

Silver-catalyzed C- to N-center Remote Arene Migration

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ABSTRACT: The first 1,4-arene migration from a carbon to a nitrogen center, induced by iminyl radicals generated from radical additions to vinyl azides, is reported. Two different modes of vinyl azide activation trigger this migration process, which offers a mild route for the synthesis of trifluoromethyl- or sulfonyl-substituted β -enamino ketones. Mechanistic studies reveal a dual role for the silver catalyst, and provide insight into the nature of the migration by demonstrating the positional influence of arene substituents on arene migratory aptitude. By in situ generation of the key migration substrate from readily available precursors, this method offers a new strategy for achieving remote C-to-N group migration, and more generally for the formal activation of C–C bonds.

Selective C–C bond cleavage is one of the most challenging topics in organic synthesis.¹ Among various strategies, radical migration reactions have recently attracted great interest.² However, these processes are mostly limited to functional group migration between carbon centers,³ whereas group migrations induced by heteroatom-centered radicals remain largely underdeveloped.⁴ The main challenge for the latter lies in the difficulty of both generating a heteroatom radical species, and triggering a subsequent, selective, functional group migration. In this context, the groups of Shi,^{4a} Nevado,^{4b} and Liu^{4c} successively reported the sole examples of arene migrations from carbon centers to N-centered aminyl or sulfonamidyl radical intermediates (Figure 1a), the generation of the nitrogen radical was achieved by amine oxidation through single electron transfer.⁴

We targeted a new method to achieve C-to-N remote group migration, in which an iminyl radical would serve as the arene acceptor. Although iminyl radicals have been exploited in a wide range of processes,⁵ including 1,5-HAT,⁶ cyclization,⁷ and hydrolysis⁸ reactions, to our knowledge this important class of N-centered radical has not been explored in functional group migrations. Vinyl azides, themselves a versatile synthon,⁹ can serve as a source of iminyl radicals via radical addition to the alkene, with subsequent loss of molecular nitrogen.^{6b,10} Building on our interests in combining silver catalysis with vinyl azide chemistry,¹¹ we questioned whether this unusual mode of iminyl radical generation could trigger novel C-to-N remote functional group migrations. Stabilization of the resulting C-centered radical would be expected to facilitate this rearrangement; we identified tertiary (hetero)aryl alcohols as potential candidates, where C–C bond cleavage would lead to a tertiary, hydroxyl-stabilized, C-centered radical. Here we describe the realization of this unprecedented silver-catalyzed iminyl radical-mediated (hetero)arene migration. This process is triggered either by the addition of trifluoromethyl radicals to pre-formed vinyl azides, or by a three-component coupling of homopropargylic alcohols, trimethylsilyl azide and sulfinate salts where in situ formation of the vinyl azide precedes sulfonyl radical addition / iminyl radical formation / migration (Figure 1b). Not only does this chemistry represent a conceptually novel strategy in radical-mediated group migrations, but also offers a mild route to synthetically useful trifluoromethyl- and sulfonyl-substituted β -enamino ketones.¹²

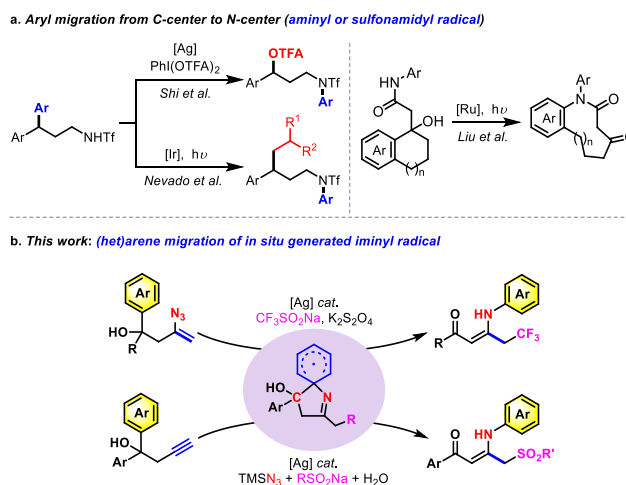


Figure 1. Remote Radical-mediated (Hetero)Aryl C- to N-Center Migrations.

