Pergamon

Tetrahedron 58 (2002) 9817–9826

TETRAHEDRON

Magnesium cation-induced *anti*-aldol selective tandem Michael/aldol reaction

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Received 8 July 2002; accepted 4 October 2002

Abstract—A mixture of magnesium thiolate or selenolate, β-substituted-α,β-unsaturated ester and aldehyde affords a Michael/aldol tandem adduct, α-phenylthio- or α-phenylselenoalkyl-β-hydroxyester, in a good yield. The reaction proceeded in *anti*-aldol selective manner, which is contrast to the products from a similar reaction in the presence of lithium cation. An NMR study and an experiment for trapping the reaction intermediates suggest that magnesium thiolate, which forms precipitate in the reaction mixture, first attacks the aldehyde, not the unsaturated ester, to give α-alkoxysulfide.

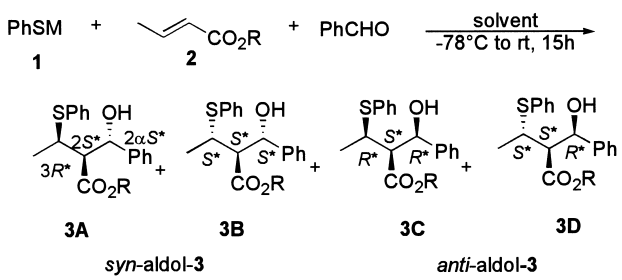
1. Introduction

Efficiency in organic synthesis is as much of interest as selectivity of organic reaction in these days. Tandem or domino strategy provides an attractive answer for this requirement.[1] The aldol and the Michael reactions are most frequently used as tools for constructing carbon backbones.[2] We have recently focused our investigation on tandemization of these two reactions[3] and reported stereoselective Michael/aldol tandem process triggered by lithium thiolates and their analogues.[4] In this process, high *syn*-aldol selectivity was observed and we have applied to stereoselective construction of tetrahydrofurans.[5] Extension of this procedure to crotonate esters, however, resulted in less aldol-selective formation of the tandem adducts, in which *anti*-Michael type selectivity was observed instead. This drawback of the methodology prompted us to improve the tandem procedure. Among many kinds of metal cations, we focused on magnesium cation for this purpose[6] and found that good *anti*-aldol selectivity was achieved.[7] In this paper, we report the full detail of our investigation on the magnesium thiolate or selenolate-induced Michael/aldol tandem reaction.

2. Results and discussion

Magnesium thiolate was generated from corresponding thiol and methyl magnesium bromide. Treatment of thiophenol, for example, with commercially available methylmagnesium bromide gave magnesium thiophenolate as a white precipitate in CH_2Cl_2. To the mixture, a solution of benzaldehyde and methyl crotonate in CH_2Cl_2 was added at −78°C; the reaction mixture was still heterogeneous but the precipitate gradually solved within 15 h. Usual work up followed by chromatographic purification gave tandem Michael/aldol adduct **3** (Scheme 1). Results are summarized in Table 1.

Desired compound **3a** was isolated in 75% yield, which was much better yield than the corresponding reaction in the presence of lithium cation. An HPLC analysis, however, indicated that the diastereomeric ratio of the adducts was 22/0/40/38. To improve the stereoselectivity, we examined *tert*-butyl crotonate for the reaction (entry 2). Similar reaction conditions for *tert*-butyl crotonate led the tandem reaction successfully to give adduct **3b** in 73% yield.



Scheme 1.

Keywords: Michael addition; diastereoselection; aldol reactions.

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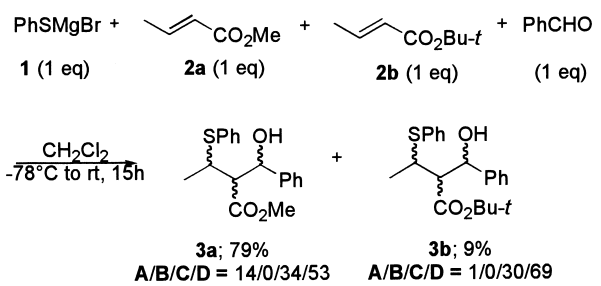
0040–4020/02/$ - see front matter
PII: S0040-4020(02)01299-1

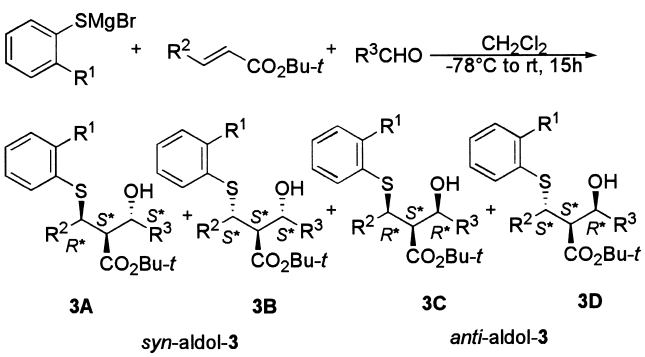
Table 1. Magnesium ion-induced Michael/aldol tandem addition to crotonate under various conditions

Entry	R	M^+	Solvent	**3**;yield (%)[a]	**A/B/C/D**[b]	*syn*(**A**+**B**)/*anti*(**C**+**D**)
1	Me	MgBr	CH_2Cl_2	**3a**; 75	22/0/40/38	22/78
2	*t*-Bu	MgBr	CH_2Cl_2	**3b**; 73	5/1/32/62	6/94
3	*t*-Bu	Li	CH_2Cl_2	**3b**; 55	53/1/45/1	54/46
4	*t*-Bu	MgBr	Ether	**3b**; 73	11/3/48/38	14/86
5	*t*-Bu	MgBr	Toluene	**3b**; 69	3/0/52/45	3/97
6	*t*-Bu	MgBr	THF	**3b**; 80	27/12/56/5	39/61
7	*t*-Bu	Na	CH_2Cl_2	**3b**; 0	–	–
8	*t*-Bu	K	CH_2Cl_2	**3b**; 0	–	–
9	*t*-Bu	ZnSPh	CH_2Cl_2	**3b**; 0	–	–

[a] Isolated yield.
[b] Determined by HPLC analyses.



Scheme 2.



Scheme 3.

Diastereomeric ratio of **3b** was found to be 5/1/32/62, i.e. two out of four possible diastereomers of **3b** were formed selectively. Comparison of NMR and HPLC data showed both of the two main adducts, diastereomer **C** and **D**, contained *anti*-aldol configuration. This selectivity was contrast to the lithium cation-induced Michael/aldol reaction that proceeded with *anti*-Michael selectivity (entry 3).[4] Ether and toluene worked as a useful solvent for the reaction (entries 4 and 5). To our surprise, THF as a solvent promoted the reaction smoothly to give the tandem adduct in good yield, but the *anti*-aldol selectivity disappeared (entry 6). Other counter cations of thiolate such as sodium, potassium or zinc were revealed to be useless for the reaction (entries 7–9). Competitive reaction between methyl and *tert*-butyl crotonates gave a mixture of **3a** and **3b** in 79 and 9% yield, respectively, but the selectivity of the reaction unchanged (Scheme 2). This indicated that methyl crotonate reacted faster than *tert*-butyl ester by about nine times.

We next apply the reaction to various of α,β-unsaturated esters, thiolates, and aldehydes (Scheme 3). Table 2 summarizes the results.

