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Copper-Catalyzed Arylation of Benzylic C−H bonds with Alkylarenes as the Limiting Reagents

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Supporting Information

ABSTRACT: A novel copper-catalyzed arylation of benzylic C−H bonds with nucleophilic arylboronic acids has been developed that provides an efficient way to synthesize various 1,1-diarylalkanes with a broad substrate scope and excellent functional group compatibility. The reactions occur at room temperature using alkylarenes as the limiting reagents, which allows access to the arylation of the more valuable and complex bioactive compounds.

1,1-Diarylalkane scaffolds are prevalent in natural products and bioactive compounds.[1] Thus, many efforts have been put into the development of efficient synthetic approaches to these structures.[2] Among them, transition-metal-catalyzed cross-coupling of benzylic electrophiles or nucleophiles with aryl reagents has been demonstrated as one of the most popular methods to access 1,1-diarylalkanes.[3] In these methods, selective prefunctionalization of alkylarenes is required for the preparation of benzylic reagents. Direct arylation of benzylic C−H bonds of alkylarenes is more attractive, as it can significantly shorten synthetic sequences and reduce the cost and waste. However, the selective C−H bond functionalization is one of the most challenging projects in organic synthesis.[4]

Inspired by highly selective enzyme catalysis,[5] researchers have successfully applied various high-valent metal oxides to oxidation of sp^3 C−H bonds via hydrogen atom abstraction (HAA).[6] Functionalization of benzylic C−H bonds could potentially take advantage of this pathway, but so far only limited types of reactions have been documented, including oxygenation,[7] halogenation,[8] and amination reactions.[9] Recently, several groups independently reported elegant studies on the direct arylation of sp^3 C−H bonds with electrophilic aryl halides as aryl reagents using photoredox and nickel dual catalysis.[10] However, most reactions were only suitable for the sp^3 C−H bonds adjacent to a heteroatom,[10] and only a few examples worked with unactivated benzylic C−H bonds.[10b,c] So far, methods for direct arylation of sp^3 C−H bonds of alkylarenes are quite limited, and more complex alkylarenes are yet to be explored as target molecules. Importantly, in all of these reactions, a large excess of the alkylarenes was required as the sp^3 C−H source, or even as a solvent. These transformations are not suitable for the late-stage functionalization of valuable and complex substrates.[11] Thus, the development of an efficient catalytic arylation system using alkylarenes as the limiting reagent would be valuable.

Recently, with a radical relay process (Scheme 1a), our group developed a highly regio- and enantioselective cyanation of benzylic C−H bonds using a chiral bisoxazoline (Box)/Cu(I) catalyst (Scheme 1b).[12a] Notably, alkylarenes were used as the limiting reagents to provide various benzyl nitriles in high yields and excellent enantiomeric excess (ee). In this reaction, benzylic radicals generated via a HAA process could be rapidly trapped by a copper(II) cyanide complex to form an sp^3 C−CN bond efficiently (Scheme 1a).[12a,b] Meanwhile, during the study on the arylation of alkenes,[13] our group revealed that benzylic radicals, generated from the addition of CF_3 to styrenes, could react with an ArCu(II) complex to form new C−C bonds. We postulate that if the benzylic radical generated in the HAA process from alkylarenes could also be captured by an ArCu (II) species, then the arylation of benzylic C−H bonds would give 1,1-diarylalkanes as a highly step-economic approach. Herein, we report a highly efficient method for the arylation of benzylic C−H bonds. Notably, alkylarenes are used as limiting reagents which enable late-stage arylation of an array of more-complex molecules bearing benzylic C−H bonds (Scheme 1c).

Based on the above hypothesis, our initial studies focused on the enantioselective arylation of 1-ethylnaphthalene (**1a**) with $PhB(OH)_2$ (**2a**) as the arylation reagent. As shown in Table 1, when the previous NFSI/Box-**L1**/Cu(I) catalytic system was employed in pure benzene,[12a] to our disappointment, the reaction failed to deliver the desired arylation product **3a**, and very low conversion of **1a** was observed (entry 1). The solvent mixture of dichloromethane (DCM) and *N*,*N*-dimethylacetamide (DMA), which was crucial in previous arylation of styrenes,[13b] was tested. Interestingly, a small amount of product

