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Nondirected, Cu-Catalyzed sp^3 C–H Aminations with Hydroxylamine-Based Amination Reagents: Catalytic and Mechanistic Studies

Anqi Wang, Nicholas J. Venditto, Julia W. Darcy, and Marion H. Emmert*

Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, 100 Institute Road, Worcester, Massachusetts 01609, United States

Abstract

This work demonstrates the use of hydroxylamine-based amination reagents $RSO_2NH-OAc$ for the nondirected, Cu-catalyzed amination of benzylic C–H bonds. The amination reagents can be prepared on a gram scale, are benchtop stable, and provide benzylic C–H amination products with up to 86% yield. Mechanistic studies of the established reactivity with toluene as substrate reveal a ligand-promoted, Cu-catalyzed mechanism proceeding through $Ph-CH_2(NTsOAc)$ as a major intermediate. Stoichiometric reactivity of $Ph-CH_2(NTsOAc)$ to produce $Ph-CH_2-NHTs$ suggests a two-cycle, radical pathway for C–H amination, in which the decomposition of the employed diimine ligands plays an important role.

Graphical Abstract

INTRODUCTION

Benzylic amines are important substructures in biologically active compounds; however, the synthesis of such structures is typically achieved through functional group interconversion processes.^{1–3} Direct aminations of benzylic C–H bonds would streamline the synthesis of benzylic amines,^{4–12} in particular, if first-row transition metals can be employed as catalyst precursors. Efforts to this end have recently produced a series of $Co^{13–15}$ and Cu catalysts^{6,16–21} that achieve nondirected, intermolecular benzylic C–H aminations. The majority of these established protocols (Scheme 1A) employ electrophilic amination reagents, such as azides^{14,15} or N-halogenated sulfonamides;^{6,7,13,17,18} alternatively, a two-reagent mixture of oxidant and amine can affect similar reactivity.^{6,10,19–21} However,

*Corresponding Author: mhemmert@wpi.edu.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00003. Experimental procedures, spectroscopic data ($^1H/^{13}C/^{19}F$ NMR, IR, HRMS), and detailed optimization data (PDF)

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commonly used reagents or reagent mixtures all suffer from specific drawbacks: The protecting group on the introduced amine functionality is typically not easily variable, as only few electrophilic amination reagents or precursors are commercially available. This limits the direct use of most known protocols in synthetic applications or requires cleavage of the introduced protecting group after C–H amination. Furthermore, the stability of many reagents is problematic and restricts their general use: Azides are explosive, while N-halogenated sulfonamides and hypervalent iodine reagents are readily hydrolyzed in the presence of water.

Due to these drawbacks, research in our group²² and by others (for example, see Scheme 1B)⁴ has focused on establishing stable and versatile, hydroxylamine-based, electrophilic amination reagents that are active reagents for non-directed C–H amination reactions. Herein, we report that these reagents can be employed in combination with Cu catalysts to achieve benzylic C_{sp}³–H aminations (Scheme 1C). The described protocol is, unlike prior Cu-based benzylic C–H amination systems, strongly affected by steric hindrance around the target C–H bonds.

Based on detailed mechanistic studies, we propose a catalytic reaction pathway proceeding through radical intermediates and two subsequent, connected catalytic cycles. Furthermore, our studies suggest that the requirement for an excess of benzylic substrate in these reactions is due to the formation of radical addition products in a second catalytic cycle. Overall, the herein reported system shows mechanistic features that have not been observed for other, similar Cu-based catalyst systems, provides interesting regioselectivities, and avoids the use of hydrolytically unstable or hazardous amination reagents.

RESULTS AND DISCUSSION

Catalytic Optimizations.

Initial screening studies with the hydroxylamine-derived reagents focused on establishing C–H amination reactivity for the functionalization of toluene. We reasoned that a catalyst able to transform primary, benzylic C–H bonds such as in toluene can also be expected to show analogous reactivity in the cleavage and amination of secondary and tertiary benzylic C–H bonds due to their lower bond dissociation energies (88.0 kcal/mol for PhCH₃, 84.0 kcal/mol for PhCH₂CH₃, 82.5 kcal/mol for PhCH(CH₃)₂).²³

Initial screenings established that C–H amination reactivity can be observed with TsNH-OAc as reagent and toluene as arene substrate and solvent, employing simple Cu salts as catalyst precursors (Table 1, entries 1–6). In order to enable distinction between small reactivity differences, all catalytic experiments were performed at least twice or until the obtained standard deviations of replicate trials were <2%.

Among the simple catalyst precursors, salts with weakly binding anions (Cu(BF₄)₂, [Cu(MeCN)₄]PF₆, Cu(OTf)₂; entries 1, 2, and 6) provided higher yields (33 to 36%), while salts with more strongly coordinating counteranions (entries 3 to 5) provided slightly lower yields. Interestingly, the oxidation state of the Cu catalyst precursor did not play a major role (entries 4/5): Use of CuCl or CuCl₂ leads to almost identical yields of C–H amination

product (27% and 30%, respectively). Overall, Cu(OTf)₂ showed the best reactivity (36% yield) among simple Cu salts.

Reactions in the absence of added Cu salts (entry 7) did not provide any benzylic C–H amination product. Furthermore, reactions performed under air instead of under N₂ atmosphere (entry 8) showed a small decrease in product yield, indicating that oxygen may interfere with the catalytic cycle.

