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Pd-Catalyzed *ortho*-Selective Oxidative Coupling of Halogenated Acetanilides with Acrylates

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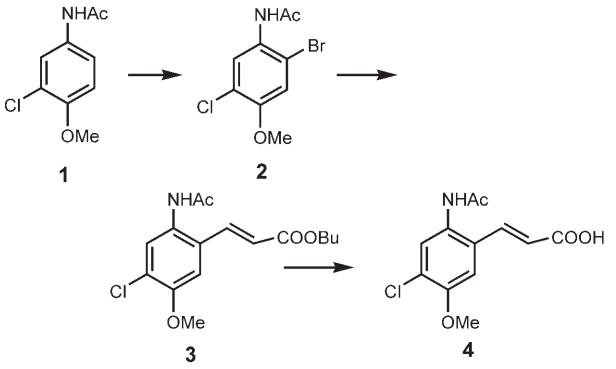
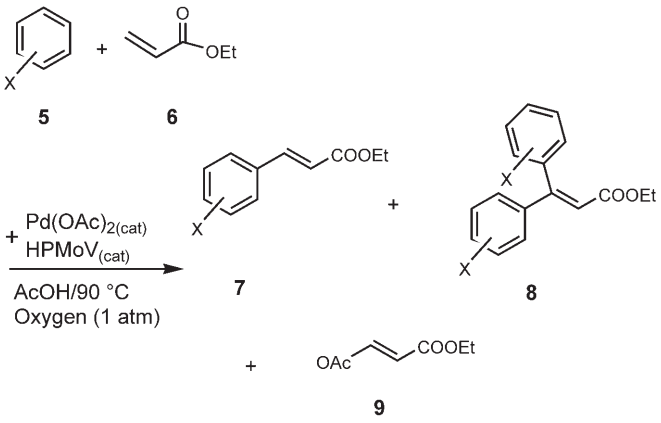
Abstract: Coupling of different halogenated acetanilides with acrylates using Pd-catalyzed *ortho*-selective C–H bond activation is reported. The yields of coupled products are low to high depending on the substrate. In general, arenes with electron-rich substituents like methoxy and methyl groups gave higher yields of the coupled products. The presence of the halogen substituent did not interfere with the activation process under these conditions

Keywords: *n*-butyl acrylate; C–H bond activation; halogenated acetanilides; oxidative cross coupling; palladium; *ortho*-selectivity



Scheme 1.

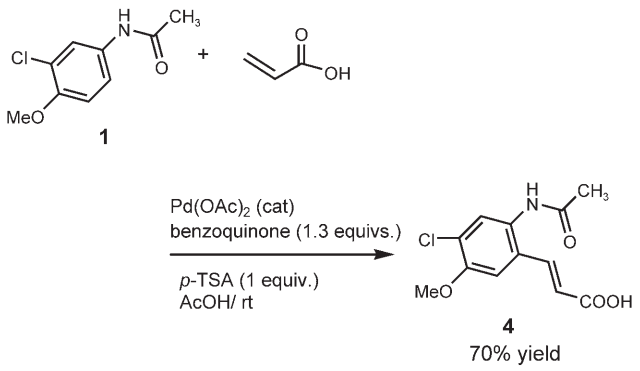


Scheme 2.

Palladium-catalyzed arylation of olefins with aryl halides, routinely referred to as the Heck reaction,[1] is a highly useful method for forming C–C bonds, and it occupies a unique place in palladium-catalyzed transformations as it is highly versatile and resourceful as evidenced by the number of articles that are published in this area. We became interested in the example shown in Scheme 1 as we needed compound **4** as an intermediate in making a pharmacologically interesting molecule.[2] Compound **4** was made in four steps starting from **1**. To introduce the acrylic function, chloroactanilide **1** was brominated to give compound **2**, which was acrylated to give **3**. A hydrolysis step was needed to make **4**.

At the outset we felt that the coupling of **1** directly with acrylic acid through the activation of the C–H bond is a simpler alternative as it avoids both bromination and hydrolysis steps. Recently, some articles were published in this direction and one such example[3] is the direct coupling of benzene with ethyl acrylate, which resulted in a mixture of products shown in Scheme 2. With substituted benzenes, the above conditions yielded an *o*-, *m*-, *p*-isomeric mixture in addition to other by-products, making this method impractical.

