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Abstract for the Contents Pages

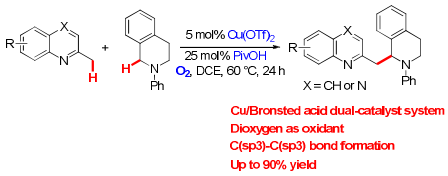
$C(sp^3)$-$C(sp^3)$ bond formation via Copper/Brønsted acid Co-catalyzed $C(sp^3)$–H bond Oxidative Cross-Dehydrogenative-Coupling (CDC) of Azaarenes

Fang-Fang Wang, Cui-Ping Luo, Guojun Deng, and Luo Yang*

Text:

A copper/Brønsted acid dual-catalyst promoted oxidative cross-dehydrogenative-coupling of alkylazaarenes and tertiary amines for $C(sp^3)$-$C(sp^3)$ bond formation was developed by using dioxygen as the terminal oxidant under mild reaction conditions.

Graphic:



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COMMUNICATION

C(sp^3)-C(sp^3) bond formation via Copper/Brønsted acid Co-catalyzed C(sp^3)–H bond Oxidative Cross-Dehydrogenative-Coupling (CDC) of Azaarenes

Fang-Fang Wang, Cui-Ping Luo, Guojun Deng and Luo Yang*

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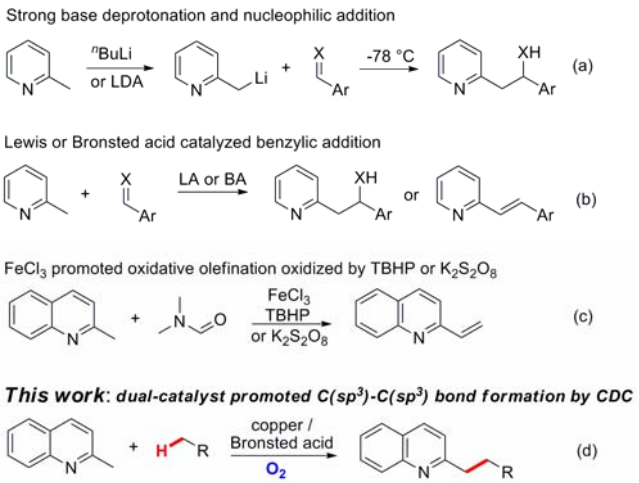
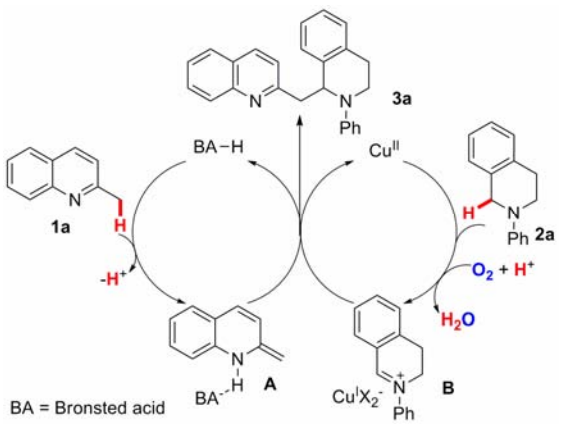
A copper/Brønsted acid dual-catalyst promoted oxidative cross-dehydrogenative-coupling of alkylazaarenes and tertiary amines for C(sp^3)-C(sp^3) bond formation was developed. This method uses dioxygen as the terminal oxidant under mild reaction conditions and would provide convenient benzylic C-H transformation of alkylazaarenes to biological active pharmaceutics.

