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# Redox-Neutral Umpolung Synthesis of α-Functionalized Amides

Rui Wang, Shaokang An, Yi-Xuan Xin, Yuan-Ye Jiang,* and Wenbo H. Liu*

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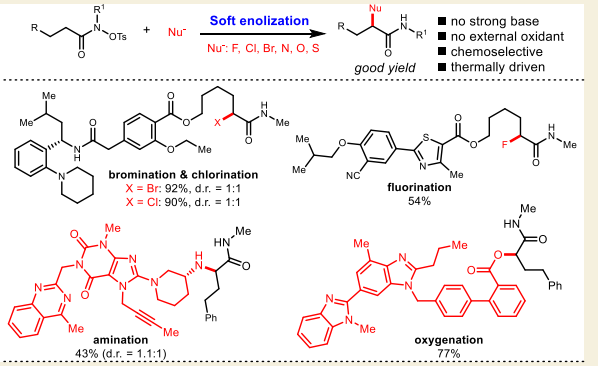
**ABSTRACT:** α-Heteroatom-substituted amides are useful as both targets and intermediates but are challenging to synthesize via conventional enolate chemistry. Herein, we describe a general and unified umpolung procedure to prepare α-heteroatom-functionalized secondary amides with various heteroatom-based nucleophiles under redox-neutral conditions. This transformation is a formal oxidation state reshuffle process from −N to −C in the hydroxamate, thereby achieving the umpolung α-heterofunctionalization of carbonyl groups without external oxidants. Regulated by the reshuffle mechanism, functionalization exclusively occurs at the α-position of the hydroxamate and precisely affords the α-functionalized amide with reliable predictability even in complex settings. Density functional theory studies support that soft enolization enabled by $Mg^{2+}$/DIPEA combination is essential to facilitate the formation of the α-lactam intermediate. This represents the first general protocol to prepare α-functionalized secondary amides.




**KEYWORDS:** *secondary amide, umpolung, α-functionalization, redox-neutral*

## INTRODUCTION

Functionalizations at the α-positions of carbonyl compounds are among the most practiced reactions in organic chemistry and can be further classified into C−C and C−Het bond formations. In particular, forging the C−Het bonds at the α-positions of carbonyl compounds is significant because (1) the products themselves are useful such as the amino acids[1,2] and (2) they are versatile synthetic intermediates, which can be readily converted to other functionalities.[3] While robust and efficient methods for aldehyde and ketone α-functionalization have been established, direct synthesis of α-functionalized secondary amides is still a challenging transformation.[4−7] Thus, these structures are usually synthesized from α-functionalized carboxylic acids and amines through detoured ways.[8] The challenges for α-heterofunctionalization of secondary amides lie in twofold: (1) due to significantly lower α-C−H acidity,[9] converting secondary amides into the corresponding enolates is not trivial and (2) to join the α-carbon with a heteroatom, special reagents in which the heteroatom is connected with a leaving group are necessary. To this end, for halogenation, amination, oxygenation, and sulfuration, highly corrosive and oxidative reagents are involved.[10,11] These reagents are not only structurally limited but also may cause side reactions due to their high oxidizing properties. Under certain circumstances, extra cleavage steps are indispensable to furnish the desired heteroatom-functionalized products, thereby further complicating the α-derivatization[12] (Figure 1a).

Since the first report by Bladon and Kirby on the α-lactam formation from hydroxamates (Figure 1b),[13] leveraging α-lactam as the key intermediate to synthesize α-functionalized amides has been disclosed occasionally.[14−16] Unfortunately, in all of these protocols, only the substrates with very acidic α-C−H bonds allow for the generation of α-lactams. Therefore, the established conditions are only suitable for the substrates with aryl[13,14,16] or carbonyl[15] substituents at the α-positions of carbonyls to enhance the α-C−H acidity. This acidic prerequisite significantly limits the synthetic potentials of this type of transformation. In the context of solving the aryl- or carbonyl-substituent issue, we describe a general and unified platform to prepare α-heteroatom-substituted secondary amides with various heteronucleophiles (including −Br, −Cl, −F, −N, −O, and −S) under redox-neutral conditions. This approach is practical and operationally simple and involves only commercially available reagents. The key to solving the α-substituent issue hinges on the identification of a compatible pair of Lewis acid and base to promote the soft enolization[17] of hydroxamates, thereby expanding the scope from arylacetic acid- or malonic acid-derived amides to all aliphatic amides. Since only mild reagents and benign conditions are engaged, this method is highly chemoselective and predictable, which has been applied to the late-stage functionalization of natural

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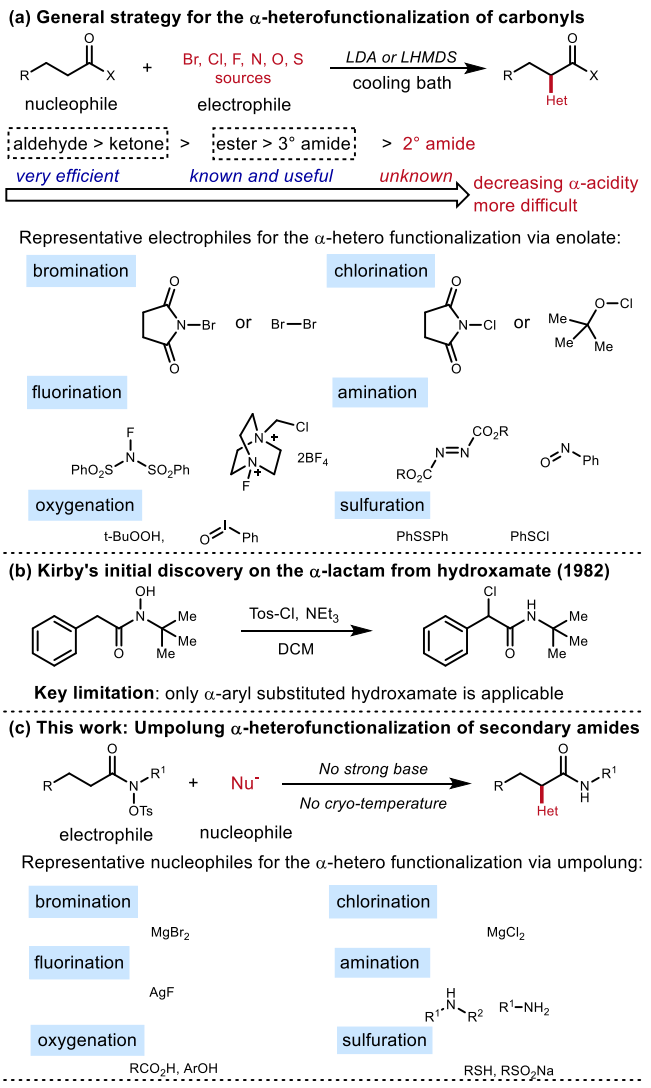