In contrast, the recently reported[4] *o*-selective Pd-catalyzed oxidative coupling of anilides with olefins through C–H bond activation using $Pd(OAc)_2$ and 1,4-benzoquinone at room temperature is highly interesting as these conditions are mild enough to make them practical. The open question was whether the *m*-chloro substituent was compatible with these reaction conditions. The original report itself did not cite any halogenated acetanilides as examples. Following the literature conditions, we treated acetanilide **1** with acrylic acid in the presence of 1,4-benzoquinone/*p*-TSA, $Pd(OAc)_2$ in acetic acid (Scheme 3). The desired **4** was isolated in 70% yield. Having this interesting result in hand, we investi-



Scheme 3.

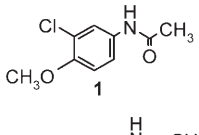
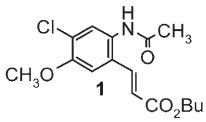
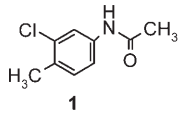
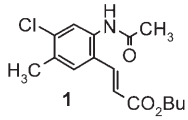
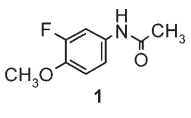
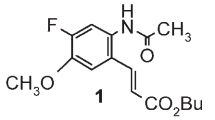
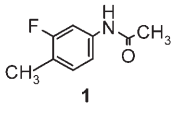
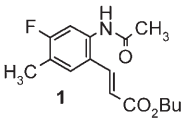
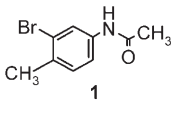
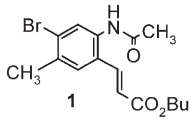
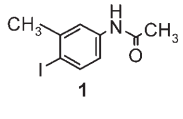
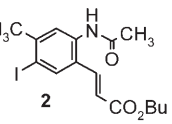
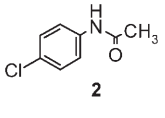
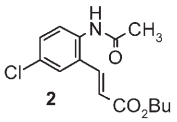
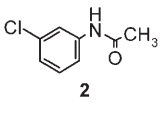
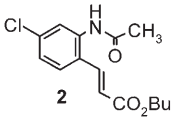
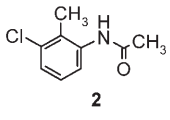
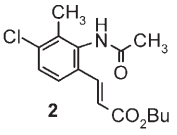
gated the generality of this reaction, coupling halogenated aromatic compounds with *n*-butyl acrylate. The results are summarized in Table 1.

In general, a number of halogenated acetanilides were found to be good substrates for this reaction. The presence of a halogen atom did not interfere in the reaction, and *o*-acrylated acetanilides were isolated in good to moderate yields depending on the substrate. Electron-rich acetanilides having methyl or methoxy substituents in the *p*-position gave higher yields of acrylated products (entries 1–5). The presence of halogen substituents in the *m*-position did not effect the yield compared to the corresponding non-halogenated cases. In other cases (entries 6–9) the yields were moderate to low.

While the preparation of our manuscript was in progress, an interesting article[5] appeared describing the catalytic coupling of anilides with chloroacrylates using one equivalent of silver triflate and $Pd(OAc)_2/PdCl_2$ as catalyst at elevated temperature (80–100 °C). In principle, these results complement the ones we obtained except that in our case the oxidative conditions are milder and benzoquinone is less expensive than silver triflate.

In summary, we have documented the coupling of halogenated acetanilides with acrylates using Pd-catalyzed *ortho* C–H activation under mild conditions.

Table 1. Oxidative coupling of halogenated acetanilides with *n*-butyl acrylate.

Entry	Acetanilide	Product	Yield [%][b]
1			82%
2			70%
3			100%
4			95%
5			67%
6			54%
7			25%
8			48%
9			28%

[a] Acetanilide (1 mol), *n*-butyl acrylate (1.1 mol), Pd(OAc)$_2$ (0.05 mol), 1,4-benzoquinone (1 mol), TsOH·H_2O (1 mol), 22 °C, 17 h.
[b] Yields were determined by HPLC analysis.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded at 500 MHz in DMSO-d_6 unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane; coupling constants (*J*) are expressed in Hertz. Melting points were measured on a Barnstead International MEL-TEMP 3.0 melting point apparatus.

