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# Synthesis of γ-Sulfur-Substituted Ketones via Rh(II)/Sc(III) Cocatalyzed Three-Component Reaction of Diazo Compounds with Thiophenols and Enones

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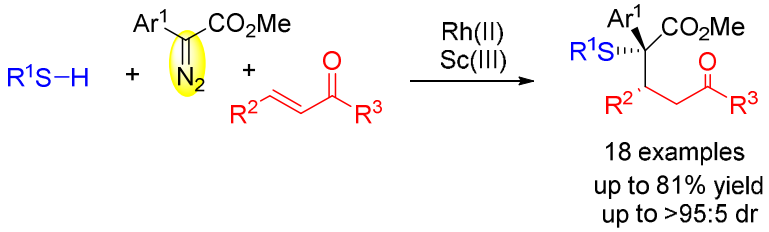
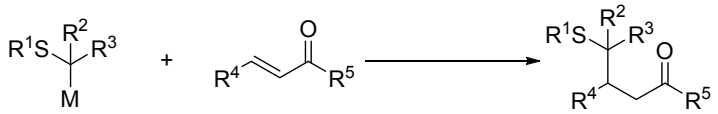
**Abstract:** A facile method for the synthesis of γ-sulfur-substituted ketones is developed via a Rh(II)/Sc(III) cocatalyzed three-component reaction of diazo compounds with thiophenols and enones. With this method, different γ-sulfur-substituted ketones were obtained in moderate to high yields with good diastereoselectivities.



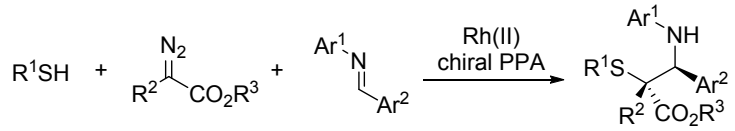

Sulfur-containing compounds are widely existed in a large number of synthetic drugs, bioactive molecules and natural products.[1] For example, all of the top 10 best-selling drugs in 2012 were sulfur-containing compounds.[2] Among different types of sulfur-containing molecules, γ-sulfur substituted carbonyl compounds have drawn considerable synthetic attention owing to their roles in various biological systems. For example, methionine, one of the amino acids that contains γ-sulfur-substituted carbonyl moiety, plays an important role both in protein structure and in metabolism.[3] The traditional ways for the synthesis of γ-sulfur carbonyl compounds include the conjugated addition of α-lithiosulphides or α-sulfur substituted alkylstannanes to α,β-unsaturated ketones (Scheme 1, part a),[4,5] which require either the use of stoichiometric amount of organolithium reagents under harsh reaction conditions or the use of highly toxic organotin reagents. As a result, it would be highly desirable to develop more efficient and straightforward approaches to build γ-sulfur carbonyl compounds under mild reaction

conditions.

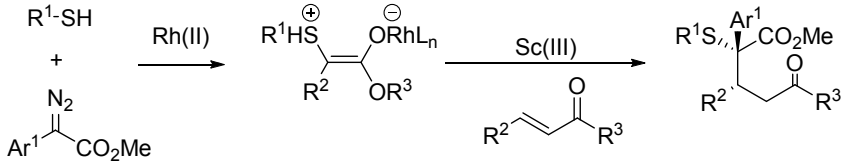
(a) Traditional methods for the synthesis of γ-sulfur substituted carbonyl compounds




(b) Our previously developed electrophilic trapping approach of active sulfonium ylide with imines



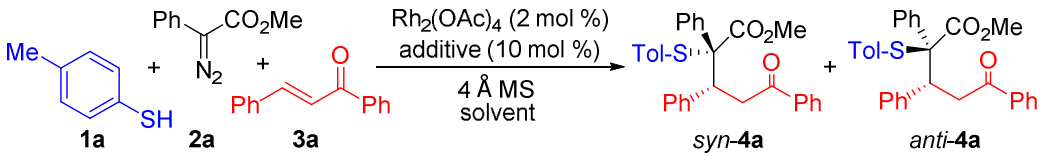

(c) **This work**: construction of γ-sulfur substituted ketones by trapping of sulfonium ylide with enones




**Scheme 1** Synthesis of γ-Sulfur-Substituted Ketones *via* the Trapping of Sulfonium Ylide with Enones.

Over the past ten years, our research group has been devoted to the development of multicomponent reactions (MCRs) *via* electrophilic trapping of *in situ* generated active intermediates from metal carbenes, therefore establish a powerful strategy for the rapid construction of complex molecules.[6-9] Within this context, we have recently developed the first example of MCR *via* electrophilic trapping of sulfonium ylide intermediates with imines by a Rh(II)/chiral phosphoric acid (CPA) cocatalyzed reaction system, to generate a series of α-sulfur-β-amino esters in good stereoselectivities (Scheme 1, part b).[8] Based on this electrophilic trapping strategy, we envisioned whether α,β-unsaturated ketones could also be used as electrophiles to undergo a Michael-type trapping of the *in situ* generated sulfonium ylide intermediates, therefore established a rapid way for the synthesis of γ-sulfur substituted ketones. However, owing to the much lower electrophilic ability of α,β-unsaturated ketones as Michael acceptors, the proposed electrophilic interception might be difficult to realize and appropriate activation of this kind of electrophile is required. Herein, we reported our successful development of a Rh(II)/Sc(III) cocatalyzed system that allows an efficient three-component reaction of diazo compounds, thiophenols and enones for the efficient construction of γ-sulfur substituted ketones.