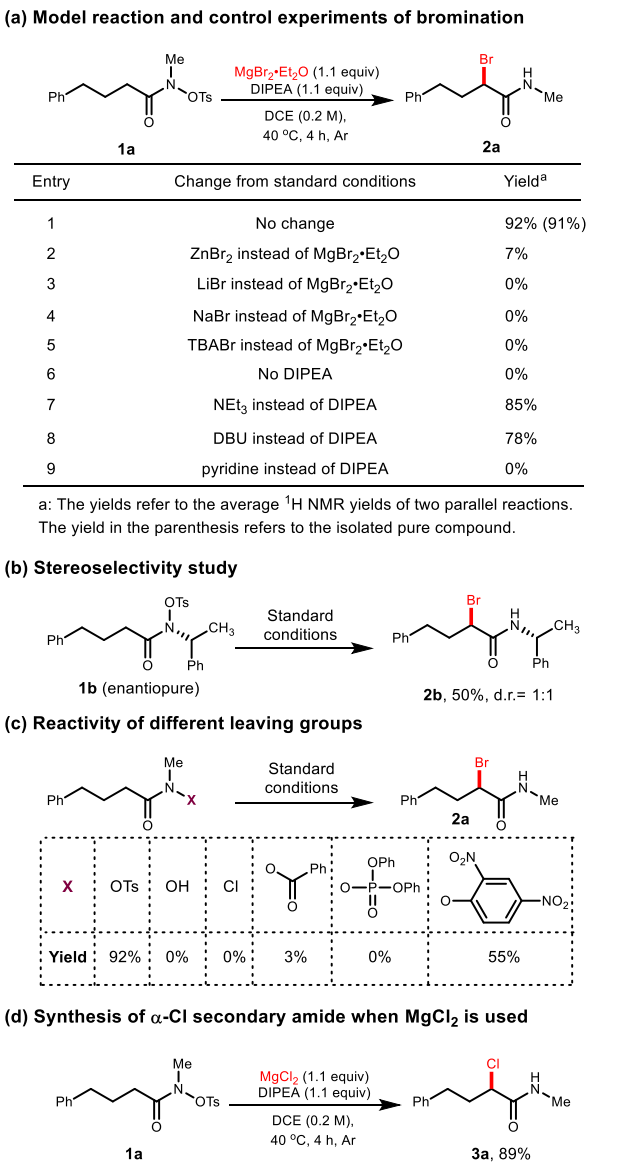

**Figure 1.** Background and this work.

products, drugs, and peptides (Figure 1c). Perhaps, most importantly, various structurally diversified O-, N-, and S-based nucleophiles can be directly applied to construct the C−Het bonds.

## RESULTS AND DISCUSSION

### Synthesis of α-Bromo and -Chloro Amides

Given that α-bromo amides are versatile in organic synthesis,[18] we initiated the investigation by selecting the transformation from nonactivated hydroxamate (**1a**) to α-bromo secondary amide (**2a**) as the target (Figure 2a). By employing the conditions reported by Kirby and others,[13−16] no desired product can be detected, which further confirms that previous protocols are only suitable for the arylacetic acid- or malonic acid-derived substrates. Following an optimization campaign, it was found that **2a** was isolated in 91% yield when the reaction was run in DCE (0.2 M) at 40 °C for 4 h with $MgBr_2{\cdot}Et_2O$ and DIPEA as the additives. To understand how each component in the standard conditions affects the reaction, control experiments were carried out. When the bromide source was changed into others, low reactivity (entry 2) or no reactivity (entries 3−5) was observed. The Lewis base is also crucial because the reaction cannot proceed without DIPEA (entry 6).




| Entry | Change from standard conditions | Yield[a] |
|---|---|---|
| 1 | No change | 92% (91%) |
| 2 | $ZnBr_2$ instead of $MgBr_2{\cdot}Et_2O$ | 7% |
| 3 | LiBr instead of $MgBr_2{\cdot}Et_2O$ | 0% |
| 4 | NaBr instead of $MgBr_2{\cdot}Et_2O$ | 0% |
| 5 | TBABr instead of $MgBr_2{\cdot}Et_2O$ | 0% |
| 6 | No DIPEA | 0% |
| 7 | $NEt_3$ instead of DIPEA | 85% |
| 8 | DBU instead of DIPEA | 78% |
| 9 | pyridine instead of DIPEA | 0% |

a: The yields refer to the average $^1$H NMR yields of two parallel reactions. The yield in the parenthesis refers to the isolated pure compound.

**Figure 2.** Model reaction, stereoselectivity study, control reactivity of other leaving groups, and synthesis of α-Cl secondary amide.

Other regular organic bases, including triethyl amine (entry 7, 85% yield) and DBU (entry 8, 78% yield), also promote this reaction in good yields, whereas pyridine is not effective for this process (entry 9). These control experiments suggest the essential roles of $Mg^{2+}$ and DIPEA to promote the functionalization of non-aryl-activated amides. The observation that $Mg^{2+}$ is effective while $Li^+$ is not (entry 3) is consistent with the fact that $Mg^{2+}$ is a Lewis acid much stronger than $Li^+$.

