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Photoredox catalyzed C(sp^3)—C(sp) coupling of dihydropyridines and alkynylbenziodoxolones

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ABSTRACT

A visible light mediated deformylative alkynylation of aldehydes is presented. Under photo irradiation, 1,4-dihydropyridine (DHP), derived from an aldehyde, generated a C(sp^3)- radical which couples with an alkynylbenziodoxolone to generate an alkyl substituted alkyne coupling product. This strategy is mild and easy to operate, a wide range of functional groups were tolerated, and 16 examples of products with 35–86% yields were obtained.

Introduction

Carbon-carbon bond formation has long remained at the center stage of organic chemistry method development [1–3]. Despite the advances accumulated via transition metal catalysis, certain cross couplings reactions are still challenging [4]. The use of nickel/photoredox and other dual catalysis have allowed a number of such methodologies to be developed [5–9]. However, circumventing the need for an extra catalyst makes these methodologies more synthetically appealing. Strategies that do not require dual catalysis were employed for the alkynylation of alkyl radicals generated from potassium trifluoroborates [10], *N*-phthalimidoyl oxalates [11], *N*-acyloxyphthalimides [10], iodides [12,13], carboxylate ions [14–17], pyridinium ions [18], C—C bonds [19–23], C—H bonds [24–28], and alkene capture of other radicals [29,30]. However these reactions generally require the use of additional oxidants, bases, radical initiators, or co-solvents. We reasoned that the use of alkynylbenziodoxolones and dihydropyridines (DHPs) as a mild radical source [31–48], would allow for simpler, more amenable, reaction conditions (Scheme 1).

While the present work was being carried out, a similar strategy for the coupling of DHPs and alkynylbenziodoxolones was reported (Scheme 1) [23]. This strategy requires moderate heating and a binary solvent mixture (MeCN/H_2O). Moreover, stoichiometric amounts of $K_2S_2O_8$ were employed as radical initiator (Scheme 1) [23].

Herein we report on an alternative photoredox catalyzed C(sp^3)—C(sp) coupling of DHPs and alkynylbenziodoxolones. The reaction is redox neutral and can be carried out at room temperature in plain acetonitrile; also, it does not require any additional radical initiator, which renders this protocol more practical and straightforward.

We started our investigation with the C(sp^3)—C(sp) bond formation of **5a** and Ph-EBX (Table 1). To our delight, the use of 1 mol% Ir(ppy)$_3$ in acetonitrile led to 95% yield of the desired product **1aa** (entry 1). Addition of Cs_2CO_3 to this reaction had a detrimental effect, lowering the yield to 51% (entry 2). Catalyst screening revealed that the reaction could be carried out in moderate to high yields with most common photoredox catalysts (51–75%) but optimal yields are achieved with Ir(ppy)$_3$ (entry 1 and entries 3–7). Similarly, solvent screening did not lead to any improvement (entries 8 and 9). Removal of either photocatalyst or light led to low yields (3% and 5% yields respectively; entries 10 and 11). Moreover, in accordance with a radical mechanism, the reaction showed itself sensible to the presence of oxygen, thus when it was carried out under air atmosphere the yield dropped to 15% (entry 12).

The alkynylation of DHP **5a** could be performed with both electron rich and electron poor ethynylbenziodoxazolones. Substrates containing fluoride, chloride, trifluoromethoxy ethers, nitriles and ketones underwent C(sp^3)—C(sp) bond formation in yields ranging from 66 to 82% (Table 2).

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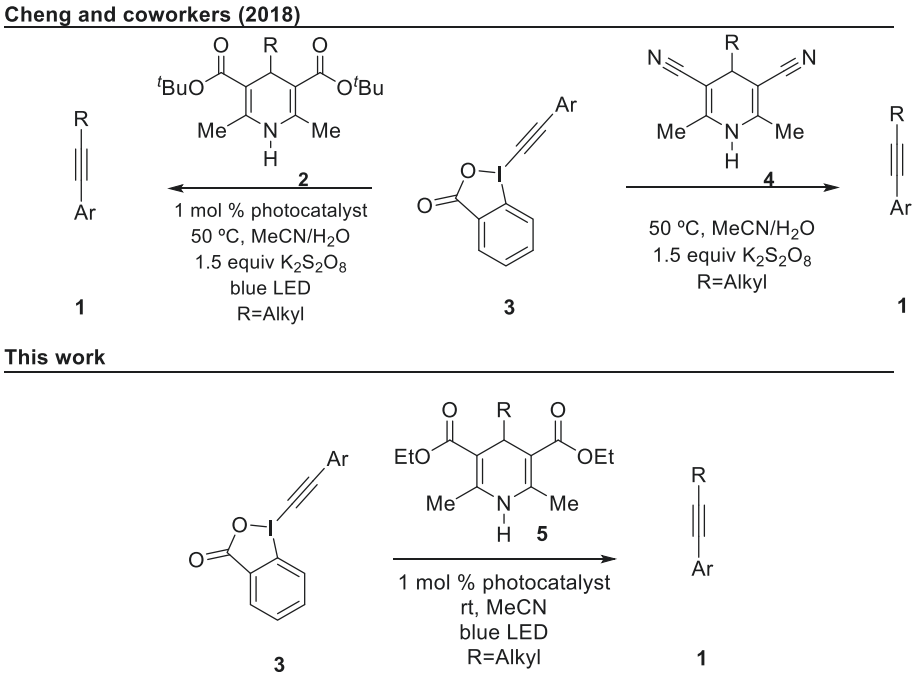


Scheme 1. Photoredox alkynylation of alkyl radicals.

