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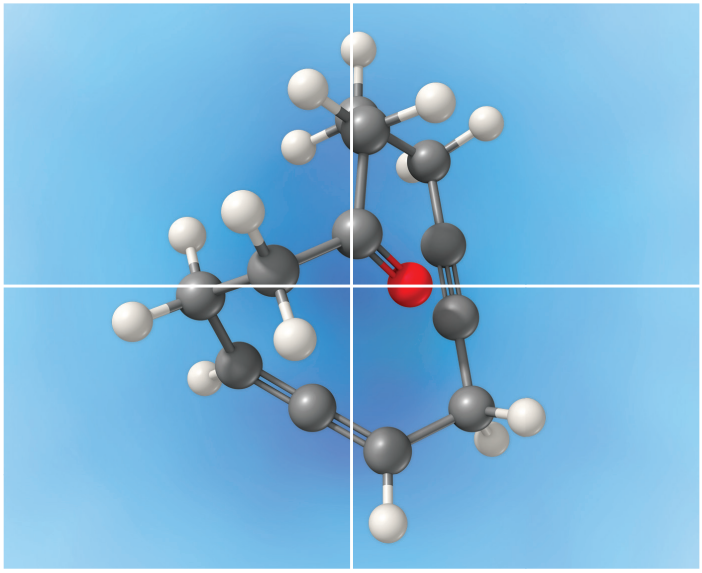

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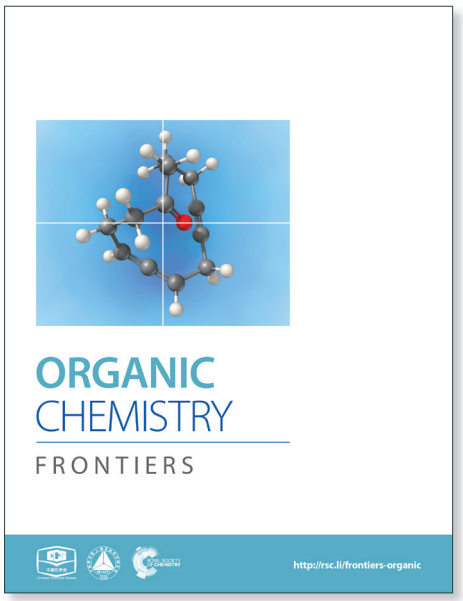

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ARTICLE

Formal Base-Free Homolytic Aromatic Substitutions via Photoredox Catalysis

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We developed a simple and convenient method to assemble biaryls exploiting a photoredox catalyst and visible light. Diazonium salts generate aryl radicals that could then add on unactivated (hetero)arenes and the sequence eventually delivers products via formal Homolytic Aromatic Substitution. The direct C-H arylation of these usually unreactive substrates is achieved at room temperature using low catalyst loadings and shows broad functional group tolerance.

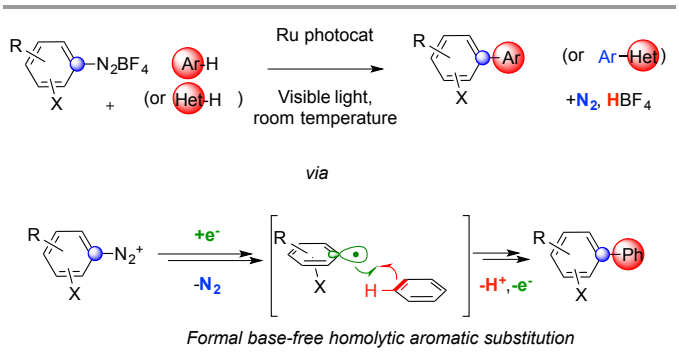
Introduction

The development of simple synthetic routes that can form biaryls from simple building blocks represents a long-standing goal for organic chemists because of the broad domain of application of functional molecules that present this structural motif. Together with catalytic methods that can activate C-H bonds,[1] in particular those of simple, unactivated arenes,[2] homolytic aromatic substitutions (HAS) are suitable free radical processes to achieve this synthetic goal. Their major pitfall is the often-required need of stoichiometric, hazardous, tin derivatives as radical mediators.[3] This issue can be addressed using stoichiometric amounts of strong bases such as alkoxides to assist chain propagation.[4]