Furthermore, when the enantiopure hydroxamate (**1b**) was subjected to the standard conditions, the corresponding product (**2b**) was obtained in a 50% combined yield with a diastereomeric ratio of 1:1 (Figure 2b). This stereoselectivity study illustrates that simply introducing a chiral center at the nitrogen atom cannot induce the chirality transfer to the newly formed C−Br bond. By switching the tosylate (−OTs) in hydroxamate (**1a**), further control experiments were performed to assess the reactivities of different leaving groups. The results reveal that among common leaving groups, −OTs exhibit the most promising reactivity (Figure 2c). Finally, when $MgBr_2{\cdot}Et_2O$ was changed into $MgCl_2$, the corresponding α-chloro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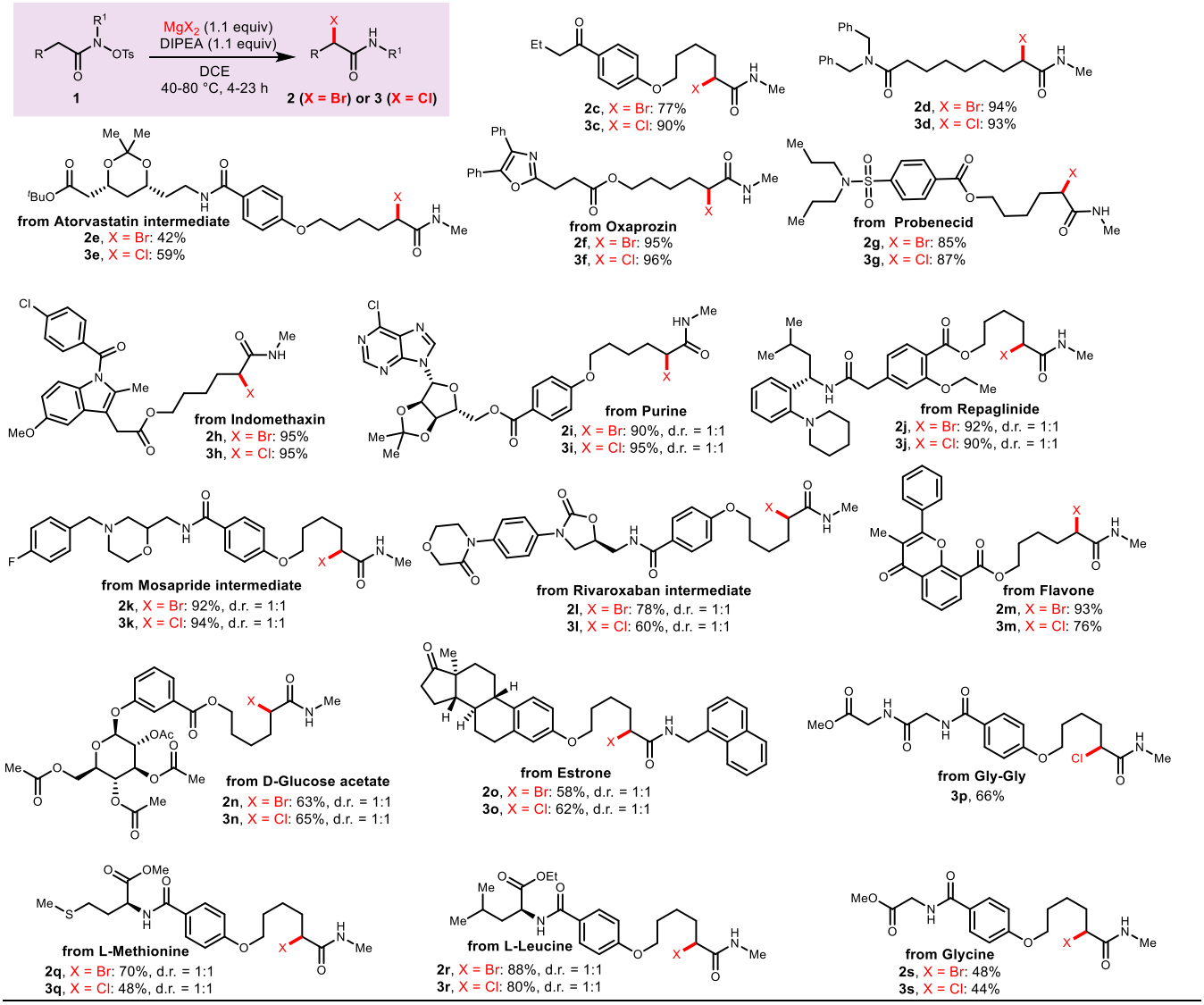


**Figure 3.** Scope of the $\alpha$-bromination and -chlorination. Bromination conditions: **1** (0.2 mmol), $MgBr_2{\cdot}Et_2O$ (1.1 equiv), DIPEA (1.1 equiv), DCE, 40 °C, 4 h. Chlorination conditions: **1** (0.2 mmol), $MgCl_2$ (1.1 equiv), DIPEA (1.1 equiv), and DCE, 40 °C, 4 h. Please see the Supporting Information for the experimental details. All the yields refer to the yields of pure isolated compounds.

secondary amide (**3a**) was smoothly obtained in 89% yield (Figure 2d).

With the efficient conditions to synthesize $\alpha$-bromo and $\alpha$-chloro amides identified, we next turned our attention to examine the generality of this protocol. Instead of simple and trivial substrates, large and densely functionalized structures with potentially interferential functional groups were intentionally chosen for the scope test (Figure 3). For example, compound **1c** contains a more reactive ketone, whereas the desired $\alpha$-Br (**2c**, 77%) and $\alpha$-Cl (**3c**, 90%) amides were isolated in high yields. In addition, in the presence of a tertiary amide, the $\alpha$-Br and $\alpha$-Cl amides can be prepared in excellent yields (**2d**, 94%; **3d**, 93%). Besides the enolizable ketones and tertiary amides, the ester is also tolerated (**2e**, 42%; **3e**, 59%). Note that apart from the acidic $\alpha$-C−H of the ester, a more acidic N−H is present in compound **1e**. These acidic protons determine that it is very difficult to prepare **2e** and **3e**. Drug derivatives including oxaprozin and probenecid with esters also proceed well (**2f**−**2g**, **3f**−**3g**). The drug indomethaxin-derived substrate comprises an amide and an enolizable ester. Nevertheless, this reaction is not interfered by these functionalities, and the corresponding products were still generated in high yields (**2h**, 95%; **3h**, 95%). A nucleic acid-derived molecule with nucleobase, sugar, and ester moieties also delivers the desired products straightforwardly (**2i**, 90%; **3i**, 95%). Furthermore, the drug repaglinide possesses an enolizable secondary amide, and its derivative was transformed into $\alpha$-bromo and -chloro secondary amides smoothly (**2j**, 92%; **3j**, 90%). Similarly, an amide-containing mosapride-derived substrate selectively leads to the products (**2k**, 92%; **3k**, 94%). Remarkably, an even more complicated substrate **1l** is compatible with the standard conditions to yield the products (**2l**, 78%; **3l**, 60%). A hydroxamate obtained from a flavone natural product is also functionalized in high yields (**2m**, 93%; **3m**, 76%). This protocol can tolerate the presence of multiple enolizable esters and acidic C−H bonds in substrates derived from D-glucose acetate (**2n**, 63%; **3n**, 65%). Although estrone is equipped with a reactive and enolizable ketone, the hydroxamate could still be converted to the $\alpha$-bromo and $\alpha$-chloro amides without affecting the ketone