Table 1
Reaction optimization for C(sp^3)—C(sp) coupling.

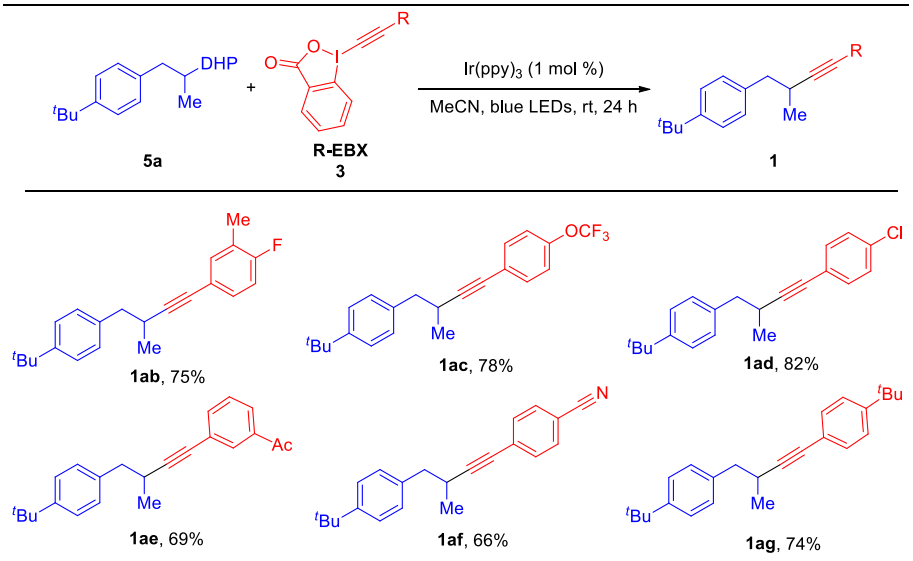
Entry	Photo-catalyst (1 mol %)	Modification	Solvent	Result (%)
1	$Ir(ppy)_3$	–	MeCN	95
2	$Ir(ppy)_3$	Cs_2CO_3 (1.5 eq)[a]	MeCN	51
3	$Ru(bpy)_3Cl_2$	–	MeCN	57
4	Catalyst 1[b]	–	MeCN	51
5	4CzIPN	–	MeCN	75
6	Catalyst 2[c]	–	MeCN	72
7	Eosin Y	–	MeCN	63
8	$Ir(ppy)_3$	–	DMF	0
9	$Ir(ppy)_3$	–	DCM	78
10	–	–	MeCN	3
11	$Ir(ppy)_3$	no LED[d]	MeCN	5
12	$Ir(ppy)_3$	presence of O_2[e]	MeCN	15

[a] 1.5 equivalents of Cs_2CO_3 added as a base to the reaction conditions.
[b] 9-Mesityl-10-methylacridinium.
[c] $Ir[dF(CF_3)ppy]_2(dtbpy)_3$.
[d] No LED or any source of light.
[e] Under air atmosphere.

Substrate compatibility was also evaluated for the DHPs. Free alcohols and Boc protected amines were well tolerated (61 and 85% yield for **1ca** and **1ba** respectively; Table 3). Substrates containing thiophene, indole, thiazole, succinimide and benzofuranone moieties delivered the corresponding C(sp^3)—C(sp) bond formation products in moderate yields (35–47% yield; **1ia**, **1fa**, **1ha**, **1ga** and **1ja**). On the other hand, compounds containing simpler alkyl or aryl substituents led to higher yields (73–86% yield; **1da**, **1ea** and **1aa**; Table 3).

A plausible reaction mechanism for this transformation is provided in Scheme 2. The reaction inhibition by O_2 is indicative of a radical mechanism while the poor results obtained in absence of light suggest the involvement of a photoredox catalytic cycle. As described by Melchiorre and coworkers, dihydropyridines **5** can cleave homolytically under photoirradiation with violet light generating the corresponding alkyl radicals [44]. We believe such a process could be sufficiently present in our system to initiate the catalytic cycle by allowing the formation of catalytic amounts of

Table 2
Scope of ethynylbenziodoxoles.



Reaction conditions: DHP **1** (0.1 mmol), ethynylbenziodoxole **3** (0.15 mmol) and $Ir(ppy)_3$ (1 mol %) MeCN (500μL), rt, 24 h.