Investigations commenced with the reaction of 3-azidyl homoallylic alcohol **1a** (formed from silver-catalyzed hydroazidation of the homopropargylic alcohol) with the Langlois reagent **2a** (Table 1). We were delighted to find that in the presence of 10 mol% of Ag₂CO₃ in DMSO at 60 °C, addition of the trifluoromethyl group indeed led to the desired arene migration product **3a**, which was obtained in 58% yield (Table 1, entry 1). A range of silver salts proved effective, with Ag₃PO₄ delivering an optimum yield of 85% (entries 2-8). The product structure (and (Z)-configuration) was confirmed via X-ray diffraction analysis. Both the silver salt and K₂S₂O₈ were found to be essential; only trace amounts of **3a** were obtained in the absence of K₂S₂O₈ (entry 8), and poor yield (20%) was observed without silver salt (entry 9). The reaction was also highly solvent-dependent, with CH₃CN and 1,4-dioxane affording only trace amounts of **3a** (entries 10 and 11). Reaction under aerobic conditions produced the desired product in a slightly decreased yield (70%) (entry 12). Finally, increasing or reducing the reaction temperature diminished the yield (entries 13 and 14).

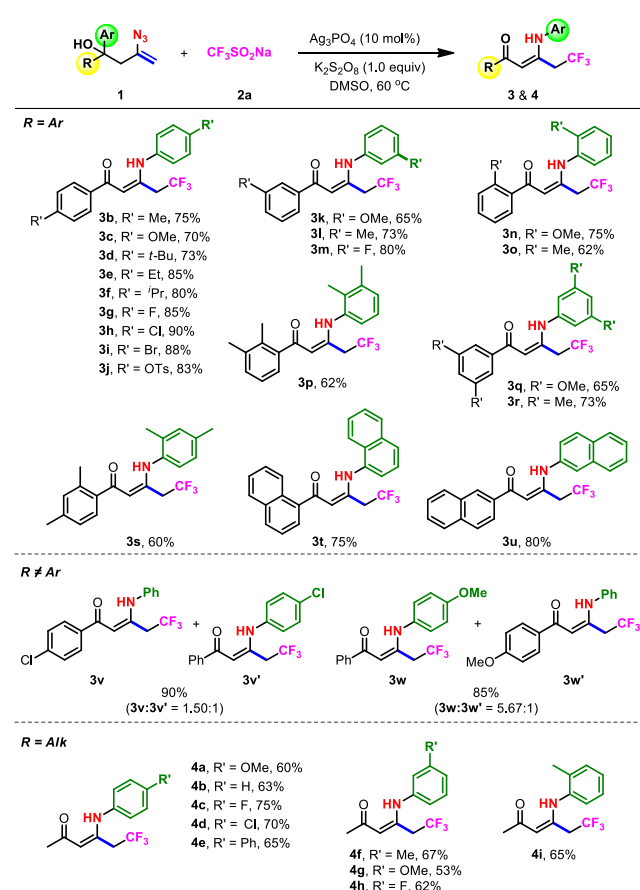
Table 1. Optimization of the Reaction Conditions^a

entry	[Ag]	amount	solvent	T (°C)	yield (%) ^d
1	Ag ₂ CO ₃	10 mol%	DMSO	60	58
2	Ag ₃ PO ₄	10 mol%	DMSO	60	85
3	AgF	10 mol%	DMSO	60	37
4	AgOAc	10 mol%	DMSO	60	35
5	AgNO ₃	10 mol%	DMSO	60	62
6	AgNO ₃	20 mol%	DMSO	60	73
7	AgNO ₃	30 mol%	DMSO	60	80
8 ^b	Ag ₃ PO ₄	10 mol%	DMSO	60	trace
9	Ag ₃ PO ₄	0	DMSO	60	20
10	Ag ₃ PO ₄	10 mol%	CH ₃ CN	60	trace
11	Ag ₃ PO ₄	10 mol%	1,4-Dioxane	60	trace
12 ^c	Ag ₃ PO ₄	10 mol%	DMSO	60	70
13	Ag ₃ PO ₄	10 mol%	DMSO	80	50
14	Ag ₃ PO ₄	10 mol%	DMSO	40	35