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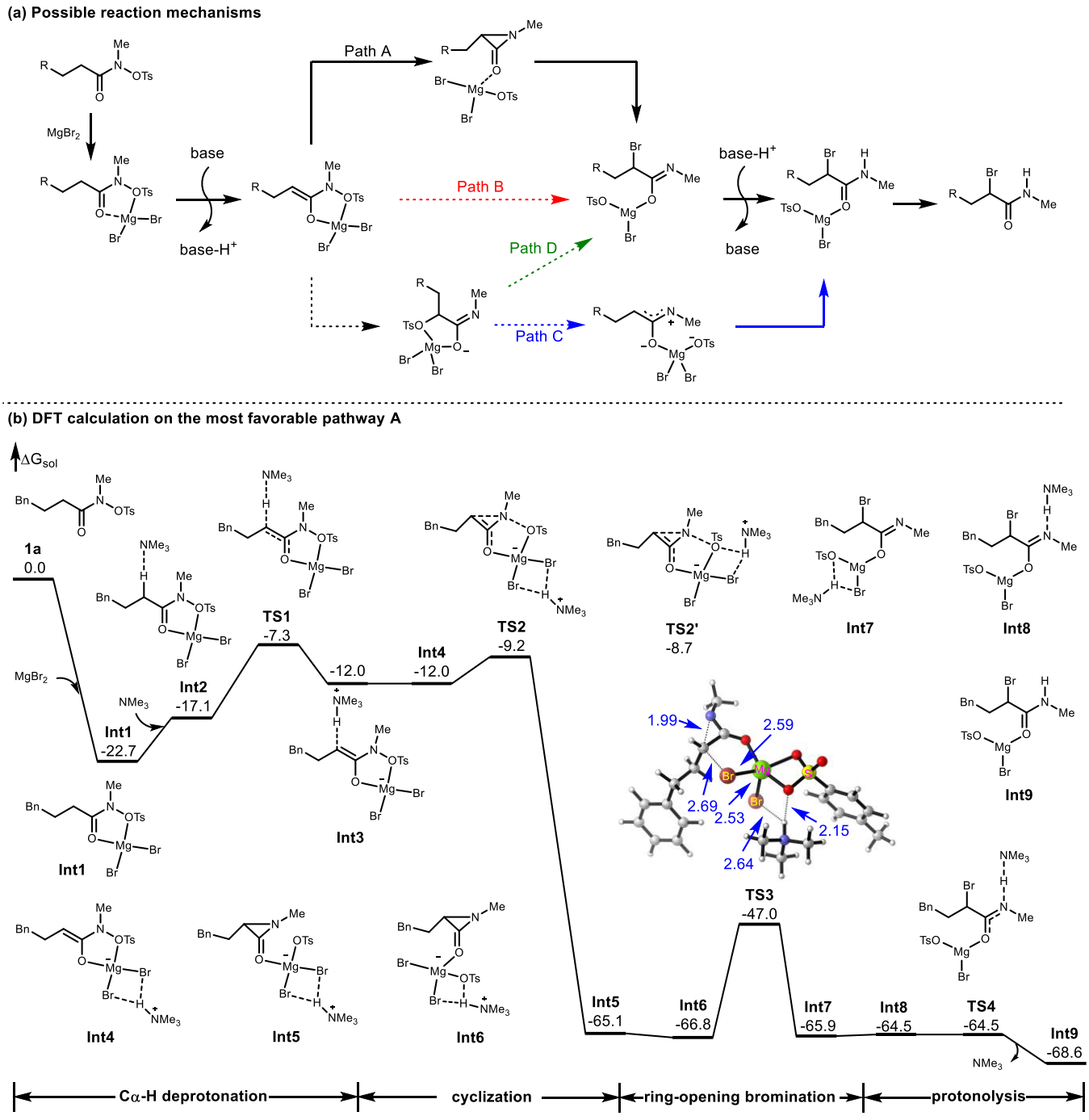


**Figure 4.** Calculated solution-phase Gibbs free energy profile of $\alpha$-bromination of amide **1a** (in kcal/mol). Interatomic distances in rate-determining transition state **TS3** are given in angstrom.

$\alpha$-C−H bonds (**2o**, 58%; **3o**, 62%). Finally, four amino acid- and peptide-derived substrates with acidic N−H and C−H bonds were investigated, which all delivered the corresponding products in good to high yields (**2q**−**2s**, **3p**−**3s**). These $\alpha$-bromo and $\alpha$-chloro amides with other potentially reactive functionalities are very challenging or even unlikely to prepare via classical enolate chemistry in high yields, thereby demonstrating the robustness and practicality of this umpolung protocol.

## DFT Calculation on the Mechanism of $\alpha$-Bromination

To rationalize the mechanism of converting hydroxamate to the $\alpha$-bromo amide, several reasonable pathways can be proposed (Figure 4a). Density functional theory (DFT) calculations were conducted to elucidate the mechanistic details (Figure 4b and also see the Supporting Information for computational details on less favored pathways). The coordination of **1a** to $MgBr_2$, the OTs moiety, and the carbonyl oxygen generates **Int1** with an energy decrease of 22.7 kcal/mol. With $NMe_3$ as a model base, the $C_\alpha$−H deprotonation of the amide could occur via **TS1** with an overall energy barrier of 9.8 kcal/mol to furnish **Int3**. Thereafter, the bromination of the magnesium enolate is considered, but this pathway is highly endergonic (path B in Figure 4a and Scheme S1), probably due to the incompatible