Aromatic aldehydes underwent smooth reaction progress with *tert*-butyl crotonate to give tandem adducts **3** in good yields (entries 1–4). The *anti*-aldol selectivity, combined

Table 2. Michael/aldol tandem addition with magnesium thiolates

Entry	R^1	R^2	R^3	**3**; yield (%)[a]	**A/B/C/D**[b]	*syn*/*anti*[b]
1	H	Me	*p*-$MeOC_6H_4$–	**3c**; 79	5/1/32/62	9/91
2	H	Me	*p*-ClC_6H_4–	**3d**; 71	1/1/28/70	2/98
3	H	Me	2,4,6-$Me_3C_6H_2$–	**3e**; 56	57/2/31/10	59/41
4	H	Me	1-$C_{10}H_7$–[c]	**3f**; 69	3/0/16/81	3/97
5	H	Me	C_5H_{11}–	**3g**; trace	n/d	
6	Me	Me	Ph	**3h**; 74	2/1/24/73	3/97
7	Me	Me	1-$C_{10}H_7$–[c]	**3i**; 94	1/0/16/83	1/99
8	Br	Me	Ph	**3j**; 85	2/0/38/60	2/98
9	Br	Me	*p*-$MeOC_6H_4$–	**3k**; 66	9/3/47/41	12/88
10	Br	Me	1-$C_{10}H_7$–	**3l**; 93	2/0/23/75	2/98
11	H	C_3H_7–	Ph	**3m**; 66	7/1/30/62	8/92
12	H	C_3H_7–	*p*-$MeOC_6H_4$–	**3n**; 68	16/2/33/49	18/82
13	Me	C_3H_7–	Ph	**3o**; 66	7/1/30/62	8/92
14	Br	C_3H_7–	Ph	**3p**; 59	3/0/38/59	3/97
15	H	Me_2CH–	Ph	**3q**; 24	3/1/14/82	4/96
16	Br	Me_2CH–	Ph	**3r**; 28	5/0/14/81	5/95

[a] Isolated yield.
[b] Determined by HPLC analyses.
[c] 1-$C_{10}H_7$–=1-naphthyl.

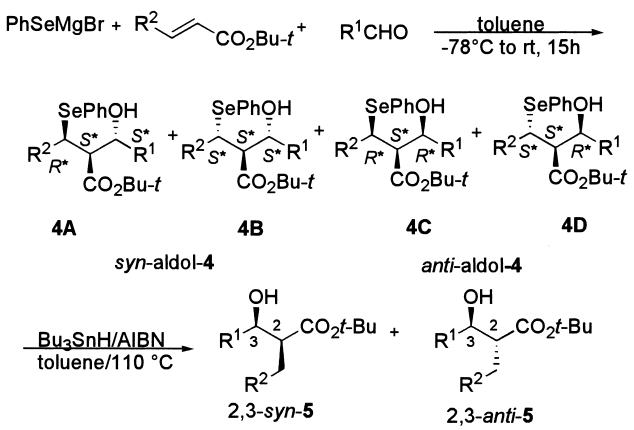
ratios of diastereomer **C** and **D**, were normally higher than 90/10 except for the reaction of 2,4,6-trimethylbenzaldehyde, in which the yield and stereoselectivity remained in the moderate level due to steric hindrance of the aldehyde (entry 3). High **D** selectivity was observed for the reaction 1-naphthaldehyde, in which **3f**-**D** was formed in more than 80/20 ratio (entry 4). Aliphatic aldehyde gave the adduct in poor yield (entry 5).

It should be remarked that use of *ortho*-substituted thiophenols always enhanced the *anti*-aldol electivity. For example, the reaction with *o*-thiocresol raised the selectivity to 3/97 (entry 3, Table 1 vs entry 6, Table 2). Existence of Br group at the *ortho* position also increased the *anti*-aldol selectivity to 2/98 (entries 8 and 10).

This procedure is also useful for the reaction with *tert*-butyl 2-hexenoate to give corresponding tandem adduct *anti*-aldol selectively (entries 11–14). Again, the presence of *ortho*-substituent in thiolate enhanced the stereoselectivity into good level (entries 13 and 14). Sterically demanding β-substituent in the enonate also gave *anti*-aldol adduct preferentially, but the yields were rather low (entries 15 and 16). Neither *tert*-butyl tiglate nor *tert*-butyl crotonamide gave the corresponding tandem adducts. This is probably due to low reactivity caused by steric and/or electronic reason.

This procedure was applied to selenolate nucleophile (Scheme 4). Results are summarized in Table 3.

Magnesium selenolate was generated by treatment of



Scheme 4.

Table 3. Michael/aldol tandem addition of magnesium selenolate

Entry	R^1	R^2	**4**; yield (%)[a]	**A/B/C/D**[b]	**5**; yield (%)[a]	*syn*/*anti*[b]
1	Ph	Me	**4a**; 69	3/0/52/45	**5a**; 89	3/97
2	*p*-MeC_6H_4–	Me	**4b**; 77	6/2/57/36	**5b**; 93	4/96
3	*p*-ClC_6H_4–	Me	**4c**; 52	4/0/57/38	**5c**; 98	2/98
4	*m*-$MeOC_6H_4$–	Me	**4d**; 59	5/1/53/41	**5d**; 99	5/95
5	C_5H_{11}–	Me	**4e**; 8	n/d		
6	Ph	C_3H_7–	**4f**; 38	4/0/46/50	**5f**; 91	2/98
7	*p*-MeC_6H_4–	C_3H_7–	**4g**; 63	9/1/50/40	**5g**; 97	6/94

[a] Isolated yield.
[b] Determined by HPLC analyses.

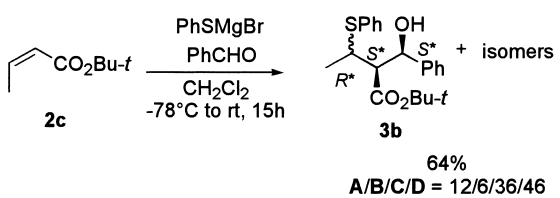
diphenyldiselenide with methyl magnesium bromide.[8] Although the half amount of selenium source was wasted by forming methylphenyl selenide, the unpleasant preparation of toxic phenyl selenol was eliminated with this procedure. Toluene was the best choice of the solvent, and tandem adducts **4** with aromatic aldehydes were obtained in good yields. The reaction of benzaldehyde and *tert*-butyl crotonate, for example, afforded tandem adduct **4a** in 69% yield in which the ratio of the four diastereomers was 3/0/52/45 (entry 1). Diastereomers **C** and **D** were again formed in a similar level of the selectivity to the tandem reaction of thiols (entries 2–4). On the other hand, aliphatic aldehydes showed poor reactivity toward the reaction and trace amounts of adduct **4e** was observed (entry 5). 2-Hexenoate also underwent the reaction to give tandem adducts in good yield (entries 6 and 7).

Removal of the phenylseleno group in **4** afforded *anti*-aldol **5** in almost diastereomerically pure form. For example, treatment of **4a** with Bu_3SnH in the presence of AIBN resulted in the formation of **5a** in 89% yield, in which *anti*-**5a** was consisted as a major component in a ratio of 97/3. Thus, this Michael/aldol and subsequent removal of the phenylseleno group provide a convenient method to prepare *anti*-aldols from β-substituted-α,β-unsaturated esters.

The stereochemistry of the tandem adducts was determined by comparison of NMR and HPLC behaviors with the compounds which have known configuration in the previous results.[4] *anti*-Aldol configuration in series of diastereomers **C** and **D**, for example, was determined by comparison with **4a**-**A**, *syn*-aldol configuration of which was unambiguously revealed in its X-ray crystallographic analysis.[4a,4c] Configuration of **3r**-**D** was determined by X-ray crystallographic analysis.[9]

It is interesting whether the geometry of the starting alkene affected to the stereoselectivity. *Z*-*tert*-Butyl crotonate **2c** was prepared in the Ando's method[10] and its tandem reaction was examined. Desired product **3b** was isolated in a similar yield and the products ratio of the four diastereomers was 12/6/36/46 (Scheme 5). The *anti*-aldol selectivity was also seen, but it was lower than the reaction from *E*-crotonate.[11]

The *anti*-aldol products **C** and **D** were obtained as major components in the most of the reactions, while the ratios of between **C** and **D** usually lay around 3/7 to 2/8. This ratio did not change much with the concentration of the substrates. For example, compound **3b** was obtained as a mixture of the four isomers in the ratio of 5/1/32/61, which was unchanged very much in the reaction under 10 times thinner conditions. Exposure of disatereomerically pure **3b**-**A** to magnesium thiolate resulted in the complete



Scheme 5.