A complementary strategy uses photoredox catalysts that harvest visible light[5] to mildly activate onium species generating aryl radicals.[6] Diazonium and iodonium derivatives can indeed regioselectively arylate various heterocycles at the 2-position *via* photoredox catalysis.[7]

Merging these two approaches, Li used a strongly reducing Ir photocatalyst to activate aryl iodides at room temperature and trigger base-assisted HAS on arenes.[8]

We report a HAS cascade that does not require the presence of any base (Scheme 1). This minimizes consumption of reagents and production of waste, therefore increasing the practical viability of the method. It allows the C-H arylation of simple arenes and heteroarenes at room temperature with remarkable functional group tolerance. Aryl radicals are readily generated from diazonium salts using a suitable Ru photoredox catalyst,[6] as originally introduced in an intramolecular fashion by Deronzier.[6a] Desired products form together with a nitrogen molecule and an equivalent of non-toxic HBF_4. The presence of protic acidic species does not inhibit the reaction and is tolerated by the photocatalyst. Under these conditions, sufficiently basic species, even in traces, could have an impact on the outcome of these experiments. The presence of water molecules and/or suitable anions could indeed vary the time required to achieve full conversion of the substrate and the selectivity towards the desired product or the reduced starting material.



Scheme 1. Base-free HAS to synthesise biaryls.

Results and discussion

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We discovered this process while attempting to develop a synthesis of biaryls merging photoredox and gold catalysis. Reasoning on the feasibility of Ru/Pd dual catalytic cascades[6b] and on the possibility to access unusual spin states via addition of aryl radicals on suitable transition metal complexes,[6c] we wondered whether it would have been possible to develop an alternative access to biaryls *via* Ru/Au joint catalysis (see ESI for details on our initial idea).[9]

In an initial experiment (Table 1, entry 1), 4-nitrophenyldiazonium tetrafluoroborate reacted with toluene (40 equiv, 1:1 mixture with acetonitrile) at room temperature for 3 hours in the presence of 0.5 mol% of $Ru(bpy)_3Cl_2$ as photocatalyst, 10 mol% of JP $Au(MeCN)SbF_6$ (JP = JohnPhos, (2-Biphenyl)di-*tert*-butylphosphine) and 2 equiv. of K_2CO_3 as base under irradiation of a blue LED. To our delight, 81% of the desired biaryl product **1a** was recovered as a mixture of its three regiosomers. Toluene was arylated in a 4:1.3:1 ratio at its *ortho*-, *meta*- and *para*- positions. Direct reduction of the diazonium salt to nitrobenzene was the main side product (17%).

However, successive experiments showed us that desired products were formed through a mechanism different from our originally envisioned one. In other words, neither gold nor the inorganic base were necessary to deliver biaryls in high yields.

The yield of **1a** resulted lower replacing the gold complex with PPh_3AuCl (63%, entry 2). We soon found that a comparable selectivity towards **1a** was observed repeating the reaction without K_2CO_3 (62%, entry 3). In both cases we observed complete conversion of the diazonium salt and nitrobenzene as main byproduct. The limited difference in yields with and without K_2CO_3 let us question our initial idea that the sequence could involve a base-assisted C-H activation by gold.[9] We then realized the importance to immediately check whether a gold salt had or not an impact on the outcome of the reaction. Biaryl **1a** formed in 66% yield in the presence of 0.5 mol% of $Ru(bpy)_3Cl_2$ without any other additive (entry 4).