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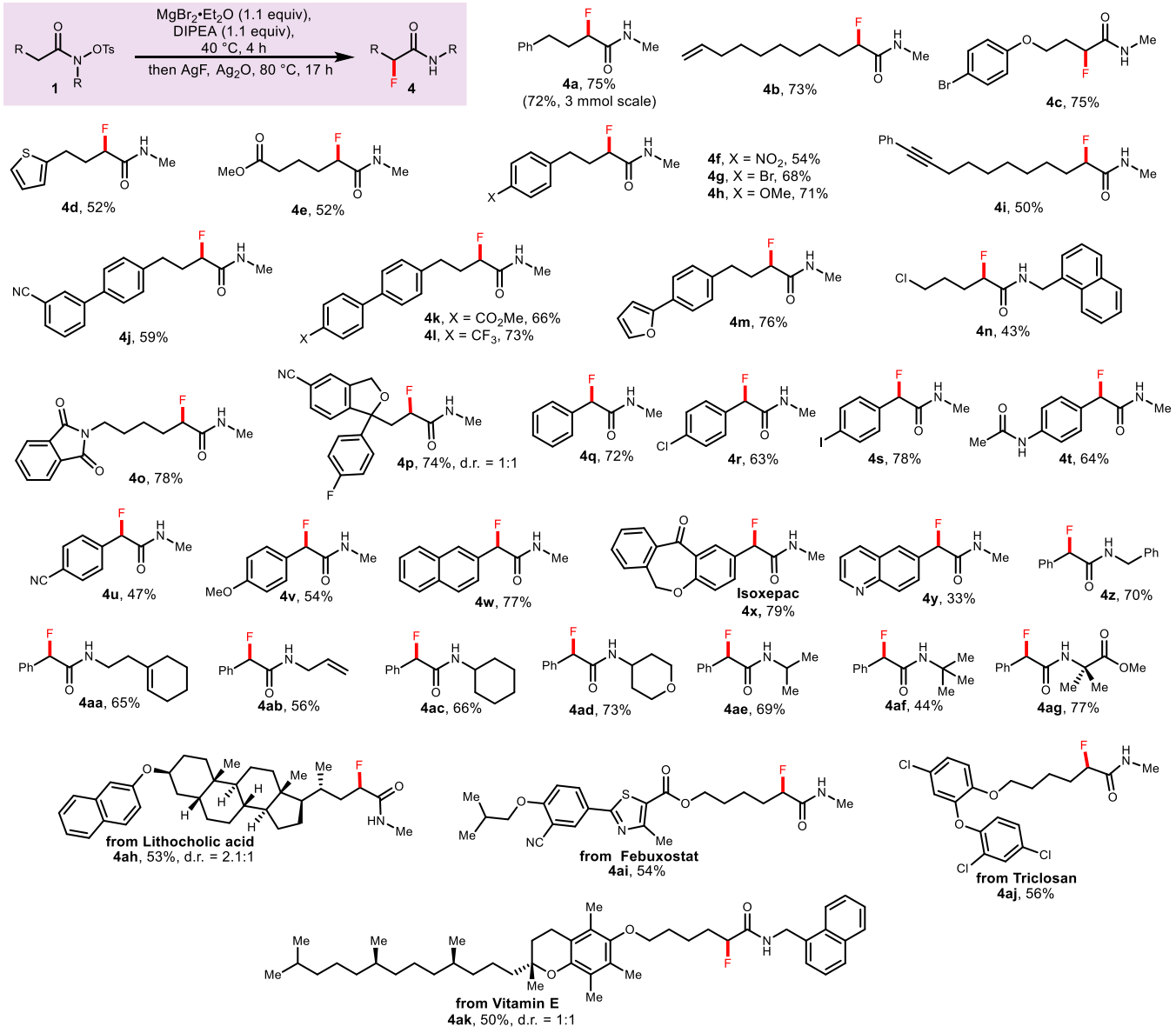


**Figure 5.** Scope of the secondary amides. Conditions: **1** (0.2 mmol), $MgBr_2 \cdot Et_2O$ (1.1 equiv), DIPEA (1.1 equiv), DCE, 40 °C, 4 h; then, AgF (3.0 equiv), $Ag_2O$ (0.3 equiv), DCE, 80 °C, 17 h. Conditions for the aryl acetic acid-derived amides: **1** (0.2 mmol), AgF (2.0 equiv), $NEt_3$ (1.1 equiv), and acetonitrile, 80 °C, 18 h. Please see the Supporting Information for the experimental details. All the yields refer to the yields of pure isolated compounds.

electronic characters of bromide and $\alpha$-carbon of the enolate (both are electron-rich). In contrast, the N−OTs bond cleavage proceeds smoothly following the $C_\alpha$−H deprotonation and leads to two pathways, which are influenced by the hydrogen bond of ammonium. Regarding the more kinetically favored pathway, ammonium forms hydrogen bonds with two bromides (**TS2**) or with one bromide and OTs (**TS2′**). The spontaneous cyclization occurs along with the N−OTs bond cleavage (energy barrier: 2.8 kcal/mol). **TS2** is slightly favored over **TS2′** and affords **Int5** with a dramatic energy decrease, thereby implying that this process might be driven by the stability of $\alpha$-lactam and the weak N−OTs bond. Subsequently, **Int5** could isomerize to **Int6** to improve the nucleophilicity of the bromide. Then, ring-opening bromination proceeds via **TS3** with an overall energy barrier of 19.8 kcal/mol. Finally, the resulting intermediate **Int7** isomerizes to **Int8** and delivers the amide product via **TS4** facilely with a small energy barrier. The calculated energy profile illustrates that the ring-opening bromination of $\alpha$-lactam is the rate-determining step for $C_\alpha$−H bromination, and the irreversible N−OTs bond cleavage of magnesium enolate is responsible for chemoselectivity.

## Synthesis of $\alpha$-Fluoro Secondary Amides

Introducing the fluorine atom into organic molecules by forming the C−F bond can alter organic molecules with beneficial properties, which have seen broad applications in medicine and materials chemistry.[19] Therefore, developing simple and efficient fluorination approaches has attracted tremendous attention over the past several decades.[20] Among known fluorination strategies, C−H fluorination with a nucleophilic fluoride source is particularly challenging but the most straightforward.[21,22] Following the establishment of $\alpha$-bromination and chlorination, $\alpha$-fluorination also received



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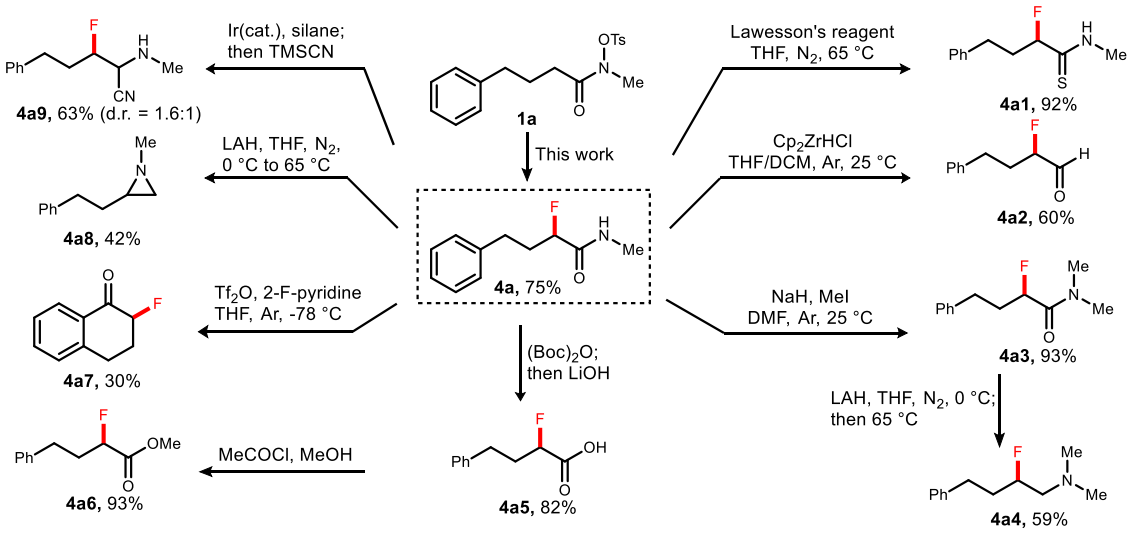


