Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5833

www.rsc.org/obc

PAPER

Ligand-free palladium-catalyzed intramolecular Heck reaction of secondary benzylic bromides†

Wei Zhou, Guanghui An, Guangqian Zhang, Jianlin Han* and Yi Pan*

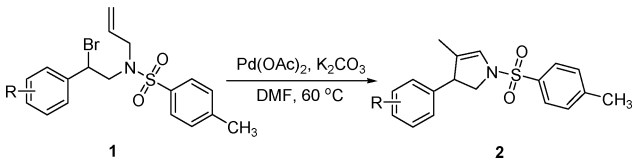
Received 14th February 2011, Accepted 26th May 2011
DOI: 10.1039/c1ob05231d

A facile ligand-free palladium-catalyzed intramolecular Heck reaction of β-hydrogen-containing secondary benzylic bromides was developed, which affords pyrroline derivatives with good regioselectivities.

Introduction

The palladium-catalyzed Heck reaction is one of the most powerful tools for carbon–carbon bond formation processes in organic synthetic chemistry,[1] and many examples have been reported for this coupling of nucleophiles with aryl or alkenyl electrophiles.[2] However, the similar coupling of alkyl electrophiles still remains a great challenge,[3–7] especially, the coupling reaction of secondary alkyl halides containing β-hydrogens. In the past five years, significant progress has been achieved in other transition-metal-catalyzed Heck-type couplings of secondary alkyl halides, which generally proceed through radical intermediates.[8,9] In contrast, the palladium-catalyzed reactions of secondary alkyl halides are still in their preliminary stages.[10]

To develop the palladium-catalyzed Heck-type reaction of β-hydrogen-containing secondary alkyl halides, several challenges need to be taken into account, which include the high activation energy barrier to the oxidative addition of secondary alkyl electrophiles to palladium[11] and the tendency of alkyl-palladium species to undergo β-hydride elimination.[5a] During our ongoing studies on the aminohalogenation reaction[12] and palladium-catalyzed reaction,[4c] we found that simple palladium acetate could efficiently catalyze the Heck reaction of secondary benzylic bromides bearing β-hydrogens, resulting in the desired coupling products. Herein, we report a ligand-free palladium-catalyzed intramolecular Heck reaction of β-hydrogen-containing secondary benzylic bromides, affording pyrroline derivatives in good yields and good regioselectivities (Scheme 1).



1 2

Scheme 1 Palladium-catalyzed intramolecular Heck reaction.

Results and discussion

The starting materials for the intramolecular Heck reaction could be easily obtained from our recently reported aminohalogenation reaction.[12] Based on the previous studies on the palladium-catalyzed cross-coupling of primary benzylic halides,[4c] the preliminary scan of the reaction conditions was focused on using $Pd(OAc)_2$ as catalyst, Bu_3N as base and DMF as solvent. The reaction afforded a product of 2-pyrroline derivative **2a** with 48% yield (Table 1, entry 1). The structure of **2a** has been confirmed by X-ray diffraction analysis (Fig. 1).

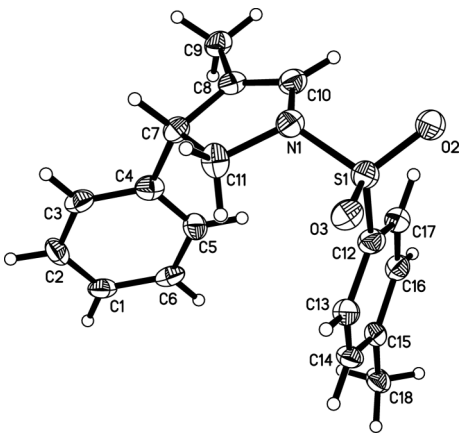


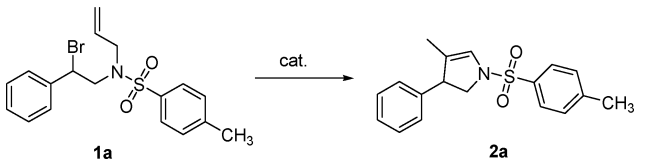
Fig. 1 ORTEP diagram drawing of **2a**.

