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Copper-Catalyzed Aminoheteroarylation of Unactivated Alkenes through Distal Heteroaryl Migration

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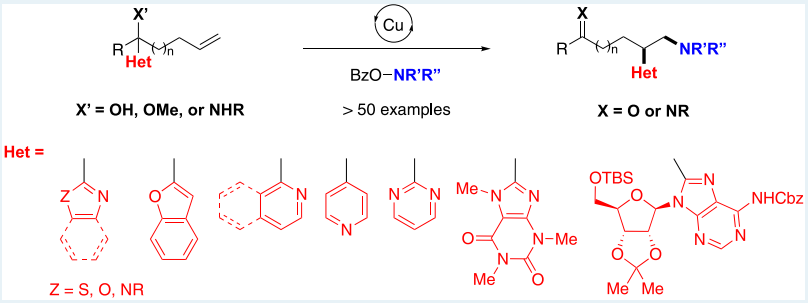

ABSTRACT: We report a copper-catalyzed aminoheteroarylation of unactivated alkenes to access valuable heteroarylethylamine motif. The developed reaction features a copper-catalyzed intermolecular electrophilic amination of the alkenes followed by a migratory heteroarylation. The method applies to alcohol-, amide-, and ether-containing alkenes, overcoming the common requirement of a hydroxyl motif in previous migratory difunctionalization reactions. This reaction is effective for the introduction of diverse aliphatic amines and has good functional group tolerance, which is particularly useful for rich functionalized heteroarenes. This migration-involved reaction was found well suited as a powerful ring-expansion approach for the construction of medium-sized rings that are in great demand in medicinal chemistry.

KEYWORDS: *unactivated olefin, copper, heteroaryl migration, N-centered radical, aminoheteroarylation*

The heteroarylethylamine core is an important structural motif found prevalently in bioactive molecules and pharmaceuticals, such as conserved in many opioid receptor ligands (Figure 1).[1] Their importance as medicinally privileged functionality has motivated the development of effective methods to access this structural motif in a rapid and diverse manner. Toward this end, an appealing strategy is 1,2-aminoheteroarylation of alkenes as a straightforward approach that enables direct installation of an amino group and a heteroaryl group on alkenes.[2,3] Particularly, the intermolecular aminoheteroarylation of unactivated alkenes presents a general, desirable manner for the rapid and modular construction of molecular diversity and complexity. A series of methods have been developed on nitrogen-tethered unactivated alkenes to afford azacyclic skeletons bearing different aryl groups by an elegant amino cyclization and a subsequent intermolecular C−C bond formation.[4] Yet, for the flexible installation of diverse amino functionalities, especially aliphatic amines that feature attractive biological activities, a few aminoheteroarylation reactions that involved an intermolecular C−N bond formation have been achieved (Scheme 1).[5] A photo-catalyzed alkene aminopyridylation reaction was reported to install secondary amides and 2-pyridyl groups (Scheme 1a).[5a] The palladium-catalyzed aminoarylation reaction reported by the Engle's group was successful for an intermolecular installation of amide, sulfonamides, and imidazole (Scheme 1b).[5b]

Zhu's group has developed a nickel-catalyzed reductive aminoarylation for the preparation of aliphatic amines but only on iodoarene-tethered alkenes (Scheme 1c).[5e] The versatile assembly of diverse heteroarylethylamine motifs remains a challenge for catalytic alkene aminoheteroarylation. To address this problem, we envisioned an alkene amino migratory heteroarylation strategy by leveraging temporary installation of a heteroaryl group onto a remote carbonyl or iminyl group (Scheme 1d). This paper reports the development of a copper-catalyzed migratory aminoheteroarylation reaction for the creation of diverse heteroarylethylamines motifs.

The key to the development of a new catalytic protocol is use of *O*-benzoyl-*N*-hydroxylamines as electrophilic aminating reagents[8] in the copper-catalyzed amination step. This intermolecular C−N bond formation not only enables the

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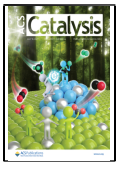

