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Palladium-Catalyzed Three-Component Coupling Reactions: 1,1-Difunctionalization of Activated Alkenes

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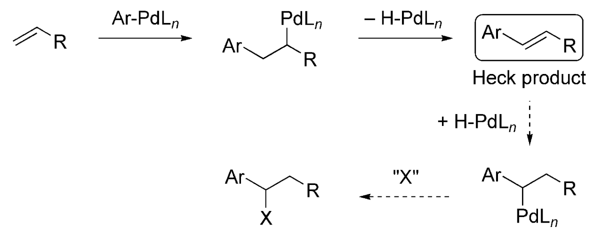
A three-component coupling reaction was developed to access 3,3-oxyarylpropionate derivatives. Each of the three reaction components can be varied, allowing the modular synthesis of a range of important chiral building blocks.

Introduction

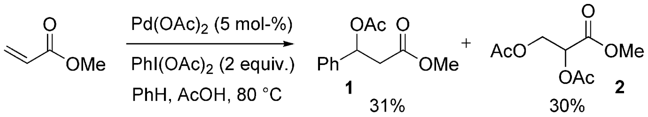
Palladium-catalyzed oxidative functionalization of olefins is a powerful technique for synthesis;[1] transformations such as 1,2-diamination,[2] 1,2-aminooxygenation,[3] 1,2-dicarbonylation[4] and 1,2-dioxygenation[5] of alkenes have been reported. We were intrigued by the oxidative Heck-type coupling reactions of benzenes with olefins[6] and wondered if the Heck intermediates could be captured and functionalized (Scheme 1). It is known that the β-hydride elimination step is very fast and reversible and this could lead to a relatively long-lived benzylic palladium(II) intermediate, which could be functionalized.[7] Such three-component coupling reactions are of interest because of the potential for reduction in the number of synthetic steps required to make target molecules.[8] Indeed, similar reactivity was demonstrated by Yoshida and coworkers and, more recently, by Sanford and coworkers, whereby aryl stannanes were coupled with terminal olefins with concomitant formation of a C–Cl bond under Pd catalysis.[9] This report details a related transformation that does not require the use of stoichiometric organometallic reagents, as arenes are coupled directly.



Scheme 1. Heck reaction mechanism and proposed capture and functionalization of Heck intermediate.

Results and Discussion

Our initial studies began with the Pd-catalyzed reaction of benzene with methyl acrylate in the presence of iodobenzene diacetate and acetic acid open to air (Scheme 2). We were pleased to discover that under our initial conditions two intriguing products were obtained in a 1:1 ratio. The first product was desired 1,1-aryloxygenated compound **1** and the second was 1,2-dioxygenated species **2**. We set out to optimize the formation of **1** and to determine the scope of the transformation.



Scheme 2. Oxidative functionalization of methyl acrylate.

Removal of acetic acid from the reaction mixture led to complete consumption of the acrylate and formation of product **1** in a modest 31% yield with no other isolable compounds identified (Table 1, Entry 1). Performing the reaction in acetic acid with one equivalent of NaOAc and no benzene led to the selective formation of product **2** in an excellent 95% yield (Table 1, Entry 2). Running the reaction in acetic anhydride led to no reaction (Table 1, Entry 3), whereas the use of DMF or MeCN as solvent provided the Heck product methyl cinnamate (**3**) in 85 and 14%, respectively (Table 1, Entries 4 and 5). In the presence of Pd(acac)$_2$ the reaction was somewhat more efficient, providing a 38% yield of **1** (Table 1, Entry 6). Utilizing 3-NO$_2$-C$_6$H$_4$I(OAc)$_2$ as oxidant instead of PhI(OAc)$_2$ led to an appreciable increase in yield, providing a 63% isolated yield

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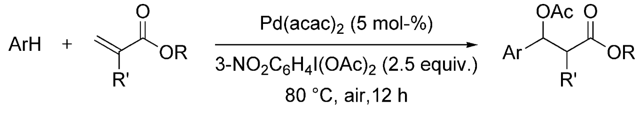
of **1** (Table 1, Entry 7). The cationic Pd source Pd(MeCN)$_4$(BF$_4$)$_2$ provided a mixture of products **1** and **2** (Table 1, Entry 8). The reaction did not occur with the use of other late-transition-metal sources such as PtCl$_2$ (Table 1, Entry 9) or with Lewis acids.[10] Running the reaction without either a Pd source or the iodinane oxidant led to no conversion to product **1** (or **2** or **3**).

