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Arylation, Vinylation, and Alkynylation of Electron-Deficient (Hetero)arenes Using Iodonium Salts

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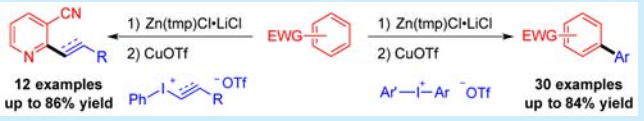
Supporting Information

ABSTRACT: Arylation, vinylation, and alkynylation of electron-deficient arenes and heteroarenes have been achieved by chemoselective C−H zincation followed by copper-catalyzed coupling reactions using iodonium salts. This approach offers a direct and general access to a wide scope of (hetero)biaryls as well as alkenylated and alkynylated heteroarenes under mild conditions. It is particularly useful and valuable for the rapid and modular synthesis of diverse (hetero)aryl compounds, as demonstrated in the synthesis of transient receptor potential vanilloid 1 (TRPV1) antagonists and angiotensin II receptor type 1 (AT1 receptor) antagonists.



Developing rapid and efficient access to diverse electron-deficient biaryl motifs is highly valuable, [1] as they have a ubiquitous presence and indispensable role in natural products,[1a] pharmaceutically important compounds,[1b,c] and functional materials[1d] (Figure 1). Complementary to traditional

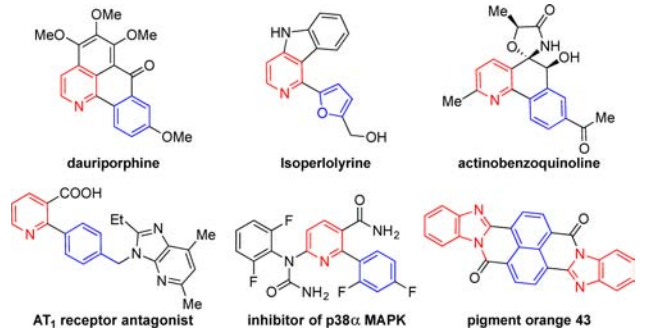
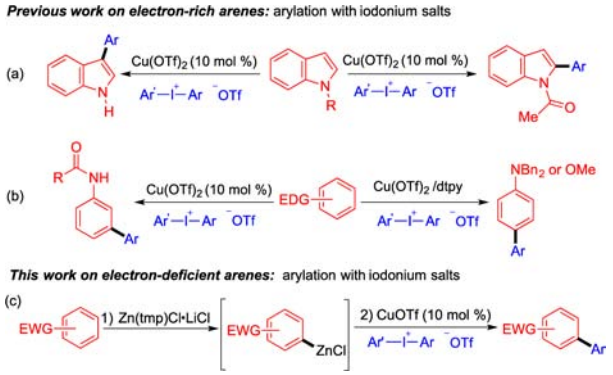


Figure 1. Electron-deficient biaryl motifs in natural products, bioactive compounds, and functional molecules.

metal catalyzed cross-coupling reactions which require multi-step preparation of organometallic reagents,[2,3] direct arylation of arenes offers an attractive and rapid strategy for the synthesis of biaryls.[4] Despite remarkable advancement in arene arylation, current methods often suffer from the limited scope of arenes bearing specific directing groups, the use of strong oxidants, and harsh reaction conditions. Thus, it is desirable to develop a general and mild arene arylation approach to diverse electron-deficient biaryl compounds.

Recently, iodonium salts have emerged as a powerful and attractive electrophilic arylation reagent alternative to aryl halides in cross-coupling reactions,[5] due to their favorable properties such as high reactivity, air and moisture stability, and convenient preparation without the need for chromatography purification.[6] For example, they have been used in the direct arylation of electron-rich aromatic compounds to directly access electron-rich biaryl compounds, such as indoles (Scheme 1a),[7a] phenols, and anilines (Scheme 1b).[7b,c] Yet, arylation of electron-deficient arenes using iodonium salts has not been reported, likely due to their weaker nucleophilicity.

Scheme 1. Arylation of Arenes with Iodonium Salts



Along with our research interests in direct functionalization of arenes,[8] we envisioned that arylation of electron-deficient arenes could be achieved in one pot by selective zincation for the formation of more nucleophilic organozinc intermediates[9] followed by copper-catalyzed arylation with iodonium salts (Scheme 1c). This approach of preparing (hetero)biaryls features a broad scope of arenes, superior functional group tolerance, and mild reaction conditions. In this letter, we report the development of such an arene arylation method using iodonium salts and its application in the synthesis of bioactive biaryl compounds. We also demonstrate such a strategy is effective for arene vinylation and alkynylation.

