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Benzylic C−H Azidation Using the Zhdankin Reagent and a Copper Photoredox Catalyst

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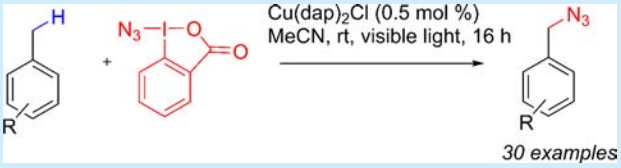
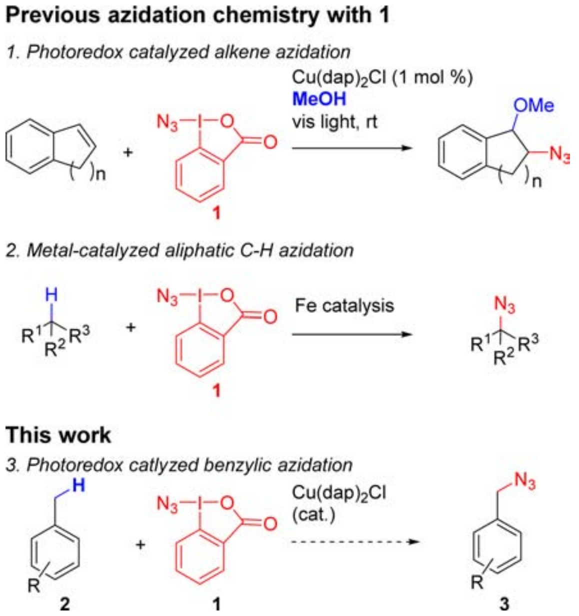
Ⓢ *Supporting Information*

ABSTRACT: An azidation method for C−N bond formation at benzylic C−H positions is described using copper-catalyzed visible light photochemistry and the Zhdankin azidoiodinane reagent. The method is applicable to a wide range of substrates bearing different functional groups and having a primary, secondary, or tertiary benzylic position, and is thought to proceed through a radical chain reaction.



The use of copper complexes in visible light photocatalysis (PRC) is a growing area of research, driven in part by the huge cost differential between copper and commonly used photoredox catalysts based on iridium and ruthenium Noble metals.[1,2] We have recently developed photoredox-catalyzed azidation chemistry using the Zhdankin azidoiodinane reagent[3] (**1**) and the Sauvage catalyst $Cu(dap)_2Cl$ (dap = 2,9-bis(*p*-anisyl)-1,10-phenanthroline),[4] which reacted smoothly with alkenes in alcohol solvents to give a range of alkoxy-azidated products (Scheme 1).[5] The compatibility of this versatile azidation reagent with copper PRC, under mild conditions, motivated us to investigate new C−N bond forming applications.

Scheme 1. Proposed Benzylic C−H Azidation



The Zhdankin reagent is increasingly being used as a versatile azidation reagent, with recent reports describing C−N bond formation at aliphatic tertiary and secondary C−H positions[6] (iron and ruthenium catalysis),[7] arenes (copper catalysis),[8] β-keto esters,[9] aldehydes (iodide catalysis),[10] and alkenes.[5,11,12] We chose to investigate **1** in benzylic C−H azidation, as classic approaches to this useful motif, starting from C−H groups, use nucleophilic azide and strong oxidizing agents, and are necessarily restricted to electron rich substrates.[13] More recent work on direct C−H azidation has featured a small number of benzylic azidations but is restricted to electron-rich secondary and tertiary substrates.[7,12b] We wondered if a combination of the Zhdankin reagent (an electrophilic azide source) and copper photoredox catalysis could deliver benzylic azides **5** across a wider range of substrates, particularly in the more challenging primary series.

We began by screening simple toluene derivatives and were pleased to obtain an encouraging result with *para*-xylene, obtaining an 80% yield of the azidated product **3a** using one equivalent of **1** and $Cu(dap)_2Cl$ (1 mol %) in a mixture of acetonitrile and *para*-xylene (1:1) (Table 1). The reaction was completely selective for the benzylic position, an important distinction, as arene azidation has been reported for toluidine substrates using the Zhdankin regent under copper catalysis.[8] Further investigation established that both $Cu(dap)_2Cl$ and visible light were required for efficient reaction, with common photoredox catalysts such as $Ru(bpy)_3Cl_2$ (entry 2) and $Ir(ppy)_3$ (entry 3) being ineffective. The simple copper salt CuBr, however, did give reasonable conversions (entry 4). Low levels of background reaction were noted in the absence of catalyst but presence of light, and absence of light but presence of $Cu(dap)_2Cl$ (entries 5 and 7). No catalyst and no light produced no reaction (entry 6). Reducing the stoichiometry of the starting *p*-xylene **2** gave a corresponding reduction in yields (entry 8),

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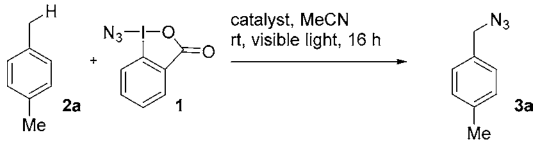
Table 1. Reaction Optimization[a]