Scheme 1. Radical Relay Process for the Benzylic C−H Bond Functionalizations

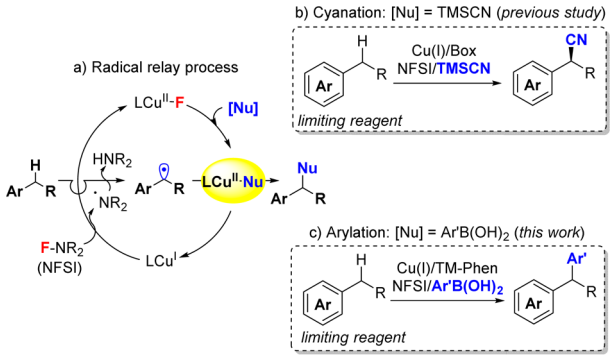

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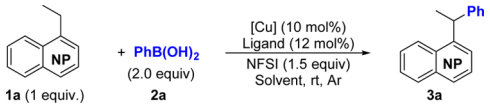
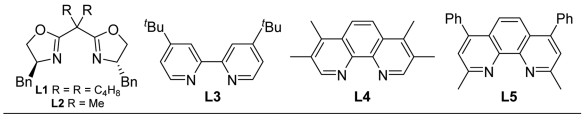
Table 1. Optimization of the Reaction Conditions[a,b]

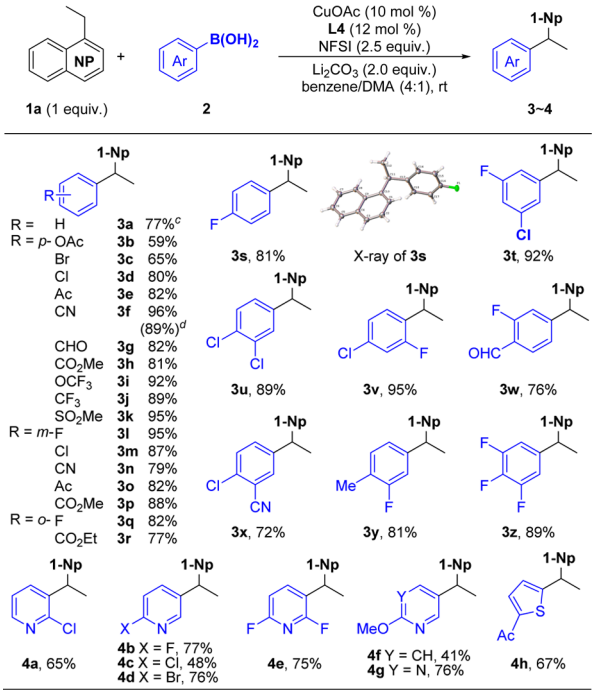


Entry	[Cu]	Ligand	Solvent	1a Conv.	3a Yield
1	$Cu(MeCN)_4PF_6$	L1	benezene (BEN)	10%	0
2	$Cu(MeCN)_4PF_6$	L1	DCM/DMA (4:1)	33%	5%[i]
3	$Cu(MeCN)_4PF_6$	L2	DCM/DMA (4:1)	12%	9%[i]
4	$Cu(OTf)_2$	L2	DCM/DMA (4:1)	23%	10%[i]
5	$Cu(OTf)_2$	L2	BEN/DMA (4:1)	31%	11%[i]
6[c]	$Cu(OTf)_2$	L2	BEN/DMA (4:1)	0	0
7[d]	$Cu(OTf)_2$	L2	BEN/DMA (4:1)	<5%	0
8	$Cu(OTf)_2$	L3	BEN/DMA (4:1)	18%	5%
9	$Cu(OTf)_2$	L4	BEN/DMA (4:1)	16%	14%
10	$Cu(OTf)_2$	L5	BEN/DMA (4:1)	22%	0
11[e]	$Cu(OTf)_2$	L4	BEN/DMA (4:1)	50%	43%
12[e]	CuOAc	L4	BEN/DMA (4:1)	46%	44%
13[e,f]	CuOAc	L4	BEN/DMA (4:1)	66%	57%
14[f,g]	CuOAc	L4	BEN/DMA (4:1)	75%	74%
15[f,g,h]	CuOAc	L4	BEN/DMA (4:1)	95%	81%



