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Copper-catalyzed oxidative C(sp³)-H/C(sp²)-H cross-coupling *en route* to carbocyclic rings†

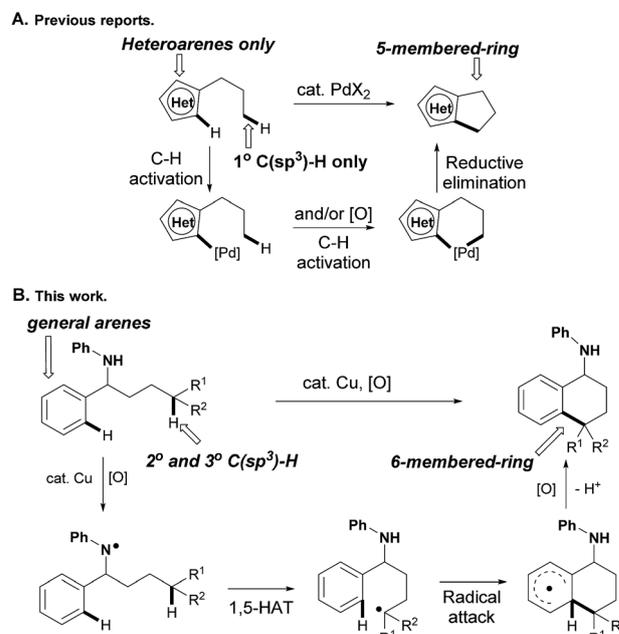
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Copper-catalyzed selective coupling of C(sp³)-H bonds with C(sp²)-H bonds has been developed. An aniline module was used as a directing group to generate an aminyl radical, which selectively cleaves the secondary and tertiary C(sp³)-H bonds *via* a 1,5-HAT process to forge six-membered carbocyclic rings.

The selective construction of C-C bonds, the essential link in organic molecules, in more efficient ways is always the central topic in synthetic chemistry.¹ In the past several decades, transition-metal-catalyzed C-C bond construction *via* the activation of ubiquitous C-H bonds has attracted increasing attention, due to the atom and step economy.² While the recent fast developments in this area offered various transformations involving mainly activation of one C-H bond,³ C-C bond formation *via* direct C-H/C-H cross-coupling is no doubt the most efficient and ideal method. Inspired by this strategy, cross-dehydrogenative coupling (CDC), termed by Li, was developed and used for the construction of diverse functional molecules.⁴ However, at least one relatively active C-H bond, such as C-H bonds adjacent to heteroatoms and carbonyl groups, or at the benzylic and allylic positions, is typically required in these reactions, and the direct cross-coupling of two inert C-H bonds still faces many challenges from issues such as reactivity and regioselectivity.

Transition-metal-catalyzed oxidative coupling of inert C-H bonds has emerged as a powerful method to construct C-C bonds in an intra- and inter-molecular manner. While the coupling of both aryl C-H bonds has been well documented for biaryl bond formation,⁵ the cross-coupling of inert aromatic and aliphatic C-H bonds selectively still remains an unsolved problem. For instance, Li and co-workers reported an intermolecular CDC of arenes with simple unactivated alkanes in 2008.⁶ While the selective activation of C(sp²)-H bonds could be realized using pyridine as the *ortho*-directing group, the regioselective activation of inert C(sp³)-H bonds was still an unsurmountable problem in this transformation. Only two examples of intramolecular C(sp²)-C(sp³) couplings involving Pd(II)-catalyzed tandem activation of C(sp²)-H and C(sp³)-H bonds successively have been reported,⁷ in which only relatively active heteroaryl C(sp²)-H and primary C(sp³)-H bonds were

compatible to produce five-membered-ring products accordingly (path A, Scheme 1). Different from the metal-catalyzed C(sp²)-H/C(sp³)-H oxidative couplings that were initiated from C(sp²)-H bond activation, we conceive that the C(sp³)-H bond could be cleaved firstly *via* radical hydrogen-atom abstraction,^{8,9} and the alkyl radical is then trapped by aryl rings to produce the final C(sp²)-C(sp³) coupling product after the following oxidation and deprotonation. While the inert C(sp³)-H bonds are almost impossible to distinguish from other aliphatic C-H bonds on the alkyl side chain, the 1,*n*-hydrogen-atom-transfer (1,*n*-HAT)⁹ strategy offers us a reliable solution, in which heteroatoms might be installed on the starting materials to generate the heteroatom radicals for directed selective cleavage of inert C(sp³)-H bonds (path B, Scheme 1).¹⁰



Scheme 1 Transition-metal-catalyzed intramolecular C(sp³)-H/C(sp²)-H cross-coupling.