In order to further improve the reactivity of the catalyst system, we explored the effects of a series of bidentate ligands. Addition of most common ligands (nacnac ligands; bisoxazolines; IPr; 1,2-diamines; diimines derived from (MeCO)₂ and arylamines) did not enhance the yield observed with simple Cu salts; however, several of the diimine ligands shown in Figure 1^{17,18} resulted in an enhancing effect when added to the reaction mixture. We then synthesized a series of ligands with *para*-substitution in the aromatic moieties (**2–5**, Figure 1) to systematically study substituent effects on catalysis.

In agreement with literature observations,¹⁸ electron-donating substituents (ligands **2** and **3**; Table 1, entries 9 and 10) showed relatively low reactivities, even though the presence of the methoxy-substituted ligand **3** resulted in a yield of 37% (entry 10), similar to the highest yields obtained in the absence of L-type ligands (36%; entry 6). Ligands **4** and **5** bearing electron-withdrawing substituents resulted in slightly higher yields (39% each; entries 11 and 12). This led us to explore a series of diimine ligands with two or more electron-withdrawing substituents (ligands **6–9**, Figure 1); of these, the C₆F₅ moiety in ligand **9** resulted in 48% yield (Table 1, entry 16). Combining ligand **9** with Cu(OTf)₂ or [Cu(MeCN)₄]PF₆, which were both effective catalyst precursors in the ligand-less optimization, did not lead to enhanced reactivity (40% and 33% yield, respectively; entries 17 and 18). This trend (lower reactivity with OTf and PF₆ counteranions) held true for reactions forming Cu^{II} catalyst precursors *in situ* through reaction of CuCl₂ with the corresponding Ag salts (entries 19–21): While the reactions catalyzed by CuCl₂/AgBF₄ afforded moderate yields (49%), reactions employing CuCl₂/AgOTf or CuCl₂/AgPF₆ provided much decreased product yields (32% and 28%, respectively). This suggests that the counteranions play a role in the catalytic activity; furthermore, Ag largely does not seem to influence the outcome of the C–H amination catalysis, which is in contrast to reactivity patterns observed in intramolecular and allylic C–H aminations.²⁴ Further optimization by adjustment of the reaction temperature resulted in the same reactivity at 120 °C as observed at 110 °C (49%; entry 22), while lower reaction temperatures (100 °C; entry 23) afforded lower yields (38%) of BnNHTs.

Overall, the reaction optimization reveals that perfluorinated, highly electron-withdrawing aryl groups (ligand **9**) are the most activating substituents. We speculate that this is due to their stability under the reaction conditions, either against hydrolysis or addition reactivity of radical intermediates. Further studies to this end will be presented in the Mechanistic Investigations section of this manuscript.

Synthesis of Different Amination Reagents.

Following catalytic optimization, we prepared a variety of amination reagents with different protecting and leaving groups to be tested in benzylic C–H amination. Most of these reagents were synthesized in a two-step procedure (Scheme 2A) in analogy to a preparation described in the literature.²⁵ This direct synthesis takes advantage of the higher nucleophilicity of the NH₂ moiety in hydroxylamine under weakly basic conditions, which determines the chemoselectivity of the first acylation step.

However, several reagents with electron-withdrawing substituents on their sulfonyl protecting groups could not be obtained cleanly using the two-step procedure; these reagents were synthesized employing a temporary protecting group strategy (Scheme 2B).²⁶

Generally, all reagent preparations were straightforward, and the majority of reagents were prepared on gram scales (examples of scales between 0.2 to 7.0 g product are described in the SI). All reagents are bench and air stable and were stored without additional precautions. Many of the prepared reagents were not known in the literature prior to this work (for complete characterizations, see SI).

Scope of Amination Reagents.

The resulting reagents were subjected to the optimized C–H amination conditions (Table 1, entry 16). Interestingly, varying the leaving group from acetate in reagent **1** to pivalate (Scheme 3, reagent **10**) or trifluoroacetate (reagent **11**) decreased the catalytic efficiency (34% and 4% yields), suggesting that the identity of the leaving group is crucial for catalysis.

Adjusting the substituents of the sulfonate group from tolyl to phenyl (reagent **12**) resulted in only a small decrease in yield to 44%, while both electron-donating (OMe, reagent **16**) and electron-withdrawing substituents on the aryl moieties (NO₂, CF₃, Cl; reagents **13–15**) afforded further lowered yields of the corresponding C–H amination products (28–35%). These data suggest that factors other than electron-donating or electron-withdrawing substituent effects may influence reactivity. One such factor may be the stability of the aromatic groups against radical addition. However, as the data show, the aromatic nature of the protecting group is not generally necessary for maintaining reactivity: mesylate-protected amination reagent **17** produced the respective amination product in 40% yield.

In contrast, no C–H amination reactivity of toluene was observed with amination reagents such as AcHN-OAc, TsAcN-OAc, TsBnN-OAc, or BzNH-O₂COR, suggesting that the activating effect of the sulfonate protecting group (possibly through stabilization of the radical character in catalytic intermediates),²⁷ the leaving group acetate, and the NH functionality of the electrophilic amination reagents are all crucial for catalytic reactivity.

Arene Substrate Scope.

Next, we explored the scope of the reaction regarding employable arene substrates (Table 2); the amination reagent that resulted in the highest yields with toluene (**1**) was employed in all these reactions. When compared to the C–H amination of toluene (48% yield; entry 1),

reactions employing substrates with secondary benzylic C–H bonds afforded similar (EtPh, 45%; entry 2) or higher C–H amination yields (PhCH₂Ph 86%; entry 3).

