Difluoroalkylation of Tertiary Amides and Lactams by an Iridium-Catalyzed Reductive Reformatsky Reaction

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ABSTRACT: An iridium-catalyzed, reductive alkylation of abundant tertiary lactams and amides using 1–2 mol % of Vaska’s complex (IrCl(CO)(PPh3)2), tetramethyldisiloxane (TMDS), and difluoro-Reformatsky reagents (BrZnCF2R) for the general synthesis of medicinally relevant α-difluoroalkylated tertiary amines is described. A broad scope (46 examples), including N-aryl- and N-heteroaryl-substituted lactams, demonstrated an excellent functional group tolerance. Furthermore, late-stage drug functionalizations, a gram-scale synthesis, and common downstream transformations proved the potential synthetic relevance of this new methodology.

The incorporation of the gem-difluoromethylene (−CF2−) group, an oxygen bioisostere, into organic molecules has gained considerable attention in pharmaceutical and agrochemical research as well as in materials science, due to the unique influence of fluorine atoms on physical, chemical, and biological properties. More specifically, the β,β-difluoro-α-amino motif represents a key building block in many bioactive molecules, owing to the electronic influence of the fluorine atoms on the neighboring nitrogen center. The strong electron-withdrawing character of β-fluorine substitution on amines or nitrogen-containing heterocycles significantly lowers their basicity and pKa, which in turn influence critical parameters in medicinal lead optimization, such as physicochemical properties, binding affinities and absorption, distribution, metabolism, and excretion (ADME). The relevance of this structural motif in drug discovery is exemplified by the large variety of β,β-difluoro-α-amino-containing pharmaceutical compounds such as gencitabine, cedazuridine, efornithine, GDC-0077, and glecaprevir (Scheme 1A). Therefore, the development of new concise and selective methods for the late-stage introduction of gem-difluoromethylene units onto nitrogen-containing scaffolds remains an attractive goal in synthetic chemistry.

In the past decade, several research groups have become involved in the challenging late-stage reductive C–C coupling of amides with organometallic reagents for the synthesis of α-functionalized amines. Stoichiometric approaches for the reductive functionalization of different amide classes, including lactams with various organometallic reagents, have been reported by Huang, Sato and Chida, and Chiba and our group. These methods employ DIBAL-H, Schwartz’s reagent (Cp2ZrHCl), triflic anhydride/metal hydride, or a NaH/NaI composite as the stoichiometric reductants. A highly chemoselective reductive functionalization of amides can be achieved
by a transition-metal-catalyzed approach, as demonstrated by our group and others. Using catalytic amounts of Vaska’s complex \( \text{IrCl(CO)(PPh}_3\text{)}_2 \) and 1,1,3,3-tetramethyldisiloxane (TMDS) led to the formation of metastable \( O \)-silylated hemiaminal intermediates, which are precursors to reactive iminium ions that can undergo subsequent nucleophilic functionalization.

Continuing our group’s ongoing efforts on reductive iridium-catalyzed \( C - C \) bond-forming reactions, we envisioned combining amide functionalization with commonly known difluoromethylene sources to form highly desirable and medicinally relevant \( \alpha \)-difluoroalkylated amines (Scheme 1B). The ethoxycarbonyl-difluoromethyl \( (-CF_2CO_2Et) \) moiety is a versatile difluoromethylene source, due to its potential as a handle for further modifications into various functional groups. In addition to cross coupling, C–H functionalization, and radical addition, this difluoro-methylene-containing unit is traditionally introduced via nucleophilic attack of the corresponding difluoro-Reformatsky reagent \( \text{BrZnCF}_2CO_2Et \) on carbonyl groups, imines, or azodicarboxylates. This long-serving reagent with its efficacious reactivity toward various electrophiles caught our attention for its potential unprecedented deployment in a general late-stage amide functionalization approach, and herein we wish to report our findings.