[a]Reactions were conducted on a 0.1 mmol scale. [b]Conversion (**1a**) and yield (**3a**) were determined by ^{1}H NMR spectroscopy with $MeNO_2$ as an internal standard. [c]**2a** was replaced by $PhBF_3K$ or PhBPin. [d]Oxidant NFSI was replaced by $PhC(O)O_2Bu^t$, $(^tBuO)_2$, or $K_2S_2O_8$. [e]Reaction was carried with Li_2CO_3 (1.5 equiv). [f]NFSI (2.5 equiv). [g]Li_2CO_3 (2.0 equiv). [h]Extra NFSI (1.25 equiv) and **2a** (1.0 equiv) were added to the mixture after 2 h. [i]Less than 5% ee was obtained in entries 2−5.

Table 2. Substrate Scope of Boronic Acids[a,b]



[a]Reactions were conducted on 0.2 mmol scale with the reaction condition of entry 14 in Table 1. [b]Isolated yield. [c]Reaction condition of entry 15 in Table 1. [d]**3f** (1.38 g) was obtained in 6.0 mmol scale.

3a could be detected (entry 2). Replacement of chiral ligand **L1** by **L2** could slightly increase the yield (from 5% to 9%, entry 3). Further screening of Cu catalysts and solvents showed that it is hard to improve the yield significantly (entries 4 and 5). Moreover, other oxidants (such as $PhCO_3{}^tBu$, $^tBuOO^tBu$, and $K_2S_2O_8$) and arylboronic reagents ($PhBF_3K$, PhBpin, and PhBneop) were ineffective (entries 6 and 7).[14] Owing to the low efficiency of Box/Cu(I), we turned our attention to other nitrogen-containing ligands. We were delighted to find out that phenanthroline-type ligand **L4** provided better reactivity (14%); sterically bulkier ligand **L5** inhibited the reaction (entries 8−10). In our previous report on the arylation of styrenes, transmetalation to form ArCu(II) was the rate-determining step.[13a] We reasoned that addition of extraneous base might be helpful. Excitingly, Li_2CO_3 proved to be a good base, and the yield was significantly increased to 43−44% (entries 11 and 12).[14] Increasing the amount of NFSI and base could further improve the yield to 74% (entries 13 and 14).[15] Owing to the excellent mass balance, addition of extra portions of NFSI and **2a** increased the yield to 81% (entry 15).

With the optimized conditions in hand, we examined the substrate scope of arylboronic acids. As shown in Table 2, a range of arylboronic acids were suitable for this reaction. The reactions of other arylboronic acids besides **2a** proceeded smoothly without extra addition of NFSI/$ArB(OH)_2$. Various 1,1-diarylalkanes (**3a**−**3z**) were formed in good to excellent yields. Notably, the reaction exhibited excellent functional group compatibility. Arylboronic acids bearing ester, halides, ketone, cyano, aldehyde, trifluoromethyl, and sulfonyl groups survived the standard conditions. Importantly, heteroarylboronic acids, such as pyridine, pyrimidine, and thiophene, were good candidates to deliver arylation products (**4a**−**4h**) in satisfactory yields (41−77%). Unfortunately, the electron-rich arylboronic acids exhibited poor reactivity toward C−H arylation reaction.[16]

Encouraged by the results above, we next surveyed the substrate scope of alkylarenes (Table 3). Simple 1-alkylnaphthylenes proved to be good substrates to afford the corresponding arylation products **5a**−**5f** in good yields (54−75%). Meanwhile, 1-alkylnaphthylenes bearing various functional groups (azide, ester, ether, imide, halides) on both alkyl chain (**5g**−**5m**) and aryl ring (**5n**−**5p**) were suitable to give desired products in good yields. It was noteworthy that the reaction of **5g**−**5j** occurred only at benzylic C−H bonds, and the C−H bonds adjacent to heteroatoms were untouched. Moreover, the tolerance of aryl halide (**5o**) allows for further transformation. 2-Alkylnaphthylenes were also compatible with the standard conditions to deliver arylation products **5q** and **5r** in satisfactory yields. In the case of 2,6-diethylnaphthylene, the reaction provided both monoarylation product **5s** (43% yield) and diarylation product **5s′** (19% yield). Furthermore, direct arylation of acenaphthene gave **5t** in 60% yield, which took six steps to make in the literature.[17] Furthermore, 1,2- and 1,1-diarylalkanes were investigated, and the arylation reaction proceeded very well to give products **5u**−**5x**. Again, this arylation process is much more favorable at the sp^3 C−H bond adjacent to naphthalene relative to benzene (**5u**, **5x**).