One exception to this trend was observed with isobutylbenzene (3%; entry 4); we speculate that the lack of reactivity may be caused by steric hindrance²⁸ at the benzylic position. Cumene as a substrate (entry 5) produces only traces of benzylic C–H amination product, which also suggests that the established catalyst system is sensitive to steric bulk around the site of C–H amination. Interestingly, no such selectivity is observed with other Cu catalyst systems that are active for benzylic C–H aminations; instead, [Cu(MeCN)₄]PF₆/TsNNaCl¹⁷ and Tp^{Br}₃Cu(NCMe)/PhI=NTs¹⁶ both readily form the product of benzylic C–H amination with cumene as substrate.

Reacting a substrate with both secondary and primary benzylic C–H bonds (entry 6) produces the secondary C–H amination product **18a** as the major product (55%), with the minor product **18b** being formed in 12% yield as a result of primary C–H bond cleavage. This observation suggests that the catalyst prefers cleavage of the C–H bond with the lower bond dissociation energy, as long as this bond is not significantly sterically hindered. Therefore, a combination of both steric and electronic factors influences C–H amination selectivity in the established systems, resulting in a reactivity order of 2° > 1° >> 3°. A competition experiment (entry 13) between ethylbenzene and cumene further supports this conclusion.

These observations are generally in agreement with literature reports on other Cu catalysts, which show a preference for the secondary benzylic C–H bond,¹⁶ but typically also attack primary, nonbenzylic C–H bonds, resulting in a mixture of three different products (**18a**, **18b**, and *p*-H₃CC₆H₄-CH₂CH₂NHTs). This suggests that the combination of Cu(BF₄)₂/**9** and amination reagent **1** is generally less reactive than comparative Cu C–H amination systems, but at the same time more selective for secondary and primary benzylic bonds.

Substituted toluenes (entries 7–9) generally afforded low to moderate yields of benzylic C–H amination product (24 to 43%); no clear trend can be delineated between electron-withdrawing and electron-donating substituents. This is in agreement with the amination reagent scope (see Scheme 3 above), in which both electron-withdrawing and electron-donating substituents on amination reagents **13** to **16** afford lower yields than the tolyl-substituted amination reagent **1**. Overall, this observation suggests that factors other than simple electronic substituent factors may play a role in the established system. As both electron-withdrawing and electron-donating substituents have shown stabilizing effects on radical centers,²⁹ the described reactivity may well be influenced by such effects. However, initial rates measured with different *para*-substituted toluenes do not show any clear correlations with Hammett parameters (σ/σ^+) or radical stabilization parameters ($\sigma^\bullet$; see SI).

In contrast to arenes with functional group substitution, arenes with cyclic alkyl substructures afforded higher yields than observed with toluene (64% and 76%, respectively; entries 10 and 11). Similarly high yields have been observed with these substrates when employing other Cu-based catalyst systems,^{17,21} and this phenomenon has previously

been associated with decreasing values of benzylic C–H bond dissociation energies for the respective substrates.²¹

Interestingly, THF is also a suitable substrate for C–H amination, providing the aminated hemiaminal product in 67% yield (entry 12). As the bond dissociation energy for the C_α–H bond in THF (70 kcal/mol) is significantly lower than the bond dissociation energy of the benzylic C–H bond in toluene,^{23,30} this finding is in agreement with the above observed higher yields for substrates with lower bond dissociation energies (entries 10/11).

Mechanistic Investigations.

As the developed reaction system shows some similarities to literature-known systems, but also distinctly different reactivity (e.g., lack of C–H amination of sterically hindered C–H bonds), we pursued mechanistic studies to gain insight into pathways involved in product and side product formation.

Our initial studies were aimed at confirming that ligand **9** binds to the Cu precatalyst under catalytic conditions. To this end, we prepared a catalytic reaction mixture in analogy to the optimized conditions (see Experimental Section for details). This reaction mixture was heated to 110 °C for 15 min, diluted with MeOH, and then analyzed by electrospray ionization mass spectroscopy (ESI-MS). The obtained mass spectrum (Scheme 4) showed the presence of [Cu^I(**9**)(H₂O)₂]⁺ in positive ion mode. This complex is likely formed from the precursor Cu(BF₄)₂·6H₂O and ligand **9** by coordination and one-electron reduction. In combination with the above-discussed similar performance of Cu^I and Cu^{II} salts as catalyst precursors, this suggests that Cu compounds of either oxidation state may provide entry into the catalytic cycle; moreover, both oxidation states may be involved during catalysis.

Interestingly, decomposition of **9** occurs upon extended reaction times: An analogous ESI-MS analysis of a reaction mixture after 24 h showed signals for complex **20** (Figure 2; for spectra, see SI), in which Cu is ligated by two diamine ligands. This suggests that the speciation of the Cu complexes in the reaction mixture changes over the course of the reaction; this changing coordination environment may at the same time cause changes in catalytic reactivity (see discussion *vide infra*).

A subsequent ligand decomposition study (see SI for details) confirms that among the tested ligands, ligand **9** is the most stable diimine and undergoes hydrolysis very slowly. In contrast, ligands with more electron-donating aryl groups (e.g., ligands **2** and **3** with C₆H₄-NMe₂/OMe substituents) hydrolyze more quickly. This suggests that the relative significant stability of ligand **9** plays a role in the catalytic amination activity.