^a Standard reaction conditions: **1a** (0.30 mmol), **2a** (0.60 mmol), K₂S₂O₈ (0.30 mmol), in DMSO (3 mL) at 60 °C under N₂ for 12 h; ^b Without K₂S₂O₈; ^c In the air; ^d Yield of isolated product.

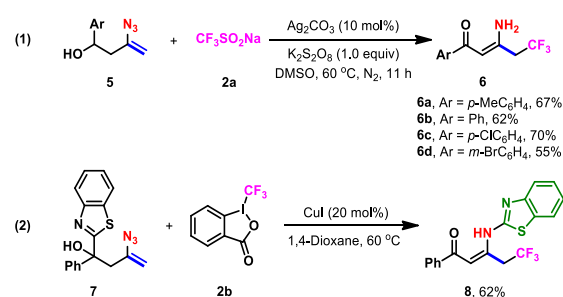
We next set out to examine the scope with respect to the 3-azidyl homoallylic alcohol (Scheme 1). Substrates with arene groups bearing electron-donating substituents at the *para*-position of the aryl ring afforded the migration products in good yields (**3b–3j**, 70–90%). Notably, halides (**3h** and **3i**, 88–90%) were tolerated in this radical reaction, providing a platform for further manipulation of the products. Meta-substituted arenes also proved effective substrates, giving products **3k–3m** in 65–80% yield. Steric hindrance did not impede product formation, with *ortho*- and *di*-substituted arenes **3n–3s** also giving the desired products in good yield (60–73%). Naphthyl groups could similarly participate smoothly in the migration process, delivering products **3t** and **3u** in 75% and 80% yield respectively. We next investigated the migrating ability of different aryl groups in non-symmetric *bis*-aryl homoallylic alcohols, and found that the electronic influence of the arene substituents played a crucial role in migration selectivity: for **1v** (phenyl / 4-chlorophenyl groups) the relatively electron-rich phenyl ring was preferentially transferred to give **3v** as the major product (**3v**/**3v'** = 1.50/1). In the more electronically-biased system **1w** (4-methoxyphenyl / phenyl), migration of more the electron-rich PMP group was observed in a higher ratio (**3w**/**3w'** = 5.67/1). We also examined 3-azidyl homoallylic alcohols containing alkyl groups; here, the reactions proceeded with complete chemoselectivity to give the arene migration product in moderate to good yields (**4a–4i**, 53–75%).

The reactivity of secondary homoallylic alcohols was also examined (Scheme 2, Eq. 1). Successful reaction was again observed, but here the hydrogen atom migration products (**6a–6d**) were obtained exclusively, irrespective of the electronics of the arene substituents.¹³ Encouraged by these results, we speculated that heteroaryl migration could also take place, for which we selected benzothiazole-substituted tertiary alcohol **7** (Eq. 2).

Scheme 1. Reaction Scope of 3-Azidyl Homoallylic Alcohols^a


^a Reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), K₂S₂O₈ (0.30 mmol), Ag₃PO₄ (10 mol%), in DMSO (3.0 mL) at 60 °C under N₂ for 12 h; Isolated yields.

Under the standard silver-catalyzed conditions using **2a** as the CF₃ source, heteroaryl migration product **8** was indeed obtained, albeit in low yield. Fortunately, switching to the Togni reagent and copper catalysis proved highly effective, delivering the desired migration product **8** in 62% yield, with complete selectivity for heteroaryl migration. To date, only one example of remote radical heteroaryl migration from C- to N-center has been reported.^{4c} Interestingly, application of these conditions to substrate **1a** was less successful, with the rearranged product recovered in low yield.

