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Transition Metal Free C−N Bond Forming Dearomatizations and Aryl C−H Aminations by in Situ Release of a Hydroxylamine-Based Aminating Agent

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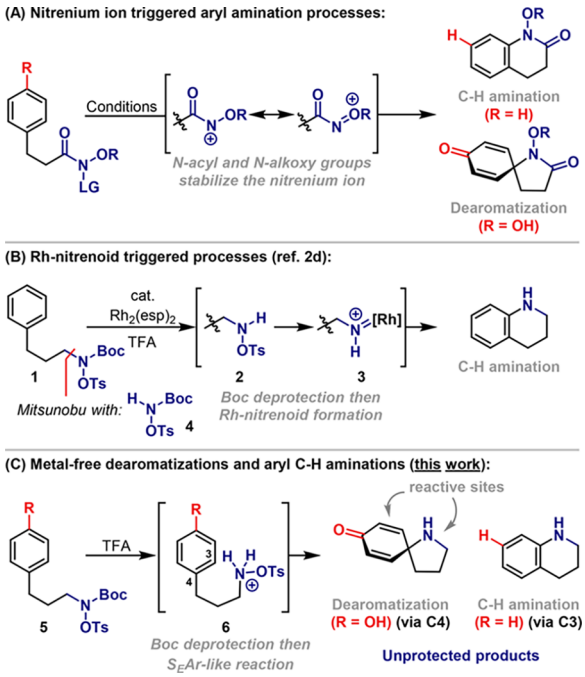
Supporting Information

ABSTRACT: We outline a simple protocol that accesses directly unprotected secondary amines by intramolecular C−N bond forming dearomatization or aryl C−H amination. The method is dependent on the generation of a potent electrophilic aminating agent released by in situ deprotection of O-Ts activated N-Boc hydroxylamines.

General methods for intramolecular electrophilic C−H amination of aromatic units are rare,[1−5] and very few of these are transferable to C−N bond forming dearomatization reactions.[1c,d,f,g,6] Classically, the most powerful approach harnesses the intermediacy of nitrenium electrophiles; however, their high reactivity necessitates stabilizing functionality, with efficient protocols restricted to the provision of lactams equipped with specific N-protecting groups (Scheme 1A).[1] To circumvent these limitations, Falck and co-workers recently disclosed intramolecular aryl C−H amination processes triggered by rhodium nitrenoids **3**; these were generated from activated hydroxylamines **2**, which, in turn, were accessed by in situ deprotection of N-Boc precursors **1** (Scheme 1B).[2d] This approach is notable because (a) it allows the direct preparation of unprotected nitrogen ring systems by aryl C−H amination and (b) precursors **1** are directly accessible by Mitsunobu alkylation of bifunctional amino-reagent **4**.

Scheme 1. Introduction



As part of an ongoing program aimed at exploiting electrophilic nitrogen sources for heterocycle synthesis,[7] we considered whether the Falck approach could be adapted to C−N bond forming dearomatizations of phenols **5** (R = OH) (Scheme 1C).[8] Such a process would allow the direct preparation of complex "3-dimensional" heterocycles from simple precursors.[9] Contrary to our initial expectations, we disclose herein that hydroxylammonium intermediates **6** are in fact sufficiently reactive that C−N bond formation occurs efficiently in the absence of a rhodium catalyst. The method can be used to promote both the envisaged C−N bond forming dearomatizations as well as aryl C−H aminations, with the former providing products equipped with nucleophilic and electrophilic functionality that can be engaged directly in further annulations. The processes are rather unusual, apparently involving direct S_EAr-like attack of the aromatic moiety onto the activated hydroxylammonium unit (**6**), which is generated in situ under mild conditions. The studies described here suggest that intermediates of this type might have the potential to facilitate a wide range of transition metal free C−N bond formations.

In initial studies, we examined the cyclization of a TFE solution of phenolic system **5a**,[10] which was prepared in high yield by Mitsunobu alkylation of **4** (see the SI). To our delight, in the presence of TFA (2 equiv) and $Rh_2(esp)_2$ (2 mol %), spirocyclic target **7a** was generated in 88% NMR yield (Table 1). However, further control experiments revealed that the rhodium catalyst was not required, with **7a** formed in 77% yield in its absence. Upon completion of the reaction, **7a** could be isolated as its TsOH salt in sufficient purity for most purposes by simply removing volatile components under reduced pressure. Alternatively, and despite its obvious sensitivity, we established that chromatographic purification of **7a** is possible using Et_3N washed silica. Fractions containing the product were acidified with TFA to afford the TFA salt of **7a**; with the nitrogen protonated, the product was relatively resistant to polymerization and other decomposition pathways (vide infra). This purification procedure was used for other sensitive products described later (see the SI).