**Scheme 2. Reaction Optimization**

| Entry | TMDS (x equiv) | 2a (y equiv) | conc. of 2a* [mol%] | 3a* | 4* | 5* |
|-------|---------------|--------------|---------------------|-----|----|----|
| 1     | 2.0           | 1.1          | 0.52                | 53  | 8  | 24 |
| 2     | 2.0           | 2.6          | 0.52                | 57  | 13 | 19 |
| 3     | 1.5           | 2.6          | 0.52                | 76  | 6  | 10 |
| 4     | 1.5           | 2.6          | 0.24                | 79 (75) | 5 | 8 |

*NMR yield using 1,3,5-trimethoxybenzene as an internal standard; isolated yield in parentheses.

**Scheme 3. Reaction Scope of Tertiary Amides and Lactams**

\( ^a \) 2.5 equiv of TMDS and 2 mol % of \( \text{IrCl(CO)(PPh}_3\text{)}_2 \) were used.

\( ^b \) 2-Methyl-THF was used as the solvent in the first step and stirred for 2 min.

\( ^c \) THF was used as the solvent in the first step.

\( ^d \) 2.5 equiv of TMDS and 2 mol % of \( \text{IrCl(CO)(PPh}_3\text{)}_2 \) were used, and the first step was stirred for 1 h.

\( ^e \) Standard conditions: amide or lactam \( 1 \) (0.15 mmol), \( \text{IrCl(CO)(PPh}_3\text{)}_2 \) (1 mol %), TMDS (0.23 mmol), toluene (1.50 mL), and \( 2a \) (0.40 mmol) in THF (1.63 mL); isolated yields are given.
Scheme 4. Reaction Scope of Difluoro-Organozinc Reagents

“Lactam 1ab (0.15 mmol), 1.5 equiv of TMDS, and 1 mol % of IrCl(CO)(PPh3)2 were used. Standard conditions: amide 1n (0.15 mmol), IrCl(CO)(PPh3)2 (2 mol %), TMDS (0.38 mmol), toluene (1.50 mL), 2a (0.40 mmol) in THF; isolated yields are given.

Scheme 5. Gram-Scale Reaction and Downstream Functionalization

“Isolated yields are given.

N,N-Dimethyl-1-naphthamide 1a was chosen as a model substrate for the reductive functionalization with difluoro-organozinc reagent 2a, which was freshly prepared from the corresponding ethyl bromodifluoroacetate (2a) and zinc in THF. We were very pleased that staged treatment of a toluene solution of 1a with 1 mol % of Vaska’s complex, 2.0 equiv of TMDS, and 1.1 equiv of difluoro-organozinc reagent 2a’ gave the desired tertiary amine 3a in promising 53% yield, alongside minor amounts of secondary alcohol 4 and overreduction product 5 (Scheme 2, entry 1). Increasing the equivalents of organozinc reagent 2a’ improved the yield of desired product 3a slightly (Scheme 2, entry 2). More significantly, lowering the amount of TMDS to 1.5 equiv drastically reduced the rate of overreduction and allowed access to synthetically useful yields of functionalization product 3a (Scheme 2, entry 3).

Finally, changing the concentration of organozinc reagent 2a’ by dilution provided a 75% isolated yield (Scheme 2, entry 4). Further changes to the reaction conditions, such as using different solvent combinations, temperatures, or reaction times, did not have a positive effect on the reaction outcome (see SI for full optimization details).