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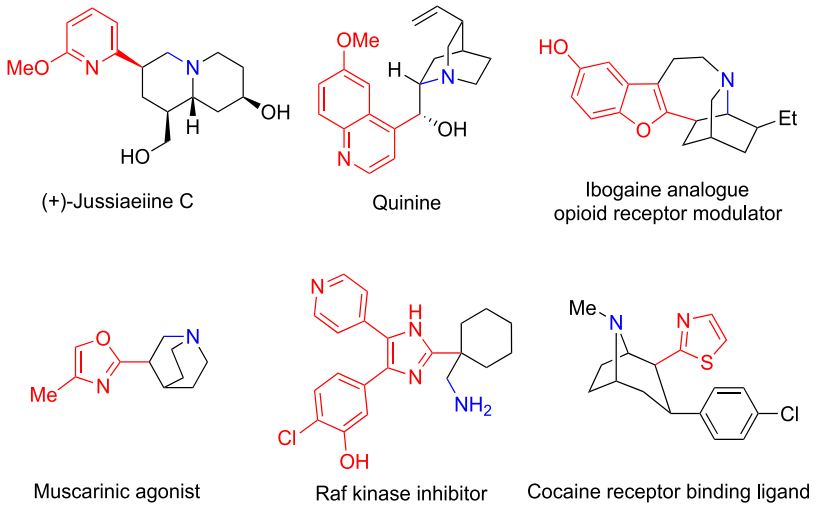
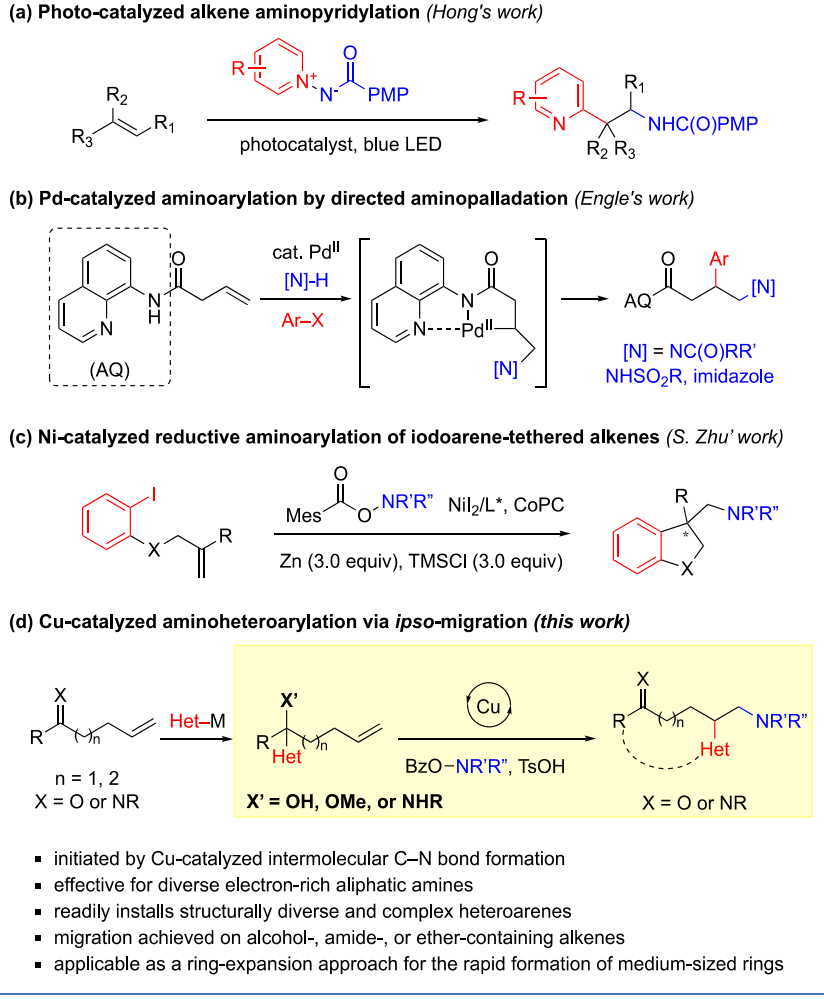


Figure 1. Heteroarylethylamines as an important motif commonly found in bioactive natural products and molecules.

Scheme 1. Aminoheteroarylation Reactions of Unactivated Alkenes via Intermolecular C−N Bond Formation



- initiated by Cu-catalyzed intermolecular C–N bond formation
- effective for diverse electron-rich aliphatic amines
- readily installs structurally diverse and complex heteroarenes
- migration achieved on alcohol-, amide-, or ether-containing alkenes
- applicable as a ring-expansion approach for the rapid formation of medium-sized rings

installation of diverse electron-rich aliphatic amines that were problematic in most existing methods but also positions the formation of carbon-radical intermediates that are expected to undergo a distal migration for the assembly of the heteroarene. Our work was inspired by radical-based functional group migration-involved transformations, particularly alcohol-assisted alkene migratory functionalization.[6,7] Different from previous migratory reactions, the catalytic protocol described here is effective on alcohol-, amide-, and even ether-containing alkenes, overcoming a common limitation for the requirement of a hydroxyl moiety and presenting the synthetic potential for broader applications. Furthermore, our method is well suited for a rapid approach to access medium-sized rings via the form of ring expansion, particularly for heteroarene-bearing

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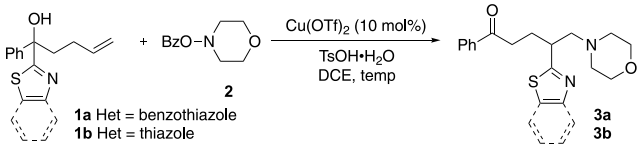
Table 1. Optimization of Aminoheteroarylation of Alkene[a]



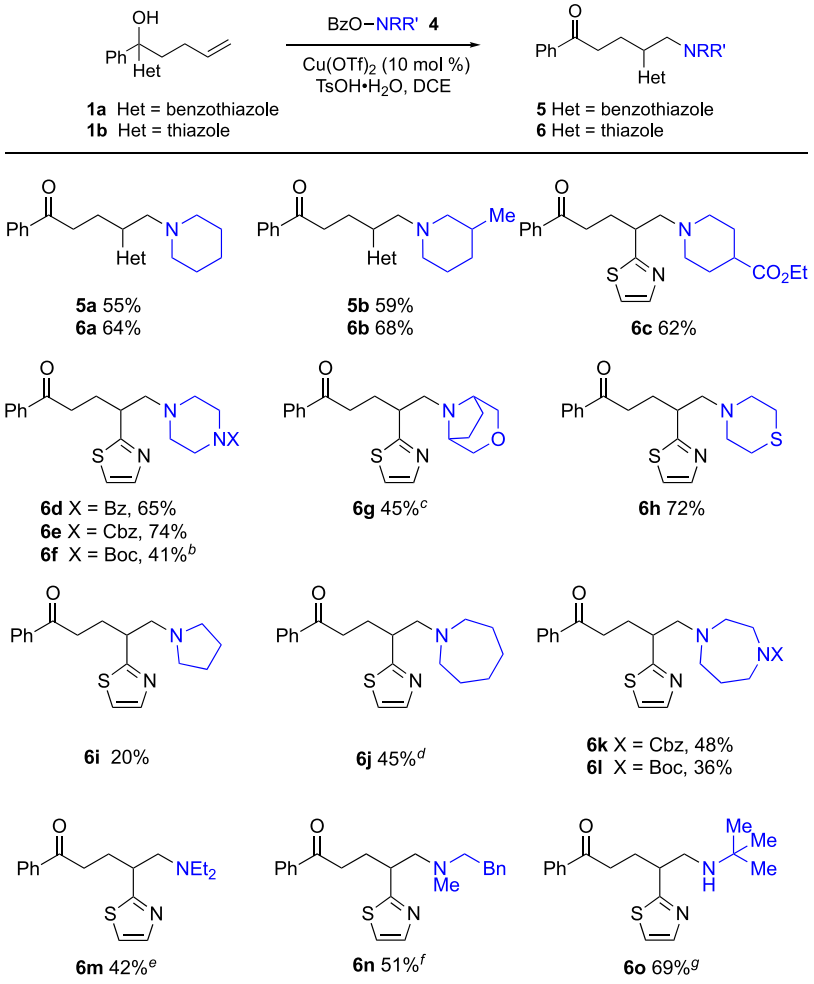
entry	1a/1b	T (°C)	time	3a/3b (%)[b]
1	**1a**	80	1 h	20
2	**1a**	80	5 min	66
3	**1a**	**60**	**20 min**	**70 (73)**[c]
4	**1a**	40	4.5 h	65
5	**1b**	**80**	**5 min**	**72 (77)**[c] **(72)**[cd]
6	**1b**	60	20 min	65
7	**1b**	40	5 h	66
8[e]	**1a**	60	20 h	trace
9[f]	**1a**	60	72 h	ND

