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# Palladium-catalyzed direct cross-coupling reaction between indenes and electron-deficient alkenes

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ABSTRACT

An efficient methodology for oxidative cross-coupling of indene and derivatives with electron-deficient olefins catalyzed by palladium was developed. The corresponding diene products were obtained in moderate to good yields.



Palladium-catalyzed activation of C–H bonds is a very efficient method among many new carbon–carbon and carbon–heteroatom bond forming methodologies.[1] Palladium-catalyzed C–H activation of arenes[2] or electron-rich heterocyclic compounds[3] has been well-studied. Several groups have reported direct C–C bond formation from unactivated $sp^3$ C–H bonds via palladium catalysis.[4] In contrast, there have been few reported coupling reactions between simple olefins.[5] Our group has previously developed a general method for the direct cross-coupling of olefins with acrylates to form dienes at 60 °C, using palladium(II) acetate as the catalyst and copper(II) acetate and oxygen gas as oxidant to regenerate Pd(II) from the Pd(0) formed during the reaction.[6] In the above-mentioned reaction, a high loading of the palladium catalyst (20 mol %) was necessary to afford satisfactory yields, which has hindered the widespread applicability of this reaction. In this Letter, we investigate the possibility of decreasing the catalyst loading and broadening the substrate scope.

Under the previously reported conditions, the direct coupling reaction between 3-methyl-1*H*-indene and *tert*-butyl acrylate afforded the desired product in 83% yield.[6] When the catalyst loading was decreased to 10 mol % without changing the other conditions, a 54% yield of the product was obtained. Further investigations also revealed that the solvent played a significant role in the coupling reaction. Of the various solvents tested, acetic acid proved to give the best result. Using sodium acetate as an additive and oxygen gas as the sole oxidant also afforded the expected product in 61% yield. The best results were obtained with a 10 mol % loading of $Pd(OAc)_2$, $Cu(OAc)_2$ (1 equiv), and $O_2$ (1 atm) as oxidant in acetic acid at 60 °C, with a 2:1 ratio of the starting materials (**1a**/**2a**), generating the desired product **3a** in 70% yield. When 5 mol % of $Pd(OAc)_2$ was used or 10 mol % of $Pd(OAc)_2$ with oxygen as the sole oxidant, we observed decreased yields of 52% and 38%, respectively.

A wide variety of electron-deficient olefins were used as coupling partners under the optimized conditions (Table 1). *tert*-Butyl acrylate, *n*-butyl acrylate, ethyl acrylate, methyl acrylate, and phenyl acrylate all afforded the corresponding products in good yields (entries 1–4 and 6). We were pleased to observe that styrene readily reacted with 3-methyl-1*H*-indene in a modest 50% yield (entry 7).

Unfortunately, acrylonitrile afforded only a 31% yield of the corresponding product, possibly due to its instability under acidic conditions (entry 5).[7] We also discovered that the electronic effect of the substituent on the olefin had a very significant influence on the yield with a low yield (19%) obtained for methyl methacrylate (entry 8). In addition, none of the desired products was obtained with acrylamide (entry 9).

Next, we briefly examined various indenes for this $Pd(OAc)_2$-catalyzed direct coupling with *tert*-butyl acrylate under the optimized conditions (Table 2). Good yields were obtained with substrates having an electron-donating group (entry 2, 71% yield) or a weak electron-withdrawing group (entries 5, 6, and 9; 52%, 62%, and 66% yield, respectively) on the benzene ring. However, the substrate **1h** with a strongly electron-withdrawing trifluoromethyl group was transformed into the desired product slowly and in low yield after 48 h (entry 8). The yield could be improved to 47% after prolonging the reaction time to 96 h (entry 8). Furthermore, substitution on position C-1 resulted in a drastic decrease in the yield which might be due to steric hindrance. For instance, substrates with 1-methyl (entry 3) and 1-phenyl groups (entry 4)

