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Cu/Pd Cooperatively Catalyzed Tandem Intramolecular anti-Markovnikov Hydroarylation of Unsaturated Amides: Facile Construction of 3,4-Dihydroquinolinones via Borylation/Intramolecular C(sp^3)-C(sp^2) Cross Coupling

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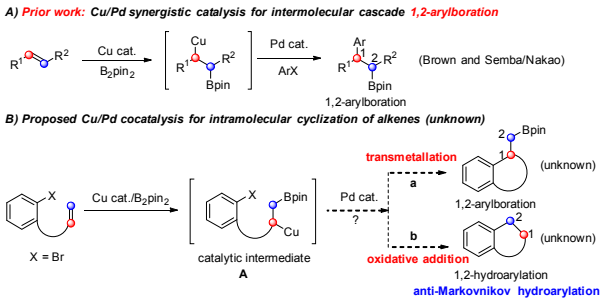
Zhijie Kuang, Bingnan Li and Qiuling Song*

An anti-Markovnikov hydroarylation of unsaturated amides via Cu/Pd synergistically catalyzed cascade borylation/intramolecular sp^2-sp^3 cross coupling has been disclosed. 3,4-Dihydroquinolinones, one type of important scaffolds prevailing in pharmaceuticals and biologically active compounds, could be readily accessible with high regio-selectivity and high yields.

Transition-metal-catalyzed cross-coupling reactions of Csp^3 nucleophiles have been proven as a powerful strategy in chemical synthesis.[1] Recently, Cu/Pd synergistic catalysis for 1,2-arylboration of alkenes have emerged as a successful and practical tool in Csp^3 nucleophiles cross couplings, which proceed via transmetallation by a catalytic nucleophile (Cu-R was converted into Pd-R, followed by arylation with ArX).[2] Although significant progress have been achieved on intermolecular 1,2-arylboration (Scheme 1A), Cu/Pd cooperatively catalyzed intramolecular cyclization of alkenes has yet been reported[3]. There are several advantages of intramolecular reactions over intermolecular counterparts: 1) versatile cyclic products will be resulted, even some unusual cyclic products could be afforded by careful design; 2) unexpected and novel reaction modes might be disclosed due to the proximity; 3) valuable drug-like heterocycles might be obtained.

We envision that two plausible pathways might be occurred from the catalytic intermediate **A** (Scheme 1B), which is formed by the attack of *in-situ* generated Cu-Bpin complex to C=C bond upon with Pd catalysis, during Cu/Pd cocatalyzed intramolecular cyclization of alkenes with B_2pin_2: a) by transmetallation with active Cu species (a nucleophile), normal 1,2-arylboration will take place with the intramolecular ArX moiety; b) instead of transmetallation, oxidative addition of Pd catalyst with ArX moiety (an electrophile) occurs first, rendering an active Pd species, which reacts with the *in-situ* generated alkyl boronate moiety to lead to 1,2-hydroarylative



Scheme 1. Cooperative Cu/Pd Catalysis in the Difunctionalization of Alkenes with B_2pin_2.

product. It is of note that the hydroarylative product is generated via an anti-Markovnikov hydroarylation mode (Scheme 1B). Literature survey indicates that intermolecular hydroarylation catalyzed by Cu/Pd cooperative catalysis were reported independently by Semba/Nakao[4] and Buchwald[5a] in 2016 (Scheme 2A), and their intermolecular hydroarylations[5b] took place via a Markovnikov mode. Our hypothesis will provide a complementary pathway to their seminar methods in terms of intramolecular pattern as well as anti-Markovnikov mode if path b occurs first over path a (Scheme 1B). How to control the two competitive pathways in one reaction and make path b occur exclusively becomes an interesting while challenging subject. Herein, we report our new disclosure in addressing this gap by the formation of anti-Markovnikov hydroarylative products via Cu/Pd synergistic catalysis with B_2pin_2 in an intramolecular borylation/Csp^3 cross-coupling protocol (Scheme 2B). This strategy is significant and in sharp contrast to prior reports in Cu/Pd co-catalyzed arylboration as well as intermolecular Markovnikov hydroarylation, therefore a novel reaction mode is resulted, which complements the existing methods in hydroarylation of alkenes.

