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Angewandte
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International Edition
www.angewandte.org

Enantioselective Intermolecular Radical Amidation and Amination of Benzylic C–H Bonds via Dual Copper and Photocatalysis

Xuemeng Chen, Zhong Lian,* and Søren Kramer*

Abstract: A method for direct access to enantioenriched benzylic amides and carbamate-protected primary benzylamines by C–H functionalization is reported. The C–H substrate is used as limiting reagent with only a small excess of the unactivated amide or carbamate nucleophile. The enantioselective intermolecular dehydrogenative C–N bond formation is enabled by a combination of a chiral copper catalyst, a photocatalyst, and an oxidant, and it takes place under mild conditions, which allow for a broad substrate scope. The method is compatible with late-stage C–H functionalization, and it provides easy access to ^{15}N-labeled amides and amines starting from cheap $^{15}NH_4Cl$.

Benzylamines are common motifs in natural products, agrochemicals, and pharmaceuticals.[1] In particular, enantioenriched chiral benzylamides and benzylamines are frequent substructures in pharmaceuticals (Scheme 1A).[2] Rapid access to a diverse range of related target structures with single-point variations is essential for medicinal chemistry. To this end, C–H amination offers the most direct strategy for late-stage diversification and installation of amines and amides.[3]

Since C–H substrates in medicinal chemistry are typically precious, the use of C–H substrate as the limiting reagent is desirable. Recently, several novel intermolecular benzylic C–H amination methods have been developed that utilize the C–H substrate as limiting reagent and lead to α-substituted primary benzylamines with easily-removed protecting groups. These methods include nitrene insertions using a manganese or a copper catalyst,[4] electrochemistry with a manganese catalyst,[5] electrophotochemistry with a
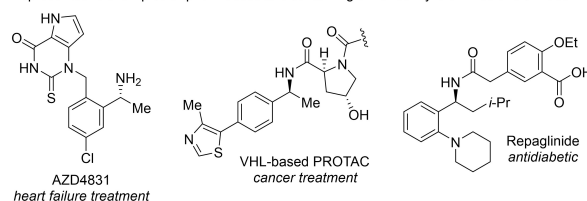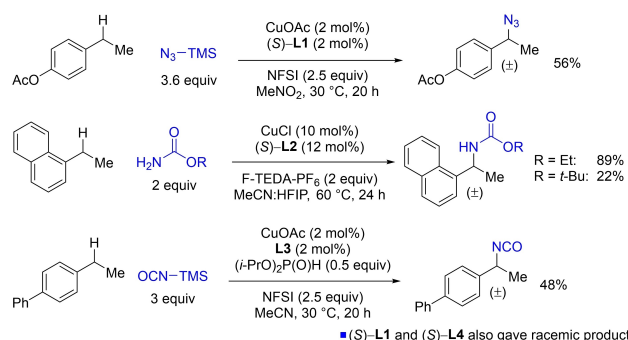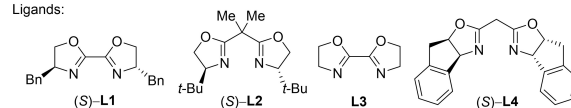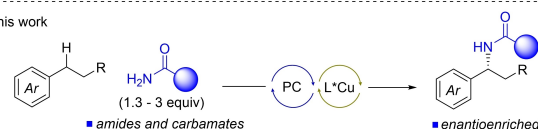
Scheme 1. Context for developing enantioselective intermolecular radical amidation and amination by benzylic C–H functionalization with copper catalysis. F-TEDA-PF$_6$ = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane bis(hexafluorophosphate), HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol.