Our studies began with model substrates 3-cyanopyridine (nicotinonitrile) **1a** and diphenyliodonium salt **2a** (Table 1). Learning from Knochel's seminal work[9] and our recent

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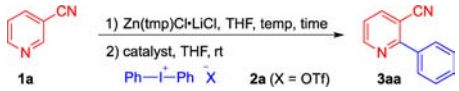
Table 1. Condition Optimization for Arylation of 1a[a]



entry	catalyst	X	temp (°C)[b]	time (h)[b]	2a (equiv)	3aa (yield, %)[c]
1	–	OTf	rt	0.75	1.2	trace
2	$Cu(OTf)_2$	OTf	rt	0.75	1.2	22
3	$Cu(OAc)_2$	OTf	rt	0.75	1.2	5
4	$Cu(acac)_2$	OTf	rt	0.75	1.2	28
5	CuCl	OTf	rt	0.75	1.2	34
6	CuBr	OTf	rt	0.75	1.2	22
7	CuOTf[d]	OTf	rt	0.75	1.2	53
8	CuOTf[d]	OTf	50	0.75	1.2	65
9	CuOTf[d]	OTf	50	0.75	2.0	79
10	CuOTf[d]	BF_4	50	0.75	2.0	65
11	CuOTf[d]	AsF_6	50	0.75	2.0	79
12	CuOTf[d]	SbF_6	50	0.75	2.0	74
13	**CuOTf[d]**	**OTf**	**50**	**1.0**	**2.0**	**82**
14[e]	CuOTf[d]	–	50	1.0	2.0	0
15[f]	CuOTf[d]	–	50	1.0	2.0	0

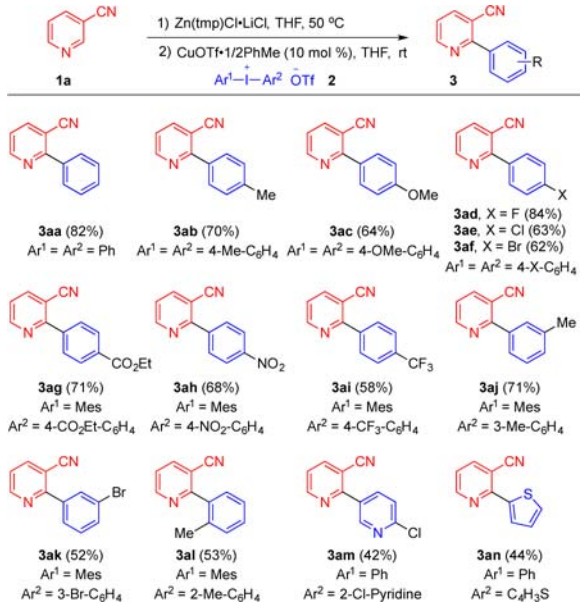
[a]Reactions conditions: **1a** (0.3 mmol), Zn(tmp)Cl·LiCl (0.6 mmol); then catalyst (0.03 mmol), THF (3 mL). [b]Deprotonation temperature and time. [c]Isolated yield. [d]CuOTf·1/2PhMe. [e]PhI was used instead of **2a**. [f]PhOTf was used instead of **2a**.

experience,[8] we chose Zn(tmp)Cl·LiCl as an effective base to promote selective H−Zn exchange for the formation of arylzinc intermediate. Upon the direct treatment of diphenyliodonium salt **2a,** desired product **3aa** was observed only in trace amounts (entry 1). To our delight, the formation of **3aa** was successful with the presence of a copper catalyst (entries 2−7). Among different copper salts, CuOTf·1/2PhMe was the most effective (entry 7). We next surveyed the conditions for generating the organozinc intermediate; elevated temperature resulted in a better yield of **3aa** (entry 8). Increasing the loading of **2a** improved the formation of **3aa** to 79% yield (entry 9). The use of other common counterions of iodonium salts such as BF_4, AsF_6, and SbF_6 did not give better results (entries 10−12). Finally, extending the deprotonation time further increased the formation of **3aa** to 82% yield, which was chosen as the standard reaction conditions (entry 13). When iodonium salt was replaced with either PhI or PhOTf under the optimized reaction conditions, no desired product **3aa** was observed (entries 14−15), indicating the superior reactivity of diphenyliodonium salt in this reaction.