**Table 1**. Catalyst Screening and Optimization of Reaction Conditions[a]



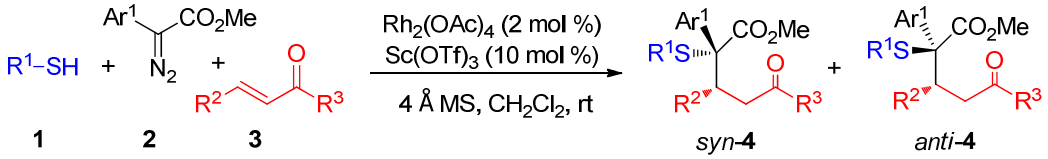

| entry | solvent | temp | additive | yield of **4a** (%)[b] | dr[c] (*syn* : *anti*) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | -- | < 5 | -- |
| 2 | $CH_2Cl_2$ | rt | $Cu((OTf)_2$ | < 5 | -- |
| 3 | $CH_2Cl_2$ | rt | $Zn(OTf)_2$ | 20 | 87:13 |
| 4 | $CH_2Cl_2$ | rt | $Yb(OTf)_3$ | 15 | 73:27 |
| 5 | $CH_2Cl_2$ | rt | $Sc(OTf)_3$ | 25 | 87:13 |
| 6 | DCE | rt | $Sc(OTf)_3$ | 15 | 84:16 |
| 7 | $CHCl_3$ | rt | $Sc(OTf)_3$ | 11 | 86:14 |
| 8 | Toluene | rt | $Sc(OTf)_3$ | 11 | 66:34 |
| 9 | THF | rt | $Sc(OTf)_3$ | < 5 | -- |
| 10[d] | $CH_2Cl_2$ | rt | $Sc(OTf)_3$ | 74 | 80:20 |
| 11[d] | $CH_2Cl_2$ | 40 °C | $Sc(OTf)_3$ | 77 | 72:28 |
| 12 | $CH_2Cl_2$ | 40 °C | -- | < 5 | -- |
| 13[e] | $CH_2Cl_2$ | 40 °C | $Sc(OTf)_3$ | < 5 | -- |

[a] Reaction conditions: 1:2:3 = 1.5:1.5:1.0. [b] Yield of isolated product after purification by column chromatography. [c] *syn*/*anti* determined by $^1$H NMR spectroscopy of the crude reaction mixture. [d] Using 3 equiv. of **1a** and **2a**. [e] Without the addition of $Rh_2(OAc)_4$.

We started our exploration by choosing 4-methylbenzenethiol (**1a**), methyl phenyl diazoacetate (**2a**) and chalcone (**3a**) as the model substrates. With $Rh_2(OAc)_4$ alone as the catalyst, the S–H insertion product between **1a** and **2a** was obtained as the major product and the desired three-component product was not observed (Table 1, entry 1). This result indicates that chalcone **3a** is not electrophilic enough to intercept the *in situ* formed sulfonium ylide intermediate. We envisioned that an appropriate Lewis acid co-catalyst might be able to activate **3a** toward the proposed electrophilic trapping process. With this thought in mind, we screened a number of Lewis acid

co-catalysts. When $Cu(OTf)_2$ was employed as the co-catalyst, the desired three-component product **4a** was not observed (Table 1, entry 2), however, the use of $Zn(OTf)_2$, $Yb(OTf)_3$ or $Sc(OTf)_3$ as the co-catalyst indeed facilitate the desired three-component reaction and $Sc(OTf)_3$ shows a superior efficiency, giving **4a** in 25% yield with 87:13 dr (Table 1, entries 3–5). Changing the solvent from $CH_2Cl_2$ to other halogenated solvents such as 1,2-dichloroethane (DCE) or $CHCl_3$ also gave **4a** but with even lower yields (Table 1, entries 6 and 7). The use of toluene or THF as the solvent failed to improve the efficiency of this transformation (Table 1, entries 8 and 9). When 3 equivalents of **1a** and **2a** was employed, the desired three-component product **4a** was obtained in a 74% isolated yield with 80:20 dr (Table 1, entry 10). Raising the reaction temperature to 40 °C gave a slightly improved yield of **4a** but with a decreased dr ratio (Table 1, entry 11). Both catalysts are indispensable for the current transformation as in the absence of $Rh_2(OAc)_4$ and/or $Sc(OTf)_3$, the desired three-component product was not observed (Table 1, entries 12 and 13). For all entries, the aldol-type 1,2-addition products were not observed.

**Table 2** Three-Component Reaction of Thiophenols with Various Diazo Compounds and Enones[a]




**1a**: $R^1$ = *p*-$CH_3C_6H_4$
**1b**: $R^1$ = *o*-$MeOC_6H_4$
**1c**: $R^1$ = *p*-$MeOC_6H_4$
**1d**: $R^1$ = *p*-$BrC_6H_4$