[a]Reaction conditions: **1a** or **1b** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), and 1,2-dichloroethane (DCE) (1 mL). The conditions in bold gave best results. [b]Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. [c]Isolated yields in parentheses. [d]Run on 2.0 mmol scale. [e]No acid was added. [f]No copper catalyst was added.

medium-sized ketones that are highly valued in medicinal chemistry, yet would be difficult to access otherwise.

Our studies began with the aminoheteroarylation reaction of 1-phenyl-1-(benzothiazolyl)pentenol **1a** using *O*-benzoyl-*N*-hydroxylmorpholine **2** as an amine precursor (Table 1). With $Cu(OTf)_2$ as the catalyst and $TsOH{\cdot}H_2O$ as an additive, the reaction at 80 °C readily proceeded to afford the desired product **3a** (entry 1). Yet, significant amounts of cyclization and elimination byproducts were formed (see the Supporting Information). To minimize these side reactions, shorter reaction times and lower temperatures were tested (entries 2–4). When the reaction was run at 60 °C for 20 min, the formation of **3a** was improved to 73% yield (entry 3). We also tested the reaction of 1-phenyl-1-(thiazolyl)pentenol **1b** at different temperatures (entries 5–7). The desired 1,2-aminothiazole product **3b** was formed in 77% yield most effectively when the reaction was run at 80 °C for 5 min (entry 5). Control experiments showed that both copper catalyst and the acid additive are imperative in this reaction (entries 8 and 9). Although we chose $Cu(OTf)_2$ as standard conditions, the reactions were also effective with other Cu(I) and Cu(II) salts as the catalysts (see the Supporting Information).

Table 2. Generality of Amine Precursors in Aminoheteroarylation Reactions[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **4** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), DCE (1 mL), and 80 °C. Isolated yields shown. [b]Run with **4f** (3.0 equiv). [c]Run at 40 °C. [d]Run with **4j** (4.0 equiv) and $TsOH{\cdot}H_2O$ (3.0 equiv) at 60 °C. [e]Run at 40 °C. [f]Run with **4n** (3.0 equiv) and $TsOH{\cdot}H_2O$ (2.25 equiv) at 60 °C. [g]Run with **1b** (0.1 mmol, 1.0 equiv), **4o** (3.0 equiv), and $TsOH{\cdot}H_2O$ (6.0 equiv).

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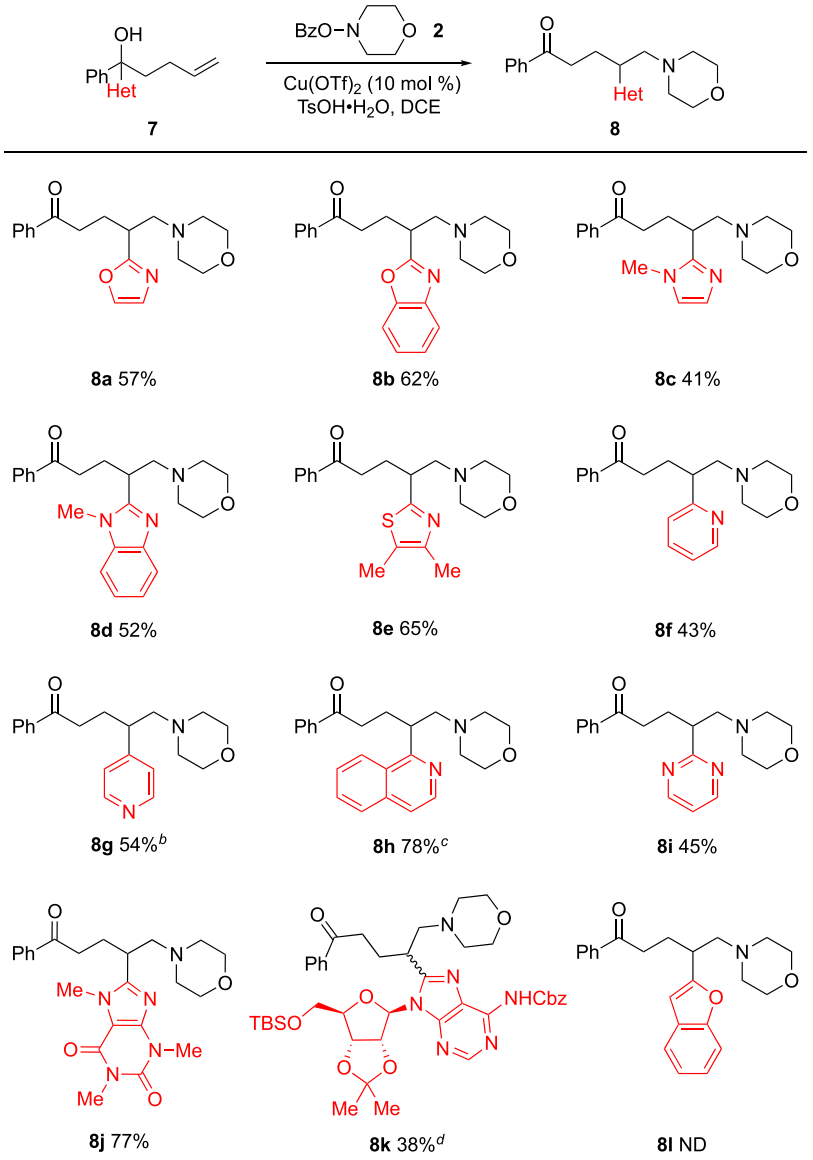
Table 3. Heteroaryl Groups in Aminoheteroarylation Reactions[a]



