Palladium-Catalyzed Direct 1,4-Addition of Heteroarenes to α,β-Unsaturated Ketones via C–H Activation

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Received: 13.03.2012; Accepted after revision: 26.04.2012

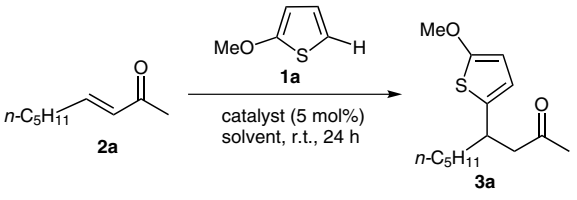
Abstract: Palladium-catalyzed direct conjugate additions of heteroarenes to α,β-unsaturated ketones via C–H activation are described. The reactions of heteroarenes with α,β-unsaturated ketones proceeded smoothly in the presence of $PdCl_2$ as a catalyst under mild conditions to give the corresponding Michael adducts in moderate to excellent yields.

Key words: palladium catalyst, direct conjugate addition, heteroarene, unsaturated ketone, C–H activation

Heteroaryl groups are frequently found in various bioactive molecules and functional materials.[1] The development of a convenient and efficient method for the synthesis of heteroaryl-group-containing compounds is still a challenge in organic synthesis.[2] Among the new $C_{(heteroaryl)}$–$C_{(aryl\ or\ alkyl)}$ bond-forming processes, palladium-catalyzed coupling reactions via the C–H activation of heteroarenes have recently emerged as an extremely powerful tool for the synthesis of heteroarene derivatives. These reactions include the cross-coupling reaction of heteroarenes with aryl halides[3] or pseudohalides[4] and arylboronic reagents,[5] the oxidative coupling between different heteroarenes,[6] the alkenylation of heteroarenes with alkenes,[7] and the alkynylation of heteroarenes with alkynes.[8] The palladium-catalyzed direct carbonylation of heteroarenes via the C–H activation of heteroarenes has also been reported recently.[9] To the best of our knowledge, no report on the palladium-catalyzed direct 1,4-addition of heteroarenes to α,β-unsaturated ketones via C–H activation is currently available.[10] From the mechanistic analysis of these cross-coupling reactions, the palladium-catalyzed direct conjugate addition of heteroarenes to α,β-unsaturated ketones is anticipated to occur via C–H activation. Thus, the palladium-catalyzed direct 1,4-addition of five-membered heteroarenes to α,β-unsaturated ketones via C–H activation was investigated in the present study, and the results are reported herein.

In our initial studies, the reaction of 2-methoxythiophene (**1a**) with (*E*)-non-3-en-2-one (**2a**) was selected as a model reaction for optimizing the reaction conditions. The results are shown in Table 1. The reaction of **1a** with **2a** was carried out under similar conditions as that employed in the palladium-catalyzed direct arylation of heteroarenes with aryl boronic acids reported by Shi et al.[11] The desired product **3a** was obtained in 50% yield (Table 1, entry 1). The use of $Pd(acac)_2$, $Pd(PPh_3)_2Cl_2$, and $PdCl_2$ as Pd source, instead of $Pd(OAc)_2$, did not give the desired product in high yield (45% to 53%, Table 1, entries 2–4). No reaction was observed in the absence of a palladium catalyst (Table 1, entry 5). The solvents were then screened using $PdCl_2$ as the catalyst (Table 1, entries 6–9). Both aprotic nonpolar (toluene and CH_2Cl_2) and polar solvents (DMF and MeCN) resulted in no reaction. Gratifyingly, the desired reaction proceeded smoothly in a protic solvent methanol (MeOH) to afford product **3a** in 97% yield (Table 1, entry 10). Therefore, the subsequent reactions of oxygen-, nitrogen-, and sulfur-atom-containing five-membered heteroarenes with α,β-unsaturated ketones were performed in the presence of $PdCl_2$ as the catalyst in MeOH at room temperature under a nitrogen atmosphere.

Table 1 Catalyst and Solvent Screening[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	AcOH	50
2	$Pd(acac)_2$	AcOH	52
3	$Pd(PPh_3)_2Cl_2$	AcOH	45
4	$PdCl_2$	AcOH	53
5[c]	none	AcOH	n.r.[d]
6	$PdCl_2$	toluene	n.r.[d]
7	$PdCl_2$	CH_2Cl_2	n.r.[d]
8	$PdCl_2$	DMF	n.r.[d]
9	$PdCl_2$	MeCN	n.r.[d]
10	$PdCl_2$	MeOH	97

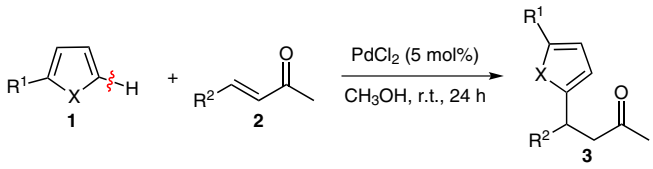
[a] Reaction conditions: **1a** (57.1 mg, 0.5 mmol), **2a** (35.1 mg, 0.25 mmol), catalyst (5 mol%), solvent (2 mL) at r.t. under a nitrogen atmosphere.
[b] Isolated yield.
[c] Reaction mixture stirred in the absence of catalyst.
[d] No reaction observed; starting materials recovered.

