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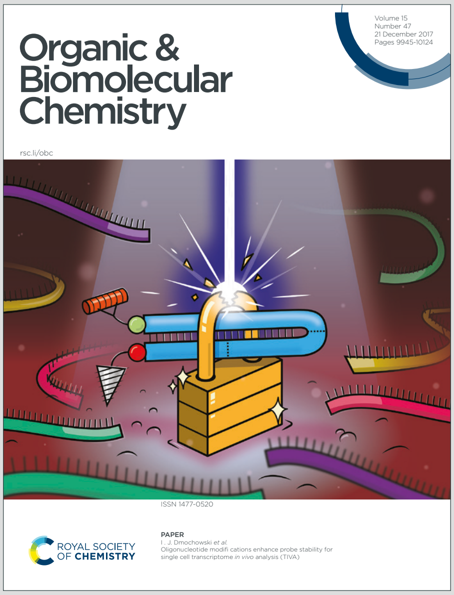

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Palladium-Catalyzed Cascade Reactions of Alkene-tethered Carbamoyl Chlorides with *N*-Tosyl Hydrazones: Synthesis of Alkene-functionalized Oxindoles

Wan Sun,[a] Chen Chen,*[a] Yuan Qi,[a] Jinghui Zhao,[a] Yinwei Bao[a] and Bolin Zhu*[a]

A palladium-catalyzed cascade reaction of alkene-tethered carbamoyl chlorides with *N*-tosyl hydrazones is described. It provided a new way to synthesize various alkene-functionalized oxindoles bearing an all-carbon quaternary center. The olefin moieties could serve as versatile handles for further elaboration. This transformation was highly efficient and showed good functional group tolerance.

Oxindoles represent a class of fused heterocyclic motifs found universally in numerous pharmaceuticals, agrochemicals and natural products.[1] Especially for 3,3-disubstituted oxindoles, which exhibit all kinds of biological activities.[2] Well known members include dioxibrassanin,[3] convolutamydines,[4] and horsifiline[5] (Figure 1). Therefore, it is important to develop efficient methodologies for the synthesis of 3,3-disubstituted oxindoles.[6] Traditional synthesis of 3,3-disubstituted oxindoles typically involve alkylation of 3-unsubstituted oxindoles and are limited only to aliphatic substitution. When the disubstituents are not identical, this approach was proven to be very challenging. In recent years, a variety of new synthetic strategies were developed for the construction of 3,3-disubstituted oxindoles, which include: a) Olefin difunctionalization of acrylamide via a free radical pathway;[7] b) Heck-type reaction via N-(2-halophenyl)acrylamide;[8] c) Difunctionalization of acrylamide via a transition-metal-catalyzed Friedel-Crafts type pathway.[9]

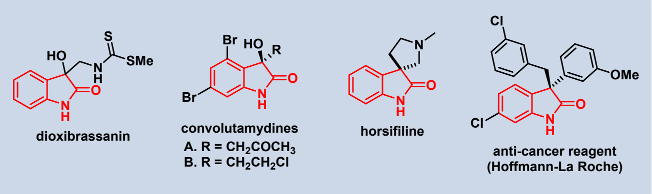

Figure 1. Representative Examples of 3,3-Disubstituted Oxindoles

Carbamoyl chlorides[10] are useful precursors for preparing oxindoles moieties via transition-metal-catalyzed domino reactions,[11-15] which could be readily prepared from corresponding secondary amines by treatment with triethylamine and triphosgene. For examples, Takemoto[12] and co-workers reported a new strategy for rapid access to various oxindoles from carbamoyl chlorides via C(sp^3)-H activation and carbosilylation. Lautens[13] and Tong[14] reported transition-metal-catalyzed intramolecular borylacylation and iodoacylation for the synthesis of boryl- and iodo-substituted oxindoles, respectively. Furthermore, Lautens[15] and co-workers reported palladium-catalyzed intramolecular cross-coupling of alkyne-tethered carbamoyl chlorides for the synthesis of methylene oxindoles (Scheme 1a).

