COMMUNICATION

Multi-component Heteroarene Couplings via Polarity-reversed Radical Cascades

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A multi-component radical addition strategy enables difunctionalization of alkenes with heteroarenes and a variety of radical precursors, including N_3, $P(O)R_2$, and CF_3. This unified approach for coupling diverse classes of electrophilic radicals and heteroarenes to vinyl ethers allows for direct, vicinal C-C as well as C-N, C-P, and C-R_f bond formation.

The unique reactivity and selectivity accessible via radical addition to alkenes has significantly enabled the synthesis of valuable medicines and materials.[1] Specifically, in the realm of drug discovery, certain privileged elements and architectures (e.g. N, P, F, heteroarenes) are frequently incorporated into a medicinal candidate to improve its pharmacological properties.[2] Among the most common radical reactions used to introduce heteroarenes in this arena is the Minisci reaction.[3,4] This two-component reaction (Fig 1a) is best suited for coupling nucleophilic radicals (e.g. α-oxy) to electrophilic heteroarenes (e.g. pyridine, quinoline). Conversely, the polarity-mismatched[5] coupling of radicals and heteroarenes that are both electron-deficient is typically disfavored – with rare exceptions.[6] However, Minisci also demonstrated that a polarity-reversing strategy could bring together three components in a radical cascade (Fig 1b).[7] This underutilized approach chemoselectively combines an *in situ* generated electrophilic radical with an electron-rich alkene in the presence of an electron-deficient heteroarene. The resulting nucleophilic radical then combines with the protonated heteroarene to afford a difunctionalized product after subsequent oxidation. In a pioneering example, Minisci generated α-carbonyl radicals from acetone using Ag/S_2O_8 to initiate this cascade.[7] Later, refluxing peroxides were employed to enable the perfluoroalkyl radical ($\bullet R_f$) variant.[8]

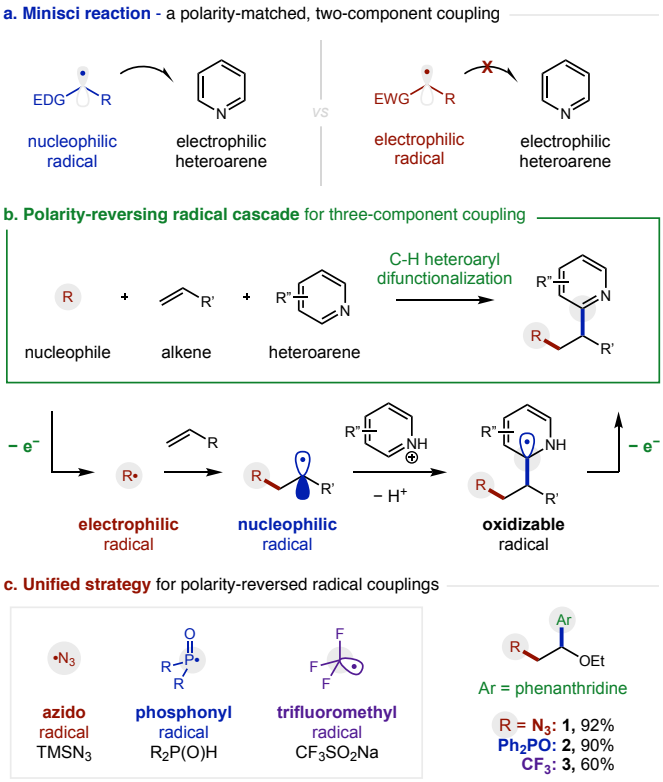

Fig. 1. Design of a unified strategy for polarity-reversal cascades

Recent efforts have focused on extending this approach to incorporate other radical partners – and to do so under milder conditions that are more suitable to medicinal applications. For example, Barriault developed a bimetallic, gold-catalyst to incorporate α-carbonyl radicals ($\bullet R_{EWG}$).[9] Herzon and Baran reported hydropyridylations (•H) with Co and Fe complexes.[10] Liu developed an azido variant ($\bullet N_3$) with iodanes, and Chu reported a photocatalytic version shortly thereafter.[11] Other photolytic methods for incorporating trifluoromethyl ($\bullet CF_3$) and phosphonyl radicals ($\bullet P(O)R_2$) have been developed by Hong, Matsunaga, and us.[12] However, in looking at the divergent

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conditions required to perform each of these specific reactions, we questioned if a single, unified strategy could be developed to enable the incorporation of multiple classes of electrophilic radicals within this cascade. The advantage of such an approach would be its utility as a robust synthetic tool to rapidly access complex molecules with vicinal substituted functionality – especially for applications in medicinal chemistry.

