Cross-Coupling

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Palladium-Catalyzed Oxidative Difunctionalization of Alkenes with α-Carbonyl Alkyl Bromides Initiated through a Heck-type Insertion: A Route to Indolin-2-ones**

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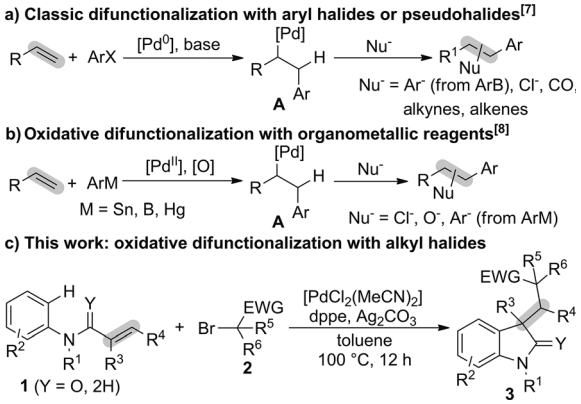
Abstract: *The oxidative interception of various σ-alkyl palladium(II) intermediates with additional reagents for the difunctionalization of alkenes is an important research area. A new palladium-catalyzed oxidative difunctionalization reaction of alkenes with α-carbonyl alkyl bromides is described, in which the σ-alkyl palladium(II) intermediate is generated through a Heck insertion and trapped using an aryl C(sp^2)–H bond. This method can be applied to various α-carbonyl alkyl bromides, including primary, secondary, and tertiary α-bromoalkyl esters, ketones, and amides.*

The Heck reaction has become one of the most important synthetic methods for the formation of various carbon–carbon bonds in organic synthesis.[1] Despite impressive advances in this research field, Heck coupling reactions that utilize alkyl halides, particularly tertiary alkyl halides, have remained rare and challenging.[1–5] Such transformations are difficult because the tertiary alkyl metal intermediate, which is generated through tertiary alkylation with α-halocarbonyl compounds, tends to undergo β-hydride elimination, generating a conjugated olefin.[1,6] Recently, some new strategies have been developed using palladium,[2] cobalt,[3] nickel,[4] or other metals[5] in catalytic systems. However, all successful transformations are limited to the classic Heck coupling process involving β-hydride elimination. Therefore, the development of methods that avoid β-hydride elimination during Heck coupling reactions with alkyl halides is desirable.

In a classic Heck coupling process, the insertion of an alkene by the active Pd^0 species and an organic electrophile forms a σ-alkyl Pd^{II} intermediate **A**.[1] Generally, intermediate **A** undergoes β-hydride elimination to furnish an alkene. An attractive alternative has been developed for the interception of this σ-alkyl palladium(II) intermediate **A**; this strategy requires additional reagents, such as alkenes,[7] alkynes, CO, or $ArB(OH)_2$, to access diverse difunctionalized products (Scheme 1a). However, examples of palladium(0)-catalyzed alkene difunctionalization reactions are rare; such reports have limited generality and often produce numerous side products from competitive β-hydride elimination and protonolysis processes. To overcome these limitations, considerable efforts have been devoted to the palladium(II)-catalyzed oxidative difunctionalization of alkenes. This process is generally triggered by an organometallic reagent to form σ-alkyl palladium(II) intermediate **A** in the presence of oxidants, followed by interception with another nucleophile (often Cl^-, O^-, or organometallic reagents).[8] However, few methods utilizing a Heck insertion process are available for the oxidative difunctionalization of alkenes with alkyl halides. We herein report a new oxidative method for trapping intermediate **A** using α-carbonyl alkyl bromides to realize alkene difunctionalization reactions using a Pd catalyst with a Ag_2CO_3 oxidant (Scheme 1c); this method proceeds through a tandem C–Br/C–H functionalization and cyclization and provides access to important indolin-2-one structures.[9]



Scheme 1. Alkene difunctionalizations that involve a Heck insertion.

