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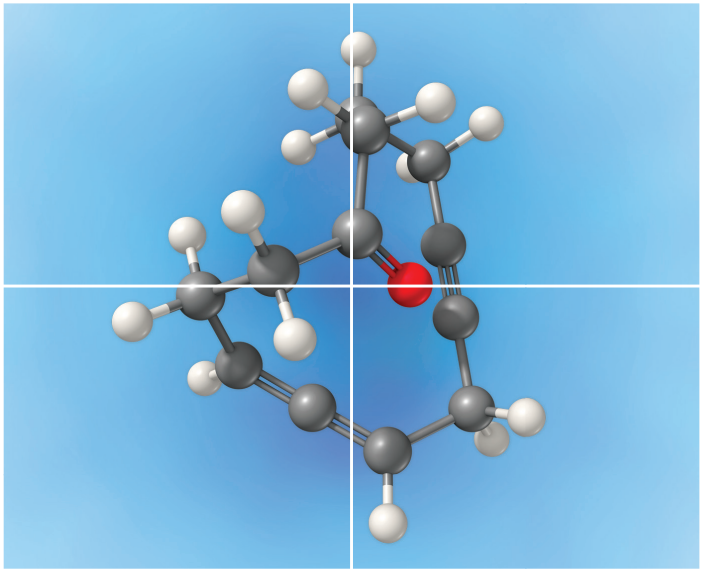

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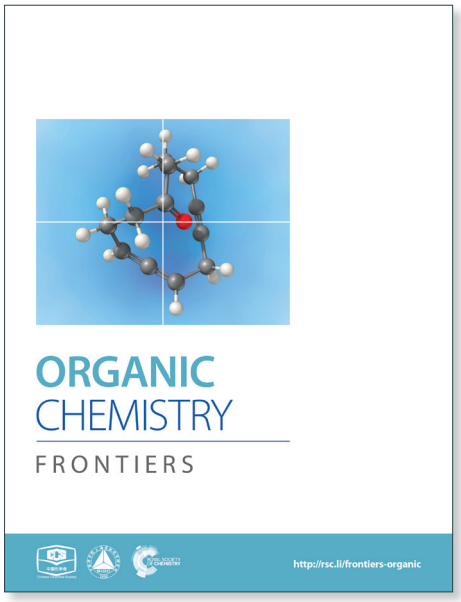

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Organic Chemistry Frontiers

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RESEARCH ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2014,
Accepted 00th January 2014

DOI: 10.1039/x0xx00000x

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Room Temperature, Open-flask C-H Arylation of Electron-deficient Heteroarenes with Triazenes: Rapid Synthesis of Heterobiaryls

Rui Wang,*[a] and John R. Falck[a]

Aryl triazenes, a source of aryl radicals, were coupled with heteroarenes via C-H functionalization to produce heterobiaryls in moderate to good yields. Couplings proceeded in open atmosphere at ambient temperature for 3-24 h. Best results were obtained with electron-deficient heteroarenes, while both electron donating and withdrawing substituents in the traizene moieties were tolerated.

Introduction

Heteroarenes are well represented in both natural products and pharmaceuticals. Nitrogen heterobiaryls are especially important. For example, Crestor, Lamictal, Viagra, Glivec, some of the commercially most successful drugs in the past decade,[1] and natural compound Micrococcin P1 contain the heterobiaryl motif (Figure 1).

