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Dirhodium Catalyzed C-H Arene Amination using Hydroxylamines

Mahesh P. Paudyal[1], **Adeniyi Michael Adebesin**[1], **Scott R. Burt**[2], **Daniel H. Ess**[2], **Zhiwei Ma**[3], **László Kürti**[3], and **John R. Falck**[1,*]

[1]Division of Chemistry, Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[2]Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602, USA

[3]Department of Chemistry, Rice University, BioScience Research Collaborative, Houston, TX 77005, USA

Abstract

Primary and *N*-alkyl arylamine motifs are key functional groups in pharmaceuticals, agrochemicals and functional materials as well as in bioactive natural products. However, there is a dearth of generally applicable methods for the direct replacement of aryl hydrogens with $–NH_2$/-NH-alkyl moieties. Here, we present a mild dirhodium-catalyzed C-H amination for conversion of structurally diverse monocyclic and fused aromatics to the corresponding primary and *N*-alkyl arylamines using either NH_2/NHalkyl-*O*-(sulfonyl)hydroxylamines as aminating agents; the relatively weak RSO_2O-N bond functions as an internal oxidant. The methodology is operationally simple, scalable, and fast at or below ambient temperature, furnishing arylamines in moderate-to-good yields and with good regioselectivity. It can be readily extended to the synthesis of fused *N*-heterocycles.

Main Text

Arylamine motifs (1, 2) are prevalent in natural products, pharmaceuticals, agrochemicals, functional materials, and dyestuffs as well as many synthetic reagents and catalysts (3–5). Most traditional methods for their synthesis from a corresponding $C(sp^2)$-H bond involve multi-step sequences and/or, harsh conditions (6–8). In many instances, the initial product (nitro, azide, azo, nitroso, chloronitroso, amide/imide/sulfonamide, or imine) requires an additional step(s) before arriving at a free amine (6). The amination of organic anions is a useful and direct alternative (9), but is generally restricted to the introduction of $–NR_1R_2$ (R_1,$R_2 \neq H$) and is not applicable to base sensitive substrates. The seminal studies of Ullman and Goldberg into metal-mediated arene $C(sp^2)$-N bond formation at the beginning of the

*Corresponding author: j.falck@utsouthwestern.edu.

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20th century were harbingers (10) of more efficient palladium catalyzed cross-couplings between aromatic halides/sulfonates and ammonia or nitrogen surrogates developed independently by Hartwig (11) and Buchwald (12) in the early 1990s. In turn, a steady succession of technical improvements, up to the present time, has been offered with the aim of mitigating the original stringent Hartwig-Buchwald reaction conditions (13–16). All of these procedures, however, are restricted by the need for a pre-functionalized arene.

In more recent years, much attention has been paid to catalytic, direct arene aminations (17–19). Many elegant atom- and step-efficient protocols have been introduced, but virtually all require a directing group while others need an excess of arene, high temperatures, or generate amides, imides, and sulfomamides instead of free amines (20–31). A noteworthy exception is the photoredox driven process of Nicewicz (32) and colleagues that circumvents many of the preceding limitations.

Based upon a combination of experimental observations and theoretical considerations, we anticipated a reaction dichotomy could be achievable between dirhodium-catalyzed aziridination, as reported previously by our laboratories (33), and direct arene amination. Following a systematic investigation, proof-of-principle for arene amination vs. aziridination was demonstrated (Fig. 1). Treatment of 1-allyl-2-methoxybenzene (*o*-allylanisole, **1**) with *O*-(2,4-dinitrophenyl)-hydroxylamine (**2**: DPH) (34) and catalytic $Rh_2(esp)_2$ (Du Bois' catalyst, **6**: 5 mol%) in 2,2,2-trifluoroethanol (TFE) at 0 °C afforded the corresponding aziridine (**3**) as the sole product whereas use of *N*-methyl-*O*-tosylhydroxylamine (**4a**) (35) as the aminating agent under otherwise identical conditions furnished exclusively the arene amination adduct 3-allyl-4-methoxy-*N*-methylaniline (**5**). Consequently, a more detailed study of the direct arene amination was begun and ultimately led to a versatile, regioselective, operationally simple and mild dirhodium-catalyzed direct arene amination suitable for both intermolecular and intramolecular applications. It should be noted that the relatively weak N-O bond of the aminating agents, many of which are commercial or readily prepared (33–37), functions as an internal oxidant when cleaved during the catalytic amination process, thus obviating the need for addition of an external oxidant to the reaction mixture. Also, the synchronous release of a stoichiometric amount of arylsulfonic acid during the amination is critical since it protonates the arylamines which would otherwise inactivate the Rh catalyst. In some instances, acid sensitive functionality such as epoxides and acetals do not survive.