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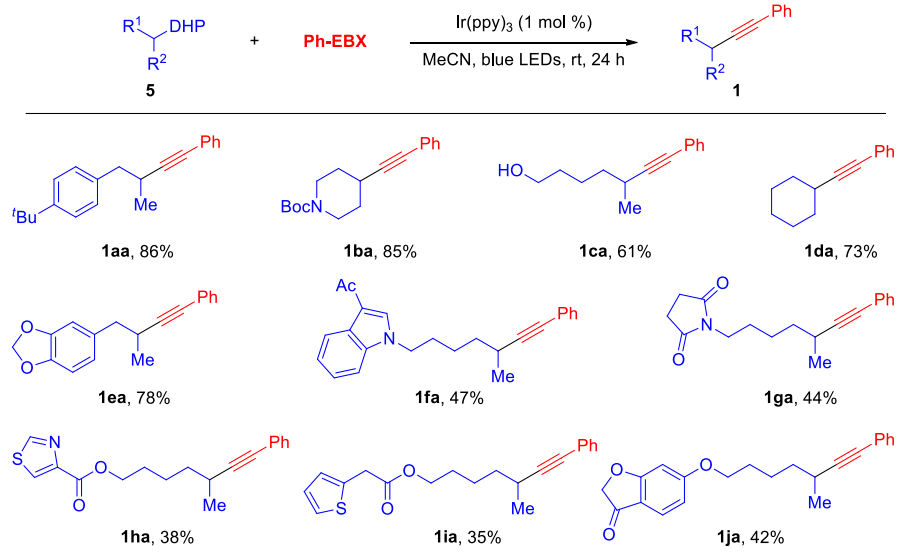
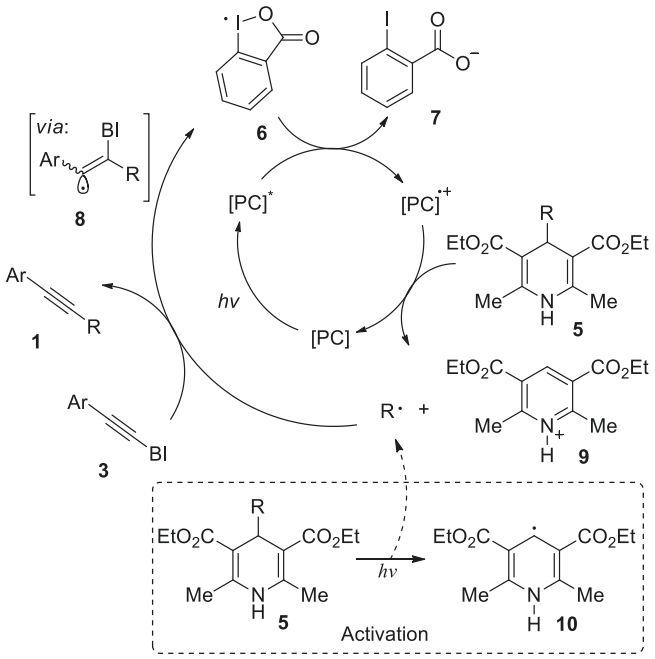
Table 3
Scope of dihydropyridines.



Reaction conditions: DHP **5** (0.1 mmol), ethynylbenziodoxole PhEBX (0.15 mmol) and $Ir(ppy)_3$ (1 mol %) MeCN (500μL), rt, 24 h.

Reaction conditions: DHP **5** (0.1 mmol), ethynylbenziodoxole PhEBX (0.15 mmol) and $Ir(ppy)_3$ (1 mol %) MeCN (500 μL), rt, 24 h.

the iodoradical **6** (after trapping of the alkyl radical by ethynylbenziodoxoles) [23]. After this initiation, the catalytic cycle would could kept going via oxidative quenching of the photocatalyst exited state by the iodoradical **6**, generating compound **7** and the oxidized form of the photocatalyst. The latter could oxidize the DHPs **5** generating compound **9** and alkyl radical that would restart the cycle.



Scheme 2. Plausible reaction mechanism.

Conclusion

In summary we report on a room temperature, photoredox catalyzed, reaction that we anticipate will, thanks to its simplicity, find use on C(sp^3)—C(sp) bond forming. The procedure does not require any additional catalyst, radical initiator or co-solvent. Since the DHPs can be readily prepared from the corresponding aldehydes, the procedure achieves formal deformylative C—C bond formation. The functional group tolerance was illustrated with substrates with diverse reactivity.

Experimental

General procedure for synthesis of alkyne coupling product **1**: DHP **5** (0.1 mmol), ethynylbenziodoxole **3** (0.15 mmol) and Ir $(ppy)_3$ (0.8 mg, 1 mol %) were added to an oven-dried vial equipped with a PTFE-coated magnetic stir bar. Then the vial was capped and purged with three cycles of vacuum/argon. Subsequently, degassed solvent MeCN (500 μL) was added through syringe under argon atmosphere. The reaction mixture was vigorously stirred for 24 h at rt under irradiation of blue LEDs. Then the vial was removed from the light source and the solid was filtered off. The filtrate was concentrated under reduced pressure and the crude product residue was purified by either flash column chromatography on silica gel or preparative TLC to give **1**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151230.

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