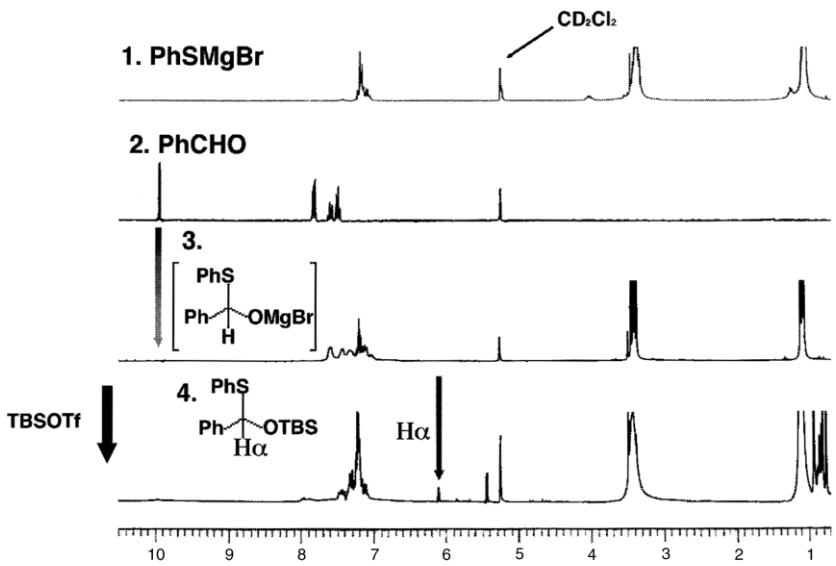


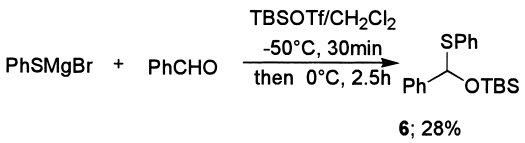
Figure 1. NMR observation of PhSMgBr in CD_2Cl_2.

recovery of pure **3b**-**A**; neither decomposed products of **3b** nor isomerized products **3b**-**C** or **3b**-**D** were observed. This suggests that product ratios of **3** under the present reaction conditions are determined kinetically and no isomerization occurs during the reaction progress.

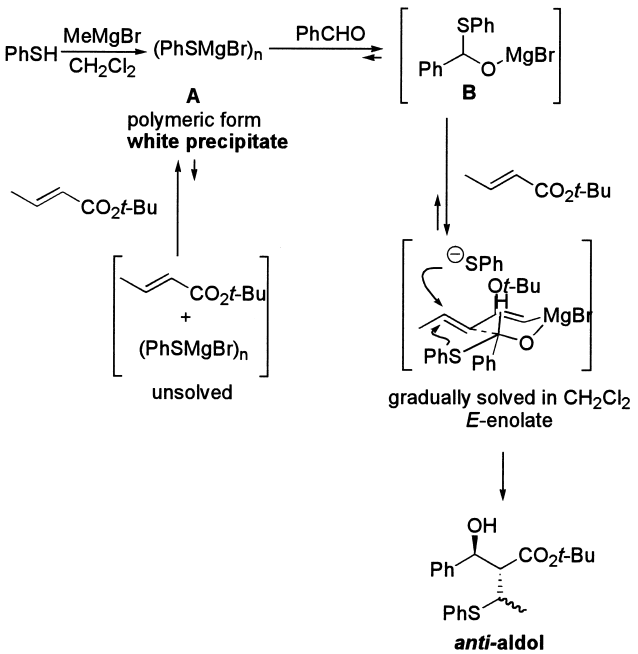
The present *anti*-aldol selectivity was in contrast to the reaction induced by lithium thiolate. This suggests that the former reaction should pass through a different mechanism from the latter. To investigate the reaction pathway, an NMR study for the reaction was attempted. The observed NMR spectra were summarized in Fig. 1.

Addition of methylmagnesium bromide to a solution of thiophenol in CD_2Cl_2 caused immediate formation of white precipitate of magnesium thiophenolate. An NMR spectrum for the supernatant of the mixture showed only small peaks in aromatic region so that the most part of thiolate existed in the solid phase, not in the solution phase (Fig. 1, chart 1). When benzaldehyde, which is shown in the second row of the charts, was added to the mixture, the spectrum changed to the third row chart, in which the peaks from the aldehyde disappeared. The reaction mixture was still heterogeneous so that most part of the aldehyde went to the solid phase by formation of complex with magnesium thiolate. To trap an intermediate, TBSOTf was added to the mixture instead of *tert*-butyl crotonate. The heterogeneous mixture turned to homogeneous and the two new peaks appeared around 5.5 and 6.2 ppm (the bottom chart in Fig. 1). The former peak was assigned to be the methylene proton of bis(phenylthio)-methane, which should be formed by the direct substitution of CH_2Cl_2 by magnesium thiolate. We wondered what species the other peak at 6.2 ppm represented and attempted to isolate it from the reaction mixture. The same reaction in a preparative scale gave the latter product, which was purified through chromatographic treatment along with partial decomposition. The compound isolated was found to be α-*tert*-butyldimethylsilyloxy phenyl sulfide **6**, the structure of which was identified by NMR and micro-analysis (Scheme 6). It is in contrast to the fact that none of **6** was formed when TBSOTf was added to the mixture of lithium thiolate and benzaldehyde. Although a mixture of **6** and *tert*-butyl crotonate in CH_2Cl_2 did not give **3b**, these results suggest that nucleophilic magnesium thiolate first attacks benzaldehyde to give 1,2-adducts in the solid phase of the reaction mixture.

Combining the NMR results and the experimental data, plausible reaction mechanism is presented in Scheme 7.



Scheme 6.



Scheme 7.

Magnesium thiolate precipitates in CH_2Cl_2. The precipitate hardly solved in CH_2Cl_2 even in the presence of crotonates or aldehydes. If the tandem reaction occurred from the three components-complex such as the reaction in the presence of lithium cation does, *syn*-aldol selectivity should be observed. In the actual experiment, however, the opposite high *anti*-aldol selectivity was achieved. Thus, the reaction passes through a different mechanism from the lithium cation induced-reaction. As seen before, PhSMgBr possesses nucleophilicity which promotes the 1,2-addition to give intermediate **B** in solid phase. The magnesium ion in this intermediate should be Lewis acidic and added crotonate coordinates to **B** in solid phase. The aldol reaction happens from this complex by internal or external attack of thiolate (structure **C**), which generate *E*-enolate giving *anti*-aldol selectively. Geometry of the starting alkene slightly affects the stereoselectivity since *Z*-crotonate underwent less selective aldol reaction (see Scheme 5) than *E*-crotonate. This should be because preference of transition structure of **C** depends on the β-substituent of the Michael acceptor, but the difference becomes small probably because isomerization of crotonate catalyzed by thiolate should occur prior to the desired reaction.

In conclusion, we have provided a new type of Michael/aldol tandem reaction triggered with magnesium thiolate. High *anti*-aldol selectivity as well as high yield of the adduct was achieved by the use of magnesium cation as the counter cation. Mechanistic study suggests that magnesium thiolate underwent 1,2-addition to aldehyde first, then the desired aldol reaction should take place from this complex. Further application of the adducts are now underway in our laboratory.

3. Experimental

3.1. General

All ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on JEOL EX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C) or Brucker Advance 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. Solvents used in the reaction described here were dried over appropriate drying agents (K for THF, Na for ether and toluene, and CaH_2 for all other solvents) and distilled under nitrogen before use. Aldehydes were purified by distillation. Bu_3SnH, thiophenol and diphenyldiselenide, which were purchased from Aldrich, were used without further purification. *E*-α,β-Unsaturated esters were prepared from corresponding acid and isobutene. *Z*-α,β-Unsaturated ester was prepared by Ando's method.

3.2. Michael/aldol tandem reaction to α,β-unsaturated esters with magnesium thiolate

3.2.1. Preparation of *tert*-butyl 2-(hydroxyphenylmethyl)-3-phenylsulfanylbutyrate (3b): general procedure. To a solution of thiophenol (0.242 g, 2.20 mmol) in CH_2Cl_2 (2 mL) was added methylmagnesium bromide in ether (3 M, 0.73 mL, 2.2 mmol) at −78°C and the resulting magnesium thiophenolate precipitated as white solid. To the heterogeneous mixture, *tert*-butyl crotonate (0.284 g, 2.00 mmol) and benzaldehyde (0.212 g, 2.00 mmol) were added at −78°C. The resulting mixture was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 5 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, crude product was purified with flash chromatography (silica gel/hexane–ether 20:1 then 3:1 v/v) and desired tandem product **3b** was obtained in 73% yield (0.512 g, 1.42 mmol) as pale yellow oil. HPLC analysis indicated disatereomeric ratio of **A/B/C/D** was 5/1/32/62. Diastereomers **A**, **C** and **D** were isolated in pure form by further chromatographic separation.