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manganese or a trisaminocyclopropenium ion catalyst,[6] and photo-induced iodine(III) catalysis.[7] Nonetheless, these methods only provide access to the racemic benzylamines; in many cases due to a reaction mechanism involving radical-polar crossover.[4–8]

Enantioselective benzylic C–H functionalization by a combination of a copper catalyst and *N*-fluorobenzenesulfonimide (NFSI) was pioneered by Stahl and Liu.[9] The exploitation of this reaction type, which proceeds through a radical relay pathway initiated by hydrogen atom transfer (HAT), has led to enantioselective benzylic C–H radical cyanation, arylation, and alkynylation.[9–11] When nitrogen-nucleophiles are used with the copper/NFSI systems, a
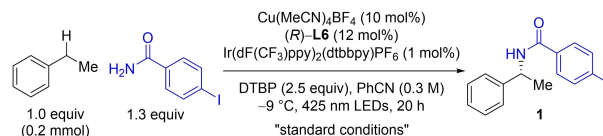
radical-polar crossover reaction mechanism is often invoked.[12] The key implication of the radical-polar crossover pathway is the difficulty of developing enantioselective variants. This is supported by the frequent observation that even the use of enantiopure chiral ligands on copper affords racemic products (Scheme 1B). Stahl and co-workers developed a racemic benzylic C–H azidation using a chiral BiOX-ligand.[12a] Landais and co-workers demonstrated the use of carbamate nucleophiles with a chiral BOX-ligand which also led to racemic C–N bond formation.[12b] Although Stahl and co-workers utilized an achiral ligand for benzylic C–H isocyanation, the use of chiral BOX-ligands also led to racemic products.[12d] Enantioselective C–N bond formation using the copper/NFSI chemistry has not been achieved.[11,13]

Despite these advances, enantioselective catalysis for the intermolecular installation of primary amines and amides by benzylic C–H functionalization remains a challenge. Particularly, since many of the existing protocols for benzylic C–H amination proceed via a radical-polar crossover mechanism.[4–7,12] Here, we describe the first intermolecular enantioselective copper-catalyzed radical C–H amidation and amination (Scheme 1C).[11,14–16] The dehydrogenative C–N bond formation is enabled by combining a chiral copper catalyst with photocatalysis—a combination which can avoid radical-polar crossover. Unlike previous HAT-initiated copper-catalyzed benzylic C–H amination reactions, the use of chiral ligands leads to enantioenriched products.
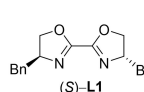
We initiated the study as part of our interest in C–H functionalization, photocatalysis, and enantioselective catalysis.[17] After substantial optimization, we identified reaction conditions that provide good yield and enantioselectivity with the C–H substrate as limiting reagent, near-equimolar amount of amide nucleophile, and a catalytic system consisting of Cu(MeCN)$_4$(BF$_4$), (R)-L6, Ir(dF-(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$, and di-*tert*-butylperoxide (DTBP) under irradiation with 425 nm light at an internal reaction temperature of −9 °C (Table 1, entry 1). Control experiments without copper, photocatalyst, light, or (R)-L6 did not lead to any significant product formation (entries 2–3). Setting up the reaction completely in air only afforded trace amounts of product; however, rigorous exclusion of air is not required as the injection of 0.1 mL air into the 4 mL reaction vial, at the outset of the reaction, did not affect the reaction outcome (entry 4). The use of a copper catalyst with a strongly coordinating counter ion or benzoyl peroxide instead of DTBP were detrimental for the amidation (entries 5 and 6). Adding more or less than 2.5 equiv. of DTBP decreased the yield but did not affect enantioselectivity (entries 7 and 8). The enantioselectivity is only slightly influenced by the reaction temperature (entry 9). Examination of a wide concentration range only showed a minor effect on the yield and no effect on the enantioselectivity (entries 10 and 11). The use of a BiOX ligand or other BOX-ligands than (R)-L6 led to lower yields and enantioselectivities (entry 12).