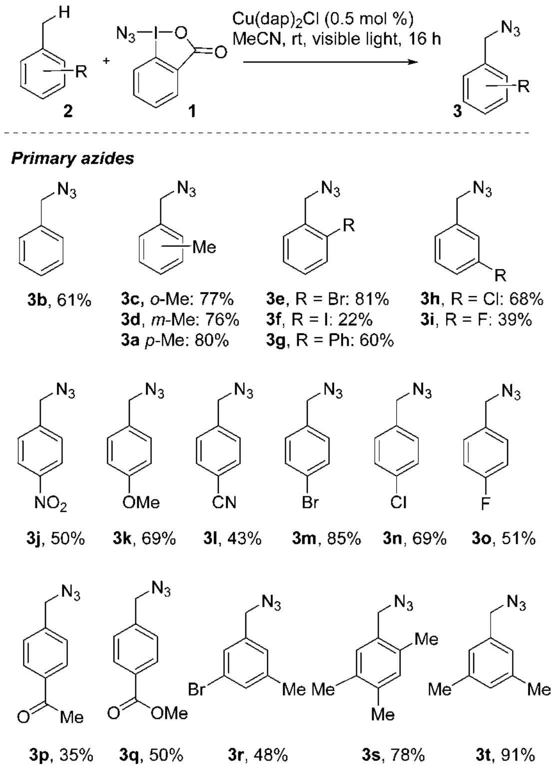
entry	catalyst	notes	yield (%)[b]
1	Cu(dap)$_2$Cl (0.5 mol %)		80
2	Ru(bpy)$_3$Cl$_2$ (1 mol %)		0
3	Ir(ppy)$_3$ (1 mol %)		0
4	CuBr (0.5 mol %)		55
5	Cu(dap)$_2$Cl (0.5 mol %)	dark	29
6	none	dark	0
7	none	light	17
8	Cu(dap)$_2$Cl (0.5 mol %)	5 equiv of xylene	39

[a] Reaction conditions: Catalyst, 1-azido-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (1.0 equiv, 0.50 mmol) and degassed MeCN/*para*-xylene (5 mL, 1:1) irradiated with a 30 W fluorescent bulb (1 cm distance) for 16 h. [b] Isolated yields.

with 5 equiv giving 39% of the azide **3a**. We could, however, recover the unreacted C—H component in each case.

Investigation of the reaction scope (Scheme 2) established a broad reactivity profile, encompassing halogenated (*para* and *meta*-Cl, *para*-, *meta*-, and *ortho*-Br, *para*- and *meta*-F, and *para*-I), electron rich (*para*-OMe, *para*-Me, and *ortho*-Ph) and even some electron poor (*para*-NO$_2$, -CN, -CO$_2$Me, and -COMe) toluenes (Scheme 2). Yields were generally good to excellent for electron-rich, brominated and chlorinated substrates, with electron-poor toluenes reacting in moderate yield. Direct azidation of this latter category of deactivated substrates, however, has rarely been reported in the literature.[13b] Substitution on each of the ortho, meta, and para positions was probed for xylene isomers, with successful azidation being observed in each case (**3a**, **3c**, and **3d**), with mesitylene and durene being similarly productive (**3s** and **3t**).

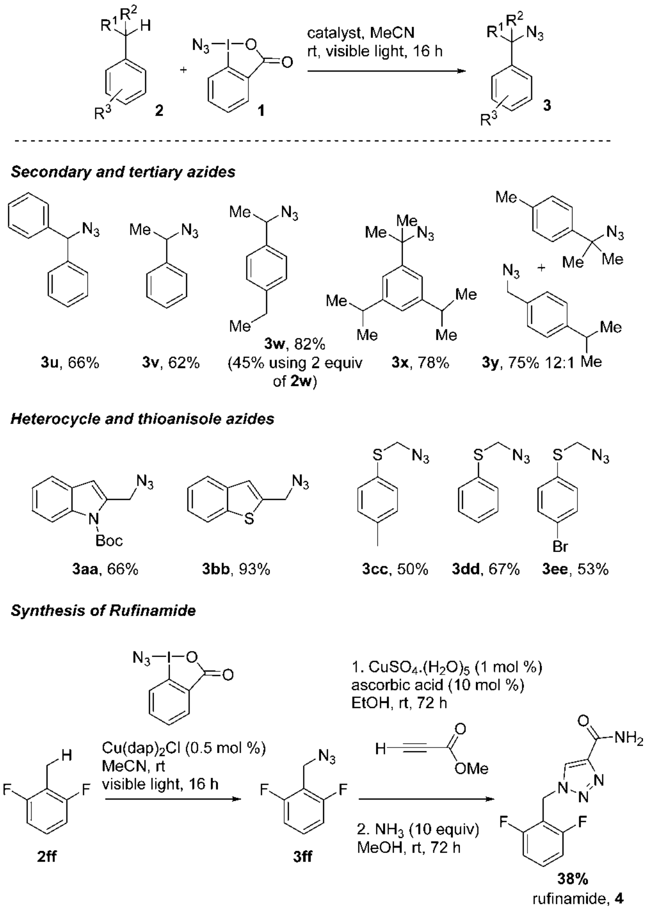
Scheme 2. Primary Azide Substrate Scope[a,b]



[a] General conditions for azidation: Cu(dap)Cl$_2$ (0.5 mol %), 1-azido-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**1**, 1.0 equiv, 0.50 mmol), degassed MeCN/substrate **2** (5 mL, 1:1) irradiated with a 30 W fluorescent bulb (1 cm distance) for 16 h. [b] Isolated yields.