| entry | **1** | $Ar^1$ | $R^2/R^3$ | **4** | yield (%)[b] | dr[c] (*syn* : *anti*) |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph (**2a**) | Ph/Ph (**3a**) | **4a** | 74 | 80:20 |
| 2 | **1a** | Ph (**2a**) | *p*-$NO_2C_6H_4$/Ph (**3b**) | **4b** | 72 | 82:18 |
| 3 | **1a** | Ph (**2a**) | *p*-$CH_3C_6H_4$/Ph (**3c**) | **4c** | 73 | 70:30 |
| 4 | **1a** | Ph (**2a**) | *p*-$BrC_6H_4$/Ph (**3d**) | **4d** | 77 | 86:14 |
| 5 | **1a** | Ph (**2a**) | Me/Ph (**3e**) | **4e** | 65 | 87:13 |
| 6 | **1a** | Ph (**2a**) | COOMe/Ph (**3f**) | **4f** | 51 | 84:16 |
| 7 | **1a** | Ph (**2a**) | Ph/*p*-$MeOC_6H_4$ (**3g**) | **4g** | 79 | 80:20 |
| 8 | **1a** | Ph (**2a**) | Ph/*p*-$ClC_6H_4$ (**3h**) | **4h** | 79 | 73:27 |
| 9 | **1a** | Ph (**2a**) | Ph/*p*-$NO_2C_6H_4$ (**3i**) | **4i** | 77 | 61:39 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | **1a** | Ph (**2a**) | *m*-$ClC_6H_4$/Me (**3j**) | **4j** | 68 | 93:7 |
| 11 | **1a** | Ph (**2a**) | Me/Me (**3k**) | **4k** | 45 | >95:5 |
| 12 | **1b** | Ph (**2a**) | Ph/Ph (**3a**) | **4l** | 62 | 82:18 |
| 13 | **1c** | Ph (**2a**) | Ph/Ph (**3a**) | **4m** | 61 | 88:12 |
| 14 | **1d** | Ph (**2a**) | Ph/Ph (**3a**) | **4n** | 77 | 83:17 |
| 15 | **1a** | *p*-$CF_3C_6H_4$ (**2b**) | Ph/Ph (**3a**) | **4o** | 81 | 83:17 |
| 16 | **1a** | *m*-$BrC_6H_4$ (**2c**) | Ph/Ph (**3a**) | **4p** | 75 | 86:14 |
| 17 | **1a** | *p*-$MeOC_6H_4$ (**2d**) | Ph/Ph (**3a**) | **4q** | 69 | 82:18 |
| 18 | **1a** | 3,4,5-$(MeO)_3C_6H_2$ (**2e**) | Ph/Ph (**3a**) | **4r** | 79 | 79:21 |

[a] Reaction conditions: 1:2:3 = 3.0:3.0:1.0. [b] Combined isolated yield of **4** (*syn* + *anti*). [c] *syn*/*anti* determined by $^1$H NMR spectroscopy of the crude reaction mixture.

With the optimal reaction conditions in hand, we then proceeded to investigate the substrate scope of this three-component reaction. Different substituted enones were first tested. Both electron-deficient and electron-rich substituents on the aryl ring of the alkenyl terminal of the enones all gave the desired three-component products in high yields with good diastereoselectivities (Table 2, entries 1–4). When methyl or ester group were present at β-position of the unsaturated ketone substrate, the reaction also proceeded albeit with slightly decreased yields (Table 2, entries 5–6). Different substituted aryl enones also gave the desired three-component products in high efficiency (Table 2, entries 7–9). Methyl enone **3j** was also a suitable substrate, yielding corresponding three-component product **4j** in 68% yield and with high diastereoselectivity (Table 2, entry 10). The alkyl unsaturated ketone **3k** gave the desired product in a relative low yield, however with an excellent diastereoselectivity (Table 2, entry 11). Different *para*-substituted thiophenols were then tested, and the desired three-component products were obtained in good yields with high diastereoselectivities (Table 2, entries 12–14). Finally, different substituted aryl diazoacetates were used as the carbene sources, and all of them could give the desired three-component products in high efficiency regardless of the electronical characters (Table 2, entries 15–18). The relative stereochemistry of products was assigned as *syn* by analogy with *syn*-**4n** as determined by single-crystal X-ray diffraction (Figure 1).[10]

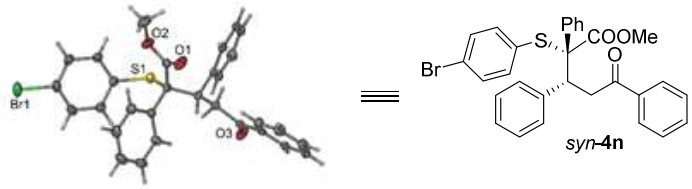
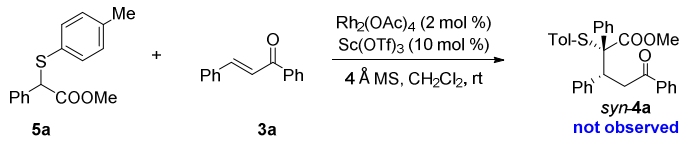
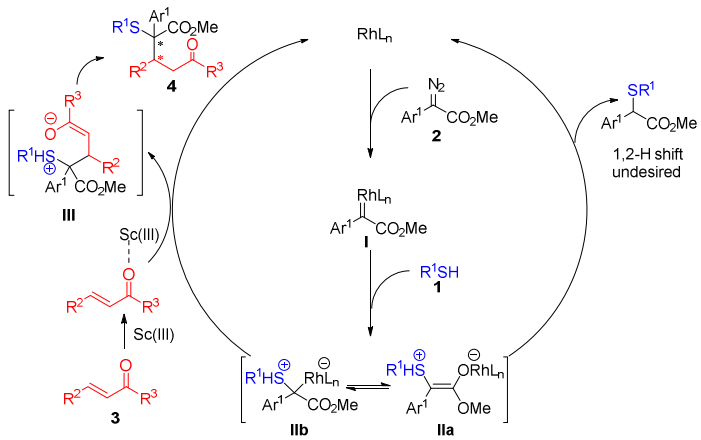



**Figure 1** X-ray crystal structure of *syn*-**4n**, ellipsoids are drawn at the 50% probability level.

To gain some insights into the possible reaction pathway, the reaction between the S–H insertion product **5a** and chalcone **3a** was conducted. However, under standard reaction conditions, the desired three-component product **4a** was not observed (eq 1). This result indicated that this three-component reaction most like proceed through an *in situ* Michael-type sulfonium ylide trapping pathway instead of a stepwise S–H insertion/Michael addition pathway. This transformation is proposed to proceed through a sulfonium ylide intermediate, which was *in situ* generated from metal carbene and thiophenol. The *in situ* generated protic sulfonium ylide was then immediately trapped by the tethered electrophilic enone unit that was activated by Sc(III), to give the desired three-component product *via* a Michael-type addition (Scheme 2).




