Palladium-catalyzed direct oxidative Heck–Cassar–Sonogashira type alkynylation of indoles with alkynes under oxygen†

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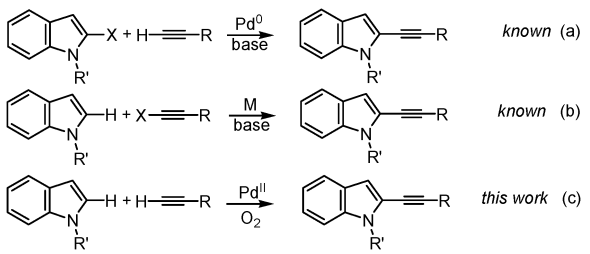
A novel Pd^{II} catalyzed direct oxidative Heck–Cassar–Sonogashira type alkynylation of indoles with terminal alkynes under an atmosphere of O_2 is developed. Unlike previous methods, the reaction does not require the pregeneration of indolyl halide or alkynyl halide. Furthermore, only a catalytic amount of base is required and oxygen was used as the ultimate "green" terminal oxidant.

The palladium catalyzed Heck–Cassar–Sonogashira (HCS) coupling of aryl halides with terminal alkynes in the presence of a stoichiometric amount of base, is among the most useful organic transformations in modern synthetic chemistry.[1] The coupling has been widely used in the synthesis of various important alkyne compounds and conducting materials.[2] Substituted indoles,[3] being a class of privileged structural motifs, exist in numerous natural products and pharmaceuticals and exhibit a wide range of privileged biological activities.[4] Recently a palladium-catalyzed intramolecular oxidative alkylation of indole was reported by Fagnou.[3i] Typically, alkynylation of indoles are realized by Pd^0 catalyzed classical HCS coupling of (pseudo)halogenated indoles and alkynes (Scheme 1, eqn (a)).[5] Alternatively, alkynylindoles can be synthesized from indoles and (pseudo)halogenated alkynes (Scheme 1, eqn (b)).[6] Herein, we report an unprecedented Pd^{II} catalyzed oxidative Heck–Cassar–Sonogashira (HCS) type alkynylation of indoles directly with terminal alkynes using O_2 as a terminal oxidant (Scheme 1, eqn (c)).[7]

We began our study by testing the reaction of 1,3-dimethylindole (**1a**) with phenylacetylene catalyzed by palladium under oxidative conditions.‡ Using a buffer system composed of 20 mol% Cs_2CO_3 and 200 mol% pivalic acid (PivOH), 1,3-dimethylindole reacted with phenylacetylene (**2a**), catalyzed by $Pd(OAc)_2$, to produce the C2 alkynylation product **3a** in



Scheme 1 Approaches for alkynylation of indoles.

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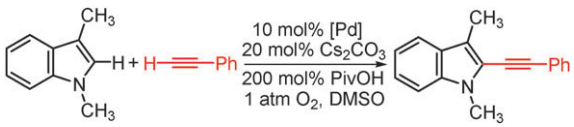
Table 1 Optimization of the Pd-catalyzed oxidative HCS-type alkynylation of indoles with terminal alkynes and O_2[a]



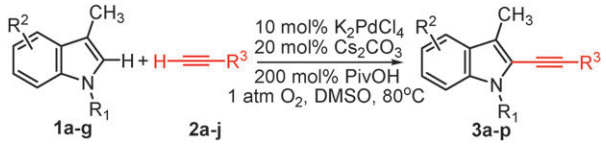
1a 2a 3a

Entry	Catalyst	T/°C	t/h	Yield[b]/%
1	$Pd(OAc)_2$	80	10	20
2	$Pd(TFA)_2$	80	10	15
3	$PdCl_2$	80	10	65
4	$(COD)PdCl_2$	80	10	44
5	$(PPh_3)_2PdCl_2$	80	10	45
6	K_2PdCl_4	80	10	51
7	K_2PdCl_4	80	10	5[c]
8	K_2PdCl_4	80	10	3[d]
9	K_2PdCl_4	80	10	51[e]
10	K_2PdCl_4	80	10	40[f]
11	K_2PdCl_4	80	10	48[g]
12	K_2PdCl_4	80	24	71 (66)
13	$PdCl_2$	80	24	66
14	K_2PdCl_4	70	24	46
15	K_2PdCl_4	90	24	42