The variation of base from Bu_3N to K_2CO_3 achieved a significant increase in the yield (entry 2). Further screening of reaction conditions revealed that **2a** could be obtained in 86%

School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, P.R. China. E-mail: hanjl@nju.edu.cn, yipan@nju.edu.cn; Fax: +86-25-83593153

† Electronic supplementary information (ESI) available: General experimental procedures, spectral data and copies of ^1H NMR and ^{13}C NMR spectra of products. CCDC reference number 780714 (**2a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05231d

Table 1 Optimization of reaction conditions[a]



entry	catalyst	base	solvent	T/°C	yield (%)[c]
1	$Pd(OAc)_2$	n-Bu_3N	DMF	100	48
2	$Pd(OAc)_2$	K_2CO_3	DMF	100	62
3	$Pd(OAc)_2$	K_2CO_3	DMF	60	86
4	$Pd(OAc)_2/PPh_3$[b]	K_2CO_3	DMF	60	<5
5	$PdCl_2$	K_2CO_3	DMF	60	38
6	$PdCl_2/PPh_3$[b]	K_2CO_3	DMF	60	<5
7	$Pd(OAc)_2$/SIMes·HBF_4[d]	K_2CO_3	DMF	60	22
8	$Pd(OAc)_2$/Xantphos[b]	K_2CO_3	DMF	60	<10
9	$Pd(OAc)_2$	K_2CO_3	DMAc	60	78
10	$Pd(OAc)_2$	K_2CO_3	THF	60	N.R.
11	$Pd(OAc)_2$	K_2CO_3	DMSO	60	N.R.

[a] Reaction conditions: 0.5 mmol substrate with 2.0 equiv base and 1 mol% catalyst in 1.0 mL solvent for 24 h under N_2. [b] 2 mol% ligand was added. [c] Isolated yields. [d] 2 mol% *t*-BuOK was added.

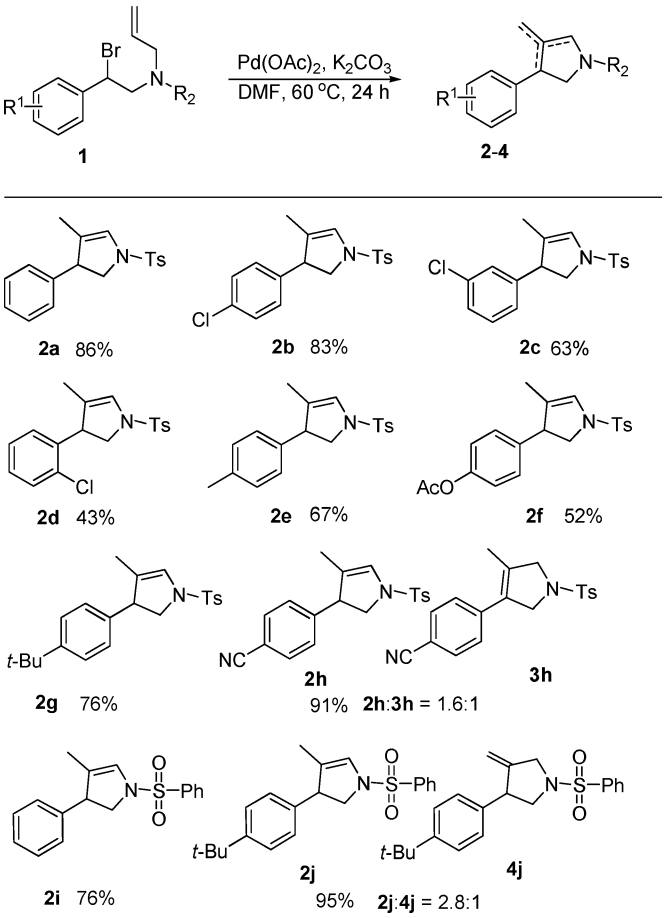
yield when the reaction temperature was decreased to 60 °C (entry 3). The combination of a palladium salt catalyst with PPh_3 did not give any improvement on the yields (entries 4 and 6). Other ligands, including SIMes·HBF_4[5a] and Xantphos[13] were also less effective (entries 7 and 8). Various solvents were tested and DMF was found to be the most efficient media for the reaction (entries 9–11).

We then examined the scope of the ligand-free palladium-catalyzed intramolecular Heck reaction by using a variety of β-hydrogen-containing secondary benzylic bromides (Table 2).