(1)




**Scheme 2** Proposed Reaction Mechanism of the Title Reaction.

In summary, we have developed a Rh(II)/Sc(III) cocatalyzed three-component reaction of diazo compounds with thiophenols and enones. With this strategy, different γ-sulfur substituted ketones were synthesized in moderate to

high yields with good diastereoselectivities. Control experiments indicate that this transformation may proceed through an electrophilic trapping of the *in situ* generated sulfonium ylide with Sc(III)-activated enones.

## EXPERIMENTAL SECTION

**General Information:** All $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on Brucker spectrometers in $CDCl_3$. Tetramethylsilane (TMS) served as an internal standard ($\delta = 0$) for $^1$H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for $^{13}$C NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Infrared (IR) spectra were recorded on a NICOLET NEXUS 670 FT-IR spectrometer, $\nu_{max}$ in $cm^{-1}$. High-resolution mass spectrometry (HRMS) was performed on IonSpec FT-ICR or Waters Micromass Q-TOF micro Synapt High Definition Mass Spectrometer. Melting points were uncorrected. Single crystal X-ray diffraction data (*syn*-**4n**) were recorded on Bruker-AXS SMART APEX II single crystal X-ray diffractometer.

**Materials**: $CH_2Cl_2$ was distilled over calcium hydride. Chalcones **3a-3d, 3g-3i** were prepared according to the literature procedure.[11] **3j** was synthesized following another literature procedure.[12] Aryl diazoacetates **2a-2e** were prepared by the treatment of corresponding arylacetate with p-acetamidobenzenesulfonyl azide (p-ABSA) in the presence of DBU following the general procedure.[13] 4Å molecular sieve was dried in a Muffle furnace at 250℃ over 5 hours. All reactions were carried out under argon atmosphere in a well-dried glassware.

**General Experimental Procedure for the Synthesis of Product 4:** A suspension of $Rh_2(OAc)_4$ (2 mol %), $Sc(OTf)_3$ (10 mol %), Chalcones **3** (0.20 mmol, 1.0 eq) and 4Å molecular sieve (0.1 g) was stirred in 2.0 mL of $CH_2Cl_2$ at room temperature, and then a mixture of the diazo compounds **2** (0.60 mmol, 3.0 eq) and thiols **1** (0.60 mmol, 3.0 eq) in 1.0 mL $CH_2Cl_2$ was introduced to the suspension for 3 h via a syringe pump. After the addition completed, the reaction mixture was continued stirred at the same temperature until the diazo compound decomposed completely. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was subjected to $^1$H NMR spectroscopy analysis for the determination of diastereoselectivity. Purification of the crude products by flash chromatography on silica gel (eluent: EtOAc/light petroleum ether = 1/50~1/20) afforded pure products **4**.

*methyl 5-oxo-2,3,5-triphenyl-2-(p-tolylthio)pentanoate (syn-***4a***)*. White solid (57 mg, 59% yield); mp 120−122 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.50 – 7.45 (m, 1H), 7.39 – 7.34 (m, 2H), 7.27 – 7.08 (m, 10H),

7.02 – 6.97 (m, 4H), 4.62 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.90 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.71 – 3.59 (m, 4H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 171.4, 139.6, 139.0, 137.4, 137.2, 136.6, 132.9, 130.6, 129.5, 129.4, 128.5, 128.0, 127.7, 127.6, 127.5, 127.1, 69.9, 52.1, 46.9, 41.5, 21.3; IR ν ($cm^{-1}$) 3064, 3032, 2949, 2918, 1711, 1687, 1597, 1492, 1448, 1431, 1348, 1289, 1221, 1003, 807, 747, 703, 586, 502; HRMS-ESI: calcd. for $C_{31}H_{28}O_3NaS$ $[M + Na]^+$: 503.1657, found: 503.1667.

*methyl 3-(4-nitrophenyl)-5-oxo-2,5-diphenyl-2-(p-tolylthio)pentanoate (syn-***4b***).* White solid (62 mg, 59% yield); mp 61−63 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 2H), 7.84 – 7.78 (m, 2H), 7.54 – 7.48 (m, 1H), 7.43 – 7.36 (m, 2H), 7.35 – 7.28 (m, 3H), 7.26 – 7.17 (m, 4H), 7.11 – 7.03 (m, 4H), 4.61 (dd, *J* = 11.6, 2.0 Hz, 1H), 4.19 (dd, *J* = 17.8, 1.8 Hz, 1H), 3.69 – 3.52 (m, 4H), 2.33 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.2, 170.9, 147.2, 146.8, 140.4, 136.7, 136.6, 136.4, 133.3, 131.8, 129.8, 129.4, 128.7, 128.3, 127.9, 127.8, 126.8, 122.3, 69.0, 52.3, 46.5, 41.3, 21.4; IR ν ($cm^{-1}$) 3060, 3025, 2949, 2921, 1728, 1685, 1597, 1519, 1491, 1447, 1346, 1282, 1228, 1181, 1110, 1002, 857, 812, 779, 709, 700, 691, 507; HRMS-ESI: calcd. for $C_{31}H_{27}NO_5NaS$ $[M + Na]^+$: 548.1508, found: 548.1524.

