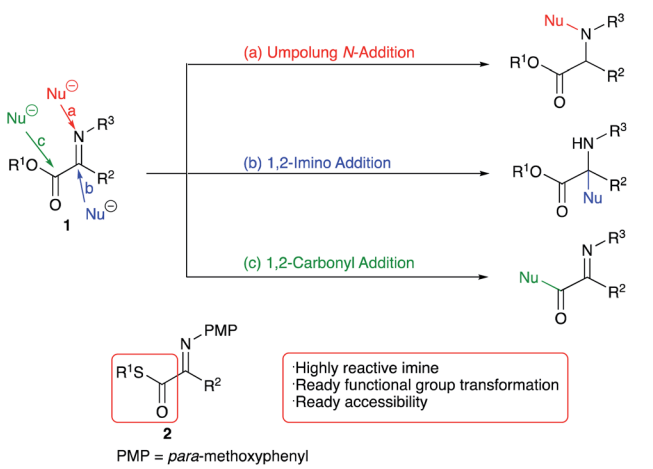
1 Introduction

The widespread existence of 1,2-amino alcohol moieties in natural products and pharmaceuticals[1] has prompted us to explore efficient synthetic methods for these important materials. Various synthetic 1,2-amino alcohol derivatives have also been employed as drugs for therapeutic purposes, chiral auxiliaries, and metal ligands in catalytic asymmetric synthesis.[2] We have reported new approaches to this class of compound *via* asymmetric reduction of 1,2-imino ketones,[3] diastereoselective addition to chiral imines,[4] titanium tetraiodide-mediated reductive addition reactions,[5] and crossed pinacol-type reductive coupling of aldehydes with imines.[6] In addition to these studies, we have been interested in the Umpolung reactions using α-imino esters **1** and related compounds, and have disclosed several interesting features.[7,8] Under certain reaction conditions an unusual Umpolung *N*-addition reaction proceeds to give *N*-alkylated products in good yields (Scheme 1, path a).

During these investigations, the thioester analogues **2** have intrigued us, since a simple calculation using the model substrates **1a** and **2a** with the Gaussian 03 program[9] indicates that in the addition reactions of a methyl anion to normal ester **1a** and thioester **2a**, the energy difference between the *C*- and the *N*-additions is larger for thioester **2a** than for normal ester **1a** (Scheme 2). This means that the Umpolung *N*-addition reaction would be easier for thioesters than for normal esters. Among α-imino thioesters α-aldimino thioester **3** has attracted our attentions since α-aldimino thioesters are expected to be more reactive than α-ketimino analogues and the subsequent reactions at the aldimino moieties would proceed to give interesting and useful products. This paper describes three-component coupling reactions consisting of *N*-alkylation/aldol reaction[10] of α-aldimino thioesters (Scheme 3).

2 Results and discussion

A further calculation using the Gaussian 03 program[9] indicates that the LUMO energies of the ethyl ester **1b** and its thio analogue are −0.0627 and −0.0756, respectively, which means that the reactivity of the α-imino thioester **2b** is higher than that of the α-imino ester **1b**. The structures **1b** and **2b** were fully optimized followed by frequency calculation on the stationary point performed using 6-31G(d) basis set for all atoms, which was employed a B3LYP density functional theory.[11] We have also found that the reactivity of the imino nitrogen atom of α-imino thioester **2b** is higher than that of α-imino ester **1b** since the Frontier electron densities are 0.176 and 0.216, respectively, leading to the increased reactivity of nitrogen atom (Scheme 4). In fact, the reaction of the α-imino ester **1b** with Et_2AlCl in DME

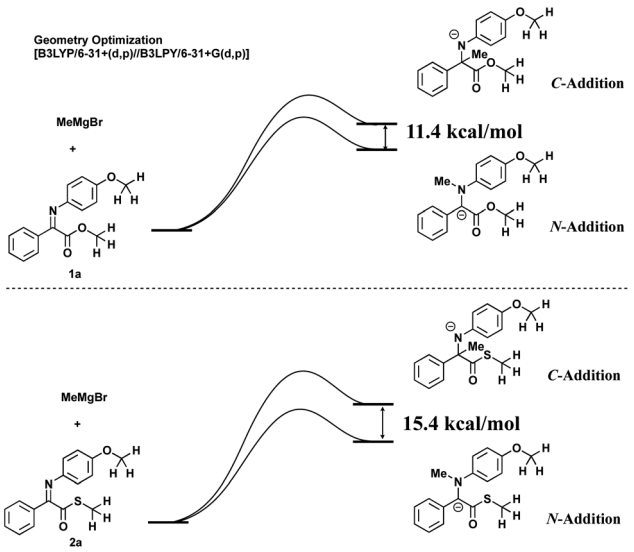


Scheme 1 Reactions of α-imino ester **1** and α-imino thioester **2**.

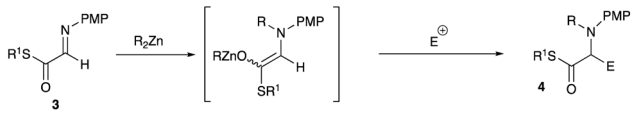
[a]*School of Energy Science and Engineering, Nanjing Tech University, Nanjing 211816, Jiangsu Province, China*

[b]*Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra02000e



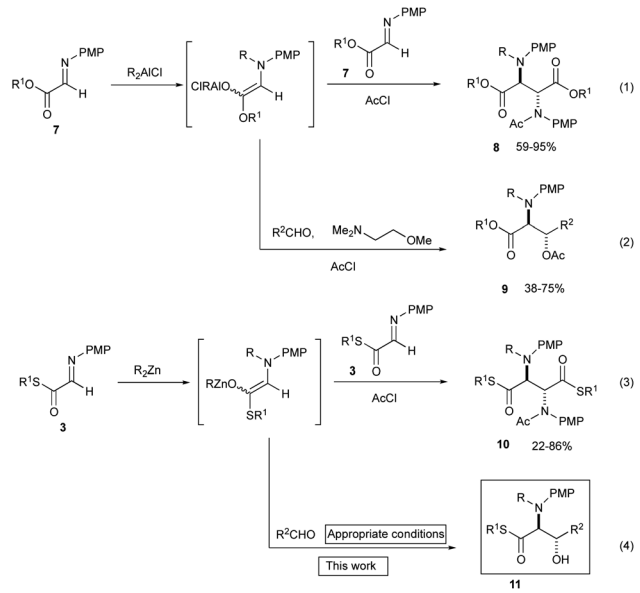
Scheme 2 Model substrates **1a** and **2a** for energy calculation.



