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Synthesis of α-Substituted Primary Benzylamines through Copper-Catalyzed Cross-Dehydrogenative Coupling

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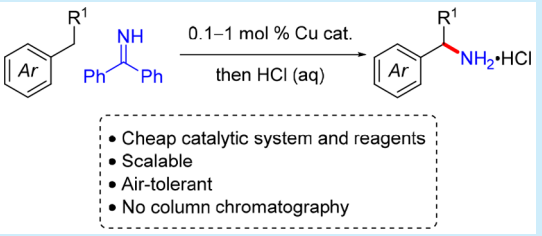
Supporting Information

ABSTRACT: A copper-catalyzed route to α-substituted, primary benzylamines by C−H functionalization of alkylarenes is described. The method directly affords the amine hydrochloride salt. Catalyst loadings down to 0.1 mol % in combination with scalability, insensitivity to air and moisture, and no need for column chromatography makes the procedure highly practical. The facile synthesis of the racemate of a blockbuster drug highlights the relevance for the development of pharmaceuticals. Preliminary mechanistic data are also included.



The incorporation of nitrogen into organic molecules is crucial for the development of pharmaceutical candidates and production of medicinally important compounds. Highlighting the pivotal role of C−N bonds in medicines, approximately 85% of the top 200 best-selling drugs in 2016 contained C−N bonds.[1] Benzylamines with α-substituents are privileged motifs within C−N containing compounds and can be found in numerous drugs for treatment of a diverse range of diseases such as bacterial infections, cardiovascular disease, and depression (Figure 1).

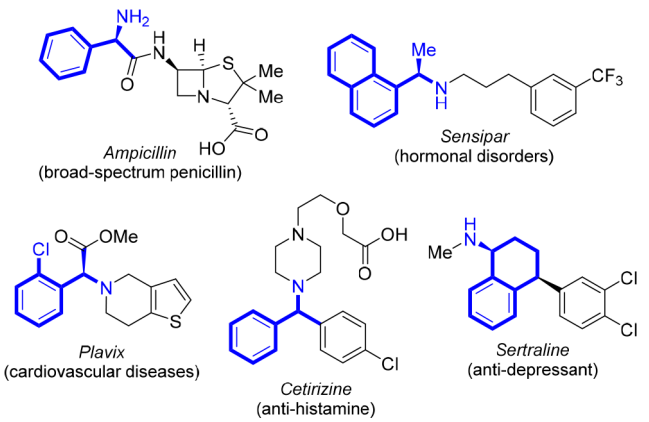


Figure 1. Examples of pharmaceuticals containing α-substituted benzylamines.

The catalytic formation of C(sp^3)−N bonds typically relies on the availability of prefunctionalized starting materials such as alkyl halides or ketones.[2] Albeit this approach generally provides excellent chemoselectivity and accordingly high yields, it is limited by the availability of starting materials bearing the required functional groups, or, alternatively, adds additional steps to a synthesis route for installation of the necessary functional group. As an alternative strategy, site-selective C−H functionalization can circumvent the need for prefunctionalization.[3] Indeed, the use of C−H functionalization for benzylic C−N bond formation has received considerable attention recently.[4,5] However, while direct routes to primary amines are highly warranted,[6] most of the benzylic C−H functionalization methods afford only protected amines and do not either address amine deprotection or require purification-separated deprotection, which can be elaborate and time-consuming.

Cross-dehydrogenative coupling reactions (CDC) are emerging as a subclass of C−H functionalizations where the use of an oxidant allows two coupling partners to be connected directly by X−H functionalization of both partners (X = C, N, O, S, etc.).[7] While many different metals can be utilized as catalysts for CDC reactions, copper is often preferred due to its availability, low cost, and catalytic efficiency. Interestingly, the CDC strategy has never been used for the direct synthesis of primary benzylamines.[8−10]

Recently, Hartwig and Hu have reported cross-coupling reactions with diarylimines as coupling partners (Scheme 1).[2d,i] After the cross-coupling reaction, facile deprotection liberates the corresponding primary amines. Interestingly, in spite of the importance of primary benzylamines, diarylimines have not been used for C−N bond formation toward this compound class. Furthermore, diarylimines have not yet been used in combination with CDC.