Initial experiments were performed on the oxidative difunctionalization reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) and methyl 2-bromopropanoate (**2a**) with a palladium source, phosphine ligands, and oxidants (Table 1). The palladium catalyst was necessary for the transformation, and $[PdCl_2(MeCN)_2]$ was the most efficient Pd source (entries 1–6). For this process, adding a ligand improved the reaction, and using dppe was optimal (entries 1 and 7–9). Whereas using PPh_3 or PCy_3 provided product **3aa** in 78% and 88% yield, respectively (entries 1 and 7), dppe increased the yield to 99% (entry 8). Although the reaction could proceed

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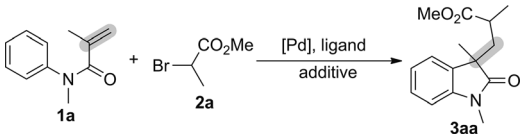
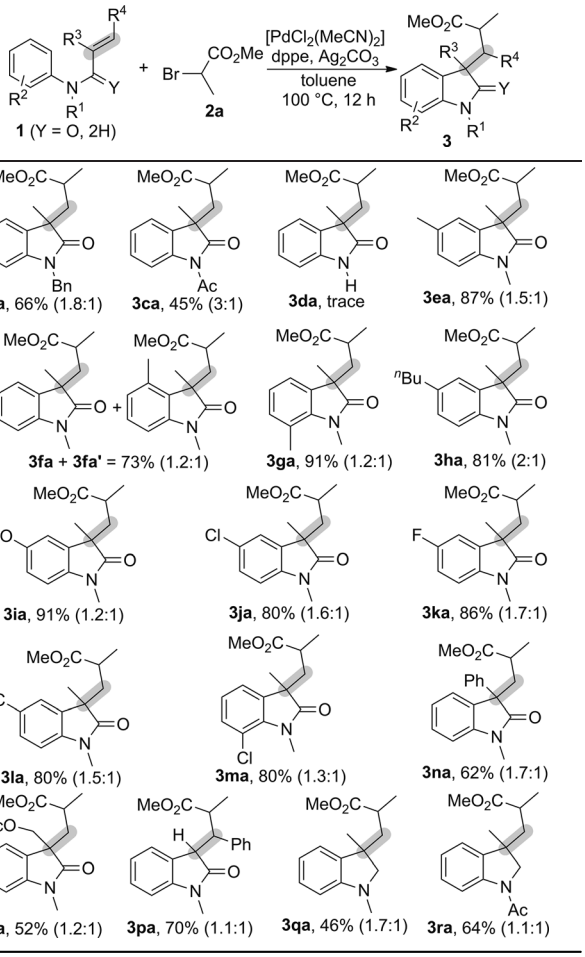
Table 1: Optimization of the reaction conditions.[a]



Entry	Palladium precursor	Ligand	Additive	Solvent	Yield [%]
1	$[PdCl_2(MeCN)_2]$	PPh_3	Ag_2CO_3	toluene	78
2	$PdCl_2$	PPh_3	Ag_2CO_3	toluene	72
3	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	toluene	75
4	$[Pd(dba)_2]$	PPh_3	Ag_2CO_3	toluene	15
5	$[Pd(PPh_3)_4]$	PPh_3	Ag_2CO_3	toluene	32
6	–	PPh_3	Ag_2CO_3	toluene	0
7	$[PdCl_2(MeCN)_2]$	PCy_3	Ag_2CO_3	toluene	88
8	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	toluene	99
9	$[PdCl_2(MeCN)_2]$	–	Ag_2CO_3	toluene	56
10[b]	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	toluene	21
11	$[PdCl_2(MeCN)_2]$	dppe	Ag_2O	toluene	85
12	$[PdCl_2(MeCN)_2]$	dppe	AgOAc	toluene	6
13[c]	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	toluene	43
14	$[PdCl_2(MeCN)_2]$	dppe	–	toluene	0
15	$[PdCl_2(MeCN)_2]$	dppe	$Cu(OAc)_2$	toluene	0
16	$[PdCl_2(MeCN)_2]$	dppe	NaOAc	toluene	0
17	$[PdCl_2(MeCN)_2]$	dppe	CsOAc	toluene	0
18	$[PdCl_2(MeCN)_2]$	dppe	Cs_2CO_3	toluene	0
19	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	1,4-dioxane	43
20	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	DMF	22
21[d]	$[PdCl_2(MeCN)_2]$	dppe	Ag_2CO_3	toluene	56

