Intermolecular Enantioselective Benzylic C(sp^3)-H Amination via Cationic Copper Catalysis

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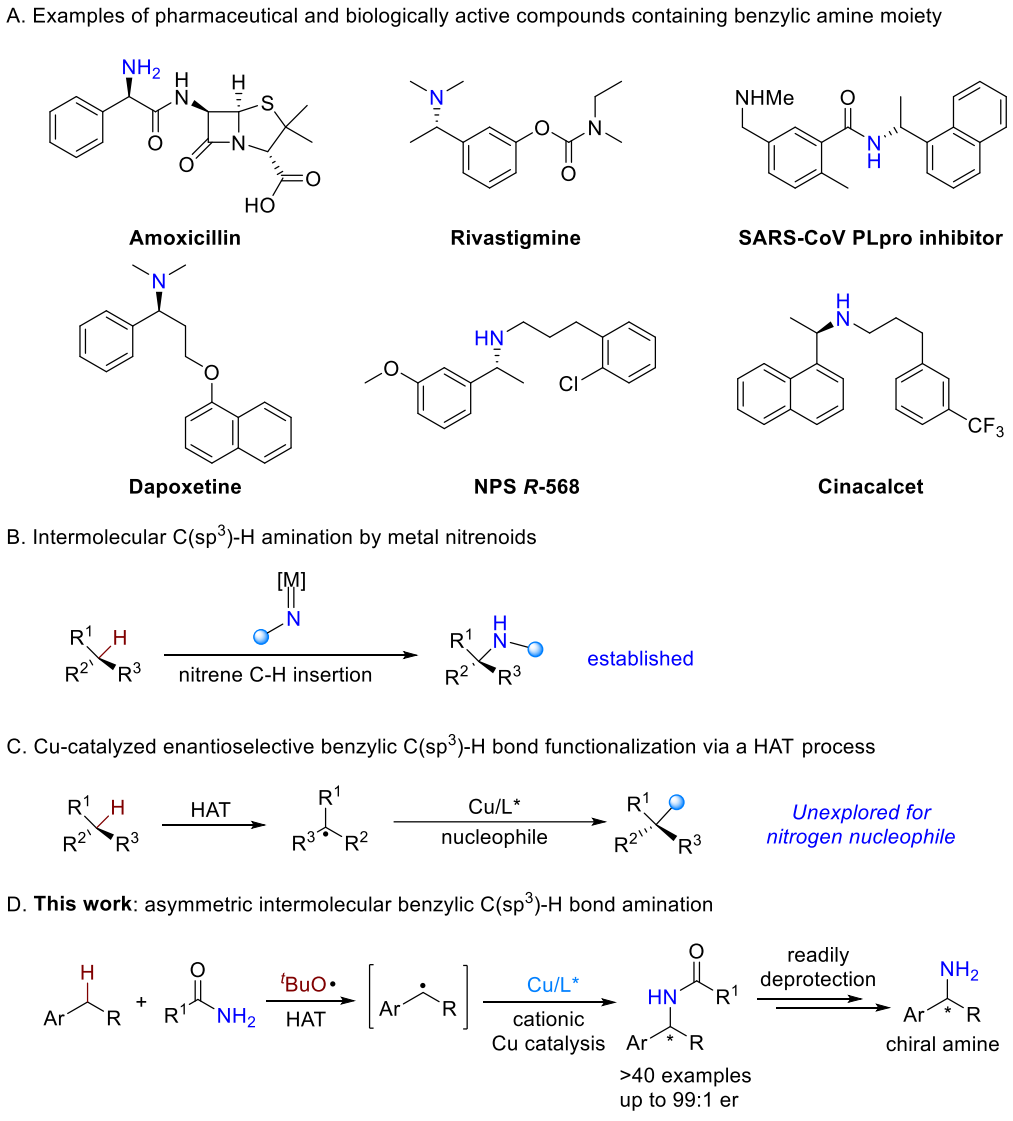
Abstract

Chiral benzylic amines are privileged motifs in pharmacologically active molecules. Intramolecular enantioselective radical C(sp3)H functionalization by a hydrogen-atom transfer (HAT) process has emerged as a straightforward and powerful tool for the synthesis of chiral amines, while intermolecular enantioselective C(sp3)H amination remains elusive. In this article, we report a cationic copper catalytic system for intermolecular enantioselective benzylic C(sp3)H amination with peroxide as oxidant. This mild yet straightforward method transforms an array of feedstock alkylarenes and amides into chiral amines with high enantioselectivities. The protocol has good functional group tolerance and broad substrate scope. More importantly, the method can be applied to synthesizing bioactive molecules and chiral drugs. Preliminary mechanistic studies indicate that benzylic radicals resulting from the HAT process are involved in the amination reaction.