3-[2-(Acetylamino)-4-chloro-5-methoxyphenyl]-2-(2*E*)-propenoic Acid (4)

Into a homogeneous mixture of acetanilide (**1**; 3.0 g, 15 mmol), 1,4-benzoquinoline (2.1 g, 19 mmol), *p*-toluenesulfonic acid monohydrate (1.43 g, 15 mmol), palladium acetate (0.2 g, 0.75 mmol) and acetic acid (20 mL), a solution of acrylic acid (1.19 g, 1.65 mmol) in toluene (12 mL) was added over 2 min. The flask was capped with a rubber septum, and the mixture was stirred at room temperature for 17 h to give a gray thick suspension. Water (50 mL) and ethyl acetate (50 mL) were added into the mixture and stirred for 15 min. The solid was filtered, washed with water (50 mL) and ethyl acetate (50 mL)

and dried to give **4** as a beige solid; yield: 2.9 g (70%); mp > 260 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.07 (3H, s), 3.49 (1H, br), 3.92 (3H, s), 6.65–6.68 (1H, d, J = 15 Hz), 7.47 (2H, s), 7.64–7.67 (1H, d, J = 15 Hz), 9.78 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 22.95, 56.45, 109.67, 120.95, 122.66, 128.11, 128.94, 130.33, 138.51, 152.31, 167.53, 169.04; MS (ESI): m/z = 270 (M + H); HR-MS (ESI): m/z = 270.0538 (calcd. for $C_{12}H_{13}ClNO_4$: 270.0533).

General Procedure for the Preparation of Acetanilides

To a pre-cooled (0 °C) solution of aniline (0.21 mol), triethylamine (0.6 mol), *N,N*-dimethylaminopyridine (0.2 g) and ethyl acetate (500 mL), a solution of acetic anhydride (0.2 mol) in ethyl acetate (80 mL) was added slowly over 1 h. The hazy mixture was warmed up to 22 °C and stirred at room temperature for 17 h to give a thick suspension. The reaction mixture was quenched with water (150 mL). The top organic layer was washed in sequence with saturated aqueous NaCl solution (150 mL), 2 N HCl solution (150 mL) and saturated NaCl aqueous solution (150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at 55 °C under vacuum to leave a viscous oil. Hexane (150 mL) was added to obtain a thick suspension at 22 °C. Acetanilides (**1**, **11**, **13**, **15**, **17**, **19**, **21**, **23** and **25**) were collected by filtration as white solids. The yield were 85–95%.

General Procedure for the Oxidative Coupling of Acetanilides with *n*-Butyl Acrylate

Into a homogeneous mixture of acetanilide (30 mmol), 1,4-benzoquinoline (30 mmol), *p*-toluenesulfonic acid monohydrate (30 mmol), palladium acetate (1.5 mmol) and acetic acid (75 mL), a solution of *n*-butyl acrylate (33 mmol) in toluene (23 mL) was added over 2 min. The flask was capped with a rubber septum, and the mixture was stirred at room temperature for 17 h. Water (150 mL) and ethyl acetate (400 mL) were added into the mixture and stirred for 15 min. Tetrahydrofuran (150 mL) was added to dissolve all insoluble solids (if necessary). The top organic layer was washed in a sequence, with water (100 mL), saturated aqueous Na_2CO_3 solution (150 mL) and saturated NaCl solution (150 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated at 55 °C under vacuum. The resulting solids were purified by silica gel column chromatography to yield the corresponding oxidatively coupled products (**10**, **12**, **14**, **16**, **18**, **20**, **22**, **24** and **26**).

