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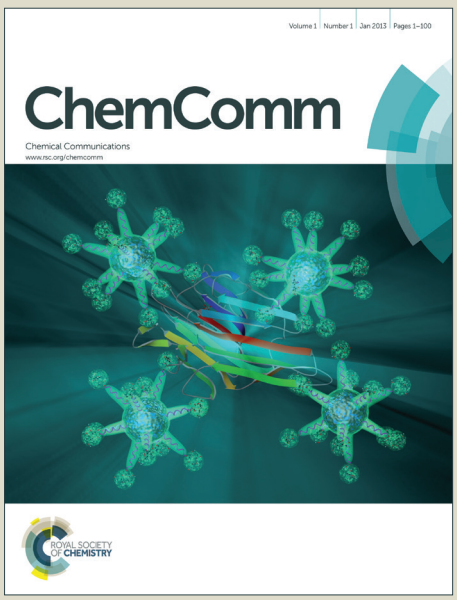

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Palladium-Catalyzed Picolinamide-Directed Coupling of C(sp^2)-H and C(sp^2)-H: a Straightforward Approach to Quinolinone and Pyridone Scaffolds

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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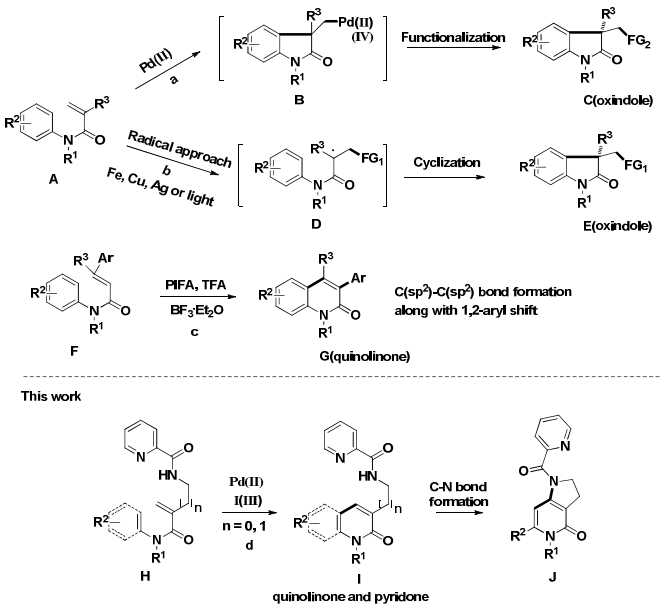
An unprecedented palladium-catalyzed picolinamide-directed coupling of C(sp^2)-H and C(sp^2)-H was developed with exclusive formation of the six-membered ring heterocyclics-quinolinone and pyridone. The method employs cyclic hypervalent iodine as oxidant and features good functional-group tolerance. A further advantage of this reaction is that sequential of C-H/C-H and C-H/N-H coupling could be achieved.

N-arylacrylamide derivatives have been widely employed as a useful substrate for the construction of heterocyclic scaffolds. Zhu,[1] Liu[2] and Li[3] presented their impressive studies on palladium-catalyzed oxidative difunctionalization of the *N*-arylacrylamides which involve the initial aryl C-H activation to form a palladium (II or IV) intermediate B via a 5-endo cyclyzation process (Scheme 1a). An al-



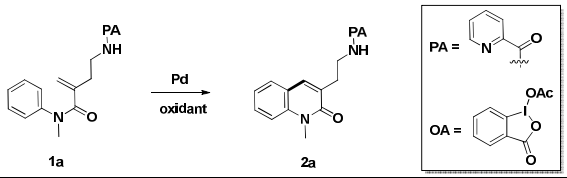
Scheme 1. C-H functionalization of *N*-aryl acrylamide derivatives.