Chiral amines, particularly chiral benzylic amines are found in many natural products and pharmaceuticals (Scheme 1A).[1] The established methods for the asymmetric synthesis of chiral amines include reductive amination,[2] olefin hydroamination,[3] and transition-metal-catalyzed coupling of nitrogen nucleophiles with alkyl halides.[4] However, with the aim of streamlining synthesis, the enantioselective amination of benzylic C(sp^3)−H bonds is highly appealing.[5] Remarkable progress has been made in the catalytic enantioselective nitrene insertion into benzylic C(sp^3)−H bonds by designing new chiral catalysts (Scheme 1B).[6] Enzyme

catalysis has also been demonstrated to be effective for intermolecular asymmetric nitrene C−H insertions.[7] Despite the success of these methods, the limited substrate scope or low level of enantiocontrol preclude their synthetic applications. Therefore, more general and efficient catalytic methods are desired for highly enantioselective intermolecular benzylic C(sp^3)−H amination.

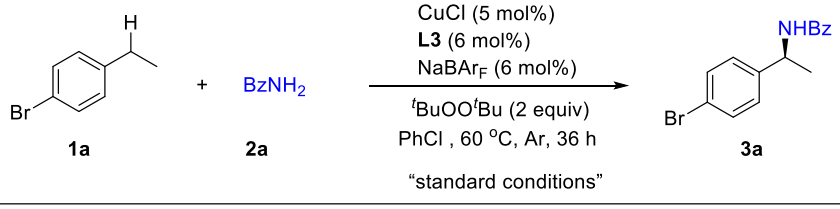
Scheme 1. Catalytic Intermolecular Benzylic C(sp^3)−H Amination Reactions

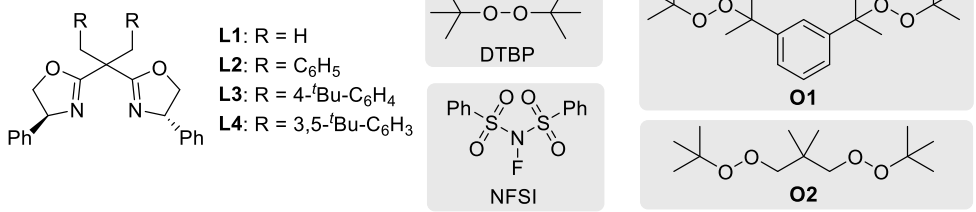


Cu-catalyzed hydrogen atom transfer (HAT) process is an efficient approach for the functionalization of benzylic C(sp^3)−H bonds.[8,9] Recently, Liu group and Stahl group achieved highly enantioselective benzylic C(sp^3)−H bond functionalization for the C–C bond formation by using copper catalyst and *N*-fluorobenzenesulfonimide

(NFSI).[10] However, when this catalytic system is used for benzylic C−N bond formation, racemic products are often obtained (Scheme 1C).[11,12] Thus new catalytic system is need to be developed for the enantioselective intermolecular C(sp^3)−H bond amination through hydrogen atom transfer (HAT) process. Here, we report a highly enantioselective intermolecular benzylic C(sp^3)−H bond amination by using chiral cationic copper catalyst and the oxidant di-*tert*-butyl peroxide (DTBP) (Scheme 1D). The reaction has a wide substrate scope and high enantioselectivity, and can be directly applied to the synthesis of chiral drugs.