*methyl 5-oxo-2,5-diphenyl-3-(p-tolyl)-2-(p-tolylthio)pentanoate (syn-***4c***).* White solid (51 mg, 51% yield); mp 146−148 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.50 – 7.45 (m, 1H), 7.40 – 7.33 (m, 2H), 7.26 – 7.16 (m, 5H), 7.15 – 7.08 (m, 2H), 7.01 – 6.96 (m, 2H), 6.95 – 6.87 (m, 4H), 4.60 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.84 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.70 – 3.58 (m, 4H), 2.28 (s, 3H), 2.23 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.9, 171.5, 139.5, 137.5, 137.2, 136.6, 135.9, 132.9, 130.4, 129.5, 129.3, 128.5, 128.3, 128.0, 127.8, 127.6, 127.5, 70.1, 52.1, 46.5, 41.6, 21.3, 21.1; IR ν ($cm^{-1}$) 3051, 3023, 2949, 2920, 1729, 1676, 1597, 1492, 1448, 1361, 1298, 1231, 1012, 814, 736, 693, 591; HRMS-ESI: calcd. for $C_{32}H_{30}O_3NaS$ $[M + Na]^+$: 517.1813, found: 517.1808.

*methyl 3-(4-bromophenyl)-5-oxo-2,5-diphenyl-2-(p-tolylthio)pentanoate (syn-***4d***).* White solid (74 mg, 66% yield); mp 126−128 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.54 – 7.46 (m, 1H), 7.43 – 7.35 (m, 2H), 7.31 – 7.26 (m, 3H), 7.23 – 7.13 (m, 6H), 7.08 – 7.00 (m, 2H), 6.84 – 6.76 (m, 2H), 4.52 (dd, *J* = 11.3, 2.2 Hz, 1H), 4.00 (dd, *J* = 17.8, 2.1 Hz, 1H), 3.63 (s, 3H), 3.55 (dd, *J* = 17.8, 11.4 Hz, 1H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.6, 171.1, 140.0, 138.1, 137.0, 136.8, 136.6, 133.1, 132.5, 130.5, 129.6, 128.6, 128.0, 127.6, 127.3, 121.2, 69.4, 52.2, 46.2, 41.2, 21.4; IR ν ($cm^{-1}$) 3058, 3030, 2948, 2921, 1728, 1686, 1596, 1580, 1489, 1447, 1432, 1356, 1283, 1227, 1181, 1076, 1010, 812, 752, 722, 700, 691, 506; HRMS-ESI: calcd. for $C_{31}H_{27}BrO_3NaS$ [M +

Na]$^+$: 581.0762, found: 581.0734.

*methyl 3-methyl-5-oxo-2,5-diphenyl-2-(p-tolylthio)pentanoate (syn-***4e***)*. Colorless sticky oil (47 mg, 57% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.18 (m, 5H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 3.74 (s, 3H), 3.53 (d, *J* = 17.2 Hz, 1H), 7.36 – 7.24 (m, 1H), 2.73 (dd, *J* = 17.5, 10.5 Hz, 1H), 2.31 (s, 3H), 1.10 (d, *J* = 6.5 Hz, 3H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.0, 171.8, 139.7, 137.5, 137.4, 136.9, 133.0, 129.4, 128.8, 128.5, 128.0, 127.7, 127.4, 127.2, 70.0, 52.2, 42.2, 34.5, 21.3, 17.3. IR ν ($cm^{-1}$) 2953, 2924, 2853, 1728, 1686, 1597, 1492, 1460, 1448, 1377, 1359, 1281, 1226, 1180, 1019, 1003, 810, 754, 691; HRMS-ESI: calcd. for $C_{26}H_{26}O_3NaS$ [M + Na]$^+$: 441.1500, found: 441.1494.

*dimethyl 3-(2-oxo-2-phenylethyl)-2-phenyl-2-(p-tolylthio)succinate (syn-***4f***)*. Colorless sticky oil (40 mg, 43% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.24 – 7.17 (m, 3H), 77.14 – 7.05 (m, 4H), 7.00 (d, *J* = 7.8 Hz, 2H), 4.32 (d, *J* = 10.0 Hz, 1H), 3.84 (s, 3H), 3.71 – 3.54 (m, 4H), 3.40 (d, *J* = 18.1 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.5, 173.1, 171.4, 139.9, 137.4, 137.0, 136.5, 133.3, 129.4, 128.6, 128.2, 128.1, 128.0, 127.7, 126.6, 66.3, 52.7, 52.2, 46.6, 38.9, 21.3. IR ν ($cm^{-1}$) 3058, 3024, 2951, 2924, 2855, 1735, 1687, 1597, 1492, 1448, 1434, 1361, 1277, 1228, 1171, 1019, 1003, 812, 756, 692; HRMS-ESI: calcd. for $C_{27}H_{26}O_5SNa$ [M + Na]$^+$: 485.1399, found: 485.1371.

*methyl 5-(4-methoxyphenyl)-5-oxo-2,3-diphenyl-2-(p-tolylthio)pentanoate (syn-***4g***)*. White solid (65 mg, 63% yield); mp 50−52 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H), 7.26 – 7.17 (m, 5H), 7.17 – 7.08 (m, 5H), 7.05 – 6.93 (m, 4H), 6.87 – 6.80 (m, 2H), 4.62 (dd, *J* = 11.1, 2.3 Hz, 1H), 3.87 – 3.76 (m, 4H), 3.68 – 3.55 (m, 4H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.3, 171.4, 163.3, 139.6, 139.1, 137.4, 136.6, 130.5, 130.3, 130.2, 129.5, 129.3, 127.7, 127.6, 127.4, 127.1, 113.6, 70.0, 55.4, 52.1, 47.0, 41.0, 21.3; IR ν ($cm^{-1}$) 3058, 3031, 2948, 2839, 1727, 1676, 1600, 1576, 1510, 1492, 1445, 1419, 1260, 1228, 1169, 1029, 993, 834, 811, 758, 702, 581, 506; HRMS-ESI: calcd. for $C_{32}H_{30}O_4NaS$ [M + Na]$^+$: 533.1763, found: 533.1788.