Since Noyori[16] and co-workers reported the cyclopropanation of alkenes with diazo compounds in 1966, diazo chemistry draws much attention from organic chemists. In the past decade, diazo compounds have been extensively explored as carbene precursors in transition-metal-catalyzed transformations.[17] In 2001, Vranken[18] and co-workers reported the first palladium-catalyzed cross-coupling reaction of (trimethylsilyl)diazomethane and benzyl halides. However, the stability and safety issues related to diazo compounds limit their wide applications. In 2007, a major breakthrough was reported by Barluenga,[19] who first utilized *N*-tosyl hydrazones as the precursor of diazo compounds in palladium-catalyzed cross-coupling reactions. Since then, a variety of useful transformations in palladium carbene involved cross-couplings[20] have been developed by Wang,[21] Valdés,[22] Van Vranken[23] and others.[24]

Although palladium-catalyzed cross-coupling reactions using *N*-tosyl hydrazones as carbene precursors have been extensively investgated in the past few years, studies on the reactions between alkylpalladium and carbenes have been rarely reported,[8b, 24a] which might be a new protocol for the construction of functionalized alkenes. With the combination of the pioneering works and our continuous effort on transition-metal-catalyzed synthetic transformations.[25] We envisioned that alkyl palladium(II) species from the palladium(0) catalyst and alkene-tethered carbamoyl chlorides would also be capable of carbene formation and alkyl migratory insertion. Herein, we report a palladium(0)-catalyzed intramolecular Heck type reaction of alkene-

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[a] Address here. Tianjin Key Laboratory of Structure and Performance for Functional Molecules, MOE Key Laboratory of Inorganic-Organic Hybrid Functional Material Chemistry, College of Chemistry, Tianjin Normal University, Tianjin 300387, P. R. China. E-mail: hxxycc@tjnu.edu.cn, hxxyzbl@tjnu.edu.cn

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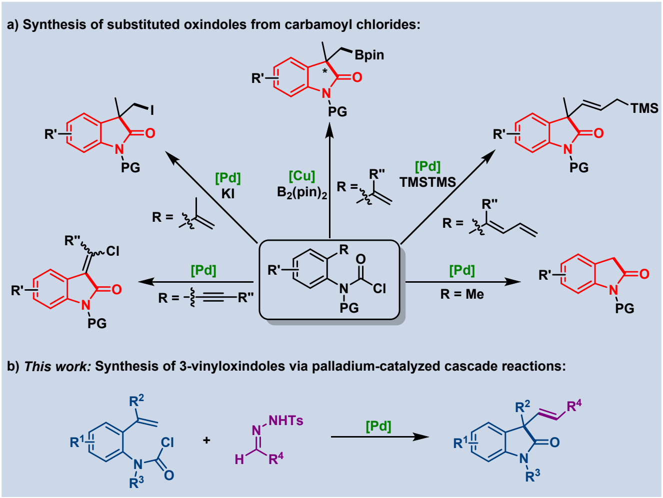
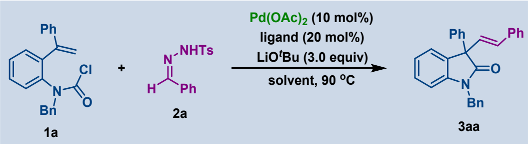
tethered carbamoyl chlorides with *N*-tosyl hydrazones to give 3-vinyloxindoles (Scheme 1b).