[a] Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), 10 mol% [Pd], 20 mol% Cs_2CO_3 and 200 mol% PivOH in DMSO (0.2 mL + 1.0 mL)[8] under 1 atm O_2; unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard; isolated yield is in parentheses. [c] Without PivOH. [d] Without Cs_2CO_3. [e] Cs_2CO_3 was replaced by K_2CO_3. [f] Cs_2CO_3 was replaced by K_3PO_4. [g] PivOH was replaced by AcOH.

20% yield (Table 1, entry 1). To suppress its homocoupling, the phenylacetylene was dissolved in DMSO and added slowly using a syringe pump.[8]

Subsequently, the catalytic activities of different palladium sources for the reaction were investigated (Table 1, entries 1–6). Among the catalysts tested, $PdCl_2$ and K_2PdCl_4 gave the best results. The use of a buffer system mentioned above was found to be crucial, possibly for the deprotonation of the terminal alkyne and reoxidation of Pd^0 to Pd^{II}. The yields dropped sharply in the absence of either the base or the acid (Table 1, entries 7 and 8). Other bases such as K_2CO_3 and K_3PO_4 can also be used (Table 1, entries 9 and 10), and pivalic acid was found to be more effective than acetic acid for the reaction (Table 1, entry 11). When the reaction time was extended to 24 h, the alkynylation yield catalyzed by K_2PdCl_4 was slightly higher than the one catalyzed by $PdCl_2$ and the NMR yield increased to 71% with a 66% isolated yield (Table 1, entries 12 and 13). The influence of temperature was also examined and lower yields were obtained when the reaction temperature was either increased or decreased (Table 1, entries 14 and 15).



Scheme 2 Pd-catalyzed oxidative HCS-type alkynylation of indoles with terminal alkynes.

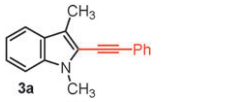
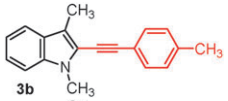
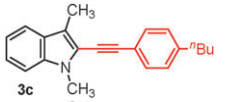
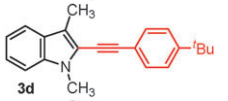
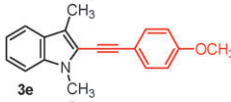
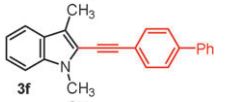
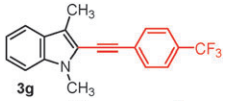
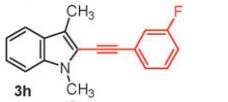
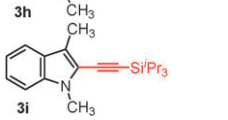
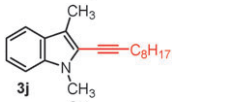
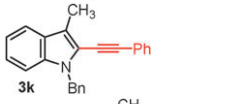
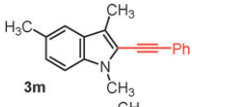
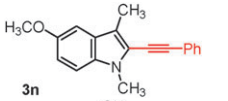
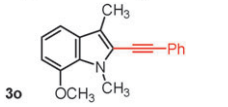
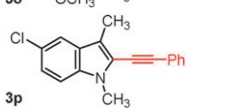
Under the optimized conditions, the substrate scope of this novel oxidative Heck–Cassar–Sonogashira-type alkynylation of indoles was explored (Scheme 2). As shown by the results in Table 2, various terminal alkynes reacted with 1,3-dimethylindoles smoothly. Aromatic alkynes with an electron-rich alkyl or alkoxyl substituent at the *para*-position coupled with **1a** effectively to furnish the alkynylation products (Table 2, entries 2–5, **3b**, **3c**, **3d** and **3e**). 4-Ethynylbiphenyl also gave the coupling product in good yield (Table 2, entry 6, **3f**). Electron-deficient aromatic alkynes were also feasible and gave the HCS coupling products in slightly lower yields (Table 2, entries 7 and 8, **3g** and **3h**). Besides aromatic terminal alkynes, (triisopropylsilyl)acetylene could be used in the coupling reaction, which would make further modifications and derivatizations of the alkynylation product **3i** readily possible (Table 2, entry 9). It is worth noting that 1-decyne could also take part in this reaction (**3j**) albeit in a lower yield (with most 1,3-dimethylindole being recovered), possibly due to the decreased electrophilic nature of the corresponding alkynyl-palladium intermediate being generated during the reaction (Table 2, entry 10).