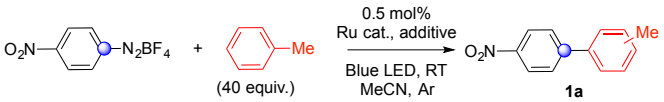
This result suggested that **1a** could in principle form under these conditions *via* HAS-like mechanism (*vide infra*) and not through our originally supposed pathway.

We were however puzzled by the difference observed comparying the yield of **1a** with and without a gold complex featuring a SbF_6^- counteranion (81% for entry 1 and 66% for entry 4). We then wondered whether counteranions of metal salts might play a role, especially in the absence of stoichiometric bases, and affect therefore the outcome of the sequence. The reaction with commercially available $Ru(bpy)_3(PF_6)_2$ catalyst provided 71% of **1a** (entry 5). For sake of comparison, similar results were achieved with the addition of either 10 mol% of JP $Au(MeCN)SbF_6$ (70%, entry 6) or 10 mol% of PPh_3AuCl complex (68%, entry 7). We then synthesized $Ru(bpy)_3(SbF_6)_2$ seeking to take advantage of the solubility properties of the non-coordinating SbF_6^- anion. The switch proved important to increase the yield of **1a** by reducing the formation of nitrobenzene as byproduct. We were indeed delighted that a selectivity comparable with our best result could be achieved performing the arylation of toluene with 0.5 mol% $Ru(bpy)_3(SbF_6)_2$ as photocatalyst (entry 8, 79%).

This result suggested that the high yield observed in our preliminary experiment using both Au and Ru salts (entry 1, 81%) might originate from anion metathesis between gold and ruthenium complexes.

Performing the reaction in the dark delivered only traces of **1a**, thus portraying the role of light irradiation (entry 9). The latter alone is similarly unable to allow significant conversion of the diazonium salt, **1a** being retrieved in 10% yield without Ru (entry 10). This back-ground reactivity is a relatively common feature in photoredox reactions.[6b,7a] Formation of products is inhibited by TEMPO. The radical scavenger traps indeed the initially generated aryl radical (see ESI). Lower yields were observed performing our experiments under air (see Table S1 in ESI). This effect is usually not observed in conceptually analogous photoredox reactions, which do not involve intermediates that could easily react with dioxigen.[5-8] Reactions became faster using wet solvents. Try as we might, reproducibility issues were invariably observed. This problem was addressed using dry solvents and adding a precise amount of water to the reaction mixture. Full conversion of the diazonium salt was observed in one hour upon addition of 200 μL of water, but the yield of **1a** sunk to 63% because of more pronounced direct reduction of the onium reagent. We then decided to continue the study using anhydrous solvents and degased mixtures.

Table 1. Optimization of reaction conditions



Entry	Catalyst, *mol %*	Additive, *mol %*	yield (%)
1[c]	$Ru(bpy)_3Cl_2$, *0.5*	[d]JP $Au(MeCN)SbF_6$, *10*	81
2[c]	$Ru(bpy)_3Cl_2$, *0.5*	PPh_3AuCl, *10*	63
3	$Ru(bpy)_3Cl_2$, *0.5*	PPh_3AuCl, *10*	62
4	$Ru(bpy)_3Cl_2$, *0.5*	--	66
5	$Ru(bpy)_3(PF_6)_2$, *0.5*	--	71
6	$Ru(bpy)_3(PF_6)_2$, *0.5*	[d]JP $Au(MeCN)SbF_6$, *10*	70
7	$Ru(bpy)_3(PF_6)_2$, *0.5*	PPh_3AuCl, *10*	68
8	$Ru(bpy)_3(SbF_6)_2$, *0.5*	--	79
9[a]	$Ru(bpy)_3(SbF_6)_2$, *2.5*	--	traces
10[b]	--	--	10

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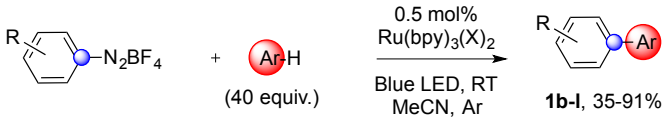
Reaction conditions: ArN_2BF_4 0.45 mmol, 0.225 M, isolated yields. [a] Without irradiation for 24h. [b] For 72h without photocatalyst. [c]With 0.9 mmol of K_2CO_3, 2 equiv., as base. [d]JP = JonhPhos, (2-Biphenyl)di-*tert*-butylphosphine.