With optimized conditions in hand, we then examined the reaction scope with respect to tertiary amides and lactams 1 (Scheme 3). Satisfyingly, several N,N-dimethyl-benzamides 1a−1f with electron-deficient and electron-rich substituents in ortho or para positions, as well as furan substrate 1g, could be successfully converted into the corresponding difluoromethylated tertiary amines 3b−3g in good isolated yields (62−84%). Pyrrolidine-, piperidine-, morpholine-, azepane-, and azocane-derived amides 3h−3o were reductively functionalized in good to excellent yields (69−98%) while demonstrating tolerance to various substituents such as boronic ester, acetal, iodo, or nitro groups. N,N-Dibenzylandamide 1p, N,N-benzylethylamide 1q, and anilide 1r were successfully employed to furnish the desired products 3p−3r in 64−87% yields. However, increased amounts of TMDS (2.5 equiv) and Vaska’s complex (2 mol %) were used to force the slow reduction step of these more challenging substrates to full conversion. Anilide 1s, bearing an ethyl ester moiety, was converted into amine 3s in the same way, albeit in a diminished 56% yield. Weinreb amide 1t reacted smoothly to product 3t in 91% yield, while α,β-unsubmersated amides gave difluoro products 3u and 3v in moderate 34% and 58% yields, which is due to competing conjugate addition. Furthermore, aliphatic amides 1w and 1x underwent reductive functionalization in 73% and 68% yields. Encouraged by these results, we also envisioned including lactams in the substrate scope. Five- and six-membered lactams in the substrate scope. Five- and six-membered lactams in the substrate scope. Five- and six-membered lactams in the substrate scope. Five- and six-membered lactams in the substrate scope.

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Next, we assessed the scope of the difluoro-organozinc reagents 2’ and were again pleased to find that azepan-1-yl(phenyl)methanone (1m) could be readily functionalized with benzyl, trimethylsilyl, and isopropyl difluoroacetates 2b’−2d’ to form 3a j−3a l in good yields (63−85%) (Scheme 4). Vaska’s complex (2 mol %) and 2.5 equiv of TMDS were used to ensure that starting amide 1n was fully converted into the silylated hemiaminal intermediate before adding the nucleophile. Employing 1-menthol- and glycerol-derived difluoroacetates 2e’ and 2f’, products 3a m and 3a n were isolated in 49% and 64% yields as 1:2:1 and 1:1 mixtures of diastereomers, respectively. Sterically demanding benzhydryl difluoroacetate 2g’ could be introduced efficiently in 74% yield to give tertiary amine 3a o. Notably, difluoroacetamide-containing zinc bromides 2h’ and 2i’ could also be used under the same reaction conditions to furnish amines 3a p and 3a q in near quantitative yields. Using morpholine-derived difluoroacetamide 2j’, 3a r was obtained in good yield (63%). Further reduction of the difluoroacetamide moiety in these products was not observed under the reported reaction conditions, which can be explained by the active iridium catalyst being quenched by the organozinc bromides upon addition. Highlighting lactams as suitable feedstock compounds, the reductive functionalization of 1a b with benzyl difluoroacetate 2b’ and difluoroacetamide 2h’ gave the C2-difluoroalkylated saturated nitrogen-containing heterocyclic amines 3a s and 3a t in 42% and 53% yields, respectively.

To showcase the synthetic utility of this methodology, we performed a gram-scale reductive difluoroalkylation of amide 1b, generating tertiary amine 3b in a 67% (1.15 g, 4.47 mmol) yield (Scheme 5), which was comparable to the small-scale reaction. Identifying the ester moiety in 3b as a useful handle for downstream derivatizations, we synthesized several CF2-containing compounds 6−10 by standard organic procedures. Primary alcohol 6 was obtained in 81% yield by reduction with sodium borohydride. Addition of a methanolic ammonia solution gave corresponding primary amide 7 in 85% yield. Tertiary alcohol 8 was formed in 61% yield, using 2.1 equiv of Grignard reagent. Saponification and subsequent acidification furnished carboxylic acid 9 in quantitative yield. Finally, enol ether 10 was installed in 42% yield by employing the Tebbe reagent under basic reaction conditions.

In conclusion, a broadly applicable and efficient method for the synthesis of acyclic and cyclic α-difluoroalkylated tertiary amines with good overall yields has been developed. The mild iridium-catalyzed reductive difluoroalkylation shows excellent functional group tolerance with respect to both coupling partners: amides/lactams and organozinc reagents, which are among other things highlighted by the late-stage derivatization of four drug molecules. Furthermore, the reaction was readily performed on a gram scale without a significant loss in yield, and several CF2-containing derivatives were made by common downstream transformations, altogether demonstrating the potential utility of the method developed herein as a useful tool in current and future drug discovery programs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00438.
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