Herein, a straightforward route to α-substituted, primary benzylamines by C−H functionalization is reported. The reaction represents the first combination of CDC and diarylimine coupling partners. The catalyst system is simple and low catalyst loadings can be used—even on a 5 mmol scale. The substrate scope mainly focuses on cheap, bulk alkylarenes thus potentially providing abundant access to pharmaceutically important building blocks.

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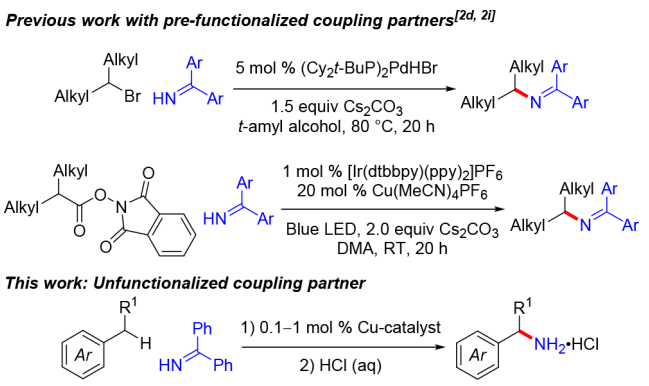
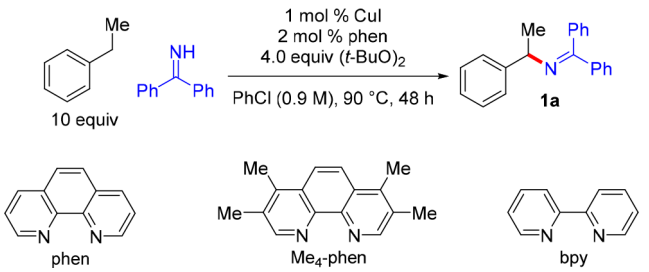
Scheme 1. Coupling Reactions with Diarylimines as Protected Amine Coupling Partners



The reaction between two cheap and commercially available starting materials, ethylbenzene and benzophenone imine, was chosen for the reaction optimization. After thorough investigation of the reaction parameters, the desired *N*-alkyl imine, **1a**, was obtained in 71% yield (Table 1, entry 1). The optimized reaction conditions consist of 1 mol % CuI,[11] 2 mol % 1,10-phenanthroline (phen), 4.0 equiv of $(t\text{-BuO})_2$, and 10 equiv of ethylbenzene in concentrated chlorobenzene at 90 °C for 48 h (Table 1, entry 1). The catalytic system, oxidant, and solvent are all cheap.[12] The presence of both CuI and phen is necessary for maintaining the high yield albeit a small background reaction is also observed (entries 2–4). As expected the oxidant is crucial to the reaction, but the addition of more than 4.0 equiv does not increase the product yield (entries 5–6). The addition of only 1 mol % phen decreases the yield; however, addition of 3 mol % is not better than 2 mol % (entries 7–8). Different copper sources and ligands were also examined. Copper(I) halide salts in general provide good yields (entries 9–10), but copper(II) salts, such as $Cu(OAc)_2$ and $Cu(OTf)_2$, gave much inferior yields (not shown).[13] In terms of ligands, the tetramethyl phenanthroline (Me_4-phen) provided almost comparable yield to phen while the yield with bipyridine (bpy) was comparable to the ligand-free reaction (entries 11–12). The neat reaction without chlorobenzene gave a comparable yield to that using the standard conditions indicating the potential for solvent-free reactions. Addition of chlorobenzene does nonetheless ensure the homogeneity of the reaction mixture, and with the aim of developing a general method, also for substrates with markedly different chemical and physical features, chlorobenzene was kept as the reaction solvent.

Table 1. Effect of Selected Reaction Parameter on the Yield of the C(sp^3)–N Bond Formation



entry	variation from "standard conditions"	yield (%)[a]
1	none	71
2	no CuI	10
3	no phen	24
4	no CuI and phen	9
5	no $(t\text{-BuO})_2$	0
6	5 equiv of $(t\text{-BuO})_2$	71
7	1 mol % phen	63
8	3 mol % phen	70
9	CuBr instead of CuI	66
10	CuCl instead of CuI	58
11	Me_4-phen instead of phen	64
12	bpy instead of phen	23
13	no PhCl	69
14	5 equiv of PhEt	52
15	under air in closed vial	70

[a]The yield was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

The last two entries deserve special attention (Table 1, entries 14–15). Importantly, the addition of 10 equiv of the benzylic substrate is not a requirement for synthetically useful yields. The use of 5.0 equiv of ethylbenzene still produces a 52% yield, which could be practical for more expensive substrates (entry 14). Finally, a reaction was performed in air completely without the use of glovebox and Schlenk techniques (entry 15). Remarkably, no decrease in yield was observed compared to the reaction under argon demonstrating that the developed reaction conditions tolerate ambient air and moisture.