Scheme 1. Synthesis of 3,3-Disubstituted Oxindoles from Carbamoyl Chlorides

We initiated our studies with the screening of reaction conditions by reacting alkene-tethered carbamoyl chloride **1a** with *N*-tosyl hydrazone **2a** in the presence of $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.3 equiv), LiO^tBu (3.0 equiv) in MeCN (2.0 mL) at 90°C under N_2 atmosphere. Gratifyingly, the desired cyclization product **3aa** was obtained in 78% yield (Table1, entry 1). Subsequently, a series of ligands including monophosphines and diphosphines were evaluated, and to our delight, the yield of **3aa** was significantly increased to 91% with the use of $P(4\text{-}F\text{-}C_6H_4)_3$ as the ligand (Table 1, entries 2-4). Decreasing the amount of $P(4\text{-}F\text{-}C_6H_4)_3$ ligand to 20 mol% delivered similar result (Table1, entry 5). Other solvents, including DMF, DMSO, toluene and 1, 4-dioxane failed to show better results (Table 1, entries 6-9). When the reaction was conducted at 70°C, a lower yield was obtained because of the low conversion of **1a** (Table1, entry 10). To our delight, the reaction was finished within 30 minutes in air and the desired product **3aa** was isolated in 95% yield (Table1, entries 11-13). Thus, the optimal condition for this transformation was determined to be as follows: simply mixing **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), $P(4\text{-}F\text{-}C_6H_4)_3$ (0.04 mmol) and LiO^tBu (0.6 mmol) in MeCN (2.0 mL) at 90 °C in air for 30 minutes.

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	time	3aa[b]
1[c]	PPh_3	MeCN	12 h	78%
2[c]	$P(4\text{-}Me\text{-}C_6H_4)_3$	MeCN	12 h	75%
3[c]	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	12 h	91%
4[d]	DPPB	MeCN	12 h	70%
5	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	12 h	89%
6	$P(4\text{-}F\text{-}C_6H_4)_3$	DMF	12 h	62%
7	$P(4\text{-}F\text{-}C_6H_4)_3$	DMSO	12 h	45%
8	$P(4\text{-}F\text{-}C_6H_4)_3$	Toluene	12 h	80%
9	$P(4\text{-}F\text{-}C_6H_4)_3$	1, 4-Dioxane	12 h	82%
10[e]	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	12 h	85%
11	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	6 h	93%
12	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	30 min	94%
13[f]	$P(4\text{-}F\text{-}C_6H_4)_3$	MeCN	30 min	95%

[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.4 mmol) $Pd(OAc)_2$ (10 mol%), ligand (20 mol%) in solvent (2.0 mL) at 90 °C under a nitrogen atmosphere. [b] Isolated yield. [c] Ligand (30 mol%). [d] Ligand (15 mol%). [e] The reaction temperature was 70 °C. [f] Without N_2.

With an optimized set of conditions in hand, we then surveyed the substrate scope of alkene-tethered carbamoyl chlorides **1** in order to survey the generality of this reaction. As shown in Table 2, **1b**-**1f** bearing electron-donating substituents on aromatic ring reacted effectively, to provide the corresponding products (**3ba**-**3fa**) in moderate to good yields (55%-88%). Moreover, electron-withdrawing substituents of the phenyl groups were also tolerated, which included fluoro, chloro and nitro groups, and the corresponding products **3ga**-**3ia** were isolated in 75%-99% yields. Notably, halide substituents were found to be compatible with this reaction, providing an opportunity to further functionalization. Furthermore, **3ja** was also readily obtained under our optimized reaction conditions albeit in a lower yield. In the presence of substituent on aromatic ring at the R^2 position, such as fluoro and chloro, the desired products **3ka**-**3ma** were obtained in high yields (93%, 96% and 74%, respectively). To our delight, the reaction of substrate **1n**, which contained a methyl group at the R^2 position, afforded **3na** in quantitative yield. The scope of the reaction by varying the substituent on the nitrogen atom was also investigated, both *p*-methoxybenzyl(PMB) (**1o**) and cyclopentyl group (**1p**) were tolerated, providing the corresponding products **3oa** and **3pa** in 57% and 99% yields, respectively.

Table 2. Variation of Alkene-tethered Carbamoyl Chlorides **1**[a,b]

