C–H Activation

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Copper-Catalyzed Dehydrogenative Cross-Coupling Reactions of *N-para*-Tolylamides through Successive C–H Activation: Synthesis of 4*H*-3,1-Benzoxazines**

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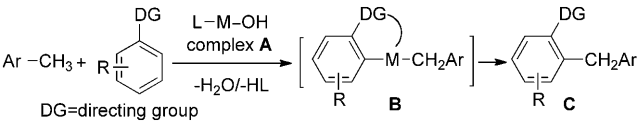
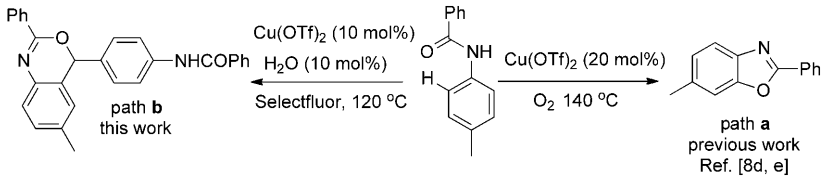
Carbon–carbon bond-formation reactions are among the most important processes in chemistry because they enable key steps in building more complex molecules from simple precursors. A transition-metal-catalyzed dehydrogenative cross-coupling (DCC) reaction from two C–H bonds will avoid the installation of functional groups and thus make synthetic routes shorter and more efficient. Some excellent pioneering progress had been achieved on this subject.[1] However, important limitations in regioselectivity and undesired homocoupling pathways still exist. A remarkable method for suppressing homocoupling relies on achieving two successive palladium-catalyzed C–H activations of two arene substrates (for example, indole and benzene) utilizing mechanistic duality.[2] Considering both regioselectivity and the elimination of homocoupling, the development of directed metalation[3] of a metal catalyst with potential dichotomous behavior for highly regioselective activation of two kinds of C–H bonds in a successive manner, might become a promising strategy for efficient DCC reactions.

From the mechanistic point of view, most of the ligand-directed transition metals (such as Pd, Ru, Rh, and Pt) catalyzed aromatic C(sp^2)–H bonds functionalizations through cyclometalated intermediates. The cyclometalated intermediates such as cyclopalladium species were known to be reluctant to undergo homocoupling reaction under $Pd^{0/II}$ conditions.[3] On the other hand, benzylic methyl C–H bonds could be activated by Ru^{II} hydroxo complexes[4] through possible ambiphilic or nucleophilic C–H activation.[5] Therefore, we hypothesized that by choosing a suitable metal hydroxo complex catalyst **A** (Scheme 1), a successive C–H activation involving ligand directed *ortho*-arene C(sp^2)–H bond and benzylic methyl C(sp^3)–H bond might take place. As a result, the formation of intermediate **B**, which contains Ar–M bond and $ArCH_2$–M bond, will lead to a DCC product **C** by reductive elimination. So far, to the best of our knowledge, there is no example of DCC reactions through transition-metal-catalyzed activation of both aromatic C(sp^2)–H and benzylic methyl C(sp^3)–H bonds.[1a,6,7]



Scheme 1. Design for DCC reactions of benzylic methyl C(sp^3)-H and ligand directed aromatic C(sp^2)–H bonds through C–H activation catalyzed by a transition-metal hydroxo complex. L = ligand.

Copper catalysts are particularly attractive in transition-metal-catalyzed direct C–H functionalization reactions because of their low cost and low toxicity.[8] Recently, a copper-catalyzed intramolecular oxidative C–O coupling of benzanilides was developed, in which the *para*-methyl group was unreactive (Scheme 2, path **a**).[8d,e] Herein, we report a novel annulation of *N-para*-tolylamides catalyzed by Cu($OTf)_2$ and with Selectfluor as the oxidant, for the synthesis of 4*H*-3,1-benzoxazines[9] through successive intermolecular C–H activated DCC reaction of aromatic C–H and benzylic methyl C–H bonds, and subsequent intramolecular C–O bond formation (Scheme 2, path **b**). During this reaction a catalytic amount of water might play an important role for in situ generation of the key copper hydroxo complex catalyst.



Scheme 2. Copper-catalyzed C–H functionalization. Tf = trifluoromethanesulfonyl.

Based on our recent studies on the palladium-catalyzed amide-directed benzylic C–H[10a] and aromatic *ortho*- or *para*-C–H[10b] amination with *N*-fluorobenzenesulfonimide (F^+ as oxidant), we sought to use Selectfluor as an oxidant to perform an amide-directed DCC reaction. Therefore, our initial testing was carried out in the presence of Selectfluor (1.0 equiv) and $HNTf_2$ (1.0 equiv), Cu($OTf)_2$ (0.1 equiv) catalyzed the reaction of *N-para*-tolylpivalamide (**1a**; Table 1). When the reaction was performed at 120 °C for

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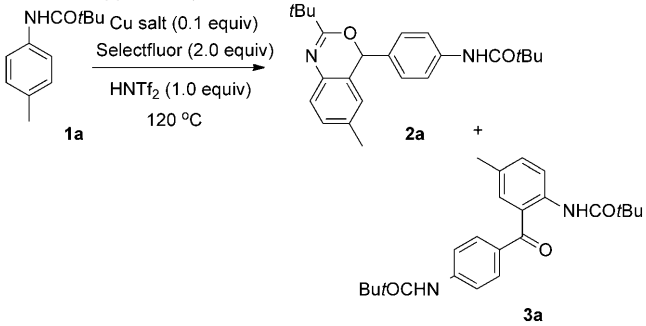
Table 1: Copper-catalyzed DCC reactions of **1a**.