The use of a broad range of arylamides as nucleophiles provided almost constant yields and enantioselectivities compared to 1 (Scheme 2). Aryl halides are well-tolerated,
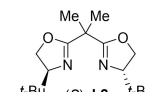
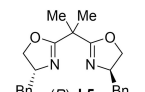**Table 1:** Optimized reaction conditions and deviation from standard conditions.

| Entry	Deviation from standard conditions	Yield [%][a]	er[b]
1	none	74 (74)	92:8
2	no Cu, or no Ir, or no light	0	-
3	no (R)-L6	3	-
4	0.1 mL air added	73 (73)	92:8
5	CuCl instead of Cu(MeCN)$_4$BF$_4$	8	58:42
6	benzoyl peroxide instead of DTBP	0	-
7	1.5 equiv DTBP	54	92:8
8	3.0 equiv DTBP	63	92:8
9	7 °C instead of −9 °C[c]	71	90:10
10	0.2 M instead of 0.3 M	66	92:8
11	0.6 M instead of 0.3 M	68	92:8
12	L1, L2, L5, L7, or L8	as shown below	
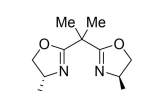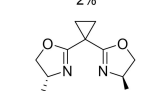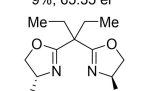
[a] Yields were determined by GC analysis using an internal standard. Isolated yields in parenthesis. [b] Enantiomeric ratios were determined by chiral HPLC. [c] Temperature of reaction mixture. For −9 °C, the chiller was set to −20 °C, and for 7 °C, the chiller was set to 0 °C.

thus providing handles for easy diversification (1–4). The inclusion of substituents in the *ortho*, *meta*, and *para*-positions (3–6) as well as both electron-withdrawing and electron-donating groups (5, 7) did not significantly change the reaction outcome. Bulky groups in the *para*-position provided slightly higher enantioselectivity (8, 9) Heterocycles, thiophene and furan, on the amide also led the desired product in good enantioselectivity (10, 11). In addition to aromatic amides, aliphatic amides, such as acetamide and butyramide, can also successfully be utilized as nucleophiles (12, 13). A primary alkyl bromide is tolerated, thus highlighting the mildness of the reaction conditions (14). An amide containing potentially competing benzylic C–H bonds also afforded the desired amide product, 15, likely due to the short linker between amide and benzylic hydrogens (see below). Notably, for an amide containing a defined α-stereocenter, the stereochemistry of the ligand overrules any potential substrate control (16, 17). The amidation reaction can be scaled as demonstrated by 65% yield, 91:9 er, obtained for 2 on a 1.0 mmol scale. Furthermore, the enantiopurity of 2 was increased to >99:1 er by a single recrystallization. The absolute stereochemistry was determined to be (R)-2 by X-ray crystallography.[18]

A broad scope for the C–H substrates was also observed (Scheme 3). For ethylarenes, tolerated functional groups include ester, ether, aryl iodide and bromide, and tosylate (Scheme 3A; 18–23). Ethylbenzenes bearing *meta*-substituents led to good yields and enantioselectivities (19, 20).
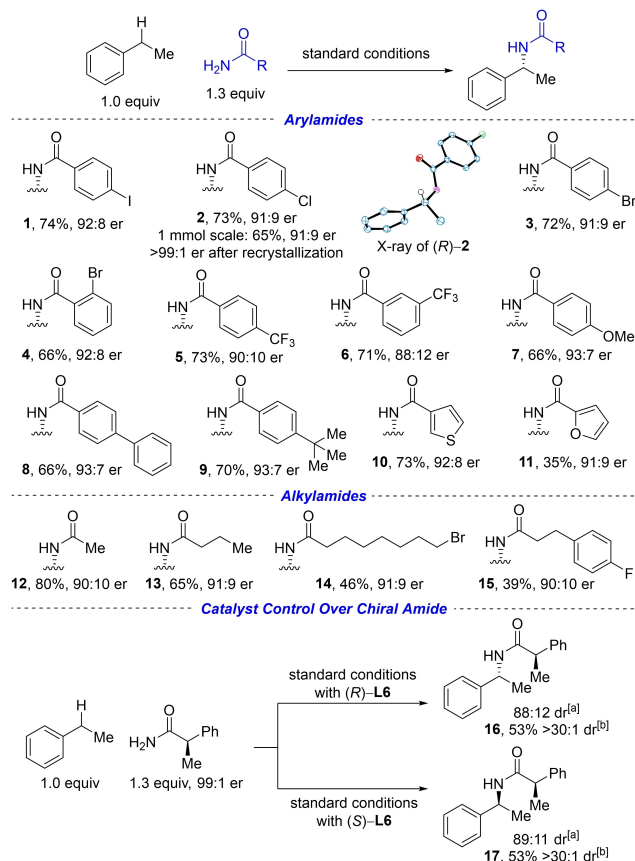
Scheme 2. Substrate scope with respect to the amide nucleophile. Isolated yields; er determined by chiral HPLC; dr determined by GC. [a] Determined in crude reaction mixture. [b] After column chromatography.