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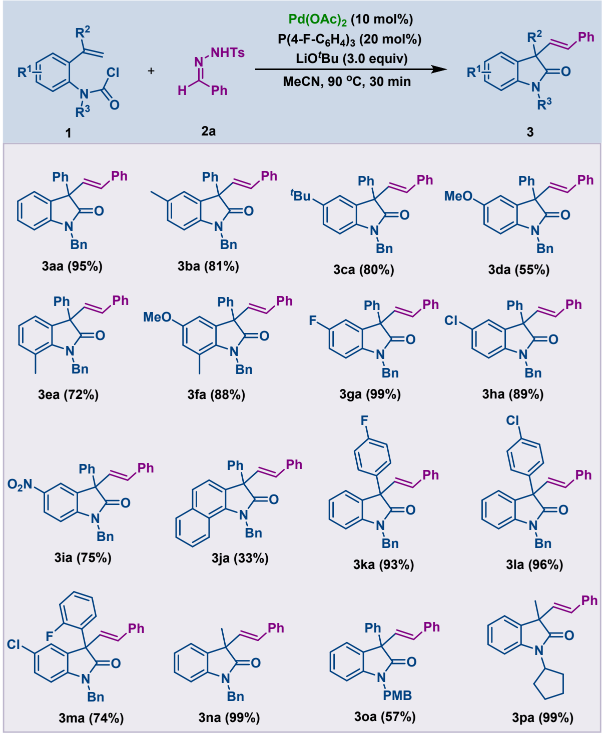
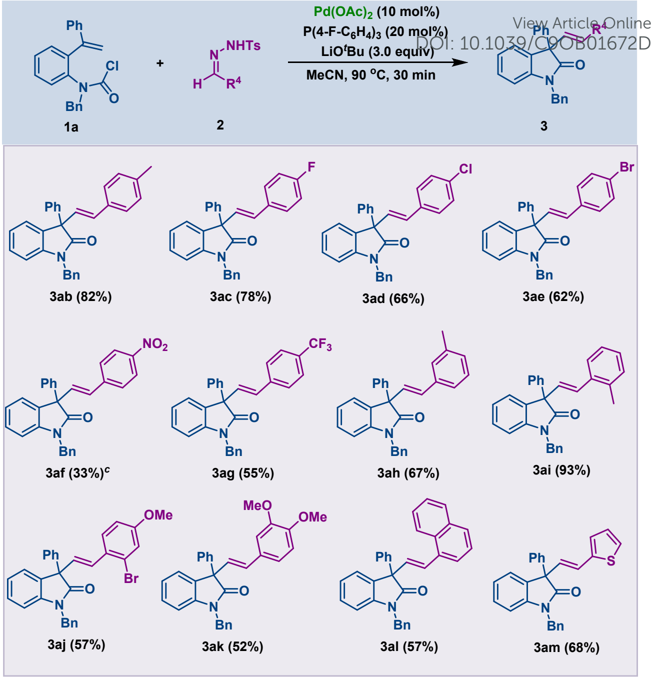


[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.4 mmol) Pd(OAc)$_2$ (10 mol%), P(4-F-C$_6$H$_4$)$_3$ (20 mol%) in MeCN (2.0 mL) at 90 °C for 30 min. [b] Isolated yield.

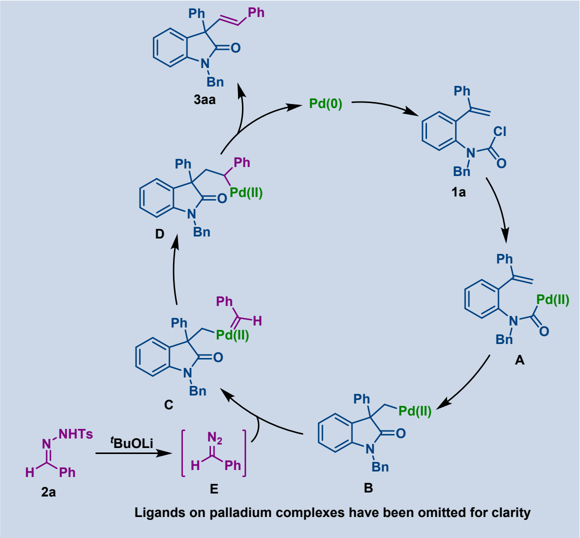
The scope of *N*-tosyl hydrazones **2** was also investigated. As shown in Table 3, a variety of electronically distinct substituents on *N*-tosyl hydrazones were tested. Substrates bearing methyl at the *para*-position of phenyl ring proceeded smoothly, afforded **3ab** in 82% yield. The *N*-tosyl hydrazones bearing a halide substitution (**2c**-**2e**) tolerated well, the desired products **3ac**-**3ae** were obtained in moderate yields, which could be easily transformed into more complex molecules via cross-couplings reactions. Strong electron-withdrawing groups were also tolerated, such as nitro and trifluoromethyl groups could provide the products in relatively low yield (**3af** and **3ag**). Furthermore, *m*-, *o*- and multisubstituted *N*-tosyl hydrazones reacted smoothly to give the corresponding products in 52%–93% yields (**3ah**–**3ak**). Reaction with *N*-tosyl 1-naphthaldehyde hydrazones **2l** provided **3al** in 57% yield. Notably, heteroaryl contained substrate **2m** was also tolerated, which reacted with **1a** to afford **3am** in 68% yield.