It is worth noting that the regioselectivity of the process did not change significantly among these reactions. The ratios of o/m/p arylation of toluene ranged between 3.6:1.3:1 and 4:1.4:1. These observations are consistent with a negligible impact of a catalytic amount of gold and/or a stoichiometric inorganic base on the sequence. The efficient formation of **1a** suggested furthermore that the reaction with a photoredox catalyst did not require the presence of a stoichiometric base and confirmed the stability of $Ru(bpy)_3^{2+}$ cations in acidic media.[6b] Slight differences in yields were thus most likely due to effects displayed by anions present in solution.[10] It is worth noting that their role is expectedly marginal in most photoredox cascades[5-8] and HAS reactions[3,4,8] as these processes usually occur in basic and neutral media.

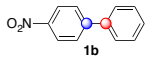
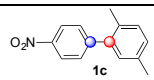
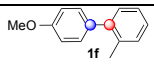
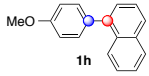
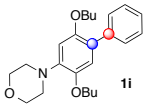
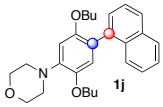
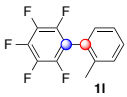
We then examined the scope of this mild arylation by screening various unactivated arenes (Table 2). On selected examples we performed reactions with different photocatalysts, varying their counterion, and adding a hexafluoroantimonate gold salt as additive to test whether they might play a role using different substrates.

Beside toluene, nitro phenyldiazonium smoothly reacts with benzene and *p*-xylene to provide biaryls **1b** and **1c** (61-80% yields, entries 1-4). While yields remain comparable, reactions with $Ru(bpy)_3Cl_2$ hexahydrate as catalyst were faster (entries 2 and 4). Chlorine substitutents are well tolerated by the cascade, delivering corresponding products **1d** and **1e** in excellent yields (73-91%, entries 5-9). The most selective reaction with benzene was the slowest one (entry 7, 91%, 24 hours). The use of $Ru(bpy)_3Cl_2$ hexahydrate as catalyst allowed full conversion of the diazonium reagent in 13 hours and the yield of **1e** sunk to 73% (entry 8). Addition of 10 mol% of a gold salt with non-coordinating SbF_6^- counterion provided full conversion of the substrate in 4 hours and delivered 86% of **1e** (entry 9). Electron rich diazonium salts were less efficient and required longer reaction times (entries 10-11, 32-37%). Employing naphthalene as acceptor the coupling occurred smoothly and delivered **1h** in 86% yield with good regioselectivity (entry 12, 5.8:1 ratio). Diazonium salts bearing *ortho* substituents could be more prone to undergo direct reduction rather than desired product, usually retrieved in moderate to good yields (see also Table S5 in ESI). Among selected examples, an onium reagent with a bulky *n*-butoxy chain can be readily coupled delivering arylated products **1i** and **1j** in 35% and 50% respectively, entries 13 and 14. The sequence tolerated esters as witnessed by formation of **1k** in 54% yield (entry 15). A perfluorodiazonium could be employed and delivered the corresponding biaryl **1l** in 71% yield, although with poor regiocontrol (1.8:1.3:1 mixture of isomers, entry 16).