Ortho-substituents are not tolerated. C–H substrates containing a pyrazole or pyridine moiety were also successfully amidated (**26**, **27**). In addition, a robustness screen with other heterocycles (Figure S-2) showed compatibility with a pyrimidine, quinoline, benzothiophene, and Boc-protected indole as well as some limitations, such as an unprotected indole. Overall, the developed method is compatible with several heterocycles frequently encountered in medicinal chemistry. In cases with potential for site-selectivity issues, the reaction displays good site-selectivity (**28**, **29**). Although many electronically different substituents are tolerated, the use of either strongly electron-withdrawing or -donating groups in the *para*-position diminishes both the yield and enantioselectivity (**30**, **31**). A series of longer-chain alkylbenzenes successfully underwent the enantioselective C–H amidation (Scheme 3B). In general, these substrates provided slightly higher enantioselectivities than ethylarenes. Propylbenzene led to the desired product in 59% yield, 93:7 er (**32**). The yield of the reaction is sensitive to sterical hindrance as a lower yield was obtained for isobutyl-substituted **33**. Functional groups such as esters, ketone, silyl ether, sulfonate, primary alkylbromide, and pyridine were all tolerated (**34–40**). The linker length between the functional group and the benzylic C–H bonds is important for

the yield, not enantioselectivity, as demonstrated by the ester series, **41–43**. In general, entries with <50% yield are accompanied by incomplete conversions (Figure S-3). Finally, we investigated the potential for application to late-stage C–H amidation of drug-like molecules (Scheme 3C). For all four substrates, the desired amidation product was obtained in good enantioselectivity and synthetically useful yield (**44–47**). Enantioselective *N*-alkylation of a drug-like amide is also feasible (**48**).

Next, carbamate-protected primary amines were examined as nucleophiles (Scheme 4). Notably, the use of $BocNH_2$ under the standard reaction conditions led to the desired product in 59% yield and 89:11 er (**49**). As diverse deprotection methods is desirable for medicinal chemistry, we also investigated the use of $TeocNH_2$ and $TrocNH_2$ as nucleophiles (**50**, **51**). Both provided the desired amination product in comparable yield to $BocNH_2$. While the enantioselectivity for $TeocNH_2$ is close to $BocNH_2$, the enantioselectivity for $TrocNH_2$ is more moderate; nonetheless, access to diverse deprotection conditions, even for racemic methodologies, is still highly valuable for applications in medicinal chemistry and late-stage functionalization. Examination of representative C–H substrates with $BocNH_2$ as nucleophile showed similar trends as the amidation (**52–57**).