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Herein we report a copper-catalyzed intramolecular cross-coupling of inert aliphatic and aryl C–H bonds with yields as high as 95%. An aniline module was used as a directing group to generate the aminyl radical, which selectively cleaves the secondary and tertiary C(sp³)–H bonds *via* a 1,5-HAT process to produce 6-membered-ring products. The initial nitrogen radical could be generated with the assistance of a catalytic amount of Cu(OAc)₂ directly from an N–H bond in aniline,¹¹ and pre-functionalized or *in situ* generated N–X bonds were not required.⁸

Our initial study commenced with **1a** as the pilot substrate in the presence of a catalytic amount of Cu(OAc)₂. After careful reaction optimization (Tables S1–S4, see ESI[†]), we found that the combination of **1a** with Cu(OAc)₂ (20 mol%) and Ag₂CO₃ (1.5 equiv.) in 1,2-dichloroethane (DCE, 2.0 mL) at 135 °C for 25 h afforded the desired product **2a** with the best yield (92%, Table 1, entry 1). Control experiments and the effects of each parameter were then examined (Table 1). It is revealed that Cu(OAc)₂ as the catalyst together with Ag₂CO₃ as the oxidant was crucial for this reaction. No product could be observed in the absence of Cu(OAc)₂ (entry 2), and other copper salts failed to catalyze the reaction. If a stoichiometric amount of Cu(OAc)₂ (3 equiv.) was used without the addition of Ag₂CO₃, only a trace amount of **2a** was detected (entry 5). Variation of the reaction temperature decreased the yield slightly (entries 9–10). When the reaction was quenched at 12 h, the desired product **2a** was isolated in 77% yield (entry 11). Upon reducing the catalyst loading of Cu(OAc)₂ or the amount of oxidant Ag₂CO₃, the yields decreased only slightly, furnishing **2a** in 83% yield even with

only 5 mol% of Cu(OAc)₂ (entry 13) and also in 83% yield with 1 equivalent of Ag₂CO₃ (entry 14).

With the optimized conditions in hand, we next sought to analyze the scope of this protocol (Table 2). With regards to the substituent effect on a phenyl ring, various substituted groups were compatible with this transformation. As for the substituents on the *para*-site of the phenyl ring, both electron-donating and -withdrawing groups were well tolerated with moderate to excellent yields, including alkyl (**2b–d**), phenyl (**2e**), methylthio (**2f**), halogen (**2g–i**) and trifluoromethyl (**2j**). In particular, the presence of halogen atoms (Br, Cl, and F) in products **2** offers the potential for further synthetic elaboration *via* known transition-metal-catalyzed coupling methods. Generally, some anilines, **1**, with different substituents, such as methyl, cyclopropyl, chloro and trifluoromethyl, at the *meta*-site on the phenyl ring could be cyclized completely at the less sterically hindered position with good yields (**2k–n**), which can be explained by the steric effect of such substituents.

Yet intriguingly, the *meta*-MeO-substituted aniline, **1o**, afforded both 5- and 7-methoxyl cyclic products in an excellent combined yield (95%, **2o** and **2o'**), but with a compromised selectivity to give the cyclized product at the more sterically hindered position as the major isomer. Even though this selectivity was not significant (1.7 : 1), it indicated that the electronic effect also plays an important role in this transformation. The cyclization of naphthalen-2-yl-derived aniline, **1p**, also proceeded smoothly to give a mixture of both tetrahydrophenanthren and tetrahydroanthracen-type products with a good total yield (60%, **2p** and **2p'**). Similar to the *meta*-methoxy substrates, aniline **2p** that cyclized at the relatively more sterically hindered position was the major isomer. The selective activation of the C(sp³)–H bond in the cycloalkanes was also successful for cross-coupling of the phenyl ring, providing a synthetically difficult spiro skeleton in 62% yield (**2q**). A symmetric aniline with two of the same C(sp³)–H bonds suitable for 1,5-hydrogen-atom abstraction in both alkyl side chains was also tested in this catalytic system. It was interesting to find that both C(sp³)–H bonds coupled with the *ortho*-C(sp²)–H bonds on the phenyl ring smoothly, followed by *in situ* elimination of aniline to afford an attractive 2,3,5,6-tetrahydro-1*H*-phenalene structure (**2r**).

