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# Pd-Catalyzed Direct Coupling of Indoles with Carbon Monoxide and Alkynes: Selective Synthesis of Linear α,β-Unsaturated Ketones

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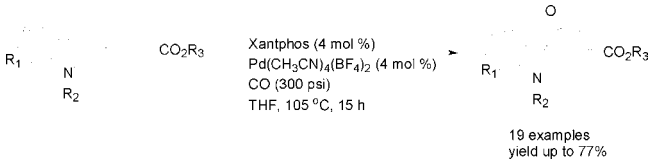
## ABSTRACT




**A new strategy is described for the direct coupling of indoles with CO and alkynes to generate α,β-unsaturated ketones. This procedure, employing Xantphos and $Pd(CH_3CN)_4(BF_4)_2$, is attractive from both environmental and operational points of view and adds value to the method for the carbonylation of alkynes by using carbon nucleophiles and affording linear regioselectivity.**

The transition-metal catalyzed addition of nucleophiles and carbon monoxide to alkynes has attracted considerable attention, since it provides a straightforward and atom-economical approach to valuable α,β-unsaturated carboxylic acid derivatives.[1] A number of catalytic systems based on transition metals, such as Rh,[2] Pt,[3] Pd,[4] and Fe,[5] have been used for this reaction. The seminal contributions by Drent made Pd-catalyzed processes one of the most useful synthetic routes to methacrylates.[4b,c] Nonetheless, several drawbacks still limit this useful protocol: first, strong acids (e.g., TsOH, $CH_3SO_3H$) are needed in most cases to generate the active palladium hydride species. Second, systems giving linear regioselectivity are rare.[6] Third, the nucleophiles are mainly restricted to heteroatoms with active protons, such as alcohols, amines, (thio)phenols, and water. To our knowledge, an analogous transformation using carbon nucleophiles to access α,β-unsaturated ketones has not been reported. On the other hand, the addition of (hetero)aromatic C−H and CO to alkenes via chelation-assisted C−H activation strategy was well established and exploited by Moore, Murai, Chatani, and co-workers.[7]

The ubiquitous presence of the indole nucleus in alkaloids and synthetic pharmaceuticals has stimulated great

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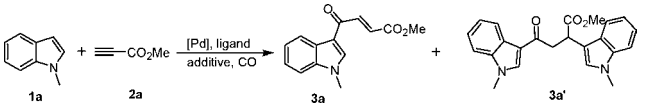
interest in functionalizing the indole skeleton. Classical and widely used methods include Friedel–Crafts acylation, alkylation, allylic alkylation, and conjugate addition, which are based on the carbon nucleophilicity of indoles.[8] Recently, transition metal-catalyzed C($sp^2$)–H bond activation has emerged as an alternative strategy. Regioselective alkylation,[9] alkenylation,[10] and arylation[11] of indoles at either the C2 or C3 position have been achieved. By contrast, direct carbonylation of indoles is not well developed, and only a few catalytic systems for esterification and amidation of indoles have been reported.[12] Herein we describe a novel protocol for the direct coupling of indoles/CO/alkynes to afford linear α,β-unsaturated ketones in a highly regioselective and chemoselective manner.

Initially, we subjected *N*-methylindole (**1a**) and methyl propiolate (**2a**) to Drent's alkoxycarbonylation conditions, and the desired α,β-unsaturated ketone **3a** was isolated in 10% yield, as well as 16% of the 1,3-diindolyl compound **3a′** (Table 1, entry 1). The strong Brønsted acid, TsOH, simultaneously promotes the carbonylation of alkynes and the Michael addition between indole **1a** and the product **3a**. Increasing the acid promoter to 20 mol % selectively furnished the product **3a′** in 46% yield (Table 1, entry 5). Employing 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene (Xantphos) gave the same tendency but showed higher activities than other phosphines, such as 2-$PyPPh_2$, $PPh_3$, dppb, and dppp. Pivalic acid, which is weak and widely employed in C($sp^2$)–H bond activation,[13] did not show any activity for this transformation (Table 1, entry 8). Based on the investigation of the mechanism for the alkoxycarbonylation of alkynes, the cationic palladium complex, $Pd(CH_3CN)_4(BF_4)_2$, was tested as a surrogate