Mesitylene (**7a**) was selected as a model arene to optimize reaction parameters. Use of 2 mol % $Rh_2(esp)_2$ and 1.5 equivalents of aminating agent **4a** in TFE as solvent smoothly generated *N*-methylaniline **8a** (75%) in just 30 min at 0 °C (Fig. 2, Entry 1); comparable yields were obtained with 1 mol% and 0.5 mol% catalyst, except the latter required 1 h for complete consumption of starting material. Combinations of TFE with CH_2Cl_2 or MeOH in ratios up to 1:1 were suitable, but aminations run in EtOH or MeOH as the only solvent delivered poor yields (~10 to 20%) and those run in only DMF, CH_3CN, THF, toluene, and dioxane failed. Amongst alternative Rh-catalysts, $Rh_2(OAc)_2$ and $Rh_2(C_8H_{15}O_2)_4$ were the next best with moderate yields (~40 to 45%) while the performance by $Rh_2(TFA)_4$ was poor. Results from other catalysts are summarized in Table S1. Generally, reactions were quenched as soon as the substrate was completely consumed to minimize by-product

formation. Air and water (5% v/v) were well tolerated making this methodology operationally convenient.

The successful transfer of a *n*BuNH- unit to **7a** from TsONH*n*Bu (**4b**) affording **8b** in 52% yield (Fig. 2, Entry 2) suggested more complex amino moieties should also be suitable. For the introduction of -NH_2 into **7a**, we used 2,4,6-$Me_3C_6H_3S(O)_2ONH_2$ (36) (**4c**, 2 equiv) as aminating agent because of its greater stability at room temperature compared with $TsONH_2$ (37). Although all of **4c** was consumed, a considerable amount of unreacted **7a** was recovered and a modest yield (49%) of **8c** was realized (Entry 3). On the other hand, the simple and expedient generation of the aminating agent *in situ* from 2,4,6-$Me_3C_6H_3S(O)_2ONH^tBoc$ (**4d**, 1.5 equiv) and CF_3CO_2H (2 equiv) proved quite effective and boosted the yield of **8c** to 70% (Entry 4), although the reaction was much slower than in the case of aminating agent **4c** (Entry 3) and appeared to be dependent upon the rate of ^{t}Boc cleavage.

The results from other representative arenes are also summarized in Fig. 2. Despite having only a single aliphatic substituent, cyclopropylbenzene (**7d**) was well behaved, affording a 1:1 *p*-/*o*-mixture (**8d** & **8e**) in 20 min at 0 ºC with no evidence of addition to the strained three-membered ring (Entry 5). The directing effect in favor of the *para*-isomer was more pronounced with anisole (**7f**) and led to a 16:1 distribution of **8f** and **8g** (Entry 6). This effect completely dominated in veratrole (**7h**) that gave **8h** as the predominant regioisomer (Entry 7) and was equally evident in the conversion of 1,3-dimethyoxybenzene (**7i**) into **8i**, although a minor amount (6%) of the *ortho*-isomer **8j** was found despite the increased steric congestion at this site (Entry 8). Addition of acetic acid to the reaction solvent for the latter three examples (i.e., Entries 6–8) improved the yields and suppressed the formation of mauve-colored by-products that we assume arose from further oxidation of the aminated adducts. The *ortho*/*para*-directing effect of electron donating substituents is typical for electrophilic aromatic additions; the preference for the *para*-isomer vs. *ortho* might reflect the steric demand of the Rh-nitrenoid complex. Consistent with these results, aromatics with only electron-withdrawing substituents, e.g., -CF_3 and –CN, fail to aminate under these reaction conditions.