[a]Reaction conditions: **7** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), DCE (1 mL), and 80 °C. Isolated yields shown. [b]Run with **2** (3.0 equiv) and $TsOH{\cdot}H_2O$ (3.0 equiv). [c]Run with **7h** (0.1 mmol, 1.0 equiv), and $TsOH{\cdot}H_2O$ (3.0 equiv). [d]Run with **7k** (2.0 equiv), **2** (0.2 mmol, 1.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (0.6 equiv), DCE (2 mL), and 80 °C.

With effective conditions established, we studied the scope of *O*-benzoylhydroxylamines for the aminoheteroarylation of alkene (Table 2). Starting from **1a** or **1b**, the reactions using piperidine and 3-methylpiperidine-derived hydroxylamines as the amine precursors smoothly afforded benzothiazole- and thiazole-containing amine products (**5a**−**5b** and **6a**−**6b**), respectively. Other six-membered cyclic amine precursors bearing different functional groups were well tolerated, providing a diverse range of *β*-aminoethyl thiazole derivatives from the reactions of **1b**, such as ester-containing piperidine (**6c**), *N*-Bz- (**6d**), *N*-Cbz- (**6e**), and *N*-Boc-(**6f**) piperazines, bridged bicyclic morpholine (**6g**) as well as thiomorpholine (**6h**). Five- and seven-membered cyclic amine precursors, specifically pyrrolidine and azepane, also participated in this reaction, affording **6i** and **6j** in 20 and 45% yield, respectively. The aminoheteroarylation reactions with *N*-Cbz- and *N*-Boc-protected 1,4-diazepane precursors successfully delivered **6k** and **6l**. The reaction was also applicable to acyclic amine precursors, demonstrated in the formation of diethylamine **6m** and methylphenethylamine **6n** in moderate yields. Noticeably, primary amine was also successfully installed on the alkene to give **6o** in 69% yield.

We next examined the generality of this alkene migratory difunctionalization strategy on diverse heteroarenes using alkene substrates bearing different heteroaryl groups (Table 3). The reactions of various azoles were found to afford the desired 1,2-amino azole products, including oxazole (**8a**), benzoxazole (**8b**), imidazole (**8c**), benzimidazole (**8d**), and 4,5-dimethylthiazole (**8e**). Six-membered azaheteroaryl groups were found to be effective in the formation of the 2-pyridyl (**8f**), 4-pyridyl (**8g**), isoquinolinyl (**8h**) products, and more electron-deficient pyrimidine (**8i**). Structurally, more complex caffeine-containing product **8j** was also formed in good yields. Even the adenosine-derived alkene was compatible with this migration, furnishing the desired product **8k** in 38% yield. These examples have demonstrated the generality of this

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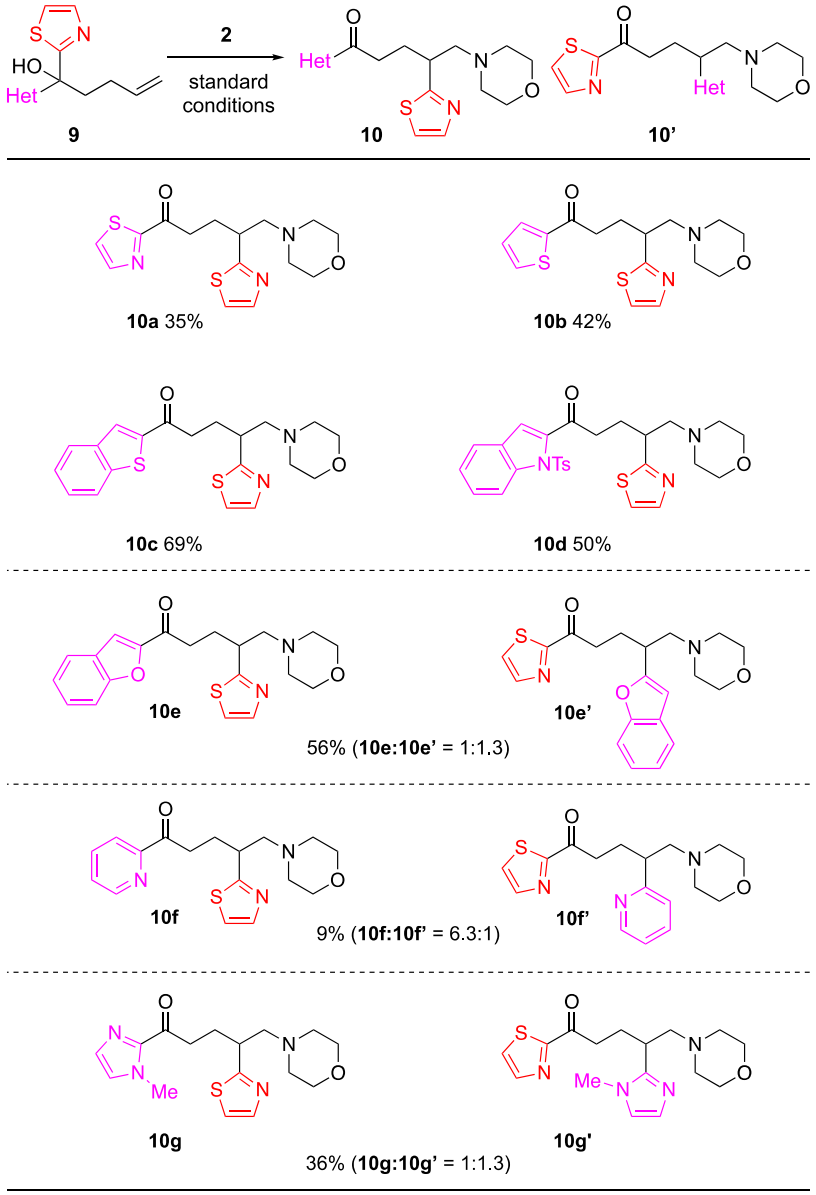
Table 4. Aminoheteroarylation of Alkenes Bearing Two Heteroaryl Groups[a]



