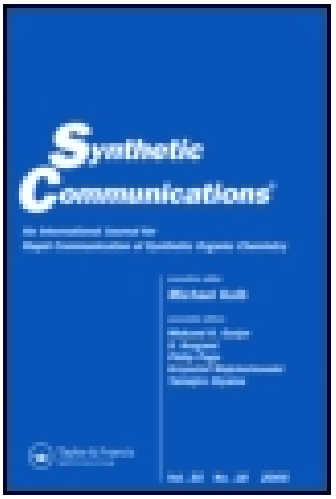

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Stereoselective Cross-Coupling of Baylis-Hillman Acetates with Diphenyl Disulfides and Diselenides Using Palladium Acetate

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STEREOSELECTIVE CROSS-COUPLING OF BAYLIS–HILLMAN ACETATES WITH DIPHENYL DISULFIDES AND DISELENIDES USING PALLADIUM ACETATE

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An efficient method is described for the stereoselective synthesis of diorganyl chalcogenides from a variety of Baylis–Hillman acetates and diaryl chalcogens using palladium catalyst. This reaction is a convenient new method to produce unsymmetrical sulfides and selenides in good yields.

Keywords: Baylis–Hillman acetates; diaryl chalcogens; stereoselective cross-coupling; thioethers

INTRODUCTION

Thioethers are versatile building blocks for the synthesis of various organosulfur compounds, and they also play an important role in biological and chemical processeses.[1] The thioether linkage has been used to prepare cyclic analogs of acyclic polypeptides to restrict their conformational mobility and thus to increase their biological activity and stability against biodegradation.[2] In recent years, organoselenium chemistry has developed an exceptional class of structures, because of oranoselenium's pivotal role in the synthesis of a large number of biological compounds and important therapeutic products ranging from antiviral and anticancer agents to naturally occuring food supplements.[3] Among the transition metals, palladium-catalyzed cross-coupling reactions of various aryl, alkyl, and vinyl halides with organoheteroatom compounds having M-M (M=S, Se, Te) bonds are now widely used for the synthesis of various diorganyl chalcogens.[4] To the best of our knowledge, similar reactions of Baylis–Hillman acetates with diphenyl diselenides and disulfides have not been reported in literature.

The Baylis–Hillman reaction is a powerful carbon–carbon-bond forming reaction between electrophiles and activated vinylic systems. The products of this reaction possess hydroxyl, alkene, and electron-withdrawing groups in close

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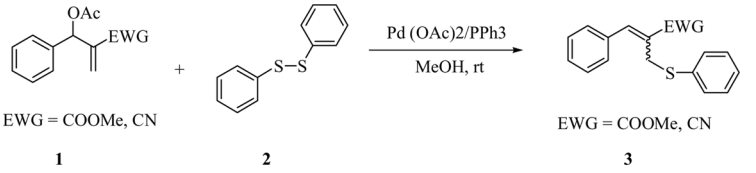


Scheme 1. Stereoselective cross-coupling of Baylis-Hillman acetates with diphenyldisulfides.

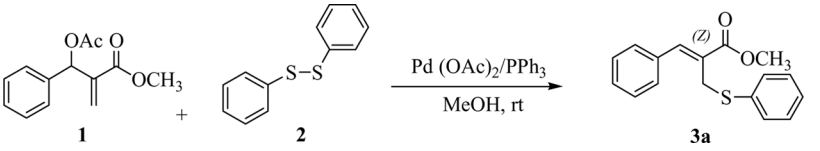
proximity, which makes them valuable in a number of stereoselective processes.[5] Baylis–Hillman adducts and their acetates are useful precursors for the synthesis of a wide variety of heterocycles and biologically active natural products including α-methylene-γ-butyrolactones and mikanecic acids, frontalin, and drugs such as trimethoprim, sarkomycin, and ilmofosine.[6] In continuation of our previous work on Baylis–Hillman acetates,[7] herein we report on our studies of the feasibility of coupling Baylis–Hillman acetates with diphenyl diselenides and disulfides using palladium catalysts (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, typical reactions with a variety of palladium catalysts and solvent systems were examined using 2-(acetoxy-phenyl-methyl)-acrylic acid methyl ester and diphenyl disulfide as model substrates (Table 1).