**Table 1.** Optimization of Reaction Conditions[a]




| entry | catalyst | additive (%) | $P_{CO}$ (psi) | **3a**[b] (%) | **3a′**[b] (%) |
|---|---|---|---|---|---|
| 1 | $PdCl_2$/$PyPPh_2$ | TsOH(5) | 300 | 10 | 16 |
| 2[c] | $PdCl_2(PPh_3)_2$ | TsOH (5) | 300 | n.d. | trace |
| 3[c] | $PdCl_2$(Xantphos) | TsOH (5) | 300 | 14 | 27 |
| 4[c] | $PdCl_2$(Xantphos) | TsOH (10) | 300 | 8 | 43 |
| 5[c] | $PdCl_2$(Xantphos) | TsOH (20) | 300 | trace | 46[d] |
| 6[c] | $PdCl_2$(Xantphos) | TsOH (30) | 300 | trace | 44 |
| 7[c] | $PdCl_2$(Xantphos) | | 300 | 29 | trace |
| 8[c] | $PdCl_2$(Xantphos) | PivOH(30) | 300 | 21 | trace |
| 9[c] | $PdCl_2$(dppb) | TsOH (20) | 300 | 10 | 11 |
| 10[c] | $PdCl_2$(dppp) | TsOH (20) | 300 | trace | 32 |
| 11[e] | $Pd^{2+}$/Xantphos | | 300 | 70 | 4 |
| 12[e] | $Pd^{2+}$/DPEphos | | 300 | 16 | 8 |
| 13[e] | $Pd^{2+}$/$^t$BuXantphos | | 300 | trace | trace |
| 14[e] | $Pd^{2+}$/Xantphos | | 200 | 33 | 9 |
| 15[e] | $Pd^{2+}$/Xantphos | | 50 | trace | trace |
| 16[e] | $Pd^{2+}$/Xantphos | | 400 | 66 | 3 |
| 17[e] | $Pd^{2+}$/Xantphos | | 500 | 62 | 3 |
| 18[f] | $Pd^{2+}$/Xantphos | | 300 | 34 | 35 |

[a] All reactions were carried out with 1.0 mmol of **1a**, 1.5 mmol of **2a**, 4 mol % of palladium precursor and ligand, 5 mL of THF, 105 °C, 15 h. [b] Isolated yield based on **1a**. [c] Using palladium complexes. [d] Molecular structure was determined by HSQC and HMQC spectra. [e] $Pd^{2+}$ = $Pd(CH_3CN)_4(BF_4)_2$. [f] 70 °C.

for the mixture of acids and palladium salts. Gratifyingly, the Xantphos/$Pd(CH_3CN)_4(BF_4)_2$ system gave the anticipated product **3a** in 70% isolated yield, also along with 4% of the dimer **3a′** (Table 1, entry 11). Similar phosphines to Xantphos, e.g., bis(2-diphenylphosphinophenyl) ether (DPEphos) and 9,9-dimethyl-4,5-bis(di-*tert*-butylphosphino)-xanthene (*t*-BuXantphos), gave unsatisfactory results for this transformation. It is noteworthy that lowering the pressure of carbon monoxide proved to be detrimental to both efficiency and selectivity (Table 1, entries 14 and 15). The outcome of this procedure also significantly depends on the nature of solvents, and THF is the best reaction solvent (for the influence of other parameters, see the full Table 1 in the Supporting Information).

With the optimized reaction conditions established, the generality of the reaction was explored using a variety of indoles (Table 2). Interestingly, the system tolerates the active NH group and smoothly converts free indole to the desired product **3b**, albeit in moderate yield (54%). The efficiency of this transformation is highly dependent upon the electronic properties of $R_2$ groups. When electron-donating groups, i.e., Bz, $^n$Bu, $^i$Pr, and $^t$Bu, were presented at the $R_2$ position, the products **3c**–**f** were isolated in good yields (63–77%; Table 2, entries 3–6). In contrast, the strongly electron-withdrawing group, Ac, totally inhibited the process (Table 2, entry 10). The system is compatible with the Reppe carbonylation candidate CC double bond and the weakly coordinating CN group. This