Table 3. Variation of *N*-Tosyl Hydrazones **2**[a,b]



[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.4 mmol), Pd(OAc)$_2$ (10 mol%), P(4-F-C$_6$H$_4$)$_3$ (20 mol%) in MeCN (2.0 mL) at 90 °C for 30 min. [b] Isolated yield. [c] 2 h

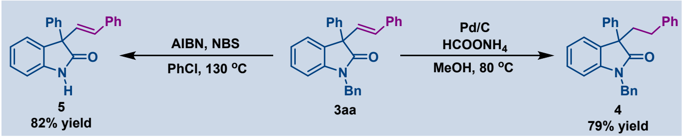
On the basis of the well-known transition-metal-catalyzed transformations of carbamoyl chloride.[11-15] A plausible mechanism for this palladium-catalyzed intramolecular Heck-type cascade reaction is proposed. As shown in Scheme 2, the reaction is initiated by oxidative addition of Pd(0) to carbamoyl chlorides to afford Pd(II) intermediate **A**. Then, intramolecular insertion of the alkene into the C-Pd(II) bond via 5-*exo* cyclization to form alkylpalladium species **B**. Diazo compound **E** is generated in situ from *N*-tosylhydrazone **2a** with treatment of base. Decomposition of diazo compound **E** by Pd(II) species **B** leads to palladium carbene intermediate **C**, followed by alkyl migratory insertion to give intermediate **D**. Finally, a *syn* β-hydride elimination process may occur to afford the 3-vinyloxindoles **3aa** and regenerates the Pd(0) catalyst.



Ligands on palladium complexes have been omitted for clarity

Scheme 2. Plausible Reaction Mechanism

To further showcase the practical utility of this protocol, two synthetic transformations were conducted. As shown in Scheme 3, a hydrogenation reaction of **3aa** proceeded smoothly to give **4** in 79% yield.[26] Moreover, **3aa** could be successfully deprotected by AIBN/NBS reagent to give *N*-unprotected 3-vinyloxindoles **5** in 82% yield.[27]



Scheme 3. Synthetic Transformations

Conclusions

In conclusion, we have developed a palladium-catalyzed Heck-type intramolecular cyclization of alkene-tethered carbamoyl chlorides with *N*-tosyl hydrazones. This reaction demonstrates excellent reactivity, good functional group tolerance and high efficiency. It provided a new way to synthesize a range of functionalized 3-vinyloxindoles bearing an all-carbon quaternary center. Investigation of the further applications of this methodology is currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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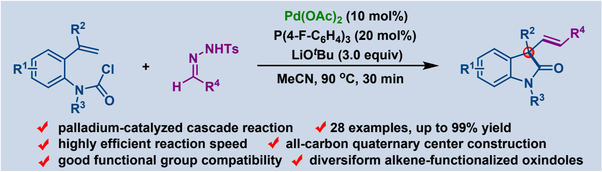

- ✓ palladium-catalyzed cascade reaction
- ✓ highly efficient reaction speed
- ✓ good functional group compatibility
- ✓ 28 examples, up to 99% yield
- ✓ all-carbon quaternary center construction
- ✓ diversiform alkene-functionalized oxindoles

An efficient approach for the construction of alkene-functionalized oxindoles was developed via palladium-catalyzed cascade reactions of alkene-tethered carbamoyl chlorides with *N*-tosyl hydrazones.