Table 1. Cu-Catalyzed Enantioselective Intermolecular Benzylic C(sp^3)−H Bond Amination. Optimization of Reaction Conditions[a]





Entry	Variation from the "standard conditions"	yield(%)[b]	er[c](%)
1	None	88(82[d])	93:7
2	without CuCl	0	-
3	without $NaBAr_F$	0	-
4	without **L3**	0	-
5	without DTBP	0	-
6	$Cu(OTf)_2$ • PhH instead of CuCl/$NaBAr_F$	16	56:44
7	$Cu(CH_3CN)_4BF_4$ instead of CuCl/$NaBAr_F$	22	64:36
8	$Cu(CH_3CN)_4PF_6$ instead of CuCl/$NaBAr_F$	36	70:30
9	**O1** instead of DTBP	16	89:11
10	**O2** instead of DTBP	31	90:10
11	NFSI instead of DTBP, 100°C	13	rac
12	Selectfluor instead of DTBP	11	rac
13	**L1** instead of **L3**	53	85:15
14	**L2** instead of **L3**	62	90:10
15	**L4** instead of **L3**	63	74:26
16	2.0 equiv of **1a**	42	93:7

[a]Reaction conditions: CuCl (5 mol %), $NaBAr_F$ (6 mol %), **L3** (6 mol %), **2a** (0.2 mmol), DTBP (2 equiv.), **1a** (4 equiv.), in PhCl (0.5 mL) under Ar at 60 °C for 36 h. [b]Yields were determined by ^1H

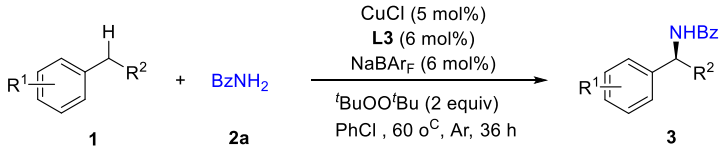
NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]Enantiomeric ratio (er) values were determined by HPLC on a chiral stationary phase. [d]Isolated yield. $NaBAr_F$, sodium tetrakis [3,5-bis(trifluoromethyl)phenyl] borate. DTBP, *di*-tert-butyl peroxide. NFSI, N-fluorobenzenesulfonimide.

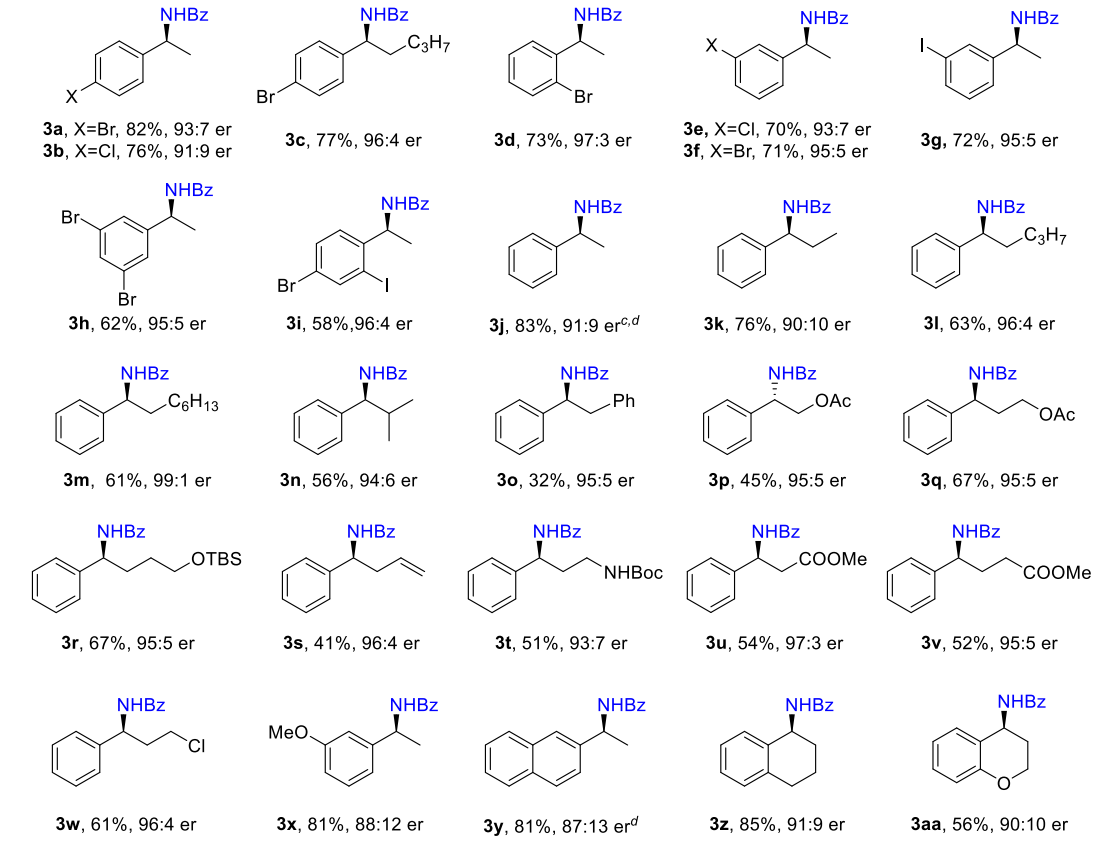