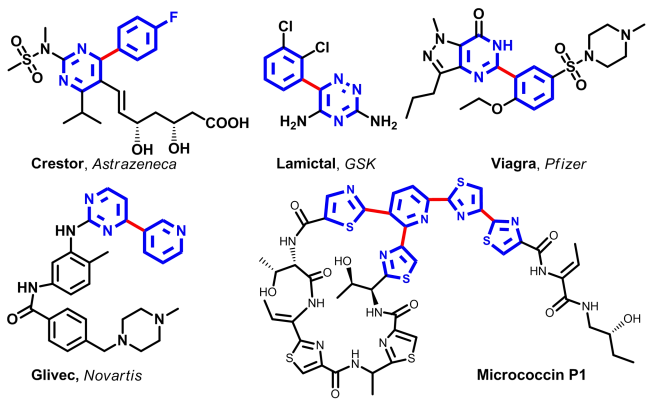
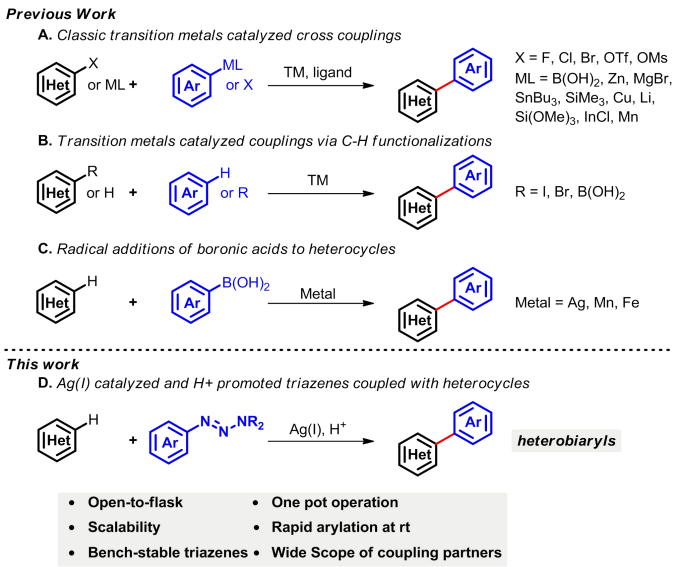


Figure 1. Examples of the heterobiaryl motifs.

Methodologies[2] for synthesizing the core heterobiaryl framework mainly rely upon (i) nucleophillic aromatic substituted reactions, (ii) couplings of pre-activated arenes (*i.e.*, haloarenes) with partners (*i.e.*, phenylboronic acids) (Suzuki-Miyaura cross-coupling reactions),[3] (iii) the vibrant C-H activation strategy,[4] and (iv) the Minisci reaction (Scheme 1).[5]

Modern arylation methods mainly rely on transition-metal-catalyzed (Pd, Cu, Rh, Ru, Ir, Fe, Zn and Ni) cross-coupling reactions.[6] Transition-metal-catalyzed Suzuki-Miyaura cross-coupling reaction has achieved dramatically over the past few decades. Recent progress in Suzuki-Miyaura cross-couplings which afforded heterobiaryls have been reported (Scheme 1, A). For example, Miura,[3b] Feringa,[3c-d] Hartwig,[3i] Buchwald,[3k] De Meijere[3l] *et al* reported that transition metals (*e.g.*, Pd, Cu, Ni) efficiently catalyzed haloarenes (*e.g.*, aryl iodides, aryl chlorides) with heterocycles. Most recently, transition-metal-catalyzed aromatic C-H bond functionalizations have been of great interest owing to their broad synthetic applications, particularly in the fields of organic synthesis and medicinal chemistry. C-H bond activations and subsequent functionalizations have many advantages comparing with classic pre-activated strategies. Direct C-H bond functionalizations[7] bypass the use of pre-activated reaction partners, thus lead to more green process. Pioneering work using C-H functionalization that afforded heterobiaryls was reported by Itami and co-workers[7i-n] in 2008 (Scheme 1, B), the arylation of electron-deficient nitrogen heterocycles with iodoarenes promoted by potassium tert-butoxide was described. Later, they reported that transition-metal-catalyzed (*e.g.*, Pd, Ni, Ir) pre-activated haloarenes (or haloheteroarenes) directly coupled with heteroarenes (or arenes) and a wide range of heterobiaryls were constructed. Unfortunately, most of these cross-coupling reactions suffer from relatively harsh reaction conditions, requirement for specific ligands, synthesis of pre-activated coupling partners. In contrast, radical reactions have many advantages comparing with many transition-metal-mediated processes. For example, many radical reactions can be performed under mild conditions, use water as a reaction medium, and are amenable to a wide range of functionalizations. Specifically, synthesis of heterobiaryls though addition of aromatic radicals to heterocycles is a challenging task. This may be primarily due to the difficulties in controlling chemo- and/or regio-selectivities, although radical method has advanced dramatically comparing with many well-established arylation methods. In 1971, the initial work, namely, addition of alkyl radicals to protonated heterocycles, was reported by Minisci and co-workers.[5] Disadvantages of these process included harsh reaction conditions and comparably narrow substrates scopes (alkyl radicals).[8] Recently, Baran *et al* reported that arylboronic acids