SYNLETT 2012, 23, 1605–1608
Advanced online publication: 13.06.2012
DOI: 10.1055/s-0031-1290382; Art ID: ST-2012-W0233-L

The reactions of five-membered heteroarenes **1a**–**d** with α,β-unsaturated ketones **2a** and **2b** were performed under optimized reaction conditions. The results are summarized in Table 2.[12] The reaction of five-membered heteroarene **1a** with α,β-unsaturated ketone (*E*)-4-phenylbut-3-en-2-one (**2b**) yielded 76% desired adduct **3b** (Table 2, entry 2).

The reactions of 2-methylfuran (**1b**) with α,β-unsaturated ketones **2a** and **2b** proceeded smoothly to give addition products **3c** and **3d** in excellent yields (98%, Table 2, entries 3 and 4, respectively). When furan (**1c**) was used as starting material, the double-alkylated product was isolated along with the monoalkylated product. Adducts **3e** (Table 2, entry 5) and **3f** (Table 2, entry 6) were obtained as

Table 2 Palladium-Catalyzed Direct 1,4-Addition of Heteroarenes **1** to α,β-Unsaturated Ketones **2**[a]



Entry	Heteroarene **1**	Ketone **2**	Product **3**	Yield (%)[b]
1	**1a**	**2a**	**3a**	97
2	**1a**	**2b**	**3b**	76
3	**1b**	**2a**	**3c**	98
4	**1b**	**2b**	**3d**	98
5	**1c**	**2a**	**3e**	67[c]
6	**1c**	**2b**	**3f**	45[d]
7	**1d**	**2a**	**3g**	70
8	**1d**	**2b**	**3h**	42[e]

[a] Reaction conditions: five-membered heteroarene **1** (1.0 mmol), α,β-unsaturated ketone **2** (0.5 mmol), $PdCl_2$ (4.4 mg, 5 mol%), MeOH (2 mL) at r.t. for 24 h under a nitrogen atmosphere.
[b] Isolated yield.
[c] Double alkylated product isolated in 15% yield.
[d] Double alkylated product isolated in 22% yield.
[e] Starting material **2b** recovered in 33% yield.

major products in 67% and 45% yields, respectively. The related double-alkylated products were isolated with 15% and 22% yields, respectively (Table 2, entries 5 and 6). By contrast, when the *N*-methylated pyrrole 1-methyl-1*H*-pyrrole (**1d**) was examined, a sole monoalkylated product was obtained. Desired product **3g** was isolated in 70% yield from the reaction of **1d** with **2a** (Table 2, entry 7). α,β-Unsaturated ketone **2b** exhibited low reactivity in the conjugate addition reaction with **1d**, which led to the formation of monoalkylated product **3h** in only 42% yield; **2b** was recovered in 33% yield (Table 2, entry 8).

To confirm the presented reaction of five-membered heteroarenes with α,β-unsaturated ketones processed via C–H activation, ^{1}H NMR analysis of a solution of **1a** in deuteromethanol (CD_3OD), and a mixture of $PdCl_2$, **1a**, and CD_3OD were performed. The results are shown in Figure 1. A double resonance for the H_a of **1a** was observed at δ = 6.60 ppm in the ^{1}H NMR spectrum (Figure 1, A). As expected, the resonance peak of H_a reduced with increasing $PdCl_2$ amount. The ^{1}H NMR spectrum of **1a** was determined in the presence of 0.5 equivalents of $PdCl_2$. At the same time, the resonance peak of H_a was reduced to half (Figure 1, B), compared with that in the ^{1}H NMR (Figure 1, A). Furthermore, the resonance peak of H_a almost disappeared, when **1a** was treated with one equivalent of $PdCl_2$ in CD_3OD (Figure 1, C). The reaction of heteroarene **1a** with $PdCl_2$ is believed to form a new palladium species **4** (Scheme 1), which could undergo a 1,4-addition reaction with a α,β-unsaturated ketone.[13]