Aryl bromide **7k** (Entry 9) and terminal alkyl bromide **7l** (Entry 10) endured to deliver **8k** and a mixture of **8l**/**8m** (3:1), respectively, leaving the halogens available for further manipulation, if desired. The presence of some functional groups, however, partially retard amination, e.g., exposure of benzyl alcohol **7n** to the standard amination conditions generated a modest amount of **8n** (42%) after 2 h (Entry 11); on the other hand, protection as silyl ether **7o** resulted in a much improved yield of **8o** (68%) (Entry 12). Fortunately, a synthetically useful yield of amine could be obtained even in the presence of an electron withdrawing substituent, e.g., **7p**→**8p** (Entry 13). The amination process was also extended to fused aromatics: naphthalene (**7q**) and 1,4-dimethylnapthalene (**7r**) gave rise to *N*-methyl-1-naphthylamine (**8q**, Entry 14) and *N*-methyl-1,4-dimethyl-2-naphthylamine (**8r**, Entry 15), respectively, while 2-methoxynaphthalene (**7s**) readily underwent amination to give **8s** in 85% yield on a 0.5 mmol scale and in 80% yield on a 5 mmol scale (Entry 16). The smooth amination of 2-methoxy-6-bromonaphthalene (**7t**) into *N*-methyl-2-methoxy-6-

bromo-1-naphthylamine (**8t**, Entry 17) succinctly illustrates the chemo- and regio-selectivities of this methodology.

To validate the suitability of this methodology for late stage functionalization of complex molecules, *O*-methylestrone (**7u**) was smoothly converted to a mixture of **8u** and **8v** (1:7.2, Entry 18) in very good combined yield while only one regioisomer **8w** (Entry 19) was obtained from the parent phenol, estrone (**7w**), thus demonstrating its applicability to substrates containing potentially sensitive benzylic, tertiary, and α-keto hydrogens. The scope was further defined with the amination of methyl naproxen **7x** to **8x** (Entry 20) and morphine derivative **7y** to **8y** (Entry 21). The latter required the addition of *p*-toluenesulfonic acid (2.5 equiv) to ensure the teriary amine was fully protonated to avoid passification of the catalyst.

The intramolecular version of the amination proved quite facile and represents one of the mildest and most efficient aza-annulations currently available to the practitioner (Fig. 3) (38, 39). The enabling amination functionality was introduced in uniformly good yields via the Mitsunobu inversion under standard conditions from the corresponding alcohols. Acidic cleavage of the ^{t}Boc and subsequent in situ amination proceeded at 0 °C. Fused aza-annulated bicycles were created in good yields irrespective of additional ring substituents, **10a→11a** (Entry 1), electron donating, **10b→11b** (Entry 2), or electron withdrawing functionality, **10c→11c** (Entry 3) and **10d→11d** (Entry 4). Control studies of the reaction of **10b** confirmed that there was less than 2% of the *ortho*-annulation product, 8-methoxy-1,2,3,4-tetrahydroquinoline, based upon ^{13}C NMR analysis of the crude reaction product (Fig. S5–S6). Secondary alcohols likewise participated readily in the Mitsunobu and aza-annulation reactions, **9e→10e→11e** (Entry 5). This 2-step sequence, when conducted using the chiral alcohol **9f**, showed no loss of stereochemical integrity (Entry 6). Incorporation of a heteroatom into the ring closure, e.g., **9g→10g→11g** (Entry 7), did not perturb the chemistry and provided easy access to the dihydrobenzoxazine class of heterocycles. The yield declined somewhat for making the 5-membered dihydroindole **11h** from alcohol **9h** (Entry 8), but improved for the 7-membered tetrahydrobenzazepine **11i** from **9i** (Entry 9).

As a beginning towards gaining insight into the mechanism of the amination, a 1:1 mixture of naphthalene (**7q**) and **7q**-d_8 was treated with a limited amount of amination reagent (**4a**, 0.5 equiv) under otherwise standard reaction conditions. Samples were taken and quenched at 10, 20, 30 and 40 min. Analysis via SIM-LC/MS revealed the product ratios remained constant at ~1:1, a ratio inconsistent with an organometallic C-H activation pathway which are typically ~3:1 or higher (40, 41). Based on density functional theory calculations, we previously suggested that aziridination of alkenes involves the dirhodium-nitrenoid intermediate **B** shown in Fig. 4 that arises from overall NH transfer from the DPH-aminating reagent to the dirhodium catalyst (33). In contrast, reaction of *O*-tosylhydroxylamine reagents with the dirhodium catalyst favor intermediate **A** because TsO^{-} is weakly basic and the equilibrium with intermediates **B** lies far to the left. The chemoselectivity might be explained by the more electrophilic nature of intermediate **A** versus nitrenoid **B**. This preliminary hypothesis is consistent with the observation that moderate to strong bases such as K_2CO_3, Et_3N, and pyridine completely inhibit amination, but not aziridination. Moreover,