*methyl 5-(4-chlorophenyl)-5-oxo-2,3-diphenyl-2-(p-tolylthio)pentanoate (syn-***4h***)*. White solid (59 mg, 58% yield); mp 130−132 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.07 (m, 10H), 7.04 – 6.95 (m, 4H), 4.62 – 4.54 (m, 1H), 3.86 (dd, *J* = 17.5, 1.8 Hz, 1H), 3.68 – 3.53 (m, 4H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.8, 171.4, 139.7, 139.3, 138.8, 137.3, 136.6, 135.5, 130.5, 129.5, 129.4, 128.8,

127.7, 127.6, 127.5, 127.2, 69.8, 52.1, 47.1, 41.5, 21.3; IR ν ($cm^{-1}$) 3030, 2921, 2852, 1732, 1684, 1588, 1492, 1399, 1285, 1228, 1091, 1011, 814, 702, 507; HRMS-ESI: calcd. for $C_{31}H_{27}ClO_3NaS$ $[M + Na]^+$: 537.1267, found: 537.1285.

*methyl 5-(4-nitrophenyl)-5-oxo-2,3-diphenyl-2-(p-tolylthio)pentanoate (syn-***4i***)*. White solid (49 mg, 47% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.17 (m, 2H), 7.94 – 7.86 (m, 2H), 7.29 – 7.07 (m, 10H), 7.04 – 7.00 (m, 2H), 6.99 – 6.94 (m, 2H), 4.56 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.97 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.70 – 3.60 (m, 4H), 2.31 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 196.9, 171.3, 150.2, 141.6, 139.8, 138.5, 137.2, 136.5, 130.5, 129.5, 129.4, 129.0, 127.8, 127.6, 127.6, 127.5, 127.4, 123.7, 69.7, 52.2, 47.3, 42.2, 21.3; IR ν ($cm^{-1}$) 3060, 3032, 2949, 2921, 1728, 1694, 1602, 1526, 1453, 1446, 1433, 1345, 1318, 1284, 1227, 1031, 1005, 855, 812, 743, 702, 506; HRMS-ESI: calcd. for $C_{31}H_{27}NO_5NaS$ $[M + Na]^+$: 548.1508, found: 548.1530.

*methyl 5-(4-nitrophenyl)-5-oxo-2,3-diphenyl-2-(p-tolylthio)pentanoate (anti-***4i***)*. White solid; (32 mg, 30% yield); mp 151−153 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.41 – 7.28 (m, 5H), 7.23 – 7.05 (m, 5H), 6.99 (d, *J* = 7.7 Hz, 2H), 6.73 (d, *J* = 7.4 Hz, 2H), 4.49 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.72 (dd, *J* = 15.9, 2.4 Hz, 1H), 3.49 – 3.38 (m, 4H), 2.27 (s, 3H);$^{13}C$ NMR (100 MHz, $CDCl_3$) δ 196.7, 171.6, 150.2, 141.4, 139.6, 137.0, 135.9, 135.8, 130.8, 130.7, 129.4, 129.2, 128.1, 127.9, 127.5, 127.4, 127.2, 123.7, 69.6, 52.0, 49.5, 43.1, 21.2; IR ν ($cm^{-1}$) 3058, 3031, 2948, 2920, 2851, 1720, 1691, 1602, 1525, 1493, 1453, 1384, 1346, 1234, 1004, 855, 811, 744, 702, 606, 506; HRMS-ESI: calcd. for $C_{31}H_{27}NO_5NaS$ $[M + Na]^+$: 548.1508, found: 548.1501.

*methyl 3-(3-chlorophenyl)-5-oxo-2-phenyl-2-(p-tolylthio)hexanoate (syn-***4j***).* White solid (57 mg, 63% yield); mp 83−85 °C; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 3H), 7.22 – 7.18 (m, 2H), 7.16 – 7.11 (m, 3H), 7.10 – 7.04 (m, 3H), 6.86 – 6.76 (m, 2H), 4.31 (dd, *J* = 11.5, 2.4 Hz, 1H), 3.63 (s, 3H), 3.56 (dd, *J* = 17.3, 2.3 Hz, 1H), 2.91 (dd, *J* = 17.3, 11.5 Hz, 1H), 2.34 (s, 3H), 1.98 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 206.3, 170.9, 140.9, 140.0, 136.5, 136.4, 133.2, 130.5, 129.6, 129.5, 129.2, 128.6, 127.9, 127.4, 127.3, 127.2, 69.2, 52.1, 46.3, 46.0, 30.8, 21.3; IR ν ($cm^{-1}$) 3059, 3022, 2949, 2922, 1728, 1595, 1571, 1492, 1445, 1431, 1359, 1279, 1226, 1160, 1084, 1021, 902, 811, 791, 713, 699, 506; HRMS-ESI: calcd. for $C_{26}H_{25}ClO_3NaS$ $[M + Na]^+$: 475.1111, found: 475.1115.