Compound **3b-A**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.43 (d, J=7.3 Hz, 3H), 2.95 (dd, J=4.3, 8.9 Hz, 1H), 3.78 (dq, J=4.6, 7.3 Hz, 1H), 5.20 (dd, J=4.2, 8.9 Hz, 1H), 7.20–7.60 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.0, 27.8, 43.6, 59.0, 73.4, 81.4, 127.1, 127.4, 128.1, 128.3, 128.9, 131.6, 136.1, 141.8, 170.2. IR: 3300–3600, 1720 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.37; H, 7.51.

Compound **3b-C**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.43 (d, J=7.3 Hz, 3H), 2.76 (dd, J=5.0, 8.9 Hz, 1H), 3.43 (qd, J=6.9, 8.9 Hz, 1H), 3.6–3.8 (br, 1H), 5.03 (d, J=5.0 Hz, 1H), 7.20–7.60 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.0, 27.8, 43.5, 58.0, 72.2, 82.2, 125.8, 126.8, 127.5, 128.2, 128.8, 130.1, 133.9, 141.8, 172.8. IR: 3300–3600, 1720 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.13; H, 7.53.

Compound **3b-D**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.34 (d, J=6.9 Hz, 3H), 2.74 (dd, J=4.6, 8.9 Hz, 1H), 3.52 (qd, J=6.9, 8.9 Hz, 1H), 3.6–3.8 (br, 1H), 5.35 (d, J=4.6 Hz, 1H), 7.15–7.51 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.5, 27.8, 42.9, 57.5, 72.3, 82.1, 125.7, 127.4, 127.5, 128.2, 128.8, 128.9, 133.1, 141.9, 172.7. IR: 3300–3600, 1720 cm^{-1}.

3.2.2. Methyl 2-(hydroxyphenylmethyl)-3-phenylsulfanylbutyrate (3a). Exact mass determination: 316.1152 (calcd $C_{12}H_{20}O_3S$: 316.1133).

Compound **3a-C**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (d, J=6.9 Hz, 3H), 2.91 (dd, J=5.9, 7.9 Hz, 1H), 3.34–3.45 (m, 2H), 3.60 (s, 3H), 5.11 (t, J=6.4 Hz, 1H), 7.23–7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.1, 43.2, 51.7, 72.5, 125.8, 127.4, 127.8, 128.4, 128.8, 132.8, 133.0, 141.5, 173.5. IR: 3300–3600, 1720 cm^{-1}.

Compound **3a-D**. ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (d, J=6.9 Hz, 3H), 2.90 (dd, J=5.9, 7.6 Hz, 1H), 3.22 (br, 1H), 3.37 (dq, J=4.3 Hz, 6.9 Hz, 1H), 3.59 (s, 3H), 5.30 (t, J=6.5 Hz, 1H), 7.25–7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.4, 42.2, 51.5, 56.8, 72.6, 125.7, 127.4, 127.7, 128.3, 128.4, 128.8, 132.9. 141.4, 173.3. IR: 3300–3600, 1720 cm^{-1}.

3.2.3. *tert*-Butyl 2-[hydroxy(4-methoxyphenyl)methyl]-3-phenylsulfanylbutyrate (3c). Anal. calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26. Found: C, 67.75; H, 7.55.

Compound **3c-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.41 (d, J=6.6 Hz, 3H), 2.72 (dd, J=3.0, 5.3 Hz, 1H), 3.37 (qd, J=6.6, 8.3 Hz, 1H), 3.81 (s, 3H), 5.00 (dd, J=5.6, 8.3 Hz, 1H), 6.85–7.44 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.1, 27.9, 43.5, 55.3, 58.2, 72.0, 82.1, 113.6, 127.1, 127.3, 128.9, 133.9, 134.0, 172.7. IR: 3300–3600, 1720 cm^{-1}.

Compound **3c-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.32 (d, J=7.3 Hz, 3H), 2.76 (dd, J=3.3, 5.3 Hz, 1H), 3.47 (qd, J=6.9, 8.3 Hz, 1H), 3.81 (s, 3H), 5.25 (dd, J=5.0, 7.3 Hz, 1H), 6.85–7.44 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.2, 27.9, 42.8, 55.3, 57.3, 72.1, 82.1, 113.7, 127.0, 127.4, 128.8, 133.0, 134.0, 159.0, 172.8. IR: 3300–3600, 1720 cm^{-1}.

3.2.4. *tert*-Butyl 2-[hydroxy(4-chlorophenyl)methyl]-3-phenylsulfanylbutyrate (3d). Anal. calcd for $C_{21}H_{25}ClO_3S$: C, 64.19; H, 6.41. Found: C, 64.02; H, 6.69.

Compound **3d-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.43 (d, J=6.9 Hz, 3H), 2.72 (dd, J=4.9, 8.9 Hz, 1H), 3.42 (qd, J=6.6, 8.9 Hz, 1H), 4.99 (d, J=5.6 Hz, 1H), 7.21–7.48 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.0, 27.9, 43.5, 57.7, 71.6, 82.5, 127.2, 127.5, 128.5, 128.9, 133.1, 133.8, 140.4, 172.6. IR: 3100–3650, 1720 cm^{-1}.

Compound **3d-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.34 (d, J=8.3 Hz, 3H), 2.67 (dd, J=4.3, 9.2 Hz, 1H), 3.54 (qd, J=6.9, 8.9 Hz, 1H), 5.34 (d, J=5.6 Hz, 1H), 7.21–7.48 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.7, 27.8, 43.0, 57.4, 71.7, 82.5, 127.1, 127.6, 128.3, 129.0, 133.0, 133.2, 133.7, 140.7, 172.6. IR: 3300–3600, 1720 cm^{-1}.

3.2.5. *tert*-Butyl 2-[hydroxy-(2,4,6-trimethylphenyl)-methyl]-3-phenylsulfanylbutyrate (3e). Anal. calcd for $C_{24}H_{32}O_3S$: C, 71.96; H, 8.05. Found: C, 71.84; H, 8.41.

Compound **3e-A**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.49 (d, J=6.9 Hz, 3H), 2.22 (s, 6H), 2.49 (s, 3H), 3.38 (dd, J=4.7, 9.6 Hz, 1H), 3.80 (dq, J=4.9, 7.0 Hz, 1H), 5.72 (dd, J=3.0, 10.0 Hz, 1H), 6.99–7.58 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.7, 20.9, 27.3, 28.2, 44.9, 56.3, 69.7, 80.8, 126.6, 128.6, 128.8, 128.9, 130.4, 131.4, 132.5, 137.5, 170.2. IR: 3100–3700, 1720 cm^{-1}.

3.2.6. *tert*-Butyl 2-(hydroxynaphthalen-1-ylmethyl)-3-phenylsulfanylbutyrate (3f). Anal. calcd for $C_{25}H_{28}O_3S$: C, 73.50; H, 6.91. Found: C, 73.17; H, 7.20.

Compound **3f-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.58 (d, J=6.6 Hz, 3H), 3.06 (dd, J=4.0, 9.2 Hz, 1H), 3.60 (qd, J=6.9, 9.2 Hz, 1H), 4.25–4.35 (br, 1H), 5.79 (br, 1H), 7.17–8.28 (12H, m, Ar). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.3, 28.3, 44.4, 56.7, 70.0, 82.8, 123.0, 124.1, 125.6, 125.9, 126.6, 127.8, 128.6, 129.3, 130.5, 132.8, 133.3, 134.1, 135.2, 137.7, 173.4.. IR: 3100–3700, 1700 cm^{-1}.

Compound **3f-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.38 (d, J=6.9 Hz, 3H), 2.97 (dd, J=3.3, 9.9 Hz, 1H), 3.79 (qd, J=6.9, 9.9 Hz, 1H), 4.25–4.35 (br, 1H), 6.15 (br, 1H), 7.11–8.03 (m, 12H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.7, 28.3, 44.6, 57.1, 70.0, 82.8, 123.3, 123.6, 125.6, 125.9, 126.7, 127.7, 128.5, 129.5, 130.5, 132.8, 133.3, 134.1, 135.2, 138.1, 173.4. IR: 3100–3700, 1700 cm^{-1}.