addition of TsOH (1.5 equiv) to the reaction of **1** with 2,4-DNPONHMe (**12**) produced only the arene amination adduct **5** and no aziridine. As an additional control, it was shown that the presence of 2,4-DNP-OH (1.5 equiv) did not alter the reaction manifold in favor of aziridination when **4a** was utilized as the aminating reagent and only **5** was observed.

It was also instructive to compare our methodology with the intermolecular Rh-catalyzed amination procedure of Du Bois to gain a perspective of their respective complementary chemoselectivities (Fig. 4) (42). Both have similar efficiency using *p*-ethylanisole (**13**), but the Du Bois procedure leads to benzylic C-H insertion only whereas our methodology gives arene amination exclusively providing **15** and **16** in a combined 67% yield.

The influence of ligands and counter ions on the reactivity of organometallics is well precedented (43, 44). However, examples of such dramatic bifurcation of the reaction manifold are rare and warrant closer study to understand the energetics and full synthetic potential of this metalloid-nitrogen umpolung for direct arene aminations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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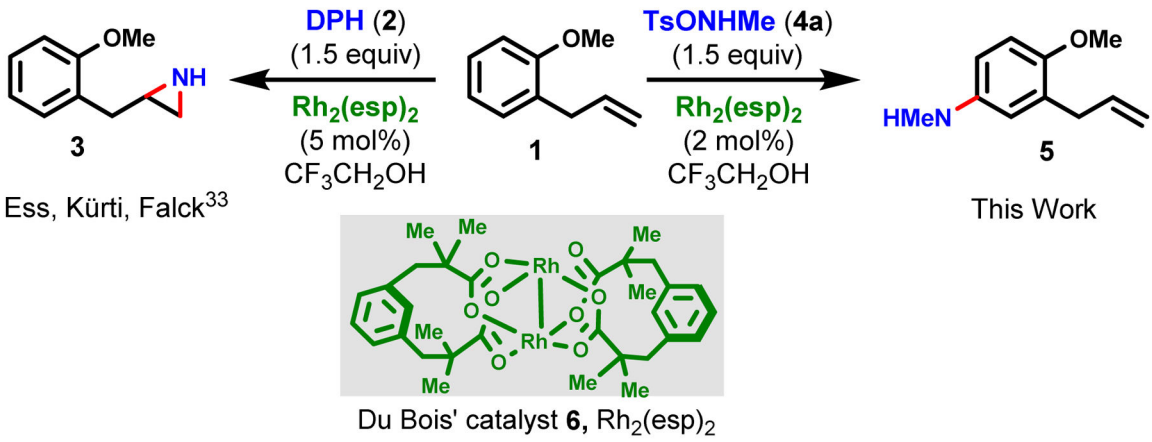

Fig. 1. A dramatic shift in chemoselectivity arises with different aminating agents

o-Allylanisole (**1**) undergoes chemoselective olefin aziridination in the presence of catalytic $Rh_2(esp)_2$ (**6**) and aminating agent DPH (**2**) in 2,2,2-trifluoroethanol (TFE = CF_3CH_2OH) to give **3**. Changing the aminating agent to TsONHMe (**4a**) furnishes the corresponding N-Me aniline (**5**).

