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Transition-metal free reductive functionalization of tertiary carboxamides and lactams for α -branched amine synthesis

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Abstract: A new protocol for the synthesis of α -branched amines by reductive functionalization of tertiary carboxamides and lactams is described. The process relies on the efficient and controlled reduction of tertiary amides by sodium hydride-sodium iodide composite, in situ treatment of the resulting anionic hemiaminal with trimethylsilyl chloride and subsequent coupling with nucleophilic reagents including Grignard reagents and tetrabutylammonium cyanide. The new protocol exhibits broad functional group compatibility, operates under transition-metal free reaction conditions, and is suitable for various synthetic applications on both sub-millimole and on multi-gram scales.

α -Branched amines and their derivatives are found as key structural and functional units in various pharmaceutical compounds and natural products (Scheme 1). Accordingly, significant efforts have been made over the years to develop new and effective methods for their construction.

Scheme 1. Selected α -branched amines currently used in the clinic

For the synthesis of acyclic α -branched amines, multicomponent approaches such as Mannich, Petasis and Strecker reactions are classical yet powerful protocols of choice.^[1] Construction of cyclic derivatives commonly relies on directed lithiation at the α -carbon of cyclic amines having an unreactive Lewis basic directing group on the nitrogen atom (such as *tert*-butoxycarbonyl) and subsequent reaction of the resulting carbanion with reactive carbon electrophiles. Although effective,

this approach requires the use of strong organometallic bases for the initial deprotonation.^[2] Recently, the α -C-H arylation/alkylation of amines by photoredox catalysis has enabled the synthesis of such constructs under much milder reaction conditions.^[3]

Another promising approach to access α -branched amines is via reductive functionalization of readily available and bench-stable carboxamides.^[4,5] In this context, several protocols have been developed by taking advantage of electrophilic activation or controlled hydride reduction (including transition-metal-catalyzed hydrosilylation) as the initiation process to enable subsequent selective functionalization whilst minimizing over-reduction. As for the initiation by electrophilic activation of amides, triflic anhydride (Tf₂O)^[6] and phosphoryl chloride (POCl₃)^[7] have been utilized. For example, Huang has demonstrated that electrophilic activation of carboxamides by Tf₂O results in formation of nitrilium ion intermediates, which could be subsequently functionalized by the sequential addition of metal hydride and Grignard reagents for the α -functionalization (Scheme 2A).^[6] Reductive activation by use of stoichiometric hydride reagents could be implemented by reduction of *N*-alkoxy amides^[8] with DIBAL-H or the Schwartz's reagent (Cp₂ZrHCl) as well as that of tertiary/secondary amides with Cp₂ZrHCl.^[9] The corresponding metallated hemi-aminal intermediates were treated with acids and carbon nucleophiles to deliver α -branched amines (Scheme 2B). Metal-catalyzed hydrosilylation of carboxamides with silane reagents has also been found useful to initiate their reductive functionalization. In this context, Nagashima's Ir-catalyzed hydrosilylation of tertiary carboxamides and lactams with 1,1,3,3-tetramethyldisiloxane (TMDS)^[10] has been developed and applied by Dixon^[11] Chida/Sato,^[12] and Huang,^[13] in which the *O*-silylated hemi-aminal intermediates were utilized for subsequent α -carbon-carbon bond forming processes with various nucleophiles (Scheme 2C). Recently, Adolfsson reported the use of molybdenum(VI) hexacarbonyl as a catalyst with TMDS to perform the reductive Strecker reaction on tertiary carboxamides (Scheme 2C).^[14]

Recently, the Chiba group disclosed a controlled hydride reduction of tertiary carboxamides for the synthesis of aldehydes using a combination of NaH and NaI in THF.^[15] Key to the success of this chemistry was the stability (prior to aqueous work up) of the anionic hemi-aminal intermediates

formed via single hydride transfer from the activated NaH to the carboxamides.^[16] Building on this discovery, we were keen to leverage further synthetic value from these intermediates in particular for the synthesis of α -branched amines. Accordingly, we sought to identify a suitable reagent that could react with the anionic hemi-aminal intermediate and facilitate its substitution with carbon-centered nucleophiles. We hypothesized that chlorosilane reagents could indeed possess the necessary oxophilicity to both trap and activate the intermediates towards downstream carbon-carbon bond formation and thus enable their conversion to α -branched amines, and herein we wish to describe our findings (Scheme 2D).