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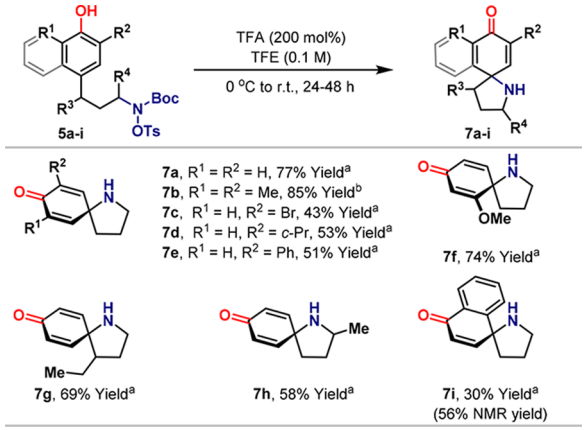
Table 1. C−N Bond Forming Dearomatizations of *para*-Phenols and Naphthols

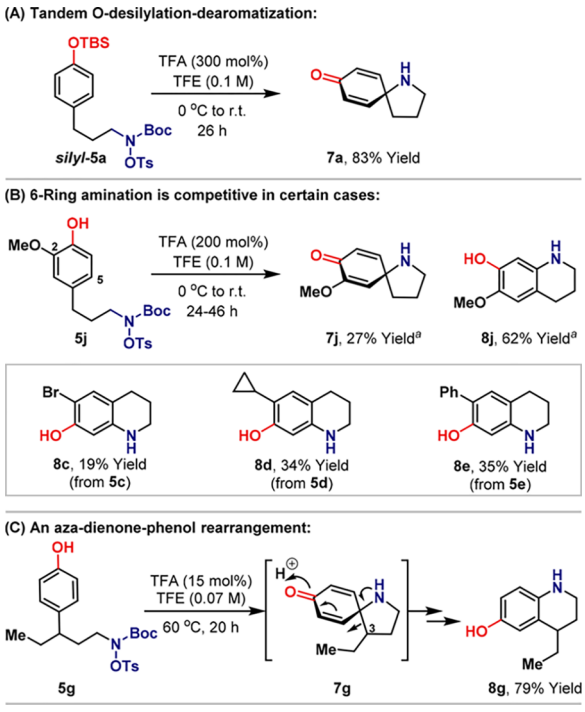


[a]Isolated as the TFA salt. [b]Isolated as the free base.

Examination of the scope of the process revealed that it tolerates a wide range of differentially substituted *para*-phenols, such that **7b−f** were all formed in synthetically useful yields (Table 1). Spirocycle **7b** exhibited good levels of stability as its free base, and this allowed unambiguous confirmation of its structure by single crystal X-ray diffraction. The process also extended to *para*-naphthol system **5i**, which provided **7i** in 56% NMR yield; purification of this product was challenging owing to its high sensitivity and the modest isolated yield (30%) reflects this. Systems with substitution on the pyrrolidine ring can also be generated, as demonstrated by the efficient synthesis of **7g** and **7h**.[11]

The studies outlined in Table 1 provided further useful and insightful observations, and these are summarized in Scheme 2. If desired from a synthetic viewpoint, the dearomatization process

Scheme 2. Key Observations



[a]Yield determined by ^{1}H NMR analysis vs 1,3,5-trimethoxybenzene.