[a]Reaction conditions: **9** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (0.3 mmol, 1.5 equiv), DCE (1 mL), and 80 °C. Isolated yields shown.

migratory aminoheteroarylation strategy on a broad scope of heteroarenes, including structurally complex ones that have been less explored but are important such as caffeine and adenosine derivatives. It should also be noted that electron-rich heteroaryl groups were found unsuccessful under the current conditions, as seen in the case of benzofuryl analogue **8l**.

We further investigated alkene substrates bearing two heteroaryl groups to evaluate the migration selectivity and the impact of the second heteroaryl group (Table 4). Subjecting *bis*-thiazole-containing alkene **9a** to standard reaction conditions led to the desired product **10a** in 35% yield, a significant drop in comparison to the formation of analogous product **3b** in 77% yield. Selective formation of *β*-thiazolyl amine products **10b**−**10d** revealed that thiazolyl migration was favored over the migration of thienyl, benzothienyl, and *N*-tosylindolyl group. Interestingly, benzofuryl- and thiazolyl-substituted substrate **9e** afforded two isomers in a 1:1.3 ratio that slightly favored the migration of benzofuryl (**10e′**) over thiazolyl (**10e**). Note that benzofuryl migration in the analogous phenyl-substituted product **8l** was unsuccessful. Thus, the change from phenyl to thiazolyl would contribute to the viability of benzofuryl migration in forming product **10e′**. The reaction of pyridyl thiazole-containing alkene **9f** also gave two products **10f** and **10f′** in a 6.3:1 ratio, via the migration of thiazolyl and pyridyl, respectively. Finally, imidazolyl thiazole-containing alkene **9g** afforded both thiazole (**10g**) and imidazole migration product (**10g′**) in comparable yields. In comparison to the formation of **3b** (77%), **8f** (43%), and **8c** (41%) from mono-azaheteroaryl substrates, the poorer yields observed in the formation of **10a** (35%), **10f** and **10f′** (9%) as well as **10g** and **10g′** (36%) from bis-azaheteroaryl-containing substrates indicated that the electronic nature of

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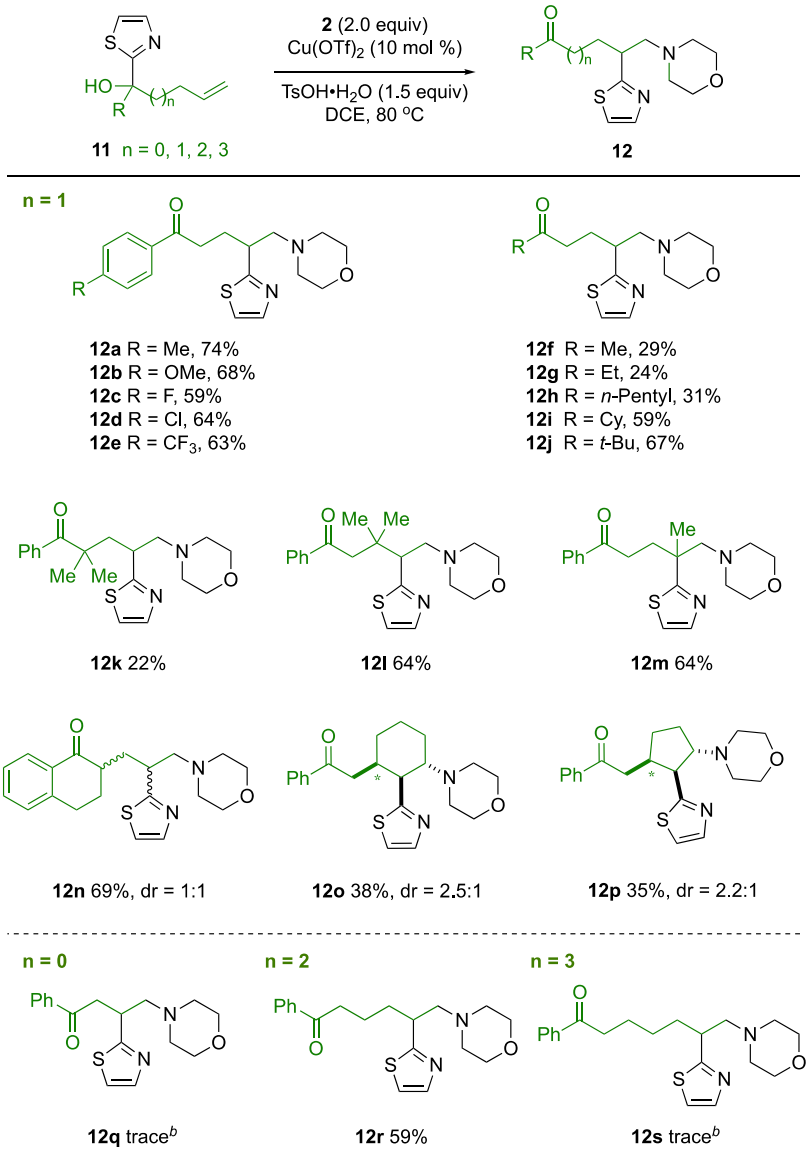
Table 5. Generality of Alkenes in Aminoheteroarylation Reactions[a]



[a]Reaction conditions: **11** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), DCE (1 mL), and 80 °C. Isolated yields shown. [b]Detected by LC/MS.

nonmigratory substituent affects the efficiency of the heteroaryl migration.