Towards our goal of a unified strategy, we sought to employ hypervalent iodanes, which are robust precursors for numerous electrophilic radicals (Fig 1c).[13] In particular, we hypothesized azido, phosphonyl, and trifluoromethyl radicals could all be accessed by iodane-scission reactions, as shown in Fig 2. In all three cases, a neutral or anionic reagent combines with a λ_3-iodane either directly or otherwise to form an electrophilic radical. Azido radicals **A** are formed via direct ligand displacement of $PhI(OAc)_2$ by $TMSN_3$, followed by homolysis of the weak N-I bond.[14] Conversely, we proposed that phosphonyl radicals **B** may be formed indirectly by H• abstraction of the weak P-H in $Ph_2P(O)H$ by $•N_3$.[14,15] Finally, trifluoromethyl radicals **C** may be generated by ligand displacement of $PhI(OTFA)_2$ with Langlois' reagent $NaSO_2CF_3$.[16]

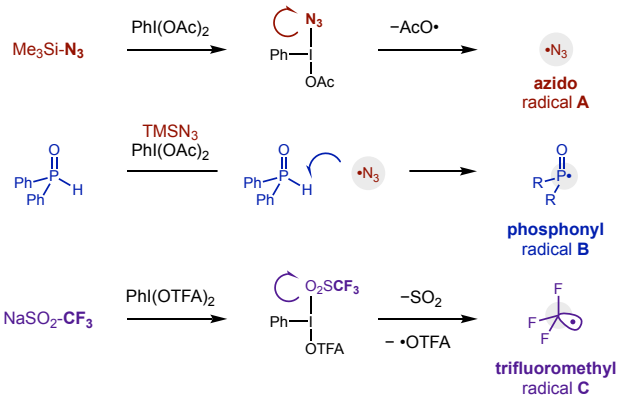
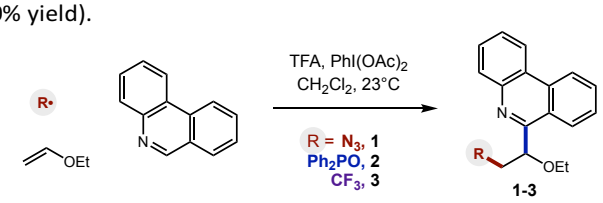


Fig. 2. Diverse electrophilic radicals from hypervalent iodanes

To our delight, upon subjecting these three, distinct radical-precursors ($TMSN_3$, $Ph_2P(O)H$, and $NaSO_2CF_3$) to an electron-rich alkene (ethyl vinyl ether) and heteroarene (phenanthridine) in the presence of $PhI(OAc)_2$ or $PhI(OTFA)_2$, all three classes of cascade reactions were accessible (**1-3;** 60-92%). As shown in Fig 3, the development of these three reactions were largely enabled by the identity of the oxidant, as well as its rate of addition. For example, in the azido variant, an initial addition of $PhI(OAc)_2$ affords only 20% yield (entry 1), likely due to rapid formation of $•N_3$ in too high of concentration. Alternatively, slow addition via syringe pump allows for efficient formation of the azido product **1** (entry 2, 92% yield). This strongly beneficial effect of slow addition was also seen for other heteroarene traps (see SI).

Next, we investigated the phosphonyl cascade reaction. As expected, direct displacement of both $PhI(OAc)_2$ and $PhI(OTFA)_2$ by diphenyl phosphine oxide is inefficient, with up to 14% yield observed only in the case of slow oxidant addition (entries 3-5). However, addition of $TMSN_3$ as an H-atom transfer mediator,[14] enables efficient formation of phosphonyl product **2** (entry 6, 90% yield).



entry	R• precursor	oxidant	addition	product	yield
1	$TMSN_3$	$PhI(OAc)_2$	t = 0	1	20%
2	**$TMSN_3$**	**$PhI(OAc)_2$**	**2 mL / hr**	**1**	**92%**
3	$Ph_2P(O)H$	$PhI(OAc)_2$	t = 0	2	0%
4	$Ph_2P(O)H$	$PhI(OTFA)_2$	t = 0	2	0%
5	$Ph_2P(O)H$	$PhI(OAc)_2$	2 mL / hr	2	14%
6	**$Ph_2P(O)H$**	**$TMSN_3$, $PhI(OAc)_2$**	**2 mL / hr**	**2**	**90%**
7	$NaSO_2CF_3$	$PhI(OTFA)_2$	2 mL / hr	3	1%
8	$NaSO_2CF_3$	$PhI(OTFA)_2$	3 mL / hr	3	35%
9	$NaSO_2CF_3$	$PhI(OTFA)_2$	6 mL / hr	3	51%
10	**$NaSO_2CF_3$**	**$PhI(OTFA)_2$**	**t = 0**	**3**	**60%**