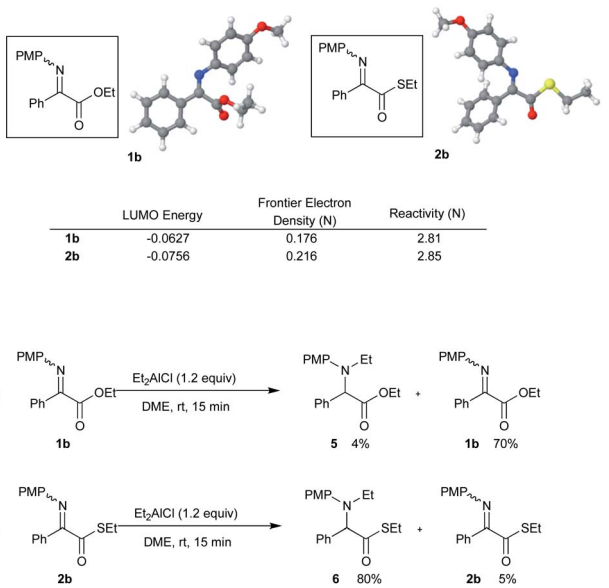
Scheme 3 The present study using α-aldimino thioester **3**.

at rt for 15 min gave the *N*-ethylation product **5** in only 4% yield, whereas the α-imino thioester **2b** underwent a similar *N*-ethylation reaction to give the product **6** in 80% yield. (Scheme 4, eqn (1) and (2)).

Our previous investigations revealed that *N*-alkylation proceeded well both with the α-aldimino ester **7**[7a] and the α-aldimino thioester **3**[7q] to give the intermediary aluminum and the zinc enolates, respectively. However, the subsequent addition reaction with the parent imines **7** and **3** proceeded very rapidly to give homo-coupling products **8** and **10**, respectively in good yields (Scheme 5, eqn (1) and (3)), and therefore, it was not trivial to carry out a cross-coupling reaction with another electrophile (eqn (2) and (4)). When the α-aldimino ester **7** was used as a substrate, the presence of an added additive ($Me_2N(CH_2)_2OMe$) facilitated a cross-coupling reaction with aldehydes to give 1,2-amino alcohols **9** in good yields (eqn (2)).[7j] In strong contrast to the cases with the α-aldimino ester **7**, however, the thioester **3** underwent only a homo-coupling reaction even in the presence of an additive ($Me_2N(CH_2)_2OMe$) to give the adduct **10** in good yield, and the cross-coupling product **11** was not obtained at all, presumably due to the enhanced electrophilicity of the imine moiety of the α-aldimino thioester **3**. We screened various organometallics (RMgBr, R_2Mg, R_3Al, R_2AlCl, $RAlCl_2$, R_2Zn and RZnBr), and among them the use of dialkylzinc recorded an acceptable yield of the homo-coupling product **10** (up to 86% yield, eqn (3)).



Scheme 5 Previous investigations using α-aldimino ester **7** and α-aldimino thioester **3**.

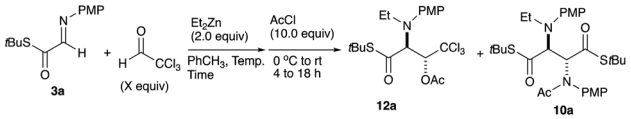


Scheme 4 Reactivity difference between α-imino ester **1b** and α-imino thioester **2b**.

We further examined the reaction conditions for cross-coupling using a series of aldehydes under various conditions. Among the aldehydes tested ($pClC_6H_4CHO$, PhCHO, PhCH = CHCHO, *n*PrCH = CHCHO, *n*BuCHO, EtOCOCHO, CCl_3CHO, *etc.*) only chloral, a reactive aldehyde gave a cross-coupling product **11**. Since the three-component coupling product, the β-hydroxy α-amino thioester obtained was unstable under air due to the oxidative cleavage previously reported,[12] it was isolated as the acetate **12a** after acetylation with AcCl at the hydroxy moiety. Table 1 summarizes the results.

As shown in Table 1, the three-component coupling reaction proceeded with the α-imino thioester **3a**, diethylzinc, and chloral in toluene to give the adduct **12a** together with the homo-coupling product **10a** as a major byproduct (entry 1). In

Table 1 Three-component coupling reaction: Examination of the reaction conditions



Entry	Chloral (equiv.)	Temp (°C)	Time (h)	**12a**[a] (%)	*anti*/*syn*[b]	**10a**[a] (%)
1	1.0	−60 to −30	2.0	19	63 : 37	29
2	1.0	−78 to −50	1.0	45	70 : 30	26
3	1.5	−78 to −50	2.0	59	64 : 36	8
4	2.0	−78 to −50	2.0	79	62 : 38	6
5	2.5	−78 to −50	2.0	76	59 : 41	5
6[c]	2.1	−78 to −50	1.0	37	65 : 35	20

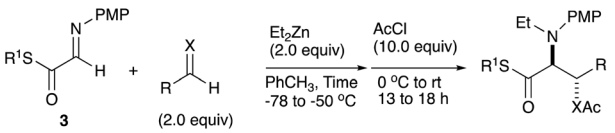
[a] Isolated yield. [b] Determined by ^{1}H NMR and/or HPLC. [c] **3a** was slowly added to a mixture of chloral and Et_2Zn.

an effort to avoid the undesirable formation of the homo-coupling product **10a**, a solution of diethylzinc was added to a mixture of the α-imino thioester **3a** and chloral at −78 °C (entry 2). An increase in the formation of the cross-coupling product **12a** was observed when 1.5 equivalents of chloral were used. The best result was obtained when the reaction was carried out with 2.0 equivalents of chloral, and in this case the desired product was obtained in 79% yield (entry 4). An additional increase in the amount of chloral did not lead to a further improvement of the product yield (entry 5). Since diethylzinc did not react with chloral at −78 °C, a solution of the thioester **3a** was added to a mixture of choral and diethylzinc. In this case, however, an increased amount of the homo-coupling product **10a** was obtained (entry 6). Under the best conditions found for the cross-coupling reaction, various aldehydes and imines were subjected to the three-component coupling reaction, and Table 2 summarizes the results.