With the optimized conditions in hand, the generality with respect to alkylarenes was examined (Scheme 2). Since the real utility of the methodology is the synthesis of benzylamines, not *N*-alkyl imines, the yields of the isolated α-substituted benzylamines as the hydrochloride salts, after deprotection, are reported. The overall two-step process is effectively a one-pot procedure separated only by a concentration of the reaction medium.

Aryl chlorides, bromides, fluorides, and even iodides are well-tolerated (**2b**–**2d**, **2p**). The bulk chemical cumine provided a good yield of the benzylamine in a reaction forming a fully substituted carbon atom (**2e**). A substrate bearing a propyl group as a longer alkyl chain also produced a good yield; however, introducing a highly sterically demanding *tert*-butyl at the adjacent carbon was detrimental to product formation (**2f**, **2g**). Cyclic substrates afforded the desired amines in good yields (**2h**, **2i**). Electron-donating groups on the arene generally led to lower yields, while a strongly electron-withdrawing group increased the yield (**2j**–**2l**). Naphthyl groups are also well-tolerated, and the identical yields for **2m** and **2n** highlight the insensitivity to sterical hindrance in the *ortho*-position. Finally, two diarylmethanes afforded the benzylamines, **2o** and **2p**, which resemble substructures of cetirizine (Figure 1).

A copper catalyst loading of 1 mol % is remarkably low for CDC; nonetheless, the catalyst loading could be even further reduced as was evident when the reaction was scaled up (Scheme 3). On a 5 mmol scale, a copper loading of just 0.1 mol % provided the benzylamine hydrochloride salt in 56% isolated yield. Notably, benzophenone, the nitrogen carrier, was reisolated in 90% yield allowing for its efficient recycling.[14]

Easy access to α-substituted primary benzylamines is crucial for the synthesis of numerous pharmaceuticals. To illustrate this point, the racemate of the active pharmaceutical ingredient in the blockbuster drug Sensipar was synthesized in one step

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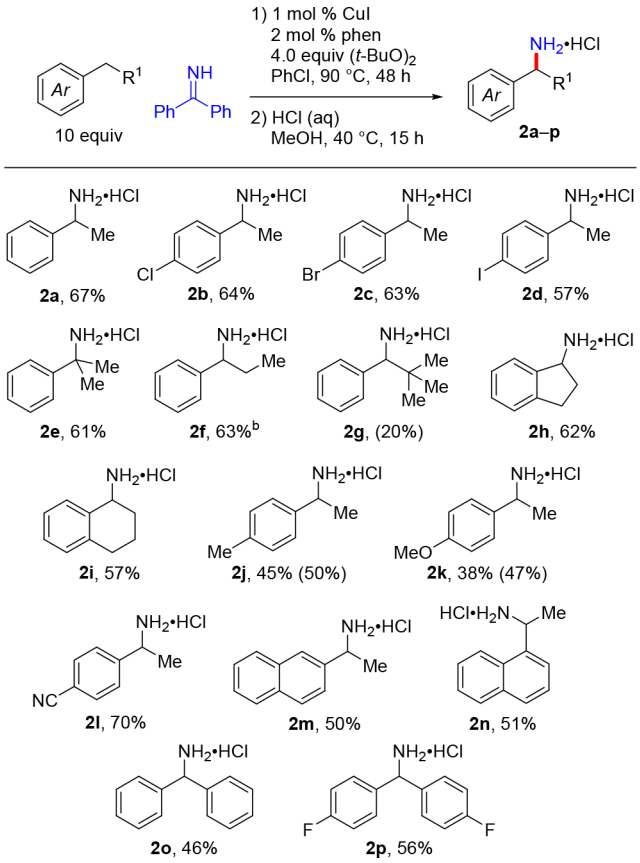
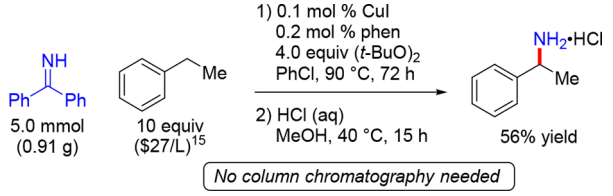
Scheme 2. Scope of Benzylic Substrates[a]