With arylation conditions established, we examined the scope of iodonium salts in their reactions with **1a** (Scheme 2). Various substituents on the iodonium salts were found to be well tolerated. For example, desired products **3aa**−**3ai**, containing either an electron-donating group (Me, MeO) or an electron-withdrawing group (F, Cl, Br, COOEt, NO_2, CF_3) at the 4-position, all readily formed in 58−84% yields. Likewise, substituents at the C-2 and C-3 positions of iodonium aryl salts were also examined with desired products **3aj**−**3al** formed smoothly. In addition, heteroarene-derived iodonium salts, such as pyridine and thiophene, were also effective in the arylation reactions and formed **3am**−**3an** in moderate yields.

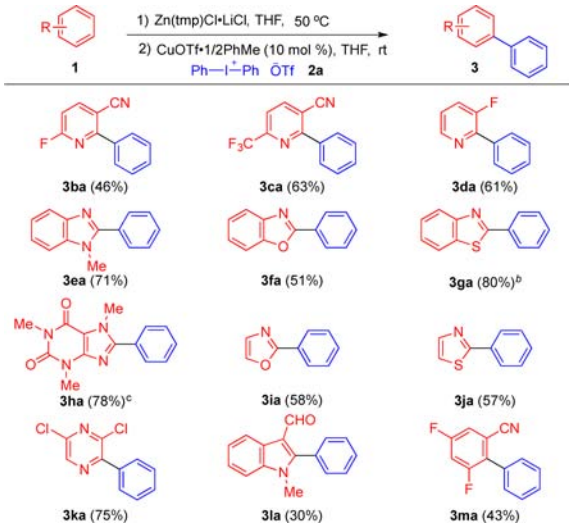
We also explored different electron-deficient hetereoarene and arene substrates using diphenyliodonium salt **2a** as the arylation reagent (Scheme 3). Similar to nicotinonitrile **1a**, 6-fluoronicotinonitrile and 6-trifluoromethylnicotinonitrile were

Scheme 2. Scope of Iodonium Salts[a]



[a]Reaction conditions: **1a** (0.3 mmol), Zn(tmp)Cl·LiCl (0.6 mmol), 50 °C, 1 h; **2** (0.6 mmol), CuOTf·1/2PhMe (0.03 mmol), 8 h.

Scheme 3. Scope of Electron-Deficient Hetereoarene and Arene Substrates[a]



[a]Reaction conditions: **1** (0.3 mmol), Zn(tmp)Cl·LiCl (0.6 mmol); **2a** (0.6 mmol), CuOTf·1/2PhMe (0.03 mmol), THF (3 mL). [b]Deprotonation step run at room temperature. [c]Reaction run in CH_2Cl_2 because of the poor solubility of caffeine in THF.

successfully arylated under standard conditions (**3ba** and **3ca**). 3-Fluoropyridine was also effective, providing the desired product **3da** in 61% yield. Besides pyridines, 1-methylbenzimidazole, benzoxazole, benzothizole, and caffeine all underwent arylation to afford **3ea**−**3ha**. Simple oxazole and thiazole also gave the desired products **3ia** and **3ja**. Finally, pyrazine, *N*-methyl-3-aldehydeindole, and even electron-poor benzo nitrile were examined and found to be effective substrates under standard conditions, affording biaryl compounds **3ka**, **3la**, and **3ma**, respectively. The high regioselectivity observed is presumably derived from the selective zinc metalation step.

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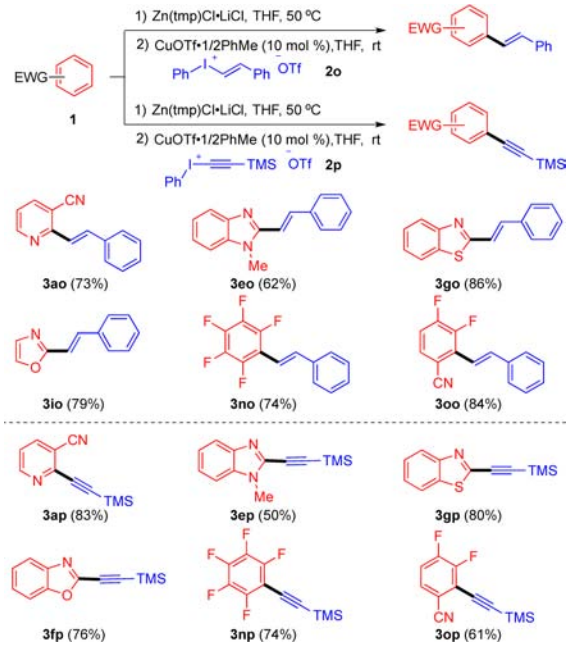
The broad scope of this reaction also demonstrates its superior functional group tolerance.

