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Domino Heck/Hiyama cross-coupling: trapping of the σ-alkylpalladium intermediate with arylsilanes†

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A palladium-catalyzed domino Heck cyclization/Hiyama coupling reaction by the trapping of the σ-alkylpalladium intermediate with arylsilanes is described. A wide range of aryl-tethered alkenes and arylsilanes are all compatible with the reaction conditions. This approach shows good yields and excellent functional group tolerance, presenting a more practical and sustainable alternative to the conventional domino Heck cyclization/Suzuki coupling reaction.

Over the past decades, the cascade reaction has emerged as a powerful and atom-economical approach for the construction of highly functionalized, diverse and complex molecules effectively while reducing waste output as well as the time and labor required for the overall transformation.[1] Typically, the intramolecular domino Heck cyclization has shown unique efficacy and attracted considerable attention since it generates, after the carbometallation of alkene, an *in situ* generated active σ-alkylmetal species that can be further functionalized.[2] The groups of Zhu,[3] Lautens,[4] Li,[5] Gu,[6] and Jia[7] have made great contributions in this respect. Among the various transformations of the σ-alkylmetal species in the domino Heck cyclization, the cross-coupling strategy provides an efficient avenue to realize diarylation of tethered alkenes. For example, Grigg's group demonstrated the first Pd-catalyzed domino Heck cyclization/Suzuki coupling reaction for the synthesis of 3,3-disubstituted oxindoles bearing quaternary all-carbon centers in the 1990s.[8] Subsequently, a domino carbopalladation cross-coupling reaction for the formation of valuable oxindole scaffolds was developed by the group of Somfai.[9] Recently, Kong's group demonstrated a nickel-catalyzed intramolecular Heck cyclization/Suzuki coupling reaction of a range of electrophiles and aryl boronic acids.[10] Another related example was reported by the same group, who demonstrated a Ni-catalyzed reductive diarylation of activated alkenes with an external stoichiometric amount of a reducing agent by domino cyclization/cross-coupling of aryl bromide.[11] Despite significant achievements made in capturing the σ-alkylmetal species by the cross-coupling processes, to the best of our knowledge, the coupling of nucleophiles was limited to boronic acids and aryl bromides, and no report has appeared using arylsilanes as nucleophiles in Heck/coupling-capture sequences for the achievement of diarylation of tethered alkenes.

On the other hand, organosilicon compounds[12] are usually employed in cross-coupling processes due to their ease of handling and/or low toxicity. The classic Hiyama cross-coupling provides an indispensable synthetic method for the preparation of useful industrial and pharmaceutical materials by utilizing arylsilanes as the coupling reagent.[13] To date, nearly all studies of the Hiyama reaction have focused on couplings of aryl or vinyl-palladium species; the Hiyama coupling of alkyl-palladium species remains scarce. In this context, we postulated that utilization of the σ-alkylpalladium species generated *in situ*[14] instead of aryl or vinyl-palladium species to couple with arylsilanes may be an effective way to realize the diarylation of tethered alkenes. Herein, we report our investigation of a palladium-catalyzed cascade Heck cyclization/Hiyama cross-coupling of aryl-tethered activated/unactivated alkenes with arylsilanes involving two sequential C(sp2)–C(sp^3) bond formations in a single synthetic sequence (Scheme 1). Compared with the previous reports of cascade Heck cyclization/Suzuki-coupling route,[8,10] this described approach avoids the limitations of difficult synthesis and purification of substrates.

We commenced the study by using *N*-(2-iodophenyl)-*N*-methylmethacrylamide (**1a**) and triethoxy(4-methoxyphenyl) silane (**2a**) as the model substrates to evaluate the feasibility of the proposed Heck cyclization/Hiyama coupling process (Table 1). Gratifyingly, the desired product **3a** was first realized in 63% yield by using 5 mol% of $Pd(OAc)_2$ as the catalyst, 10 mol% of PCy_3 as the ligand, and Bu_4NF as the silane activator in MeCN at 80 °C for 12 h (entry 1). Subsequently, extensive