Scheme 2. Reactions of Secondary and Heteroaryl-substituted Alcohols.


Approaches that do not require pre-formation of the vinyl azide would offer a significant advance in the efficiency of the migration process. Given that silver catalysis is used to effect alkyne hydroazidation¹¹ as well as iminyl radical formation, we

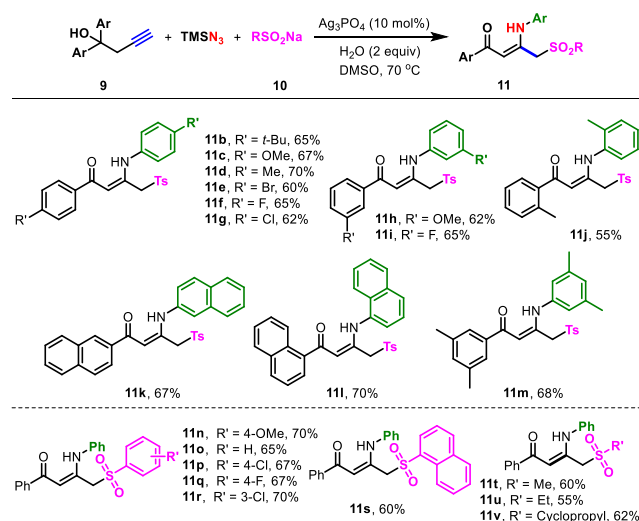
questioned whether it would be possible to realize a novel multicomponent *C*-center to *N*-center radical-mediated remote arene migration reaction starting from a homopropargylic alcohol, azide source, and radical precursor. After some experimentation, it was found that the combination of trimethylsilyl azide as the nitrogen atom source, and sodium sulfinates as radical precursors, indeed enabled this one-pot alkyne hydroazidation / sulfonylation / arene transfer sequence. As shown in Scheme 3, the reaction of homopropargylic alcohol **9a**, TMSN_3 and sodium *p*-toluenesulfinate **10a**, in the presence of Ag_3PO_4 (10 mol%) and H_2O (2 equiv.) in DMSO at 70 °C, delivered product **11a** in 64% yield, the structure of which was confirmed by X-ray crystallography (for full details of reaction optimization, see the Supporting Information). To our knowledge, this is the first *C*-to-*N* arene in which incorporation of the migrating group and acceptor *N*-center into a single molecular structure is achieved in situ.⁴ In the present setting, this represents a conceptually new entry to synthetically useful β -enamino- δ -ketosulfones.¹²

Scheme 3. Optimization of a Multicomponent Alkyne Hydroazidation / Sulfonylation / Arene Transfer Sequence.



Having developed conditions for efficient *C*-to-*N* aryl migration of homopropargylic alcohol **9a**, the scope of the process was investigated using a range of alcohols and sulfinates (Scheme 4). Migrating arene groups bearing *para*-electron-donating substituents (**11b–11d**) and electron-withdrawing halogen groups (**11e–11g**) gave the migration products in uniformly good yields (60–70%). *Meta*-substituted arenes also proved effective, affording products **11h** and **11i** in 62% and 65% yield respectively. Substrates with increased steric bulk on the

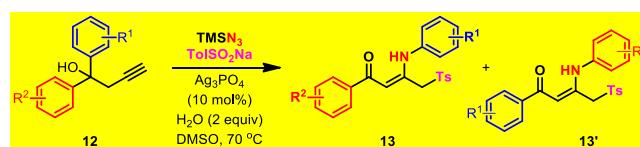
Scheme 4. Reaction Scope: Symmetrical Homopropargylic Alcohols and Sulfinates



migrating group were again successful, with *ortho*-tolyl migration proving only slightly less effective (**3j**), as were naphthyl groups (**11k** and **11l**, 67% and 70% yield respectively) and disubstituted arenes (**11m**). The sulfinate scope was surveyed using homopropargylic alcohol **9a**; pleasingly, a range of sulfinates proved suitable, delivering the corresponding addition / migration products in good yields. The electronic properties of the aryl sulfinate showed a relatively small influence, affording β -enamino- δ -ketosulfones (**11n–11s**) with comparable efficiency. Alkyl sulfinates also furnished the desired migration products (**11t–11u**) in reasonable yields.