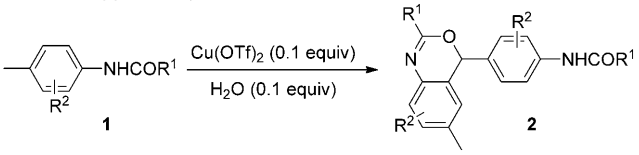
Entry	Catalyst	Solvent	H_2O [equiv]	*t* [h]	Yield of **2a** (**3a**) [%][a]
1	$Cu(OTf)_2$	DCE	–	6.0	0
2	$Cu(OTf)_2$	DCE	1.0	2.5	63 (12)
3	$Cu(OTf)_2$	DCE	0.05	2.0	81
4	**$Cu(OTf)_2$**	**DCE**	**0.1**	**1.5**	**88**
5	$Cu(OTf)_2$	DCE	0.2	3.5	74
6	$Cu(OTf)_2$	DCE	0.5	3.0	67 (6)
7	$Cu(OTf)_2$	$Cl_2CHCHCl_2$	0.1	2.0	78
8	$Cu(OTf)_2$	$C_6H_5NO_2$	0.1	2.0	74
9[b]	$Cu(OTf)_2$	DCE	0.1	2.0	80
10	$Cu(OAc)_2$	DCE	0.1	12.0	0
11	$CuCl_2$	DCE	0.1	12.0	0
12	CuF_2	DCE	0.1	12.0	43[c]
13	CuI	DCE	0.1	12.0	27[d]

[a] Yield of the isolated product. [b] *N*-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate was used instead of Selectfluor. [c] 38% of **1a** was recovered. [d] 59% of **1a** was recovered. Also, the same result was obtained by adding 0.1 equiv of 1,10-phenanthroline and without $HNTf_2$.

6.0 hours with anhydrous 1,2-dichloroethane (DCE) as the solvent, no reaction occurred (Table 1, entry 1). Surprisingly, when 1.0 equivalent of H_2O was added to the above reaction, an intermolecular annulation product 4*H*-3,1-benzoxazine **2a** was generated in 63% yield, along with 12% of **3a** (Table 1, entry 2). When 0.05, 0.1, 0.2 or 0.5 equivalents of H_2O were added, **2a** was obtained in 81%, 88%, 74%, and 67% yield, respectively (Table 1, entries 3–6). These results showed that during the transformation from **1a** into **2a**, a catalytic amount of H_2O played an important role. Therefore, 0.1 equivalent of H_2O (Table 1, entry 4) was used for further optimization of the reaction condition. When the reactions were performed with $Cl_2CHCHCl_2$ and $C_6H_5NO_2$ as solvents, **2a** were obtained in 78% and 74% yield, respectively, along with some unidentified by-products (Table 1, entries 7 and 8). With *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the oxidant, **2a** could also be obtained in 80% yield (Table 1, entry 9). Other copper salts such as $Cu(OAc)_2$ and $CuCl_2$ were not effective, and most of the **1a** was recovered (Table 1, entries 10 and 11). Copper salts CuF_2 and CuI were less effective, and gave **2a** in 43% and 27% yield, respectively (Table 1, entries 12 and 13). No reaction was observed in the absence of the copper salts. Interestingly, during the transformation from **1a** into **2a**, no intramolecular C–O coupling benzoxazole product (Scheme 2, path **a**) and homocoupling by-products were detected.

Under the optimized reaction conditions (Table 1, entry 4), various 4*H*-3,1-benzoxazines were generated with this new method. As described in Table 2, substrates with electron-withdrawing or electron-donating groups on the benzene ring worked well (Table 2, entries 1–12). Reactions

Table 2: Copper-catalyzed DCC reactions of **1b–q**.[a]



Entry	1	R^1	R^2	*t* [h]	Yield [%][b]
1	**1b**	*t*Bu	3-Me	1.5	76
2	**1c**	*t*Bu	2-Me	3.0	54
3	**1d**	*t*Bu	3-F	2.0	67
4	**1e**	*t*Bu	3-Cl	1.8	62
5	**1f**	*t*Bu	3-Br	3.0	61
6	**1g**	*t*Bu	3-Ph	1.1	79
7	**1h**	*t*Bu	2-Ph	1.5	87
8	**1i**	*t*Bu	2-(4-MeC_6H_4)	1.3	82
9	**1j**	*t*Bu	2-(4-ClC_6H_4)	2.0	84
10	**1k**	*t*Bu	2-(3-$CF_3C_6H_4$)	2.0	73
11	**1l**	*t*Bu	2-C_6H_3-5-Me	2.0	76
12	**1m**	*t*Bu	2-(4-MeC_6H_4)-5-Me	1.4	80
13	**1n**	Ph	3-Me	1.8	84
14	**1o**	Ph	3-Cl	1.2	80
15	**1p**	Ph	H	2.0	91
16[c]	**1q**	CH=$CHCH_3$	H	2.5	62