Fig. 3. Development of three radical cascade reaction classes [a]

[a] **N_3**: Heteroarene (0.1 mmol), TFA (1 eq), $TMSN_3$ (2 eq), alkene (4 eq), $PhI(OAc)_2$ (2 eq), CH_2Cl_2 (0.05 M), 23 °C, 30 min. **P**: Heteroarene (0.1 mmol), TFA (2 eq), $TMSN_3$ (1 eq), phosphine oxide (6 eq), alkene (2 eq), $PhI(OAc)_2$ (2 equiv), CH_2Cl_2 (0.05 M), 23 °C, 30 min. **CF_3**: Heteroarene (0.1 mmol), TFA (1 eq), $NaSO_2CF_3$ (2 eq), alkene (2 eq), $PhI(OTFA)_2$ (2 eq), MeCN (0.1 M), 23 °C, 45 min. Yields determined by NMR.

Finally, we investigated the trifluoromethyl radical-mediated variant of this cascade. Knowing that $NaSO_2CF_3$ does not efficiently displace the ligands of $PhI(OAc)_2$ at room temp, we used the more reactive oxidant, $PhI(OTFA)_2$. Interestingly, in the event of slow oxidant addition, slow rates of both iodane substitution and ensuing formation of $•CF_3$ resulted in low reactivity (entries 7-9). Thus, for the CF_3 cascade reaction, we found that addition of the reagent at t = 0 is optimal, affording trifluoromethyl product **3** (entry 10, 60% yield).

With a unified, iodane-mediated strategy in hand for heteroaryl difunctionalization of alkenes by a polarity-reversing radical cascade, we wished to investigate the generality of these three classes of reactions. In the azido three-component coupling (Fig. 4), we were pleased to find the phenanthridine-based protocol could be extended to include several other electronically diverse heteroarenes. For example, both isoquinolines (**4**-**10**) and quinolines (**11**-**12**), bearing various functional groups, including ketones, esters, amides, and halides, were tolerated. Additionally, in place of ethyl vinyl ether, 2,3-dihydrofuran could be used as the alkene partner to afford azido furan **13** as a single diastereomer (> 20:1 d.r.). Unfortunately, non-ethereal alkenes were inefficient coupling partners – providing diminished reactivity in all three radical cascades.[17]