Benzaldehyde did not react with the intermediary zinc enolate, but only the homo-coupling product **10a** was obtained (entry 1). The use of the cyclohexylthio ester recorded a slightly better diastereoselectivity of 69 : 31, whereas in the case of the ethylthio ester the ratio of the diastereomers was improved to 83 : 17, although the product yields were moderate (entry 3 and 4). Bromal also reacted with the enolate to give the three-component coupling product **12d** in moderate yield, presumably due to the decreased reactivity of bromal compared with that of chloral (entry 5). Ethyl glyoxylate and acrolein did not serve as a good electrophile in this three-component coupling reaction, and the addition reaction gave moderate yields of the products (entries 6 and 7). Regarding the use of imines, a simple imine derived from *para*-chlorobenzaldehyde and anisole did not give the addition product, nor did its *para*-tosyl derivative, a relatively reactive imine (entries 8 and 9). The imine derived from ethyl glyoxylate is a better electrophile in this three-component coupling reaction to give the *anti*-coupling adduct as a sole product, in which the ethylthio ester served as a better substrate (entries 10 and 11). We further examined the use of other dialkylzinc reagents as the initial *N*-alkylation reagent. Table 3 summarizes the results.

The use of diisopropylzinc and diphenylzinc was examined besides diethylzinc. Diisopropylzinc underwent

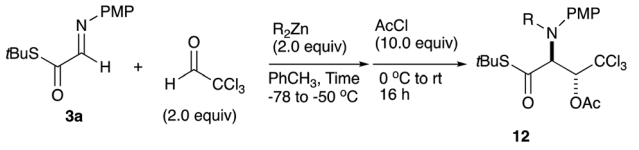
Table 2 Three-component coupling reaction



Entry	**3** : R^1	Electrophile	Time (h)	**12** : Yield[a] (%)	*anti* : *syn*[b]
1	**3a** : *t*Bu		2.0	0	—
2	*t*Bu		1.0	**12a** : 79	62 : 38
3	**3b** : Et		1.0	**12b** : 54	83 : 17
4	**3c** : Cy		1.0	**12c** : 47	69 : 31
5	*t*Bu		2.0	**12d** : 43	50 : 50
6	*t*Bu		3.0	**12e** : 26	50 : 50
7	*t*Bu		4.0	**12f** : 32	62 : 38
8	*t*Bu		2.0	0	—
9	*t*Bu		3.0	0	—
10	*t*Bu		1.0	**12g** : 45[c]	100 : 0
11	Et		1.0	**12h** : 64[c]	100 : 0

[a] Isolated yield. [b] Determined by 1H NMR and/or HPLC. [c] 1.0 equiv of the electrophile (imine) was used.

Table 3 Comparison of dialkylzinc reagents

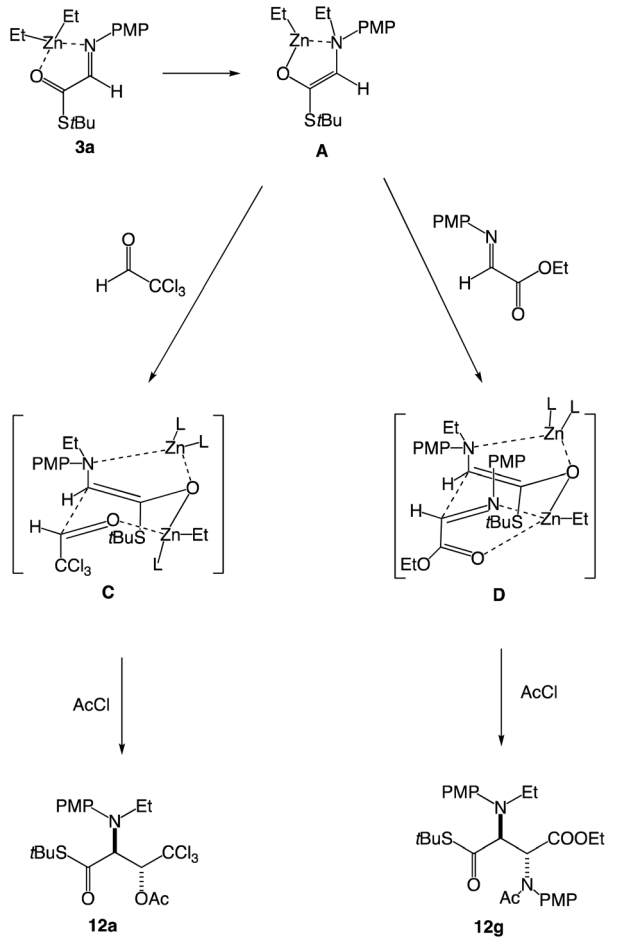


Entry	R	Time (h)	12[a] (%)	*anti*/*syn*[b]
1	Et	1.0	**12a** : 79	62 : 38
2	*iso*-Pr	1.5	**12i** : 75	56 : 44
3	Ph	3.5	0	—

[a] Isolated yield. [b] Determined by ^{1}H NMR and/or HPLC.

a similar *N*-alkylation reaction to give the three-component coupling product **12i** in 75% yield, whereas diphenylzinc did not add to the α-imino thioester **3a**, but only the starting thioester **3a** was recovered (entries 2 and 3). Regarding the reaction mechanisms the following Scheme 6 shows possible pathways.

First, diethylzinc coordinates with the α-imino thioester **3a** and *N*-ethylation proceeds to give the zinc enolate **A**, which reacts with chloral to form the β-hydoroxy α-amino thioester **12a** *via* a six-membered transition state **C**. In the case of the reaction with an imine, the addition also proceeds *via* a six-membered transition state **D** to give the α,β-diamino thioester **12g**. Since there exist three chelated metallacycles in the TS **D**, a relatively fixed intermediate would be involved in this model having an *N*,*O*-chelated electrophilic imine, leading to a formation of the *anti*-adduct **12g** with high diastereoselectivity. In contrast, in the TS **C** for the addition with chloral, since there are only two metllacycles and no chelation is available between the aldehyde substituent (CCl_3) with the zinc atom, the *anti*-selectivity would be affected compared with the case of the imine as an electrophile.



Scheme 6 Plausible reaction pathways.