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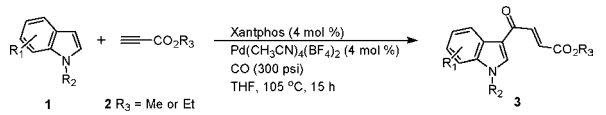
**Table 2.** Synthesis of α,β-Unsaturated Ketones[a]



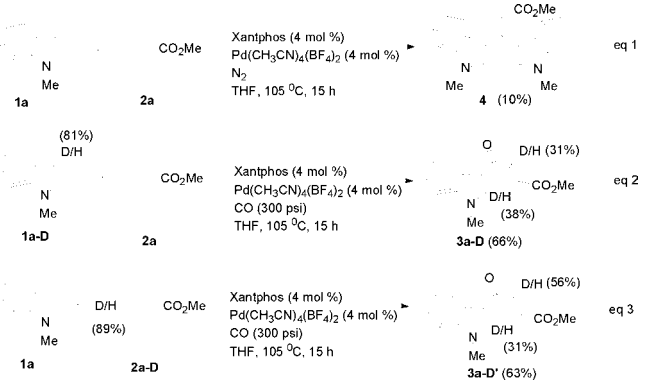

| entry | 1 | $R_1$ | $R_2$ | 3 | yield (%)[b,c] |
|---|---|---|---|---|---|
| 1 | **1a** | H | Me | **3a** | 70 |
| 2 | **1b** | H | H | **3b** | 54 |
| 3 | **1c** | H | Bz | **3c** | 71 |
| 4 | **1d** | H | $^n$Bu | **3d** | 63 |
| 5 | **1e** | H | $^i$Pr | **3e** | 77 |
| 6 | **1f** | H | $^t$Bu | **3f** | 77 |
| 7 | **1g** | H | 1-Adamantyl | **3g** | 60 |
| 8 | **1h** | H | $CH_2CH_2CN$ | **3h** | 54 |
| 9 | **1i** | H | $CH_2CH{=}CH_2$ | **3i** | 56 |
| 10 | **1j** | H | Ac | **3j** | 0 |
| 11 | **1k** | 5-MeO | Me | **3k** | 55 (6) |
| 12 | **1l** | 5-Me | Me | **3l** | 62 (7) |
| 13 | **1m** | 6-Me | Me | **3m** | 66 (11)[d] |
| 14 | **1n** | 7-Et | Me | **3n** | 61 (12)[d] |
| 15 | **1o** | 5-Ph | Me | **3o** | 57 (7) |
| 16 | **1p** | 5-Cl | Me | **3p** | 36 |
| 17[e] | **1q** | H | Me | **3q** | 60 |
| 18 | **1r** |  | | **3r** | 0 |
| 19 | **1s** |  | | **3s** | 60 |

[a] All reactions were carried out with 1.0 mmol of **1**, 1.5 mmol of **2a**, 4 mol % of $Pd(CH_3CN)_4(BF_4)_2$ and Xantphos, 5 mL of THF, 300 psi of CO, 105 °C, 15 h. [b] Isolated yield based on indoles. [c] Isolated yield of the corresponding 1,3-diindolyl compounds in parentheses. [d] Determined by NMR. [e] $R_3$ = Et.

transformation also tolerates different substituents, such as Me, MeO, Ph, and Cl, on the phenyl subunit of indoles. However, it is worth mentioning that the electron-rich $R_1$ (Table 2, entries 11−14) groups boosted the Michael addition between the indoles and the products, which gives the corresponding 1,3-diindolyl compounds as accompanying products. The catalytic system was not useful for substrates with strong coordination properties, perhaps because the highly electrophilic cationic palladium species are prone to be poisoned by a Lewis base (Table 2, entry 18). This system represents acceptable catalytic activities to pyrrole derivatives yet expresses poor regioselectivity between α and β positions in pyrrole rings. For example, free pyrrole gave the α-carbon carbonylated product in 23% and the β-carbon carbonylated product in 18%, and *N*-isopropylpyrrole afforded the two products in 14% and 23% yields, respectively. *N*-*tert*-Butylpyrrole selectively furnished the β-carbon carbonylated product **3s** in 60% yield, owing to the strong steric hindrance from the bulky *tert*-butyl group to the α carbon (Table 2, entry 19).