^{15}N-labeled NH_4Cl is a very cheap source of ^{15}N, even more so when compared to the ^{15}N-labeled nucleophiles needed for most previous benzylic C–H amidation/amination reactions (Scheme 5). Acylation or Boc-protection of $[^{15}N]$-NH_4Cl directly provide access to the labeled nitrogen-nucleophiles. Subsequent amidation afforded the ^{15}N-labeled amide **9** in 71%, 93:7 er. Deprotection by Schwartz's reagent gave the ^{15}N-labeled free primary amine **58** in 72% yield, 93:7 er. Alternatively, the ^{15}N-labeled free primary amine **58** can be obtained from $[^{15}N]$-$BocNH_2$ and deprotection by dilute acid. Finally, access to enantioenriched ^{15}N-labeled secondary amine **59** is also straightforward by reduction of the amide with BH_3.

The dual catalytic system used in this enantioselective intermolecular benzylic C–H amidation combines the ability of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$/DTBP to generate *tert*-butoxy radicals for HAT under mild conditions[19] with the ability of chiral copper complexes to perform enantioselective amidation of carbon-centered radical intermediates.[15] Under the standard reaction conditions with 4-chlorobenzamide as nucleophile, we only observe trace amounts (<3%) of chloride-free benzamide product **60** (Scheme 6A). This minor product likely stems from a Ritter-type pathway involving radical-polar crossover and trapping by the solvent, benzonitrile. The low yield for the Ritter-type pathway suggests that radical-polar crossover is only occurring to a very limited extent. The addition of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl; 20 mol%) to the standard reaction conditions completely inhibited the reaction (Scheme 6B). In contrast, the addition of $CBrCl_3$ (1.5 equiv) did not prevent product formation; however, 29% of brominated ethyl benzene (**61**) was detected, which is consistent with a free radical intermediate (Scheme 6B).[9] Finally, a small primary kinetic isotope effect was observed, thus indicating that the C–H bond cleavage is at least partly
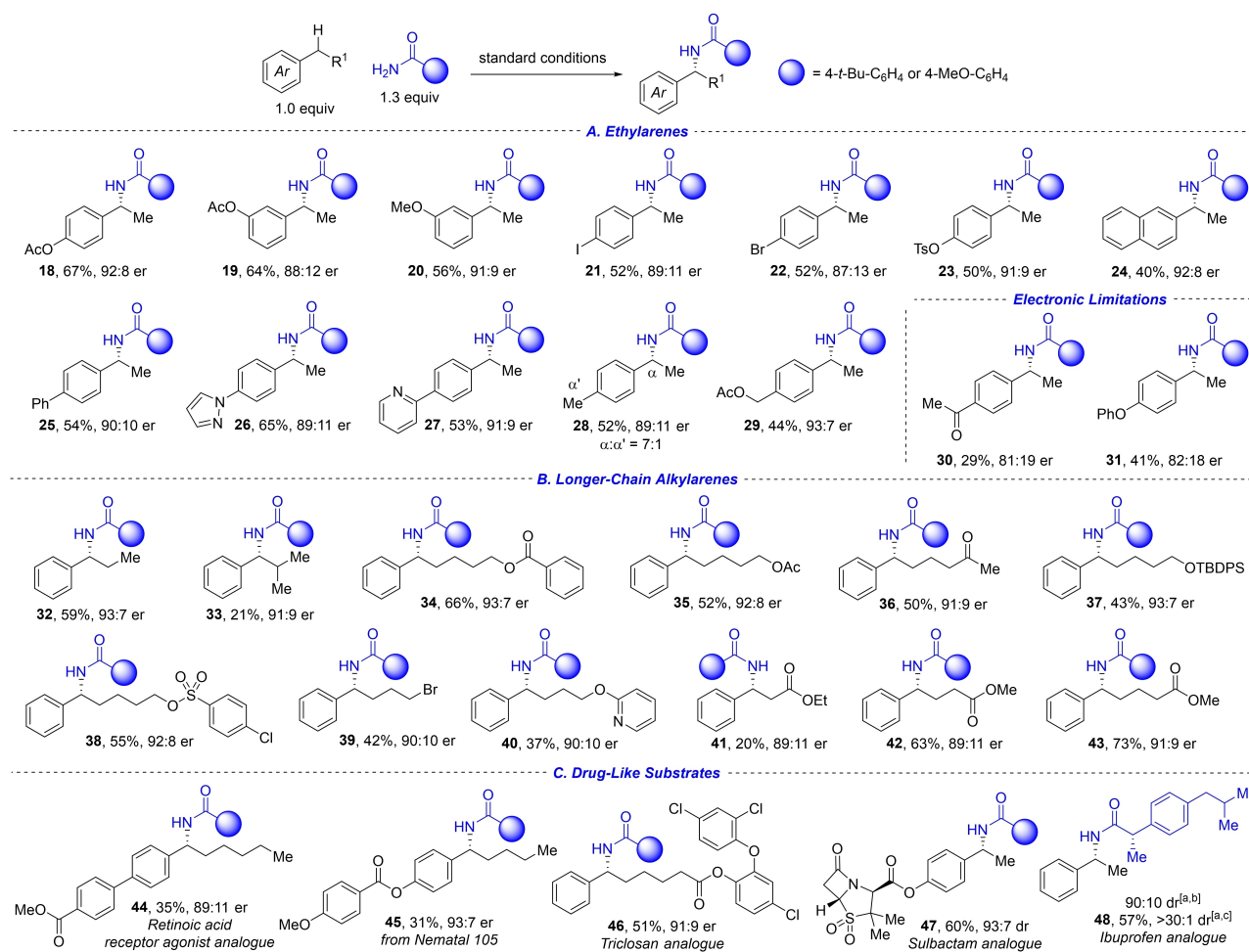
Scheme 3. Substrate scope with respect to the C–H substrate. Isolated yields; er determined by chiral HPLC; dr determined by GC or chiral HPLC. [a] Amide (1.0 equiv), ethylbenzene (2.0 equiv). [b] Determined in crude reaction mixture. [c] After column chromatography.