We began our study with an exploration of reaction conditions for the oxidative coupling of 1-bromo-4-ethylbenzene (**1a**) and benzamide (**2a**), and the results were summarized in Table 1 (see Supplementary Tables S1 for details). After extensive examination of copper source, ligand, oxidant and solvent, we found that the optimal reaction conditions are: CuCl (5.0 mol%), $NaBAr_F$ (6 mol %), chiral bisoxazoline ligand **L3** (6.0 mol%) and DTBP (2.0 equiv.), at 60 °C for 36 h. Under these conditions, the desired amination product **3a** was obtained in 82% yield with 93:7 er. (Table 1, entry 1). Control experiments showed that CuCl, $NaBAr_F$, **L3**, and DTBP are critical for the reaction (entries 2–5). Various copper catalyst precursors were evaluated in the reaction with ligand **L3**, and the nature of the counterions of catalysts was found to have a strong influence on the enantioselectivity and yield of the reaction. The neutral Cu catalyst precursor CuCl could not provide target product (entry 3), and $Cu(OTf)_2$ gave the amination product in low yield (16%) and low enantioselectivity (56:44 er) (entry 6). When $CuBF_4$ and $CuPF_6$ were used as catalyst precursor, both the yield and enantioselectivity of the reaction were increased, indicating that weakly coordinated counterion benefits to the reaction (entries 7 and 8). Encouraged by this, we employed copper precursor with large and non-coordination counterion BAr_F^- (tetrakis[3,5-bis(trifluoromethyl)phenyl]borane), resulting in a significant improment in the yield and enantioselectivity of the reaction. These results suggested that the reaction requires an electron-deficient catalytic copper(I) center, which is easier to bind to weakly nucleophilic amides.