-ternatively intriguing difunctionalization of *N*-aryl acrylamide is by virtue of the radical approach catalyzed by various transition metal catalysts or induced by light (Scheme 1b).[4] Compared to the construction of the five-membered oxindole ring, the synthetic route to six-membered quinolinone ring from *N*-arylacrylamides is much less reported. Zhao et.al demonstrated that phenyliodine bis(trifluoroacetate) (PIFA) could mediate formation of arylquinolin-2-one compounds (Scheme 1c) from *N*-aryl acrylamides.[5] Hu and co-workers also showed one example of synthesis of the 1-methylquilolin-2(1*H*)-one from *N*-arylacrylamide derivative.[6] Although in term of limited substrate scopes, the two methods provide an endo-cyclization pathway to six-membered quinolinone. Given the importance of quinolinone with broad biological activities,[7] there still needs to develop efficient synthetic methods.

Recently, bidentate directing groups have been widely used in a number of transformations of C-H bonds.[8] Among these, picolinamide-directed functionalizations of C(sp^2)-H and C(sp^3)-H bonds have received much attention.[9] Herein, we present an unprecedented palladium-catalyzed picolinamide-directed or C(sp^2)-H/C(sp^2)-H coupling (Scheme 1d), with the exclusive formation of the six-membered ring via an endo-cyclization pathway, providing a convenient approach to the privileged quinolinone and pyridone scaffolds. Furthermore, we demonstrated that the second C-H/N-H coupling could be achieved by the judicious choice of reaction conditions, which allowed for construction of fused heterocycle by terminal difunctionalization of the alkene.

A preliminary study was performed with *N*-aryl acrylamide **1a** as a benchmark substrate (Table 1). Exposure of **1a** to various oxidants (2 equiv) including hypervalent iodines (III), persulfate salts and oxigen (see supporting information) in toluene at 80 °C for 24 h in the presence of $Pd(OAc)_2$ (10 mol%) found that the cyclic hypervalent iodine OA (III) gave the best result. The six-membered ring product was obtained in 34% yield (entry 1). Interestingly, lowering the $Pd(OAc)_2$ loading from 10 to 2.5 mol% increased the yield to 49% (entry 2). Investigation of solvents showed that xylene was the optimal solvent (entry 4). Finally, a study of Pd sources revealed that various counter anions of palladium (II) could be tolerated and $PdBr_2$ proved to be the most efficient catalyst (entry 8).

Table 1. Optimization of palladium catalyzed C(sp^2)-H/C(sp^2)-H coupling of *N*-arylacrylamide.[a]

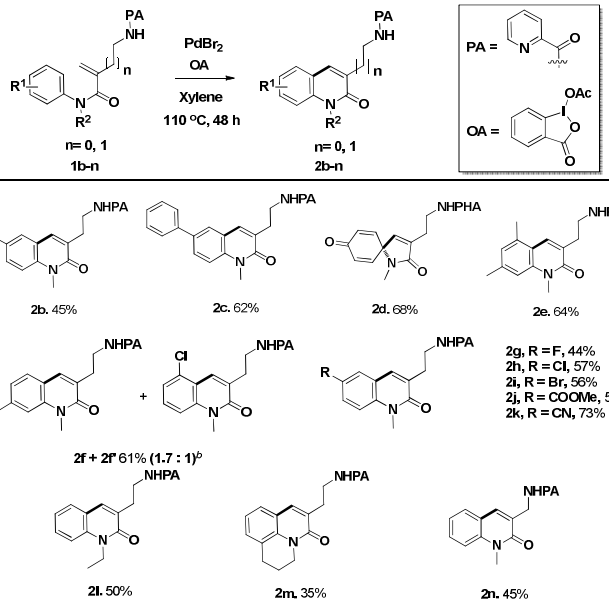


Entry	Pd [mol%]	Oxidant [equiv]	Solvent	*t* [h]	T [^oC]	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	OA (2)	Toluene	24	80	34
2	$Pd(OAc)_2$ (2.5)	OA (2.5)	Toluene	36	110	49
3	$Pd(OAc)_2$ (2.5)	OA (2.5)	$PhCF_3$	48	110	48
4	$Pd(OAc)_2$ (2.5)	OA (2.5)	Xylene	48	110	61
5	$PdCl_2$ (2.5)	OA (2.5)	Xylene	48	110	49%
6	$PdCl_2(MeCN)_2$ (2.5)	OA (2.5)	Xylene	48	110	43%
7	$Pd(acac)_2$ (2.5)	OA (2.5)	Xylene	48	110	63%
8	$PdBr_2$ (2.5)	OA (2.5)	Xylene	48	110	65%(60)[c]

[a] General reaction conditions: **1a** (0.2 mmol), Pd (mol%), oxidant (equiv), solvent (2.0 mL). [b] Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [c] Yields of isolated products are given in parentheses.