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), palladium precursor (5 mol%), ligand (10 mol%), additive (2 equiv), and solvent (2 mL) at 100°C for 12 hours. The d.r. value (1:1) was determined by ^1H NMR analysis. [b] $[PdCl_2(MeCN)_2]$ (2 mol%). [c] Ag_2CO_3 (1 equiv). [d] At 80°C. Cy = cyclohexyl, dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphino)ethane.

Table 2: Variation of the *N*-arylalkene **1**.[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $[PdCl_2(MeCN)_2]$ (5 mol%), dppe (10 mol%), Ag_2CO_3 (2 equiv), and toluene (2 mL) at 100°C for 12 hours. The d.r. value is given in parenthesis.

without ligands, only a moderate yield was obtained (entry 9). However, the yield decreased from 99% to 21% at a reduced catalyst loading of $[PdCl_2(MeCN)_2]$ (2 mol%; entry 8 vs. entry 10). Extensive screening revealed that silver salts were crucial for the reaction (entries 8 and 11–18). A good yield was achieved using Ag_2O instead of Ag_2CO_3 (entry 11), but replacing Ag_2CO_3 with AgOAc furnished product **3aa** in low yield (entry 12). Notably, the yield decreased from 99% to 43% when one equivalent of Ag_2CO_3 was used (entry 13), and reactions in the absence of a silver salt did not generate a detectable amount of product **3aa**, even in the presence of an oxidant ($Cu(OAc)_2$) or various bases, including NaOAc, CsOAc, and Cs_2CO_3 (entries 14–18). Previous reports indicated that silver salts could be used as oxidants to trigger radical transformations.[10] Therefore, silver salts may act as oxidants instead of bases in this process. After varying solvent and reaction temperature, we found that the reaction in toluene at 100°C provided the best results (entry 8 vs. entries 19–21).

After the standard reaction conditions had been determined, we examined the scope of this difunctionalization process, varying the *N*-arylalkene **1** and the α-carbonyl alkyl bromide **2**. As shown in Table 2, the standard conditions were compatible with various functionalized *N*-arylalkenes, including *N*-arylacrylamides **1b–p** and *N*-(2-methylallyl)anilines **1q–r**. In the presence of $[PdCl_2(MeCN)_2]$, dppe, and Ag_2CO_3, acrylamides **1b** and **1c**, which bear benzyl and acetyl groups on the nitrogen atom, respectively, reacted with methyl 2-bromopropanoate (**2a**), affording the corresponding products (**3ba** and **3ca**) in moderate yield. Unfortunately, *N*-phenylamide **1d**, which contained an unprotected N–H group, was not suitable for this reaction (Product **3da**). Several substituents, including Me, *n*Bu, MeO, Cl, F, and CF_3, were well tolerated on the aryl ring of the aniline derivative (**3ea–ma**). For example, *N*-arylacrylamides **1e–g**, which bear a methyl group at the *para*, *meta*, or *ortho* position, successfully underwent the difunctionalization transformation, furnishing the desired products (**3ea–ga**) in 87%, 73%, and 91% yield, respectively. Notably, the reaction of *meta*-methyl-substituted *N*-arylacrylamide **1f** produced a mixture of regioisomers (**3fa** and **3fa′**) in a 1.2:1 ratio, based on ^1H NMR analysis of the unpurified mixture. The standard reaction conditions could be applied to halogen-substituted *N*-arylacrylamides, such as **1j**, **1k**, and **1m**; these compounds were converted into products **3ja**, **3ka**, and **3ma** in high yields. Substrates with either a Ph or an AcO group in place of the methyl group at the 2 position of the acrylamide moiety also performed well under the standard conditions (**3na–oa**). *N*-Methyl-*N*-phenylcinnama-

mide (**1p**), which contains an internal alkene, smoothly underwent the difunctionalization reaction to afford product **3pa** in 70% yield. Unactivated alkenes **1q–r** were also investigated under the standard conditions: They were found to be suitable substrates for the reaction, generating **3qa** and **3ra** in moderate yields.