[a] Reactions were carried out with **1** (0.3 mmol), $Cu(OTf)_2$ (0.1 equiv), H_2O (0.1 equiv), Selectfluor (2.0 equiv), and $HNTf_2$ (1.0 equiv) in anhydrous DCE (2 mL) at 120°C. [b] Yield of the isolated product. [c] With *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the oxidant.

of substrates with *ortho*- and *meta*-methyl groups on the benzene ring (for example, **1b** and **1c**), provided the highly regioselective *para*-methyl-substituted annulation products. Products containing fluoride **2d**, chlorides **2e**, **2j,** and **2o** as well as bromide **2f** could be obtained in good to high yields. The tolerance for chlorides and bromide on the aromatic ring in this transformation offers an opportunity for further cross-coupling. When *meta*-substituted substrates were used, C–C coupling occurred exclusively at the less-hinder site (Table 2, entries 1, 3–6, 13, and 14). We also found that **2n–q** could be obtained by changing the acyl directing groups (Table 2, entries 13–16), in which benzamido was identified as the best directing group in the transformation from **1** into **2** (Table 2, entries 13–15). However, no reaction occurred with substrate *N*-*para*-tolylacetamide, 3-methyl-*N*-*para*-tolylbutanamide, and 2-phenyl-*N*-*para*-tolylacetamide, which may result from their lack of directing ability when using $Cu(OTf)_2$ in the transformation.[11] In addition, starting from substrate *N*-(4-ethylphenyl)benzamide with an ethyl group *para* to the direct amide group, no reaction occurred.

To help ascertain the character of the key copper complex catalyst that is generated in situ, the corresponding ^{19}F NMR and ESI/MS experiments were performed.[12] The Cu–F bond region of ^{19}F NMR spectra of a mixture of CuI (1.0 equiv), 1,10-phenanthroline (1.0 equiv), and *N*-fluoro-2,4,6-trime-

thylpyridinium tetrafluoroborate (3.0 equiv) showed a single signal at $\delta = -256$ ppm. The results of ESI/MS experiment under the above conditions indicates the formation of the in situ generated $Cu^{III}FOH$ complex catalyst.[12] Moreover, when the reaction of **1a** was performed under the conditions described in Table 1, entry 9, but with 1.0 equivalent of $Cu(OTf)_2$, after 20 minutes, the Cu–F bond region exhibited a single signal at $\delta = -227$ ppm as shown in the ^{19}F NMR spectra.[12] In our experiment, the formation of C–C coupling/oxidation product **3a** (Table 1) might indicate that during the formation of **2**, C–C bond coupling occurred before the coupling of the C–O bond. Therefore, the transformation from **1** into **2** might begin with the successive activation of both benzylic methyl and aromatic C–H bonds by the $Cu^{III}FOH$ complex catalyst that is generated in situ to provide the intermolecular C–C bond-coupling intermediate as described in Scheme 1. The next intramolecular C–O coupling reactions give the final annulation products **2**. Further investigation of the mechanism of this transformation is under way.[13–15]

In conclusion, we have reported a novel $Cu(OTf)_2$-catalyzed annulation for the construction of benzoxazine derivatives from readily available *N-para*-tolylamides in the presence of Selectfluor and water through the first intermolecular C–H activated dehydrogenative cross-coupling reaction of benzylic methyl $C(sp^3)$–H and aromatic $C(sp^2)$–H bonds, and subsequent intramolecular C–O bond formation. This strategy might inspire the development of additional new catalyst for DCC reaction between two different kinds of unactivated C–H bonds. Studies are ongoing to apply this DCC cascade for the synthesis of other heterocycles.

Experimental Section

N-para-tolylpivalamide **1a** (57.3 mg, 0.3 mmol), $Cu(OTf)_2$ (10.8 mg, 0.03 mmol), Selectfluor (212.6 mg, 0.6 mmol), and $HNTf_2$ (84 mg, 0.3 mmol) were added to an over-dried screw-cap test tube equipped with a magnetic stir bar while in a glovebox. The test tube was then sealed off with a screw-cap and taken out of the glovebox. Then solvent (2.0 mL; from a mixture of 10 mL DCE and 2.7 μL H_2O) was added, the vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times). The reaction mixture was stirred at 120 °C for the 1.3 h. After cooling to RT, the mixture was poured on ice-water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered over Celite, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a gradient eluent of *n*-hexane and ethyl acetate to afford the product **2a** (49.9 mg, 88 %).

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