As with trifluoromethyl radical addition, the use of non-symmetric homopropargylic alcohols again raises an interesting question on the chemoselectivity of the migration, the answer to which could provide useful mechanistic information (see below), as well as affording more functionalized products. To this end, a range of non-symmetric biaryl propargylic alcohols **12a–12p** were prepared and subjected to the optimized rearrangement conditions (Table 2). Competition between various arenes and phenyl (Entries 1–10) again revealed a clear trend for preferential migration of the more electron-rich arene. These results suggested that the least efficient migrating group (*p*-trifluoromethylphenyl, Entry 10) could serve as a 'dummy' substituent, enabling the selective migration of other arenes. Pleasingly, this indeed turned out to be the case, with an optimum selectivity ratio of 7.21:1 in the competition between *p*-MeO- and *p*-CF₃-substituted arenes (Entry 11). This principle could be applied to

Table 2. Migratory Aptitude Study^a



Entry	12	R ¹	R ²	major migration	yield (%) ^b	ratio (13 : 13') ^c
1	12a	4- <i>t</i> -Bu	H	4- <i>t</i> -BuC ₆ H ₄	75	4.20 : 1
2	12b	4-MeO	H	4-MeOC ₆ H ₄	65	3.34 : 1
3	12c	4-Me	H	4-MeC ₆ H ₄	67	2.85 : 1
4	12d	3-MeO	H	3-MeOC ₆ H ₄	72	1.22 : 1
5	12e	3-Me	H	3-MeC ₆ H ₄	64	1.15 : 1
6	12f	4-F	H	C ₆ H ₅	62	1 : 1.25
7	12g	3-Cl	H	C ₆ H ₅	64	1 : 1.35
8	12h	3-CF ₃	H	C ₆ H ₅	50	1 : 1.41
9	12i	4-Cl	H	C ₆ H ₅	60	1 : 1.75
10	12j	4-CF ₃	H	C ₆ H ₅	60	1 : 2.34
11	12k	4-MeO	4-CF ₃	4-MeOC ₆ H ₄	72	7.21 : 1
12	12l	3-MeO	4-CF ₃	3-MeOC ₆ H ₄	66	5.75 : 1
13	12m	4-MeO	4-Cl	4-MeOC ₆ H ₄	65	4.64 : 1
14	12n	3-MeO	4-Cl	3-MeOC ₆ H ₄	62	3.74 : 1
15	12o	4-Me	4-CF ₃	4-MeC ₆ H ₄	60	4.82 : 1
16	12p	4-Cl	3-CF ₃	4-ClC ₆ H ₄	55	1.76 : 1

^a Conditions: **12** (0.5 mmol), TMSN_3 (1.0 mmol), **10a** (1.0 mmol), H_2O (1.0 mmol), in DMSO (2 mL), 70 °C, 4 h, under air; Yields are isolated yields. ^b Total yield of two isomers. ^c Isomer ratio determined by integration of the CH_2Ts signals in the ¹H NMR spectrum of the crude reaction mixture.