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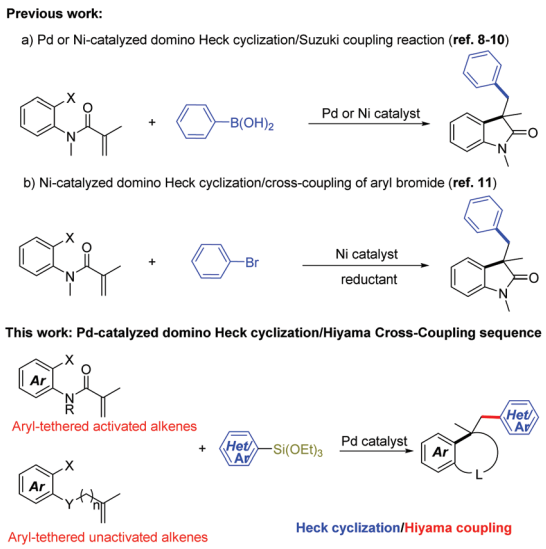
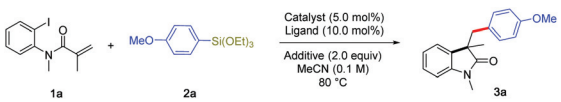


Scheme 1 Design plan for the Heck cyclization/Hiyama coupling process.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Ligand	Additive	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	Bu_4NF	63
2	$Pd(OAc)_2$	$P(p\text{-}MeOC_6H_5)_3$	Bu_4NF	69
3	$Pd(OAc)_2$	$P(2\text{-furyl})_3$	Bu_4NF	72
4	**$Pd(OAc)_2$**	**PPh_3**	**Bu_4NF**	**85**
5	$Pd(OAc)_2$	DPPF	Bu_4NF	<5
6	$Pd(OAc)_2$	DPPB	Bu_4NF	<5
7	$Pd(OAc)_2$	DPEphos	Bu_4NF	0
8	$Pd(OAc)_2$	PPh_3	$NEt_3{\cdot}3HF$	62
9	$Pd(OAc)_2$	PPh_3	$TBAF{\cdot}3H_2O$	79
10	$Pd(OAc)_2$	PPh_3	CsF	<10
11	$Pd(OAc)_2$	PPh_3	KF	<10
12	$Pd(OAc)_2$	PPh_3	CaF_2	<10
13	$Pd(OAc)_2$	PPh_3	NH_4F	<10
14[c,d]	$Pd(OAc)_2$	PPh_3	Py·HF	0
15	$Pd_2(dba)_3$	PPh_3	Bu_4NF	50
16	$Pd(TFA)_2$	PPh_3	Bu_4NF	76
17	$[Pd(C_3H_5)Cl]_2$	PPh_3	Bu_4NF	69
18	$PdCl_2(PPh_3)_2$	PPh_3	Bu_4NF	77
19	$Pd(OAc)_2$	PPh_3	—	0

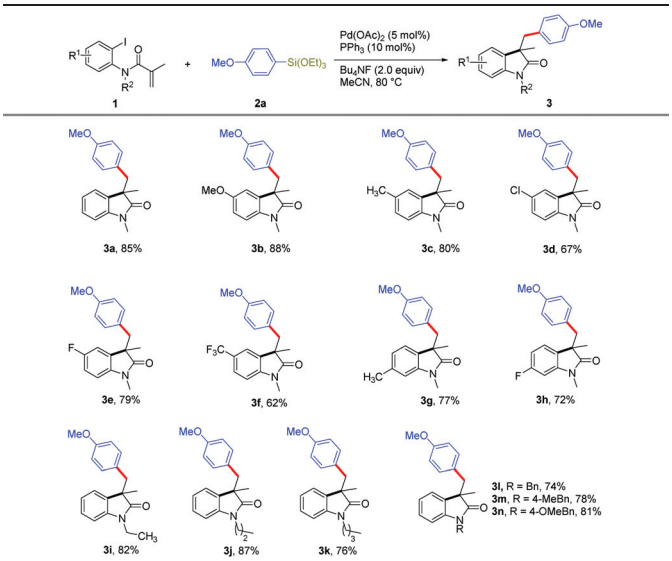
[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol%), ligand (10 mol%), MeCN (2.0 ml, 0.1 M), additive (0.4 mmol), 80 °C, 12 h under argon atmosphere conditions. [b] Isolated yields. [c] TBAI as the additive. [d] TBAB as the additive.