**Figure 6.** Synthetic application of $\alpha$-fluoro secondary amide. Conditions: (a) **4a** (0.2 mmol), Lawesson's reagent (2.0 equiv), THF, $N_2$, 65 °C, 9.5 h; (b) **4a** (0.2 mmol), $Cp_2ZrHCl$ (2.0 equiv), THF/DCM, Ar, 25 °C, 5 h; (c) **4a** (0.2 mmol), NaH (3.0 equiv), MeI (3.0 equiv), DMF, Ar, 25 °C, 5 h; (d) **4a3** (0.18 mmol), $LiAlH_4$ (4.0 equiv), THF, $N_2$, 0 to 65 °C, 11.5 h; (e) **4a** (0.2 mmol), $Boc_2O$ (2.0 equiv), DMAP (1.05 equiv), $Et_3N$ (1.05 equiv), DCM, air, 25 °C, 12.5 h; then LiOH (3.0 equiv), THF/$H_2O$, air, 25 °C, 2.5 h; (f) **4a5** (0.16 mmol), acetyl chloride (0.5 equiv), MeOH, air, 25 °C, 13 h; (g) **4a** (0.2 mmol), $Tf_2O$ (1.1 equiv), 2-fluoropyridine (1.1 equiv), DCM, Ar, −78 °C, 10 min; then 0 °C, 10 min; (h) **4a** (0.2 mmol), $LiAlH_4$ (6.0 equiv), THF, $N_2$, 0 to 65 °C, 19.5 h; (i) **4a** (0.2 mmol), $[IrCl(COE)_2]_2$ (1 mol %), $Et_2SiH_2$ (2.0 equiv), DCM, Ar, 0 to 25 °C, 1 h, then $BF_3{\cdot}Et_2O$ (1.5 equiv), Ar, 0 °C, 0.5 h; then TMSCN (2.5 equiv), Ar, 0 to 25 °C, 11 h.

our attention. Unfortunately, by switching $MgBr_2{\cdot}Et_2O$ to $MgF_2$ under standard conditions of bromination (Figure 2a), the desired fluorination product cannot be detected. After extensive optimization, the one-pot, two-step protocol to convert hydroxamate to the $\alpha$-fluoro amides was developed. Under standard conditions (Figure 5), **1a** was transformed into $\alpha$-fluoro amide **4a** in 75% yield (72% yield in a 3 mmol scale).

To investigate the generality of this fluorination approach, the scope was evaluated as well. We were glad to find that this fluorination is a general process with a broad substrate scope and functional group compatibility. Important functional groups, such as olefin (**4b**, 73%), −Br (**4c**, 75%; **4g**, 68%), −Cl (**4n**, 43%; **4r**, 63%), −I (**4s**, 78%), ester (**4e**, 52%; **4k**, 66%), nitro (**4f**, 54%), nitrile (**4j**, 59%; **4p**, 74%), alkyne (**4i**, 50%), and ketone (**4x**, 79%), are tolerated, and the desired $\alpha$-fluoro secondary amides are obtained in good to high yields. Moreover, numerous heterocycles, including thiophene (**4d**, 52%), furan (**4m**, 76%), phthalimide (**4o**, 78%), and quinoline (**4y**, 33%), are compatible under standard conditions. In addition to the variation of the carboxylic acid moiety, the amine motif can also be widely diversified. The substitutes for nitrogen can be methyl (**4b**, 73%), naphthyl methylene (**4n**, 43%), benzyl (**4z**, 70%), primary alkyl (**4aa**, 65%), allyl (**4ab**, 56%), secondary alkyl (**4ac**, 66%; **4ad**, 73%; **4ae**, 69%), tertiary alkyl (**4af**, 44%), and even amino ester (**4ag**, 77%). In addition, complex-molecule-derived $\alpha$-fluoro secondary amides are also prepared in good to high yields. It is worth noting that this redox-neutral C−H fluorination does not involve strong oxidants, such as hypervalent iodine reagents and N−F-based oxidants, which determines that the oxidizable functional groups, including olefin (**4b**, **4aa**, **4ab**), alkyne (**4i**), iodine (**4s**), benzylic C−H bonds (**4q**−**4y**), electron-rich arenes (**4v**, **4ak**), quinoline (**4y**), thiophene (**4d**), and furan (**4m**), are compatible. From a practical standpoint, this fluorination has several advantages: (1) all of the reagents required in this fluorination are commercially available, which renders this protocol easily adopted; (2) it can be readily scaled up without appreciable yield loss; (3) due to the almost identical polarity, a notorious challenge in the C−H fluorination field is that the fluorinated product is very difficult to purify from the C−H precursor when the conversion is not complete. However, the current C−H fluorination does not suffer from this issue thanks to the in situ release of a polar tosylate group; and (4) all the operations are performed in one pot without isolating any intermediate.

As introduced previously, secondary amides are versatile compounds, which can be readily diversified.[23,24] To illustrate the synthetic application of this fluorination, $\alpha$-fluoro secondary amide **4a** was successfully converted to other functionalities (Figure 6). For example, $\alpha$-fluoro thioamide **4a1** was afforded in 92% yield under standard Lawesson conditions. By using Schwartz's reagent, $\alpha$-fluoro aldehyde **4a2** was smoothly prepared in 60% yield. The difference between secondary amides and tertiary amides is that the NH site of the secondary amide is available for further derivatization, which represents a particular advantage compared to the tertiary amide. A standard alkylation allowed for the synthesis of $\alpha$-fluoro tertiary amide **4a3** in 93% yield from **4a**. Moreover, $\beta$-fluoro amine **4a4** was afforded in 59% yield from **4a3**. The $\alpha$-fluoro secondary amide was hydrolyzed to the corresponding acid **4a5** in 82% yield, which can be further transformed into the fluorinated ester **4a6** in 93% yield. When triflic anhydride was employed to activate **4a**, an intramolecular cyclization occurred to deliver the $\alpha$-fluoro ketone **4a7** in 30% yield. In addition, when **4a** was subjected to reductive conditions (LAH), aziridine **4a8** was isolated in 42% yield. This aziridine is presumably formed from the $\beta$-fluoro amine intermediate. Considering the importance and challenge to prepare the *N*-alkyl aziridine,[25] this method provides an alternative pathway to access those structures. Finally, by using Dixon's reductive Strecker protocol,[26] the highly functionalized $\beta$-fluoro-$\alpha$-amino nitrile **4a9** was produced diastereoselectively in 63% yield. The rapid synthesis of diverse fluorine-containing compounds and *N*-alkyl aziridine demonstrates the potential