In order to verify our hypothesis, *N*-(2-bromo-4-chlorophenyl)-*N*-methylmethacrylamide (**1a**) was chosen as the template substrate, due to its ready accessibility (two-steps synthesis) and the likelihood of cyclization (five-member-

Institute of Next Generation Matter Transformation, College of Chemical Engineering, College of Material Sciences Engineering, Huaqiao University, Xiamen, Fujian 361021, China. E-mail: qsong@hqu.edu.cn; Fax: +86-592-6162990

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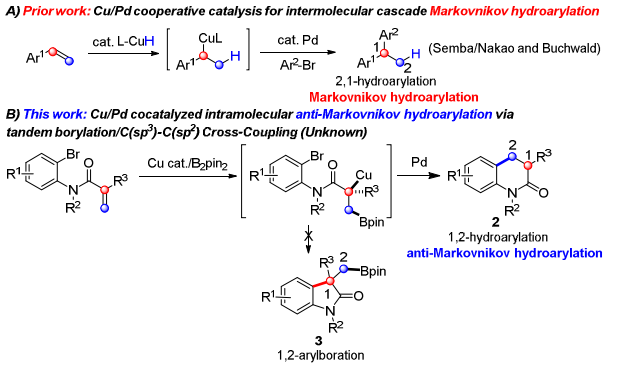
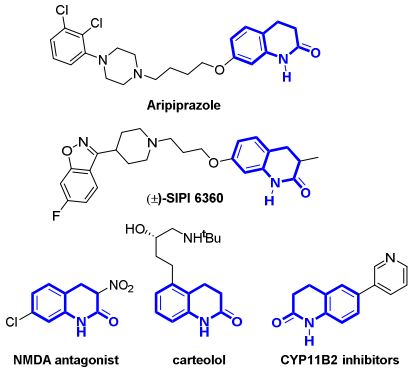


Scheme 2. Cu/Pd Synergistic Catalysis in Hydroarylation of Alkenes.

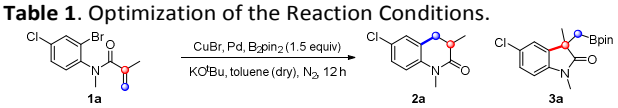
ed 2-oxindoline (path a) or six-membered 3,4-dihydroquinolinone (path b), with the participation of Pd and Cu/B_2pin_2. It is noteworthy that 3,4-dihydroquinolinones are important molecular scaffolds in bioactive compounds and pharmaceuticals[6-7], such as in the antipsychotic drug Aripiprazole[8], atypical schizophrenia drug (±)-SIPI 6360[9], the dear PMPA (NMDA antagonist)[10], carteolol eye drops[10] and CYP11B2 dual Inhibitors[11] (Scheme 3). The development of efficient methods for the construction of this valuable skeleton therefore becomes highly desirable in organic synthesis.



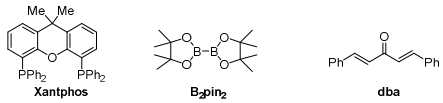
Scheme 3. Representive Pharmaceuticals and Drugs Containing the 3,4-Dihydroquinolinone Skeletons.

It is not surprising that a significant amount of the five-membered 2-oxindoline **3a** was generated in addition to the formation of six-membered 3,4-dihydroquinolinone **2a** (Table 1, entry 1), because of the favorable propensity to the formation of a five-membered **3a** from compound **1a**. Thus suppressing the formation of **3a** becomes a big challenge in our hypothesis. Preliminary co-catalyst screening (entries 1-3) suggested that $Pd(dba)_2$ and CuBr were able to control the selectivity for a single target product (**2a**) (entry 3). Subsequent changes in different variables, such as temperature (entry 4 and entry 6), time (entry 5) and the amount of base (entries 7-9) did not lead to significant improvements. Then the ratio of Cu and Pd catalysts were carefully adjusted since we realize that Cu-Bpin complex addition over C=C bonds should be prior to the competitive oxidative addition of Pd catalyst into ArX, the ratio of Cu salt to Pd salt would be critical to the desired transformation. We