screening of ligands revealed that monophosphine ligands (entries 2–4) performed better than bis(phosphine) ligands (entries 5–7) in this reaction. More gratifyingly, the inexpensive PPh_3 was the most effective ligand to generate the product **3a** in 85% yield (entry 4). Several fluoride additives were evaluated and had a pronounced influence on the transformation: $NEt_3{\cdot}3HF$ and $Bu_4NF{\cdot}3H_2O$ showed inferior performance in comparison with Bu_4NF, while other fluorides such as CsF, KF, CaF_2, NH_4F and Py·HF were ineffective in activating the inert C–Si bond and facilitating the transmetalation from silicon to the palladium catalyst (entries 8–14). In addition, TBAI or TBAB were also ineffective for the transformation (entry 14). Furthermore, a careful survey of palladium catalysts was then performed, which showed that $Pd(OAc)_2$ was still the best choice. Finally, a control experiment revealed that none of the product **3a** was obtained without the addition of the fluoride activator (entry 19).

With the optimized reaction conditions established, we next investigated the scope of the Heck cyclization/Hiyama coupling procedure by testing various methacrylamides **1** in the reaction with **2a**. As shown in Table 2, *para*- and *meta*-substituents of aryl iodides, such as methoxy, methyl, halide, trifluoromethoxy, and ester groups, were well tolerated to give the products **3b–3h** in 62–88% yields. The substrates with an *N*-Et, *N*-^{n}Pr, or *N*-^{n}Bu protecting group were efficient reaction partners, giving access to the corresponding products **3i–3k** in satisfactory yields. Moreover, various *N*-benzyl groups (Bn, 4-MeBn, and 4-OCH_3Bn) could also be readily converted to the corresponding products **3l–3n** in 74–81% yields.

The substrate scope with respect to arylsilanes **2** was investigated next (Table 3). Arylsilanes with electron-donating substituents (phenyl, methyl and methoxyl) or electron-withdrawing substituents (trifluoromethoxyl and ester) were found to be suitable substrates and underwent the cascade Heck cyclization/Hiyama coupling reaction with acrylamide with good yields (**3o–3t**). Additionally, organosilicon with a benzothiophenyl backbone was also a pertinent precursor (**3u** and **3v**). Notably, aryl-tethered unactivated alkenes also worked well in

Table 2 Scope of acrylamide[a,b]



[a] Reaction conditions unless otherwise noted: **1** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Bu_4NF (0.4 mmol), MeCN (2.0 ml, 0.1 M), 80 °C, 12 h under argon atmosphere conditions. [b] Isolated yields.

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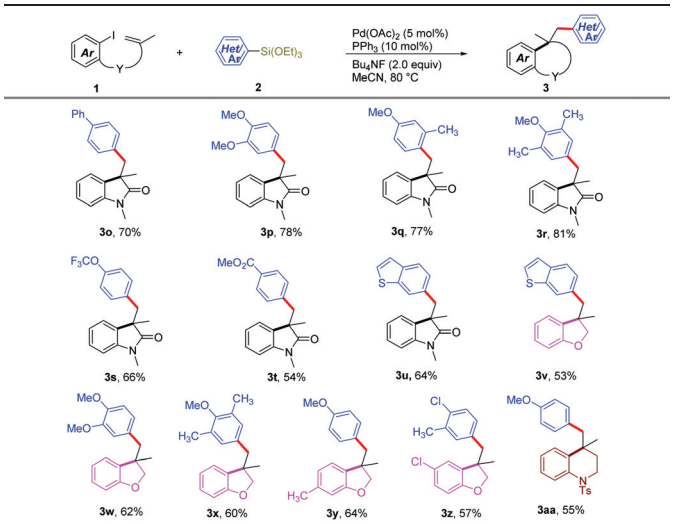
Table 3 Substrate scope of the Heck cyclization/Hiyama coupling process[a,b]