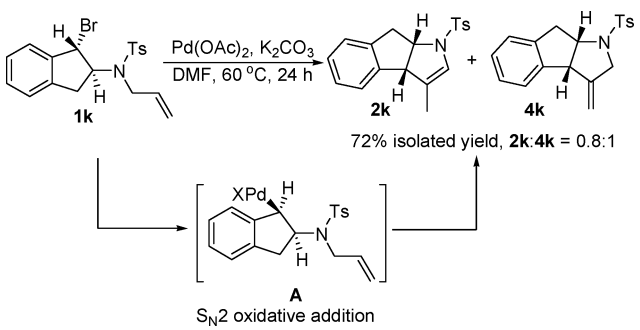
The intramolecular cyclization can proceed smoothly for a wide range of substrates, resulting in moderate to excellent chemical yields. The substrates with a chloro substituent on the aromatic ring were well tolerated, and gave good yields (**2b–2d**). The aromatic rings with electron-donating groups were also good substrates for the reaction (**2e** and **2g**). In the case of **1h**, two different cyclic products were obtained in a total 91% yield (**2h** : **3h** = 1.6 : 1). We then examined variation on the nitrogen atom, and found that the phenylsulfonyl group could also work well, resulting in 76% yield (**2i**). For the substrate **1j**, the desired product was obtained in 70% yield, along with 25% yield of product containing exocyclic double bond. Furthermore, excellent regioselectivities were detected for almost all the cases without the aid of any ligands. The cyclic products obtained belong to an important type of biologically active compounds, and can also be easily transformed into pyrrole analogues.[14]

As in previous reports, the palladium complex catalyzed Heck reactions of alkyl halides bearing β-hydrogens proceed through an alkylmetal intermediate,[5a,15] which are different from the processes catalyzed by other metals.[6,7] To find whether the current ligand-free palladium-catalyzed system follows the alkylmetal or radical pathway, an *anti*-bromoamine containing a five-member ring (**1k**) was prepared, which was subjected to the reaction under the optimized conditions (Scheme 2). Only the isomers (**2k** and **4k**) are obtained from the reaction, and this stereochemistry reveals that our ligand-free palladium-catalyzed reaction proceeds *via*

Table 2 Intramolecular Heck reactions[a,b]



[a] Reaction conditions: 0.5 mmol substrate with 2.0 equiv K_2CO_3 and 1 mol% $Pd(OAc)_2$ in 1.0 mL DMF at 60 °C for 24 h under N_2. [b] Isolated yields.



Scheme 2 Mechanism study of the intramolecular Heck reaction.

benzylpalladium intermediate (**A**) with an S_N2 mechanism for oxidative addition. This pathway is different from the other metal-catalyzed related radical transformations.

Experimental section

General information

Solvents were dried and distilled prior to use. Melting points are uncorrected. IR spectra were collected on Bruker Vector

22 in KBr pellets. ^{1}H and ^{13}C NMR (TMS used as internal standard) spectra were collected in $CDCl_3$ with a Bruker ARX 300 spectrometer. High resolution mass spectra for all the new compounds were done by a Micromass Q-Tof instrument (ESI). Thin layer chromatography was carried out on Silica Gel 60 F-254 TLC plates. 20 cm × 20 cm Gel 60 F-254 TLC plates were used for Isolation. Flash chromatography was performed on silica gel 60 (200–300 mesh).

Typical procedure for the intramolecular Heck reaction

Into a dry vial was added substrate **1** (0.5 mmol), freshly dried K_2CO_3 (138 mg, 1 mmol), $Pd(OAc)_2$ (1.1 mg, 1 mol%) and freshly distilled DMF (1.0 mL) under a nitrogen atmosphere. The mixture was stirred at 60 °C for 24 h. After cooling, the reaction was quenched with water (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, concentrated and purified by column (EtOAc/petroleum ether, 1 : 20 v/v) to give the product.