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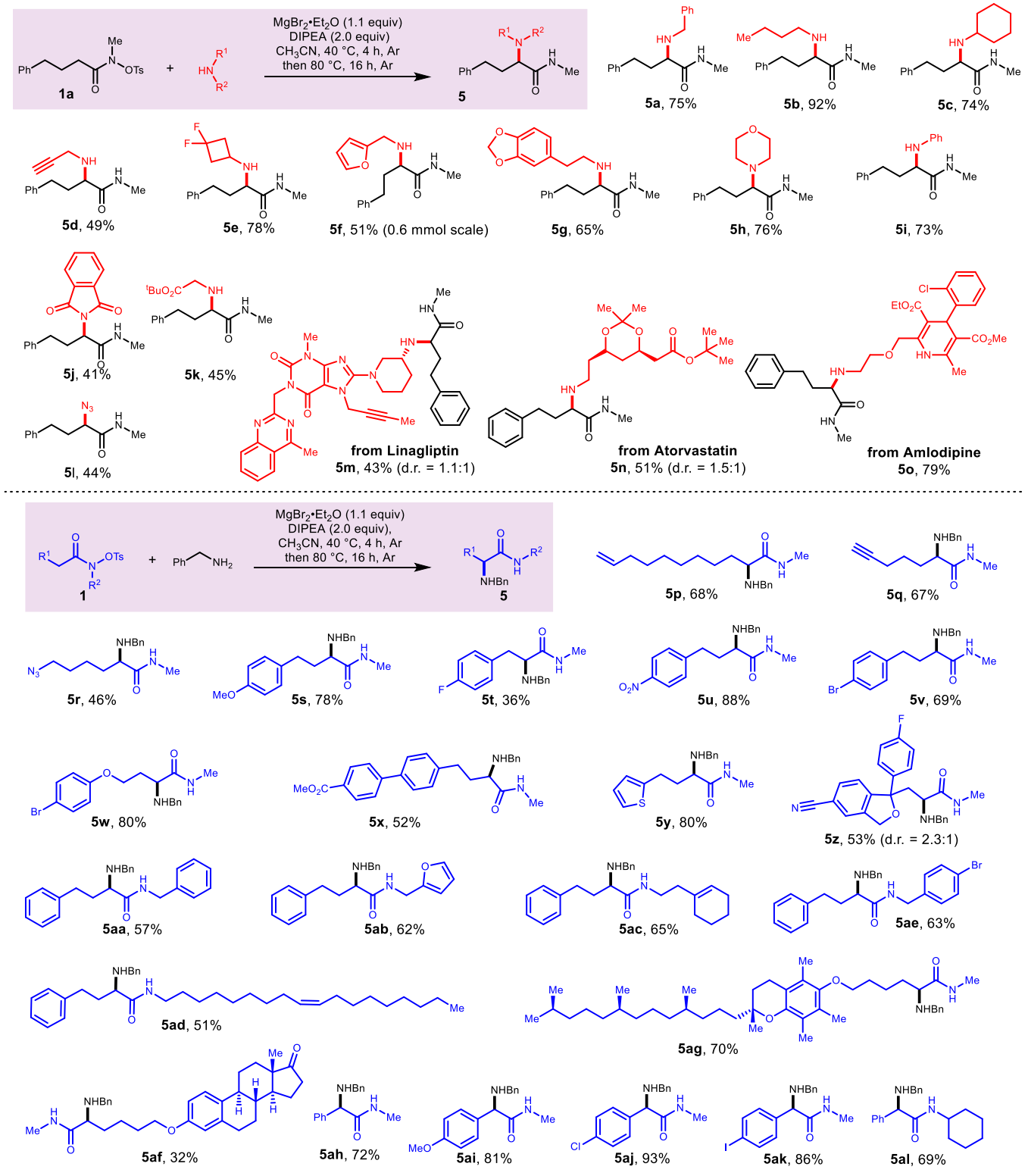


**Figure 7.** Scope of amines (top) and hydroxamates (bottom) of $\alpha$-amination. Conditions: **1** (0.2 mmol), $MgBr_2 \cdot Et_2O$ (1.1 equiv), DIPEA (2.0 equiv), $CH_3CN$, 40 °C, 4 h; then, the corresponding amine (1.5 equiv), $CH_3CN$, 80 °C, 16 h. Please see the Supporting Information for the experimental details. All the yields refer to the yields of pure isolated compounds.

synthetic utility of this fluorination method in organic synthesis.

## Synthesis of $\alpha$-Aminated Amides

$\alpha$-Amino acids are building blocks of enzymes, and they also frequently occur in many natural products and pharmaceuticals. Therefore, incorporating amine functionalities into the $\alpha$-position of carbonyls is particularly important.[27,28] Subsequent to the development of $\alpha$-halogenation, we found that a diverse range of amines also serve as potent nucleophiles to achieve the $\alpha$-amination by reacting with $\alpha$-bromo amide intermediates



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in situ derived from hydroxamates without any additional oxidant (Figure 7, top). A wide range of primary amines (**5a**–**5g**, 49–92%), secondary amine (**5h**, 76%), aniline (**5i**, 73%), phthalimide (**5j**, 41%), amino acid (**5k**, 45%), and azide (**5l**, 44%) proceed well and allow for the rapid synthesis of $\alpha$-aminated amides. Complex amines, such as linagliptin (**5m**), atorvastatin precursor (**5n**), and amlodipine (**5n**), also furnish the desired $\alpha$-amino amides in good yields (43–79%).

With benzylamine as the amino donor, the scope of hydroxamates was also tested (Figure 7, bottom). Numerous hydroxamates with important functional groups are compatible. For example, alkene (**5p**, 68%), alkyne (**5q**, 67%), −azide (**5r**, 46%), $-NO_2$ (**5u**, 88%), −Br (**5v**, 69%; **5w**, 80%), ester (**5x**, 52%), thiophene (**5y**, 80%), and −CN (**5z**, 53%) are all tolerated, and the desired amination products are isolated in good to high yields. Besides the carboxylic acid moiety, the amine motif could be diversified, as well. For instance, benzylamine (**5aa**, 57%; **5ae**, 63%), furan-type amine (**5ab**, 62%), and aliphatic amines with an olefin (**5ac**, 65%; **5ad**, 51%) are feasible substrates. Some natural products with complex functionality do not interfere with the amination process (**5af**, 32%; **5ag**, 70%). Finally, a wide range of aryl acetic acid-derived hydroxamates allow for the synthesis of the $\alpha$-amino amides (**5ah**–**5al**, 69–93%) in good to high yields. The broad scope of the hydroxamates and amines suggests the potential applications of these amination protocols.

