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Micelle enabled C(sp²)–C(sp³) cross-electrophile coupling in water *via* synergistic nickel and copper catalysis[†]

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A robust and sustainable $C(sp^2)-C(sp^3)$ cross-electrophile coupling was developed *via* nickel/copper synergistic catalysis under micellar conditions. This protocol provided a general method to access alkylated arenes with good to excellent yields on a very large scale.

Metal catalyzed C(sp²)-C(sp³) bond formation reactions are widely applied in academia and the industrial area.^{1,2} Although the traditional cross coupling reaction is carried out using preformed organometallic reagents as the coupling partner,³ there is increasing interest in cross-electrophile coupling which serves as an alternative method to forge $C(sp^2)-C(sp^3)$ bonds.4-11 In 2010, Weix reported the first general nickelcatalyzed cross-electrophile coupling of aryl halides with unactivated alkyl halides.¹² This seminal report generated high expectations and several follow-up efforts to further extend and improve the methodology. Nevertheless tedious operations are still required to ensure high quality in the end product, due to the extent of side-reactions, and the high amount of residual components inherent to such transformations. In addition, such chemistry tends to happen in the flagged reprotoxic polar aprotic solvents, such as DMA, DMF or NMP. Meanwhile, chemistry-in-water technology has become more and more popular owing to the demand of the environmental footprint.¹³ Lipshutz's group reported aryl-alkyl cross coupling using micelle enabled Pd catalysis.¹⁴ This work sheds light on the further development of related chemistry in terms of sustainability. In collaboration with Lipshutz, we also revisited the methodology to make it more amenable for large scale production and reported the iron-catalyzed reductive couplings

of the terminal (hetero)aryl alkenes and alkyl halides under aqueous micellar conditions that addressed these issues in the specific reported case.¹⁵ With the aim to derive an even more general and robust sustainable catalytic system, herein, we report a Ni/Cu co-catalyzed $C(sp^2)-C(sp^3)$ cross-electrophile coupling under micellar conditions, in water as the bulk medium (Scheme 1).

With this objective in mind, our investigation started with the coupling of ethyl 4-bromobenzoate (1a) and iodocyclohexane (2a) as model substrates (Table 1). Brief variations of the standard conditions led us to the best conditions of 2.5 mol% Ni(OAc)₂·4H₂O, 3 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline (L1), 0.75 mol% of copper oxide, and zinc as the



Scheme 1 Synthesis of alkylated arenes via cross-electrophile couplings.

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En	try Reac	tion condition ^a		Yield ^b (%)
1	With	Without Ni(OAc)·4H ₂ O		0
2	With	Without zinc		0
3	With	Without L1		0
4	With	out Cu ₂ O	50	
5	With	out 2 wt% TPG	27	
6	With	out 2-Me-THF	60	
7	Stan	dard conditions	92(89)	
8	L2 in	stead of L1	80	
9	L3 in	stead of L1	68	
10	L4 in	stead of L1	62	
11	L5 in	stead of L1	78	
12	L6 in	stead of L1	79	
13	L7 in	stead of L1	58	
14	L8 in	stead of L1	11	
15	CuI i	nstead of Cu2O	67	
16	CuO	instead of Cu2C	72	
17	Cu(C	$Ac)_2$ instead of	75	
18	25 °C	C instead of 45	81	
19	THF	THF instead of 2-Me-THF		60
20	Aceto	Acetone instead of 2-Me-THF		41
21	MeC	MeCN instead of 2-Me-THF		32
22	Wate	Water instead of TPGS-750-M 70		
	$- \underbrace{\searrow}_{N} \underbrace{\bigvee}_{L1} \underbrace{\bigvee}_{L2} \underbrace{\bigvee}_{L3} \underbrace{\bigvee}_{L4} \bigvee$			Bu N N L4
	MeO N L5	$Ph \xrightarrow{Ph}_{N} \xrightarrow{Ph}_{L6}$	MeO N N L7	DMe N N L8

^{*a*} Reaction were performed with **1a** (4.38 mmol), **2a** (6.58 mmol), 2-Me-THF (10 mL), 2 wt% TPGS-750-M/H₂O (10 mL) at 45 °C for 16 h. ^{*b*} Yields determined by HPLC using 1,3,5-trimethoxybenzene as an internal standard. Value within parentheses is isolated yield.

reducing agent in the co-solvent system of 2 wt% TPGS aqueous solution and 2-Me-THF leading to the full consumption of the starting material 1a and an 89% isolated yield of the desired product 3aa (entry 7). This finding on the crucial role of copper co-catalysis came from originally contaminated aryl bromide with copper trace. Careful investigations on the challenges we faced when working with analytically pure aryl bromide that would not react any longer led us to find out that Cu₂O was essential to the process. Control experiments indicated that this transformation could not occur in the absence of either nickel, ligand or zinc (entries 1-3). The catalytic amount of copper also plays an important role as the yield dropped to 50% without copper (entry 4).¹⁶ The nano-micelle environment was necessary for the reaction since a low yield was obtained in sole organic solvent (entry 5). Besides L1, other phenanthroline and bi-pyridine type ligands also showed effectiveness for this reaction, albeit in lower yields (11-80%, entries 8-14). Other copper sources including CuI, CuO and Cu(OAc)₂ also worked well for the reaction and the yields varied from 67–75%, as shown in entries 15–17. To our delight, this reaction could also be performed at room temperature, producing the desired product **3aa** in 81% yield (entry 18). 2-Me-THF is selected as the best co-solvent as other common solvents such as THF, acetone and MeCN yielded more modest results (entries 19–21). A lower yield was observed compared with the micellar conditions (entry 22) when only water was used in addition to challenging physical operations.