Scheme 2. Synthesis of α -branched amines by reductive functionalization of carboxamides.

We targeted the reductive functionalization of *N,N*-dimethyl-2-naphthamide (**1a**) with phenylmagnesium bromide as the model reaction (Scheme 3A). A brief survey of various reaction parameters allowed us to identify trimethylsilylchloride (TMSCl) as the preferred silylating reagent, as well as efficient and general reaction conditions. These comprised treatment of **1a** (0.5 mmol) with NaH (3 equiv) and NaI (1 equiv) in THF at 60 °C to form the anionic hemi-aminal **A**, followed by sequential addition of TMSCl (2.5 equiv) and phenylmagnesium bromide (2 equiv) at 0 °C and further stirring of the reaction mixture for 2 h at 25 °C before work up afforded the α -branched amine **2a** in 86% yield. As **2a** was not formed if the TMSCl was not added,

the intermediacy of the *O*-trimethylsilyl hemiaminal **B** was implied.^[17] Elimination of trimethylsiloxide, presumably assisted by MgBr_2 present in the Schlenk equilibrium, generates reactive iminium ion **C** that is subsequently attacked by PhMgBr to provide product **2a**. Not only was this protocol simple to perform, it was also found to be easily up-scaled to 30 mmol of substrate and was applicable for the synthesis of *N,N*-diethylamine **2b** as well as pyrrolidine (**2c**), piperidine (**2d**), and morpholine (**2e**) (Scheme 3B).

Scheme 3. Reductive functionalization of 2-naphthamides **1** using phenylmagnesium bromide. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of 2-naphthamides. [b] The reaction was carried out on 30 mmol scale (see the SI for details).

We next investigated the scope of the reaction with respect to the Grignard reagent using 2-naphthamide substrates (Scheme 4). The method was found to be compatible with use of both electron-rich and electron-deficient aryl Grignard reagents as well as sterically hindered 2,6-dimethylphenylmagnesium bromide, providing the corresponding amines **3-5** in good yields (Scheme 4A). Installation of heteroaryl moieties such as 2-thienyl (for **6**) and pyridyl motifs (for **7** and **8**)^[18] could be implemented efficiently. Similarly, the protocol allowed the introduction of vinyl and acetylenic moieties, providing allylamine **9** and propargylamine **10**, respectively, in good yields. As for alkyl Grignard reagents (Scheme 4B), our method was suitable for installing methyl (for **11** and **12**) as well as primary alkyl groups including allyl and benzyl (for **13-15**). More sterically demanding secondary alkyl groups such as isopropyl and cyclopropyl (for **16** and **17**) could be introduced efficiently, and, impressively, use of 1-adamantylmagnesium bromide resulted in formation of the corresponding amine **18** albeit in slightly reduced yield (38%). Notably, the method was also compatible with the use of phenyldimethylsilyllithium in the presence of MgBr_2 , affording α -silylamine **19** in good yield.

A. Aryl/alkenyl/alkynyl Grignard reagents

B. Alkyl Grignard reagents

Scheme 4. Scope with respect to the Grignard reagents. [a] The reactions were conducted using 0.5 mmol of carboxamides.