With the optimal reaction conditions in hand, we set up to explore the scope of substrates (Table 2). Substrates bearing methyl and benzenyl groups on the benzene ring gave moderate to good yields (**2b-c**). Interestingly, a spiro product was obtained in 68% yield for substrate with incorporation of OMe (**2d**). Substrate incorporating a 3, 5-dimethyl group (**2e**) also worked well, indicating that the reaction system was insensitive to steric hindrance. Of note, halogen-

Table 2. Palladium catalyzed C(sp^2)-H/C(sp^2)-H coupling of *N*-arylacrylamides.[a]

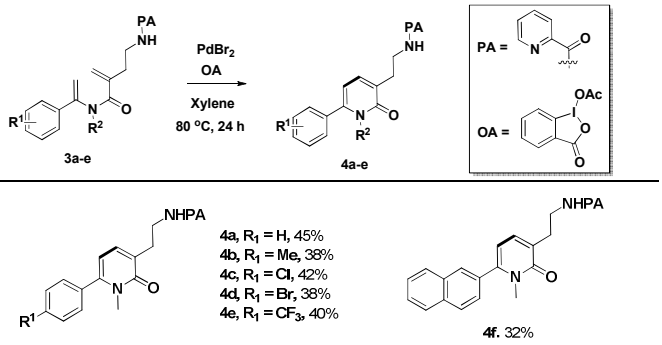


[a] General reaction conditions: **1b-n** (0.2 mmol), $PdBr_2$ (5 mol%), oxidant (2.5 equiv), xylene (2.0 mL) at 110 °C, 48 h. [b] The ratio of 2f and 2f' was determined by ^1H-NMR.

-ns such as F, Cl and Br, ester and cyano groups were tolerated well (**2g-k**) with reaction conditions. Variation of the *N*-substituents found substrates with ethyl group (**2l**) and tetrahydroquinolinyl core (**2m**) could smoothly furnish the products. Reduction of the carbon chain by one carbon atom resulted in a slightly lower yield (**2n**).

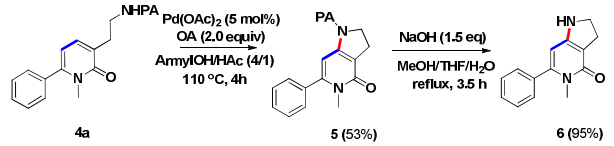
Next, we turned attention to *N*-alkenyl acrylamide substrates (Table 3), aiming to provide a new entry to the pyridone scaffold. Gratifyingly, slight modification of standard conditions could achieve the cyclization of **3a**, giving the pyridone **4a** in 45% yield. Various substituents on the benzene were then investigated. Me (**4b**), Cl (**4c**), Br (**4d**) and CF_3 (**4e**) groups were tolerated well. Substrates bearing naphthalene (**4f**) could also be transformed to the corresponding product.

Table 3. Palladium catalyzed C(sp^2)-H/C(sp^2)-H coupling of *N*-alkenylacrylamides.[a]



[a] General reaction conditions: **3a-e** (0.2 mmol), $PdBr_2$ (5 mol%), oxidant (2.0 equiv), xylene (2.0 mL) at 80 °C, 24 h.

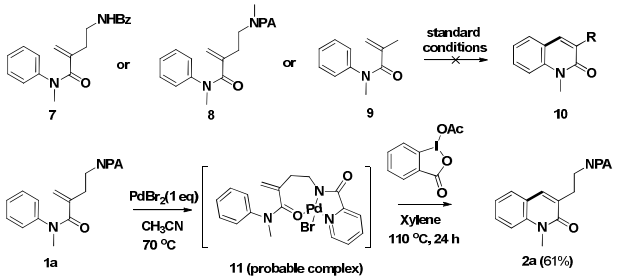
Subsequently, to further broaden application of the reaction system, we were eager to achieve the second C-H/N-H coupling directed by the picolinamide, which would allowed for construction of fused heterocycle by terminal difunctionalization of the alkene. The pyridone **4a** was chosen to test our hypothesis. However, the established conditions by Chen,[9b] Daugulis[9c] and Shi,[10] can not be applied to **4a** at all. After extensive attempts, we found that treatment of **4a** with $Pd(OAc)_2$ and OA in ArmylOH/HAc (v/v, 4/1) at 110 °C for 4 h yielded the desired product **5** in 53% yield (Scheme 2). Control of the reaction time is the key to achieve this transformation owing to reversibility of the C-H/N-H coupling. It was also demonstrated that the picolinamide directing group could be readily removed by hydrolysis to give the bicyclic compound **6**.