Table 1. Optimization of the Reaction Conditions.



entry	CuBr (x mol %) xantphos (x mol %)	Pd (x mol %)	KO^{t}Bu (x equiv)	T (°C)	yield (%) 2a 3a
1	10	$Pd_2(dba)_3$ (5)	1.5	110	37 15
2	10	$Pd_2(dba)_3$•$CHCl_3$ (5)	1.5	110	17 38
3	10	$Pd(dba)_2$ (5)	1.5	110	41 1
4	10	$Pd(dba)_2$ (5)	1.5	120	28 --
5[b]	10	$Pd(dba)_2$ (5)	1.5	110	43 --
6	10	$Pd(dba)_2$ (5)	1.5	100	21 --
7	10	$Pd(dba)_2$ (5)	1.2	110	37 5
8	10	$Pd(dba)_2$ (5)	2.0	110	50 --
9	10	$Pd(dba)_2$ (5)	3.0	110	35 7
10	20	$Pd(dba)_2$ (10)	2.0	110	91 1
11	16	$Pd(dba)_2$ (8)	2.0	110	89 --
12	**15**	**$Pd(dba)_2$ (7.5)**	**1.8**	**110**	**90 -- 78[c] --**
13[d]	15	$Pd(dba)_2$ (7.5)	1.8	110	-- --
14[e]	15	$Pd(dba)_2$ (7.5)	1.8	110	-- --



[a] Reaction conditions: all reactions were performed on 0.2 mmol scale with respect to **1a**; yields were determined by GC by utilizing dodecane as internal standard. The reaction mixture contained H_2O approximately 0.3% w/w. [b] For 24 h. [c] The yield was isolated one and $Pd(dba)_2$ was used in 7.5 mol %.[d] No B_2pin_2. [e] In air.

simultaneously increased the amount of palladium and copper salts, but kept the amount of copper salt twice to that of palladium salt (entry 10). To our delight, both selectivity, conversions as well as yields were dramatically increased along with the changes. Based on the result in entry 10, we finely tuned the reaction conditions resulting in the optimal one—entry 12. It was noteworthy that the reaction didn't proceed at all in air (entry 13) or in the absence of B_2pin_2 (entry 14), which proves that B_2pin_2 is a prerequisite for the success of the transformation, and oxygen plays deteriorate role in this reaction. More conditions screenings are available in Supporting Information (SI).

With the optimal conditions in hand, we next examined the scope of this intramolecular anti-Markovnikov hydroarylation via Cu/Pd synergistically catalyzed tandem borylation/cross coupling. (Scheme 4) We first tested the substrates with electron-withdrawing group on the aromatic ring (**2a**-**2f**, **2h**). Fluorine-containing compounds usually have different special properties and widely existed in pharmaceutical, material science as well as agro-chemicals, we specially investigated a series of fluorine-containing substrates (**2b**-**2g**), and the medium to excellent yields (60-90%) were obtained with high selectivity. Cyano group was also tolerated under the standard conditions albeit in a low yield (**2h**, 32% yield). Subsequently, the substrates with electron-donating group, such as CF_3O, ^{i}Pr, Me, MeO, on the aromatic rings were also inspected (**2g**, **2i**-**2n**), they were well compatible under the standard conditions. It is of note that the positions of substituents on the phenyl ring did not significantly affect the efficiency of the reactions, as observed in products **2j**-**2l**. We further examined the influence of the substituents on the *N* atom to investigate the universality of reactions. With Et- (**2o**), Bn- (**2p**) or Me- (**2r**)