### Synthesis of $\alpha$-Oxygen- and Sulfur-Functionalized Amides

In addition to halogen and nitrogen nucleophiles, the developed umpolung protocol can also extend to other heteroatom nucleophiles (Figure 8). Numerous oxygen-based nucleophiles, including phenolate (**6a**, 46%; **6b**, 48%) and carboxylate (**6c**–**6f**, 52–77%), smoothly react with $\alpha$-bromo amide intermediates derived from hydroxamates to form the $\alpha$-oxygen-functionalized amides. It is important to highlight that although an ester or phenyl ether is incorporated at the $\alpha$-positions of carbonyl, the esters can be further hydrolyzed to afford the $\alpha$-hydroxy amides, which are very useful structures.[29] Sulfur-based nucleophiles, including sulfone (**7a**, 58%) and aryl and alkyl thiolate (**7b**–**7d**, 47–67%), also participate in this reaction effectively. In principle, other heteroatom nucleophiles, including −Se, −Te, and −P, may also afford the corresponding $\alpha$-functionalized products via this platform. These examples collectively demonstrate that umpolung $\alpha$-functionalization is a general process.

A general and unified redox-neutral umpolung protocol to synthesize $\alpha$-heteroatom-functionalized secondary amides from hydroxamates is presented. Bromide, chloride, fluoride, nitrogen, oxygen, and sulfur-based nucleophiles have been successfully applied to this platform. Complementary to classical enolate chemistry, this protocol provides an efficient method to access $\alpha$-heteroatom-functionalized amides without relying on strong bases and oxidative electrophiles. Due to mild conditions, various functional groups are tolerated, and the late-stage modification of complex molecules can be achieved. Beyond the synthesis of $\alpha$-heteroatom-functionalized secondary amides, thanks to the versatile reactivity profile of amides, other important functional groups can also be synthesized indirectly, as demonstrated in the section of fluorination (Figure 6). Considering the ready availability of both starting materials, the simple reaction conditions, and the versatility of products, it will be a useful and easily adopted reaction for organic chemists.

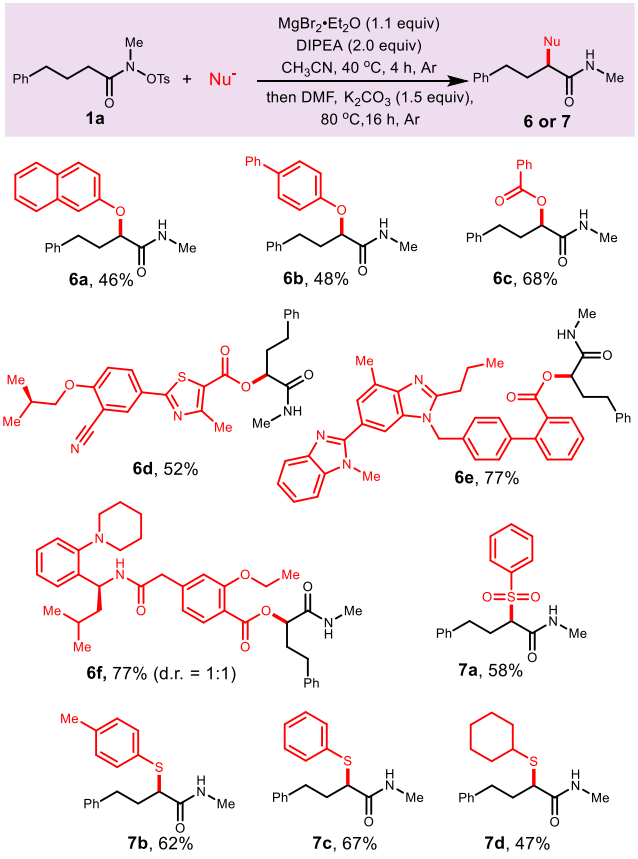


**Figure 8.** Scope of other heteroatom nucleophiles. Conditions: **1a** (0.2 mmol), $MgBr_2{\cdot}Et_2O$ (1.1 equiv), DIPEA (2.0 equiv), $CH_3CN$, 40 °C, 4 h; then, the corresponding nucleophile (1.5 equiv) and $K_2CO_3$ (1.5 equiv), DMF, 80 °C, 16 h. Please see the Supporting Information for the experimental details. All the yields refer to the yields of pure isolated compounds.

## METHODS

### Procedures for the Synthesis of $\alpha$-Br Secondary Amide (2a)

Under an argon atmosphere, *N*-methyl-4-phenyl-*N*-(tosyloxy)-butanamide **1a** (69.4 mg, 1.0 mmol, 1.0 equiv), magnesium bromide ethyl etherate (56.8 mg, 1.1 mmol, 1.1 equiv), 1,2-dichloroethane (1.0 mL), and *N*-ethyldiisopropylamine (38.0 $\mu$L, 1.1 mmol, 1.1 equiv) were added successively to a 10 mL Schlenk tube with a magnetic bar. The sealed tube was then stirred at 40 °C for 4 h. The reaction mixture was washed with $H_2O$ (1.0 mL) and then extracted with dichloromethane (3 × 1.0 mL). After that, the organic phase was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residual was purified by column chromatography on silica gel (gradient eluent: petroleum ether/ethyl acetate = 5:1 to 2:1) to afford 2-bromo-*N*-methyl-4-phenylbutanamide **2a** as a white solid (47 mg, 91% yield).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00767.

Experimental details and characterization data (PDF)



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## AUTHOR INFORMATION


### Corresponding Authors

**Yuan-Ye Jiang** − *Key Laboratory of Catalytic Conversion and Clean Energy in Universities of Shandong Province, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, P.R. China;* orcid.org/0000-0002-4763-9173; Email: yuanyejiang@qfnu.edu.cn

**Wenbo H. Liu** − *School of Chemistry, Sun Yat-sen University, Guangzhou 510006, P.R. China;* orcid.org/0000-0001-8442-2697; Email: liuwb29@mail.sysu.edu.cn

### Authors

**Rui Wang** − *School of Chemistry, Sun Yat-sen University, Guangzhou 510006, P.R. China*

**Shaokang An** − *School of Chemistry, Sun Yat-sen University, Guangzhou 510006, P.R. China*

**Yi-Xuan Xin** − *Key Laboratory of Catalytic Conversion and Clean Energy in Universities of Shandong Province, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, P.R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.4c00767


### Author Contributions

⬢R.W., S.A., and Y.X. contributed equally to this work. R.W. and S.A. performed chemistry experiments. Y.X. and Y.J. performed DFT studies. W.L. conceived the study and prepared the manuscript with the input from other authors. All authors analyzed the data.

### Notes

The authors declare no competing financial interest.

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