***Butyl 3-[2-(Acetylamino)-4-chloro-5-methoxyphenyl]-2-(2E)-propenoate* (10):** White solid; mp 186–187 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.38–1.43 (2H, m, J = 7 Hz), 1.61–1.66 (2H, m, J = 7 Hz), 2.07 (3H, s), 3.93 (3H, s), 4.16–4.18 (2H, t, J = 7 Hz), 6.75–6.78 (1H, d, J = 15 Hz), 7.47–7.49 (2H, d, J = 15 Hz), 7.70–7.72 (1H, d, J = 15 Hz), 9.77 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 14.01, 18.70, 20.66, 30.26, 56.48, 63.75, 109.73, 119.72, 122.93, 128.04, 128.70, 130.54, 139.08, 152.32, 166.25, 168.91; MS (ESI): m/z = 326 (M + H); HR-MS (ESI): m/z = 326.1159 (calcd. for $C_{16}H_{21}ClNO_4$: 326.1159).

***Butyl 3-[2-(Acetylamino)-4-chloro-5-methylphenyl]-2-(2E)-propenoate* (12):** White solid; mp 143–144 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.38–1.43 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.09 (3H, s), 2.32 (3H, s), 4.15–4.17 (2H, t, J = 7 Hz), 6.59–6.62 (1H, d, J = 15 Hz), 7.54 (1H, s), 7.72–7.75 (1H, d, J = 15 Hz), 7.85 (1H, s), 9.89 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.61, 18.64, 18.88, 23.11, 30.26, 63.73, 119.18, 126.06, 126.98, 128.94, 132.66, 134.75, 135.86, 139.01, 166.15, 168.85; MS (ESI): m/z = 310 (M + H); HR-MS (ESI): m/z = 310.1205 (calcd. for $C_{16}H_{21}ClNO_3$: 310.1210).

***Butyl 3-[2-(Acetylamino)-4-fluoro-5-methoxyphenyl]-2-(2E)-propenoate* (14):** White solid; mp 180.5–181.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.38–1.43 (2H, m, J = 7 Hz), 1.61–1.66 (2H, m, J = 7 Hz), 2.07 (3H, s), 3.91 (3H, s), 4.15–4.18 (2H, t, J = 7 Hz), 6.70–6.73 (1H, d, J = 15 Hz), 7.29–7.31 (1H, d, J = 12 Hz), 7.54–7.56 (1H, d, J = 9 Hz), 7.72–7.75 (1H, d, J = 15 Hz), 9.83 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.48, 18.64, 22.91, 30.28, 56.31, 63.66, 111.03, 114.17, 114.30, 118.85, 125.19, 130.67, 130.73, 139.09, 145.12, 145.19, 151.34, 152.99, 166.34, 168.88; MS (ESI): m/z = 310 (M + H); HR-MS (ESI): m/z = 310.1450 (calcd. for $C_{16}H_{21}FNO_4$: 310.1455).

***Butyl 3-[2-(Acetylamino)-4-fluoro-5-methylphenyl]-2-(2E)-propenoate* (16):** White solid; mp 151–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.36–1.41 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.09 (3H, s), 2.22 (3H, s), 4.14–4.16 (2H, t, J = 7 Hz), 6.53–6.56 (1H, d, J = 15 Hz), 7.29–7.31 (1H, d, J = 7 Hz), 7.74–7.68 (1H, d, J = 15 Hz), 7.79–7.81 (1H, d, J = 7 Hz), 9.90 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.49, 13.63, 18.64, 23.16, 30.27, 63.65, 63.65, 112.13, 112.30, 118.28, 121.66, 121.79, 124.06, 136.47, 136.54, 139.14, 160.47, 162.12, 166.25, 168.80; MS (ESI): m/z = 294 (M + H); HR-MS (ESI): m/z = 294.1494 (calcd. for $C_{16}H_{21}FNO_3$: 294.1505).

***Butyl 3-[2-(Acetylamino)-4-bromo-5-methylphenyl]-2-(2E)-propenoate* (18):** White solid; mp 168–169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.35–1.41 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.09 (3H, s), 2.34 (3H, s), 4.14–4.17 (2H, t, J = 7 Hz), 6.61–6.64 (1H, d, J = 15 Hz), 7.69 (1H, s), 7.70–7.73 (1H, d, J = 15 Hz), 7.85 (1H, s), 9.88 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.51, 18.64, 21.66, 23.11, 30.26, 63.74, 119.24, 125.57, 127.54, 128.63, 129.31, 134.52, 135.83, 139.11, 166.15, 168.88; MS (ESI): m/z = 354 (M + H); HR-MS (ESI): m/z = 354.0722 (calcd. for $C_{16}H_{21}BrNO_3$: 354.0705).