3.2.7. *tert*-Butyl 2-(hydroxyphenylmethyl)-3-*o*-tolylsulfanylbutyrate (3h). Exact mass determination: 372.1729 (calcd $C_{22}H_{28}O_3S$: 372.1759).

Compound **3h-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.42 (d, J=6.6 Hz, 3H), 2.41 (s, 3H), 2.79 (dd, J=4.6, 8.9 Hz, 1H), 3.46 (qd, J=6.0, 8.9 Hz, 1H), 5.05 (d, J=4.6 Hz, 1H), 7.12–7.50 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.8, 20.8, 27.8, 43.0, 57.8, 72.0, 82.2, 125.8, 126.4, 127.3, 127.5, 128.2, 128.3, 132.6, 133.5, 140.4, 141.7, 172.8. IR: 3100–3650, 1690 cm^{-1}.

Compound **3h-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.32 (d, J=6.9 Hz, 3H), 2.40 (s, 3H), 2.82 (dd, J=5.0, 8.3 Hz, 1H), 3.50 (qd, J=6.9, 8.3 Hz, 1H), 5.27 (d, J=5.3 Hz, 1H), 7.12–7.64 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.2, 20.8, 27.8, 42.1, 57.7, 72.4, 82.2, 125.8, 126.4, 127.4, 127.5, 128.2, 128.3, 130.4, 133.0, 140.4, 141.9, 172.6. IR: 3100–3650, 1690 cm^{-1}.

3.2.8. *tert*-Butyl 2-(hydroxynaphthalen-1-ylmethyl)-3-*o*-tolylsulfanylbutyrate (3i). Anal. calcd for $C_{26}H_{30}O_3S$: C, 73.90; H, 7.16. Found: C, 73.53; H, 7.24.

Compound **3i-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.57 (d, J=6.6 Hz, 3H), 2.39 (s, 3H), 3.05 (dd, J=5.3, 9.3 Hz, 1H), 3.65 (quint, J=6.5 Hz, 1H), 4.39 (br, 1H), 5.82 (br, 1H), 7.11–8.05 (m, 11H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.5, 20.8, 27.4, 43.2, 55.9, 69.5, 82.1, 122.3, 123.5, 124.8, 125.1, 126.1, 126.3, 126.9, 127.1, 128.4, 129.0, 130.0, 130.3, 133.7, 136.4, 137.1, 140.0, 172.9. IR: 3100–3600, 1680 cm^{-1}.

Compound **3i-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.33 (d, J=6.9 Hz, 3H), 2.45 (s, 3H), 3.02 (dd, J=3.6, 9.6 Hz, 1H), 3.72 (quint, J=7.5 Hz, 1H), 4.30 (br, 1H), 6.12 (br, 1H), 7.11–8.05 (m, 11H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.9, 20.8, 27.7, 43.2, 56.5, 69.1, 82.2, 122.8, 123.2, 124.8, 125.0, 125.4, 126.2, 126.4, 127.3, 128.0, 128.8, 130.4, 132.8, 133.6, 135.2, 137.5, 140.0, 172.8. IR: 3100–3600, 1680 cm^{-1}.

3.2.9. *tert*-Butyl 3-(2-bromophenylsulfanyl)-2-(hydroxyphenylmethyl)butyrate (3j). *Compound* **3j-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.49 (d, J=6.6 Hz, 3H), 2.84 (dd, J=5.0, 8.3 Hz, 1H), 3.72 (dq, J=5.6, 6.3 Hz, 1H), 5.09 (d, J=4.9 Hz, 1H), 7.04–7.59 (m, 8H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.7, 27.7, 42.5, 57.7, 71.9, 82.0, 125.7, 127.3, 127.5, 127.8, 128.1, 128.1, 131.1, 133.0, 135.7, 141.5, 172.1. IR: 3100–3600, 1680 cm^{-1}. Anal. calcd for $C_{21}H_{25}BrO_3S$: C, 57.67; H, 5.76. Found: C, 57.62; H, 6.04.

Compound **3j-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.38 (d, J=6.9 Hz, 3H), 2.87 (dd, J=5.3, 8.3 Hz, 1H), 3.62 (qd, J=6.9, 8.3 Hz, 1H), 5.24 (d, J=5.3 Hz, 1H), 7.04–7.59 (m, 8H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.5, 27.7, 41.5, 57.3, 72.2, 82.0, 125.7, 127.4, 127.6, 127.8, 128.1, 128.1, 132.1, 133.0, 133.1, 141.5, 172.0. IR: 3120–3650, 1690 cm^{-1}. Anal. calcd for $C_{21}H_{25}BrO_3S$: C, 57.67; H, 5.76. Found: C, 57.44; H, 5.53.

3.2.10. *tert*-Butyl 3-(2-bromophenylsulfanyl)-2-[hydroxy(4-methoxyphenyl)methyl]butyrate (3k). Anal. calcd for $C_{22}H_{27}BrO_4S$: C, 56.53; H, 5.82. Found C, 56.86; H, 6.06.

Compound **3k-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.43 (d, J=6.6 Hz, 3H), 2.81 (dd, J=5.5, 7.9 Hz, 1H), 3.46 (quint, J=7.1 Hz, 1H), 3.74 (s, 3H), 5.04 (d, J=5.9 Hz, 1H), 6.83 (d, J=6.6 Hz, 2H), 7.01–7.58 (m, 6H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.8, 27.7, 42.3, 55.0, 58.0, 71.7, 81.9, 113.4, 126.1, 127.0, 127.3, 127.7, 130.8, 132.0, 133.5, 136.3, 158.8, 172.0. IR: 3300–3600, 1710 cm^{-1}.

Compound **3k-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.36 (d, J=7.0 Hz, 3H), 2.85 (dd, J=6.4, 7.6 Hz, 1H), 3.52 (quint, J=7.1 Hz, 1H), 3.76 (s, 3H), 5.09 (d, J=6.2 Hz, 1H), 6.86 (d, J=6.6 Hz, 2H), 7.01–7.58 (m, 6H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.8, 27.7, 41.2, 55.0, 57.0, 72.0, 81.8, 113.5, 125.8, 127.0, 127.4, 127.5, 132.9, 133.0, 133.4, 135.7, 158.9, 172.0. IR: 3300–3600, 1710 cm^{-1}.

3.2.11. *tert*-Butyl 3-(2-bromophenylsulfanyl)-2-(hydroxynaphthalen-1-ylmethyl)butyrate (3l). Exact mass determination: 486.0886 (calcd $C_{25}H_{27}BrO_3S$: 486.0864).

Compound **3l-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.68 (d, J=6.9 Hz, 3H), 3.15–3.20 (m, 1H), 3.80–3.88 (m, 1H), 4.14 (br, 1H), 5.91 (br, 1H), 7.11–8.05 (m, 11H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.8, 27.6, 42.8, 55.6, 69.1, 82.2, 122.3, 123.5, 125.0, 125.1, 125.7, 127.4, 127.6, 127.8, 128.0, 128.8, 130.6, 133.0, 133.5, 133.5, 136.2, 137.0, 172.3. IR: 3300–3600, 1710 cm^{-1}.

Compound **3l-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.47 (d, J=6.9 Hz, 3H), 3.15 (dd, J=4.0, 8.9 Hz, 1H), 3.96 (qd, J=6.9, 8.6 Hz, 1H), 4.14 (br, 1H), 6.07 (br, 1H), 7.11–8.05 (m, 11H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.3, 27.6, 42.8, 56.4, 69.6, 82.2, 122.8, 123.3, 124.9, 125.3, 126.0, 126.1, 127.7, 127.8, 128.0, 128.8, 129.9, 132.0, 133.1, 133.5, 136.0, 137.1, 172.3. IR: 3300–3600, 1710 cm^{-1}.

3.2.12. *tert*-Butyl 2-(hydroxyphenylmethyl)-3-phenylsulfanylhexanoate (3m). Anal. calcd for $C_{23}H_{30}O_3S$: C, 71.46; H, 7.82. Found: C, 71.37; H, 8.04.