Following those positive results with primary substrates, we explored the possibility of substitution at secondary and tertiary benzylic positions and were pleased to find smooth transformation of diphenylmethane (**3u**), ethylbenzene (**3v**), 1,4-diethylbenzene (**3w**), and tri-isopropylbenzene (**3x**) in good yield (Scheme 3).

Scheme 3. Secondary and Tertiary Azide Synthesis[a,b]



[a] General conditions for azidation: Cu(dap)Cl$_2$ (0.5 mol %), 1-azido-1λ_3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**1**, 1.0 equiv, 0.50 mmol), degassed MeCN/substrate **2** (5 mL, 1:1) irradiated with a 30 W fluorescent bulb (1 cm distance) for 16 h. [b] Isolated yields.

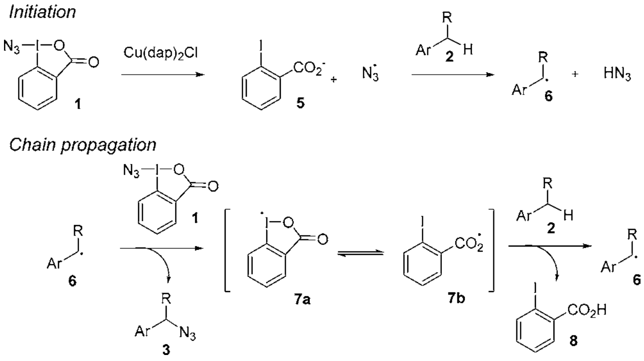
Lowering the stoichiometry to two equivalents, in the case of 1,4-diethylbenzene, gave a 45% yield of the azide **3w**. Cymene azidation was selective for the tertiary azide over the primary, in line with expectations of a radical mechanism and cleavage of the weaker tertiary C—H bond (*vide infra*). Finally, we examined some heterobenzylic substrates and could successfully synthesize the indole (**3aa**) and benzothiophene (**3bb**) azides in good to excellent yield, respectively.

In the course of substrate screening we uncovered some anomalous behavior for the *p*-thiomethoxytoluene **2cc**. In contrast to the *p*-methoxy analogue (**2k**), the major product **3cc** occurred from azidation at the SMe group (50%), with only 10% azidation taking place at the tolyl position. The radical-stabilizing effect of sulfur was exemplified through azidation of thioanisole **3dd** and *p*-bromo-thioanisole **3ee**, compounds previously prepared by Pummerer-type chlorination and azide addition. The N_3CH_2SAr moiety has been reported as a synthon for NH_2^+, reacting with aryl Grignard reagents to give anilines after hydrolysis.[14]

We could apply the direct azidation methodology in the synthesis of a drug, rufinamide (**4**), an antiepileptic medication from Novartis. Previous routes utilize benzylic halogenation and displacement with sodium azide, both at elevated temperatures.[15] Here, we could effect direct benzylic azidation of 1,3-difluorotoluene **2ff** under benign conditions to give the azide **3ff** in 38% yield, which underwent Cu-catalyzed 1,3-dipolar addition and aminolysis in quantitative yield to afford rufinamide **4**, without recourse to halogenation reagents or sodium azide in the synthetic sequence.

Radical chain reactions have been implicated in C−H azidation reactions of **1** since Zhdankin's initial work on the reagent, initiated by homolysis of the weak I−N bond.[3,7b,10,16] Here, it is likely that electron transfer from the photoexcited $Cu(dap)_2^+$ reductively cleaves **1** to generate a source of azide radicals, which can then abstract a benzylic hydrogen atom from substrate **2**. The reaction is then propagated through benzyl radical **6** abstracting azide from **1**, generating the chain-carrying iodane radical **7**, which can abstract a hydrogen atom from benzylic substrate **2** (Scheme 4). Control reactions with radical quenchers TEMPO and BHT were found to suppress the reaction, consistent with the proposed radical chain process.

Scheme 4. Proposed Mechanism



To conclude, we have described a direct azidation of benzylic C−H positions that occurs at room temperature, under mild conditions, using an earth-abundant first row transition metal photoredox catalyst. The scope of the reaction is broad and tolerant of many functional groups, encompassing primary, secondary, and tertiary benzylic positions, and a formal azido-Pummerer pathway has been identified for thioanisole derivatives. Further photoredox-catalyzed azidation transformations are being investigated in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00512.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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