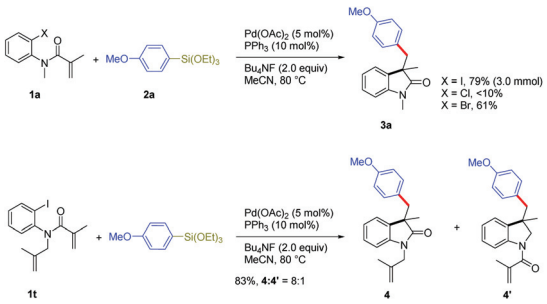


[a] Reaction conditions unless otherwise noted: **1** (0.2 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $P(PPh)_3$ (10 mol%), Bu_4NF (0.4 mmol), MeCN (2.0 ml, 0.1 M), 80 °C, 12 h under argon atmosphere conditions. [b] Isolated yields.

this transformation, leading to **3v**, **3w**, **3x**, **3y**, and **3z**, respectively, all in acceptable yields under the standard reaction conditions. Most remarkably, the substrate *N*-(3-methylbut-3-en-1-yl)aniline was also applicable to the reaction and yielded the corresponding product **3aa** in 55% yield.

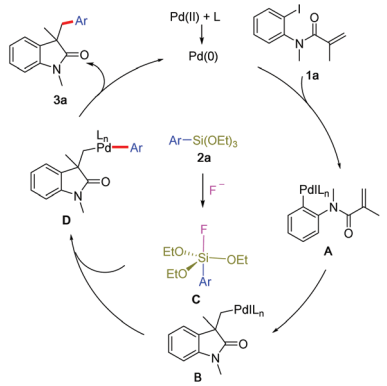
A gram-scale experiment of **1a** with **2a** was carried out to examine the scalability, and 79% yield of **3a** was isolated on a 3.0 mmol scale under the standard conditions. As a comparison, a lower yield was obtained for the reaction of aryl bromide and almost no product was observed when using aryl chloride as the substrate, which showed that the disconnection of C–X bonds of different substrates had a great effect on this cascade Heck cyclization/Hiyama coupling reaction. In addition, the reaction of **1t** bearing *N*-allyl and *N*-methylacryl moieties forming 2-indolinone **4** predominantly in a good yield showed good regioselectivity (Scheme 2).

To demonstrate both the application prospect and the functional group tolerance of this method, as shown in Scheme 3,



Scheme 2 Gram-scale reaction and synthetic regioselectivity.

Scheme 3 The cascade Heck cyclization/Hiyama coupling of the ezetimibe derivative.



Scheme 4 Proposed reaction mechanism.

the reaction of **1a** with arylsilane **5** derived from ezetimibe, a drug known to inhibit cholesterol absorption, was performed, which proceeded through Heck cyclization/Hiyama coupling to yield oxindole functionalized ezetimibe **6** in 74 yield with a 1.2 : 1 dr value. This transformation shows great promise for drug discovery and development as a powerful tool for the synthesis of ezetimibe analogues.

A mechanistic pathway is proposed in Scheme 4. Oxidative addition of Pd(0) to the carbon–halogen bond takes place followed by intramolecular carbopalladation to generate the primary $C(sp^3)$–Pd(II) species **B**. Subsequent transmetalation with the pentavalent silicate **C** generated *in situ* by the fluoride ion results in the formation of intermediate **D**, which undergoes reductive elimination to produce product **3a**, meanwhile regenerating the Pd(0) species for the catalytic cycle.

Conclusions

In conclusion, an efficient strategy for the palladium-catalyzed domino Heck cyclization/Hiyama coupling reaction of aryl-tethered activated/unactivated alkenes with arylsilanes has been presented. Outstanding functional group tolerance and broad substrate scope were demonstrated. This protocol presents a more practical and sustainable alternative to the previous domino Heck cyclization/Suzuki coupling reaction. Further investigations toward exploring this type of domino reaction and the application of this novel technique in the late-stage modification of complex molecules are ongoing in our laboratory.

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Conflicts of interest

The authors declare no competing financial interest.

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