generate aryl radicals, which can be subsequently added to heterocycles under ambient temperature. Consequently, considerable heterobiaryls were synthesized from a vide range of aromatic boronic acids and heterocycles (Scheme 1, C).[9]



Scheme 1. Major strategies for the construction of heterobiaryls.

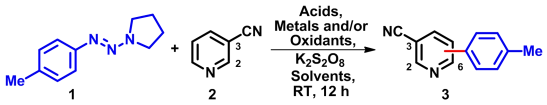
Although arylation of heterocycles has been achieved greatly in the past decades, the need for newly synthetic method that is able to address existed shortcomings, *e.g.*, harsh reaction condition, remains urgent. In recent years, aromatic trizene has gained substantial interests due to its considerable benefits.[10] Aromatic triazenes as a kind of activated aryl groups, are easily and rapidly prepared from bench-available anilines, comparatively stable under ambient temperature, tolerated with broadly functional groups, and readily scaled-up beyond a hundred gram level. In view of their advantages, aryl triazenes have attracted extensive interest in the chemistry community.[10a-d,i] Herein, we disclose first general protocol to furnish heterobiaryls through a mild, open-flask arylations of heteroarenes using triazenes *via* C-H bond functionaliztions. Notably, the transformation is amenable to a wide range of functionalities and readily performed on a multigram scale.

Results and discussion

To generate reactive species from triazenes capable of adding to heteroaromatics, we chose a mild oxidizing environment consisting of potassium persulfate (3 equiv), silver nitrate (20 mol %); as a model system, 4-tolyltriazene (**1**) and 3-cyanopyridine (**2**) were chosen.

A screen[11] of common solvents (Table 1, entries 1-5) revealed that only a two-phase system of CH_2Cl_2 and water (3:4) afforded a synthetically useful yield of **3** (88%); $CHCl_3$, in sharp contrast, gave **3** in just 45% yield. With the best solvents system in hand, we next sought an inexpensive oxidant (Table 1, entries 6-10). Benzoquinone and DDQ as oxidants gave low conversions. With hypervalent iodine reagents such as iodobenzene diacetate, we observed a moderate conversion. Peroxides TBHP and ^{t}BuOOBz also failed to provide any promising results. Actually, a comprehensive oxidants screening was tested, all failed.[11] Next, a complete list of acids[11] was also evaluated, the best result was obtained when trifluoroacetic acid was employed (Table 1, entries 3, 11-13). Among aqueous acids, 36% hydrochloric acid provided low yields while acetic acid and 65% perchloric acid gave 60% and 70% yields, separately. We coincidentally discovered that an excess of acid generally improved the yield of **3**. Further investigations revealed that excess addition of trifluoroacetic acid (10.5 equiv) afforded the best result (Table 1, entries 3).[11] Polar effect[5b,5f,12,13] and greater solubility may account for the high transformation efficiency. Interestingly, pure boron trifluoride provided a low yield (Table 1, entry 14).[14]

Table 1. Optimized reaction conditions.[a]



