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Cu(II)-Mediated *N*–H and *N*-Alkyl Aryl Amination and Olefin Aziridination

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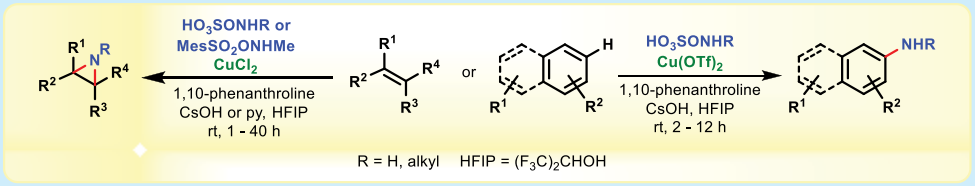
Supporting Information



ABSTRACT: Cu(II)-mediated direct NH_2 and NH alkyl aryl aminations and olefin aziridinations are described. These room-temperature, one-pot, environmentally friendly procedures replace costly Rh_2 catalysts and, in some instances, display important differences with comparable Rh_2- and Fe-supported reactions.

Aliphatic and aromatic amines are ubiquitous. Their structural and functional roles range from the building blocks of life and pharmaceuticals to catalysts, cosmetics, dyestuff, agrochemicals, polymers, and specialty materials.[1] Accordingly, a myriad of procedures exists for the creation of C–*N* bonds.[2] The advent of electrophilic amination,[3] transition-metal cross-coupling,[4] and C–H activation[5] methodologies provide access to a wider substrate scope and functional group tolerance, but typically employ (i) activated nitrogens (e.g., *N*-Ts, *N*-phth) or surrogates (e.g., azides), (ii) prefunctionalized substrates, (iii) directing groups, and/or (iv) vigorous reaction conditions. Often, additional procedures are required to obtain the free amine. In this context, the direct introduction of unactivated NH, NH_2, and NH alkyl moieties, especially at sp^2 carbons, has been more challenging.[6]

In 2014, our laboratory,[7a] in collaboration with those of Ess and Kürti, introduced a direct Rh_2-catalyzed synthesis of unactivated NH/N(alkyl) aziridines from olefins using *O*-2,4-dinitrophenylhydroxylamines (DNPs) as the aminating agents (Figure 1). By pivoting away from DNPs to *O*-arylsulfonylhydroxylamines, we were able to extend the method in 2016 to C–H arene NH_2/NH(alkyl) aminations.[8] More recently, Kürti et al.[9] demonstrated that inexpensive, water-soluble hydroxylamine-*O*-sulfonic acid (HOSA) and its *N*-alkyl derivatives could be used instead of *O*-2,4-dinitrophenylhydroxylamines for Rh_2-catalyzed aziridinations (Figure 1). Herein, we report on common Cu^{II} salts that are effective replacements for the costly Rh_2 catalysts for both NH_2/NH(alkyl) arene aminations and NH/N(alkyl) aziridinations using either HOSA or *O*-arylsulfonylhydroxylamines (Figure 1).

Having identified copper salts as promising catalysts from among common transition metals, we optimized the reaction conditions using the conversion of mesitylene (**1**) to aniline **2** as the model system and HOSA as aminating agent (Table 1). The combination of $Cu(OTf)_2$ (10 mol %) and CsOH in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) provided a modest amount of **2** over 24 h (Table 1, entry 1). The yield and reaction rate could be improved by coordination with 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine (PyBox) and still further with 1,10-phenanthroline, even on a 4 mmol scale (Table 1, entries 2 and 3, respectively). There was no amination in the absence of $Cu(OTf)_2$ (Table 1, entry 4).

Lower catalyst loadings (Table 1, entries 5 and 6) saw a modest decline in yields and much slower reaction rate. A sampling of other amino ligands (Table 1, entries 7–9) resulted in little if any **2**; similarly, variations of base (Table 1, entries 10–13) and copper catalyst (Table 1, entries 14–20) gave poor results.

As observed by Kürti,[9] the choice of solvent in the use of HOSA is critical; under the same reaction conditions as entry 3 in Table 1, aniline **2** was not observed in 2,2,2-trifluoroethanol (TFE) (Table 1, entry 21) or α,α,α-trifluorotoluene (TFT) (Table 1, entry 22) as well as DMSO, DMF, MeOH, $(HOCH_2)_2$, and THF even at 60 °C (data not shown).