We also investigated the generality of alkenes in this aminoheteroarylation reaction using different thiazole-bearing unsaturated alcohols **11** (Table 5). First, all the reactions of 1-phenyl-substiuted tertiary alcohols provided desired 1,2-aminothiazole-containing products, regardless of the presence of electron-donating or electron-withdrawing groups on the phenyl ring (**12a**−**12e**). The alkyl-substituted tertiary alcohols were also capable of delivering thiazole migration products (**12f**−**12j**). The substrates bearing more sterically bulky alkyl groups resulted in higher efficiencies, suggesting that the steric bulkiness would facilitate the migration of neighboring thiazole group. The backbone substituents of the alkenes were found to affect the transformation dramatically, as seen in the cases of **12k**−**12l**, wherein the varied gem-dimethyl position resulted in steric interference hindering the migration step. This reaction from 1,1-disubstituted alkene was capable of forming quaternary carbon-containing product **12m** in 64% yield. Cyclic alkene substrates were also evaluated. A α-tetralone-derived precursor (as a mixture of 1:1 diastereomers) delivered **12n** in 69% yield (a mixture of 1:1 diastereomers), which indicated that this migration process could occur via both *cis* and *trans* fused (5:6) bicyclic transition states. Cyclic internal alkenes successfully provided 1,2-aminothiazole products **12o** and **12p**, via fused 5:6 and 5:5 bicyclic transition states, respectively. The diminished yields of **12o**−**12p** resulted from competing pathways that led to intramolecular aminooxygenation[8b] and aza-Wacker type[9] byproducts.

We also examined alkenes **11q**−**11s** under the standard reaction conditions to gain more insight on the reactivity of 1,n-migration involved in this aminoheteroarylation transformation. The formation of **12q** and **12s**, presumably via 1,3- and 1,6-migration, was observed in a trace amount by LC/MS, while aza-Wacker type allylic amination products were formed instead. On the other hand, the 1,5-migration product **12r** was smoothly formed in 59% yield. These results support that the readily formed five- and six-membered cyclic transition states

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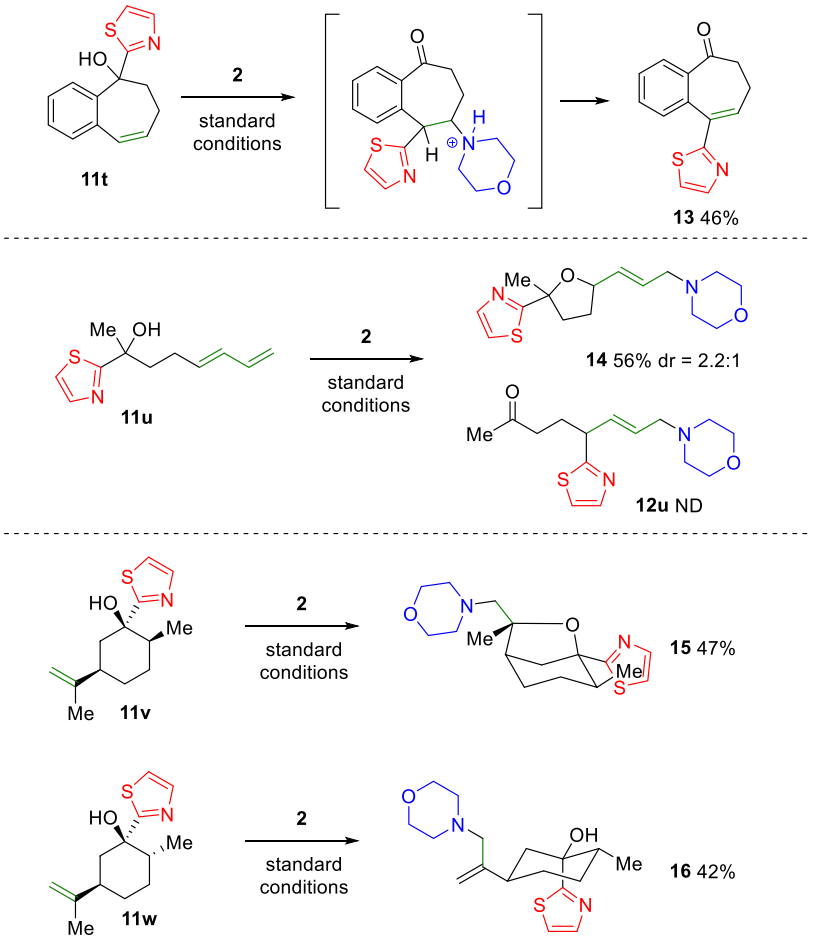
Scheme 2. Competing Reaction Pathways[a]



[a]Reaction conditions: **11** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), DCE (1 mL), and 80 °C. Isolated yields shown.

facilitated the 1,4- and 1,5-migratory aminoheteroarylation reactions, while 1,3- and 1,6-migration is hampered by unfavorable four- and seven-membered transition-state ring formation.

During the investigation of these alkene aminoheteroarylation reactions, we observed several possible competing reaction pathways (Scheme 2). For example, subjecting styrene-derived substrate **11t** to standard reaction conditions led to the formation of thiazolyl-substituted alkene **13** in 46% yield, presumably owing to the elimination-prone ammonium species under acidic conditions. Another common competing pathway is the formation of cyclic ether products by an intramolecular aminooxygenation reaction. For example, the reaction of conjugated diene precursor **11u** formed cyclic ether **14** exclusively, with no desired product **12u** observed. The reaction of carvone derivative **11v** also gave amino oxycyclization product **15**, as the migration would involve a conformationally strained bicyclic transition state. Interestingly, the reaction of another carvone derivative **11w** provided aza-Wacker type allylic amination product **16** as the major product, when the oxycyclization was conformationally disfavored. The unsuccessful migration of the thiazolyl group placed at the opposite side of the alkene in both substrates **11v** and **11w** supported the presence of five-membered cyclic transition state for the 1,4-heteroaryl migration.