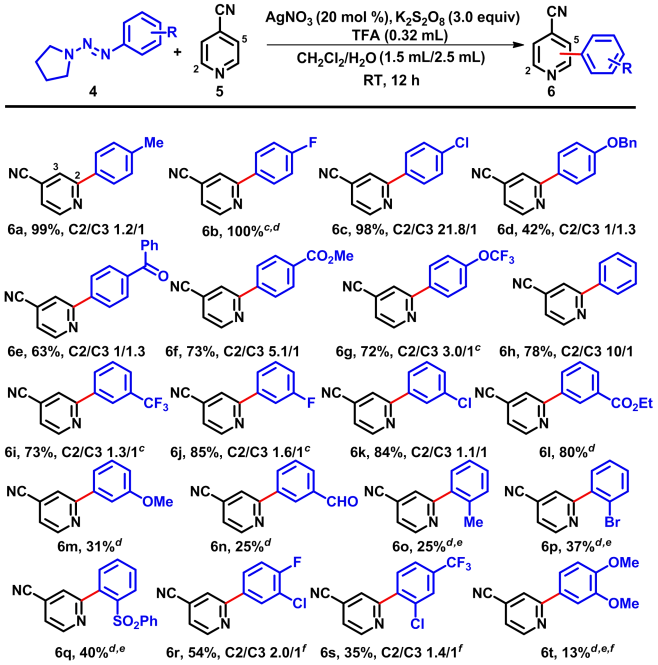
Entry	Solvent(s)	Oxidant	Acid	Yield (%)
1	DMF/H_2O	$AgNO_3$	TFA	20
2	THF/H_2O	$AgNO_3$	TFA	29
3	**CH_2Cl_2/H_2O**	**$AgNO_3$**	**TFA**	**80[b]**
4	$CHCl_3/H_2O$	$AgNO_3$	TFA	45
5	CH_3NO_2	$AgNO_3$	TFA	trace
6	CH_2Cl_2/H_2O	BQ	TFA	0
7	CH_2Cl_2/H_2O	DDQ	TFA	0
8	CH_2Cl_2/H_2O	$PhI(OAc)_2$	TFA	0
9	CH_2Cl_2/H_2O	TBHP	TFA	0
10	CH_2Cl_2/H_2O	^{t}BuOOBz	TFA	0
11	CH_2Cl_2/H_2O	$AgNO_3$	36% HCl	0
12	CH_2Cl_2/H_2O	$AgNO_3$	AcOH	60[b]
13	CH_2Cl_2/H_2O	$AgNO_3$	65% $HClO_4$	70[b]
14	CH_2Cl_2/H_2O	$AgNO_3$	$BF_3{\cdot}OEt_2$	0

[a] 3-Cyanopyridine **2** (0.2 mmol), 4-tolyltriazene **1** (0.3 mmol), TFA (0.16 mL), CH_2Cl_2/H_2O (0.75 mL/1.25 mL), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3.0 equiv), RT, 12 h. [b] C2/C6 ratio approx. 1.1/1.

With the optimized reaction conditions in hand, we next screened the triazenes scopes partnered with 4-cyanopyridine (**5**) (Chart 1). Triazenes with both electron-withdrawing and electron-donating substituents in the *para*-position provided good to excellent yields. 4-Tolyltriazene provided a high yield of coupled adduct **6a**, but there was no regioselectivity (C2/C3-arylation = 1.2/1). Electron-deficient substrates such as 4-fluoro- and 4-chlorophenyltriazenes showed high conversions and isolated yields of **6b** and **6c**, respectively. This reflected that the increased nucleophilic character of the radical intermediates induced by the electron withdrawing groups on the phenyl rings and consequently were more efficiently coupled with protonated heterocycles.[5b,12] Not surprisingly, these reactions were both highly regioselective, favoring couplings at the more electrophilic and sterically accessible ortho positions on the protonated pyridines. Protonated heteroaromatics were electron-poor substrates, which reacted with nucleophilic radicals with high regioselectivities to yield the arylated heterobiaryls. Functional groups such as an ether, carbonyl, and ester