Next, we investigated the kinetics of product formation over time (Scheme 5) under the optimized reaction conditions, employing toluene as substrate and **1** as amination reagent. Scheme 5 shows that formation of the C–H amination product BnNHTs (blue line) mainly occurs after 4 h and is mostly complete after 16 h. However, the amination reagent TsNHOAc (**1**; purple line in Scheme 5) is consumed within the first 4 h of the reaction. This suggests that BnNHTs is not formed directly from the amination reagent and that another

reaction intermediate may accumulate during the first 4 h, which then affords BnNHTs in a second reaction step.

In contrast to the kinetics of product formation, the highest rate of TsNH₂ formation (red line in Scheme 5) is detected during the first 4 h of the reaction; its yield decreases minimally in the latter part of the reaction from 52% at 4 h to 45% after 48 h. The kinetics for formation of the other side product, bitolyl (black dotted line), are more similar to the kinetics of product formation: slow formation in the initial 4 h and accelerated formation after 4 h. These observations combined imply that the reaction mechanism involves an intermediate which is formed directly from amination reagent **1**; this reaction produces TsNH₂ as a side product. In a second step after the first 4 h, the accumulated intermediate is then transformed into the product BnNHTs; this second step also forms bitolyl as the side product.

Importantly, ¹H NMR analyses of the crude reaction mixtures suggested that a broad peak at 4.23 ppm may be associated with the proposed intermediate, as the peak grows in over the first 4 h and then disappears. Isolation of the intermediate from the reaction mixture (11% yield), spectroscopic characterization, and independent synthesis (see SI for details) identify the intermediate as BnTsN-OAc, in which the N–O bond is still intact.

In a subsequent investigation, we studied the temperature dependence of the formation of product, intermediate, and side products under otherwise unchanged optimized reaction conditions. Scheme 6 illustrates that the yields of TsNH₂ and BnTsN-OAc are similar at 70 and 90 °C, suggesting that these two products are formed through a common catalytic cycle. Moreover, the combined yields of BnTsN-OAc and BnNHTs under these conditions are close to the observed yield of TsNH₂, suggesting that formation of BnNHTs from BnTsN-OAc does not produce TsNH₂.

Furthermore, the temperature dependence of the yields for intermediate and BnNHTs suggests that reaction pathways producing BnTsN-OAc can be accessed at lower temperatures (28% at 70 °C; 43% at 90 °C) than the formation of product (3% BnNHTs at 70 °C; 8% at 90 °C). This observation implies that the activation barrier for the formation of BnTsN-OAc is significantly lower than the activation barrier for the conversion of BnTsN-OAc to BnNHTs.

Reactions of isolated BnTsN-OAc under conditions analogous to the optimized catalytic reaction conditions (Scheme 7) support this hypothesis: Only 6% of BnNHTs is obtained after 24 h with the optimized catalyst system, suggesting a relatively slow transformation of BnTsNOAc into BnNHTs associated with a high activation barrier.

Interestingly, the conversion of BnTsN-OAc to product shows a dependence on the catalyst used: when employing simple Cu(BF₄)₂·6H₂O, the obtained yield of BnNHTs (84%) is much higher. Furthermore, conversion of BnTsN-OAc to BnNHTs requires Cu as catalyst, as shown by a lack of reactivity in the absence of Cu; the presence of air also inhibits the formation of BnNHTs from BnTsNOAc.

In combination, the studies illustrated in Scheme 7 demonstrate that BnTsN-OAc is a likely catalytic intermediate for the formation of BnNHTs. The data also imply that the transformation of BnTsN-OAc into the product may be catalyzed by a nonligated Cu species under C–H amination conditions. Together with the finding that ligand **9** decomposes to form diamine complex **20**, this suggests that ligand decomposition (e.g., by radical addition or diimine hydrolysis) may need to occur in the reaction mixture before the product can be formed efficiently, which is one possible explanation for the observed “timelag” in the reaction kinetics (see Scheme 5 above).

In order to gain further insight into the role of the ligand in catalysis, a similar time course study was undertaken in the absence of ligand. The respective rates of substrate disappearance, intermediate, and product formation under conditions with and without ligand are illustrated in Scheme 8.

Interestingly, consumption of the amination reagent **1** is significantly slower in the absence of ligand **9**, suggesting that the electron-donating features of Cu ligation by **9** accelerate the reaction of the catalyst with the amination reagent. At the same time, the rates of formation for TsNH₂ and the intermediate BnTsN-OAc are both significantly slower in the absence of **9**, which suggests that both products are formed in the same reaction cycle. In contrast, formation of the product BnNHTs is not significantly affected by ligand presence or absence in the first 6 h of the reaction. Similarly, the rates of bitolyl formation with and without ligand **9** only deviate from each other at longer reaction times. Both of the latter observations imply that a change in catalytic species may be occurring at extended reaction times and/or that a different species than a Cu species ligated to **9** may be responsible for conversion of BnTsNOAc to BnNHTs.

Mechanistically, all of the studies above are consistent with a mechanism that proceeds through two catalytic cycles: The first cycle forms BnTsN-OAc and TsNH₂ with a relatively low energetic barrier; then, a second catalytic cycle with a higher activation barrier transforms BnTsN-OAc into BnNHTs and produces bitolyls as side products. In agreement with our experimental findings and prior mechanistic work in related, Cu-catalyzed C–H amination systems,²⁰ we thus propose a reaction mechanism for the herein described catalytic protocol, as shown in Scheme 9.