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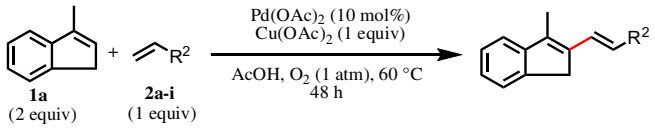
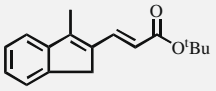
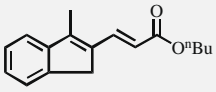
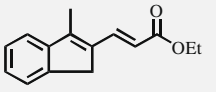
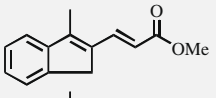
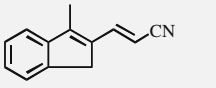
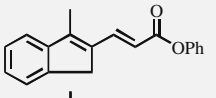
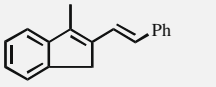
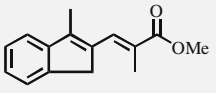
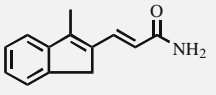
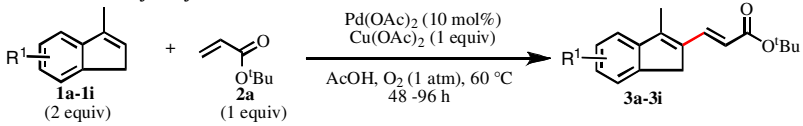
**Table 1**
Direct cross-coupling of the 3-methyl-1*H*-indene with various coupling partners[a,b]

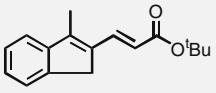
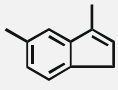
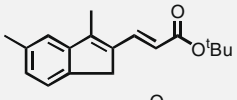
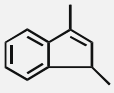
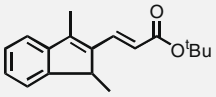
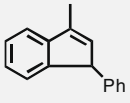
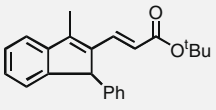



| Entry | Olefin | | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | **2a** |  | 70 |
| 2 |  | **2b** |  | 70 |
| 3 |  | **2c** |  | 69 |
| 4 |  | **2d** |  | 68 |
| 5 |  | **2e** |  | 31 |
| 6 |  | **2f** |  | 62 |
| 7 |  | **2g** |  | 50 |
| 8 |  | **2h** |  | 19 |
| 9 |  | **2i** |  | — |

[a] The reactions were run with 3-methyl-1*H*-indene (0.4 mmol), coupling partner (0.2 mmol), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (1 equiv) at 60 °C in AcOH (0.5 mL) with $O_2$ (1 atm).
[b] Isolated yield based on substrate **2**.

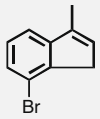
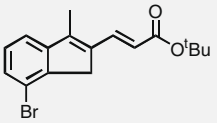
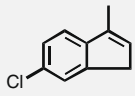
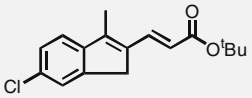
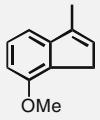
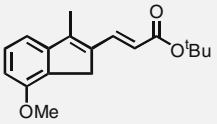
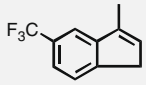
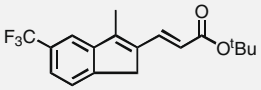
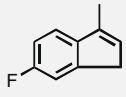
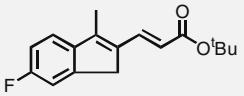
**Table 2**
Direct coupling reaction between olefins with *tert*-butyl acrylate[a,b]