were also tolerated, yielding **6d, e, f**, **g** in moderate to good yields, respectively. Likewise, triazenes with electron-withdrawing substituents in the 3-position favored better yields, *e.g.*, **6i, j, k, l**, while a methoxy in this position led to adduct **6m** in modest yield; despite having an electron-withdrawing group, the 3-formyl example **6n** was inexplicably obtained in low yield accompanied by several minor by-products. The presence of substituents, either electron-rich or deficient, adjacent to the triazenes on the phenyl rings were detrimental (see **6o-q**).[15] Polysubstituted systems were more complicated. For instance, the combination of 4-fluoro-3-chloro-substituents furnished just a 54% yield of **6r,** whereas only 35% of **6s** was formed. In the latter case, the 2-chloro-substituent clearly overshadowed the otherwise favorable effect of the 4-trifluoromethyl group. On the other hand, 3,4-dimethoxy reinforced the negative influence of electron-donating groups and allowed a mere 13% of **6t**. Unfortunately, heteroaryl triazenes failed to provide arylated heterobiaryls, whether at ambient temperature or elevated temperature (60 °C). Their ability to act as good radical acceptors is a likely factor.

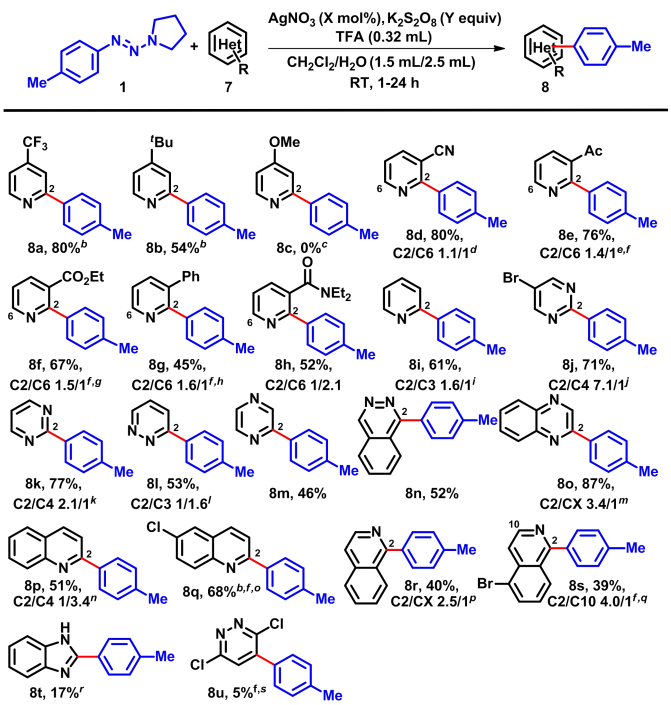
Chart 1. Scope of aryltriazene (**4**) coupling with 4-cyanopyridine (**5**).[a, b]



[a] Unless otherwise specified, all reactions were performed on following scale: 4-Cyanopyridine (**5**) (0.4 mmol), aryltriazene (0.6 mmol), TFA (0.32 mL), CH_2Cl_2/H_2O (3:4, 3.75 mL), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3.0 equiv), RT, 12 h. [b] All yields and ratios were isolated results. [c] Reaction time ≤ 3 h. [d] One isomer only. [e] Addition of a second round of $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3.0 equiv) was needed. [f] Reactions were run twice and crude products were purified by SiO_2 flash chromatography, then prep TLC.