While we still do not have enough unambiguous mechanistic evidence of the actual role of the synergistic effect of copper, and are currently actively working on elucidating it, we proposed the following dual catalytic cycles depicted as Scheme 2 based on key literature precedents.^{16–18} Nickel is assumed to have the expected role in oxidative addition and reductive elimination, while copper could facilitate the transmetalation of the alkyl species to nickel.^{19,20} Nickel and copper catalytic cycles should be matched well in order to deliver the desired compound in a good manner. We are currently investigating the mechanistic aspects of the process and will share more insights in due course.

With these best conditions in hand, the scope and limitations of this cross-electrophile coupling were examined with a variety of aryl halides (Scheme 3). Besides aryl bromide, the more reactive aryl iodides could obviously undergo this transformation smoothly to afford the desired product with 94% yield (3aa, X = I, X' = I). Cyclohexyl bromide also worked well under the standard conditions, albeit in a lower yield (3aa, X = Br, X' = Br). Aryl halides bearing various functional groups at the para-position could be prepared in moderate to good yields (65–85%), including acetyl (3ca), trifluoromethyl (3db), methoxyl (3eb), cyanide (3fa), formyl (3ha), amide (3ia), sulfonyl (3ja) and phenyl (3ka) groups. meta and ortho substituted aryl halides such as 3-bromobenzoate and 2-bromobenzoate also serve as good candidates in this reaction, affording the desired coupling product with 76% and 55% yields, respectively (3ga and 3ma). The reaction of 2-bromonaphthalene with Boc protected 4-iodo-piperidine successfully resulted in the corresponding product in a 62% yield (3la). Other heterocyclic halides including indole (3na), carbazole (3oa), benzofuran (3pa), benzothiophene (3qa), 3-coumaranone (3ra), and pyridine (3sa and 3ta) could also be employed to produce the corresponding coupling products in 59% to 75% yields. Note that this chemistry could also be implemented to the pharmaceutically relevant



Scheme 2 Proposed mechanistic cycle for the dual catalysis.

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COOEt

3ae, 72%

COOF



ĊOOEt ĊOOEt ĊOOEt 3af, 81% 3ag, 77% 3ai, 72% 3ah, 54% NBoc FtOOC ĊOOEt ĊOOEt ĊOOEt 3aj, 61% 3ak, 63% 3al, 55% 3am, 68% Scheme 4 Substrate scope of alkyl halides. afforded the desired product 3ab in an 82% yield. Not only secondary alkyl iodides, but also primary alkyl iodides such as

Ni(OAc)2•4H2O (2.5 mol%)

L1(3 mol%)

Cu₂O (0.75 mol%)

Zn (2.5 equiv.)

2-Me-THF/2 wt% TPGS-750-M/H2O

45 °C, 16 h

COOEt

ĊOOEt

3ac, 71%

COOEt

3ad, 75%

Br

COOEt

3ab,82%

à

ethyl 4-iodobutanoate could also be used to give 3ac in a 71% yield. Isopropyl iodide and cyclopentyl iodide are both active candidates to produce the corresponding product in 75% and 81% yields, respectively. The presence of both chloride and iodide in the alkyl partner leads to complete selectivity for coupling at the iodide (3ae). Alkyl iodide bearing heteroatoms such as hydropyran (**3ah** and **3ak**) and azetidine (**3aj**) could also be well tolerated. Notably, this method was applicable to drug like analogues, or subsections thereof, as one example shown in 3al. It is emphasized that the challenging substrate cyclopropyl iodide could also act as a good coupling partner under these micellar conditions and afford the desired product 3am in 68% yield.

In conclusion, a robust nickel and copper catalysed C(sp²)-C(sp³) cross-electrophile coupling within aqueous nanoreactors under very mild conditions has been developed. The present synergistic approach²² allows the expedient synthesis of a wide variety of functionalized adducts with considerable generality, good-to-excellent yields, cost-efficiency and high chemoselectivity.

molecules such as 3ua to afford the desired coupling target in a good yield (55%).²¹

We next explored the scope of this cross electrophile coupling by using different alkyl iodides (Scheme 4). As mentioned in Scheme 2, the 4-iodopiperidine derivative reacted well and

Notably, all reactions were conducted on a gram-scale, demonstrating good scalability. Moreover, the implementation of this protocol in drug substrate synthesis^{23–25} with kilo gram scale was conducted and will be reported shortly. Further study will focus on the detailed investigation of the reaction mechanism, as well as expansion of this tool box to more challenging $C(sp^2)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ cross-electrophile couplings.²⁶

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Conflicts of interest

There are no conflicts to declare.

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