3 Conclusions

In conclusion, α-imino thioesters are useful substrates for the Umpolung *N*-addition of dialkylzinc reagents to form the zinc enolates. A simple theoretical calculation explains the high reactivity of α-imino thioesters.[9,13] Since the intermediary zinc enolates formed upon the *N*-alkylation rapidly react with the parent α-imino thioesters to give homo-coupling products, cross-coupling reactions are not readily carried out. In the present study, we found that the addition of dialkylzinc to a mixture of α-imino thioester and reactive aldehydes or imines at low temperature gave three-component coupling products in good yields with high *anti*-selectivity. The formed β-hydroxy α-amino thioesters and α,β-diamino thioesters are potentially useful intermediates for further functional group interconversions with respect to the thioester moieties.[14] Since the present procedure offers a rapid assembly of three components efficiently, this methodology is useful in addition to the existing precedents for the synthesis of 1,2-hydroxy amines[1,2] and 1,2-diamines.[15]

4 Experimental

General aspects

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. High-performance liquid chromatography (HPLC) was carried out on a Hitachi L-4200 detector and a Hitachi L-6200 pump. Toluene ($PhCH_3$), was dried over CaH_2, distilled, and stored over molecular sieves 4 Å. 1,2-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 or Wako Gel B-5F). The staring materials **1b**, **2b**, **3a–c** were prepared as reported.[7d,q,s]

Ethyl 2-[ethyl(4-methoxyphenyl)amino]-2-phenylacetate 5

Under an argon atmosphere, a suspension of the α-imino ester **1b** (42.5 mg, 0.15 mmol) in DME (0.50 mL) was stirred at rt for 5 min, and to it was slowly added Et_2AlCl in *n*hexane (0.17 mL,

0.18 mmol, 1.05 M). After the mixture was stirred for 15 min, it was quenched with an aq. solution of Rochelle's salt (5.0 mL, 30.0 g in 75 mL H_2O), and the mixture was stirred at rt for 30 min. The whole mixture was extracted with ethyl acetate (5.0 mL × 5). The combined extracts were washed with an aq. solution of Rochelle's salt, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 5 : 1) under an argon atmosphere to give the title compounds **5** (1.84 mg, 4%) and the recovered **1b** (30.5 mg, 70%). The spectral data were identical with those reported.[7d]

Yield 4% (1.84 mg); a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.17 (t, 3H, J = 7.3 Hz), 3.03–3.29 (m, 2H), 3.78 (s, 3H), 4.06–4.23 (m, 2H), 5.26 (s, 1H), 6.76–6.94 (m, 4H), 7.15–7.48 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 14.1, 43.9, 55.5, 60.8, 68.7, 114.3, 119.8, 128.0, 128.4, 128.7, 136.6, 142.6, 153.7, 172.0; IR (neat) 2950, 1755, 1520, 1260, 1190, 1040, 825, 700 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}NO_3$ $(M)^+$ 313.1678, found 313.1692.

S-Ethyl 2-[ethyl(4-methoxyphenyl)amino]-2-phenylethanethioate 6

Under an argon atmosphere, a suspension of the α-imino thioester **2b** (44.9 mg, 0.15 mmol) in DME (0.50 mL) was stirred at rt for 5 min, and to it was slowly added Et_2AlCl in *n*hexane (0.17 mL, 0.18 mmol, 1.05 M). After the mixture was stirred for 15 min. The reaction was quenched with an aq. solution of Rochelle's salt (5.0 mL, 30.0 g in 75 mL of H_2O), and the mixture was stirred at rt for 30 min. The whole mixture was extracted with ethyl acetate (5.0 mL × 5). The combined extracts were washed with an aq. solution of Rochelle's salt, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified on silica gel TLC (*n*hexane : ethyl acetate = 5 : 1) under an argon atmosphere to give the title compounds **6** (40.5 mg, 80%) and the recovered **2b** (2.3 mg, 5%).

Yield 80% (40.5 mg, 80%); a yellow oil; R_f = 0.80 (*n*hexane : ethyl acetate = 10 : 1, developed twice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (dd, J = 7.0, 7.0 Hz, 3H), 1.22 (dd, J = 7.3, 7.3 Hz, 3H), 2.91–2.81 (m, 2H), 3.05 (dq, J = 7.0, 14.0 Hz, 1H), 3.15 (dq, J = 7.0, 14.0 Hz, 1H), 3.76 (s, 3H), 6.83–6.80 (m, 2H), 5.27 (s, 1H), 6.91–6.88 (m, 2H), 7.32–7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 14.5, 23.3, 44.2, 55.5, 76.4, 114.3, 120.5, 128.0, 128.3, 129.3, 135.8, 142.0, 154.0, 201.9; IR (neat) 2971, 2931, 2833, 1684, 1510, 1452, 1375, 1244, 1180, 1038, 966, 819, 761, 702 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}NO_2S(M)^+$ 329.1450, found 329.1447.

(2*R**,3*S**)-4-(*tert*-Butylthio)-1,1,1-trichloro-3-[ethyl(4-methoxyphenyl)amino]-4-oxobutan-2-yl acetate 12a: general procedure for the three-component coupling reaction

In a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed *S*-(*tert*butyl) 2-[(4-methoxyphenyl)imino] ethanethioate **3a** (37.7 mg, 0.15 mmol), and chloral (0.029 mL, 0.30 mmol) in toluene (3.0 mL) at −78 °C, and to it was slowly added Et_2Zn (0.30 mL, 1.00 M, 0.30 mmol). After the mixture was stirred for 2 h at −78 to −50 °C, to it was added AcCl (0.11 mL, 1.50 mmol) and stirred for 15.5 h at 0 °C. The mixture was quenched with aq. $NaHCO_3$ (10.0 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 (toluene : ethyl acetate = 8 : 1) to give the title compound **12a** (55.5 mg, 79%) and *S*,*S*-di-*tert*-butyl (2*S**,3*R**)-2-[ethyl(4-methoxyphenyl)amino]-3-[*N*-(4-methoxyphenyl)acetamido]butanebis(thioate) **10a** (5.2 mg, 6%).