To probe radical intermediates that may be involved in the migration step, control experiments were performed with **1b** and **11r** under the standard reaction conditions, in the presence of a radical scavenger (Scheme 3a). When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was present, the reactions of **1b** and **11r** provided the reduced yield of migrated heteroarylation products and resulted in the formation of TEMPO-trapped products **17** and **18**, respectively. The addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) also deteriorated the formation of *β*-aminoethyl thiazole product and gave rise to BHT-derivatives **19** and **20**. The formation of **17**−**20** all implied the presence of nitrogen- and carbon-radical species under the reaction conditions. Based on these experimental results, a plausible reaction mechanism is proposed for the aminoheteroarylation reaction (Scheme 3b). The active Cu(I) catalyst can be generated from the Cu(II) precatalyst through disproportionation.[10] The oxidative addition of *O*-benzoylhydroxylamine to Cu(I) catalyst would generate an amide Cu(III) species (**A**) or a Cu(II) nitrogen-based radical complex (**A′**). Subsequent intermolecular amination of alkene **1b** through either (**A**) or (**A′**) would produce the corresponding Cu(III) species (**B**) or a carbon radical (**B′**). Note that the electron-rich amine group would be protonated in the presence of TsOH.[11] The migration of the heteroaryl group onto the carbon radical

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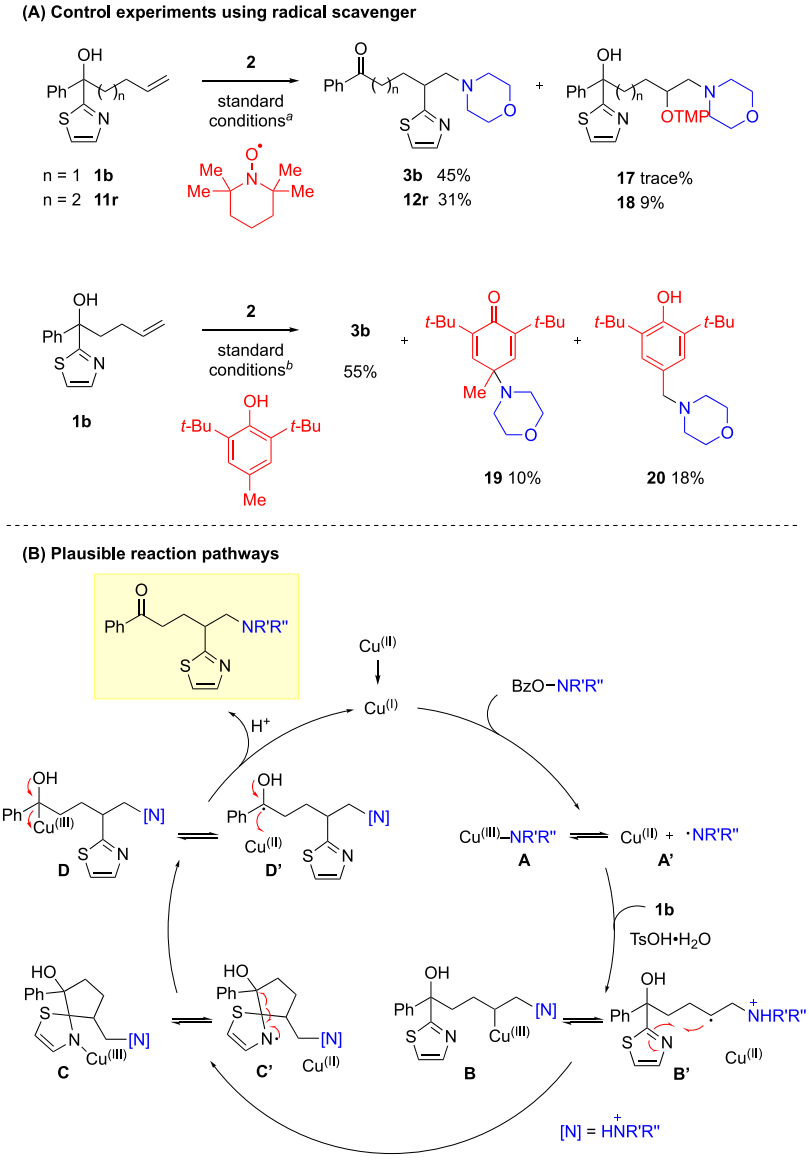
Scheme 3. Mechanistic Studies on Aminoheteroarylation Reactions



[a]Run under standard conditions with TEMPO (1.0 equiv). [b]Run under standard conditions with BHT (1.0 equiv). Isolated yields shown.

may occur either through a cyclic Cu(III) intermediate (**C**) or via an alkyl radical intermediate (**C′**). Subsequent C−C σ-bond breaking would provide a hydroxyalkyl Cu(III) intermediate (**D**) or a hydroxyalkyl radical (**D′**),[12] finally leading to the formation of the desired product by an elimination step (from **D**) or a SET oxidation (from **D′**), as well as the regeneration of the Cu(I) catalyst.