*methyl 3-methyl-5-oxo-2-phenyl-2-(p-tolylthio)hexanoate (syn-***4k***)*. Colorless sticky oil (32 mg, 45% yield);$^1H$

NMR (400 MHz, $CDCl_3$) δ7.29 – 7.21 (m, 3H), 7.20 – 7.13 (m, 2H), 7.09 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 7.9 Hz, 2H), 3.70 (s, 3H), 3.14 – 3.00 (m, 2H), 2.30 (s, 3H), 2.16 – 2.00 (m, 4H), 1.01 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.5, 171.7, 139.7, 137.2, 136.8, 129.4, 128.8, 127.6, 127.4, 127.1, 69.6, 52.1, 47.2, 34.1, 30.6, 21.3, 17.2. IR ν ($cm^{-1}$) 3022, 2950, 2923, 1728, 1492, 1446, 1433, 1360, 1226, 1162, 1033, 1019, 812, 703, 509; HRMS-ESI: calcd. for $C_{21}H_{24}O_3NaS$ $[M + Na]^+$: 379.1344, found: 379.1367

*methyl 2-((2-methoxyphenyl)thio)-5-oxo-2,3,5-triphenylpentanoate (syn-***4l***)*. White solid (50 mg, 51% yield); mp 131−133 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.52 – 7.46 (m, 1H), 7.42 – 7.31 (m, 4H), 7.27 – 7.24 (m, 5H), 7.09 – 7.00 (m, 3H), 6.91 – 6.79 (m, 4H), 4.54 (dd, *J* = 11.5, 2.0 Hz, 1H), 4.35 (dd, *J* = 17.9, 2.0 Hz, 1H), 3.63 (s, 3H), 3.59 (s, 3H), 3.56 – 3.49 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 170.9, 161.1, 139.2, 139.1, 137.4, 136.7, 132.8, 131.7, 130.9, 129.8, 128.5, 127.9, 127.6, 127.1, 127.0, 126.7, 120.6, 119.0, 110.9, 69.7, 55.6, 51.9, 46.1, 41.5; IR ν ($cm^{-1}$) 3061, 3032, 2950, 2920, 2837, 1727, 1686, 1582, 1475, 1448, 1432, 1276, 1229, 1180, 1023, 770, 753, 702, 603; HRMS-ESI: calcd. for $C_{31}H_{28}O_4NaS$ $[M + Na]^+$: 519.1606, found: 519.1630.

*methyl 2-((4-methoxyphenyl)thio)-5-oxo-2,3,5-triphenylpentanoate (syn-***4m***)*. White solid (53 mg, 54% yield); mp 158−160 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.50 – 7.45 (m, 1H), 7.39 – 7.33 (m, 2H), 7.28 – 7.21 (m, 3H), 7.20 – 7.15 (m, 4H), 7.14 – 7.08 (m, 3H), 7.04 – 6.98 (m, 2H), 6.75 – 6.69 (m, 2H), 4.62 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.89 (dd, *J* = 17.8, 2.1 Hz, 1H), 3.76 (s, 3H), 3.72 – 3.61 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.9, 171.4, 160.8, 139.0, 138.4, 137.5, 137.2, 132.9, 130.5, 129.4, 128.5, 128.0, 127.6, 127.5, 127.1, 121.8, 114.1, 70.1, 55.3, 52.1, 46.7, 41.6; IR ν ($cm^{-1}$) 3059, 3030, 2947, 2837, 1727, 1685, 1592, 1569, 1493, 1447, 1287, 1249, 1225, 1173, 1029, 1003, 830, 750, 701, 527; HRMS-ESI: calcd. for $C_{31}H_{28}O_4NaS$ $[M + Na]^+$: 519.1606, found: 519.1583.

*methyl 2-((4-bromophenyl)thio)-5-oxo-2,3,5-triphenylpentanoate (syn-***4n***)*. White solid (70 mg, 64% yield); mp 122−124 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 2H), 7.50 – 7.44 (m, 1H), 7.39 – 7.32 (m, 2H), 7.26 – 7.20 (m, 5H), 7.20 – 7.08 (m, 7H), 7.06 – 6.96 (m, 2H), 4.69 (dd, *J* = 10.1, 2.8 Hz, 1H), 3.82 – 3.63 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 171.5, 138.8, 137.9, 137.6, 137.0, 133.0, 131.5, 130.8, 130.3, 129.0, 128.5, 128.0, 127.8, 127.8, 127.8, 127.5, 123.9, 70.4, 52.3, 47.5, 41.7; IR ν ($cm^{-1}$) 3062, 3033, 2948, 2918, 1720, 1688, 1597, 1494, 1472, 1448, 1432, 1384, 1287, 1229, 1180, 1069, 1010, 814, 748, 703, 591, 488; HRMS-ESI: calcd.

for $C_{30}H_{25}BrO_3NaS$ $[M + Na]^+$: 567.0605, found: 567.0630.

*methyl 5-oxo-3,5-diphenyl-2-(p-tolylthio)-2-(4-(trifluoromethyl)phenyl)pentanoate (syn-***4o***)*. White solid (74 mg, 67% yield); mp 148−150 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H), 7.52 – 7.44 (m, 3H), 7.40 – 7.30 (m, 4H), 7.16 – 7.09 (m, 5H), 7.02 – 6.96 (m, 4H), 4.71 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.85 (dd, *J* = 17.7, 2.2 Hz, 1H), 3.69 – 3.56 (m, 4H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.4, 170.8, 141.6, 140.0, 138.5, 137.0, 136.5, 133.1, 130.3, 130.1, 129.8, 129.5, 129.5, 129.2, 128.5, 128.0, 127.7, 127.5, 127.2, 125.4, 124.3, 124.3, 122.7, 120.0, 69.8, 52.3, 47.0, 41.2, 21.3; IR ν ($cm^{-1}$) 3062, 3032, 2951, 2922, 1735, 1683, 1619, 1597, 1493, 1449, 1329, 1228, 1169, 1121, 1073, 1018, 817, 747, 706, 690, 509; HRMS-ESI: calcd. for $C_{32}H_{27}F_3O_3NaS$ $[M + Na]^+$: 571.1531, found: 571.1553.