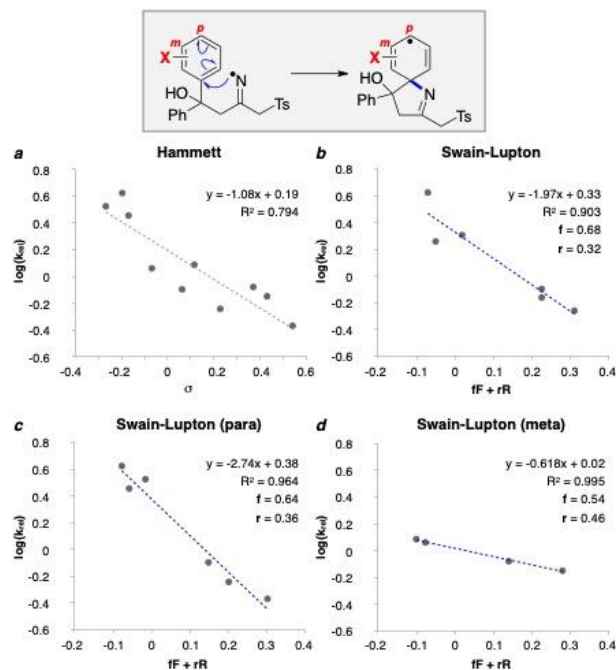


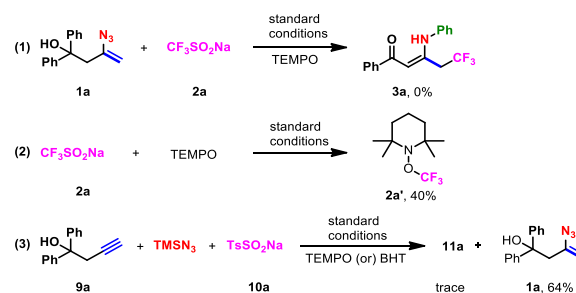
Figure 2. Hammett and Swain-Lupton Analysis of Chemoselectivity in the Arene Migration

a variety of other migrations (Entries 12-16), and could even favor migration of an electron-deficient *p*-chlorophenyl group (compare Entry 16 with Entry 9).

The migratory aptitude results in Table 2 led us to consider whether linear free energy relationships could provide further insight into the nature of the rearrangement. Figure 2a shows a Hammett plot (based on Entries 1-10 of Table 2), the general trend of which reflects a modest buildup of positive charge on the arene in the migration ($\rho = -1.08$, $r^2 = 0.79$), which would be consistent with a radical-based mechanism. To explore the relative contributions of inductive and mesomeric effects, we performed a Swain-Lupton analysis (Figure 2b);¹⁴ *f* (field) and *r* (resonance) values of 0.68 and 0.32 suggest a balance of these factors is important. Interestingly, separate Swain-Lupton analyses of *para* and *meta* substituents (Figure 2c and 2d) revealed quite different susceptibilities of the migration to electronic effects, and a better fit of the LFERs ($r^2 > 0.95$). For *para* substituents, a more pronounced influence of the substituent is observed ($\rho = -2.74$) compared to *meta* substituents ($\rho = -0.62$), which would be consistent with the greater ability of *para* substituents to influence the stability of a radical on the adjacent carbon atom in the putative spirocyclic migration intermediate.¹⁵

Further mechanistic insight into both reactions was obtained by conducting the reactions in the presence of the radical trapping agents TEMPO or butylated hydroxytoluene (BHT) (Scheme 5). The formation of **3a** from **1a** was completely inhibited when TEMPO (2.5 equiv.) was added to the reaction mixture, with adduct **2a'** observed along with 85% recovery of **1a** (Eq. 1). In addition, **2a'** was directly isolated from the reaction of $\text{CF}_3\text{SO}_2\text{Na}$ with TEMPO under the standard reaction conditions (40% yield, identity determined by ^{19}F NMR spectroscopy) (Eq. 2). Furthermore, attempted reaction of **9a** in the presence of TEMPO or BHT led solely to the isolation of vinyl azide **1a** (64%). These results show that while vinyl azide formation itself does not involve radical intermediates, the