***Butyl 3-[2-(Acetylamino)-4-methyl-5-iodophenyl]-2-(2E)-propenoate* (20):** White solid; mp 191–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.93 (3H, t, J = 7 Hz), 1.35–1.41 (2H, m, J = 7 Hz), 1.59–1.62 (2H, m, J = 7 Hz), 2.07 (3H, s), 2.35 (3H, s), 4.13–4.16 (2H, t, J = 7 Hz), 6.59–6.62 (1H, d, J = 15 Hz), 7.39 (1H, s), 7.62–7.65 (1H, d, J = 15 Hz), 8.23 (1H, s), 9.84 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.53, 18.63, 23.11, 27.47, 30.26, 63.71, 97.35, 119.08, 127.49, 128.19, 136.27, 137.09, 138.47, 143.25, 166.18, 168.68; MS (ESI): m/z = 402 (M + H); HR-MS (ESI): m/z = 402.0579 (calcd. for $C_{16}H_{21}INO_3$: 402.0566).

***Butyl 3-[2-(Acetylamino)-5-chlorophenyl]-2-(2E)-propenoate* (22):** White solid; mp 140–141 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.36–1.41 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.09 (3H, s), 3.32 (3H, s), 4.15–4.17 (2H, t, J = 7 Hz), 6.66–6.69 (1H, d, J = 15 Hz), 7.43–7.47 (2H, m), 7.69–7.72 (1H, d, J = 15 Hz), 7.91 (1H, s), 9.87 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 11.18, 16.29, 20.75, 27.90, 61.47, 117.96, 124.01, 125.73, 127.62,

127.71, 127.91, 133.52, 136.39, 163.74, 166.45; MS (ESI): $m/z = 296$ (M + H); HR-MS (ESI): $m/z = 296.1057$ (calcd. for $C_{15}H_{19}ClNO_3$: 296.1053).

***Butyl 3-[2-(Acetylamino)-4-chlorophenyl]-2-(2E)-propenoate* (24):** White solid; mp 154–155 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.36–1.41 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.11 (3H, s), 3.32 (3H, s), 4.15–4.17 (2H, t, J = 7 Hz), 6.59–6.61 (1H, d, J = 15 Hz), 7.26–7.27 (1H, d, J = 8 Hz), 7.61 (1H, s), 7.76–7.78 (1H, d, J = 15 Hz), 7.84–7.86 (1H, d, J = 8 Hz), 9.98 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.50, 18.51, 23.19, 30.26, 63.77, 119.49, 125.346, 125.52, 126.81, 128.49, 134.47, 138.20, 138.90, 166.11, 168.91; MS (ESI): $m/z = 296$ (M + H); HR-MS (ESI): m/z = 296.1056 (calcd. for $C_{15}H_{19}ClNO_3$: 296.1053).

***Butyl 3-[2-(Acetylamino)-3-methyl-4-chlorophenyl]-2-(2E)-propenoate* (26):** White solid; mp 120–121 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.91–0.94 (3H, t, J = 7 Hz), 1.37–1.42 (2H, m, J = 7 Hz), 1.60–1.65 (2H, m, J = 7 Hz), 2.11 (3H, s), 2.20 (3H, s), 4.14–4.16 (2H, t, J = 7 Hz), 6.57–6.60 (1H, d, J = 15 Hz), 7.40–7.42 (1H, d, J = 8 Hz), 7.64–7.67 (1H, d, J = 15 Hz), 7.72–7.74 (1H, d, J = 8 Hz), 9.78 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 13.50, 15.41, 18.66, 22.34, 30.24, 63.92, 115.62, 119.63, 125.10, 127.83, 134.39, 135.49, 137.34, 139.84, 166.07, 168.65; MS (ESI): m/z = 310 (M + H); HR-MS (ESI): m/z = 310.1212 (calcd. for $C_{16}H_{21}ClNO_3$: 310.1210).

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