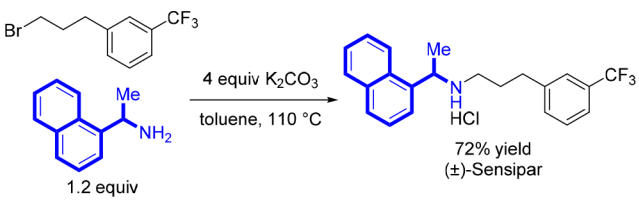
[a]The listed yields are of purified products. Yields in parentheses refer to ^{1}H NMR yield of the first step. [b]Isolated yield of 85:15 mixture of regioisomers (1-phenylpropan-1-amine and 1-phenylpropan-2-amine). For **2h–j**, regioselectivities were ≥95:5. For the rest of the substrate scope, only one regioisomer of product was detected.

Scheme 3. Scale-Up of Reaction with 0.1 mol % Copper Catalyst



from the amine **2n** (Scheme 4). Noticeably, the direct incorporation of the nitrogen atom originating from benzophenone imine demonstrates the potential for easy access to ^{15}N-labeled pharmaceuticals from ^{15}N-labeled ammonia since only one step is required for the synthesis of benzophenone imine from benzophenone and ammonia.[16]

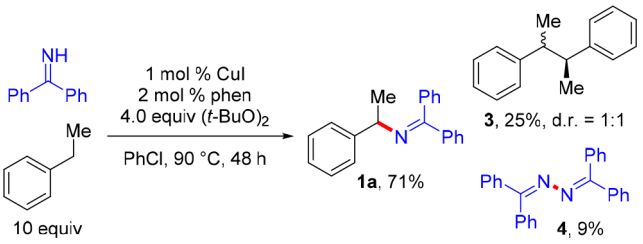
Scheme 4. Synthesis of the Hydrochloride Salt of (±)-Cinacalcet ((±)-Sensipar)



The developed method focuses on quick access to primary benzylamine building blocks as well as scalable synthesis of such compounds under simple, cheap, and practical conditions. For late-stage C−H functionalization of precious and more advanced intermediates, other methods are much more suitable such as the elegant method recently developed by White and co-workers.[4g] However, while White et al. uses a limiting amount of the substrate undergoing C−H functionalization, the preparation of the active manganese catalyst requires a separate synthesis and uses 1 equiv of $AgSbF_6$. Deprotection of the amine takes place in a separate step after purification, and 10 equiv of Cu/Zn metal are required in addition to HCl. In comparison, our method uses significant excess of one reagent; accordingly, appropriate substrates should be abundant and cheap, preferably bulk chemicals. Importantly, we can use down to 100-fold less catalyst loading (copper vs silver/manganese), the nitrogen protecting group can potentially be recycled, and deprotection takes place in a one-pot procedure needing only HCl instead of 10 equiv of metals.[17] Notably, direct or simple one-pot routes to unprotected primary amines, without the need for elaborate deprotection, has recently been mentioned as a key challenge in catalysis.[6]

Having established an effective method for the synthesis of primary benzylamines by C−H functionalization as well as examined air tolerance, generality, scalability, and utility, the attention was turned to mechanistic aspects. During the standard reaction, a few byproducts were observed and quantified by both ^{1}H NMR and GC-FID/MS (Scheme 5).

Scheme 5. Detection of Byproducts during the Standard Reaction. Depicted Yields are Relative to Benzophenone Imine



In addition to the desired product, homocoupling of both ethylbenzene and the imine was detected, albeit only to a limited extent. The observation of dimerized ethylbenzene (**3**) in combination with the diastereomeric ratio could suggest the formation of benzylic radicals during the reaction.[18] The dimerization of the imine, forming **4**, is likely a reversible copper-catalyzed equilibrium rather than an irreversible side reaction.[19,20]

Since the involvement of radical intermediates was suspected, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) was added to a standard reaction (Scheme 6a). Indeed, the presence of TEMPO inhibited the reaction which supports the suggestion that radical intermediates are involved in product formation. Furthermore, the observed regioselectivities during the substrate scope investigation correlates with C−H bond strengths and indicates that radical formation is likely product-determining. Potentially, benzylic radicals could be generated by hydrogen abstraction by a *tert*-