Other 1,3-dialkylindoles with different substituents were also applicable to this oxidative HCS-type alkynylation (Table 2). 1-Benzyl-3-methyl indoles reacted with **2a** effectively to produce **3k** and **3l**, in 54% and 58% yields, respectively (Table 2, entries 11 and 12). The presence of either electron-donating (methyl and methoxyl) or electron-withdrawing (chloro) substituents at the C5 or C8 position of indoles had no obvious influence on the coupling reaction (Table 2, entries 13–16, **3m**, **3n**, **3o** and **3p**). However, under the same reaction conditions, 1-methylindole and 1,2-dimethylindole were not reactive and >95% of the starting materials were recovered; the cause of which is under further investigation.

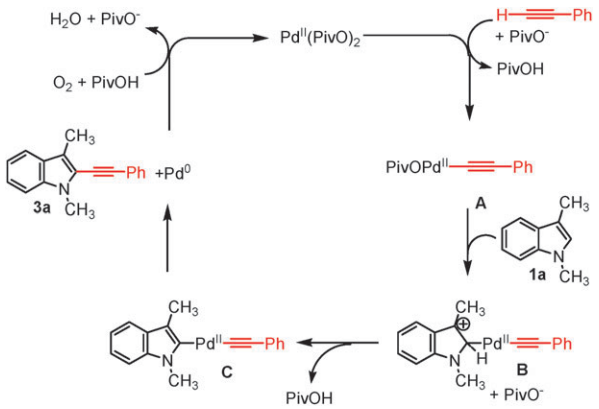
A tentative mechanism to rationalize this novel palladium-catalyzed oxidative HCS-type coupling is illustrated in Scheme 3. First, neutralization of pivalic acid with Cs_2CO_3 produces CsOPiv, which reacts with Pd^{II} and the terminal alkyne **2a** to form alkynylpalladium species **A**.[9] Second, the electrophilic attack of intermediate **A** at the C2 position of indole **1a** generates intermediate **B**, which will be deprotonated by CsOPiv to yield intermediate **C**. Then, reductive elimination of intermediate **C** produces the alkynylated product **3a** and Pd^0, which will be reoxidized to Pd^{II} in the presence of O_2 and PivOH.[3h] Alternatively, the reaction may start with palladation of the indole derivatives.[3a] Subsequent generation of a similar intermediate **C** and its reductive elimination results in the oxidative Heck–Cassar–Sonogashira type product **3a**.[10]

In summary, we have developed a novel Pd^{II} catalyzed direct oxidative Heck–Cassar–Sonogashira type alkynylation of indoles with terminal alkynes under an atmosphere of O_2. Unlike the classical palladium-catalyzed HCS-type alkynylation between

Table 2 Substrate scope for the Pd-catalyzed oxidative HCS-type alkynylation of indoles with terminal alkynes[a]

Entry	Product	Yield[b]/%
1	 **3a**	66
2	 **3b**	62
3	 **3c**	72
4	 **3d**	73
5	 **3e**	68
6	 **3f**	72
7	 **3g**	47
8	 **3h**	51
9	 **3i**	72
10	 **3j**	15
11	 **3k**	54
12	 **3l**	58
13	 **3m**	73
14	 **3n**	66
15	 **3o**	68
16	 **3p**	66

[a] Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, slowly added by syringe pump), 10 mol% K_2PdCl_4, 20 mol% Cs_2CO_3 and 200 mol% PivOH in DMSO (0.2 mL + 1.0 mL)[8] under 1 atm O_2 at 80 °C for 24 h; unless otherwise noted. [b] Isolated yield.