rate-determining (Scheme 6C). In combination with the observed enantioselectivity, these experiments support the hypothesis that the reaction proceeds through a radical pathway initiated by a HAT event. Whether the C–N bond formation takes place via Cu^{III} reductive elimination, outer-sphere attack on Cu^{II}-amide, or Cu^{I}-bound radical-radical coupling is unclear at this point and such elucidation would require a separate study.[20] It is noteworthy that the major pathway in our system stays within the radical regime, rather than the radical-polar crossover pathway that is inferred for many related benzylic C–N bond formation reactions which are initiated by a benzylic HAT.[6b,7,12,21] Importantly, this mechanistic difference—enabled by the combination of copper catalysis and photocatalysis—offers a solution to the limitations of radical-polar crossover pathways in terms of enantioselectivity.

In summary, we report a method for enantioselective intermolecular installation of amides and primary amines by benzylic C–H functionalization using dual copper and photocatalysis. Key features include the use of C–H substrate as limiting reagent, the direct use of unactivated amides and carbamates as nucleophiles, easy and cheap ^{15}N-labeling, good atom economy, and the use of a simple and cheap chiral ligand and oxidant. The nucleophile is used in only a slight excess, thus allowing the use of diverse and precious nucleophiles. Furthermore, our method involves a conceptually distinct mode of operation which, for the first time, enables enantioselective catalysis for HAT-initiated intermolecular benzylic C–N bond formation using copper catalysis.