We propose that the amination reagent reacts with two Cu^I catalysts, resulting in the formation of a Cu^{II} amide **20** and a Cu^{II} acetate species. Species like **20** have previously been proposed to be active in C–H cleavage,²⁰ which results in formation of a benzylic radical. In a parallel reaction, the Cu^{II} acetate species can react with a second equivalent of amination reagent to produce AcOH and a new Cu^{II} species **21**, in which the N–O bond remains unbroken. **21** then can react with the benzylic radical to form a new C–N bond in coordinated intermediate BnTsN-OAc; release of BnTsN-OAc and TsNH₂ subsequently reforms the two [Cu^I] species.

The intermediate BnTsN-OAc then enters the second catalytic cycle and undergoes N–O bond cleavage, oxidizing two [Cu^I] species to the corresponding Cu^{II} compounds. Complex **22** is a Cu^{II} amide species capable of H atom abstraction in analogy to the reactivity

proposed for cycle 1. However, intermediate **22** can be expected to be less electrophilic than **20**, which might provide a rationale for the higher activation barrier of cycle 2. The higher reactivity of nonligated Cu catalysts for cycle 2 can be explained with an analogous rationale: Nonligated Cu^{II} salts would be expected to be more electrophilic than Cu^{II} species coordinated to a diimine ligand and thus might be more active for H atom abstraction in cycle 2. Upon reaction between **22** and 1 equiv of toluene, a Cu^I complex **23** is formed that releases the product BnNHTs and reforms 1 equiv of catalyst. However, formation of **23** through H atom abstraction also causes the formation of a benzylic radical, which can react with another equivalent of substrate in a radical addition pathway; the resulting bitolyl radical may then react with the Cu^{II} acetate species to form AcOH and regenerate 1 equiv of [Cu^I] catalyst.

The proposed mechanism suggests that bitolyl is formed concurrently with the product BnNHTs, in agreement with the kinetic data (see Scheme 5 above) and with the observation that bitolyls are formed as side products in all productive stoichiometric reactions of the intermediate BnTsN-OAc (Scheme 7 above). However, it is possible that the benzylic radical formed in cycle 1 also undergoes bitolyl formation instead of reaction with Cu^{II} species **21**. This reaction may be occurring particularly if the reaction of the Cu^{II} acetate species with the second equivalent of amination reagent is slow, which is a scenario that would likely occur at low concentrations of amination reagent (i.e., after 2 h under the catalytic conditions shown in Scheme 5). Alternatively, a benzylic radical formed in cycle 2 may also react with **21**; as such, crossover between the two catalytic cycles may be possible.

Such “crossover” reactivity may be responsible for the higher yields observed when employing substrates with lower C–H bond dissociation energies. In these cases, the respective benzylic radicals R• are relatively long-lived. This may enable a reaction between [Cu^{II}]-OAc and the byproduct TsNH₂ to form [Cu^{II}]-NHTs; this species in turn could then undergo a radical rebound reaction with the benzylic radical R• and form R-NHTs. This hypothesis is further in agreement with the slow consumption of TsNH₂ observed in the time study upon extended reaction times (Scheme 5).

The mechanistic hypothesis described in Scheme 9 has several consequences: (1) The need to use an excess of toluene as substrate is explained by the need for cycle 2 to access the product BnNHTs. As such, reactions with 1 equiv substrate may be possible when a catalytic system that only undergoes cycle 1 can be developed. (2) Similarly, the high reaction temperature required to access BnNHTs may stem from the higher activation barrier of cycle 2, likely caused by the less electrophilic nature of the Cu^{II} amide species **22**. (3) The strong preference for sterically unhindered C–H bonds may be rationalized by the significant steric hindrance at Cu^{II} amide species **21** that recombines with the benzylic radical for C–N bond formation. (4) The mechanism in Scheme 9 proposes radical species as key intermediates due to the observed formation of bitolyl.

In order to gain insight into the feasibility of the proposed radical intermediates, we synthesized a benzylic substrate **24** with a neighboring cyclopropyl moiety. This substrate has previously been used to obtain information on the radical character of related reactions.

³¹ When subjecting **24** to the standard catalytic reaction conditions (Scheme 10), 5% of the

ring-opened product **25** was observed; no direct C–H amination product **26** with the cyclopropyl moiety still intact was obtained.

This suggests that benzylic radicals, such as proposed in the mechanistic hypothesis (Scheme 9), are feasible intermediates of the described benzylic C–H amination protocol. We speculate that the low yield of amination product **25** obtained is due to the significant steric hindrance of the benzylic C–H bond in **24**; similarly hindered substrates generally show low yields of amination product under the herein established conditions (see entries 4 and 5, Table 2).

SUMMARY AND CONCLUSIONS

In summary, we have established new types of reagents for the Cu-catalyzed amination of benzylic C_{sp}³–H bonds. The employed electrophilic amination reagents can be synthesized and stored on gram scales, eliminating the need to form reagents *in situ* (e.g., as for PhI=NR) and potential explosion hazards (e.g., as for azides). Importantly, the established reagents allow variations of the introduced protecting group.

Various arene substrates with weak, benzylic C–H bonds as well as THF have been successfully employed as substrates under the optimized conditions. Unlike in previously reported systems, tertiary or sterically crowded secondary C–H bonds undergo C–H amination only in low yields, suggesting that a sterically crowded intermediate may be responsible for C–N bond formation or C–H abstraction in the catalytic cycle.

Our detailed mechanistic studies suggest a new mechanism for C–N bond formation that proceeds through two subsequent catalytic cycles, a previously undocumented type of reactivity in Cu-catalyzed benzylic C–H aminations. As the first catalytic reaction that yields BnTsN–OAc can be performed at relatively low temperatures, future catalyst developments will focus on improving the chemoselectivity for this reaction, which has the potential to reduce the required arene substrate loading.