We also examined the compatibility of various carboxamides in the present protocol, using phenylmagnesium bromide as the coupling reagent (Scheme 5). As for aromatic amides, the process was not detrimentally influenced by the presence of biaryl and sterically demanding 2-tolyl groups (for **20** and **21**) and tolerated substituents with differing electronic properties such as electron-donating groups (for **22-24**) and electron-withdrawing groups including a bromine atom (for **25** and **26**) (Scheme 5A). Amides based on electron-rich 5-membered (hetero)aromatic rings such as ferrocene **27**, pyrrole **28**, indole **29**, and benzothiophene **30** as well as electron-deficient 6-membered ring quinoline **31** were also compatible. Reductive phenylation of α,β -unsaturated amide gave α -branched allylamine **32** in 48% yield. We then surveyed a range of aliphatic amides for the reductive functionalization (Scheme 5B). Sterically congested α -quaternary amides could be smoothly converted to the corresponding amines **33** and **34** in good yields. The reactions of carboxamides having enolizable α -protons proceeded well to afford the corresponding amines **35-39** in good yields, however, for **40** derived from a linear primary alkyl carboxamide the yield was slightly diminished (48%). It is worthy of note that synthesis of amines **38** and **39** by the functionalization of *N,N*-diethyl-2-(1-naphthyloxy)propanamide (known as napropamide used as a herbicide)^[19] and (1*R**,2*R**)-*N,N*-dimethyl-2-phenylcyclopropane-1-carboxamide, respectively, proceeded with moderate to good diastereoselectivity.

A. Aryl/alkenyl amides

B. Aliphatic amides

Scheme 5. Scope with respect to the carboxamides. [a] The reactions were conducted using 0.5 mmol of carboxamides (see the SI for details).

Significantly, the present protocol was amenable to transform lactams to C2-functionalized saturated nitrogen-containing heterocycles, which are mainstream in small molecule libraries for drug discovery programs (Scheme 6).^[20] Treatment of *N*-benzyl-2-piperidinone with NaH-NaI followed by TMSCl and Grignard reagents allowed for installation of (hetero)aryl (for **41-45**), vinyl (for **46**), alkynyl (for **47**), and alkyl (for **48-51**) motifs onto the piperidine core in good yields. Again, the scalable nature of this protocol was confirmed by demonstrating synthesis of **41** on 30 mmol scale. Synthesis of functionalized pyrrolidines **52** and **53** as well as tetrahydroisoquinoline and azepane derivatives **54** and **55** could also be readily achieved using our method.

Scheme 6. Reductive functionalization of lactams. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of lactam substrates (see the SI for details). [b] The reaction was carried out on 30 mmol scale.

Finally, as an extension of the protocol to generate α -amino nitriles, we sought to explore the reductive Strecker reaction of carboxamides under the transition-metal free protocol (Scheme 7). Following preliminary scouting studies, we identified that use of tetrabutylammonium cyanide in place of Grignard reagents enabled the synthesis of structurally varied α -aminonitriles **56–70** from both tertiary carboxamides and lactams in yields ranging from 48–91%.

The key enabling advance in the present method takes advantage of the unique hydric reactivity of NaH in the presence of NaI for controlled reduction of tertiary carboxamides including lactams. Subsequent treatment of the resulting anionic hemi-aminal intermediates with TMSCl and Grignard reagents or tetrabutylammonium cyanide allows for deoxygenative installation of the carbon functionality to afford α -branched amines. Thus, the present protocol operates under transition-metal free reaction conditions, circumventing the requirement for stoichiometric use of expensive metal hydride reagents or transition-metal catalysts. Efforts are currently underway to extend the new protocol to new reactions and to explore its applicability to the synthesis of more complex molecules.

Scheme 7. Reductive Strecker reactions. [a] The reactions were conducted using 0.5 mmol of carboxamides (see the SI for details).

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Keywords: amines • amides • lactams • sodium hydride • Grignard reagents

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Entry for the Table of Contents

A practical, scaleable, and transition-metal free protocol for the synthesis of α -branched amines from tertiary carboxamides and lactams with carbon-centered nucleophiles has been developed. The process relies on the controlled reduction of tertiary amides by sodium hydride-sodium iodide composite, in situ treatment of the resulting anionic hemiaminal with trimethylsilyl chloride and subsequent coupling with nucleophilic reagents including Grignard reagents and tetrabutylammonium cyanide.