*methyl 2-(3-bromophenyl)-5-oxo-3,5-diphenyl-2-(p-tolylthio)pentanoate (syn-***4p***)*. White solid (72 mg, 65% yield); mp 63−65 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.51 – 7.46 (m, 1H), 7.41 – 7.35 (m, 3H), 7.26 – 7.20 (m, 2H), 7.17 – 7.09 (m, 6H), 7.05 – 6.95 (m, 4H), 4.63 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.85 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.67 – 3.56 (m, 4H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.6, 170.8, 140.0, 139.6, 138.5, 137.1, 136.5, 133.0, 130.6, 130.4, 129.5, 128.9, 128.5, 128.1, 128.0, 127.6, 127.4, 127.3, 121.5, 69.7, 52.2, 47.1, 41.1, 21.3; IR ν ($cm^{-1}$) 3060, 3030, 2948, 2921, 1729, 1686, 1595, 1581, 1492, 1474, 1448, 1432, 1287, 1226, 1180, 1080, 1019, 1002, 811, 762, 747, 701, 690, 505; HRMS-ESI: calcd. for $C_{31}H_{27}BrO_3NaS$ $[M + Na]^+$: 581.0762, found: 581.0764.

*methyl 2-(4-methoxyphenyl)-5-oxo-3,5-diphenyl-2-(p-tolylthio)pentanoate (syn-***4q***)*. White solid (58 mg, 57% yield); mp 121−123 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.54 – 7.48 (m, 1H), 7.43 – 7.37 (m, 2H), 7.24 – 7.16 (m, 4H), 7.16 – 7.10 (m, 3H), 7.06 (m, 2H), 7.04 – 6.96 (m, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.61 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.95 (dd, *J* = 17.6, 2.2 Hz, 1H), 3.85 (s, 3H), 3.72 – 3.58 (m, 4H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.9, 171.4, 158.9, 139.6, 139.0, 137.2, 136.5, 132.9, 130.9, 130.7, 129.4, 129.1, 128.4, 127.9, 127.8, 127.4, 127.0, 112.7, 69.4, 55.3, 52.0, 46.9, 41.3, 21.3; IR ν ($cm^{-1}$) 3033, 2949, 2835, 1736, 1682, 1608, 1512, 1448, 1285, 1255, 1222, 1182, 1033, 813, 748, 703, 690, 569; HRMS-ESI: calcd. for $C_{32}H_{30}O_4NaS$ $[M + Na]^+$: 533.1763, found: 533.1772.

*methyl 5-oxo-3,5-diphenyl-2-(p-tolylthio)-2-(3,4,5-trimethoxyphenyl)pentanoate (syn-***4r***)*. White solid (71 mg, 62%

yield); mp 50−52 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.53 – 7.46 (m, 1H), 7.40 – 7.35 (m, 2H), 7.19 – 7.13 (m, 5H), 7.11 – 7.07 (m, 2H), 7.05 – 7.00 (m, 2H), 6.35 (s, 2H), 4.65 (dd, *J* = 10.5, 2.3 Hz, 1H), 3.89 (dd, *J* = 17.8, 2.3 Hz, 1H), 3.83 (s, 3H), 3.76 – 3.69 (m, 4H), 3.66 (s, 6H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.0, 171.5, 152.0, 139.7, 139.1, 137.5, 137. 1, 136.6, 133.0, 132.9, 130.4, 129.4, 128.5, 127.9, 127.8, 127.6, 127.3, 107.1, 70.4, 60.9, 56.0, 52.2, 47.0, 41.8, 21.3; IR ν ($cm^{-1}$) 2953, 2925, 2853, 1727, 1685, 1585, 1509, 1492, 1449, 1413, 1324, 1278, 1227, 1181, 1127, 1004, 813, 748, 701, 691; HRMS-ESI: calcd. for $C_{34}H_{34}O_6NaS$ $[M + Na]^+$: 593.1974, found: 593.1962.

*Methyl 2-phenyl-2-(p-tolylthio)acetate (**5a**)*: The diazo compound **2a** (70.4 mg, 0.40 mmol) and thiols **1a** (49.6 mg, 0.40 mmol) in 2.0 mL $CH_2Cl_2$ were added to a suspension of $Rh_2(OAc)_4$ (1.8 mg, 0.004 mmol) and 4 Å molecular sieve (100 mg) in 2.0 mL of $CH_2Cl_2$ dropwise for 1 h. After completion of the addition, stirring was continued until the diazo compound decomposed completely. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The crude product was purified by chromatography on silica gel using petroleum ether : ethyl acetate = 100:1. Colorless oil (89 mg, 82% yield). Data for **5a**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.36 – 7.22 (m, 5H), 7.07 (m, 2H), 4.84 (s, 1H), 3.66 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.0, 138.4, 135.8, 133.4, 129.9, 129.8, 128.7, 128.5, 128.3, 56.8, 52.7, 21.2; HRMS-ESI: calcd. for $C_{16}H_{16}O_2NaS$ $[M + Na]^+$: 295.0769, found: 295.0775.

## ASSOCIATED CONTENT

### Supporting Information

$^1$H NMR, $^{13}$C NMR and HRMS spectra of all compounds. X-ray data for compound *syn*-**4n**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(10) CCDC 1530984 (*syn*-**4k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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