

Cross-Coupling

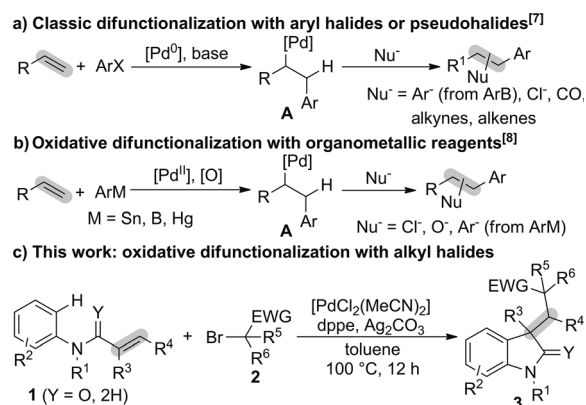
Palladium-Catalyzed Oxidative Difunctionalization of Alkenes with α -Carbonyl Alkyl Bromides Initiated through a Heck-type Insertion: A Route to Indolin-2-ones**

Jian-Hong Fan, Wen-Ting Wei, Ming-Bo Zhou, Ren-Jie Song, and Jin-Heng Li*

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,



Scheme 1. Alkene difunctionalizations that involve a Heck insertion.

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]

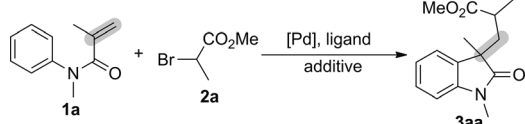
Initial experiments were performed on the oxidative difunctionalization reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) and methyl 2-bromopropanoate (**2a**) with a palladium source, phosphine ligands, and oxidants (Table 1). The palladium catalyst was necessary for the transformation, and $[PdCl_2(MeCN)_2]$ 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

[*] J.-H. Fan, W.-T. Wei, M.-B. Zhou, Dr. R.-J. Song, Prof. Dr. J.-H. Li
State Key Laboratory of Chemo/Biosensing and Chemometrics
College of Chemistry and Chemical Engineering, Hunan University
Changsha 410082 (China)
E-mail: jhli@hnu.edu.cn

Prof. Dr. J.-H. Li
State Key Laboratory of Applied Organic Chemistry, Lanzhou
University
Lanzhou 730000 (China)

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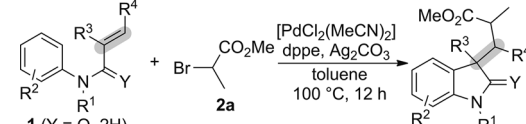
Table 1: Optimization of the reaction conditions.^[a]


Entry	Palladium precursor	Ligand	Additive	Solvent	Yield [%]
1	[PdCl ₂ (MeCN) ₂]	PPh ₃	Ag ₂ CO ₃	toluene	78
2	PdCl ₂	PPh ₃	Ag ₂ CO ₃	toluene	72
3	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	toluene	75
4	[Pd(dba) ₂]	PPh ₃	Ag ₂ CO ₃	toluene	15
5	[Pd(PPh ₃) ₄]	PPh ₃	Ag ₂ CO ₃	toluene	32
6	—	PPh ₃	Ag ₂ CO ₃	toluene	0
7	[PdCl ₂ (MeCN) ₂]	PCy ₃	Ag ₂ CO ₃	toluene	88
8	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO ₃	toluene	99
9	[PdCl ₂ (MeCN) ₂]	—	Ag ₂ CO ₃	toluene	56
10 ^[b]	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO ₃	toluene	21
11	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ O	toluene	85
12	[PdCl ₂ (MeCN) ₂]	dppe	AgOAc	toluene	6
13 ^[c]	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO 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 ₂ CO ₃	toluene	0
19	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO ₃	1,4-dioxane	43
20	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO ₃	DMF	22
21 ^[d]	[PdCl ₂ (MeCN) ₂]	dppe	Ag ₂ CO 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] [PdCl₂(MeCN)₂] (2 mol %). [c] Ag₂CO₃ (1 equiv). [d] At 80 °C. Cy = cyclohexyl, dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphino)ethane.

without ligands, only a moderate yield was obtained (entry 9). However, the yield decreased from 99 % to 21 % at a reduced catalyst loading of [PdCl₂(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 Ag₂O instead of Ag₂CO₃ (entry 11), but replacing Ag₂CO₃ with AgOAc furnished product **3aa** in low yield (entry 12). Notably, the yield decreased from 99 % to 43 % when one equivalent of Ag₂CO₃ 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 Cs₂CO₃ (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 [PdCl₂(MeCN)₂], dppe, and Ag₂CO₃,