12a. Yield 79% (55.5 mg, *anti* : *syn* = 62 : 38); a yellow oil; R_f = 0.63 (toluene : ethyl acetate = 7 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (dd, J = 6.9, 6.9 Hz, 1.11H), 1.06 (dd, J = 6.9, 6.9 Hz, 1.89H), 1.44 (s, 5.67H), 1.45 (s, 3.33H), 1.99 (s, 1.89H), 2.12 (s, 1.11H), 3.20 (dq, J = 6.9, 7.2 Hz, 1.26H), 3.29 (dq, J = 6.9, 7.2 Hz, 1.26H), 3.40 (dq, J = 7.0, 7.1 Hz, 0.74H), 3.94 (dq, J = 7.0, 7.1 Hz, 0.74H), 3.77 (s, H), 3.78 (s, H), 4.61 (d, J = 7.6, 0.63H), 4.78 (d, J = 8.7, 0.37H), 6.02 (d, J = 8.7, 0.37H), 6.34 (d, J = 7.6, 0.63H), 6.83–6,94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 13.2, 20.5, 20.6, 29.5, 29.6, 40.7, 42.1, 48.7, 49.1, 55.5, 55.5, 71.4, 71.4, 76.4, 77.2, 98.5, 98.7, 114.4, 114.5, 118.1, 119.1, 140.0, 141.1, 153.2, 153.5, 168.2, 168.7, 194.3, 195.5; IR (neat) 2965, 2930, 2835, 1767, 1676, 1511, 1368, 1246, 1205, 1040, 805, 768 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{26}C_{l3}NO_4S$ $(M)^+$ 469.0648, found 469.0645.

10a. Yield 6% (5.2 mg, *anti* : *syn* = 100 : 0); a yellow oil; R_f = 0.40 (*n*hexane : ethyl acetate = 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, J = 6.8, 6.8 Hz, 3H), 1.40 (s, 9H), 1.43 (s, 9H), 1.78 (s, 3H), 3.15–3.32 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 4.39 (d, J = 11.3 Hz, 1H), 6.05 (d, J = 11.3 Hz, 1H), 6.75–7.12 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.1, 23.2, 29.5, 29.8, 40.1, 48.4, 48.6, 55.4, 60.8, 70.9, 114.0, 114.4, 119.6, 131.0, 131.9, 140.8, 153.4, 159.4, 170.8, 195.1, 196.5; IR (neat) 2965, 1674, 1511, 1456, 1365, 1293, 1250, 1036, 731, 647 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{42}N_2O_5S_2$ $(M)^+$ 574.2535, found 574.2517.

(2*R**,3*S**)-1,1,1-Trichloro -4-(ethylthio)-3-[ethyl(4-methoxyphenyl)amino]-4-oxobutan-2-yl acetate 12b

Yield 54% (36.1 mg, *anti* : *syn* = 83 : 17); a yellow oil; R_f = 0.65 (toluene : ethyl acetate = 8 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (dd, J = 7.1 Hz, 2.49H), 1.09–1.13 (m, 0.51H), 1.23 (dd, J = 7.3 Hz, 0.51H), 1.23 (dd, J = 7.3 Hz, 2.49H), 1.98 (s, 0.51H), 2.12 (s, 2.49H), 2.81–2.92 (m, 2H), 3.26–3.54 (m, 2H), 3.77 (s, 0.51H), 3.77 (s, 2.49H), 4.69 (d, J = 6.9 Hz, 0.17H), 4.85 (d, J = 8.2 Hz, 0.83H), 6.06 (d, J = 8.2 Hz, 0.83H), 6.41 (d, J = 6.4 Hz, 0.17H), 6.78–6.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 13.1, 14.5, 14.7, 20.6, 21.0, 23.7, 23.7, 41.2, 43.1, 55.5, 55.5, 71.8, 71.8, 76.5, 77.2, 98.5, 98.8, 114.4, 114.7, 118.0, 119.3, 140.0, 140.8, 153.2, 153.6, 168.3, 168.6, 193.9, 196.2; IR (neat) 2971, 2932, 1772, 1679, 1511, 1371, 1247, 1202, 1039, 797, 764 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}C_{l3}NO_4S(M)^+$ 441.0335, found 441.0347.

(2*R**,3*S**)-1,1,1-Trichloro-4-(cyclohexylthio)-3-[ethyl(4-methoxyphenyl)amino]-4-oxobutan-2-yl acetate 12c

Yield 47% (35.3 mg, *anit* : *syn* = 69 : 31); a yellow oil; R_f = 0.58 (*n*hexane : ethyl acetate = 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (dd, J = 6.87 Hz, 2.07H), 1.09 (dd, J = 6.87 Hz, 0.93H), 1.19–1.62 (m, 6H), 1.66–1.69 (m, 2H), 1.85–1.95 (m, 2H), 1.99 (s, 0.93H), 2.12 (s, 2.07H), 3.23–3.38 (m, 1H), 3.44–3.53 (m, 2H),

3.77 (s, 0.93H), 3.78 (s, 2.07H), 4.67 (d, J = 6.87 Hz, 0.31H), 4.81 (d, J = 8.24 Hz, 0.69H), 6.05 (d, J = 8.24 Hz, 0.69H), 6.39 (d, J = 6.87 Hz, 0.31H), 6.79–6.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 13.2, 20.6, 20.6, 25.4, 25.4, 25.8, 25.9, 32.6, 32.7, 32.8, 33.0, 41.0, 42.8, 42.9, 55.4, 55.5, 71.7, 71.8, 76.4, 76.5, 98.5, 98.7, 114.4, 114.4, 118.1, 119.4, 140.0, 141.0, 153.2, 153.6, 168.3, 168.7, 193.6; IR (neat) 2933, 2854, 1770, 1675, 1511, 1371, 1247, 1203, 1039, 910, 797, 764, 732 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{28}Cl_3NO_4S(M)^+$ 495.0805, found 495.0805.

(2*R,3*S**)-1,1,1-Tribromo-4-(*tert*-butylthio)-3-[ethyl(4-methoxyphenyl)amino]-4-oxobutan-2-yl acetate 12d**

Yield 43% (38.7 mg, *anti* : *syn* = 50 : 50); a yellow oil; R_f = 0.63 (toluene : ethyl acetate = 7 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (m, 3H), 1.45 (s, 9H), 2.03 (s, 1.5H), 2.14 (s, 1.5H), 3.22–3.25 (m, 1H), 3.47 (dq), 3.60 (dq), 3.78 (s, 3H), 4.55 (d, J = 6.9 Hz, 0.5H), 4.75 (d, J = 7.8 Hz, 0.5H), 5.96 (d, J = 7.8 Hz, 0.5H), 5.34 (d, J = 7.6 Hz, 0.5H), 6.82–6.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 13.2, 20.7, 20.8, 29.5, 29.6, 41.0, 41.1, 42.1, 48.7, 49.1, 55.4, 55.5, 72.4, 72.7, 77.2, 77.5, 77.5, 114.3, 114.4, 118.4, 119.0, 140.0, 140.9, 153.1, 153.3, 168.2, 168.7, 194.3, 195.7; IR (neat): 2964, 2929, 1763, 1676, 1511, 1366, 1246, 1205, 1039, 696, 648 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{26}Br_3NO_4S$ (M)$^+$ 600.9133, found 600.9128.