The greatest yields of the product were obtained when the reaction was carried out in methanol using 2 mol% of palladium acetate and 10 mol% of triphenylphosphine at room temperature. No reaction was observed in the absence

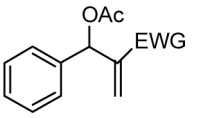
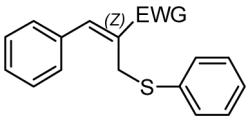
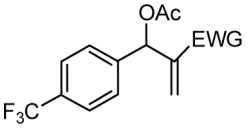
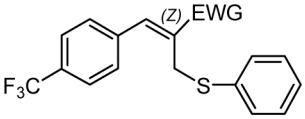
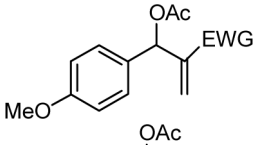
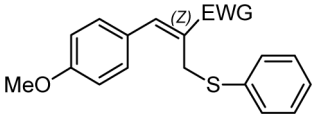
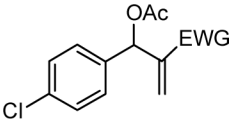
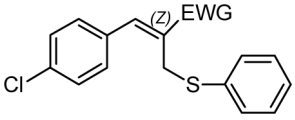
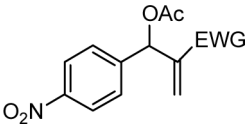
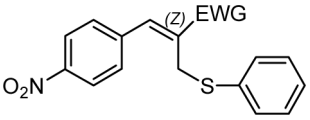
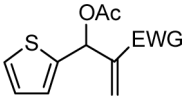
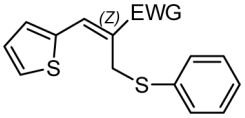
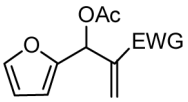
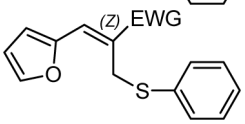
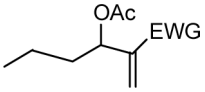
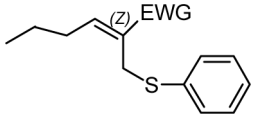
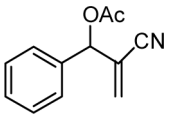
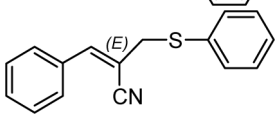
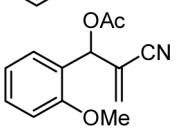
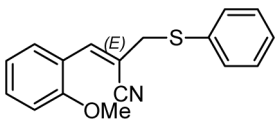
Table 1. Optimization of reaction conditions for the preparation of diorganyl chalcogenides from Baylis–Hillman acetates



Entry	Pd catalyst	Solvent	Yield (%)
1	$Pd(OAc)_2$	Methanol	0
2	$PdCl_2$	Methanol	0
3	$Pd(OAc)_2/PPh_3$	Methanol	82
4	$PdCl_2$/PPh3	Methanol	20
5	PPh_3	Methanol	0
6	$Pd(OAc)_2/PPh_3$	THF	65
7	$Pd(OAc)_2/PPh_3$	Moulene	75
8	$Pd(OAc)_2/PPh_3$	DMSO	71
9	$Pd(OAc)_2/PPh_3$	Acetonitrile	45

Note. Reactions conditions: 1 (1 mmol), 1 (0.6 mmol), Pd catalyst (2 mol%), PPh_3 (10 mol%), and solvent (3 ml) at rt for 12 h.