4-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2a)

White solid, m.p. 64–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.71 (m, 2H), 7.34–7.38 (m, 2H), 7.14–7.17 (m, 3H), 6.74–6.77 (m, 2H), 6.26–6.27 (m, 1H), 3.94 (t, J = 10.7 Hz, 1H), 3.71–3.77 (m, 1H), 3.38 (dd, J = 6.1, 10.8 Hz, 1H), 2.48 (s, 3H), 1.43 (t, J = 1.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.52, 141.44, 131.99, 129.42, 128.24, 127.58, 126.98, 126.61, 125.26, 124.72, 55.68, 51.71, 21.17, 11.50 ppm; IR (KBr): υ = 3094, 2947, 1662, 1597, 1493 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{18}H_{19}NO_2SNa$: 336.1029, Found: 336.1019.

3-(4-Chlorophenyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2b)

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.69 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.10–7.15 (m, 2H), 6.67–6.72 (m, 2H), 6.25–6.26 (m, 1H), 3.92 (t, J = 11.0 Hz, 1H), 3.74–3.68 (m, 1H), 3.34 (dd, J = 6.0, 10.9 Hz, 1H), 2.49 (s, 3H), 1.42 (t, J = 1.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.93, 140.36, 132.82, 132.46, 129.77, 128.80, 128.72, 127.98, 126.04, 124.45, 55.88, 51.57, 21.62, 11.85 ppm; IR (KBr): υ = 2921, 1489 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{18}H_{18}ClNO_2SNa$: 370.0639, Found: 370.0629.

3-(3-Chlorophenyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2c)

White solid, m.p. 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.07–7.17 (m, 2H), 6.70–6.72 (m, 1H), 6.61–6.62 (m, 1 H), 6.26–6.27 (m, 1H), 3.95 (t, J = 11.0 Hz, 1H), 3.73–3.69 (m, 1H), 3.33 (dd, J = 6.0, 11.0 Hz, 1H), 2.48 (s, 3H), 1.43 (t, J = 1.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.18, 144.00, 134.62, 132.14, 129.89, 129.85, 127.94, 127.35, 127.28, 126.25, 125.83, 124.17, 55.75, 51.88, 21.75, 11.92 ppm; IR (KBr): υ = 2979, 1650, 1476 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{18}H_{18}ClNO_2SNa$: 370.0639, Found: 370.0646.

3-(2-Chlorophenyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2d)

White solid, m.p. 122–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.3 Hz, 2H), 7.26–7.32 (m, 3H), 7.11–713 (m, 1H), 7.01–7.08 (m, 1H), 6.63–6.64 (m, 1H), 6.31–6.32 (m, 1H), 4.26–4.31 (m, 1H), 3.92 (t, J = 10.8 Hz, 1H), 3.38 (dd, J = 5.2, 11.0 Hz, 1H), 2.46 (s, 3H), 1.52 (t, J = 1.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.83, 139.11, 133.56, 132.57, 129.71, 129.41, 128.20, 128.08, 127.90, 127.24, 126.86, 123.84, 55.25, 47.77, 21.61, 12.09 ppm; IR (KBr): υ = 2975, 1469 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{18}H_{18}ClNO_2SNa$: 370.0639, Found: 370.0650.

4-Methyl-3-*p*-tolyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2e)

White solid, m.p. 46–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 7.9 Hz, 2H), 6.23–6.24 (m, 1H), 3.92 (t, J = 10.7 Hz, 1H), 3.68–3.74 (m, 1H), 3.34 (dd, J = 6.2, 10.8 Hz, 1H), 2.49 (s, 3H), 2.28 (s, 3H), 1.43–1.41 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.76, 138.79, 136.64, 132.44, 129.71, 129.31, 128.02, 127.31, 125.48, 125.16, 56.10, 51.83, 21.66, 21.06, 11.92 ppm; IR (KBr): υ = 2925, 2855, 1463 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{19}H_{21}NO_2SNa$: 350.1185, Found: 350.1194.

4-(4-Methyl-1-tosyl-2,3-dihydro-1*H*-pyrrol-3-yl)phenyl acetate (2f)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 2H), 7.34 (d, J = 7.7 Hz, 2H), 6.90–6.85 (m, 2H), 6.77–6.73 (m, 2H), 6.25–6.24 (t, J = 1.6 Hz, 1H), 3.91 (t, J = 10.8 Hz, 1H), 3.77–3.71 (m, 1H), 3.34 (dd, J = 6.0, 10.8 Hz, 1H), 2.46 (s, 3H), 2.27 (s, 3H), 1.42 (t, J = 1.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.42, 149.60, 143.90, 139.29, 132.38, 129.79, 128.36, 127.98, 125.85, 124.75, 121.71, 55.96, 51.60, 21.61, 21.14, 11.94 ppm; IR (KBr): υ = 2923, 1758, 1597, 1503 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{20}H_{21}NO_4SNa$: 394.1084, Found: 394.1080.