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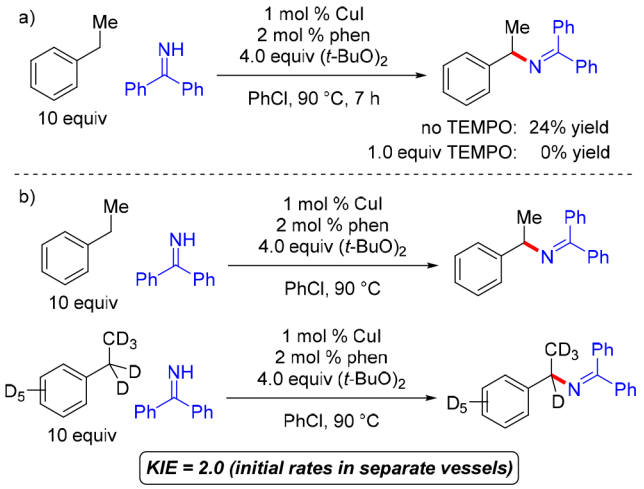
Scheme 6. (a) Reaction Inhibition by TEMPO; (b) Detection of a Kinetic Isotope Effect by Independent Rate Measurements



butoxy radical generated from $(t\text{-BuO})_2$. In order to examine if the rate-determining step involves cleavage of the benzylic C−H bond, absolute rate measurements for ethylbenzene and ethylbenzene-d_{10} were performed (Scheme 6b). The observation of a primary kinetic isotope effect clearly indicates that the C−H bond cleavage is the rate-determining step. Overall, the mechanistic data are consistent with previously reported observations for related reactions.[7,9,10]

In summary, a copper-catalyzed route to α-substituted, primary benzylamines by C−H functionalization is reported. The method directly affords the unprotected amine and relies on a cheap catalyst system and simple, commercially available reagents. The reaction can be performed on a 5 mmol scale with only 0.1 mol % of copper iodide, and reisolation of benzophenone allows for potential recycling of the protecting group. In terms of practicality, the reaction tolerates air and moisture, is a one-pot procedure, and does not require column chromatography. The relevance for pharmaceuticals was demonstrated by a short route to the racemate of Sensipar. Also, the reaction holds potential for straightforward ^{15}N-labeling of pharmaceutical candidates from ^{15}N-labeled ammonia. Preliminary mechanistic studies showed rate-limiting cleavage of the benzylic C−H bond and indicate the intermediacy of radicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03505.

Experimental procedures and NMR spectroscopic data of all products (PDF)

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Notes

The author declares no competing financial interest.

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(11) To avoid potential catalysis by trace metal impurities, 99.999% CuI was used.

(12) Chorobenzene is considered as "green" as acetonitrile, toluene, heptane, and methyl-THF, and greener than commonly used solvents such as THF, 1,4-dioxane, cyclohexane, DMA, MTBE, and benzene: Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, C. R.; Sherwood, J. Tools and Techniques for Solvent Selection: Green Solvent Selection Guides. *Sustainable Chem. Processes* **2016**, *4*, 7. $(t\text{-BuO})_2$ is one of the most stable organic peroxides and requires elevated temperatures for uncatalyzed decomposition.

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(17) In terms of practicality, the method by White et al. is sensitive to light and air, while our method can be performed in air without the exclusion of light. Ph_2CNH is commercially available ($188/25g), while White's nitrogen reagent (2.0 equiv used) has to be synthesized from 2,2,2-trichloroethyl sulfamate ($306/10g) and $PhI(OAc)_2$ ($144/100g) providing a 47% yield (prices are from www.sigmaaldrich.com). For simple, commercially available substrates, starting from scratch, our method requires two steps (one-pot) to the unprotected amine, while the method reported by White et al. requires five steps (includes catalyst synthesis, nitrogen reagent synthesis, and deprotection).

(18) In the absence of CuI/phen, 1% of **3** was formed.

(19) Ryan, M. C.; Martinelli, J. R.; Stahl, S. S. Cu-Catalyzed Aerobic Oxidative N−N Coupling of Carbazoles and Diarylamines Including Selective Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 9074−9077.

(20) In the absence of CuI/phen, 0.5% of **4** was observed.

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