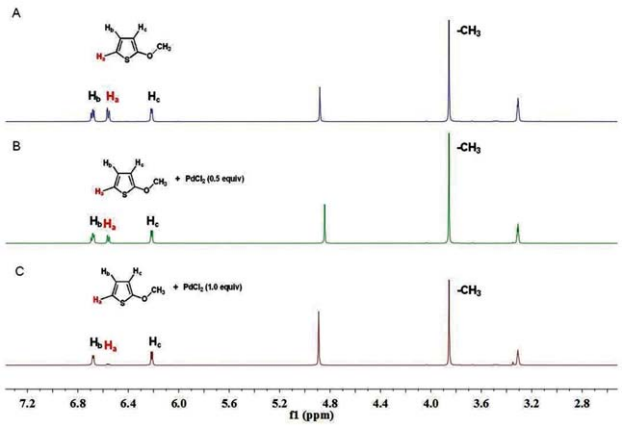


Figure 1 ^{1}H NMR spectra obtained in deuteromethanol (CD_3OD). A: **1a**; B: **1a** + $PdCl_2$ (0.5 equiv); C: **1a** + $PdCl_2$ (1.0 equiv).

Scheme 1

In summary, a convenient and efficient method for the synthesis of heteroaryl-group-containing compounds via the palladium-catalyzed C–H activation of heteroarenes has been developed in the present study. The palladium-catalyzed direct conjugate addition of heteroarenes to α,β-unsaturated ketones proceeded smoothly under mild reaction conditions to give Michael adducts in moderate to excellent yields. The present study is the first to demonstrate the use of the catalytic C–H activation protocol in the direct conjugate addition of heteroarenes to α,β-unsaturated ketones. Further studies on the extension of the reaction scope and the asymmetric direct conjugate addition are currently under way.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (No. 21002010) for their financial support. This work was also supported by the Fundamental Research Funds for the Central Universities [DUT10RC(3)28].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure**

To a mixture of $PdCl_2$ (0.025 mol, 4.4 mg), α,β-unsaturated ketone **2** (0.5 mmol), and MeOH (2.0 mL), heteroarene **1** (1.0 mmol, 2.0 equiv) was added. After the resultant mixture was stirred at r.t. for 24 h, the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (eluent: PE–EtOAc = 10:1 to 20:1, v/v) to afford the desired product **3**.

4-(5-Methoxythiophen-2-yl)-4-phenylbutan-2-one (3b)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.31 (m, 5 H), 6.37 (d, *J* = 3.8 Hz, 1 H), 5.94 (d, *J* = 3.8 Hz, 1 H), 4.62 (t, *J* = 7.4 Hz, 1 H), 3.80 (s, 3 H), 3.18 (dd, *J* = 16.6, 7.5 Hz, 1 H), 3.07 (dd, *J* = 16.6, 7.3 Hz, 1 H), 2.10 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 165.1, 143.4, 134.0, 128.7, 127.6, 126.9, 121.2, 102.8, 60.2, 50.6, 42.0, 30.7. IR (neat): 3413, 3026, 2925, 1715, 1559, 1505, 1451, 1430, 1355, 1203, 1153, 990, 762, 698 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{16}O_2S$ $[M]^+$: 260.0871; found: 260.0876.

4-(Furan-2-yl)nonan-2-one (3e)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 1.8, 0.8 Hz, 1 H), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1 H), 5.98 (dd, *J* = 3.2, 0.8 Hz, 1 H), 3.22–3.30 (m, 1 H), 2.78 (dd, *J* = 16.3, 7.6 Hz, 1 H), 2.63 (dd, *J* = 16.3, 6.6 Hz, 1 H), 2.07 (s, 3 H), 1.49–1.66 (m, 2 H), 1.21–1.26 (m, 6 H), 0.85 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6, 157.5, 140.9, 110.0, 105.1, 48.0, 34.5, 34.0, 31.6, 30.3, 26.8, 22.5, 14.0. IR (neat): 2956, 2929, 2858, 1719, 1360, 1159, 1148, 1010, 729 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{13}H_{20}O_2$ $[M + Na]^+$: 231.1361; found: 231.1364.

4-(1-Methyl-1*H*-pyrrol-2-yl)nonan-2-one (3g)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (t, *J* = 1.8, 1.9 Hz, 1 H), 6.04 (t, *J* = 3.1, 3.0 Hz, 1 H), 5.84 (dd, *J* = 3.2, 1.8 Hz, 1 H), 3.57 (s, 3 H), 3.19–3.26 (m, 1 H), 2.74 (dd, *J* = 16.7, 7.5 Hz, 1 H), 2.65 (dd, *J* = 16.6, 6.5 Hz, 1 H), 2.04 (s, 3 H), 1.50–1.56 (m, 2 H), 1.19–1.26 (m, 6 H), 0.84 (t, *J* = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.3, 136.7, 120.9, 106.8, 104.1, 50.2, 36.6, 33.9, 32.0, 31.8, 31.0, 27.1, 22.7, 14.2. IR (neat): 2954, 2927, 2856, 1716, 1489, 1359, 1299, 1162, 702 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{14}H_{23}NO$ $[M + Na]^+$: 244.1677; found: 244.1684.

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