Next, we explored the structural varieties in the heterocyclic coupling partners (Chart 2). Electron-withdrawing groups on the *para*-position of pyridines gave excellent yields, for example, cyano (**6a**) and trifluoromethyl (**8a**); while the moderate electron-donating *tert*-butyl group provided a modest 54% isolated yield of **8b** and the strongly donating substituent methoxy failed to give any arylation product **8c** that may also be due to the polar effects.[5b,5f,12,13] *Meta*-substituted pyridine derivatives including cyano (**7d**), acetyl (**7e**), carboethoxy (**7f**), phenyl (**7g**), and diethylamide (**7h**) gave adducts **8d-h** in moderate yields as expected. These substituents can't interact directly with the pyridyl nitrogens that may account for their low conversion, and addition of a second round $AgNO_3/K_2S_2O_8$ in order to completely consume all of the starting pyridines was required. The regioselectivities appeared to favor regions of low electron density. Pyridine itself gave a 61% yield of **8i** with a regioselectivity ratio 1.6/1. Notably, *ortho*-substituents (*e.g.*, fluoro, chloro, bromo and methyl) completely suppressed couplings and the unreacted pyridines could be recovered. Other heteroarenes such as 5-bromopyrimidine (**8j**), pyrimidine (**8k**), pyridazine (**8l**), pyrazine (**8m**), phthalazine (**8n**), qunioxaline (**8o**), quinoline (**8p**, **8q**), isoquinoline (**8r**, **8s**), were all acceptable coupling partners. In contrast, *1H*-benzimidazole led to coupling product **8t** in less than 20% yield. Interestingly, 3,6-dichloro-pyridazine gave arylated product **8u** in only 5% isolated yield.

Chart 2. Scope of heteroarenes (**7**) coupling with 4-tolyltriazene (**1**).[a]

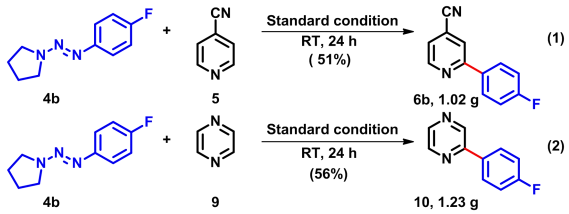


[a] Unless otherwise specified, all reactions were performed on following scale: heteroarenes (0.4 mmol), 4-tolyltriazene (0.6 mmol), TFA (0.32 mL), CH_2Cl_2/H_2O (3:4, 3.75 mL), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (3.0 equiv), RT, 12 h. All yields were based upon isolated material and brsm. [b] One isomer only. [c] Starting material was recovered. [d] Trace amount of starting material was detected. [e] 25% starting material was recovered after 48 hrs. [f] Addition of a second round $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (3.0 equiv) was needed. [g] 40% starting material was recovered after 24 hrs. [h] 48% starting material was recovered after 24 hrs. [i] Only two isomers were detected. [j] C2 was isolated alone; other positional isomers were collected as mixtures. [k] C5 isomer was not detected. [l] 1 mmol scale. [m] C2 arylation product along with acid-catalyzed hydrolysis product. [n] Two isomers were isolated. [o] Only one isomer was detected though second round addition of $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (3.0 equiv). [p] 30% starting material was recovered along with C1 arylation product and mixture of other positional isomers. [q] C9 arylation product was not found. [r] Isolated yield after 48 hrs. [s] 5% isolated product; most starting material was recovered.

Encouraged by the results above, we subsequently conducted the practical arylation reaction, it was deemed important to validate the practicality of the methodology on a gram-scale (Scheme 2).[16] When

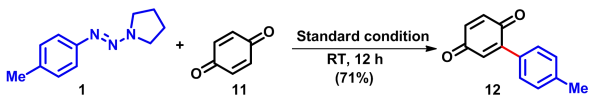
substrates **5** and **9** were primary arylated with triazene **4b** under our standard reaction conditions, the corresponding heterobiaryls **6b** and **10** were obtained in similar chemical yields.

Scheme 2. Scale-up of heterocycles coupling with aryltriazene (**4b**).