Compound **3m-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (t, 3H), 1.34 (s, 9H), 1.40–1.86 (m, 5H), 2.95 (dd, J=5.6, 7.6 Hz, 1H), 3.25 (dt, J=5.9, 7.3 Hz, 1H), 5.08 (d, J=5.6 Hz, 1H), 7.22–7.47 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 19.4, 27.9, 35.0, 48.7, 56.1, 72.4, 81.3, 126.1, 127.0, 127.6, 128.3, 128.8, 132.2, 135.1, 141.7, 172.7. IR: 3300–3600, 1710 cm^{-1}.

Compound **3m-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.34 (s, 9H), 1.40–1.86 (m, 5H), 2.79 (dd, J=4.6, 9.2 Hz, 1H), 3.44 (dt, J=3.3, 8.9 Hz, 1H), 5.42 (d, J=4.3 Hz, 1H), 7.22–7.47 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.8, 19.8, 27.8, 35.1, 49.1, 57.1, 72.1, 82.1, 125.7, 127.2, 127.3, 128.2, 128.9, 132.5, 135.0, 142.0, 173.1. IR: 3100–3700, 1730 cm^{-1}.

3.2.13. *tert*-Butyl 2-[hydroxy-(4-methoxyphenyl)methyl]-3-phenylsulfanylhexanoate (3n). Anal. calcd for $C_{24}H_{32}O_4S$: C, 69.20; H, 7.74. Found: C, 69.12; H, 8.01.

Compound **3n-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81 (t, J=6.9 Hz, 3H), 1.39 (s, 9H), 1.49 (m, 3H), 1.68 (m, 2H), 2.93 (t, J=6.6 Hz, 1H), 3.15 (q, J=6.6 Hz, 1H), 3.79 (s, 3H), 5.05 (d, J=6.3 Hz, 1H), 6.86–7.44 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.6, 19.6, 28.0, 35.5, 48.6, 55.3, 56.1, 72.3, 82.0, 113.7, 126.9, 127.1, 128.8, 130.8, 133.7, 135.0, 159.1, 172.6. IR: 3150–3700, 1740 cm^{-1}.

Compound **3n-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, J=6.9 Hz, 3H), 1.30 (s, 9H), 1.53 (m, 3H), 1.74 (m, 2H), 2.78 (dd, J=5.0, 8.6 Hz, 1H), 3.36 (dt, J=3.0, 8.6 Hz, 1H), 3.79 (s, 3H), 5.31 (d, J=5.0 Hz, 1H), 6.86–7.44 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 20.0, 27.9, 34.8, 49.0, 55.3, 57.0, 71.9, 82.0, 113.6, 127.0, 127.4, 128.9, 131.9, 132.5, 134.1, 158.9, 173.0. IR: 3150–3700, 1740 cm^{-1}.

3.2.14. *tert*-Butyl 2-(hydroxy-phenyl-methyl)-3-*o*-tolylsulfanylhexanoate (3o). Anal. calcd for $C_{24}H_{32}O_3S$: C, 71.96; H, 8.05. Found C, 71.58; H, 8.26.

Compound **3o-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (t, 3H), 1.34 (s, 9H), 1.50 (m, 3H), 1.73 (m, 2H), 2.39 (s, 3H), 2.98 (dd, J=5.9, 7.3 Hz, 1H), 3.31 (td, J=6.0, 7.3 Hz, 1H), 5.06 (d, J=5.6 Hz, 1H), 7.10–7.40 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.8, 19.1, 20.8, 27.9, 35.0, 47.7, 55.5, 72.3, 82.1, 126.1, 126.3, 126.7, 127.1, 127.6, 128.0, 131.4, 134.7, 139.5, 141.6, 172.7. IR: 3100–3650, 1690 cm^{-1}.

Compound **3o-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, 3H), 1.30 (s, 9H), 1.50 (m, 3H), 1.73 (m, 2H), 2.37 (s, 3H), 2.86 (dd, J=5.3, 8.3 Hz, 1H), 4.38 (dt, J=3.0, 7.3 Hz, 1H), 5.24 (d, J=5.3 Hz, 1H), 7.10–7.40 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 19.6, 20.7, 27.8, 34.8, 47.9, 56.9, 72.5, 82.0, 125.9, 126.4, 126.8, 127.4, 128.2, 130.3, 132.0, 139.4, 141.8, 172.8. IR: 3100–3650, 1690 cm^{-1}.

3.2.15. *tert*-Butyl 3-(2-bromophenylsulfanyl)-2-(hydroxyphenylmethyl)hexanoate (3p). Anal. calcd for $C_{23}H_{29}BrO_3S$: C, 59.35; H, 6.28. Found: C, 59.52; H, 6.49.

Compound **3p-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.37 (s, 9H), 1.60 (m, 2H), 1.80 (m, 2H), 3.04 (dd, J=5.9, 7.3 Hz, 1H), 3.45 (q, J=6.3 Hz, 1H), 3.75–3.85 (br, 1H), 5.12 (d, J=3.9 Hz, 1H), 7.04–7.57 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 19.1, 27.7, 35.0, 47.6, 55.6, 72.2, 82.0, 125.5, 126.0, 127.0, 127.6, 128.1, 130.7, 131.6, 132.9, 137.1, 141.5, 172.2. IR: 3100–3650, 1680 cm^{-1}.

Compound **3p-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, 3H), 1.34 (s, 9H), 1.60 (m, 2H), 1.80 (m, 2H), 2.94 (dd, J=5.3, 8.3 Hz, 1H), 3.58 (dt, J=3.0, 8.3 Hz, 1H), 3.65–3.75 (br, 1H), 5.25 (d, J=4.9 Hz, 1H), 7.04–7.57 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.8, 19.6, 27.7, 34.5, 47.7, 56.9, 72.3, 81.9, 125.8, 127.2, 127.4, 127.6, 128.1, 130.5, 131.6, 133.0, 136.8, 141.6, 172.5. IR: 3100–3650, 1680 cm^{-1}.

3.2.16. *tert*-Butyl 2-(hydroxyphenylmethyl)-4-methyl-3-phenylsulfanylpentanoate (3q). Exact mass determination: 386.1899 (calcd $C_{23}H_{30}O_3S$: 386.1916).

Compound **3q-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (d,

J=6.6 Hz, 3H), 1.12 (d, J=6.6 Hz, 3H), 1.19 (s, 9H), 1.98 (m, J=2.6, 6.6 Hz, 1H), 2.92 (dd, J=2.6, 11.6 Hz, 1H), 3.77 (dd, J=2.6, 11.6 Hz, 1H), 4.04 (d, J=10.6 Hz, 1H), 5.62 (dd, J=2.3, 10.6 Hz, 1H), 7.19–7.69 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.3, 22.2, 27.6, 31.8, 57.4, 57.8, 71.8, 82.1, 125.4, 126.4, 126.9, 128.0, 128.9, 130.9, 137.8, 142.5, 173.7. IR: 3300–3500, 1690 cm^{-1}.

3.2.17. *tert*-Butyl 3-(2-bromophenylsulfanyl)-2-(hydroxyphenylmethyl)-4-methylpentanoate (3r). *Compound* **3r-D**. Mp 115°C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.07 (d, J=6.6 Hz, 6H), 1.17 (s, 9H), 1.97 (dm, J=2.3, 6.6 Hz, 1H), 2.94 (dd, J=2.6, 11.6 Hz, 1H), 3.89 (dd, J=2.3, 11.5 Hz, 1H), 4.06 (d, J=10.6 Hz, 1H), 5.42 (d, J=2.3, 10.6 Hz, 1H), 7.01 (dt, J=1.3, 7.6 Hz, 1H), 7.19–7.32 (m, 6H), 7.52 (dd, J=1.3, 7.9 Hz, 1H), 7.82 (d, J=1.3, 7.9 Hz, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.3, 21.7, 27.5, 31.6, 57.0, 57.2, 71.8, 82.2, 124.0, 125.2, 126.8, 126.9, 127.9, 128.0, 130.6, 132.8, 138.7, 142.1, 173.5. IR: 3300–3500, 1690 cm^{-1}. Anal. calcd for $C_{23}H_{29}BrO_3S$: C, 59.35; H, 6.28. Found: C, 59.28; H, 6.33.