3-(4-*tert*-Butylphenyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (2g)

White solid, m.p. 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.20–7.16 (m, 2H), 6.71–6.66 (m, 2H), 6.26–6.25 (m, 1H), 3.93 (t, J = 10.6 Hz, 1H), 3.76–3.70 (m, 1H), 3.38 (dd, J = 6.2, 10.7 Hz, 1H), 2.50 (s, 3H), 1.44 (t, J = 1.4 Hz, 3H), 1.29 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.85, 143.75, 138.66, 132.56, 129.77, 128.04, 127.05, 125.49, 125.46, 125.26, 56.05, 51.74, 34.41, 31.36, 21.66, 12.03 ppm; IR (KBr): υ = 2960, 2868, 1596, 1509 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{22}H_{27}NO_2SNa$: 392.1655, Found: 392.1666.

4-(4-Methyl-1-tosyl-2,3-dihydro-1*H*-pyrrol-3-yl)benzonitrile (2h)

White solid, m.p. 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.69 (m, 2H), 7.43–7.47 (m, 2H), 7.35 (d, J = 7.8 Hz, 2H), 6.90–6.87 (m, 2H), 6.29–6.30 (m, 1H), 3.91 (t, J = 10.8 Hz, 1H), 3.75–3.80 (m, 1H), 3.35–3.40 (dd, J = 5.2, 10.9 Hz, 1H), 2.49 (s, 3H), 1.42 (t, J = 1.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.32, 144.16, 132.54, 132.23, 129.87, 128.19, 127.98, 126.71, 123.75, 118.66, 111.04, 55.55, 52.09, 21.68, 11.93 ppm; IR (KBr): υ = 2924, 2882, 2223, 1601 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{19}H_{18}N_2O_2SNa$: 361.0981, Found: 361.0973.

4-(4-Methyl-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl)benzonitrile (3h)

White solid, m.p. 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.73 (m, 2H), 7.64–7.60 (m, 2H), 7.33 (d, J = 7.8 Hz,

2H), 7.30–7.27 (m, 2H), 4.39–4.44 (m, 2H), 4.20–4.22 (m, 2H), 2.43 (s, 3H), 1.81 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.82, 138.41, 133.82, 132.81, 132.33, 129.95, 128.67, 128.07, 127.57, 118.62, 111.13, 60.07, 57.18, 21.61, 13.05 ppm; IR (KBr): υ = 2921, 2853, 2226, 1602 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{19}H_{18}N_2O_2SNa$: 361.0981, Found: 361.0987.

4-Methyl-3-phenyl-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (2i)

White solid, m.p. 143–145 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 2H), 7.67–7.64 (m, 1H), 7.60–7.55 (m, 2H), 7.18–7.15 (m, 3H), 6.76–6.72 (m, 2H), 6.28–6.27 (m, 1H), 3.97 (t, J = 10.8 Hz, 1H), 3.78–3.72 (m, 1H), 3.38 (dd, J = 6.3, 10.8 Hz, 1H), 1.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.70, 135.43, 132.99, 129.16, 128.71, 128.24, 127.96, 127.37, 127.08, 125.51, 56.07, 52.20, 11.93 ppm; IR (KBr): υ = 3064, 2878, 1581 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{17}H_{17}NO_2SNa$: 322.0872, Found: 322.0870.

3-(4-*tert*-Butylphenyl)-4-methyl-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (2j)

White solid, m.p. 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 2H), 7.68–7.64 (m, 1H), 7.60–7.57 (m, 2H), 7.20–7.16 (m, 2H), 6.70–6.67 (m, 2H), 6.28–6.27 (m, 1H), 3.95 (t, J = 10.8 Hz, 1H), 3.77–3.71 (m, 1H), 3.38 (dd, J = 6.4, 10.8 Hz, 1H), 1.44 (t, J = 1.1 Hz, 3H), 1.28 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.90, 138.52, 132.98, 129.16, 127.97, 127.80, 127.03, 125.58, 125.38, 125.31, 56.10, 51.69, 34.45, 31.36, 12.04 ppm; IR (KBr): υ = 3061, 2961, 2870, 1510, 1468 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{21}H_{25}NO_2SNa$: 378.1498, Found: 378.1486.