Among the hydrogen atom transfer reagents tested, the di-*tert*-butyl peroxide (DTBP) showed particular activity in yielding the desired coupling product. Other peroxides and NFSI, and selectflour all gave low yield and low enantioselectivity or racemic product (entries 9–12. also see Supplementary Tables S1 for details). Ligand

study showed that other structurally related bisoxazoline ligands (**L1**, **L2**, **L4**) are also effective, but with lower enantioselectivities (entries 13–15). However, when the amount of alkylarene substrate **1a** was reduced to 2.0 equiv., the yield of product **3a** dropped dramatically (entry 16). It is worth mentioning that most of the unreacted ethylbenzene could be recovered (55%) after the reaction.

Scheme 2. Alkylarene Substrate Scope in the Benzylic C(sp^3)–H Amination[a,b]





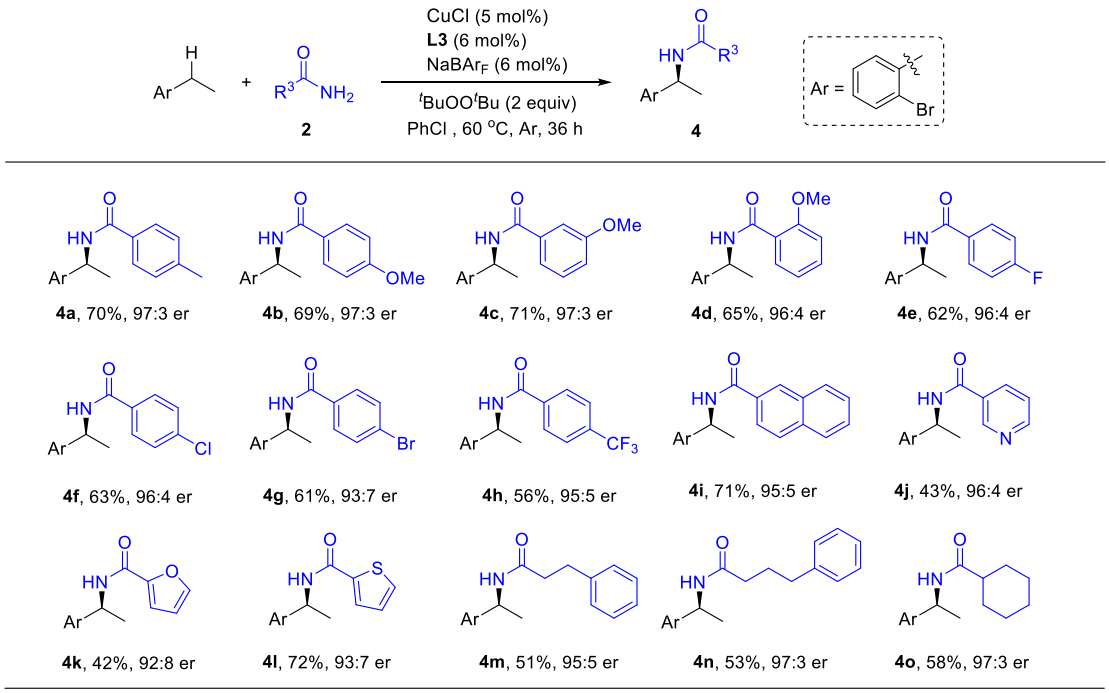
[a]Reaction conditions: CuCl (5 mol %), $NaBAr_F$ (6 mol %), **L3** (6 mol %), **2a** (0.2 mmol), DTBP (2 equiv.), **1** (4 equiv.), in PhCl (0.5 mL) under Ar at 60 °C for 36 h. [b]Isolated yield. Er values were determined by HPLC on a chiral stationary phase. [c]PhEt (8 equiv.). [d]16 h.

With the optimized reaction conditions in hand, we investigate the alkylarene substrate scope of the asymmetric amination of benzylic C(sp^3)–H bonds. As shown in

the Scheme 2, the electron-withdrawing substituents (Cl, Br, I) in alkylarene substrates were well-tolerated, giving the desired products (**3a-3i**) in good yields with high enantioselectivities (up to 97:3 er). The halide substituents in the products allowed an additional opportunity for further synthetic manipulations/transformations. The alkyl group on the benzene ring of alkylarenes **1** has a little effect on the yield and enantioselectivity of the reaction, and the substrate **1m** having a long alkyl group afforded the highest enantioselectivity (99:1 er). For isobutylbenzene **1n**, which contains both benzylic and tertiary aliphatic C−H bonds, the reaction occurred majorly at the benzylic position (**3n**, 56% yield, 94:6 er), but was also accompanied by a reaction at tertiary aliphatic C−H bond (18% yield). Notably, the reaction exhibited good compatibility with the functional groups on the alkyl chain of the substrates. The alkylarenes having esters (**3p**, **3q**, **3u**, **3v**), ether (**3r**), olefin (**3s**), amine (**3t**) and halide (**3w**) on the alkyl chains all gave the corresponding amination products with high enantioselectivities. Cyclic alkylarenes containing six-membered rings, including the tetralin and the common pharmacophore chroman, were also compatible in the reaction and produced related products (**3z**, **3aa**).

We then examined the amide substrate scope. As shown in the Scheme 3, a wide range of aromatic amides with electron-donating group (Me, OMe) and electron-withdrawing group (F, Cl, Br, and CF_3) can react with alkylarene to yield benzylic C(sp^3)−H amination products (**4a**–**4h**) in moderate to good yields (56–71%) with excellent enantioselectivities (95:5–97:3 er). Furthermore, the heteroaromatic amides (bearing a pyridine, or furan, or thiophene) could also undergo the reaction to afford the amination products (**4j**–**4l**) in moderate yields with good to excellent enantioselectivities (up to 96:4 er). The reaction of 3-pyridylamide is noteworthy because the coordination of pyridinyl group to copper is strong ad usually prevent catalysis. Moreover, aliphatic amides can also be applied to the reaction, affording the corresponding amination products (**4m**–**4o**) with high enantioselectivities (95:5–97:3 er).