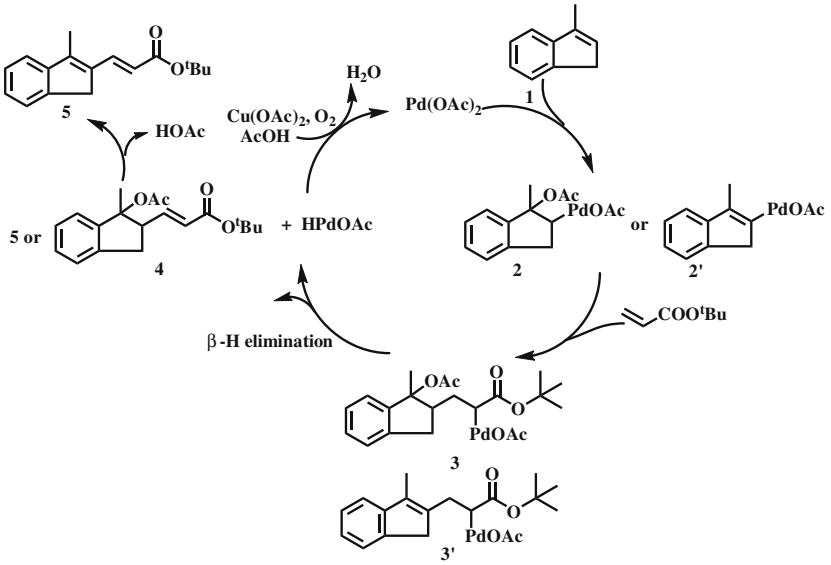

| Entry | Starting material | | Product | | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  | **1a** |  | **3a** | 48 | 70 |
| 2 |  | **1b** |  | **3b** | 48 | 71 |
| 3 |  | **1c** |  | **3c** | 48 | 49 |
| 4 |  | **1d** |  | **3d** | 72 | 40 |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Starting material | | Product | | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 5 |  | **1e** |  | **3e** | 48 | 52 |
| 6 |  | **1f** |  | **3f** | 48 | 62 |
| 7 |  | **1g** |  | **3g** | 48 | 63 |
| 8 |  | **1h** |  | **3h** | 48 (96) | 30 (47) |
| 9 |  | **1i** |  | **3i** | 72 | 66 |

[a] The reactions were run with indene derivative (0.4 mmol), *tert*-butyl acrylate (0.2 mmol), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (1 equiv) at 60 °C in AcOH (0.5 mL) with $O_2$ (1 atm).
[b] Isolated yield based on acrylate used.




**Scheme 1.** Proposed mechanism for the cross-coupling reaction.

afforded the corresponding products in only 49% and 40% yields, respectively.

Finally, we propose the following mechanism for this palladium-catalyzed direct cross-coupling reaction (Scheme 1). 3-Methyl-1*H*-indene reacts with $Pd(OAc)_2$ to afford two possible palladium intermediates **2** or **2′** which can coordinate with the acrylate with subsequent insertion to give σ-Pd complex **3** or **3′**.[5c] Upon *β*-hydride elimination from complex **3** or **3′**, the desired product **5** or intermediate **4** (which could undergo elimination of AcOH to give the final product **5**) would be formed. Oxygen and $Cu(OAc)_2$ would then reoxidize the palladium catalyst for use in the next cycle.

In summary, we have reported an efficient method for the palladium-catalyzed cross-coupling reaction between simple olefins in moderate to good yields.[8] Further expansion of the scope of this coupling reaction to other olefins is currently in progress.

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8. General procedure for the coupling reaction of indenes with *tert*-butyl acrylate: To an acetic acid solution (0.5 mL) in a 5 mL round bottom flask was added $Pd(OAc)_2$ (0.02 mmol, 10 mol%), $Cu(OAc)_2$ (0.2 mmol, 1 equiv) and 3,5-dimethyl-1*H*-indene (0.4 mmol, 2 equiv). The mixture was stirred for 10 min at 60 °C under 1 atm $O_2$. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and was filtered through a plug of Celite. The filtrate was washed with saturated $NaHCO_3$ (2 mL), water (3 mL), water (5 mL), and brine (5 mL). The organic layer was dried with anhydrous $MgSO_4$ and filtered; the crude product was obtained by evaporating the organic solvent under vacuum. The desired product was isolated by column chromatography (EtOAc/hexane = 1:19).
Compound **3b**: (*E*)-*tert*-Butyl 3-(3,5-dimethyl-1*H*-inden-2-yl)acrylate. *trans*:*cis* >99:1; $R_f$ = 0.35. This compound was obtained as a colorless oil. Yield = 71%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$ = 15.5 Hz, 1H), 7.32 (d, $J$ = 7.6 Hz, 1H), 7.20 (s, 1H), 7.09 (d, $J$ = 7.6 Hz, 1H), 5.97 (d, $J$ = 15.5 Hz, 1H), 3.49 (s, 2H), 2.43 (s, 3H), 2.27 (t, $J$ = 1.7 Hz, 3H), 1.56 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 167.1, 146.3, 145.0, 139.9, 137.2, 136.8, 136.3, 127.6, 123.4, 120.7, 118.6, 80.2, 36.7, 28.3, 21.5, 10.8. FTIR (NaCl, cm$^{-1}$): 3019, 1692, 1615, 1313, 1215, 1150, 759, 668. HRMS (ESI) $m/z$ calculated for $C_{18}H_{22}O_2Na$ $[M+23]^+$: 293.1518, found 293.1517.