Table 2. Arylation of simple arenes



1b-l, 35-91%

Entry	Ar-H	time (h)	major isomer	yield (%)	regio selectivity[a]
1		23	 **1b**	80	--
2[b]		8		79	--
3		7	 **1c**	69	--
4[b]		3		61	--
5		4	**1d**	84	3.3:1.2:1 (*o:m:p*)
6[b]		4		83	4:1.3:1
7		24	**1e**	91	--
8[b]		13		73	--
9[b,c]		4		86	--
10		48	 **1f**	32	4.5:1.6:1
11		96	**1g**	37	--
12		24	 **1h**	86	5.8:1 (α:β)
13		48	 **1i**	35	--
14		24	 **1j**	50	4.2:1 (α:β)
15		36	**1k**	54	4.1:1 (α:β)
16		12	 **1l**	71	1.8:1.3:1 (*o:m:p*)

Reaction conditions: as Table 1, entry 8. Reaction time determined by analyzing samples *via* ^{1}H NMR. Isolated yields based on the average of at least two runs. *a*: determined by NMR, spectra in ESI; *b*: with 0.5 mol% of $Ru(bpy)_3Cl_2$ hexahydrate as photocatalyst; *c*: with 10 mol% of JP $Au(MeCN)SbF_6$.

We next examined the scope of the reaction using various functionalized arenes and heterocycles as radical acceptors (Table 3). Benzonitrile can be arylated preferentially at the 2-position by an electron poor diazonium salt (**2a**, 67%, entry 1). Remarkably, yields could range from poor to excellent with subtle changes on the catalytic system (37%-87%, entries 2-4). The use of $Ru(bpy)_3(SbF_6)_2$ as catalyst provided the highest yield of **2b** (87%, entry 2) and 24 hours were required to achieve full conversion of the diazonium reagent. Full conversion of the latter was attained in 7 hours with

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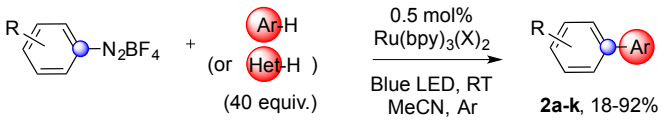
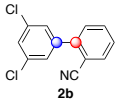
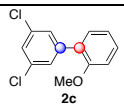
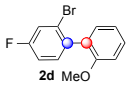
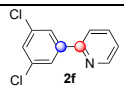
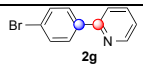
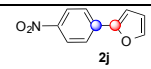
$Ru(bpy)_3Cl_2$ hexahydrate, but a significantly lower yield was observed in this case (37%, entry 3). Addition of 10 mol% of JP Au(MeCN)SbF_6 provided full conversion in 7 hours and 82% of **2b** (entry 4). Anisole too is an efficient coupling partner towards various polyhalogenated diazonium salts, delivering **2c** and **2d** in 92% and 72% yield respectively in one hour (entries 5-7). The method is suitable towards functionalization of fluorinated arenes, biaryl **2e** being isolated in 71% yield (entry 8). We then tested pyridine as reagent. The reaction with a chlorinated diazonium salt delivered biaryl **2f** in 55% yield with good regioselectivity (7:3 ratio of isomers, entry 9). A lower selectivity was observed using $Ru(bpy)_3Cl_2$ hexahydrate (39% yield, entry 10). Surprisingly, the favored isomer of the product became the *meta*-arylated pyridine when the reaction is carried out with 2 equivalents of potassium carbonate to neutralize *in-situ* generated HBF_4 (73%, 1:8 ratio of isomers, entry 11). The yield was limited using a diazonium salt with a para-bromo substituent (**2g**, 21% and 18% yield respectively, entry 12-13). Selective *ortho*-arylation prevails with a donating methoxy group too, product **2h** being retrieved in 63% yield (7:3 mixtures of isomers, entry 14). A 15.6:1 ratio was observed in the presence of a base (72%, entry 15). Complete regioselectivity towards *ortho*-arylation was observed with a nitro-substituted diazonium salt (entry 16, 41% yield). The preference for β functionalisation is usually not observed in homolytic aromatic substitutions (*vide infra*).[7,11] Taken together these results suggested that the behavior of pyridine and a protonated pyridine could differ in these sequences. We did not managed yet to fully control and predict the reactivity of nitrogen heterocycles. Switching to electron rich heterocycles, our method selectively arylated furan at the 2- position, albeit with moderate yields (47% and 34% for entries 17 and 18 respectively).