3-(4-*tert*-Butylphenyl)-4-methylene-1-(phenylsulfonyl)pyrrolidine (4j)

White solid, m.p. 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2H), 7.65–7.62 (m, 1H), 7.60–7.56 (m, 2H), 7.32–7.28 (m, 2H), 7.06–7.02 (m, 2H), 5.03 (d, J = 2.0 Hz, 1H), 4.69 (d, J = 2.2 Hz, 1H), 4.16–4.09 (m, 1H), 3.96–3.90 (m, 1H), 3.83–3.75 (m, 2H), 3.24–3.15 (m, 1H), 1.30 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.04, 136.39, 132.99, 129.18, 127.97, 127.87, 127.79, 127.02, 125.61, 109.23, 55.52, 52.49, 48.92, 34.44, 31.35 ppm; IR (KBr): υ = 3061, 2960, 2868, 1510, 1470 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{21}H_{25}NO_2SNa$: 378.1498, Found: 378.1503.

3-Methyl-1-tosyl-1,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole (2k)

White solid, m.p. 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.75 (m, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.16–7.24 (m, 4H), 6.03 (s, 1H), 4.54–4.61 (m, 1H), 4.00–4.04 (m, 1H), 3.41–3.55 (m, 2H), 2.46 (s, 3H), 1.76–1.75 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.76, 141.20, 140.89, 133.75, 129.84, 129.73, 127.70, 127.50, 126.73, 125.12, 124.14, 124.05, 64.28, 57.71, 41.22, 21.68, 12.28 ppm; IR (KBr): υ = 2975, 2922, 1452 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{19}H_{19}NO_2SNa$: 348.1029, Found: 348.1016.

3-Methylene-1-tosyl-1,2,3,3a,8,8a-hexahydroindeno[2,1-*b*]pyrrole (4k)

White solid, m.p. 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.20–7.24 (m, 4H), 5.12–5.14 (m, 1H), 4.95–4.97 (m, 1H), 4.41–4.44 (m, 1H), 4.04–4.07 (m, 1H), 3.92 (s, 2H), 3.52 (dd, J = 2.1, 17.4 Hz, 1H), 3.29 (dd, J = 6.3, 17.4 Hz, 1H), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.92, 143.66, 141.31, 134.37, 129.83, 129.78, 127.80, 127.70, 126.93, 125.15, 123.97, 107.79, 65.09, 55.25, 53.29, 40.15, 21.62 ppm; IR (KBr): υ = 2914, 2857, 1666, 1595 cm^{-1}; MS (HRMS/[M + Na]$^+$) Calcd for $C_{19}H_{19}NO_2SNa$: 348.1029, Found: 348.1022.

Conclusions

In summary, we have reported a facile palladium-catalyzed intramolecular Heck reaction of β-hydrogen-containing secondary benzylic bromides. This system tolerated a wide scope of substrates, affording excellent regioselectivities without the use of any ligands. The reaction was proved to proceed *via* a benzylpalladium intermediate with an S_N2 mechanism for the oxidative addition step, and additional mechanistic studies on this system are currently underway.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 20772056 and 20932004). The Jiangsu 333 program (for Pan), the set-up fund of Nanjing University and Changzhou Jin-Feng-Huang program (for Han) are also acknowledged.

Notes and references

1 (*a*) F. Diederich and P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 1998; (*b*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489; (*c*) G. T. Crisp, *Chem. Soc. Rev.*, 1998, **27**, 427–436; (*d*) G. Poli, G. Giambastiani and A. Heumann, *Tetrahedron*, 2000, **56**, 5959–5989.

2 (*a*) M. Oestreich, *The Mizoroki–Heck Reaction*, Wiley, Chichester, 2009; (*b*) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066.