We next explored this approach for vinylation and alkynylation of arenes by using phenylvinyl and phenylalynyl iodoium salts (Scheme 4). Different heteroarenes including

Scheme 4. Vinylation and Alkynylation of Electron-Deficient Aromatic Substrates[a]

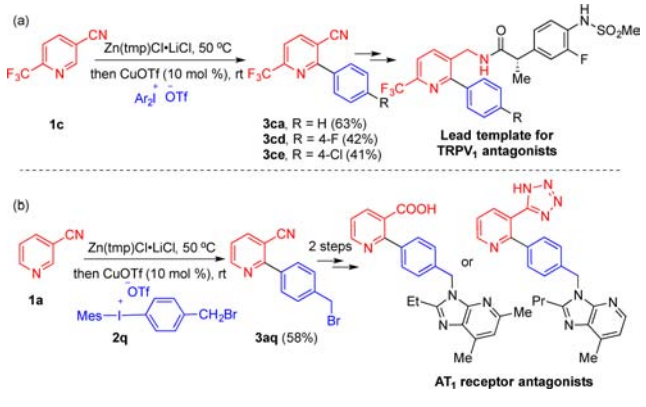


[a]Reaction conditions: **1** (0.3 mmol), Zn(tmp)Cl·LiCl (0.6 mmol), **2** (0.6 mmol), CuOTf·1/2PhMe (0.03 mmol), THF (3 mL).

nicotinonitrile, 1-methylbenzimidazole, benzothizole, and oxazole, when subjected to standard conditions with phenylvinyl iodoium salt **2o**, readily afforded *E*-alkenylated heteroarenes **3ao**−**3io** in good yields. Electron-deficient pentafluorobenzene and benzonitrile also effectively underwent vinylation and afforded products **3no** and **3oo** in good yields, respectively. Similarly, the alkynylation of different arenes were also achieved by the analogous reactions using phenylalynyl iodoium salt **2p**.

We next examined this simple arylation protocol in the synthesis of biaryl-containing compounds of valuable biological and pharmacological properties (Scheme 5). For example, key

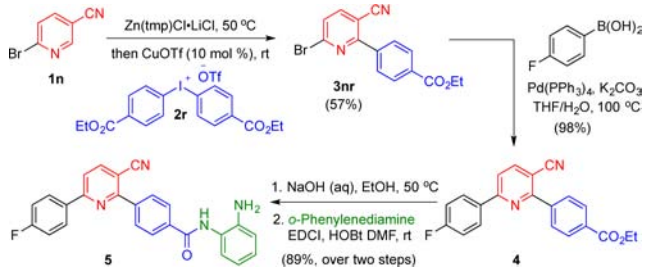
Scheme 5. Rapid Access to TRPV1 Antagonists and AT1 Receptor Antagonists



precursors of TRPV1 antagonists,[10] **3ca**, **3cd**, and **3ce**, were readily obtained using economical nicotinonitrile **1c** by this one-pot arylation protocol with iodonium salts under standard conditions. Biaryl **3aq**, a key intermediate of AT1 receptor antagonists,[11] was readily prepared from nicotinonitrile **1a** in one step (Scheme 5b).

We also applied this transformation for a rapid synthesis of compound **5**, which has inhibitory activity of histone deacetylases (HDAC) and antiproliferative effects on cancers[12] (Scheme 6). Starting from 6-bromonicotinonitrile **1n**, arylation

Scheme 6. Rapid Synthesis of HDAC Inhibitor



with iodonium salt **2r** afforded **3nr** in 57% yield. The subsequent Suzuki cross-coupling reaction provided diarylnicotinonitrile **4** in 98% yield. Hydrolysis of **4** followed by amidation with 1,2-diaminobenzene gave target molecule **5** in 89% yield over two steps. This synthesis also highlights the advantageous compatibility of copper-catalyzed arylation using iodonium salts with halides for further cross-coupling reactions, as a valuable strategy complementary to existing cross-coupling arylation reactions[2−4] to access biaryl compounds.

In conclusion, we have developed a general approach for arylation, vinylation, and alkynylation of electron-deficient (hetero)arenes by selective C−H deprotonative zincation followed by copper-catalyzed C−C coupling reactions with iodonium salts. This approach is valuable and useful for rapid synthesis of biologically significant biaryl compounds that are the core framework in natural products, pharmaceuticals, and functional materials. Our future work will extend such functionalization strategies to other C−H bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02550.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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