In all cases halogenated reagents successfully react leaving their C-X bonds untouched and suitable for further functionalisation.

Table 3. Arylation of substituted arenes and heterocycles



Entry	Ar-H	time (h)	major isomer	yield (%)	regio selectivity[a]
1		8	**2a**	67	3.5:1:1.4 (o:m:p)
2		24	 **2b**	87	5.5:1:2.3
3[b]		7		37	5.8:1:2.1
4[b,c]		7		82	5.7:1:2.2
5		1	 **2c**	91	4.1:1:1.2
6[b]		1		92	4.6:1:1.2
7[d]		1	 **2d**	72	3.3:1:1.5
8		12	**2e**	71	1:3.2:6
9		1	 **2f**	55	7:3 (α:β)
10[b]		1		39	α
11[e]		1		73	1:8
12		1	 **2g**	21	2:1
13[b]		1		18	α
14		5	**2h**	63	7:3
15[e]		5		72	15.6:1
16		2	**2i**	41	--
17		1	 **2j**	47	--
18		1	**2k**	34	--

Reaction conditions: as Table 1, entry, 8. Reaction time determined by analyzing samples *via* ^{1}H NMR. Isolated yields based on the average of at least two runs. *a*: determined by NMR, spectra in ESI; *b*: with 0.5 mol% of $Ru(bpy)_3Cl_2$ hexahydrate as photocatalyst; *c*: with 10 mol% of JP Au(MeCN)SbF_6; *d*: 72% yield on 2.25 mmol scale (20 h); *e*: with 2 equiv. of K_2CO_3 to neutralize in-situ generated HBF_4.

A possible rationale for the mechanism of this cascade is presented in Scheme 2.[5,6] Visible light allows Ru(II) complex $\mathbf{I_{red}}$ to pass to its excited form $\mathbf{I^*}$. The latter can deliver an electron to diazonium salt **3**. This SET provides Ru(III) complex $\mathbf{I_{ox}}$ together with radical **4**, that can then liberate aryl radical **5** and N_2. The former could then add to an arene yielding cyclohexadienyl radical **6**. At this stage, two competitive manifolds could be imagined. On one hand, $\mathbf{I_{ox}}$ can conclude the photocatalytic cycle by oxidizing radical **6**, which provides biaryl **1** upon deprotonation. However, analogous mechanisms reported in the literature suggest that a radical chain reaction might compete (highlighted in pink in Scheme 2).[7a] In this scenario, its propagation step would feature the electron transfer between **6** and another molecule of **3**, generating Wheland-type cation **7** together with **4** that could