Overall, this manuscript describes a new reaction protocol for Cu-catalyzed C–H amination of relatively weak C_{sp}³–H bonds that proceeds through a radical pathway. A previously undocumented, two stage mechanistic hypothesis provides a rationalization for unusual, stepwise reaction kinetics. However, the high reaction temperature, limited commercial availability of the reagents, and the requirement to use an excess of benzylic substrates are currently limiting the practicality of the protocol.

EXPERIMENTAL SECTION

Representative Procedures for Synthesis of Electrophilic Amination Reagents.

N-Hydroxymethanesulfonamide.—*N*-Hydroxymethanesulfonamide was synthesized in analogy to a literature known procedure:²⁵ 16.7 g (240 mmol, 2.00 equiv) of hydroxylamine hydrochloride was dissolved in 24 mL of DI water at 0 °C. A solution of 33.2 g (240 mmol, 2.00 equiv) of K₂CO₃ dissolved in 36 mL water was added dropwise into the hydroxylamine hydrochloride solution while maintaining the internal reaction temperature (thermometer in the reaction mixture) between 5 and 15 °C with an external ice/water bath. After stirring the

solution for 15 min, 120 mL of tetrahydrofuran and 30 mL of methanol were added; subsequently, 15.4 mL (21.3 g, 120 mmol, 1.00 equiv) of methanesulfonyl chloride was added portionwise while maintaining the internal reaction temperature between 5 and 15 °C. Upon complete addition, the reaction temperature was allowed to rise to room temperature. After stirring for 4 h at room temperature, the organic solvents were removed under reduced pressure (rotary evaporator). The resulting aqueous suspension was extracted with 2 × 200 mL diethyl ether. The combined organic layers were dried over MgSO₄. The solvent of the mixture was then removed under reduced pressure and dried under high vacuum to afford 15.1 g (73% yield) of crude *N*-hydroxymethanesulfonamide, which was used for the next synthetic step without further purification. This compound has been previously reported; the observed ¹H and ¹³C NMR spectra were consistent with the data reported in the literature.²⁵

***N*-Acetoxymethanesulfonamide.**—*N*-Acetoxymethanesulfonamide was synthesized in analogy to a literature known procedure:²² 4.85 g (43.7 mmol, 1.00 equiv) of *N*-hydroxymethanesulfonamide was dissolved in 120 mL of tetrahydrofuran at –78 °C, and 3.82 mL (5.30 g, 52.4 mmol, 1.20 equiv) of triethylamine was added dropwise. After stirring the mixture for 15 min at –78 °C, 3.74 mL (4.11 g, 52.4 mmol, 1.20 equiv) of acetyl chloride was added dropwise. The reaction mixture was stirred for 4 h at –78 °C. The reaction mixture was then allowed to warm to room temperature, and the precipitate formed in the reaction was filtered off. The solvent of the filtrate was evaporated to afford a white solid. The resulting solid was dissolved in 50 mL of dichloromethane and washed with 2 × 20 mL of 1 M aqueous HCl. The organic phase was dried over MgSO₄ and filtered, and the solvent of the filtrate was removed under reduced pressure. The thus obtained crude product was dissolved in a boiling solvent mixture of 10 mL of ethyl acetate and 30 mL of hexane. The resulting solution was stored at 2 °C overnight. The crystals formed were isolated by filtration and dried under high vacuum to afford 3.1 g (47% yield) of the title compound as a white solid.

¹H NMR (500 MHz, CDCl₃, 25 °C): δ [ppm] = 8.60 (br, 1H; NH), 3.10 (d, 2H; CH₂SO₂[–]), 2.28 (s, 3H; –COCH₃). ¹³C NMR (125 MHz, CDCl₃, 25 °C): δ [ppm] = 169.5, 39.0, 18.5. IR (ATR): $\tilde{\nu}$ [cm^{–1}] = 3128 (s), 1758 (s), 1390 (s), 1329 (s), 1194 (s), 1160 (s), 1060 (s), 1008 (s), 979 (s), 961 (s), 935 (s), 862 (s), 795 (s), 715 (s), 646 (s). HRMS calcd 175.9988 (M + Na), found 175.9975.

Representative Procedure for Cu-Catalyzed, Benzylic C–H Amination of Toluene.—In a nitrogen-filled glovebox, Cu(BF₄)₂·6H₂O (2.3 mg, 6.3 μmol, 5.0 mol %), ligand **9** (3.0 mg, 6.3 μmol, 5.0 mol %), amination reagent **1** (28.7 mg, 0.125 mmol, 1.00 equiv), and dry toluene (2.00 mL, 146 equiv) were added in this sequence to a 4 mL scintillation vial, equipped with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined vial cap and heated to 110 °C on a preheated vial plate under vigorous stirring (1500 rpm). After stirring the mixture for the required reaction time, the vial was taken off the heating block, and the mixture was allowed to cool to room temperature. Volatiles were removed under reduced pressure (rotary evaporator). A solution containing 1,3-dinitrobenzene (5.0 mg, 29 μmol) as NMR standard in 0.5 mL CDCl₃ was added into the reaction vial. The resulting mixture was filtered through Celite. The filtrate was used directly

for quantitative ^1H NMR measurements (15 s relaxation time, NS = 32) to determine the product yield by measuring the ratio of integrals for the two benzylic protons of PhCH_2NHTs (peak at 4.11 ppm) and the aromatic signal of 1,3-dinitrobenzene at 8.55 ppm (for details see SI).