Table 2. Palladium-catalyzed reaction of disulfides and diselenides with Baylis–Hillman acetates[a]

Entry	Substrate **1** (EWG=COOMe)	Product[b] **3**	Time (h)	Yield (%)[c]
a			12	82
b			12	75
c			12	80
d			14	73
e			24	40
f			12	80
g			12	75
h			16	60
i			12	90[d]
j			12	67[d]

[a]Reaction conditions: Baylis–Hillman acetate (1.0 mmol), diaryl disulfide (0.6 mmol), $Pd(OAc)_2$ (2 mol%), PPh_3 (10 mol%) in methanol (3 mL) at rt.

[b]Products with (*Z*)-stereoselectivity.

[c]Isolated yields.

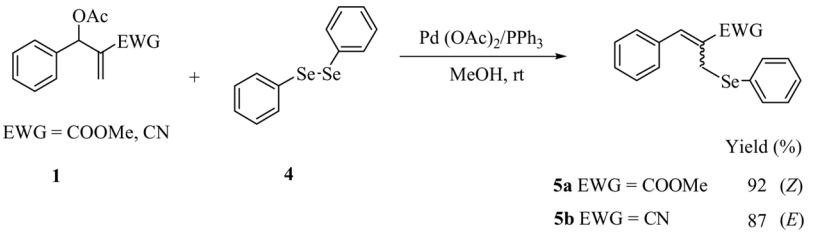
[d]Product with (*E*)-stereoselectivity.

of palladium catalyst or triphenylphosphine. Among the different solvents screened, methanol was the solvent of choice because product **3a** was formed in 82% yield. Although the reaction proceeded well while using toluene, acetonitrile (ACN), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO), the yields of the product slightly decreased.

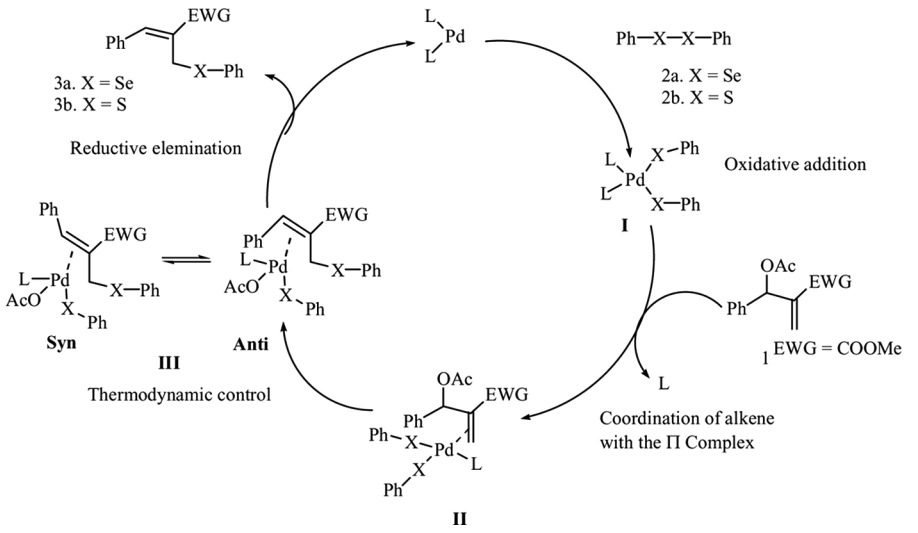
Under the optimized conditions, a wide range of structurally diverse substituted Baylis–Hillman acetates underwent reaction with diphenyl disulfides by this procedure to produce corresponding products in good yields with high stereoselectivity, and the results are summarized in Table 2. The results demonstrate that the Baylis–Hillman acetates derived from *p*-methoxy, *p*-trifluoromethyl, and *p*-chloro benzaldehydes were more reactive and gave the products in good yields (entries a–d). Baylis–Hillman acetates derived from *p*-nitrobenzaldehyde afforded the corresponding product in poor yield (entry e). Hetero-aryl Baylis–Hillman acetates were equally effective as aryl-substituted Baylis–Hillman acetates (entries f and g). Alkyl-substituted Baylis–Hillman acetate required longer reaction time, and the corresponding product was obtained in moderate yield (entry h). Similarly, Baylis–Hillman acetate **1** underwent reaction with diphenyl diselenide under identical conditions and gave the coupled product in excellent yield (Scheme 2). Further, the reaction of Baylis–Hillman acetates derived from acrylonitrile with both diphenyl disulfide and diselenide gave the coupling products (**3i**, **3j**, and **5b**) in excellent yield with (*E*)-stereoselectivity.