Ethyl (2*R,3*S**)-2-acetoxy-4-(*tert*-butylthio)-3-[ethyl(4-methoxyphenyl)amino]-4-oxobutanoate 12e**

Yield 26% (16.3 mg, *anti* : *syn* = 50 : 50); a yellow oil; R_f = 0.65 (toluene : ethyl acetate = 8 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.22 (m, 6H), 1.45 (s, 4.5H), 1.46 (s, 4.5H), 2.09 (s, 1.5H), 2.11 (s, 1.5H), 3.18–3.46 (m, 2H), 3.76 (s, 1.5H), 3.77 (s, 1.5H), 3.99–4.15 (m, 2H), 4.63 (d, J = 7.3H, 0.5H), 4.84 (d, J = 5.3 Hz, 0.5H), 5.44 (d, J = 7.3 Hz, 0.5H), 5.71 (d, J = 4.6 Hz, 0.5H), 6.79–6.90 (m, 3H), 7.07–7.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 10.8, 13.1, 14.2, 24.5, 24.5, 29.6, 29.8, 39.8, 39.8, 48.5, 48.6, 55.2, 55.4, 60.4, 65.2, 69.1, 72.3, 76.4, 77.6, 113.4, 114.1, 119.9, 119.9, 130.2, 130.2, 137.7, 141.2, 153.4, 156.8, 173.5, 173.5, 194.9, 197.8; IR (neat) 2964, 1734, 1675, 1510, 1463, 1244, 1179, 1038, 995, 834, 755 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{31}NO_6S$ (M)$^+$ 425.1872, found 425.1875.

(3*S,4*S**)-5-(*tert*-Butylthio)-4-[ethyl(4-methoxyphenyl)amino]-5-oxopent-1-en-3-yl acetate 12f**

Yield 32% (18.1 mg, *anti* : *syn* = 62 : 38); a yellow oil; R_f = 0.62 (toluene : ethyl acetate = 8 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99–1.07 (m, 3H), 1.44 (s, 3.42H), 1.44 (s, 5.58H), 1.95 (s, 1.14H), 2.02 (s, 1.86H), 3.27 (dq, J = 7.0, 7.0 Hz, 0.76H), 3.32 (dq, J = 7.0, 7.2 Hz, 1.24H), 3.77 (s, 3H), 4.22 (d, J = 8.2 Hz, 0.38H), 4.25 (d, J = 9.2 Hz, 0.62H), 5.18–5.25 (m, 1H), 5.28–5.37 (m, 1H), 5.80–5.92 (m, 2H), 6.75–6.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 13.2, 20.9, 29.7, 40.6, 41.2, 48.3, 48.3, 55.5, 71.7, 71.9, 73.7, 74.8, 114.4, 118.3, 118.6, 118.8, 118.9, 133.5, 133.8, 141.3, 142.0, 153.2, 153.3, 169.4, 169.5, 197.6, 197.8; IR (neat) 2965, 2930, 2867, 2834, 1749, 1675, 1511, 1365, 1230, 1039, 936, 817 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{29}NO_4S$ (M)$^+$ 379.1817, found 379.1822.

***S*,*S*-Di-*tert*-butyl (2*S**,3*R**)-2-[ethyl(4-methoxyphenyl)amino]-3-[*N*-(4-methoxyphenyl)acetamido]butanebis(thioate) 12g**

Yield 45% (35.9 mg, *anti* : *syn* = 100 : 0); an orange oil; R_f = 0.25 (*n*hexane : ethyl acetate = 2 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (dd, J = 6.9, 6.9, 3H), 1.17 (dd, J = 7.3, 7.3 Hz, 3H), 1.40 (s, 9H), 1.78 (s, 3H), 3.17 (dq, J = 6.9, 7.0 Hz, 1H), 3.24 (dq, J = 6.9, 7.0 Hz, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.03 (dq, J = 7.3, 10.8 Hz, 1H), 4.12 (dq, J = 7.3, 10.8 Hz, 1H), 4.44 (d, J = 11.3 Hz, 1H), 5.53 (d, J = 11.3 Hz, 1H), 6.60–7.58 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 13.9, 23.0, 29.7, 40.1, 48.4, 55.4, 58.2, 61.3, 70.9, 114.2, 114.5, 118.9, 131.2, 132.9, 141.0, 153.3, 159.4, 171.2, 171.6, 195.2; IR (neat) 2965, 2934, 2870, 1735, 1668, 1511, 1463, 1377, 1296, 1248, 1183, 1036, 986, 840, 755 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{38}N_2O_6S$ (M)$^+$ 530.2451, found 530.2432.

Ethyl (2*R*,3*S*)-3-[ethyl(4-methoxyphenyl)amino]-4-(ethylthio)-2-[*N*-(4-methoxyphenyl)acetamido]-4-oxobutanoate 12h

Yield 64% (48.2 mg, *anti* : *syn* = 100 : 0); a pale yellow oil; R_f = 0.28 (toluene : ethyl acetate = 7 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (dd, J = 7.1, 7.1 Hz, 3H), 1.18 (dd, J = 7.3, 7.3 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H), 1.78 (s, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.17 (dq, J = 7.1, 14.3 Hz, 1H), 3.21 (dq, J = 7.1, 14.3 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.02–4.17 (m, 2H), 4.55 (d, J = 11.0 Hz, 1H), 5.57 (d, J = 11.0 Hz, 1H), 6.75–7.48 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 13.9, 14.7, 23.0, 23.3, 40.5, 55.4, 58.6, 61.3, 70.9, 114.2, 114.4, 119.2, 131.1, 132.8, 140.9, 153.5, 159.4, 170.8, 171.6, 195.1; IR (neat): 2934, 2837, 1736, 1667, 1511, 1376, 1297, 1247, 1183, 1034, 839, 754 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{34}N_2O_6S$ (M)$^+$ 502.2138, found 502.2160.