Scheme 2. C-H/N-H coupling and auxiliary removal.

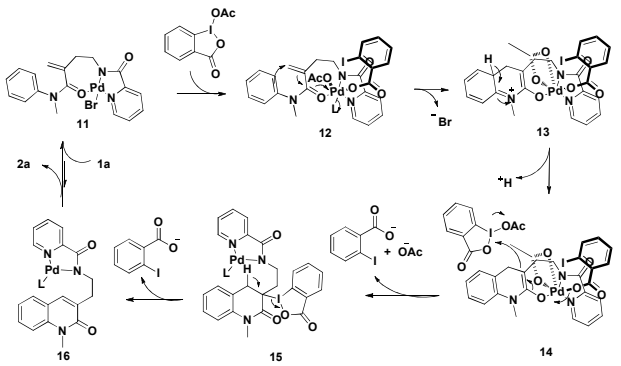
To understand the preliminary mechanism, some control experiments were carried out as shown in Scheme 3. Replacement of picolinamide with benzamide (**7**), block the NH of picolinamide with methyl group (**8**) or removal of picolinamide (**9**) completely shut down the reaction, which indicates that the picolinamide directing group is essential for the transformation. Aromatic C-H cleavage is not a rate-determining step by kinetic effect (K_H/K_D) study in either intramolecular or intermolecular experiments.[11] A radical mechanism can be ruled out because addition of the radical

scavenger (TEMPO) has no significant impact on the yield. Treatment of **1a** with 1.0 equiv. $PdBr_2$ in CH_3CN gave a palladium complex[12], which was smoothly converted to the desired product in 61% yield upon treatment of the cyclic hypervalent iodine (III).



Scheme 3. Control experiments.

Based on these observations above, a possible mechanism is depicted in Scheme 4. First, reaction of **1a** with $PdBr_2$ affords a palladium (II) complex **11**. Upon treatment of **11** with the cyclic hypervalent iodine (III), the palladium (II) is oxidized to the palladium (IV) **12** which dramatically enhanced the Lewis acidity of palladium, thus leading to activation of the acrylamide, with subsequent nucleophilic attack of the arene and elimination of a ligand and proton. Then the enolate intermediate **14** is further trapped by the cyclic hypervalent iodine (III) to give the intermediate **15**. Elimination of 2-iodobenzoic acid affords the intermediate **16**, which undergoes ligand exchange with substrate **1a** to give the product **2a**.



Scheme 4. Proposed mechanism of cyclyzation.

Conclusions

In conclusion, we have developed a novel picolinamide-directed aryl or alkenyl C(sp^2)-H/alkenyl C(sp^2)-H coupling of *N*-aryl or alkenyl acrylamide derivatives. This new reaction system provides a straightforward approach to the six-membered quinolinone and pyridone scaffolds. Furthermore, the second C-H/N-H coupling could be achieved, allowing for construction of fused heterocycle by terminal difunctionalization of the alkene. Future directions of the work will involve elucidating the detailed reaction mechanism and expanding the application.

We gratefully acknowledge financial support from the National Natural Science Foundation of China Grants (91229204 and 81220108025), Major Project of Chinese National Programs for Fundamental Research and Development (2015CB910304), National High Technology Research and Development Program of China (2012AA020302), National Basic Research Program of China (2012CB518005).

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details and additional spectra. See DOI: 10.1039/c000000x/

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11 For detailed analysis, please see supporting information.
12 The characteristic data for palladium complex please see supporting information.