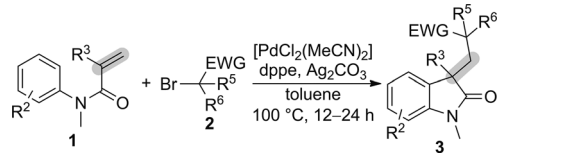
This difunctionalization method was applicable to various α-carbonyl alkyl bromides (**2b–2k**), including α-bromoalkyl amides, ketones, and esters (Table 3). Secondary α-bromoalkyl amide **2b** and ketones **2c** and **2d** smoothly reacted with acrylamide **1a** in the presence of $[PdCl_2(MeCN)_2]$, dppe, and Ag_2CO_3 in moderate yields (Products **3ab–ad**). The primary α-bromoalkyl ester **2e** and ketones **2f–i** were transformed into the desired products (**3ae–i**) in moderate to good yields, and the order of their reactivity is as follows: ester > electron-rich aryl ketone > electron-deficient aryl ketone. To our delight, both tertiary α-bromoalkyl ester **2j** and ketone **2k** were compatible with the standard conditions and reacted with acrylamides **1a**, **1e**, **1j**, and **1s** to produce products **3aj**, **3ej**, **3jj**, **3sj**, and **3ak** in 62–90% yield. For example, the reaction of *ortho*-SMe-substituted acrylamide **1s** with substrate **2j** in the presence of $[PdCl_2(MeCN)_2]$, dppe, and Ag_2CO_3 successfully generated product **3sj** in 67% yield.

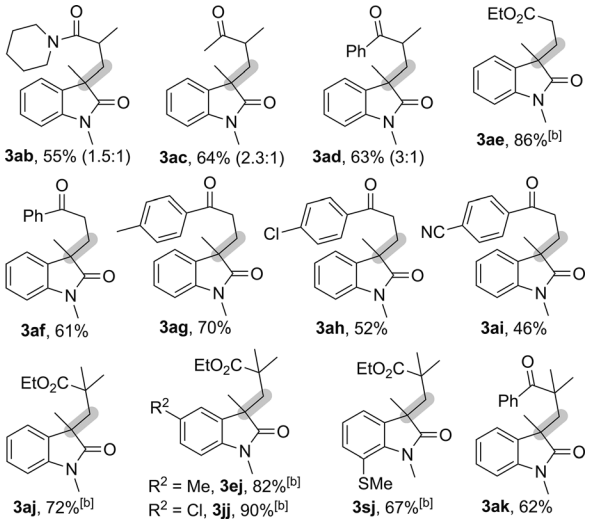
To elucidate the mechanism of the current reaction, two radical inhibitors, namely 2,2,6,6-tetramethylpiperidinyloxyl [TEMPO; Eq. (1)] and 1,1-diphenylalkene [Eq. (2)], were added to the difunctionalization reaction. The addition of 2.5 equivalents of TEMPO completely inhibited a reaction of acrylamide **1a**; instead, substrate **2a** reacted with TEMPO to form methyl 2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**4**) in 83% yield. In the presence of 1,1-diphenylalkene and *N*-arylalkene **1a** or **1q**, methyl 2-methyl-4,4-diphenylbut-3-enoate (**5**) was obtained as the major product. Therefore, an α-carbonyl alkyl radical is formed, and the classic Heck reaction, which generates an unactivated alkene through β-hydride elimination, occurs before the difunctionalization reaction with the *N*-arylalkene.