Quinoline and isoquinoline derivatives are among the most common skeletons in natural alkaloids and pharmaceutics with various interesting biological activities. [1] As a result, great effort has been directed to the functionalization of these azaarenes. While the traditional benzylic transformation via deprotonation of the weak acidic benzylic proton and subsequent nucleophic substitution/addition to highly reactive polar electrophiles requires strong base such as ^{n}BuLi or LDA (Scheme 1, route a), [2] the recent research[3] revealed this transformation can be accelerated by shifting the alkylazaarene to its enamine counterpart using a suitable Lewis [4a-d, 6a-c] or Brønsted acid (Scheme 1, route b). [5a-c] However the substrate scope remains mostly limited to highly reactive polar electrophiles, such as imines, [4] carbonyl groups, [5] Michael acceptors[7] and olfins[7]. The benzylic nucleophilic reaction of alkylazaarenes with other electron-neutral reagents is rare. Recently, the oxidative olefination of 2-methylazaarenes using TBHP, $K_2S_2O_8$ or DDQ as oxidant was reported by Wang[8a], Xu[8b] and Tian[8c] (Scheme 1, route c). A convenient benzylic C-H cross-dehydrogenative-coupling of alkylazaarenes with electron-neutral reagents to form C(sp^3)-C(sp^3) would be highly expected (Scheme 1, route d).

In line with our interests in the C-H activation and nucleophilic additions, [5a, 9] our previous studies [5a] discovered that Brønsted acids turned out to be effective catalyst for the benzylic C-H addition to carbonyl groups. On the other hand, the oxidation of



Scheme 1. Benzylic C-H nucleophilic functionalization of azaarenes



Scheme 2. Possible catalytic cycle for Dual-catalyst promoted CDC of azaarenes

C-H bonds adjacent to nitrogen[10, 11] is one of the most important and successful strategies for C-H functionalization to form electrophilic iminium ions in the presence of a copper catalyst. In this context, we envisioned a C(sp^3)-C(sp^3) bond forming process of 2-methylazaarenes and tetrahydroisoquinolines promoted by a dual-catalyst system composed of a Brønsted acid and a copper catalyst, in which the Brønsted acid can convert the 2-

Key Laboratory for Environmentally Friendly Chemistry and Application of the Ministry of Education,
Department of Chemistry, Xiangtan University, Hunan, 411105, China
Fax: +86-731-58292251; Tel: +86-731-58298351;
E-mail: yangluo@xtu.edu.cn

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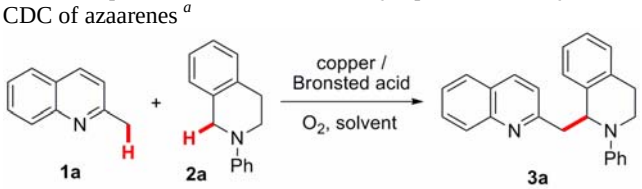
methylazaarene to its more nucleophic enamine counterpart (Scheme 2, intermediate **A**) and the copper catalyst can generate the reactive electrophilic iminium ion (intermediate **B**) [10k] assisted by oxidant.

Though the most common and widely used combination for the oxidation of C-H bonds adjacent to nitrogen is copper/TBHP, 10 obviously the copper/dioxygen combination should be much more attractive considering dioxygen is readily available, cheap and environmentally benign with only water as byproduct. [10l] With this in mind, we first examined the reaction of 2-methylquinoline (**1a**) and N-phenyltetrahydroisoquinoline (**2a**) catalyzed by CuI and pivalic acid (PivOH) under O_2 atmosphere based on our early work (Table 1, entry 1). To our delight, the desired oxidative cross-dehydrogenative-coupling product **3a** was obtained in 32% yield. During the following optimization study, we first examined the influence of different copper catalysts. Common copper catalysts such as CuBr, CuCl, $Cu(OAc)_2$ and $Cu(OTf)_2$ were screened and $Cu(OTf)_2$ turned out to be the most effective one (entries 2-5). Next, Brønsted acids with varied acidity were tested and the relatively weak pivalic acid was found to match $Cu(OTf)_2$ best (entries 6-8). The quantity of Brønsted acids can be decreased to 10 mol% and a comparable yield was observed (entry 9). Instead of the O_2 atmosphere, much lower yield was obtained when the CDC was conducted in air (entry 11). Gratifyingly, the reaction can proceed at room temperature with moderate yield (entry 12), but at higher temperature, the desired product **3a** would undergo further oxidation monitored by the GC-MS (entry 14). Next, the effect of solvent on this reaction was investigated and the most satisfactory yield was obtained in low polarity dichloroethane (DCE), other polar or even protic solvents were also applicable (entries 15-19). It is worthy noting that both the copper catalyst and the Brønsted acid were essential for the CDC revealed by the control experiments (entries 20 and 21). Without the copper catalyst, no product **3a** was detected and without the Brønsted acid the reaction resulted in very low yield.