The scope of the newly defined reaction conditions (Table 1, entry 3) was explored with a representative panel of arenes **3** (Table 2). Amination of cyclopropylbenzene afforded a 3:1 *para*-/*ortho*-mixture (**4a** and **4b**), comparable in yield to $Rh_2(esp)_2$ catalysis,[8] and with no evidence of addition to the strained three-membered ring. While the combined yields of **4c**/**4d** from anisole were similar for both $Rh_2(esp)_2$ and $Cu(OTf)_2$, the former catalyst[8] showed a pronounced bias for the *para*-isomer **4c** (16:1), whereas the latter catalyst furnished a 1:2 ratio favoring the *ortho*-isomer **4d**, an advantage for library development applications. Despite the presence of a free hydroxyl, the same preference for the *ortho*-regioisomer was again evident with 2-phenoxyethanol, which furnished

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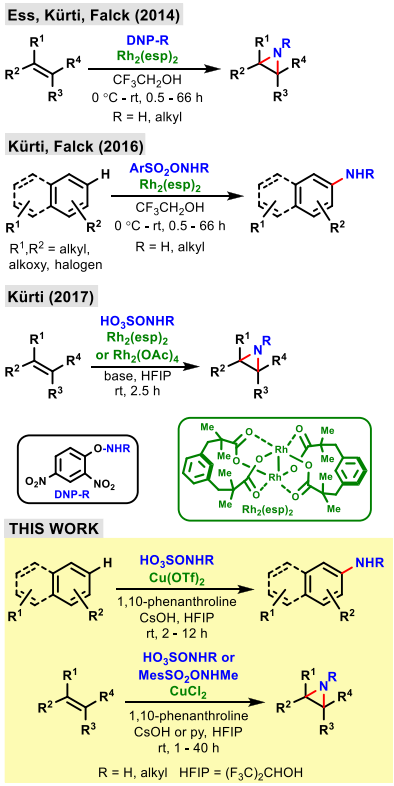

Figure 1. Direct synthesis of arylamines and aziridines using Cu(II) and Rh_2 catalysts. Cu(II) salts catalyze direct aryl-NH_2/-NH(alkyl) aminations and -*NH*/-*N*(alkyl) aziridinations of unactivated olefins with some important differences with comparable Rh_2- and Fe-catalyzed transformations.

1,3-dimethoxybenzene led to **4g**/**4h** in a 20:1 ratio versus 13.5:1 for $Rh_2(esp)_2$,[8] suggesting that other factors are also operative. The broader versatility of $Cu(OTf)_2$ to mediate arene *N*-alkylamination using other animating agents was confirmed by the synthesis of **4i** and **4j** from mesitylene using *O*-mesitylenesulfonyl-*N*-methylhydroxylamine and *N*-cyclohexylhydroxylamine-*O*-sulfonic acid, respectively, although the former required heating at 60 °C. The generation of **4k** from *O*-benzyl-L-tyrosine methyl ester in good yield demonstrated that this amination process is compatible with a variety of functional groups and was in stark contrast with the complete lack of reaction using $Rh_2(esp)_2$ under our previously published conditions.[8]

Amination of the fused aromatic dibenzofuran was instructive. Attempted amination using $Rh_2(esp)_2$/$TsONH_2$ under the conditions reported[8] previously proved very sluggish, whereas the current reaction methodology furnished a 1:1.5 mixture of the 3- and 1-amino derivatives **4l** and **4m** in 73% combined yield. This contrasts with the mixture of all four possible amino regioisomers (combined 61%) reported by Legnani et al.,[6e] using $FeSO_4$/$MsONH_3^+OTf^-$, one of the few[6c] base-metal-catalyzed direct NH_2 aminations. 2-Methoxynaphthalene readily underwent amination to give **4n**/**4o** (2:1) and methyl naproxen gave rise to **4p**/**4q** (2:1). $Rh_2(esp)_2$ catalysis,[8] on the other hand, generates only **4o** and **4q**.

For aziridinations, a survey of the copper salts and reaction conditions revealed $CuCl_2$ and 1,10-phenanthroline in HFIP with CsOH or pyridine as base was the most effective combination (see the Supporting Information (SI)). The isolation of *cis*-aziridine **6a** as the sole product from *cis*-styrene (Table 3) at rt demonstrated the addition under these conditions is stereospecific and, therefore, likely concerted.