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


Product	Yield [%]	d.r.
3ba	66%	(1.8:1)
3ca	45%	(3:1)
3da	trace	—
3ea	87%	(1.5:1)
3fa + 3fa'	73%	(1.2:1)
3ga	91%	(1.2:1)
3ha	81%	(2:1)
3ia	91%	(1.2:1)
3ja	80%	(1.6:1)
3ka	86%	(1.7:1)
3la	80%	(1.5:1)
3ma	80%	(1.3:1)
3na	62%	(1.7:1)
3oa	52%	(1.2:1)
3pa	70%	(1.1:1)
3qa	46%	(1.7:1)
3ra	64%	(1.1:1)

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), [PdCl₂(MeCN)₂] (5 mol %), dppe (10 mol %), Ag₂CO₃ (2 equiv), and toluene (2 mL) at 100 °C for 12 hours. The d.r. value is given in parenthesis.

acrylamides **1b** and **1c**, which bear benzyl and acetyl groups on the nitrogen atom, respectively, reacted with methyl 2-bromopropionate (**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 CF₃, 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-

amide (**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 -bro-

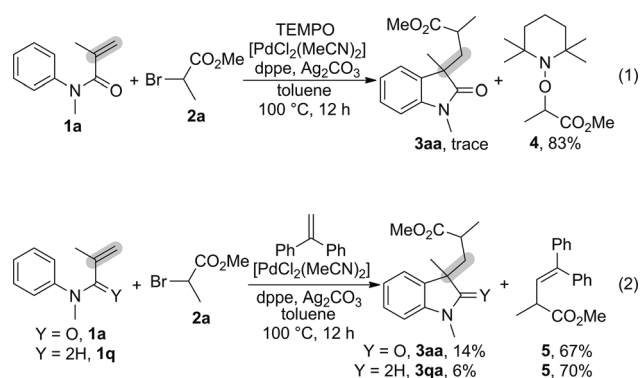
Table 3: Variation of the α -carbonyl alkyl bromide **2**.^[a]

	3ab , 55% (1.5:1)
	3ac , 64% (2.3:1)
	3ad , 63% (3:1)
	3ae , 86% ^[b]
	3af , 61%
	3ag , 70%
	3ah , 52%
	3ai , 46%
	3aj , 72% ^[b]
	3ej , 82% ^[b]
	3jj , 90% ^[b]
	3sj , 67% ^[b]
	3ak , 62%

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $[\text{PdCl}_2(\text{MeCN})_2]$ (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.

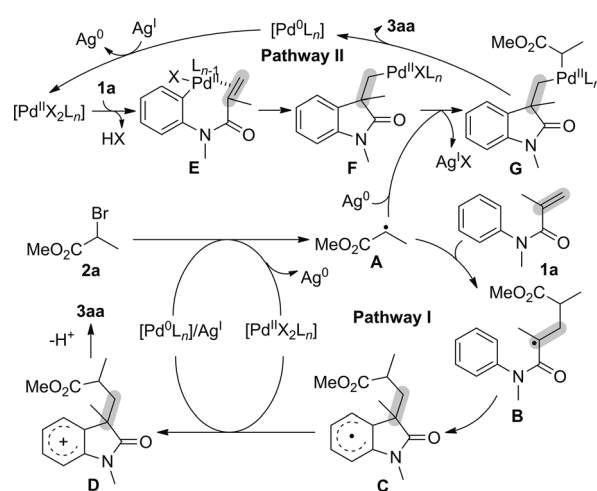
moalkyl amide **2b** and ketones **2c** and **2d** smoothly reacted with acrylamide **1a** in the presence of $[\text{PdCl}_2(\text{MeCN})_2]$, dppe, and Ag_2CO_3 in moderate yields (Products **3ab–ad**). The primary α -bromoalkyl ester **2e** and ketones **2f–i** were transformed into the desired products (**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 $[\text{PdCl}_2(\text{MeCN})_2]$, 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-tetramethylpiperidin-1-yloxy [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



Scheme 2. Two possible reaction mechanisms.

between methyl 2-bromopropanoate (**2a**) and the active $[\text{Pd}^0\text{L}_n]$ species (generated in situ from $[\text{PdCl}_2(\text{MeCN})_2]$ and dppe); the active $[\text{Pd}^0\text{L}_n]$ species is oxidized into a $[\text{Pd}^{\text{II}}\text{L}_n]$ 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 $[\text{Pd}^{\text{II}}\text{L}_n]$ 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 $\text{Pd}^{\text{II}}/\text{Pd}^0$ catalytic cycle.^[10,11] The active $[\text{Pd}^{\text{II}}\text{X}_2\text{L}_n]$ 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

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 $[\text{Pd}^0\text{L}_n]$ species. The active $[\text{Pd}^{\text{II}}\text{X}_2\text{L}_n]$ species is regenerated from the $[\text{Pd}^0\text{L}_n]$ species with the Ag^1 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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