can be performed with equal levels of efficiency from silyl protected phenols. For example, we found that O-TBS system ***silyl*-5a** (the precursor to **5a**) generated **7a** in 83% yield simply by using an extra equivalent of TFA in the dearomatization reaction (Scheme 2A). In certain cases, we observed the formation of tetrahydroquinoline products in addition to the desired spirocyclic targets. This competing process was most apparent for methoxy-substituted system **5j**, which cyclized to provide a 1:2 mixture of spirocycle **7j** and tetrahydroquinoline **8j** (Scheme 2B). C−H amination is likely facilitated by the electron donating methoxy group, which activates the *para*-position (C5) of **5j**. This side process was observed to a lesser extent for other systems possessing *para*-directing substituents at C2. Indeed, in addition to spirocycles **7c−e**, tetrahydroquinolines **8c−e** were also isolated in 19−35% yield. **7d** was recovered unchanged when resubjected to the reaction conditions, supporting the idea that tetrahydroquinoline **8d** arises via a direct aryl C−H amination pathway rather than by rearrangement of **7d**. Although side products of this type were not observed for the other examples studied in Table 1, we have found that in certain cases other tetrahydroquinoline substitution patterns can be accessed via a mechanistically distinct pathway. When the cyclization of **5g** was run using only 15 mol % TFA at 60 °C (vs 200 mol % at r.t. in Table 1), **7g** was not observed and, instead, tetrahydroquinoline **8g** formed in 79% yield (Scheme 2C). Control experiments indicate that initial spirocyclization does occur, but the lower equivalents of acid mean that the amine of **7g** is not fully protonated and so its lone pair can trigger a thermally promoted aza-dienone-phenol rearrangement to provide **8g**.[1c,d,2a,12,13] This process was not readily achieved for systems without a substituent at C3, likely due to the lower migratory aptitude of the associated C−C bond.[14]

The C−N bond forming dearomatization method can be extended to *ortho*-substituted phenols and naphthols (Table 2). Spirocyclization of phenols **5k** and **5l** provided **7k** and **7l** in 91% and 78% yield, respectively. Note that **7k** formed cleanly, which highlights the high efficiency of the process in favorable cases. Naphthol systems **5m−q** also participated smoothly to provide targets **7m−q** in generally good yield. In certain cases (e.g., **5q** to **7q**), the addition of CH_2Cl_2 cosolvent was necessary to mitigate the low solubility of the substrate in TFE. Overall, the results in Tables 1 and 2 show that the dearomatization method has a useful level of scope with respect to the arene.

The processes described here provide, for the first time, a direct C−N bond forming dearomatization approach to unprotected pyrrolidine derivatives, and so further manipulations can be achieved by direct reaction at nitrogen. N-Acylation of **7a** and **7g** with phenylacetyl chloride provided amides **9a** and **9g**, which, upon treatment with LHMDS, cyclized to provide tricycles **10a** and **10g** with good levels of efficiency (Scheme 3). The relative stereochemistry of the major diastereomer of **10g** was determined by single crystal X-ray diffraction and other assignments were supported by NOE studies (see the SI). Reaction of **7g** with phenyl isocyanate provided directly tricyclic urea **11g** in 75% yield and 4:1 d.r. Similar processes were investigated on spirocycle **7k**, which was used without purification after the dearomatization step. Here, N-acylation with phenylacetyl chloride was followed by 1,2-addition of the lithium enolate onto the carbonyl to generate product **12k** in >15:1 d.r. Reaction of **7k** with phenyl isocyanate afforded urea **11k** in 68% yield. The processes in Scheme 3 validate simple and direct entries to complex natural product-like structures.

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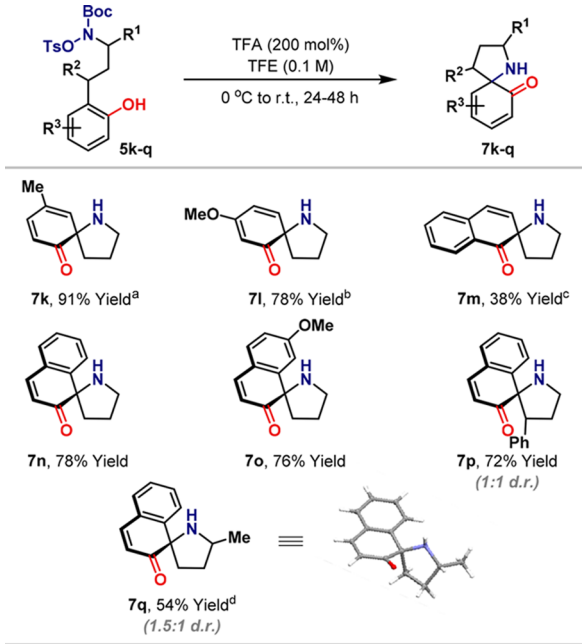
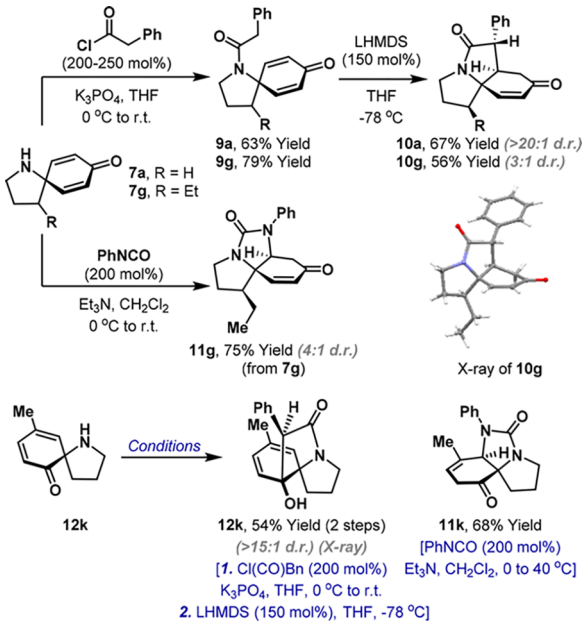
Table 2. C−N Bond Forming Dearomatizations of *ortho*-Phenols and Naphthols