3 For recent reviews on coupling reactions of alkyl electrophiles, see: (*a*) A. C. Frisch and M. Beller, *Angew. Chem., Int. Ed.*, 2005, **44**, 674–688; (*b*) M. R. Netherton and G. C. Fu, In *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*, J. Tsuji, Ed., Springer, New York, 2005, pp 85-108.

4 For palladium-catalyzed Heck reaction of activated alkyl electrophiles, see: (*a*) Z. Q. Liu, C. Q. Shi and Y. W. Chen, *Synlett*, 2008, 1734–1736; (*b*) H. Narahashi, A. Yamamoto and I. Shimizu, *Chem. Lett.*, 2004, **33**, 348–349; (*c*) Y. M. Hu, J. Zhou, X. T. Long, J. L. Han, C. J. Zhu and Y. Pan, *Tetrahedron Lett.*, 2003, **44**, 5009–5010; (*d*) K. Higuchi, K. Sawada, H. Nambu, T. Shogaki and Y. Kita, *Org. Lett.*, 2003, **5**, 3703–3704; (*e*) P. Kumar, *Org. Prep. Proced. Int.*, 1997, **29**, 477–480; (*f*) G. Z. Wu, F. Lamaty and E. Negishi, *J. Org. Chem.*, 1989, **54**, 2507–2508; (*g*) F. Glorius, *Tetrahedron Lett.*, 2003, **44**, 5751–5754.

5 For palladium-catalyzed Heck reaction of unactivated alkyl halides containing β-hydrogens, see: (*a*) L. Firmansjah and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 11340–11341; (*b*) K. S. Bloome and E. J. Alexanian, *J. Am. Chem. Soc.*, 2010, **132**, 12823–12825.

6 For a recent review on cobalt-catalyzed coupling of alkyl electrophiles, see: G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435–1462.

7 For selected examples on nickel-catalyzed coupling of alkyl electrophiles, see:(*a*) M. R. Netherton and G. C. Fu, *Adv. Synth. Catal.*, 2004, **346**, 1525–1532; (*b*) G. A. Molander, O. A. Argintaru, I. Aron and S. D. Dreher, *Org. Lett.*, 2010, **12**, 5783–5785; (*c*) S. P. Singh, J. Terao and N. Kambe, *Tetrahedron Lett.*, 2009, **50**, 5644–5646.

8 For a review on secondary alkyl halides in cross-coupling reactions, see: A. Rudolph and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 2656–2670.

9 For recent selected examples on other metal-catalyzed coupling of secondary alkyl halides bearing β-hydrogens, see: (*a*) Z. Lu and G. C. Fu, *Angew. Chem., Int. Ed.*, 2010, **49**, 6676–6678; (*b*) F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 8347–8349; (*c*) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani and A. Moyeux, *Adv. Synth. Catal.*, 2008, **350**, 1484–1488; (*d*) H. Ohmiya, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2006, **128**, 1886–1889; (*e*) R. R. Chowdhury, A. K. Crane, C. Fowler, P. Kwong and C. M. Kozak, *Chem. Commun.*, 2008, 94–96.
10 For palladium-catalyzed coupling reaction of secondary alkyl halides, see: (*a*) A. Rudolph, N. Rackelmann, M. O. Turcotte-Savard and M. Lautens, *J. Org. Chem.*, 2009, **74**, 289–297; (*b*) G. Altenhoff, S. Würtz and F. Glorius, *Tetrahedron Lett.*, 2006, **47**, 2925–2928; (*c*) A. Rudolph, N. Rackelmann and M. Lautens, *Angew. Chem., Int. Ed.*, 2007, **46**, 1485–1488.
11 I. D. Hills, M. R. Netherton and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 5749–5752.
12 (*a*) G. Q. Zhang, G. H. An, J. Zheng, Y. Pan and G. Li, *Tetrahedron Lett.*, 2010, **51**, 987–989; (*b*) H. Sun, S. J. Zhi, J. L. Han, G. Li and Y. Pan, *Chem. Biol. Drug Des.*, 2010, **75**, 269–276.
13 A. López-Pérez, J. Adrio and J. C. Carretero, *Org. Lett.*, 2009, **11**, 5514–5517.
14 F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213–7256.
15 E. M. Beccalli, E. Borsini, S. Brenna, S. Galli, M. Rigamonti and G. Broggini, *Chem.–Eur. J.*, 2010, **16**, 1670–1678.