Table 1. Optimization studies for Pd-catalyzed coupling reactions.[a]

Entry	Catalyst	Solvent	Oxidant	Yield[b] / % (**1/2/3**)
1	Pd(OAc)$_2$	PhH	PhI(OAc)$_2$	31:0:0
2[c]	Pd(OAc)$_2$	AcOH	PhI(OAc)$_2$	0:95:0
3	Pd(OAc)$_2$	Ac$_2$O	PhI(OAc)$_2$	0:0:0
4[d]	Pd(OAc)$_2$	DMF	PhI(OAc)$_2$	0:0:85
5	Pd(OAc)$_2$	MeCN	PhI(OAc)$_2$	0:0:14
6	Pd(acac)$_2$	PhH	PhI(OAc)$_2$	38:0:0
7	Pd(acac)$_2$	PhH	3-NO$_2$C$_6$H$_4$I(OAc)$_2$	63:0:5
8	Pd(MeCN)$_4$(BF$_4$)$_2$	PhH	PhI(OAc)$_2$	30:30:0
9	PtCl$_2$	PhH	PhI(OAc)$_2$	0:0:0

[a] Methyl acrylate, benzene, catalyst (5 mol-%), oxidant (2 equiv.), solvent, air. [b] Isolated yields. [c] No benzene, NaOAc (1 equiv.). [d] Reaction run at 153 °C.

Under the optimized conditions (i.e. those in Table 1, Entry 7) a range of different arenes and acrylate derivatives were found to be successful in the reaction (Scheme 3, Table 2).[11] Toluene reacted efficiently with methyl acrylate to provide the desired product as a mixture of regioisomers (Table 2, Entry 2). *p*-Xylene was found to react sluggishly with methyl acrylate to provide only a modest yield of coupled product; possibly palladation is hindered by sterics (Table 2, Entry 3). Bromobenzene and chlorobenzene reacted smoothly to generate the aldol-type products in 46 and 55% yield, respectively (Table 2, Entries 4 and 5). *tert*-Butyl acrylate was found to react with benzene with similar efficiency to that of methyl acrylate, providing a 65% yield (Table 2, Entry 6). Benzyl acrylate was a less-effective substrate, as the Heck product was isolated alongside the aldol compound (Table 2, Entry 7). The methacrylates (Table 2, Entries 8–10) were converted into product more efficiently by the less-reactive oxidant PhI(OAc)$_2$ than were the acrylates, furnishing up to 67% yield of the aldol-type products.[12] Increasing the size of the alkene α-substituent from a methyl to an ethyl group resulted in a slight drop in yield, providing a reasonable 51% yield of product (Table 2, Entry 11). Dibutyl itaconate was somewhat less successful in the reaction, supplying a modest 20% yield with PhI(OAc)$_2$ as oxidant (Table 2, Entry 12), whereas with the 3-nitrobenzene-derived oxidant only the Heck coupled product was produced. Interestingly, reaction of methyl 2-phenylacrylate furnished none of the coupled products but instead resulted in epoxidation of the alkene.[13]



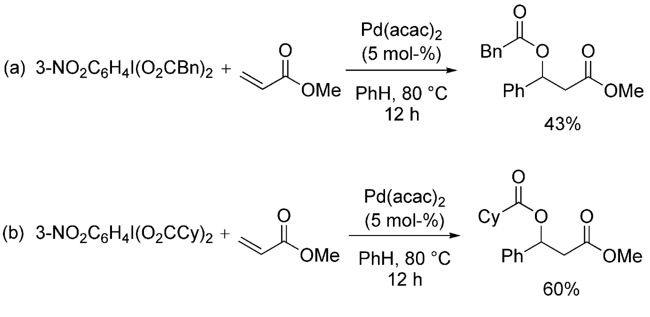
Scheme 3. Reaction scope under optimized conditions.

Table 2. Substrate scope for the three-component coupling reaction.

Entry	Arene	R	R′	Yield[a] / %
1	benzene	Me	H	63
2	toluene	Me	H	72[b]
3	*p*-xylene	Me	H	25
4	bromobenzene	Me	H	46[c]
5	chlorobenzene	Me	H	55[d]
6	benzene	*t*Bu	H	65
7	benzene	Bn	H	43
8	benzene	Me	Me	61[e,f]
9	benzene	*n*Bu	Me	67[e,f]
10	benzene	*t*Bu	Me	57[f]
11	benzene	Et	Et	51[f]
12	benzene	*n*Bu	CH$_2$CO$_2$*n*Bu	20[e,f]

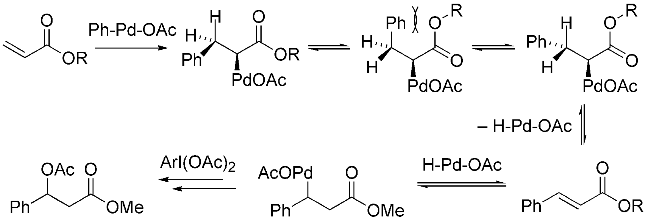
[a] Isolated yields. [b] *o*/*m*/*p*, 1:4:4. [c] *o*/*m*/*p*, 1:2.8:1.6. [d] *o*/*m*/*p*, 1:2.2:2.1. [e] PhI(OAc)$_2$ was used in place of 3-NO$_2$C$_6$H$_4$I(OAc)$_2$. [f] Mixture of diastereomers (generally less than 2.5:1).