(2*R,3*S**)-4-(*tert*-Butylthio)-1,1,1-trichloro-3-(isopropyl(4-methoxyphenyl)amino)-4-oxobutan-2-yl acetate 12i**

Yield 75% (54.4 mg, *anti* : *syn* = 56 : 44); a yellow oil; R_f = 0.53 (*n*hexane : ethyl acetate = 5 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.4 Hz, 1.32H), 1.17 (d, J = 6.9 Hz, 1.64H), 1.22 (d, J = 6.9 Hz, 1.32H), 1.32 (d, J = 6.4 Hz, 1.64H), 1.41 (s, 5.04H), 1.52 (s, 3.96H), 1.97 (s, 1.68H), 2.09 (s, 1.32H), 3.72–3.83 (m, 0.56H), 3.76 (s, 1.68H), 3.79 (s, 1.34H), 3.94 (dq, J = 6.7, 6.6 Hz, 0.44H), 4.45 (d, J = 7.3 Hz, 0.56H), 4.46 (d, J = 6.9 Hz, 0.44H), 5.91 (d, J = 7.3 Hz, 0.44H), 6.46 (d, J = 6.9 Hz, 0.56H), 6.76–7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.7, 21.3, 21.6, 22.1, 23.8, 29.5, 29.7, 48.3, 48.9, 50.4, 50.8, 55.3, 55.4, 70.1, 72.4, 76.0, 78.2, 99.0, 99.4, 113.5, 113.9, 122.8, 129.5, 138.4, 139.6, 154.3, 156.5, 168.2, 168.8, 197.5, 197.9; IR (neat) 2966, 2835, 1768, 1679, 1513, 1367, 1244, 1205, 1039, 808, 766, 734 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{28}Cl_3NO_4S(M)^+$ 483.0805, found 483.0822.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B) and on Innovative Areas "Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances" from JSPS and MEXT.

Notes and references

1 (*a*) H. Ito, T. Taguchi and Y. Hanzawa, *Tetrahedron Lett.*, 1992, **33**, 4469–4472; (*b*) D. Guijarro and M. Yus, *Tetrahedron*, 1993, **49**, 7761–7768; (*c*) A. Clerici, L. Clerici and O. Porta, *Tetrahedron Lett.*, 1995, **36**, 5955–5958; (*d*) C. Z. Ding, *Tetrahedron Lett.*, 1996, **37**, 945–948; (*e*) F. Machrouhi and J.-L. Namy, *Tetrahedron Lett.*, 1999, **40**, 1315–1318; (*f*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561–2576; (*g*) B. W. Lee, J. H. Lee, K. C. Jang, J. E. Kang, J. H. Kim, K.-M. Park and K. H. Park, *Tetrahedron Lett.*, 2003, **44**, 5905–5907; (*h*) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer and T. Zelinski, *Angew. Chem., Int. Ed.*, 2004, **43**, 788–824; (*i*) H. Maekawa, Y. Yamamoto, H. Shimada, K. Yonemura and I. Nishiguchi, *Tetrahedron Lett.*, 2004, **45**, 3869–3872; (*j*) D. Y. Jung, S. Kang, S. Chang and Y. H. Kim, *Synlett*, 2006, 86–90; (*k*) M. Barbazanges, C. Meyer and J. Cossy, *Org. Lett.*, 2007, **9**, 3245–3248; (*l*) E. Skucas, J. R. Zbieg and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 5054–5055; (*m*) O. K. Karjalainen and A. M. P. Koskinen, *Org. Biomol. Chem.*, 2012, **10**, 4311–4326; (*n*) D. Ghislieri and N. J. Turner, *Top. Catal.*, 2014, **57**, 284–300; (*o*) T. Sehl, Z. Maugeri and D. Rother, *J. Mol. Catal. B: Enzym.*, 2015, **114**, 65–71; (*p*) J. L. Schwarz, R. Kleinmans, T. O. Paulisch and F. Glorius, *J. Am. Chem. Soc.*, 2020, **142**, 2168–2174.

2 For reviews, see: (*a*) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835–876; (*b*) F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159–2232; (*c*) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033–8061; (*d*) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650–1667; (*e*) B. Alcaide and P. Almendros, *Eur. J. Org. Chem.*, 2002, 1595–1601; (*f*) H. Nakano, I. A. Owolabi, M. Chennapuram, Y. Okuyama, E. Kwon, C. Seki, M. Tokiwa and M. Takeshita, *Heterocycles*, 2018, **97**, 647–667.

3 (*a*) M. Shimizu, K. Tsukamoto and T. Fujisawa, *Tetrahedron Lett.*, 1997, **38**, 5193–5196; (*b*) M. Shimizu, K. Tsukamoto, T. Matsutani and T. Fujisawa, *Tetrahedron*, 1998, **54**, 10265–10274.

4 (*a*) M. Shimizu, M. Kawamoto and Y. Niwa, *Chem. Commun.*, 1999, 1151–1152; (*b*) M. Shimizu, Y. Hayashi, R. Hamanaka and I. Hachiya, *Heterocycles*, 2007, **73**, 191–195.

5 (*a*) M. Shimizu, Y. Takeuchi and T. Sahara, *Chem. Lett.*, 2001, **30**, 1196–1197; (*b*) M. Shimizu and T. Sahara, *Chem. Lett.*, 2002, **31**, 888–889.