The stereochemistry of the products was established by nuclear Overhauser effect (NOE) experiments, which clearly showed the presence of diagnostic NOEs between the olefinic proton and methylene protons. However, in products **3a** and **3b**, no NOE was found between methylene and olefinic protons, which confirms the (*Z*)-stereoselectivity.

On the basis of these results, together with the literature reports,[5,8] we propose a plausible mechanism (Scheme 3). The first step involves the oxidative addition of diphenyl diselenide or sulfide at the palladium metal center. Coordination of **I** with the Baylis–Hillman adduct to form Π-complex **II**, followed by intramolecular insertion of X-Ph to form **III** and reductive elimination of metal, affords the product with more stable (*Z*)-stereoselectivity and regenerates the low-valent palladium species. The (*Z*)-stereoselectivity is presumably a consequence of thermodynamic control.



Scheme 2. Stereoselective cross-coupling of Baylis-Hillman acetates with diphenyldiselenides.



Scheme 3. Plausible mechanism for the stereoselective cross-coupling of Baylis-Hillman acetates with diphenyldisulfides/diphenyldiselenides.

CONCLUSION

In conclusion, we describe here the stereoselective synthesis of diorganyl chalcogenides from a variety of Baylis–Hillman acetates and diaryl chalcogens using palladium catalyst. This reaction is a convenient new method to produce unsymmetrical sulfides and selenides. The cross-coupling reactions are stereoselective and applicable to many types of substrates.

EXPERIMENTAL

Typical Experimental Procedure

To a solution of Baylis–Hillman acetate **1** (1 mmol) and diphenyl disulfide or diphenyl diselenide **2** (0.6 mmol) in methanol (3 ml), Pd $(OAc)_2$ (2 mol%) and triphenyl phosphine (10 mol%) were added. The reaction mixture was stirred at room temperature and monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was concentrated and purified by column chromatography to give the desired product **3**.

Spectroscopic Data for the Products

Compound 3a: 3-Phenyl-2-phenylsulfanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 4.12 (s, 2H), 7.13–7.43 (m, 10H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.41, 52.16, 126.76, 128.33, 128.62, 128.88, 128.97, 129.46, 130.95, 135.92, 141.51, 167.66. ESI MS (m/z): 284 (M^+).

Compound 3b: 2-Phenylsulfanylmethyl-3-(4-trifluoromethyl-phenyl)-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 3.94 (s, 2H), 7.21–7.43 (m, 7H), 7.56 (d, 2H, $J = 8.0$ Hz), 7.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.33, 52.45, 122.08, 125.43 (q, $J_{C\text{-}F} = 3.3$ Hz), 125.68, 127.23, 128.91, 129.34, 130.27, 130.67 (d, $J_{C\text{-}F} = 3.3$ Hz), 131.70, 135.09, 138.29, 139.25, 167.16. ESI MS (m/z): 373 $(M + Na)^+$.

Compound 3c: 3-(4-Methoxy-phenyl)-2-phenylsulfanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.74 (s, 3H), 3.80 (s, 3H), 3.94 (s, 2H), 7.02 (d, 2H, $J = 8.0$ Hz), 7.25–7.34 (m, 7H) 7.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.41, 52.33, 55.51, 114.01, 126.67, 127.3, 129.15, 131.99, 134.29, 140.18, 160.10, 167.79. ESI MS (m/z): 314 (M^+).

Compound 3d: 3-(4-Chloro-phenyl)-2-phenylsulfanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 3.95 (s, 2H), 7.19–7.30 (m, 7H), 7.35 (d, 2H, $J = 7.9$ Hz), 7.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.15, 51.92, 126.76, 127.98, 128.32, 128.85, 129.11, 134.43, 135.74, 141.31, 167.52. LC MS (m/z): 318 $(M)^+$.