Acknowledgements
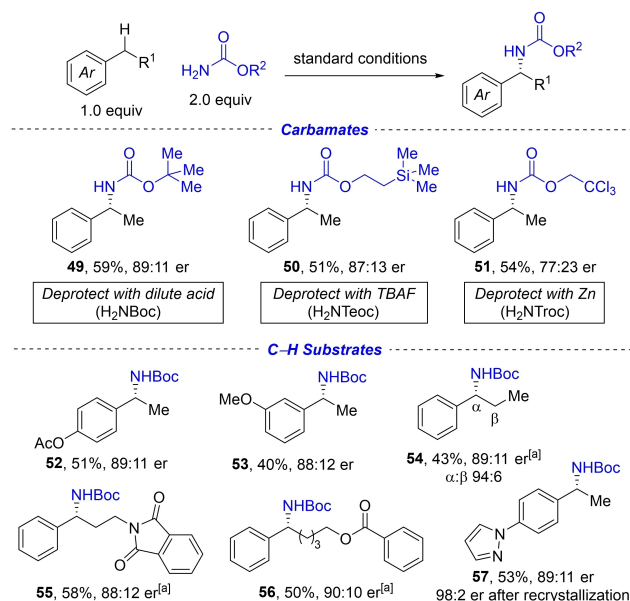
Scheme 4. Substrate scope with respect to carbamate nucleophiles. Isolated yields; er determined by chiral HPLC. [a] 3.0 equiv. BocNH₂ used.
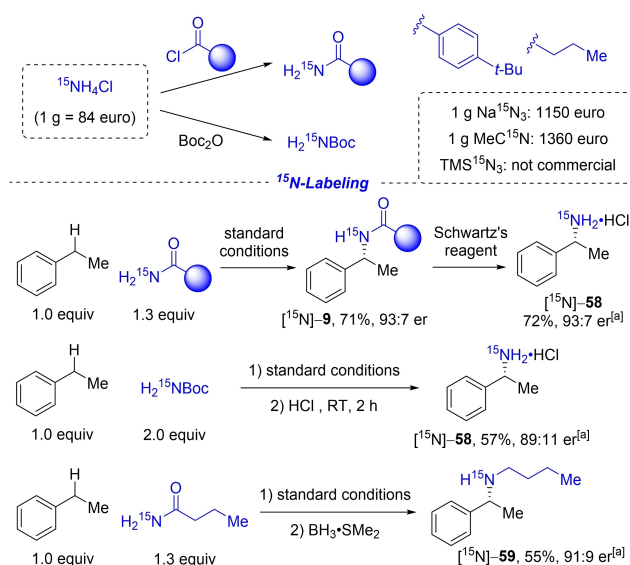

Scheme 5. ¹⁵N-Labeling and conversion to primary and secondary amines. Prices from sigmaaldrich.com. Isolated yields; er determined by chiral HPLC. [a] Er determined after acylation.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.
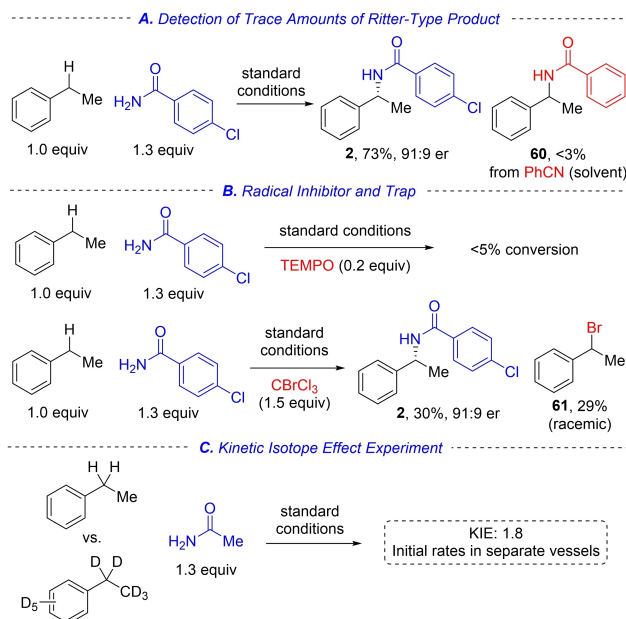
Scheme 6. Mechanistic experiments. Yields were determined by GC using an internal standard. er determined by chiral HPLC.

Keywords: Benzylamides · Benzylamines · Copper · Enantioselectivity · Photocatalysis

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