Isolation of C–H Amination Product N-Benzyl-4-methyl-benzenesulfonamide from Reaction Mixture.—In a glovebox, $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (11.5 mg, 31.5 μmol , 5.0 mol %), ligand **9** (15.0 mg, 31.5 μmol , 5.0 mol %), amination reagent **1** (143.5 mg, 0.625 mmol, 1.00 equiv), and toluene (10.0 mL, 146 equiv) were added in this sequence to a 20 mL scintillation vial equipped with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined vial cap and heated to 110 °C on a preheated vial plate under vigorous stirring (1500 rpm). After 48 h, the vial was taken off the heating block, and the mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. CHCl_3 (5 mL) was added to the mixture, and the resulting suspension was filtered through Celite. The filtrate was concentrated under vacuum (rotary evaporator) to yield the crude product which was purified by column chromatography using ethyl acetate/hexanes (1:4) as eluent. 73 mg (45% yield) of pure title compound was obtained. ^1H and ^{13}C NMR analysis are in agreement with literature reported spectra.³²

Isolation of Reaction Intermediate BnTsN-OAc from Catalytic Reaction Mixture.—In a glovebox, $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (46 mg, 126 μmol , 5.0 mol %), ligand **9** (60 mg, 126 μmol , 5.0 mol %), TsNH-OAc (**1**) (574 mg, 2.5 mmol, 1.00 equiv), and dry toluene (40.0 mL, 34.7 g, 376 mmol, 146 equiv) were added in this sequence to a 100 mL nitrogen flask, equipped with a Teflon-coated stirbar. The flask was sealed tightly and removed from the glovebox, and the reaction was heated for 4 h to 110 °C in a preheated heating block under vigorous stirring. The flask was removed from the heating block, and the mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. CHCl_3 (5 mL) was added to the mixture. The resulting suspension was filtered through Celite. 25 mL of hexanes was added to the filtrate. The precipitated white solid (TsNH_2) was filtered off. The solvent of the resulting filtrate was removed under reduced pressure to afford an off-white solid as crude product, which was purified by column chromatography using hexanes and ethyl acetate (5:1; R_f of the product is 0.20 in this mixture) as eluent. 87 mg (11% yield) of the title compound were isolated as a white solid.

^1H NMR (500 MHz, CDCl_3 , 25 °C): δ [ppm] = 7.84 ppm (d, 2H; Ar–H), 7.43 ppm (d, 2H; Ar–H), 7.30 ppm (m, 5H; Ar–H), 4.20 ppm (br, 2H; $\text{PhCH}_2\text{NH-}$), 2.50 ppm (d, 2H; CH_2SO_2^-). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C): δ [ppm] = 168.6, 145.9, 133.0, 130.1, 130.0, 129.8, 129.7, 128.7, 128.6, 56.9, 21.9, 18.8. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2908(s), 1789 (s), 1358 (s), 1160 (s), 1088 (s), 994 (s), 843 (s), 817 (s), 776 (s), 742 (s), 693 (s), 658 (s). HRMS calcd 320.0951 (M + H), found 320.0963.

Independent Synthesis of BnTsN-OAc.—1.00 g (4.37 mmol, 1.0 equiv) of TsNHOAc and 745 μL (539 mg, 5.33 mmol, 1.20 equiv) of triethylamine were added to 5.0 mL (5.5 g, 43.4 mmol, 10 equiv) benzyl chloride at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred vigorously overnight, and the resulting suspension was filtered. A vacuum distillation was performed to remove benzyl chloride from the filtrate.

The resulting residue in the distillation flask was dissolved in 50 mL of dichloromethane and washed with 2 × 25 mL of 1 M aqueous HCl. The organic phase was dried over MgSO₄ and filtered. The solvent of the filtrate was removed under reduced pressure to afford an off-white solid, which was dissolved in 3 mL of hot ethyl acetate; the resulting solution was stored at −30 °C overnight. The solid was isolated by filtration to afford 900 mg (75% yield) of the product as white crystals. The ¹H NMR, ¹³C NMR, and IR spectra obtained were identical to the spectra determined for BnTsN-OAc that had been isolated from the catalytic reaction mixture.

ESI-MS Analysis of Reaction Solution To Indicate Binding of Ligand 9.—In a glovebox, Cu(BF₄)₂·6H₂O (2.3 mg, 6.3 μmol, 5.0 mol %), ligand **9** (3.0 mg, 6.3 μmol, 5.0 mol %), TsNH-OAc (**1**) (28.7 mg, 0.125 mmol, 1.00 equiv), and 2.00 mL of toluene (1.94 g, 21 mmol, 146 equiv) were added in this sequence to a 20 mL scintillation vial equipped with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined vial cap and heated to 110 °C on a preheated vial plate under vigorous stirring (1500 rpm). After 15 min, the vial was taken off the heating block, and the mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure. MeOH (5 mL) was added and the resulting suspension was filtered through Celite. The filtrate was diluted with 8 mL of HPLC-grade MeOH and was used directly for ESI-MS analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Structures of diimine ligands promoting C–H amination reactivity in combination with $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$.

Figure 2.

Complex ion **20** detected by ESI-MS in a reaction mixture after 24 h.

A. Reagents & Reagent Combinations Used Previously in Cu Catalyzed Benzylic C-H Amination

B. Reported Hydroxylamine-Derived Reagent/Catalyst Systems for Rh Catalyzed Benzylic C-H Amination

C. This Work

Scheme 1.