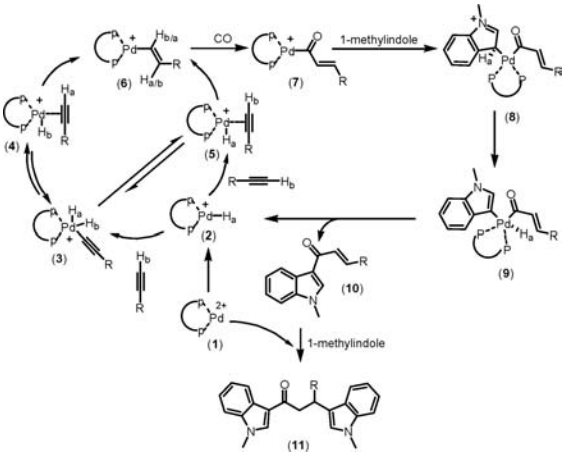
To gain mechanistic insight for the reaction, the following experiments were conducted (Scheme 1). Performing the reaction under nitrogen resulted in 3,3-bis(1-methylindol-3-yl)propionic acid methyl ester (**4**) in 10% yield. When 1-methyl-3-D-indole (81% D incorporation) was subjected to the standard reaction conditions, the deuterated 4-(1-methylindol-3-yl)-4-oxo-(2*E*)-butenoic acid methyl ester (**3a-D**) was obtained in 66% yield, with 38% D incorporation at the 2 position and 31% D incorporation at the 3 position. Increasing the amounts of propiolate **2a** does not change the percentage of D incorporation in **3a-D**, which excludes the possibility of direct H/D exchange under the reaction conditions. Moreover, using methyl 3-D-propiolate (**2a-D**, 89% D incorporation) afforded the deuterated **3a-D′** in 63% yield, with 56% D incorporation at the 3 position and 31% D incorporation at the 2 position.

**Scheme 1**




On the basis of the above observations, a possible mechanism for this transformation is outlined in Scheme 2. There are two parallel pathways to produce the Pd−(σ-vinyl) intermediate **6** from terminal alkynes and the active palladium hydride species **2**, which is in situ generated from the cationic palladium complex $Pd(CH_3CN)_4(BF_4)_2$.[14] In pathway A, the palladium hydride **2** may be oxidized by terminal alkynes to the Pd(IV) species **3**, followed by the formation of two isomers **4** and **5**. The insertion of the coordinated alkyne in **4** or **5** into the Pd−H bond affords the Pd−(σ-vinyl) intermediate **6**. In pathway B, terminal alkynes are directly captured by the electrophilic cationic palladium complex **2** to give the intermediate **5**. The mechanism involving two competing pathways is believed responsible for the

**Scheme 2.** Possible Reaction Mechanism



deuterium distribution in deuterium-labeling reactions (Scheme 1, eq 2 and 3). The acylpalladium species **7** is obtained by CO insertion into the Pd−C bond, which is more electrophilic relative to the corresponding intermediate **6** and thus facilitates the nucleophilic attack of indoles to furnish **8**. Rearomatization of **8** generates the Pd(IV)−H intermediate **9**, which is subseqentially reduced to the Pd(II)−H **2** by forming the product **10**. Meanwhile, the cationic palladium species (either **1** or **2**) catalyzes the addition of indoles to the α,β-unsaturated ketone **10** to form the accompanying product **11**.

In summary, a novel strategy for the synthesis of α,β-unsaturated ketones was developed for the first time based on cationic palladium-catalyzed direct coupling of indoles/CO/alkynes. This acid-free protocol tolerates a variety of indoles with weak coordination, electron-donating, and electron-withdrawing groups and enriches the method for the carbonylation of alkynes by using carbon nucleophiles and giving linear selectivity, albeit restricted to active terminal alkynes.

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**Supporting Information Available.** Experimental procedures, characterization data, and NMR spectra for all the starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.