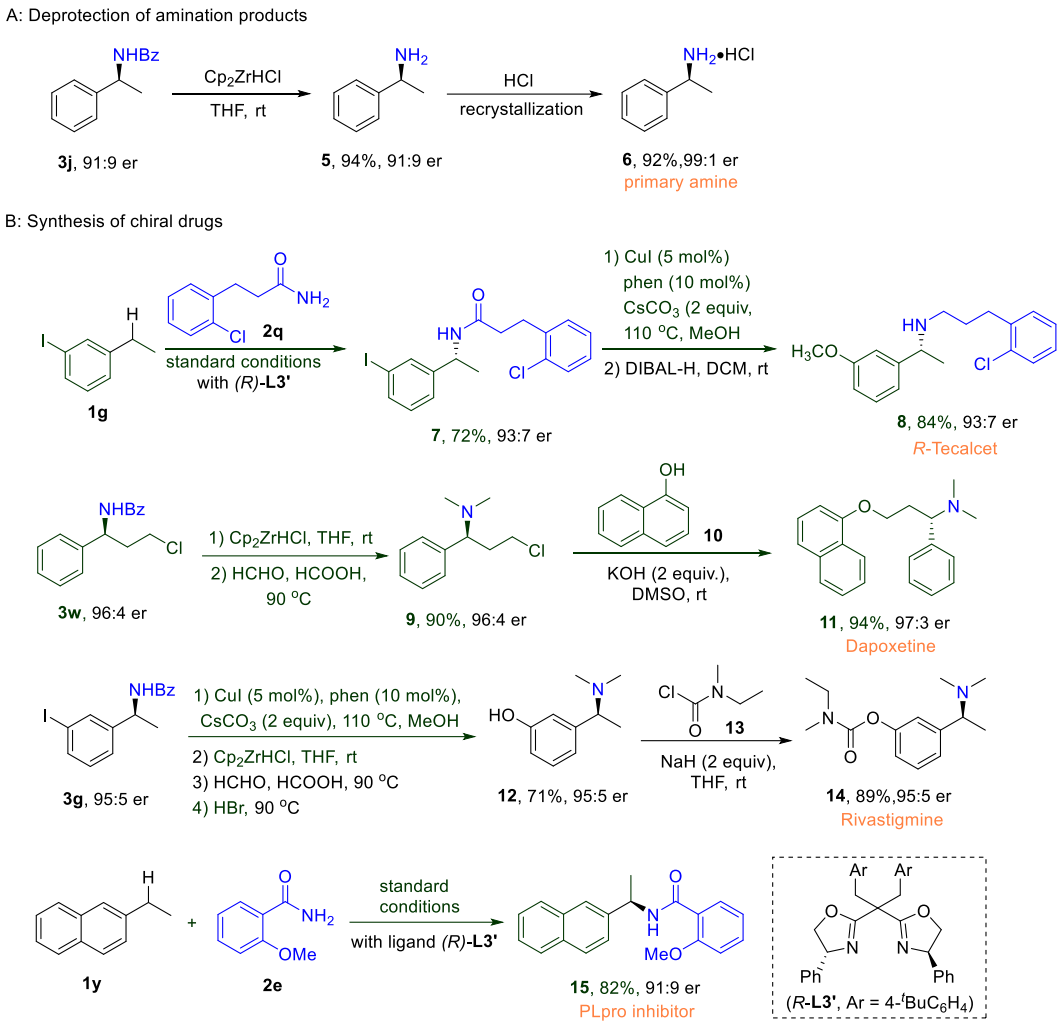
Scheme 3. Amide Substrate Scope in the Benzylic C(sp^3)−H Amination[a,b]



[a]Reaction conditions: CuCl (5 mol %), NaBAr$_F$ (6 mol %), **L3** (6 mol %), **2** (0.2 mmol), DTBP (2 equiv.), 1-bromo-ethylbenzne (4 equiv.), in PhCl (0.5 mL) under Ar at 60 °C for 36 h. [b]Isolated yield. Er values were determined by HPLC on a chiral stationary phase.

To illustrate the synthetic utility of the reaction, we carried out the transformations of the amination products and synthesis of chiral drugs (Scheme 4). The amide **3j** was deprotected to chiral primary amine by using Schwartz reagent at mild conditions without losses of enantiomeric purity (Scheme 4A).[13] The clinically used chiral drugs tecalcet (**8**), a calcimimetic compound for the treatment of hyperparathyroidism,[14] dapoxetine (**11**) for the treatment of premature ejaculation,[15] and rivastigmine (**14**) for the treatment of Alzheimer's disease [16] were readily prepared by using the enantioselective amination as the key steps (Scheme 4B). Also, the SARS-CoV PLpro inhibitor[17] (**15**) was synthesized in one step. The syntheses of these chiral drugs and biologically active molecules further demonstrated that this amination reaction is a powerful method for the synthesis of chiral compounds containing a benzylic amine moiety.