Table 1. Optimization of Mesitylene Amination[a]

entry	catalyst (mol %)	base	ligand (mol %)	solvent	time (h)	yield (%)
1	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	–	HFIP	24	30
2	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	PyBox[c] (10)	HFIP	6	57
3	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	4	75/71[b]
4	–	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	0[c]
5	$Cu(OTf)_2$ (5)	$CsOH·H_2O$	1,10-phenanthroline (5)	HFIP	20	70
6	$Cu(OTf)_2$(1)	$CsOH·H_2O$	1,10-phenanthroline (1)	HFIP	20	60
7	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	TMEDA[d] (10)	HFIP	6	5
8	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	8-hydroxyquinoline (10)	HFIP	6	0
9	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	quinoline (10)	HFIP	6	0
10	$Cu(OTf)_2$ (10)	DABCO[d]	1,10-phenanthroline (10)	HFIP	6	40
11	$Cu(OTf)_2$ (10)	Na_2CO_3	1,10-phenanthroline (10)	HFIP	6	10
12	$Cu(OTf)_2$ (10)	Et_3N	1,10-phenanthroline (10)	HFIP	6	10
13	$Cu(OTf)_2$ (10)	pyridine	1,10-phenanthroline (10)	HFIP	6	40
14	CuTC[d] (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	20
15	$Cu(BF_4)_2$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	10
16	Cu(HFacac)[d] (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	5
17	CuCl (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	44
18	$Cu(Br)_2$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	0
19	$CuSO_4$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	0
20	CuF_2 (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	HFIP	6	0
21	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	TFE	16	0
22	$Cu(OTf)_2$ (10)	$CsOH·H_2O$	1,10-phenanthroline (10)	TFT	16	0

[a]Reaction conditions: 0.4−0.5 mmol **1**, unless otherwise stated, at room temperature (rt) in the indicated solvent (~0.2 M). [b]Yield on 0.4 and 5 mmol scale, respectively. [c]rt to 60 °C. [d]PyBox = 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, CuTC = copper(I) thiophene-2-carboxylate, HFacac = copper(II) hexafluoroacetylacetonate.

4e/**4f** as a 1:2 mixture. While it is tempting to ascribe this to steric differences between the Rh and Cu catalysts, Despite the increased steric congestion, addition to the trisubstituted styrene, 1-phenylcyclohexene, was fast (1−3 h)

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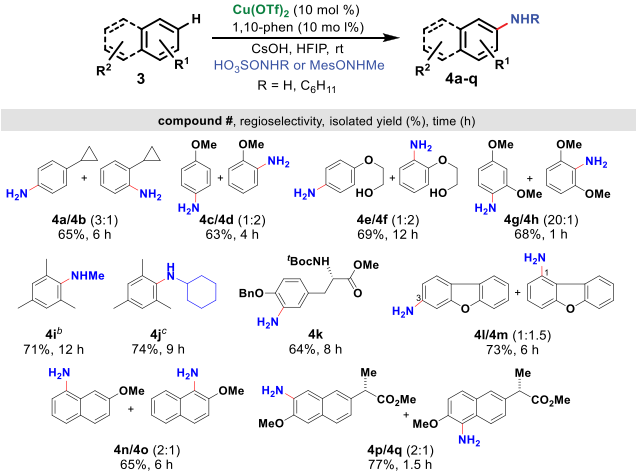
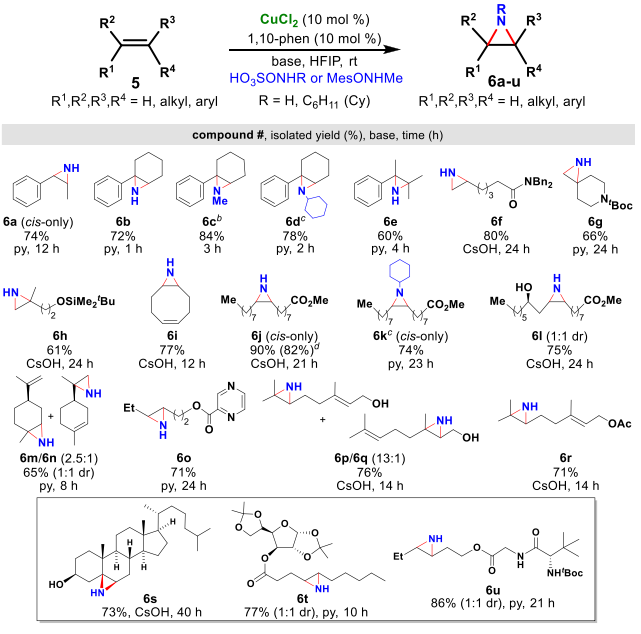
Table 2. Cu(OTf)$_2$-Catalyzed Intermolecular NH$_2$/NH(alkyl) Amination of Arenes[a]