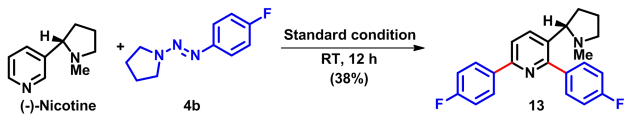
To seek its further application in synthetic community, we were delighted to find that 4-tolyltriazene **1** was able to react with benzoquinone **11** with formation of arylated adduct **12** under the standard reaction conditions in 73% isolated yield (Scheme 3). This result indicated that benzoquinone derivatives were also good radical acceptors under the current reaction condition, which provided an interesting synthetic approach to constructions of arylated benzoquinone derivatives.

Scheme 3. Arylation of benzoquinone derivatives (**11**).



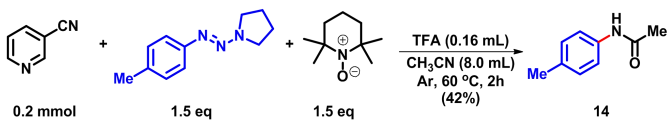
To demonstrate the usage of this method, we also found that under the optimized reaction condition, triazenes **4b** could be coupled with (-)-Nicotine, a-natural-existed compound, with pyrrolidine functional group, providing di-arylated heterocycle **13** in 38% isolated yield (Scheme 4).[17]

Scheme 4. Synthetic application.



Preliminary experiment to evaluate the plausible reaction pathway is provided in Scheme 5. We were delighted to isolate the *N*-(p-tolyl)acetamide (**14**) in 42% isolated yield under the reaction condition,[9c] which was involved the radical process.[18]

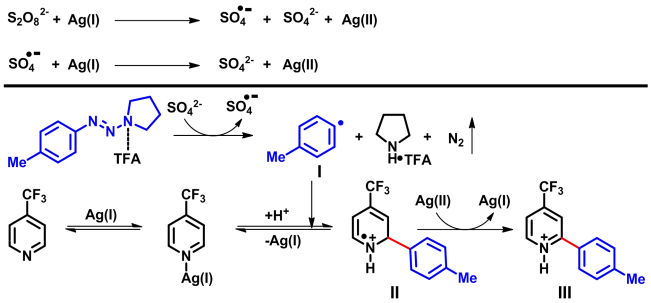
Scheme 5. Mechanistic investigation.



Based upon our results and relevant investigations by other groups, [5,9,11,19] we provided a plausible reaction pathway as shown in Scheme 6.

It is known[20] that in the presence of Ag(I)-salts, a persulfate anion disproportionates into a sulfate dianion and a sulfate radical anion. The Ag(I) salt is oxidized to a Ag(II) species by peroxydisulfate or a sulfate radical anion.

Scheme 6. Plausible reaction pathway.



Consequently, the sulfate dianion reduces the TFA-activated triazene, providing an aryl radical **I** with release of pyrrolidine salt, nitrogen and a sulfate radical anion. Further addition of this aryl radical **I** to the protonated heterocycle, providing radical cation **II**, which is oxidized by Ag(II), affording the arylated product **III** and regenerating the Ag(I) catalyst.

Conclusions

In conclusion, we reported the first example of a rapid, open-flask, single-pot, and scalable process in which aryl radicals were added to pyridine derivatives and a benzoquinone using readily available triazenes as coupling partners. In this transformation, a wide range of substrates and functional groups were compatible. Electron-withdrawing and donating group on *para*, *meta* and *ortho* positions of triazenes and pyridine derivatives were tolerated and the reaction proceeded smoothly to produce heterobiaryls in moderate to good yields. Triazenes are readily synthesized from anilines and can be easily amenable to scale up, thus the strategy provides an efficient and practical tool for the productions of useful heterobiaryls.

Notes and references

[a] Division of Chemistry, Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas, 75390-9038 United State. E-mail: rwang9@albany.edu

† Electronic Supplementary Information (ESI) available: General procedure, 1H and 13 C NMR spectrum, mechanism studies, triazenes synthesis. See DOI: 10.1039/c000000x/

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