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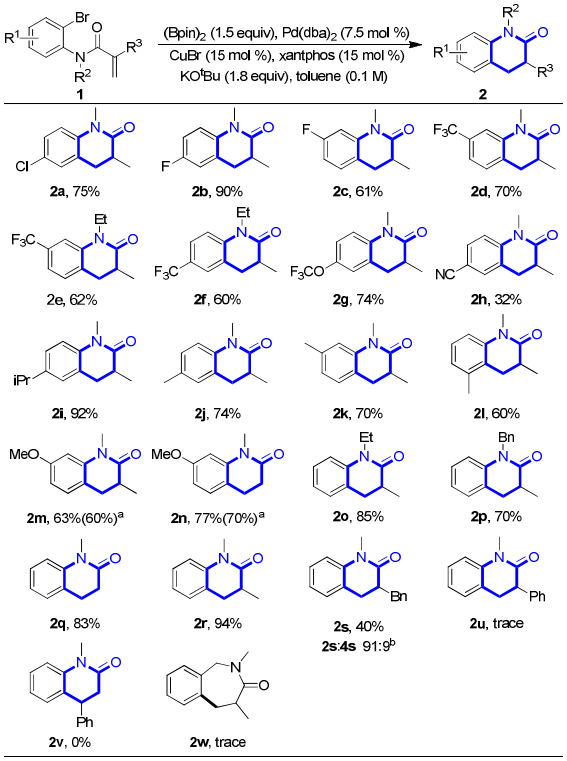
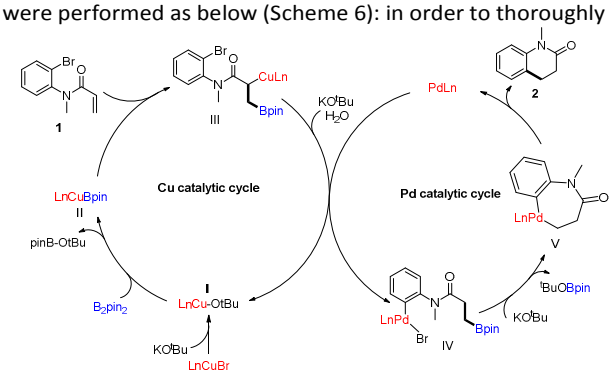
substituents on N atom, the reactions went out smoothly with excellent yields. However, the substituents on α position of carbonyls had a great influence on the smooth progress of the reaction (**2q**-**2u**). The H atom (**2q**) or Me group (**2r**) on the α location promoted the conversion, however, the Bn group (**2s**) or phenyl group (**2u**) seriously affected the transformation and the corresponding yields were reduced to 40% and trace. At the same time, we tried the compatibility of internal olefin, the example for a phenyl group at the beta-position was not successful, and no desired product (**2v**) was formed. We also investigated benzyl amine (**1w**), as expected, **2w** was not obtained due to the reluctant formation of disfavored seven-membered ring.



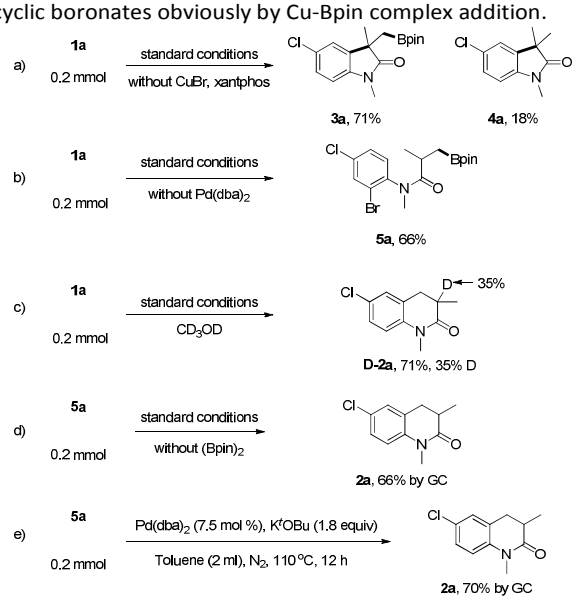
Scheme 4. Scope of the Substrates. Reaction conditions: all reactions were performed under the standard conditions. The yields were isolated ones. [a] On 1.5 mmol; [b] The ratio was determined by NMR.