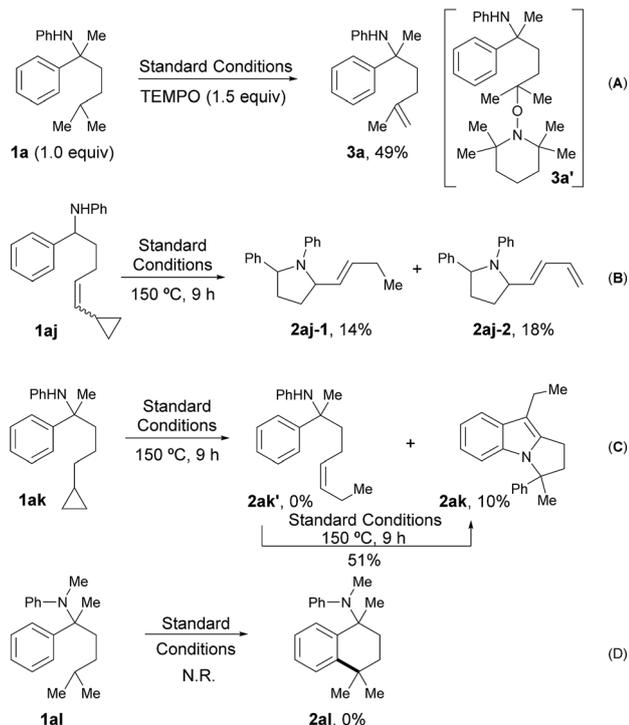
The substituents at the α -position of the nitrogen atom had an obvious effect on the transformation. While the corresponding yields decreased along with the increase of steric hindrance of the alkyl groups (**2s–u**), the cyclization of *N*- α , α -biphenyl aniline proceeded quite smoothly with excellent yield (90%, **2v**). It is important to point out that the hydrogen atom at the α -position of the nitrogen atom, well known to be activated *via* a radical path, could be well tolerated in this reaction (75%, **2w**), which further indicated that the regioselectivity of this method was determined by a 1,5-HAT process. In order to demonstrate the synthetic potential of this method, we tried to synthesize **2x**, an analogue of UCI-30002, which has been proven to play an inhibition role on several acetylcholine receptors.¹² As expected, **2x** could be obtained in 53% yield under our standard conditions. While aniline **1x** could be prepared from readily available compounds like benzonitrile and 4-nitroaniline

Table 1 Control experiments and the effects of each reaction parameter^a

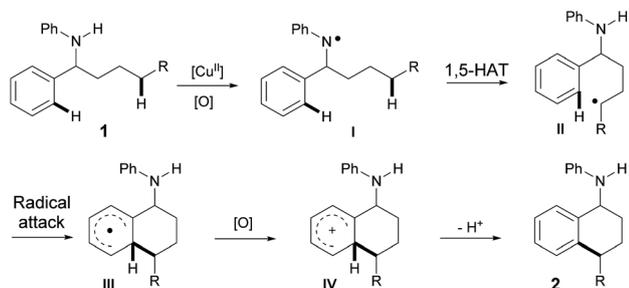
Entry	Variation from the standard conditions	Yield (%)
1	None	92
2	Without Cu(OAc) ₂	n.d.
3	Cu(OTf) ₂ instead of Cu(OAc) ₂	n.d.
4	Cu(acac) ₂ instead of Cu(OAc) ₂	Trace
5	Cu(OAc) ₂ instead of Ag ₂ CO ₃	Trace
6	AgOAc instead of Ag ₂ CO ₃	38
7	O ₂ instead of Ag ₂ CO ₃	18
8	TEMPO instead of Ag ₂ CO ₃	n.d.
9	120 °C instead of 135 °C	60
10	150 °C instead of 135 °C	78
11	12 h instead of 25 h	77
12	10 mol% instead of 20 mol% Cu(OAc) ₂	87
13	5 mol% instead of 20 mol% Cu(OAc) ₂	83
14	100 mol% instead of 150 mol% Ag ₂ CO ₃	83

^a Unless otherwise noted, the reaction conditions were as follows: **1a** (0.1 mmol), Cu(OAc)₂ (20 mol%) and Ag₂CO₃ (1.5 equiv.) in 1,2-DCE (2.0 mL) at 135 °C for 25 h. Isolated yields were reported. n.d., not detected.





Scheme 2 Control experiments designed to probe the radical path.



Scheme 3 Proposed mechanism.

Based on all of the results above and the previous reports, a plausible mechanism for the amine-directed selective activation of inert $C(sp^3)$ -H bonds for $C(sp^3)$ -H/ $C(sp^2)$ -H cross-coupling is outlined in Scheme 3. The initial interaction of $Cu(OAc)_2$ with amine **1** generates the nitrogen radical **I**,¹¹ which selectively abstracts the hydrogen atom at the remote aliphatic C-H bond *via* a 1,5-hydrogen-atom transfer to afford the carbon center radical **II**. The carbon radical **II** is subsequently captured by a phenyl ring, and the final 6-membered product **2** is afforded after the following oxidation and deprotonation.

Conclusions

In summary, we have developed a copper-catalyzed amine-directed selective activation of $C(sp^3)$ -H bonds for cross-coupling of inert $C(sp^3)$ -H and $C(sp^2)$ -H bonds. The catalytic cycle was initiated from the selective cleavage of inert secondary

or tertiary $C(sp^3)$ -H bonds *via* a 1,5-HAT process, affording the 6-membered-ring products with high efficiency and broad scope. Further efforts to develop more novel transformations with this method are still ongoing in our lab.

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