6 M. Shimizu, A. Iwata and H. Makino, *Synlett*, 2002, 1538–1540.

7 For *N*-alkylation to α-iminoesters in our laboratory: (*a*) M. Shimizu and Y. Niwa, *Tetrahedron Lett.*, 2001, **42**, 2829–2832; (*b*) Y. Niwa, K. Takayama and M. Shimizu, *Tetrahedron Lett.*, 2001, **42**, 5473–5476; (*c*) Y. Niwa, K. Takayama and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1819–1825; (*d*) Y. Niwa and M. Shimizu, *J. Am. Chem. Soc.*, 2003, **125**, 3720–3721; (*e*) M. Shimizu, H. Itou and M. Miura, *J. Am. Chem. Soc.*, 2005, **127**, 3296–3297; (*f*) I. Mizota, K. Tanaka and M. Shimizu, *Tetrahedron Lett.*, 2012, **53**, 1847–1850; (*g*) S. Hata, T. Maeda and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 1203–1205; (*h*) M. Shimizu, Y. Takao, H. Katsurayama and I. Mizota, *Asian J. Org. Chem.*, 2013, **2**, 130–134; (*i*) M. Shimizu, D. Kurita and I. Mizota, *Asian J. Org. Chem.*, 2013, **2**, 208–211; (*j*) T. Sano, I. Mizota and M. Shimizu, *Chem. Lett.*, 2013, **42**, 995–997; (*k*) I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka and M. Shimizu, *Org. Lett.*, 2013, **15**, 4206–4209; (*l*) H. Tanaka, I. Mizota and M. Shimizu, *Org. Lett.*, 2014, **16**, 2276–2279; (*m*) M. Shimizu, M. Tateishi and I. Mizota, *Chem. Lett.*, 2014, **43**, 1752–1754; (*n*) I. Mizota, T. Maeda and M. Shimizu, *Tetrahedron*, 2015, **71**, 5793–5799; (*o*) T. Tanaka, I. Mizota, K. Umezu, A. Ito and M. Shimizu, *Heterocycles*, 2017, **95**, 830–843; (*p*) M. Kawanishi, I. Mizota, K. Aratake, H. Tanaka, K. Nakahama and M. Shimizu, *Bull. Chem. Soc. Jpn.*, 2017, **90**, 395–403; (*q*) I. Mizota, Y. Nakajima, A. Higashino and M. Shimizu, *Arabian J. Sci. Eng.*, 2017, **42**, 4249–4261; (*r*) K. Nakahama, M. Suzuki, M. Ozako, I. Mizota and M. Shimizu, *Asian J. Org. Chem.*, 2018, **7**, 910–913; (*s*) I. Mizota, C. Ueda, Y. Tesong, Y. Tsujimoto and M. Shimizu, *Org. Lett.*, 2018, **20**, 2291–2296; (*t*) I. Mizota, Y. Tadano, Y. Nakamura, T. Haramiishi, M. Hotta and M. Shimizu, *Org. Lett.*, 2019, **21**, 2663–2667; (*u*) M. Shimizu, M. Mushika, I. Mizota and Y. Zhu, *RSC Adv.*, 2019, **9**, 23400–23407; (*v*) I. Mizota, M. Mori and M. Shimizu, *J. Heterocycl. Chem.*, 2020, **57**, 3002–3010; (*w*) M. Shimizu, Y. Furukawa, I. Mizota and Y. Zhu, *New J. Chem.*, 2020, **44**, 152–161; (*x*) I. Mizota, M. Maeda, K. Imoto and M. Shimizu, *Org. Lett.*, 2020, **22**, 3079–3083; (*y*) M. Shimizu, T. Morimoto, Y. Yanagi, I. Mizota and Y. Zhu, *RSC Adv.*, 2020, **10**, 9955–9963; (*z*) K. Ota, S. Fukumoto, T. Iwase, I. Mizota, M. Shimizu and I. Hachiya, *Synlett*, 2020, **31**, 1930–1936.

8 For reviews and accounts, see: (*a*) M. Shimizu, *Pure Appl. Chem.*, 2006, **78**, 1867–1876; (*b*) J. S. Dickstein and M. C. Kozlowski, *Chem. Soc. Rev.*, 2008, **37**, 1166–1173; (*c*) M. Shimizu, I. Hachiya and I. Mizota, *Chem. Commun.*, 2009, 874–889; (*d*) T. Nishi, I. Mizota and M. Shimizu, *Pure Appl. Chem.*, 2012, **84**, 2609–2617; (*e*) I. Mizota and M. Shimizu, *Chem. Rec.*, 2016, **16**, 688–702; (*f*) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2017, **117**, 8326–8419.

9 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko,

P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. P. Challacombe, M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision C.02*, Gaussian, Inc., Wallingford CT, 2004.

10 For aldol reaction, see: (*a*) T. Mukaiyama, *Org. React.*, 1982, **28**, 203–331; (*b*) D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23–32; (*c*) I. Paterson, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, vol. 2, pp. 301–319; (*d*) E. M. Carreira, A. Fettes and C. Martl, *Org. React.*, 2006, **67**, 1–216; (*e*) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600–1632; (*f*) H. Zhang, M. Han, T. Chen, L. Xu and L. Yu, *RSC Adv.*, 2017, **7**, 48214–48221; (*g*) Y. Yamashita, T. Yasukawa, W.-J. Yoo, T. Kitanosono and S. Kobayashi, *Chem. Soc. Rev.*, 2018, **47**, 4388–4480.

11 (*a*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785–789; (*b*) A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098–3100.

12 M. Shimizu and H. Makino, *Tetrahedron Lett.*, 2001, **42**, 8865–8868.

13 M. Springborg, *Methods of Electronic-Structure Calculations from Molecules to Solids*, John Wiley & Sons, New York, 2000.

14 (*a*) N. A. Mcgrath and R. T. Raines, *Acc. Chem. Res.*, 2011, **44**, 752–761; (*b*) H. M. Burke, L. McSweeney and E. M. Scanlan, *Nat. Commun.*, 2017, **8**, 15655; (*c*) V. Hirschbeck, P. H. Gehrtz and I. Fleischer, *Chem.–Eur. J.*, 2018, **24**, 7092–7107.

15 (*a*) D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580–2627; (*b*) A. Viso, R. Fernández de la Pradilla, A. García and A. Flores, *Chem. Rev.*, 2005, **105**, 3167–3196; (*c*) S. S. R. S. Kotti, C. Timmons and G. Li, *Chem. Biol. Drug Des.*, 2006, **67**, 101–114; (*d*) F. Cardona and A. Goti, *Nat. Chem.*, 2009, **1**, 269–275; (*e*) A. Viso, R. Fernández de la Pradilla, M. Tortosa, A. García and A. Flores, *Chem. Rev.*, 2011, **111**, PR1–PR42; (*f*) K. Muñiz, L. Barreiro, R. M. Romero and C. Martínez, *J. Am. Chem. Soc.*, 2017, **139**, 4354–4357; (*g*) S. Lee, Y. J. Jang, E. J. T. Phipps, H. Lei and T. Rovis, *Synthesis*, 2020, **52**, 1247–1252.