Based on the above results and previous reports,[4,7,8,10,11] we propose two possible mechanisms for this system (Scheme 2). Initially, alkyl radical **A** is formed by the reaction between methyl 2-bromopropanoate (**2a**) and the active $[Pd^0L_n]$ species (generated in situ from $[PdCl_2(MeCN)_2]$ and dppe); the active $[Pd^0L_n]$ species is oxidized into a $[Pd^{II}L_n]$ species with the aid of a Ag^I oxidant.[4,8,10] Intermediate **A** then adds to the C=C bond in substrate **1a**, yielding radical intermediate **B**. Subsequently, **B** cyclizes to form radical intermediate **C**. Oxidation of **C** by the $[Pd^{II}L_n]$ species occurs to produce cationic intermediate **D**.[4] Finally, intermediate **D** is deprotonated, generating product **3aa**.

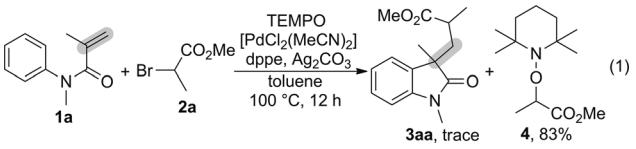
We cannot rule out another pathway that involves a Pd^{II}/Pd^0 catalytic cycle.[10,11] The active $[Pd^{II}X_2L_n]$ species can initiate the reaction by *ortho* palladation of the aniline ring in substrate **1a** to form σ-aryl palladium(II) intermediate **E**. Carbopalladation between **E** and the C=C bond gives σ-alkyl

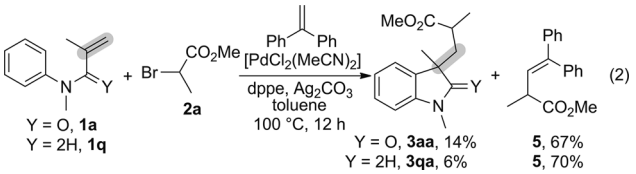
Table 3: Variation of the α-carbonyl alkyl bromide **2**.[a]

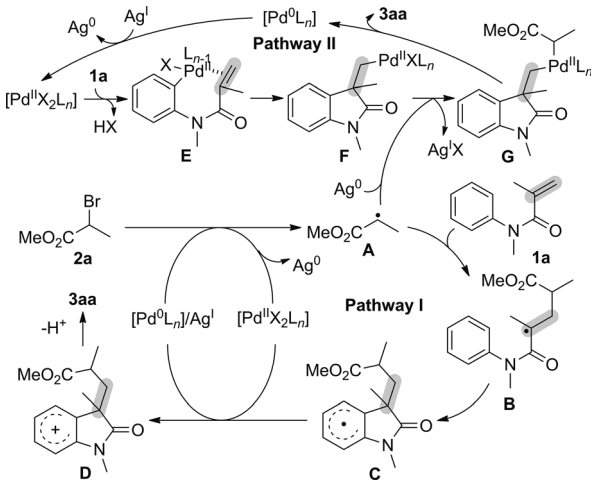




[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $[PdCl_2(MeCN)_2]$ (5 mol%), dppe (10 mol%), Ag_2CO_3 (2 equiv), and toluene (2 mL) at 100°C for 24 hours. The d.r. value is given in parenthesis. [b] 12 hours.







Scheme 2. Two possible reaction mechanisms.

palladium(II) intermediate **F**, which would be trapped by α-carbonyl radical **A** with the aid of the Ag^0 species,[11] leading to σ-alkyl palladium(II) intermediate **G**. Reductive elimination of intermediate **G** affords the desired product **3aa** and the $[Pd^0L_n]$ species. The active $[Pd^{II}X_2L_n]$ species is regenerated from the $[Pd^0L_n]$ species with the Ag^I salt to start a new catalytic cycle.

In summary, the first palladium-catalyzed oxidative difunctionalization of *N*-arylalkenes with α-carbonyl alkyl bromides is reported; this reaction is initiated through a Heck insertion and requires the addition of Ag_2CO_3. This transformation includes tandem C–Br/C–H functionalization and cyclization steps that occur through an oxidative radical pathway. This process features a broad substrate scope and excellent functional-group tolerance. Further extensions of the current method and mechanistic studies are currently underway in our laboratory.

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