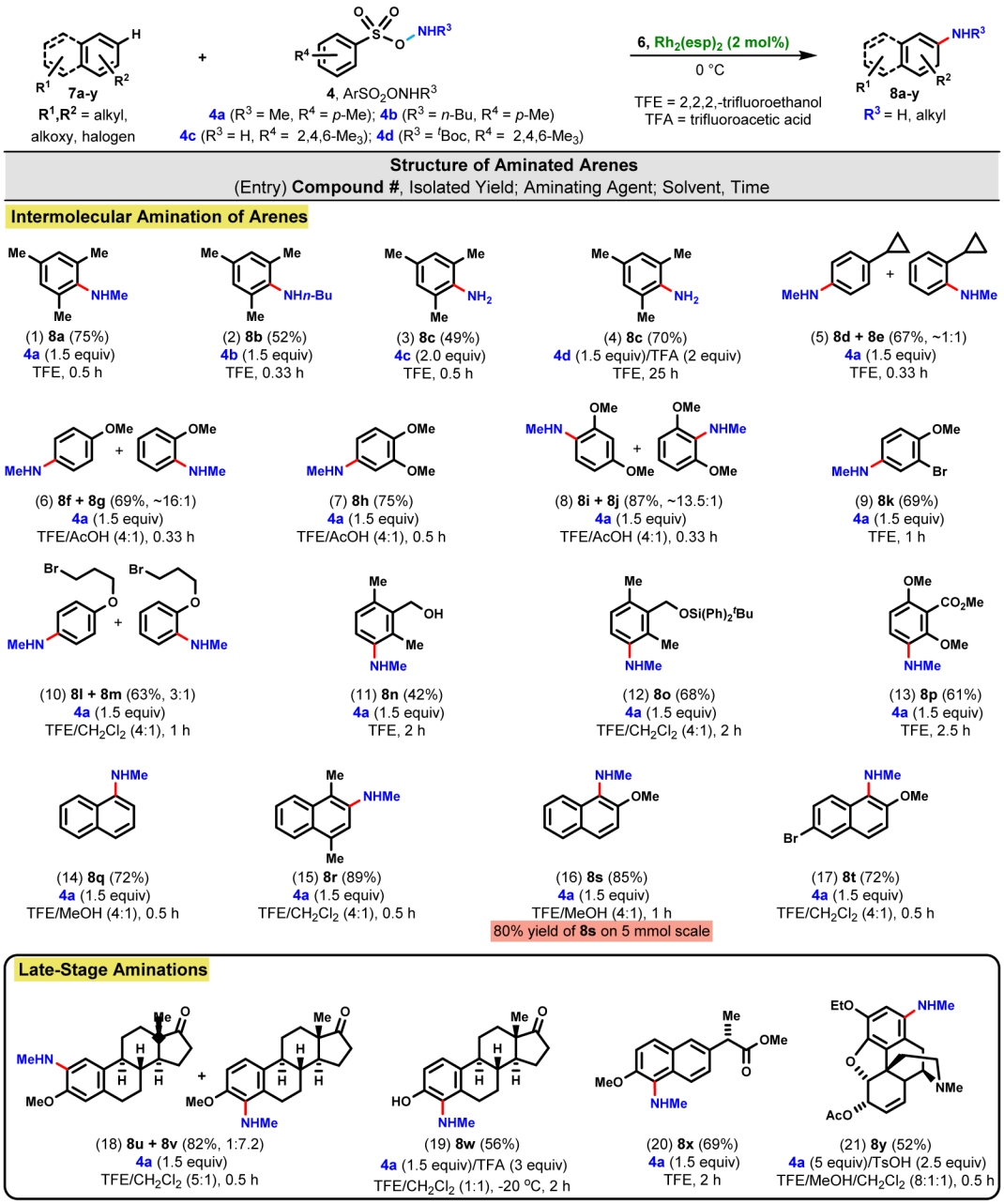

Fig. 2. Direct intermolecular amination of arenes

Reactions were conducted on a 0.1–0.5 mmole scale at 0.1 M using 2,2,2-trifluoroethanol (TFE = CF_3CH_2OH) as solvent or using mixtures of TFE and other solvents as indicated.