The third component of the coupling reaction, that is, the ester, can also be varied. 3-NO$_2$C$_6$H$_4$I(O$_2$CBn)$_2$ provided the corresponding ester upon reaction with methyl acrylate, and 3-NO$_2$C$_6$H$_4$I(O$_2$CCy)$_2$ furnished the cyclohexyl ester (Scheme 4).[14] Importantly, only I^{III} dicarboxylates were found to be successful in this process. For example, iodobenzene dichloride (PhICl$_2$) leads only to the 1,2-dichlorinated product with no benzene incorporation, whereas iodosobenzene (PhIO) and [hydroxy(tosyloxy)-iodo]benzene [PhI(OH)OTs] lead to no conversion of acrylate.



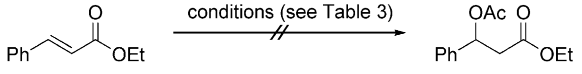
Scheme 4. (a) Use of a benzoic acid derived iodinane. (b) Use of a cyclohexane carboxylic acid derived iodinane.

The mechanism of this transformation is proposed to proceed through electrophilic attack on Pd^{II} by the arene followed by Heck-type addition to the alkene in a similar fashion to that proposed by Fujiwara.[6f] This Heck intermediate then undergoes β-hydride elimination, and the resulting Pd-H species readds to place the Pd at the benzylic site. This elimination and readdition of Pd-H is very fast and reversible and is a common process in palladium chemistry.[7] Oxidation of Pd^{II} to Pd^{IV} by the hypervalent iodine reagent followed by displacement with acetate with inversion of configuration or reductive elimination could then provide the observed products (Scheme 5).[15,16] The use of Dess–Martin periodinane as oxidant resulted in an inseparable 1:1.5 ratio of the AcO$^-$ and 2-IC$_6$H$_4$CO$_2$$^-$ incorporated products. This suggests that hypervalent iodine plays a key role in the final C–O bond formation.



Scheme 5. Postulated mechanism for three-component coupling.

In order to rule out the possibility of a simple conjugate addition reaction of acetic acid or acetate to the Heck intermediate, ethyl cinnamate was subjected to a range of conditions (Scheme 6, Table 3). Heating ethyl cinnamate with five equivalents of either NaOAc or AcOH in benzene resulted in complete recovery of the starting material (Table 3, Entries 1 and 2). Likewise, Pd(acac)$_2$ did not catalyze the conjugate addition of either NaOAc or AcOH (Table 3, Entries 3 and 4).[17] Interestingly, subjecting ethyl cinnamate to the coupling reaction conditions also led to complete recovery of the starting material (Table 3, Entry 5). These results clearly indicate that conjugate addition to the cinnamate intermediate does not occur, which therefore supports the mechanism proposed.



Scheme 6. Conjugate addition to cinnamate?

Table 3. Mechanistic investigations.

Entry	Conditions	Conversion / %
1	NaOAc (5 equiv.), PhH, 80 °C, 15 h	0
2	AcOH (5 equiv.), PhH, 80 °C, 15 h	0
3	Pd(acac)$_2$ (5 mol-%), NaOAc (2 equiv.), PhH, 80 °C, 15 h	0
4	Pd(acac)$_2$ (5 mol-%), AcOH (2 equiv.), PhH, 80 °C, 15 h	0
5	Pd(acac)$_2$ (5 mol-%), PhI(OAc)$_2$ (2 equiv.), PhH, 80 °C, 15 h	0

Conclusions

In summary, we developed a Pd-catalyzed three-component coupling reaction to access aldol-type products. This process uses cheap, readily available starting materials and is straightforward to carry out. We have shown that each of the three components of the reaction can be varied and that the reaction efficiency is dependent on the oxidant utilized. Current work is focused on expanding the scope of this transformation and delineating the mechanism.

Experimental Section

General Procedure: A flask was charged with an alkene (0.58 mmol), Pd(acac)$_2$ (9 mg, 0.029 mmol), the iodinane (1.45 mmol) and an arene (1 mL) and heated at reflux for 12 h open to air. The volatiles were removed in vacuo, and the mixture was purified by flash chromatography [silica gel; petroleum ether (40–60)/EtOAc, 20:1] to give the corresponding product.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and characterization data for all new compounds.

Acknowledgments

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[10] The reaction was also unsuccessful with AuCl$_3$, (Ph$_3$P)$_2$NiCl$_2$, CuI and BF$_3$·OEt$_2$.

[11] The reactions can be performed with just one equivalent of oxidant; however, sometimes they stall; the addition of an excess amount of oxidant prevents this from happening.

[12] Interestingly, 3-NO$_2$C$_6$H$_4$I(OAc)$_2$ provided no improvement in yields for these substrates.

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[15] A number of other mechanisms could be proposed; however, experimentation appears to rule out a Heck-type process fol-

lowed by conjugate addition of acetate (all attempts to add acetate to ethyl cinnamate were unsuccessful), and the addition of radical inhibitors does not affect the outcome of the reaction, ruling out a radical pathway.

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