We then shifted our attention to the reaction of alkylbenzenes. Unfortunately, the simple alkylbenzenes exhibited poor reactivity (generally <30%). However, conjugated biphenyl alkylarenes (**6a**−**6d**) and diphenyl ether (**6e**) were effective toward arylation to give products in good yields (50−83%). It was noteworthy that valuable and more-complex substrates were also suitable for this transformation to achieve late-stage arylation reactions, which are extremely useful for enriching a complex molecule library. For instance, the reactions of 2-ethylfluorene (**6f**, **6g**) occurred at the benzylic C2 position with a high regioselectivity.

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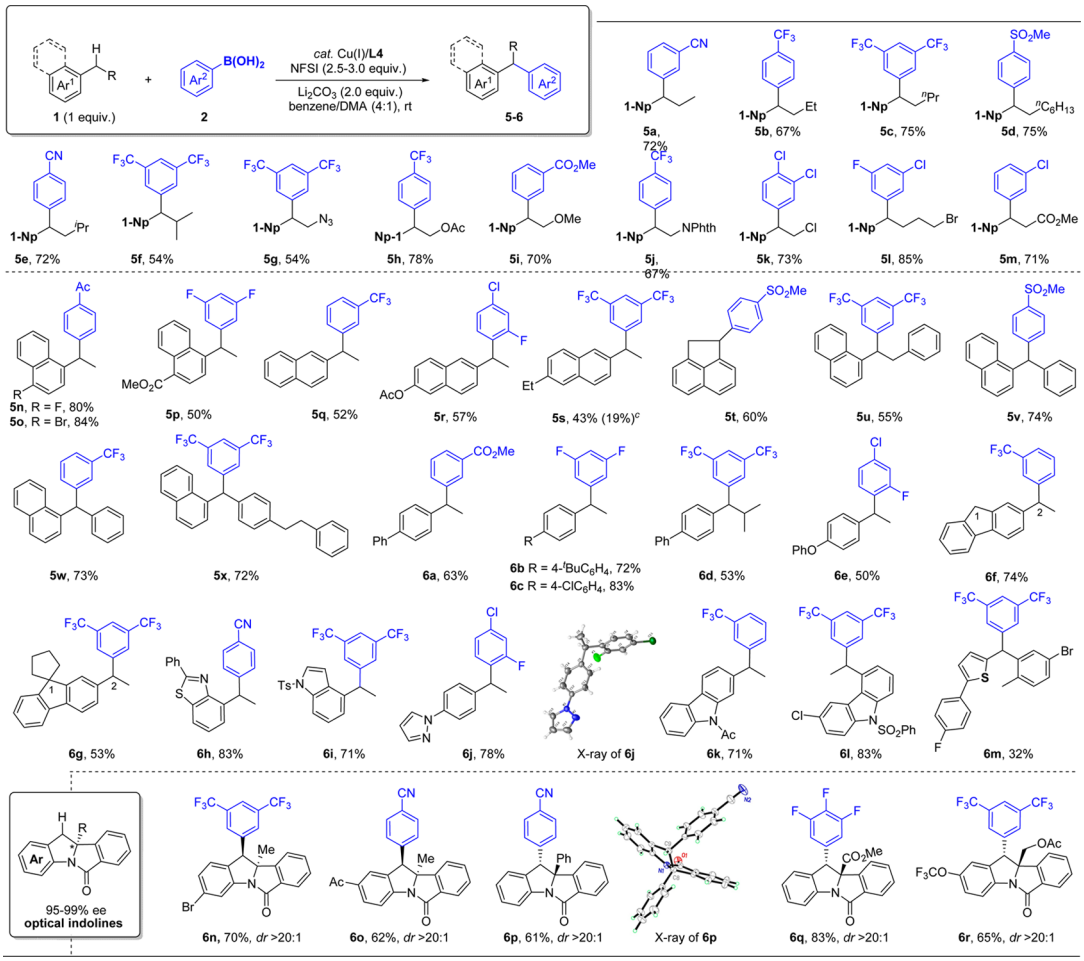
Table 3. Substrate Scope of Alkylarenes[a,b]