Table 1. Optimization of the dual-catalyst promoted benzylic CDC of azaarenes [a]



Entry	Cu (5 mol%)	BA (mol%)	Temp. [°C]	Solvent	Yield [%][b]
1	CuI	PivOH (25)	60	DCE	32
2	CuBr	PivOH (25)	60	DCE	50
3	CuCl	PivOH (25)	60	DCE	19
4	$Cu(OAc)_2$	AcOH (25)	60	DCE	67
5	**$Cu(OTf)_2$**	**PivOH (25)**	**60**	**DCE**	**90**
6	$Cu(OTf)_2$	AcOH (25)	60	DCE	67
7	$Cu(OTf)_2$	$PhCO_2H$ (25)	60	DCE	60
8	$Cu(OTf)_2$	*p*-TSA (25)	60	DCE	64
9	$Cu(OTf)_2$	PivOH (**10**)	60	DCE	85
10	$Cu(OTf)_2$	PivOH (**50**)	60	DCE	62
11[c]	$Cu(OTf)_2$	PivOH (25)	60	DCE	49
12	$Cu(OTf)_2$	PivOH (25)	**25**	DCE	66
13	$Cu(OTf)_2$	PivOH (25)	**40**	DCE	73
14	$Cu(OTf)_2$	PivOH (25)	**80**	DCE	42
15	$Cu(OTf)_2$	PivOH (25)	60	1,4-dioxane	69
16	$Cu(OTf)_2$	PivOH (25)	60	Toluene	54
17	$Cu(OTf)_2$	PivOH (25)	60	DMF	63
18	$Cu(OTf)_2$	PivOH (25)	60	^{t}BuOH	75
19	$Cu(OTf)_2$	PivOH (25)	60	CH_3CN	74
20	--	PivOH (25)	60	DCE	Trace
21	$Cu(OTf)_2$	--	60	DCE	23

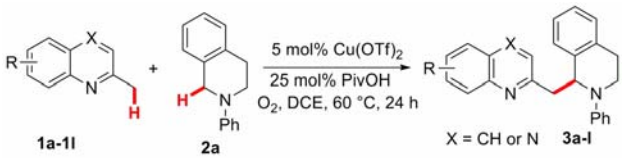
[a] Conditions: **1a** (0.4 mmol), **1b** (0.2 mmol), Cu/Brønsted acid (BA), solvent (0.5 mL), reacted for 36 h under O_2 (1 atm) unless otherwise noted.

[b] Isolated yields.

[c] Reacted under air (1 atm).

Under the optimized conditions (Table 1, entry 5), the substrate scope and limitation[12] of this dual-catalyst promoted CDC was explored. The effect of substituents on the alkylquinoline moiety is listed in Table 2. 2-Methylquinoline bearing electron donating or withdrawing substituents were successfully transformed into the desired products in moderate to high yields, such as methyl (**1b**), methoxyl (**1c**), halo (**1d-1g**), phenyl (**1h**), trifluoromethyl (**1i**) and nitro (**1g**). Besides 2-methylquinolines, the optimized dual-catalyst system can also be applied to the CDC of 2-methylquinoxaline (**1k**) or 2,3-dimethylquinoxaline (**1l**) with N-phenyltetrahydroisoquinoline (**2a**). However, the reaction of 2-methylpyridine (or 2,6-lutidine) under the same conditions was failed for unknown reason. At elevated temperature (80 °C), the N-phenyltetrahydroisoquinoline (**2a**) was oxidized to N-phenyl-3,4-dihydroisoquinolin-1-one and with the 2-methylpyridine remained intact. [13] Next, the effect of substituents on the phenyl group of tetrahydroisoquinoline moiety was also investigated (Table 3). We were pleased to observe that the substituents on the phenyl group such as methyl (**2b**), methoxyl (**2c**) and halo (**2d-2f**) were all tolerated.