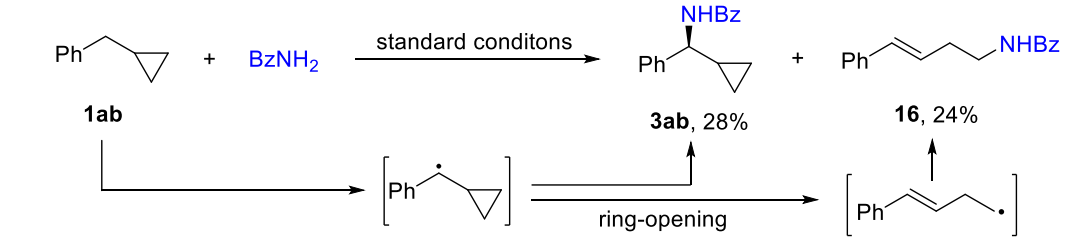
Scheme 4. Synthetic Applications of Amination Products



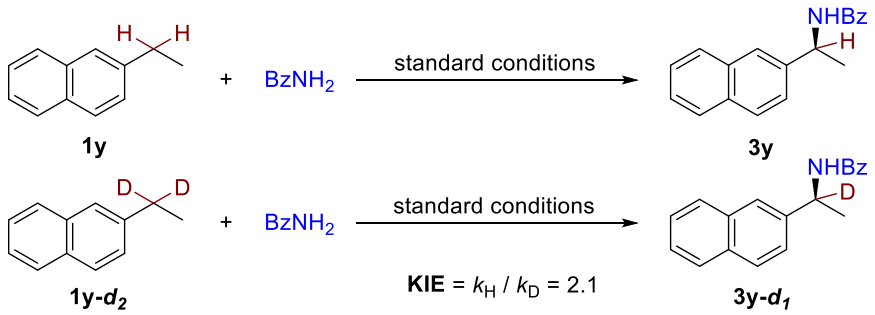
To understand the mechanism of the Cu-catalyzed benzylic C(sp^3)–H amination reaction, a radical clock experiment was conducted (Scheme 5A, also see Supporting Information for details). The amination reaction of cyclopropylmethylbenzene (**1ab**) at standard conditions furnished a mixture of amination product **3ab** and an ring-opening compound **16**, thus supporting the presence of alkyl radical intermediate.[18] A parallel kinetic isotope effect (KIE) study revealed a KIE of 2.1, indicating that the hydrogen atom abstraction of C–H by *tert*-butoxy radicals might be the rate limiting step for the reaction (Scheme 5B).[19] Plotting log(er) against Hammett σ_p of benzamides showed a linear correlation between the enantioselectivity of the reaction and the electronic effect of the benzamide *para*-substituents (Scheme 5C).[20] The negative slope of the plot indicated that the electron-rich amide is favorable for bonding with electron-deficient copper catalyst to form transient Cu(III) intermediates ligated by a benzyl and amide.

Scheme 5. Mechanistic Investigation on the Cu-Catalyzed Benzylic C(sp^3)−H Amination Reaction