A tentative mechanism which contains two individual cycles for this transformation is depicted in Scheme 5, which was based on the previous work by Cazin's group [5b]. Initially, L_nCuBr is activated by base resulting in L_nCuO^tBu (**I**), which further reacts with B_2pin_2, rendering the copper-boron species (**II**). Intermediate **II** attacks the C=C bond in substrate **1** to lead to 1,2-copperboration product **III** or 1,4-copperboration one [11]. In the presence of KO^tBu as well as water (from the solvent, reagents as well as glassware), intermediate **I** is regenerated to complete Cu catalytic cycle with the release of the protonated boronate; meanwhile oxidative addition of PdLn into ArX moiety of the protonated boronate results in intermediate **IV**. Subsequent intramolecular cross coupling delivering the seven-membered palladacycle intermediate **V**, reductive elimination eventually affords target product **2** as well as PdLn, completion of palladium catalytic cycle. To gain more insights into the mechanism of reaction, several control experiments were performed as below (Scheme 6): in order to thoroughly



Scheme 5. Mechanism Profile.

understand the roles of copper catalyst and Pd catalyst in this transformation, the reactions under the standard conditions without copper salt and ligand as well as in the absence of Pd catalyst were carried out respectively (Scheme 6a and 6b), oxindoles **3a** and **4a** with the isolated yields of 71%, 18% were obtained in the former case, while acyclic boronate **5a** was afforded in the latter case with the yield of 66%. The two reactions clearly demonstrated that both Cu and Pd are indispensable to the transformation and in the absence of Cu catalyst, five-membered 2-oxindole compounds were exclusively formed by typical Heck reaction pathway; while C=C bond were consumed without Pd catalyst rendering the acyclic boronates obviously by Cu-Bpin complex addition.



Scheme 6. Control Experiments.

By comparison with the above two experiments, we could draw the conclusion that copper catalytic cycle took precedence over palladium catalytic cycle. To prove our assumption, deuterium-labeled experiment was conducted under the standard conditions with the addition of CD_3OD, to our delight, D-**2a** was obtained in 71% yield with 35% deuterium-labeling on the α-position of carbonyl group

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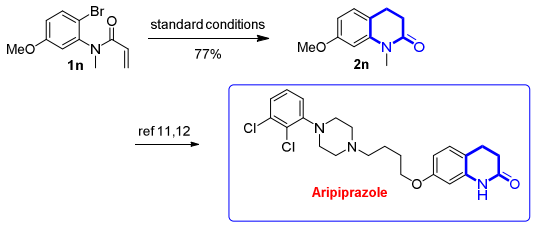
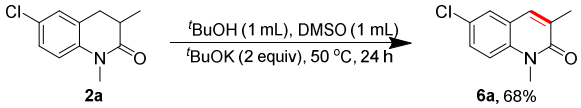
(Scheme 6c). In order to validate that **5a** was the key intermediate in this transformation, two more control experiments (Scheme 6d and 6e) were also performed, as we expected that the target product **2a** were well obtained, no matter under standard conditions (no B_2pin_2) or just with palladium and base, which highlighted the validity of our conjecture.



Scheme 7. One of the Top 200 Pharmaceutical Products by US Retail Sales in 2012.

Considering the widespread existence of the product skeletons in biologically active compounds, drug molecules, and natural products, we provide an alternative for the transformation of one of the products (**2n**). With our methodology, the 7-methoxy-1-methyl-3,4-dihydroquinolin-2(1H)-one (**2n**) was obtained in 77%, which could be further converted into a highly complex aripiprazole after four steps of known transformation[12-13]. (Scheme 7) It is worth noting that aripiprazole is a new atypical antipsychotic drug for the treatment of schizophrenia, which is one of the top 200 pharmaceutical products by US retail sales in 2012.



Scheme 8. Mild Oxidation Experiment.

Quinolin-2(1*H*)-ones is the backbone of many biological enzymes [14-15] and plays an important role in the pesticides, such as HIV-1 integrate inhibitor elvitegravir, *Penicillium* and *Aspergillums* produce. The product (**2a**) was mildly oxidized [16] to 6-chloro-1,3-dimethylquinolin-2(1*H*)-one with the isolated yield of 68% without expensive DDQ.

In conclusion, we developed an unusual intramolecular hydroarylation of unsaturated amides via Cu/Pd cocatalyzed tandem borylation/cross coupling with diboron reagents, rendering 2-quinolones which are important skeleton in pharmaceuticals and biologically active compounds in high regioselectivity and good yields, further transformations from 2-quinolones were also performed in our work.

Conflicts of interest

The authors declare no competing financial interest.

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