Table 2. The effect of substituents on the 2-methylazaarene moiety [a]



1a	R = H, X = CH	**1b**	R = 6-CH_3, X = CH
1c	R = 6-OCH_3, X = CH	**1d**	R = 6-F, X = CH
1e	R = 6-Cl, X = CH	**1f**	R = 6-Br, X = CH
1g	R = 6-I, X = CH	**1h**	R = 6-Ph, X = CH
1i	R = 6-CF_3, X = CH	**1j**	R = 6-NO_2, X = CH
1k	R = H, X = N	**1l**	R = 3-CH_3, X = N

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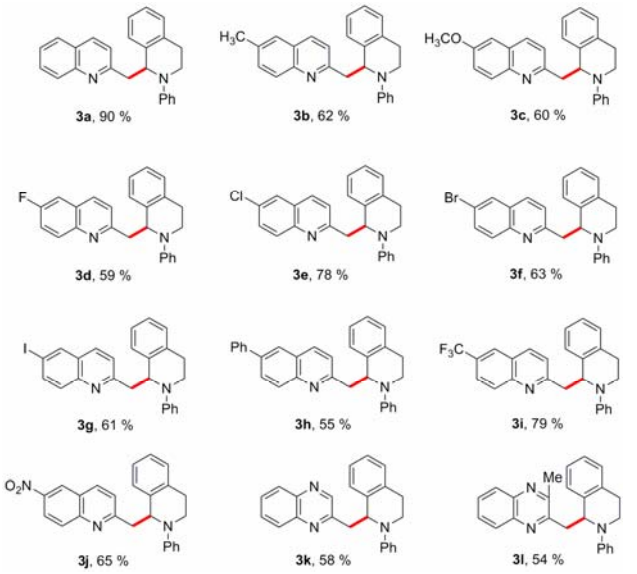
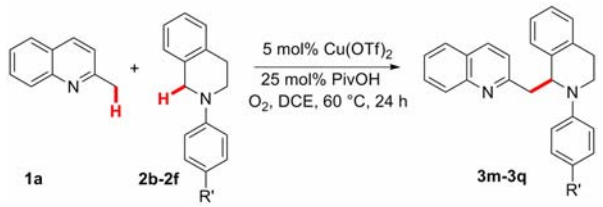


[a] Conditions: **1a**-**1l** (0.4 mmol), **2a** (0.2 mmol), $Cu(OTf)_2$ (3.6 mg, 5 mol%, 0.01 mmol), pivalic acid (5.1 mg, 25 mol%, 0.05 mmol), DCE (0.5 mL), reacted for 24 h at 60 °C under 1 atm O_2 unless otherwise noted. Isolated yields.

Table 3. The effect of substituents on the phenyl group of tetrahydroisoquinoline moiety [a]



entry	Substrate **2b-2f**		Product **3m-3q**	Yield **(%)**[a]
1	**2b**	R' = CH_3	**3m**	74
2	**2c**	R' = OCH_3	**3n**	87
3	**2d**	R' = F	**3o**	69
4	**2e**	R' = Cl	**3p**	78
5	**1f**	R' = Br	**3q**	72

[a] Conditions: **1a** (0.4 mmol), **2b-2f** (0.2 mmol), $Cu(OTf)_2$ (3.6 mg, 5 mol%, 0.01 mmol), pivalic acid (5.1 mg, 25 mol%, 0.05 mmol), DCE (0.5 mL), reacted for 24 h at 60 °C under 1 atm O_2 unless otherwise noted. Isolated yields.

In conclusion, we have developed an efficient $C(sp^3)$-$C(sp^3)$ bond forming process by the oxidative-cross-coupling of benzylic C-H bond of alkylazaarenes and tetrahydroisoquinolines, which was promoted by the copper/Brønsted acid dual-catalyst system and using dioxygen as the terminal oxidant under mild reaction conditions. This reaction would provide an efficient method for the benzylic C-H transformation of 2-alkylazaarenes to biological active pharmaceutics.

Acknowledgements

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The authors declare no competing financial interest.

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12 The optimized reaction conditions can also be applied to 2-ethylquinoline, but with much lower yield (31%) and moderate diastereoselectivities (*trans*/*cis* = 86 : 14).

13 The reaction of 2-methylpyridine with tetrahydroisoquinoline has been tried both at 60 °C (which is the optimized temperature) or 80 °C, but no CDC product was found indicated by GC-MS.