Scheme 3 Proposed mechanism for the Pd-catalyzed oxidative HCS-type alkynylation of indole **1a** with terminal alkyne **2a** and oxygen.

aryl halides and alkyne together with stoichimetric base, the current palladium-catalyzed oxidative HCS-type reaction (1) does not require the pregeneration of indolyl halide or alkynyl halide; (2) furthermore, only a catalytic amount of base is required; (3) in addition, oxygen was used as the ultimate "green" terminal oxidant, and (4) "water" was generated as a benign side-product. The results provide a basis for similar oxidative HCS-type coupling between terminal alkyne and other arenes with oxygen as terminal oxidant. The scope, mechanism and application of this catalytic reaction are ongoing.

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Notes and references

‡ A general experimental procedure for the oxidative HCS-type coupling is described as following: An oven-dried reaction vessel was charged with 1,3-dimethylindole **1a** (14.5 mg, 0.1 mmol), K_2PdCl_4 (3.27 mg, 0.01 mmol, 10 mol%), Cs_2CO_3 (6.5 mg, 0.02 mmol, 20 mol%), pivalic acid (20.4 mg, 0.2 mmol, 200 mol%) and DMSO (0.2 mL). After being stirred for 15 min at room temperature, the vessel was vacuumed and refilled with O_2. Then, the vessel was linked to an O_2 cylinder and a flow of 1 mL min^{-1} maintained. Phenylacetylene **2a** (22 μL, 0.2 mmol, 2 equiv.) dissolved in DMSO (1.0 mL) was added slowly in 24 h using a programmable syringe pump at 80 °C (the needle should be inserted into the reaction mixture). The resulting mixture was cooled to room temperature, poured into aqueous $NaHCO_3$ solution (10%, 10 mL), extracted with ethyl acetate (3 × 10 mL), and washed with brine (2 × 10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was chromatographed by TLC (20 cm × 20 cm) and developed with a mixture of cyclohexane and benzene (10 : 1) to give pure alkynylation product **3a**. Characterization of the product 1,3-dimethyl-2-(phenylethynyl)-1*H*-indole (**3a**): Mp 82.0 °C; IR (cm^{-1}) 2202; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 7.56–7.59 (m, 3H), 7.36–7.41 (m, 3H), 7.26–7.28 (m, 2H), 7.11–7.14 (m, 1H), 3.84 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm) 137.4, 131.6, 128.7, 128.6, 127.7, 123.6, 123.3, 120.5, 119.49, 119.5, 117.2, 109.4, 97.9, 80.9, 30.9, 10.1; HRMS (ESI) *m*/*z*: $[M + 1]^+$ calcd. for $C_{18}H_{16}N$, 246.1277; found: 246.1275.

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5 For examples, see: (*a*) D. Facoetti, G. Abbiati, L. d'Avolio, L. Ackermann and E. Rossi, *Synlett*, 2009, 2273; (*b*) D.-W. Yue and R. C. Larock, *Org. Lett.*, 2004, **6**, 1037; (*c*) H. Zhang and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7048.

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7 During the preparation of this manuscript, a gold-catalyzed ethynylation of arenes using hypervalent iodine as oxidant was reported, see: T. de Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512.

8 Phenylacetylene (**2a**) dissolved in 1.0 mL DMSO and was pumped into the reaction tube using a syringe pump, see ESI† for details.

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10 For other examples of C–C bond formation through the oxidative reaction of C–H and C–H bonds, see: (*a*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*b*) C. J. Scheuermann, *Chem.–Asian J.*, 2010, **5**, 436; (*c*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633.