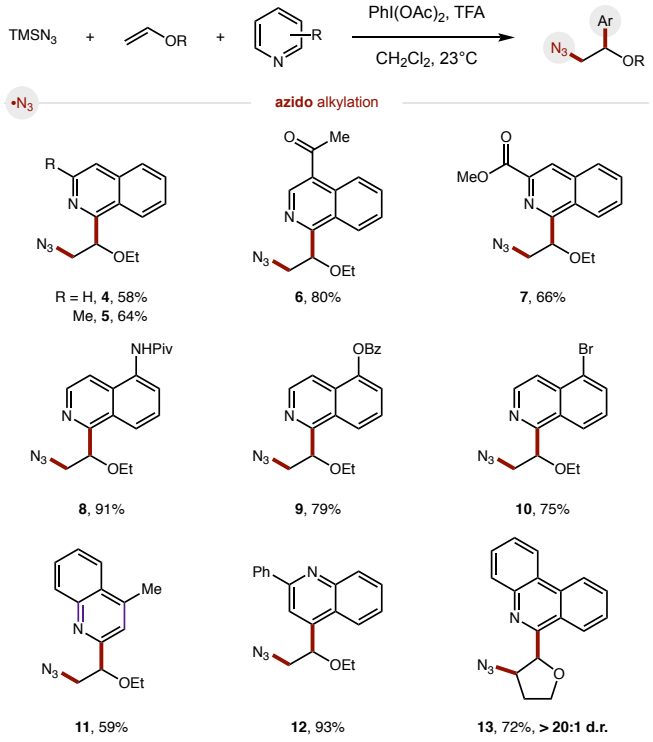


Fig. 4. Azido three-component coupling

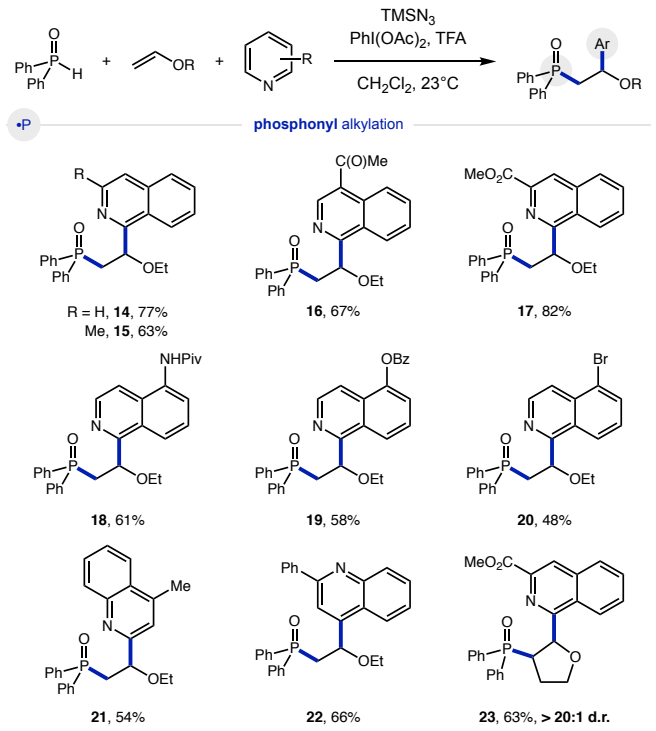


Fig. 5. Phosphonyl three-component coupling

Due to the importance of phosphorus motifs in materials and medicines, we then turned our attention to exploring the scope of the phosphonyl three-component coupling (Fig. 5). As in the case of the azide variant, the incorporation of diphenyl phosphine oxide through phosphinylalkylation of heteroarenes was efficient and synthetically generalizable. Similarly, both isoquinolines (**14**-**20**, **23**) and quinolines (**21**-**22**) were tolerated. Synthetic utility was again demonstrated by the incorporation of various functional groups, including ketones, esters, amides, and halides. Notably, aryl bromide **20**, which may undergo deleterious halide abstraction by phosphonyl radicals, was tolerated. And as before, both the 2- and 4- positions of quinoline are susceptible to efficient addition when the other position is blocked with a substituent. To our delight, furan derivative **23** was also accessed from the cyclic precursor in high diastereoselectivity (> 20:1 d.r.).

Finally, given the ubiquity of trifluoromethyl groups in medicine, we also sought to explore the generality of the trifluoromethyl three-component coupling (Fig. 6). Despite the use of the more reactive oxidant, $PhI(OTFA)_2$, the reaction scope appears similarly general to the other two cascade reaction classes. To test this reaction in more complex and challenging cases, ketones and halides were included in the heteroarene component at varying positions without issue (**24**-**27**). Similarly, a cyclic alkene was employed – affording a single diastereomer of the fluoroalkylated heteroarene (> 20:1 d.r.).

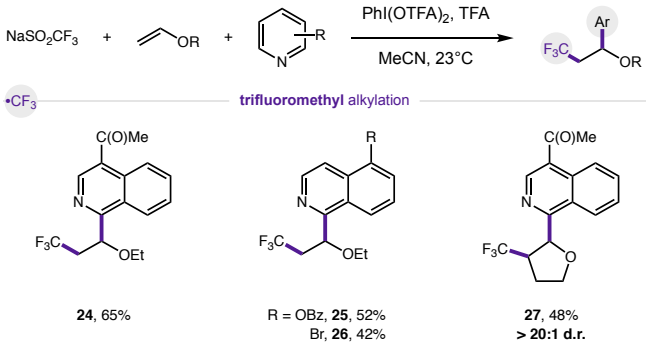


Fig. 6. Trifluoromethyl three-component coupling

In conclusion, we have demonstrated the development of a unified, modular strategy for three-component couplings to access alkyl heteroarenes in which three contiguous carbons contain biologically valuable substitution (N, P, R_f, O, pyridine). The synthetically facile approach employs hypervalent iodine reagents to generate azido, phosphonyl, and trifluoromethyl radicals, which chemo- and regio-selectively combine with enol ethers and heteroarenes. The mildness of the platform permits wide functional group tolerance and enables the synthesis of diverse classes of heteroarenes with medicinal relevance.

Conflicts of interest

There are no conflicts to declare

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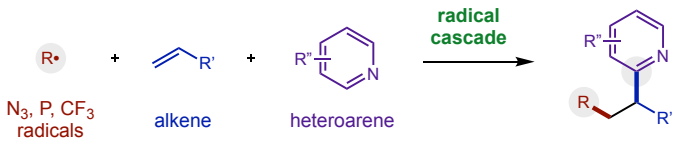
17 Non-ethereal alkenes afford the following yields for each reaction: N_3 (53%), P (35%), and CF_3 (10%). A likely explanation is the decreased nucleophilicity of the intermediate, non-ketyl, alkyl radical is less suited to heteroarene addition than to competing pathways (e.g. oxidation or H-atom transfer).

TOC Graphic



A unified strategy enables multi-component radical addition cascades to couple alkenes, heteroarenes, and various radicals, including N_3, $P(O)R_2$, and CF_3.