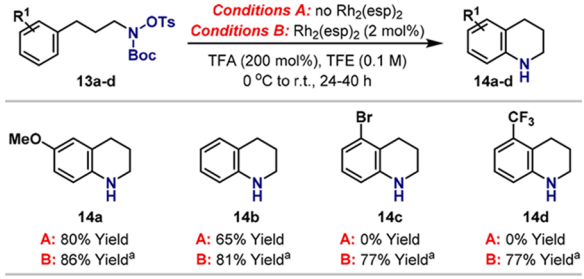
[a]Isolated as the TsOH salt by concentration of the reaction mixture. [b]Isolated as the TFA salt. [c]30:1 TFE:CH_2Cl_2 was used as solvent. [d]5:1 TFE:CH_2Cl_2 was used as solvent.

Scheme 3. Derivatizations of the Dearomatization Products



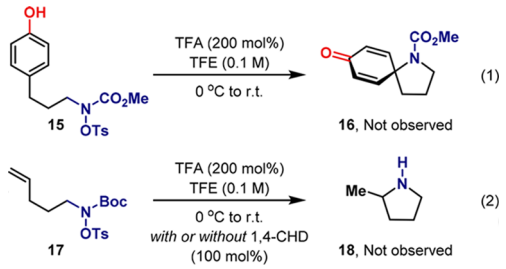
The earlier observation of a competing aryl C−H amination pathway (see Scheme 2B) prompted us to examine the limitations of this process with respect to the electronics of the aromatic unit. In Falck's original report a series of systems was investigated using $Rh_2(esp)_2$ as catalyst, but control experiments where this component was omitted were not disclosed.[2d] Accordingly, it was unclear whether the Rh-catalyst is required for intramolecular C−H amination. Indeed, in it absence, we found that cyclization of methoxy-system **13a** occurred in 80% yield (vs 86% with $Rh_2(esp)_2$). Phenyl-based system **13b** also cyclized efficiently under Rh-free conditions to generate **14b** in 65% yield (vs 81% with $Rh_2(esp)_2$). More electron deficient aromatic precursors **13c** and **13d** cyclize efficiently in the presence of $Rh_2(esp)_2$ but do not undergo aryl C−H amination in its absence. Thus, two competing aryl C−H amination pathways appear to be operative, with the Rh-catalyzed protocol enabling aminations of less nucleophilic arenes. Nevertheless, the ability to promote efficient metal free aryl C−H aminations of electron neutral and electron rich aromatic units is of high significance (Table 3).[15]

Table 3. Scope of the Metal Free C−H Amination Process



[a]Yield reported by Falck and co-workers (see ref 2d).