Previously Established, Intermolecular, Nondirected Benzylic C-H Amination Systems and the Catalytic System Described in This Manuscript

A. Two-Step Synthesis of Reagents. R = *p*-tolyl, Ph, Me, *p*-MeOC₆H₄

B. Alternative Four-Step Synthesis for Electron-Deficient Aryl Substituents. Ar = *p*-F₃C/NO₂/ClC₆H₄

Scheme 2.
Synthesis of Amination Reagents

Scheme 3. Scope of Amination Reagents^a

^aConditions: Toluene (2.00 mL, 1.73 g, 18.8 mmol, 146 equiv), amination reagent (0.125 mmol, 1.00 equiv), $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (2.3 mg, 6.3 μmol , 5.0 mol %), ligand **9** (3.0 mg, 6.3 μmol , 5.0 mol %), 110 °C, 48 h, N_2 . Yields were determined by quantitative ^1H NMR analysis of the crude reaction mixtures, using 1,3-dinitrobenzene as internal standard.

Scheme 4. ESI-MS Spectrum (Positive Ion Mode) and Predicted Spectrum for $[\text{Cu}^{\text{I}}(9)(\text{H}_2\text{O})_2]^+{}^a$

^a The difference in the m/z axis reflects a known 0.3 amu calibration discrepancy.

Scheme 5. Product Formation vs Time^a

^a Conditions: Toluene (2.00 mL, 1.73 g, 18.8 mmol, 146 equiv), **1** (0.125 mmol, 1.00 equiv), Cu(BF₄)₂·6H₂O (2.3 mg, 6.3 μmol, 5.0 mol %), ligand **9** (3.0 mg, 6.3 μmol, 5.0 mol %), 110 °C, N₂.

Scheme 6.

Products after 48 h at Different Reaction Temperatures

Scheme 7.

Reactivity of Catalytic Intermediate Demonstrating Formation of BnNHTs

Scheme 8.
Comparison of Rates of Product Formation and Substrate Disappearance with/without Ligand 9

For Relatively Stable Radicals $Bn\cdot$ (Low C-H Bond Dissociation Energy in Bn-H & Slow Radical Dimerization):

Scheme 9.

Plausible Mechanistic Hypothesis for Cu-Catalyzed, Benzylic C-H Amination

Scheme 10.
Reactivity of Radical Clock Substrate 24

Table 1.

Reaction Optimization and Background^a

entry	conditions	yield (%) ^b
1	Cu(BF ₄) ₂ ·6H ₂ O	33
2	[Cu(MeCN) ₄]PF ₆	33
3	Cu(OAc) ₂	21
4	CuCl	27
5	CuCl ₂	30
6	Cu(OTf) ₂	36
7	no Cu	<1
8	Cu(BF ₄) ₂ ·6H ₂ O, air	27
9	Cu(BF ₄) ₂ ·6H ₂ O, 2	14
10	Cu(BF ₄) ₂ ·6H ₂ O, 3	37
11	Cu(BF ₄) ₂ ·6H ₂ O, 4	39
12	Cu(BF ₄) ₂ ·6H ₂ O, 5	39
13	Cu(BF ₄) ₂ ·6H ₂ O, 6	34
14	Cu(BF ₄) ₂ ·6H ₂ O, 7	33
15	Cu(BF ₄) ₂ ·6H ₂ O, 8	25
16	Cu(BF₄)₂·6H₂O, 9	48
17	Cu(OTf) ₂ ·6H ₂ O, 9	40
18	[Cu(MeCN) ₄]PF ₆ , 9	33
19	CuCl ₂ , AgBF ₄ (10 mol %), 9	49
20	CuCl ₂ , AgOTf (10 mol %), 9	32
21	CuCl ₂ , AgPF ₆ (10 mol %), 9	28
22	Cu(BF ₄) ₂ ·6H ₂ O, 9 , 120 °C	48
23	Cu(BF ₄) ₂ ·6H ₂ O, 9 , 100 °C	38

^a Conditions (unless noted otherwise): Toluene (2.00 mL, 1.73 g, 18.8 mmol, 146 equiv), Cu catalyst (5.0 mol %), ligand (5.0 mol %), amination reagent **1** (28.7 mg, 0.125 mmol, 1.00 equiv), 110 °C, 48 h, N₂.

^b Yields were determined by quantitative ¹H NMR analysis of the crude reaction mixtures, using 1,3-dinitrobenzene as internal standard; yields are reported as average yields of at least 2 experimental trials; corresponding standard deviations are generally <2% (see SI).

Table 2.

Arene Substrate Scope^a

entry	substrate	product	NMR yield (isolated) (%) ^b
1	PhCH ₃		48 (45)
2	PhEt		45 (42)
3	PhCH ₂ Ph		86 (72)
4			3
5	Ph ^t Pr		trace
6			18a: 55 (43) 18b: 12
7			40
8			43

entry	substrate	product	NMR yield (isolated) (%) ^b
9			24
10			64 (56)
11			76 (75)
12			67
13			19a: 27 19b: 5

^aConditions: Substrate (2.00 mL, 94–197 equiv), Cu(BF₄)₂·6H₂O (2.3 mg, 6.3 μmol, 5.0 mol %), ligand **9** (3.0 mg, 6.3 μmol, 5.0 mol %), amination reagent **1** (28.7 mg, 0.125 mmol, 1.00 equiv), 110 °C, 48 h, N₂.

^bNMR yields were determined by quantitative ¹H NMR analysis of the crude reaction mixtures, using 1,3-dinitrobenzene as internal standard; yields are reported as average yields of at least 2 experimental trials; corresponding standard deviations are generally <2% (see SI).