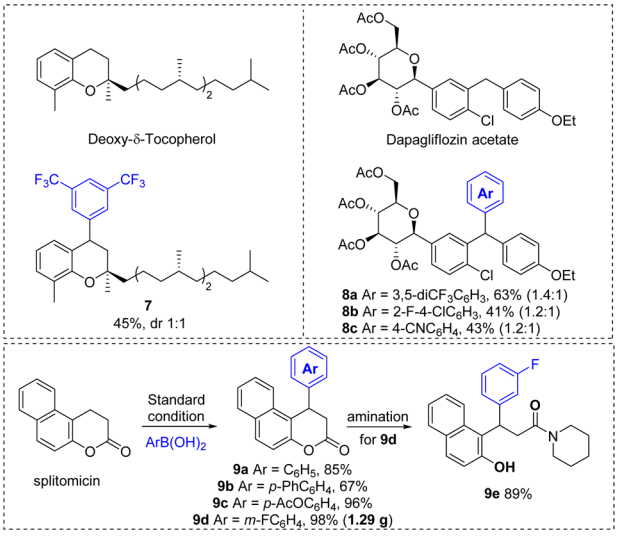


[a]All reactions were conducted on 0.2 mmol scale in benzene/DMA (4/1). [b]Isolated yield. [c]Yield in parentheses is that of the bis-arylation product.

Heteroarenes such as benzothiazole (**6h**), indole (**6i**), pyrazole (**6j**), and carbazole (**6k**, **6l**) were good substrates for the reaction to deliver a variety of arylated heteroarenes in good yields. Excitingly, thiophene substrates, a valuable synthon for Canagliflozin, could be easily arylated to give product **6m** in 32% yield in one step. Finally, a series of optically pure indolines (95−99% ee) with a quaternary stereogenic centers were successfully arylated with high diastereoselectivities to provide various enantiomerically pure products **6n**−**6r** in good yields (61−83%). The structures of **6j** and **6p** were characterized by X-ray analyses.

Finally, the late-stage arylation of bioactive compounds was investigated. As shown in Scheme 2, deoxy-δ-tocopherol, a derivative from δ-tocopherol, as a type of Vitamin E, can be selectively arylated at the benzylic C−H bonds to give product **7** in 45% yield (dr 1:1). Dapagliflozin acetate is derived from Dapagliflozin, an approved drug for use as an inhibitor of SGLT2.[18] Dapagliflozin acetate can be easily arylated with various arylboronic acids to give products **8a**−**8c** in moderate yields. Upon hydrolysis, the products are valuable in drug discovery. Moreover, as an inhibitor of Sir2p,[19] Splitomicin can be arylated efficiently to give products **9a**−**9d** in good yields. Compound **9a**, named as NSC-17364, is an inhibitor of sirtuin.[20] Meanwhile, product **9d** can be obtained in 98% yield in gram scale and can be smoothly converted to compound **9e** in 89% yield via an aminolysis step, which has the potential for bioactivity as a ROR-γ modulator.[21]

Scheme 2. Late-Stage Arylation of Bioactive Compounds



In conclusion, we have developed a Cu-catalyzed arylation of benzylic C−H bonds via a radical relay process. In this reaction, alkylarenes were used as limiting reagents to provide various 1,1-diarylalkanes efficiently. A broad substrate scope of alkylarenes

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and arylboronic acids and excellent functional group compatibilities make this method an ideal tool to achieve late-stage arylation of bioactive compounds. Further mechanism investigations of the mechanism and asymmetric reaction are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03781.

Syntheses, characterization, and additional data (PDF)
X-ray crystallographic data for 3s (CCDC 1549166), 6j (CCDC 1549168), and 6p (CCDC 1549169) (CIF)

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Notes

The authors declare no competing financial interest.

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(14) For more details, see the Supporting Information.

(15) With the optimized reaction conditions, the Box ligand still exhibited poor reactivity toward arylation of **1a** (<30% yield).

(16) The reactions of p-$RC_6H_4B(OH)_2$ provided the desired products in 30% (R = Me), 22% (R = ^{t}Bu), and <5% yield (R = OMe).

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