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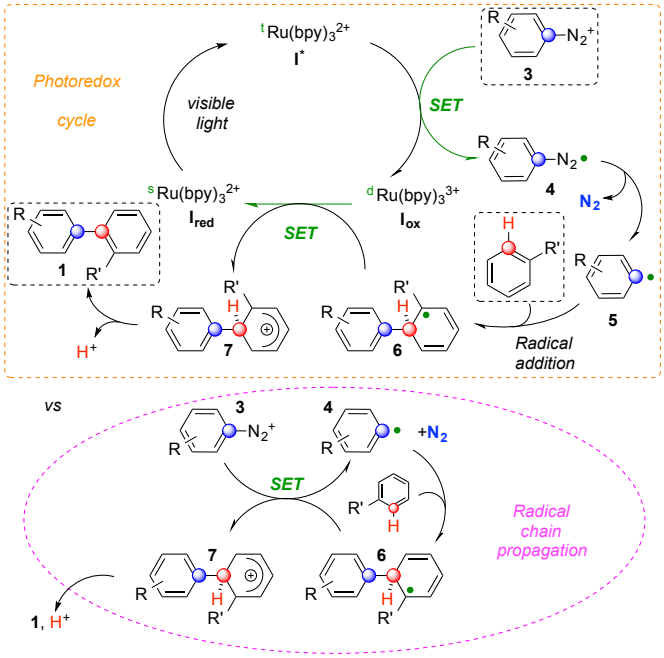
then add on another arene molecule. Rearomatization of the former would eventually provide product **1**. Whether a radical chain mechanism operates in these sequences, its termination step is likely ensured by an oxidizing Ru species rather than *via* free radical recombination. We did not observe indeed any traces of homocoupling products. It is worth noting that, even if the concentration in solution of both **6** and **I*** is most likely low, aryl radicals are weaker reducing agent than ^{d}Ru(bpy)$_3^{3+}$ and might thus not be sufficient to support chain propagation.[12] This hypothesis is confirmed by calculating the ΔG of these two competitive redox reactions. Oxidation of radical **6** by **I*** is accompanied by a large negative ΔG (-26.4 kcal/mol). The SET between **6** and cation **3** to generate a diazoyl radical has instead a positive calculated ΔG of +0.6 kcal/mol. The most energetically favored pathway appears therefore the oxidation of radical **6** by ruthenium.



Scheme 3. Plausible reaction mechanisms

Diazonium salts bearing withdrawing groups led to higher yields than their peers with donating substituents. This can correlate with the relatively higher reduction potential of the former compared to the latter. Furthermore, upon loss of N_2, the resulting aryl radical is more electrophilic and could thus better add on electron rich arenes.[3] Among these reagents, substituted ones such as toluene and naphthalene react faster and provide better yields than benzene. Beside heterocycles,[7,9] the control of regiochemistry is limited and the distribution of isomers is not statistical. When multiple regioisomers could form, the favored one usually feature substituent *ortho* to the aryl-aryl bond. Remarkably, electronic effects do not affect this preference for *ortho*-arylation.[1] A comparable regioselectivity is indeed achieved replacing toluene or anisole with benzonitrile. This is consistent with the relative extra stabilization of the *ortho*-substituted cylohexadienyl radical **6** compared to its isomers. The regioselectivity of the process should be indeed determined by the relative stability of different isomers of cyclohexadienyl radical **6**. All these features are hallmarks of homolytic aromatic substitutions[3,4] and our base-free photoredox cascade might be considered an example of HAS that mildly generates aryl radicals triggering the C-H arylation of simple arenes.

These reactions are often performed with stoichiometric bases but could remain very efficient processes in neutral and acidic media. In this case, it has been possible to observe differences by subtle tuning conditions. Remarkably, traces of different counterions and/or water molecules could change the time necessary to achieve full conversion of the onium reagent and the yield of the biaryl product (compare entries 7-9, Table 2 and 2-4, Table 3). Reactions with nitrogen heterocycles showed significant changes in regioselectivity depending on the acidity of the media. On the contrary, no significant effect on regioselectivity is observed in reactions involving unactivated arenes. This could result from the formal deprotonation of Wheland-type cation **7** that delivers a molecule of product **1**. This step is generally assisted by a sufficiently basic species. In acidic mediums, chloride anions and molecules of water or acetonitrile, which we used as solvent, could become the most basic species and might thus impact on time necessary to consume starting material and on the selectivity towards either desired biaryls or (undesired) reduced onium reagents.

Conclusions

We developed a catalytic method for the synthesis of biaryls exploiting a suitable Ru photocatalyst and visible light. The study of these formal C-H arylations revealed several analogies with homolytic aromatic substitutions, a prototypical free-radical process. Simple arenes could be readily activated under very mild conditions and with broad functional group tolerance.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, synthesis of photocatalyst, characterization of products, copies of NMR spectra. See DOI: 10.1039/b000000x/

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