At the present stage, our collective observations are consistent with the reaction pathway outlined in Scheme 1C. TFA promoted deprotection of **5** releases the protonated O-tosyl hydroxylammonium unit of **6**, which may be attacked directly by the tethered arene (S_EAr) in the C−N bond forming step. This would account for the requirement of a relatively nucleophilic aromatic partner for C−N bond formation, although we are unaware of a direct precedent for this type of attack of an arene onto an electrophilic primary N(sp^3)-center.[15] Attempted spirocyclization of methyl carbamate system **15** resulted in no reaction (eq 1), which



supports the idea that N-Boc deprotection occurs prior to C−N bond formation. We suggest that nitrogen is protonated during the C−N bond forming step because this alleviates electronic repulsion that would otherwise exist between the incoming arene and the N-lone pair of the corresponding hydroxylamine (cf. **2**). The possibility that cyclization occurs via a nitrenium ion or a (protonated) aminyl radical cannot be discounted.[16] However, as discussed earlier, it is well established that nitrenium ion triggered cyclizations are not efficient in the absence of stabilizing functionality.[1] To ascertain whether a discrete N-centered radical might be involved, alkenyl system **17** was exposed to the reaction conditions in both the absence and presence of 1,4-cyclohexadiene. In both cases only decomposition occurred and pyrrolidine **18**, the potential product of 5-*exo* cyclization of an N-centered radical, was not observed (eq 2).[16] Addition of either TEMPO or BHT to the spirocyclization of **5a** had an inhibitory effect, but this was largely overridden using slightly elevated reaction temperatures.[17]

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To conclude, we outline a conceptually simple, but highly unusual method for achieving C−N bond forming dearomatizations and aryl C−H aminations. Upon treatment with acid, and under metal free conditions, a potent electrophilic aminating agent is generated, and this interacts efficiently with pendant arenes in a process that resembles an S_EAr amination. Although C−C bond forming dearomatizations triggered by intramolecular attack of phenols onto primary C(sp^3)-sulfonates were first reported 60 years ago,[18] the studies described here are the first aza-variants of this process. The method represents a step change in efficiency vs conventional nitrenium ion mediated processes, suggesting that a diverse range of new C−N bond formations might be achievable by exploiting the untapped potential of electrophilic intermediates related to **6**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07830.

Experimental details, characterization data and crystallographic data (PDF)
Data for $C_{11}H_{15}NO$ (CIF)
Data for $C_{14}H_{15}NO$ (CIF)
Data for $C_{19}H_{21}NO_2$ (CIF)
Data for $C_{18}H_{19}NO_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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(7) See: Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. *Chem. Sci.* **2017**, *8*, 5248 and references cited therein.

(8) Existing C−N bond forming dearomatizations of phenols involve oxidation of the arene to a carbocation in advance of trapping by an NH-nucleophile. This necessitates specific protecting groups on nitrogen, and oxidatively sensitive functionality can compromise reaction efficiency. Leading references: (a) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (b) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (c) Liang, H.; Ciufolini, M. A. *Chem. - Eur. J.* **2010**, *16*, 13262. (d) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. In certain settings, secondary amines have been used as the nucleophile: (e) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (f) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411.

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(10) Other solvents were less efficient. For example, PhMe or CH_2Cl_2 provided **7a** in 40% and 41% yield, respectively. **7a** was not formed using MeOH, THF, EtOAc, or dioxane as solvent.

(11) Higher reaction temperatures provide faster conversion of starting material but lower yields of the dearomatization products. So far, we have been unable to extend the method to the synthesis of spirocyclic piperidines.

(12) (a) Dienone-phenol rearrangement: Arnold, R. T.; Buckley, J. S.; Richter, J. *J. Am. Chem. Soc.* **1947**, *69*, 2322. (b) A similar aza-variant has been invoked but not confirmed: Kawase, M.; Kikugawa, Y. *Chem. Pharm. Bull.* **1981**, *29*, 1615.

(13) The free base of **7g** was heated at 60 °C in TFE and **8g** was obtained in 57% yield after 25 h. **8g** was obtained in 50% yield (+26% recovered **7g**) using 15 mol% TFA in TFE at r.t. (48 h).

(14) Marx, J. N.; Argyle, J. C.; Norman, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 2121.

(15) A full study on the metal free C−H amination protocol will be reported in due course. Metal free intramolecular aryl C−H aminations using primary hydroxylamine derivatives have been reported previously, but forcing conditions were required (see ref 12b).

(16) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337 Conventionally, aminyl radicals are generated from N-chloroamines under either photochemical or strongly acidic conditions. In general, primary N-chloroamines, and therefore primary aminyl radicals, are difficult to access because polychlorination of the amine precursor is problematic.

(17) Full details are given in the SI. The reaction is unaffected by the presence or absence of light, and very similar results are obtained using distilled or nondistilled TFA/TFE.

(18) (a) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756. (b) Masamune, S. *J. Am. Chem. Soc.* **1961**, *83*, 1009.

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