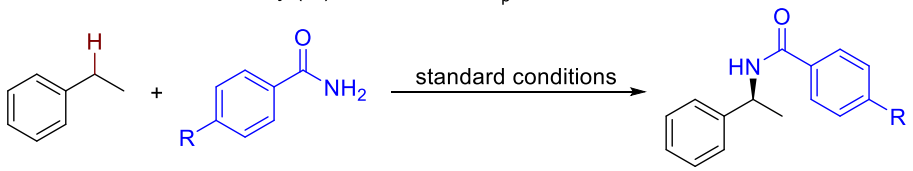
A) Radical clock experiment

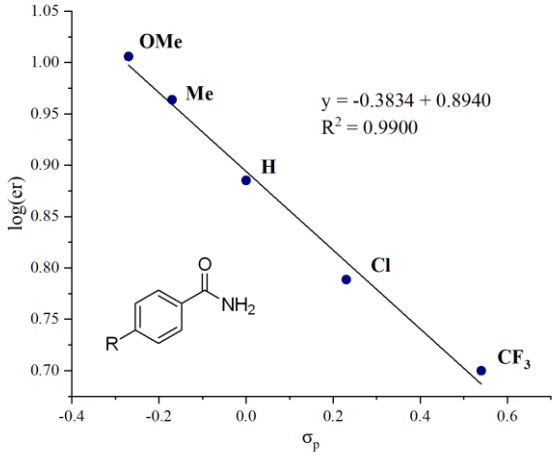


B) Parallel KIE experients



C) Corellation of enantioselectivity (er) with Hammett σ_p of benzamides

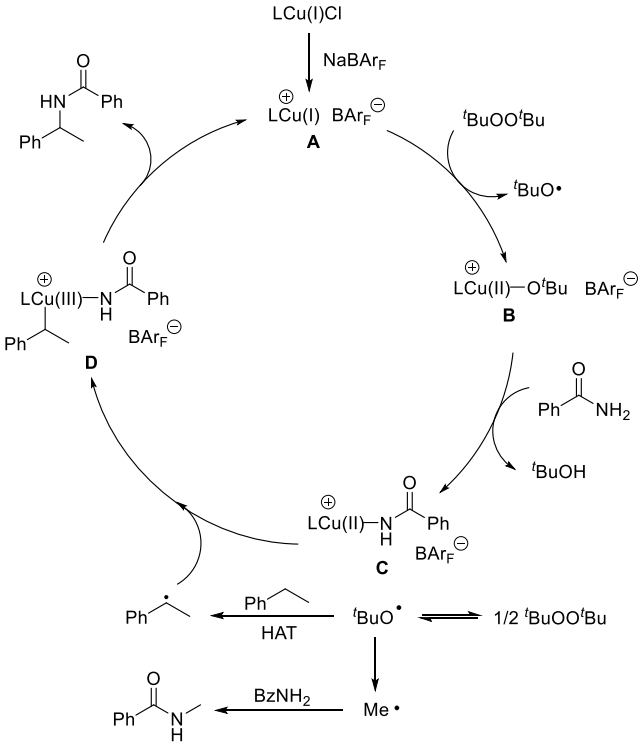




Based on the experimental observation and previous reports,[12] we proposed a mechanism for the asymmetric benzylic C(sp^3)−H amination, as shown in Scheme 6. Initially, CuCl complexed with a BOX-type ligand and exchanged anion with $NaBAr_F$ to generate copper (I) complex **A**, which is active catalyst for the amination reaction.[13]

The complex **A** promote the homolytic cleavage of DTBP to form the key alkoxy copper(II) intermediate **B** along with *tert*-butoxy radical. Then, substitution of the *tert*-butoxy group on the copper of intermediate **B** with benzamide generates copper(II) intermediate **C**. Subsequently, *tert*-butoxy radical abstracts a benzylic hydrogen atom to produce the corresponding benzylic radical, which is trapped by **C** to form a copper(III) intermediate **D** containing a benzyl and an amido groups. The intermediate **C** undergoes reductive elimination to furnish amination product and liberate the copper(I) complex **A**. Since the trapping of alkyl radical by the copper(II) intermediate **C** is a probably reversible process,[10a] the enantioselectivity may be determined by the subsequent reductive elimination step. We observed *N*-Methyl benzamide (~10%) in the reaction, which might be formed by the reaction of benzamide with methyl radical from the decomposition of *tert*-butoxy.

Scheme 6. Proposed Catalytic Cycle for the Benzylic C(sp^3)−H Amination Reaction



In conclusion, we have established a cationic copper-catalyzed intermolecular asymmetric radical oxidative coupling of benzylic C(sp^3)−H bonds with amides,

providing an efficient and straightforward approach to chiral benzylic amine with good to excellent enantioselectivities. The protocol has high potential for applications in the synthesis of bioactive compounds containing chiral benzylic amine moiety. Mechanistic studies suggested that the amination likely undergoes via a radical mechanism, in which C−H bond cleavage is the rate-limiting step. Future efforts will focus on applying this strategy to the enantioselective functionalization of benzylic C(sp^3)–H bonds with other nucleophiles.

ACKNOWLEDGMENT

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