Based on the mechanistic hypothesis, we expect that this aminoheteroarylation strategy was potentially extendable beyond alcohol-containing alkenes in previous migratory difunctionalization reactions. We examined the aminoheteroarylation conditions on alkene-containing α-tertiary amides and ether derivatives (Scheme 4). Both sultam **21a** and phosphinamide **21b** were found effective to promote the migration functionalization in a manner analogous to tertiary alcohols. *N*-sulfonylimine **22** from **21a** was successfully isolated in 41% yield, whereas *N*-phosphinylimine from **21b** was not stable under acidic conditions, with ketone product **3b** obtained in 52% yield. Furthermore, the reactions of analogous methyl ethers **23a**−**23b** also afforded the desirable products **3b** and **8f**. These examples demonstrated that this aminoheteroarylation is applicable to nonalcohol substrates and is not limited by the presence of a hydroxyl moiety which was commonly required in previous migration methods. Excitingly, this reaction proved to be a viable strategy for the synthesis of cyclic ketone systems. Subjecting **24a** and **24b** to standard conditions readily constructed eight- and nine-membered cyclic amines **25a** and **25b**, respectively. Such ring-expansion reactions present an attractive, useful approach to rapidly access medium-sized nitrogen-containing ring systems known to be synthetically challenging yet highly desirable in medicinal chemistry.[13]

In summary, we have developed copper-catalyzed aminoheteroarylation of alkenes for the synthesis of valuable heteroarylethylamine motifs. This method features selective migration, good tolerance of functional groups, as well as a broad scope of alkenes, heteroarenes, and amines under mild conditions. Mechanistic studies have implied the presence of

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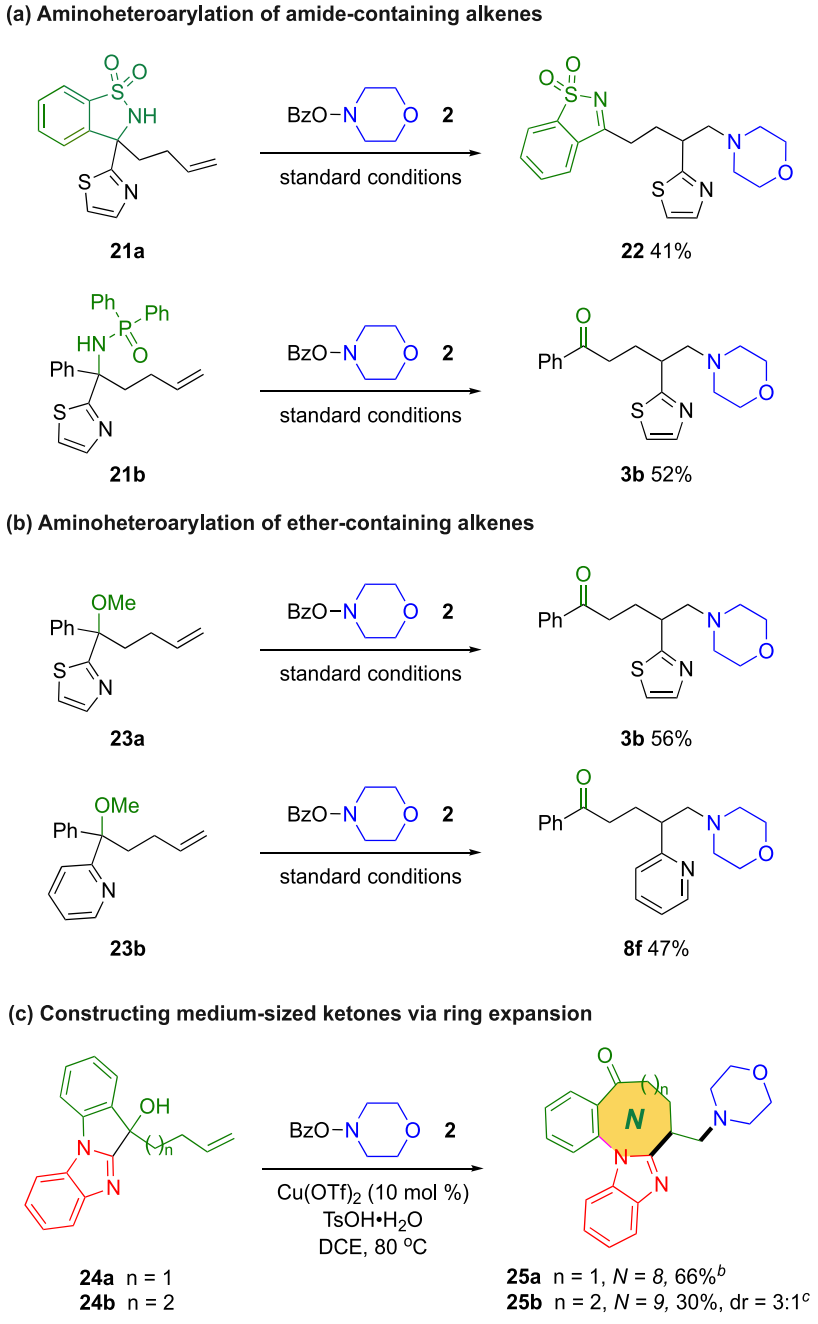
Scheme 4. Expanding the Generality and Application of Alkene Aminoheteroarylation[a]



[a]Reaction conditions: alkene (1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol %), $TsOH{\cdot}H_2O$ (1.5 equiv), DCE, and 80 °C. [b]Run with **2** (3.0 equiv), $TsOH{\cdot}H_2O$ (2.0 equiv), DCE, and 80 °C. [c]Run with **2** (5.3 equiv), $TsOH{\cdot}H_2O$ (4.8 equiv), DCE, and 80 °C. Isolated yields shown.

nitrogen- and carbon-radical species under reaction conditions. Such an alkene migratory aminoheteroarylation reaction is also well suited as a rapid approach to construct medium-sized rings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01001.

Condition optimizations; experimental procedures; compound characterization; and NMR spectra (PDF)

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Author Contributions

†Y.K. and W.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(11) Although the roles of acid additive such as TsOH in this reaction remain to be fully understood, the acid additive likely contributes to the protonation of amine intermediate/product to release the coordination of copper-catalyst to the amine group. The acid may have additional roles of facilitating the N−O cleavage of BzO−NRR' or the migration of heteroaryl group, although the protonation is not required in either N−O bond cleavage or the migration step.

(12) We can't exclude the involvement of the protonated heteroaryl form in the migration step with the presence of $TsOH{\cdot}H_2O$ under standard reactions. Yet the migration of heteroaryl groups does not necessarily require the protonation, which was supported by the formation of 10e′, control experiment with NSFI in the absence of TsOH (see the SI), and related migration reactions such as those in ref 7.

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