[a]Reaction conditions: 0.4−0.5 mmol arene, Cu(OTf)$_2$ (10 mol %), 1,10-phenanthroline (1,10-phen; 10 mol %), HOSA (1.5 equiv), and CsOH·H$_2$O (1.5 equiv) at rt in HFIP (~0.2 M). [b]*O*-Mesitylenesulfonyl-*N*-methylhydroxylamine (MesONHMe) (1.5 equiv), 60 °C. [c]*N*-Cyclohexylhydroxylamine-*O*-sulfonic acid (1.5 equiv), rt.

Table 3. CuCl$_2$ Catalyzed *NH*/*N*(alkyl)-Aziridination of Unactivated Olefins[a]



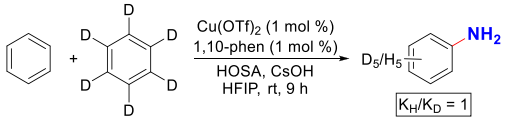
[a]Reaction conditions: 0.4−0.5 mmol alkene **5**, CuCl$_2$ (10 mol %), 1,10-phenanthroline (1,10-phen; 10 mol %), HOSA (1.5 equiv), and base (1.5 equiv) at rt in HFIP (~0.2 M). [b]*O*-Mesitylenesulfonyl-*N*-methylhydroxylamine (MesONHMe) (1.5 equiv), no base. [c]*N*-Cyclohexylhydroxylamine-*O*-sulfonic acid (1.5 equiv). [d]5 mmol scale.

and efficiently generated **6b**−**6d** from HOSA, *O*-mesitylenesulfonyl-*N*-methylhydroxylamine and *N*-cyclohexylhydroxylamine-*O*-sulfonic acid, respectively. Even a tetrasubstituted olefin, which gave way to **6e**, was well-behaved. As a practical matter, pyridine was superior to CsOH with all of the styrenyl substrates, except **6c**, that did not require added base. As anticipated, complex product mixtures were generated from these styrenyl substrates using FeSO$_4$/MsONH$_3^+$OTf$^-$.[6e]

Aliphatic aziridines **6f**−**6k** were all smoothly garnered in good yields from the corresponding terminal, 1,1-disubstituted, cyclic, and 1,2-disubstituted olefins, albeit more slowly than the more electron-rich styrenes. Methyl ricinoleate yielded **6l** and (*R*)-(+)-limonene yielded **6m**/**6n**, all as 1:1 diastereomeric ratio (dr) mixtures, insensitive to the presence of adjacent chiral centers. Importantly, heterocycles are compatible with the reaction conditions, e.g., **6o**.[7,9] It was also possible to distinguish between the subtly different olefins in the monoterpenoid geraniol and its acetate, which furnished **6p**/**6q** (13:1) and **6r**, respectively. The potential utility of this methodology for the modification of pharmaceuticals and natural products was further illustrated with three late-stage molecules, i.e., steroid **6s**, furanoside **6t**, and peptide **6u**.

To gain additional mechanistic insight, an equimolar mixture of benzene and perdeuterobenzene was subjected to competitive amination utilizing Cu(OTf)$_2$ (1 mol %)/1,10-phenanthroline (1 mol %) (Scheme 1). In concert with related Rh$_2$- and

Scheme 1. Kinetic Isotope Effect[a]



[a]Crude reaction product was treated with excess Ac$_2$O in CH$_2$Cl$_2$ at rt and the ratio of *N*-acetylanilides measured via ^{1}H/^{13}C NMR after isolation and purification.

Fe(II/III)-mediated reactions,[6e,8] the K_H/K_D ratio was 1, indicating that the C−H cleavage is not the rate-determining step and is inconsistent with an organometallic C−H activation pathway.[10]

In summary, the foregoing results document the next step in the evolution of unactivated NH/N(alkyl) arene aminations and stereospecific aziridinations into cost-effective, scalable, inherently safer, and environmentally friendly processes that should find wide application even with late-stage, polyfunctional molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00586.

Supplementary tables, experimental procedures, spectroscopic data, and NMR charts (PDF)

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Notes

The authors declare no competing financial interest.

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