3.3. Competitive reaction between *tert*-butyl and methyl crotonate (Scheme 2)

To a solution of thiophenol (0.1258 g, 1.14 mmol) in CH_2Cl_2 (2 mL) was added methylmagnesium bromide in ether (3 M, 0.4 mL, 1.2 mmol) at −78°C. To the heterogeneous suspension, a mixture of *tert*-butyl crotonate (0.1374 g, 0.968 mmol), methyl crotonate (0.0998 g, 0.997 mmol) and benzaldehyde (0.1143 g, 1.07 mmol) was added at −78°C. The resulting mixture was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 5 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the crude product was purified with flash chromatography (silica gel/hexane–ether 20:1 then 3:1 v/v) and desired tandem products **3a** and **3b** were isolated in 79% (0.2660 g, 0.84 mmol) and 9% (0.0347 g, 0.967 mmol), respectively. HPLC analyses revealed disatereomeric ratio of **A/B/C/D** was 14/0/34/53 for **3a** and 1/0/30/69 for **3b**.

3.4. Michael/aldol tandem reaction to α,β-unsaturated esters with magnesium selenolate

3.4.1. Preparation of *tert*-butyl 2-(hydroxyphenylmethyl)-3-phenylselanylbutyrate (4a): general procedure. To a solution of diphenyldiselenide (1.034 g, 3.31 mmol) in toluene (6 mL) was added methylmagnesium bromide in ether (3 M, 1.1 mL, 3.3 mmol) at room temperature and the resulting mixture was allowed to stir for 30 min. Benzaldehyde (0.360 g, 3.38 mmol) was added to the mixture at −50°C and the reaction mixture was allowed to stir at the same temperature for 10 min. *tert*-Butyl crotonate (0.415 g, 2.92 mmol) was added at −78°C and the reaction mixture was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 5 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, crude product was purified with flash chromatography (silica gel/hexane–ether 20:1 then 3:1 v/v) and desired tandem product **4a** was obtained in 69% yield (0.813 g, 2.00 mmol) as pale yellow oil. HPLC analysis indicated disatereomeric ratio of **A/B/C/D** was 3/0/52/45.

Compound **4a-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (br, 1H), 1.35 (s, 9H), 1.55 (d, J=6.9 Hz, 3H), 2.79 (dd, J=5.9, 7.9 Hz, 1H), 3.29 (quint, J=6.9 Hz, 1H), 5.05 (d, J=5.6 Hz, 1H), 7.23–7.51 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.5, 27.9, 38.4, 58.9, 73.0, 82.3, 126.0, 127.5, 127.6, 128.2, 128.7, 128.9, 135.0, 141.7, 172.7. IR: 3300–3600, 1720 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_3Se$: C: 62.22; H, 6.46. Found: C, 62.23; H, 6.39.

Compound **4a-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.40 (d, J=6.9 Hz, 3H), 2.72 (dd, J=5.0, 8.6 Hz, 1H), 3.46 (quint, J=6.9 Hz, 1H), 3.55–3.65 (br, 1H), 5.24 (d, J=4.6 Hz, 1H), 7.15–7.51 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.4, 27.8, 37.9, 58.2, 73.1, 82.2, 125.7, 127.4, 127.9, 128.2, 128.4, 129.0, 135.5, 141.9, 172.8. IR: 3300–3600, 1720 cm^{-1}. Anal. calcd for $C_{21}H_{26}O_3Se$: C: 62.22; H, 6.46. Found: C, 62.35; H, 6.51.

3.4.2. *tert*-Butyl 2-(hydroxy-*p*-tolylmethyl)-3-phenylselanylbutyrate (4b). Anal. calcd for $C_{22}H_{28}O_3Se$: C, 63.00; H, 6.73. Found: C, 62.85; H, 6.90.

Compound **4b-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.51 (d, J=6.9 Hz, 3H), 2.31 (s, 3H), 2.80 (dd, J=5.6, 8.2 Hz, 1H), 3.20 (quint, J=7.0 Hz, 1H), 3.40–3.50 (br, 1H), 5.02 (d, J=6.3 Hz, 1H), 7.09–7.54 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.8, 21.0, 27.8, 38.4, 58.9, 72.9, 81.9, 126.0, 127.5, 128.7, 128.8, 128.8, 134.9, 137.1, 138.6, 172.5. IR: 3150–3700, 1700 cm^{-1}.

Compound **4b-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.45 (d, J=6.9 Hz, 3H), 2.31 (s, 3H), 2.77 (t, J=6.9 Hz, 1H), 3.44 (quint, J=7.5 Hz, 1H), 3.50–3.60 (br, 1H), 5.21 (d, J=4.6 Hz, 1H), 7.09–7.54 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.8, 21.6, 27.8, 37.6, 57.8, 72.9, 81.9, 125.7, 127.7, 128.7, 128.8, 128.8, 135.2, 136.9, 138.7, 172.4. IR: 3150–3700, 1700 cm^{-1}.

3.4.3. *tert*-Butyl 2-[(4-chloro-phenyl)-hydroxy-methyl]-3-phenylselanylbutyrate (4c). Anal. calcd for $C_{21}H_{25}ClO_3Se$: C, 57.35; H, 5.73. Found: C, 57.19; H, 5.81.

Compound **4c-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.53 (d, J=6.9 Hz, 3H), 2.73 (dd, J=4.6, 8.6 Hz, 1H), 3.24 (t, J=7.4 Hz, 1H), 3.72 (d, J=7.6 Hz, 1H), 4.99 (dd, J=5.9, 7.6 Hz, 1H), 7.16–7.57 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.4, 27.8, 37.7, 57.9, 72.3, 82.3, 127.4, 127.9, 128.0, 128.2, 128.9, 133.2, 135.0, 140.5, 172.3. IR: 3100–3650, 1720 cm^{-1}.

Compound **4c-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.46 (d, J=7.3 Hz, 3H), 2.71 (dd, J=4.6, 8.6 Hz, 1H), 3.49 (dd, J=7.3, 8.6 Hz, 1H), 3.82 (d, J=8.6 Hz, 1H), 5.26 (dd, J=4.6, 8.6 Hz, 1H), 7.21–7.48 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.3, 27.7, 38.1, 58.6, 72.4, 82.3, 127.1, 127.7, 128.2, 128.5, 129.0, 133.0, 135.4, 140.3, 172.5. IR: 3100–3650, 1720 cm^{-1}.

3.4.4. *tert*-Butyl 2-[hydroxy-(3-methoxyphenyl)methyl]-3-phenylselanylbutyrate (4d). Anal. calcd for $C_{22}H_{28}O_4Se$: C, 60.69; H, 6.48. Found: C, 60.44; H, 6.46.

Compound **4d-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.56 (d, J=6.9 Hz, 3H), 2.78 (m, 1H), 3.29 (dt, J=7.3, 7.9 Hz, 1H), 3.73 (s, 3H), 5.03 (t, J=6.8 Hz, 1H), 6.76–7.55 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.0, 27.7, 37.6, 55.0, 57.8, 73.0, 82.0, 110.9, 113.1, 118.0, 127.8, 128.9, 129.1, 134.7, 135.3, 143.5, 159.4, 172.5. IR: 3100–3700, 1700 cm^{-1}.

Compound **4d-D**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.48 (d, J=7.3 Hz, 3H), 2.78 (dd, J=5.6, 7.3 Hz, 1H), 3.47 (quint, J=7.5 Hz, 1H), 3.72 (s, 3H), 5.25 (dd, J=5.3, 7.9 Hz, 1H), 6.76–7.55 (m, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.2, 27.8, 38.2, 55.0, 58.8, 72.9, 82.0, 111.3, 113.3, 118.3, 127.5, 128.7, 129.1, 134.7, 135.3, 143.1, 159.4, 172.4. IR: 3100–3700, 1700 cm^{-1}.

3.4.5. *tert*-Butyl 2-(hydroxyphenylmethyl)-3-phenylselanylhexanoate (4f). Exact mass determination: 434.1345 (calcd $C_{23}H_{30}O_3Se$: 434.1360).

Compound **4f-C**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.79 (t, J=6.9 Hz, 3H), 1.38 (s, 9H), 1.44–1.90 (m, 4H), 2.99 (t, J=6.6 Hz, 1H), 3.12 (q, J=6.9 Hz, 1H), 5.13 (d, J=6.3 Hz, 1H), 7.19–7.57 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.6, 20.5, 27.9, 36.4, 45.7, 56.6, 73.3, 82.2, 125.7, 127.3, 127.7, 128.2, 129.0, 129.2, 135.0, 141.5, 172.6. IR: 3100–3700, 1700 cm^{-1}.