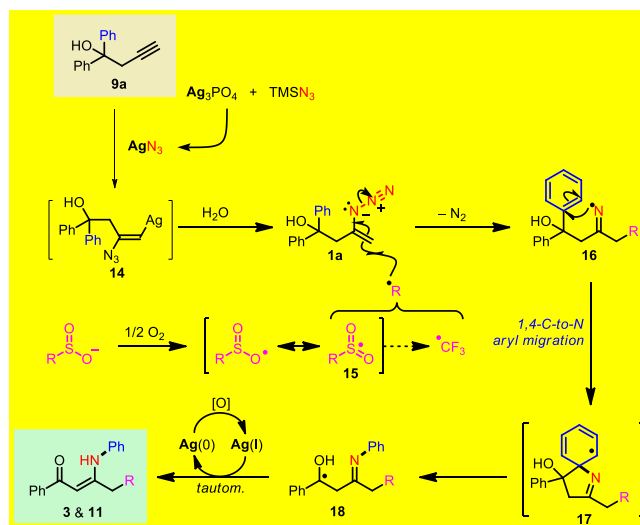
Scheme 5. Mechanistic Studies



decomposition of the vinyl azide to the putative iminyl radical via addition of trifluoromethyl or sulfinyl group likely does.

Based on these observations, and established sulfonyl radical¹⁶ and vinyl azide chemistry,⁹ a plausible pathway for these transformations is outlined in Scheme 6. Initial reaction of Ag_3PO_4 and TMSN_3 generates silver azide,¹⁷ which adds to the alkyne to generate the *trans*-alkenylmetal complex **14**. Protonation of **14** by water generates vinyl azide **1a**.^{11c} Meanwhile, sulfonyl radical **15** is produced either from aerobic oxidation of the sulfinate ion,¹⁶ or from silver-mediated oxidation. The latter could proceed from an Ag(II) complex generated from persulfate oxidation of Ag(I) , or indeed from the Ag(I) salt itself. In the case of the trifluoromethyl addition, loss of SO_2 to generate the CF_3 radical is presumably more rapid than addition of the sulfinyl radical to the vinyl azide, whereas for aryl / alkyl sulfinyl groups, direct addition is observed. In either case, an iminyl radical **16** is generated via expulsion of molecular nitrogen.^{11b,8c} Following 5-*exo* intramolecular radical attack on the arene substituent of the homopropargylic alcohol, the key transient spiro radical **17** is formed, with C-to-N aryl migration giving **18** by cleavage of the C-C bond to the alcohol-bearing carbon. This mode of cyclization is consistent with mechanistic explorations in previous iminyl radical cyclization reactions, where in the present case the driving force of generating a radical stabilized by both a benzene ring and hydroxyl group enables productive fragmentation.¹⁸ Subsequently, **17** is oxidized by silver(I) to produce a cationic intermediate, which gives products **3a** and **11a** by loss of a proton and tautomerization. The silver(0) species generated in this process can be re-oxidized to Ag(I) by oxygen, or $\text{S}_2\text{O}_8^{2-}$.

Scheme 6. Possible Mechanism for C-to-N Arene Migration



In conclusion, we have developed an unprecedented remote C-to-N arene migration induced by in situ generation of iminyl radicals from vinyl azides. Two different radical precursors are demonstrated to trigger this process, either through reaction of 3-azidyl homoallylic alcohols with trifluoromethyl radical, or a multicomponent reaction of homopropargylic alcohols, trimethylsilyl azide, and sulfinate salts. Both reactions afford synthetically useful products from readily available starting materials. Mechanistic insight was provided through migratory aptitude and radical trapping experiments, with LFER analyses further supporting a radical-based mechanism. This work opens new avenues for exploration of rarely reported radical-mediated C-to-N functional group migrations using variety of radical 'triggers'; studies to expand this migration chemistry to other functional groups are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and copies of NMR spectra are available free of charge via the Internet at (<http://pubs.acs.org/page/jacsat/submission/authors.html>).

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Notes

The authors declare no competing financial interest.

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