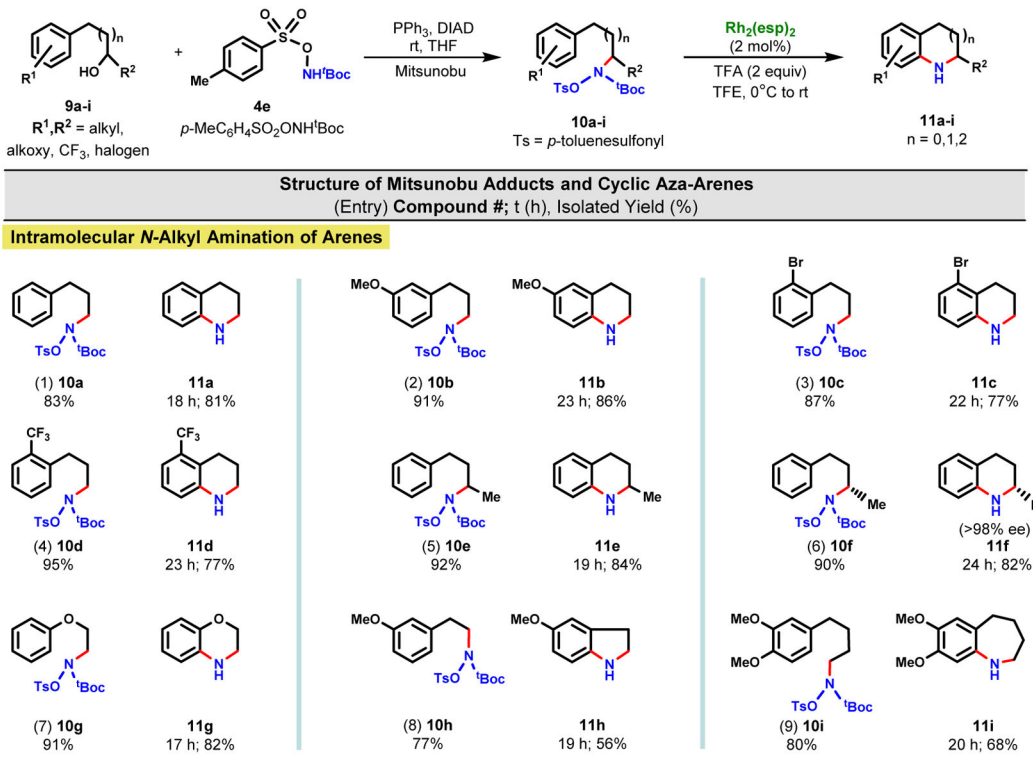

Fig. 3. Direct intramolecular cyclization (aza-annulation) of arenes

Cyclizations were conducted at 0.1 M using 2,2,2-trifluoroethanol (TFE = CF_3CH_2OH) as the solvent on a 0.1–0.3 mmol scale unless otherwise indicated.

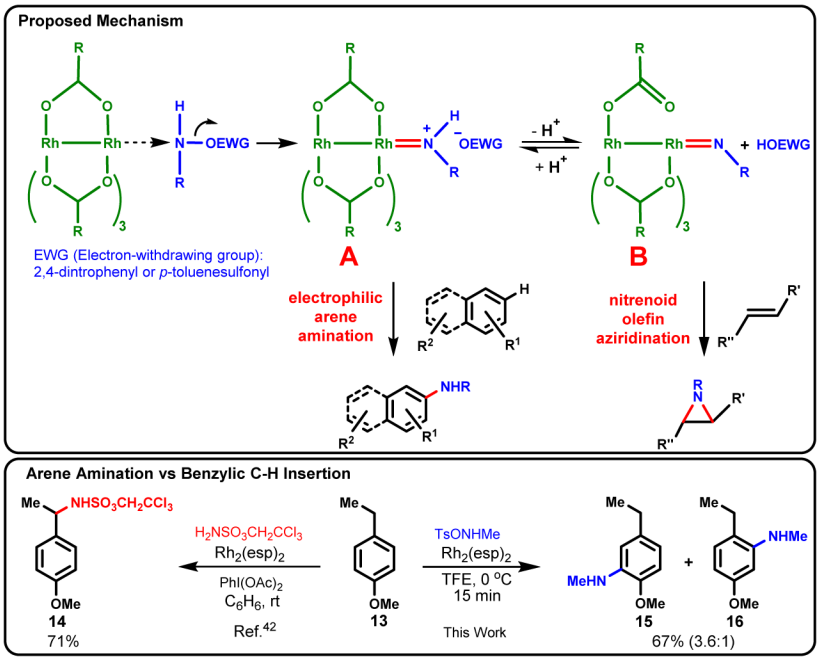

Fig. 4.

Proposed intermediates leading to amination versus aziridination and control study of arene amination vs benzylic C-H insertion.