Compound 3e: 3-(4-Nitro-phenyl)-2-phenylsulfanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.84 (s, 3H), 3.90 (s, 2H), 7.22–7.25 (m, 3H), 7.31–7.37 (m, 2H), 7.40 (d, 2H, $J = 8.3$ Hz), 7.68 (s, 1H), 8.15 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.43, 52.66, 123.64, 127.55, 128.99, 129.85, 131.15, 138.19, 167.56. LC MS (m/z): 350 $(M + Na)^+$.

Compound 3f: 2-Phenylsulfanylmethyl-3-thiophen-2-yl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 3H), 4.17 (s, 2H), 7.06 (dd, 1H, $J = 3.8$ Hz), 7.17–7.27 (m, 3H), 7.31 (d, 1H, $J = 3.8$ Hz), 7.42 (d, 2H, $J = 6.8$ Hz), 7.47 (d, 1H, $J = 4.5$ Hz), 7.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.41, 52.21, 126.24, 128.15, 129.20, 132.49, 134.50, 136.56, 140.37, 167.72. ESI MS (m/z): 290 (M^+).

Compound 3g: 3-Furan-2-yl-2-phenylsulfanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.76 (s, 3H), 4.23 (s, 2H), 6.40–6.43 (m, 1H), 6.60 (d, 2H, $J = 3.7$ Hz), 7.16–7.25 (m, 2H), 7.38–7.43 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.55, 52.05, 112.12, 116.37, 126.75, 126.81, 128.50, 132.02, 144.56, 167.10. ESI MS (m/z): 274 (M^+).

Compound 3h: 2-Phenylsulfanylmethyl-hex-2-enoic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.86 (t, 3H, $J = 7.5$ Hz), 1.25–1.39 (m, 2H, $J = 6.7$ Hz), 1.92 (q, 2H, $J = 7.5$ Hz), 3.74 (s, 3H), 3.76 (s, 2H), 6.77 (t, 1H, $J = 7.6$ Hz), 7.19–7.28 (m, 3H), 7.39 (d, 2H, $J = 7.6$ Hz). ESI MS (m/z): 250 (M^+).

Compound 3i: 3-Phenyl-2-phenylsulfanylmethyl-acrylonitrile. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.72 (s, 2H), 7.21–7.41 (m, 10H), 7.90 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 41.08, 110.23, 117.03, 127.95, 128.65, 128.77, 129.14, 130.38, 132.05, 132.90, 144.73. ESI MS (m/z): 290 $(M + K)^+$.

Compound 3j: 3-(2-Methoxy-phenyl)-2-phenylsulfanylmethyl-acrylonitrile. ^{1}H NMR (300 MHz, $CDCl_3$): 3.86 (s, 3H), 4.07 (s, 2H), 6.87 (d, 1H, $J = 8.3$ Hz), 7.02 (t, 1H, $J = 7.6$ Hz), 7.28–7.46 (m, 6H), 7.70 (s, 1H), 7.98 (d,

1H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 41.12, 55.56, 106.34, 110.71, 118.34, 120.75, 128.31, 127.25, 128.47, 130.11, 131.68, 139.69, 157.41. ESI MS (m/z): 281 (M^+).

Compound 5a: 3-Phenyl-2-phenylselanylmethyl-acrylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 4.01 (s, 2H), 7.18–7.30 (m, 10H), 7.78 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.93, 52.16, 127.42, 128.44, 128.64, 129.28, 129.75, 134.20, 139.85, 167.72. ESI MS (m/z): 331 (M^+).

Compound 5b: 3-Phenyl-2-phenylselanylmethyl-acrylonitrile. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.68 (s, 2H), 7.22–7.99 (m, 10H), 7.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.08, 104.30, 117.10, 127.41, 128.62, 128.71, 128.76, 131.72, 134.12, 140.21. ESI MS (m/z): 321 $(M + Na)^+$.

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