Compound **4f-D**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J=7.0 Hz, 3H), 1.24 (s, 9H), 1.38–1.74 (m, 4H), 2.87 (dd, J=4.5, 9.2 Hz, 1H), 3.45 (dt, J=3.7, 9.2 Hz, 1H), 3.65 (d, J=8.8 Hz, 1H), 5.43 (dd, J=4.4, 8.1 Hz, 1H), 7.21–7.57 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 20.9, 27.8, 35.8, 45.8, 57.7, 72.9, 82.1, 125.7, 126.5, 127.2, 128.6, 128.1, 128.3, 129.0, 134.9, 142.1, 173.2. IR: 3100–3700, 1700 cm^{-1}.

3.5. Deselenohydrogenation of 4: general procedure

A mixture of **4a** (0.492 g, 1.21 mmol, **A/B/C/D**=3/0/52/45), Bu_3SnH (0.39 mL, 1.46 mmol) and AIBN (0.04 g, 0.24 mmol) in toluene (10 mL) was heated to 110°C for 2 h. The resulting mixture was cooled and subjected to flash chromatography (hexane, hexane–ether 10:1 then hexane–ethyl acetate 3:1) to give **5a** in 89% yield (0.270 g, 1.08 mmol). HPLC analysis revealed diastereomeric ratio was 3/97.

3.5.1. *anti-tert*-Butyl 2-(hydroxyphenylmethyl)butyrate (5a). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H), 1.40 (s, 9H), 1.64 (dt, J=5.3 Hz, 7.3 Hz, 2H), 2.58 (ddd, J=4.9, 7.3, 9.6 Hz, 1H), 3.12 (d, J=6.3 Hz, 1H), 4.76 (t, J=6.6 Hz, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.4, 22.8, 27.9, 55.1, 74.9, 81.0, 126.3, 127.5, 128.2, 142.3, 174.6. Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.60; H, 9.16.

3.5.2. *anti-tert*-Butyl 2-(hydroxy-*p*-tolylmethyl)butyrate (5b). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J=7.3 Hz, 3H), 1.43 (s, 9H), 1.52–1.63 (m, 2H), 2.34 (s, 3H), 2.57 (ddd, J=5.0, 7.6, 9.6 Hz, 1H), 2.94 (br, 1H), 4.71 (d, J=6.9 Hz, 1H), 7.15 (d, J=8.3 Hz, 2H), 7.23 (d, J=8.3 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.5, 21.1, 22.9, 28.1, 55.1, 75.0, 81.4, 126.3, 129.0, 137.4, 139.3, 174.7. Exact mass determination: 264.1723 (calcd $C_{16}H_{24}O_3$: 264.1725).

3.5.3. *anti-tert*-Butyl 2-[(4-chlorophenyl)hydroxymethyl]butyrate (5c). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, J=7.2 Hz, 3H), 1.39 (s, 9H), 1.25–1.68 (m, 2H), 2.52 (ddd, J=5.3, 9.2, 11.8 Hz, 1H), 3.36 (d, J=6.6 Hz, 1H), 4.73 (t, J=6.6 Hz, 1H), 7.26 (d, J=8.9 Hz, 1H), 7.31 (d, J=8.6 Hz, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.5, 22.9, 28.2, 54.8, 76.5, 81.4, 127.7, 128.4, 133.3, 140.9, 174.5. Anal. calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 62.81; H, 7.56.

3.5.4. *anti-tert*-Butyl 2-[hydroxy-(3-methoxyphenyl)-methyl]butyrate (5d). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H), 1.41 (s, 9H), 1.34–1.65 (m, 1H), 2.63 (ddd, J=5.0, 7.6, 9.6 Hz, 1H), 3.18 (br, 1H), 3.80 (s, 3H), 4.72 (t, J=6.3 Hz, 1H), 6.81 (dd, J=2.6, 8.3 Hz, 1H), 6.89–6.91 (m, 2H), 7.24 (t, J=8.7 Hz, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.5, 22.9, 28.0, 55.0, 55.2, 74.9, 81.5, 111.7, 113.3, 118.7, 129.1, 144.0, 159.6, 174.7. Exact mass determination: 280.1656 (calcd $C_{16}H_{24}O_4$: 280.1675).

3.5.5. *anti-tert*-Butyl 2-(hydroxyphenylmethyl)hexanoate (5f). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (t, J=7.3 Hz, 3H), 1.26–1.35 (m, 4H), 1.39 (s, 9H), 1.57–1.66 (m, 2H), 2.64 (ddd, J=4.6, 7.0, 9.6 Hz, 1H), 3.19 (br, 1H), 4.74 (d, J=6.9 Hz, 1H), 7.28–7.35 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 22.6, 28.2, 29.4, 29.6, 53.5, 75.4, 81.3, 126.5, 127.8, 128.5, 142.6, 175.1. Exact mass determination: 278.1886 (calcd $C_{17}H_{26}O_3$: 278.1882).

3.6. Michael/aldol tandem reaction from *Z-tert*-butyl crotonate (Scheme 5)

To a solution of PhSH (0.1214 g, 1.1 mmol) in CH_2Cl_2 (1 mL) was added methyl magnesium bromide in ether (3 M, 0.37 mL, 1.1 mmol) at −78°C and the resulting heterogeneous mixture was allowed to stir at −50°C for 30 min. PhCHO (0.1196 g, 1.12 mmol) and *Z-tert*-butyl crotonate (0.1388 g, 0.94 mmol) in this were added to the mixture in this order and the reaction mixture was allowed to warm to room temperature for 15 h. After a similar work-up mentioned before, **3b** was isolated in 64% yield. HPLC analysis for crude **3b** indicated the diastereomeric ratio being **A/B/C/D**=12/6/36/46.

3.6.1. Isolation of intermediate 6 (Scheme 6). To a solution of PhSH (0.2456 g, 2.23 mmol) in CH_2Cl_2 (2 mL) was added methyl magnesium bromide in ether (3 M, 0.75 mL, 2.25 mmol) at −78°C and the resulting heterogeneous mixture was allowed to stir at −50°C for 30 min. PhCHO (0.2238 g, 2.11 mmol) was added to the mixture at −50°C and the reaction mixture was allowed to stir at the same temperature for 30 min. TBSOTf (0.5016 g, 2.12 mmol) was added to the mixture at −50°C; 30 min later, the heterogeneous mixture turned to yellow gel. CH_2Cl_2 (5 mL) was added and the resulting mixture was allowed to warm to room temperature for 1.5 h. The mixture

was concentrated in vacuo and the residue was filtered on glass filter after CH_2Cl_2 (1 mL) was added. The filtrate was concentrated and the residue was purified through flash chromatography (hexane then hexane–ether 10:1) to give *tert*-butyldimethyl-(phenylphenylsulfanylmethoxy)silane **6** in 28% yield (0.1986 g, 0.6 mmol).

^{1}H NMR (270 MHz, $CDCl_3$) δ −0.07 (s, 3H), 0.00 (s, 3H), 0.91 (s, 9H), 6.22 (s, 1H), 7.28–7.56 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.3, −4.7, 18.1, 25.6, 83.6, 125.9, 127.7, 127.9, 128.2, 128.5, 133.1, 135.3, 141.7. Anal. calcd for $C_{19}H_{26}OSSi$: C, 69.04; H, 7.93. Found: C, 68.97; H, 7.94.

3.7. NMR observation of the reaction mixture (Fig. 1)

In septum-sealed NMR tube (5 mm diameter), PhSH (0.0103 g, 0.093 mmol) and CD_2Cl_2 (99.6%d, 0.8645 g) was charged by syringe. Methylmagnesium bromide in ether (3 M, 40 μL, 0.12 mmol) was added at room temperature, and the resulting heterogeneous mixture was measured by NMR. PhCHO (0.0113 g, 1.06 mmol) and TBSOTf (0.0215 g, 0.81 mmol) was added to the mixture subsequently and spectra were measured by each time at room temperature.

Acknowledgements

The present work was partially supported by the Grant-in-Aid (11640536) from the Ministry of Education, Science and Culture, Japan.

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