Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N–C/O–C Cleavage

Guangchen Li,[†] Chong-Lei Ji,[‡] Xin Hong,[*,‡] and Michal Szostak[*,†]

[†]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States
[‡]Department of Chemistry, Zhejiang University, Hangzhou 310027, China

Supporting Information

ABSTRACT: The amide bond is one of the most fundamental functional groups in chemistry and biology, and plays a central role in numerous processes harnessed to streamline the synthesis of key pharmaceutical and industrial molecules. Although the synthesis of amides is one of the most frequently performed reactions by academic and industrial scientists, the direct transamidation of tertiary amides is challenging due to unfavorable kinetic and thermodynamic contributions of the process. Herein, we report the first general, mild and highly chemoselective method for transamidation of *unactivated* tertiary amides by a direct acyl N–C bond cleavage with non-nucleophilic amines. This operationally-simple method is performed in the absence of transition-metals and operates under unusually mild reaction conditions. In this context, we further describe the direct amidation of abundant *alkyl* esters to afford amide bonds with exquisite selectivity by acyl C–O bond cleavage. The utility of this process is showcased by a broad scope of the method, including various sensitive functional groups, late-stage modification and the synthesis of drug molecules (>80 examples). Remarkable selectivity towards different functional groups and *within* different amide and ester electrophiles that is not feasible using existing methods was observed. Extensive experimental and computational studies were conducted to provide insight into the mechanism and the origin of high selectivity. We further present a series of *guidelines* to predict the reactivity of amides and esters in the synthesis of valuable amide bonds by this user-friendly process. In light of the importance of the amide bond in organic synthesis and major practical advantages of this method, the study opens up new opportunities in the synthesis of pivotal amide bonds in a broad range of chemical contexts.

Introduction

The amide bond is a quintessential functional group in chemical synthesis, biology and drug discovery.[1–3] Because of the importance of amide bonds, the amide bond forming reactions rank as *the* most frequently executed reaction in the synthesis of active pharmaceutical ingredients.[4,5] The central role of amides in natural products, synthetic intermediates and biological and synthetic polymers means that the development of new methods for the synthesis of amides is an important direction in chemical industry.[6–8] Transamidation reactions are particularly promising in this respect as a way to diversify the amide bonds intrinsic to many biologically-active molecules[9] and provide unconventional disconnection for the synthesis of broadly valuable amides.[10]

The high stability of the N–C(O) linkage resulting from $n_N \rightarrow \pi^*_{C=O}$ conjugation has significantly hindered the utility of amides in direct transamidation reactions (Figure 1A).[11–13] The direct transamidation of tertiary amides is extremely challenging due to unfavorable kinetic and thermodynamic contributions of the process.[14] Recent years have witnessed the development of new methods for the construction of amides by transamidation reactions, including ground-state-destabilization that triggers the amide bond towards unconventional N–C(O) cleavage reactivity.[15–17] In these examples, the secondary carboxamide bond is preactivated to kinetically and thermodynamically favor amide exchange reactions.[18] However, in contrast to secondary amides, N-preactivation of the tertiary amide bond is not easily feasible and the N–C(O) linkage suffers from significant steric hindrance around the amide bond, which collectively render the selective transamidation a formidable challenge.

Very few examples of the efficient transamidation of tertiary amides have been reported (Figure 1B). Early studies demonstrated that selective transamidation of tertiary amides under thermodynamic equilibrium conditions is feasible using Al- or Zr-catalysis;[19,20] however, these conditions typically afforded equilibrium mixtures. More recently, a reductive transamidation process mediated by Mn in the presence of phen ligand was developed.[21] Despite being a major advance, this chemistry highlighted a number of limitations, including the necessity for high temperature (120 °C) to overcome the kinetic barrier for transamidation as well as the use of expensive ligands and toxic NMP as a solvent.

A direct amidation of abundant *alkyl* esters using non-nucleophilic amines has only recently begun to be addressed.[22,23] Studies have shown that the direct amidation of esters is feasible using Ni-catalysis.[22] However, this chemistry requires high loading of toxic and air-sensitive transition-metal, extremely high temperatures (140 °C) and is feasible only with more reactive methyl and ethyl esters. Similar to amides, esters can be primed towards high reactivity by ground-state-destabilization that partially overcomes

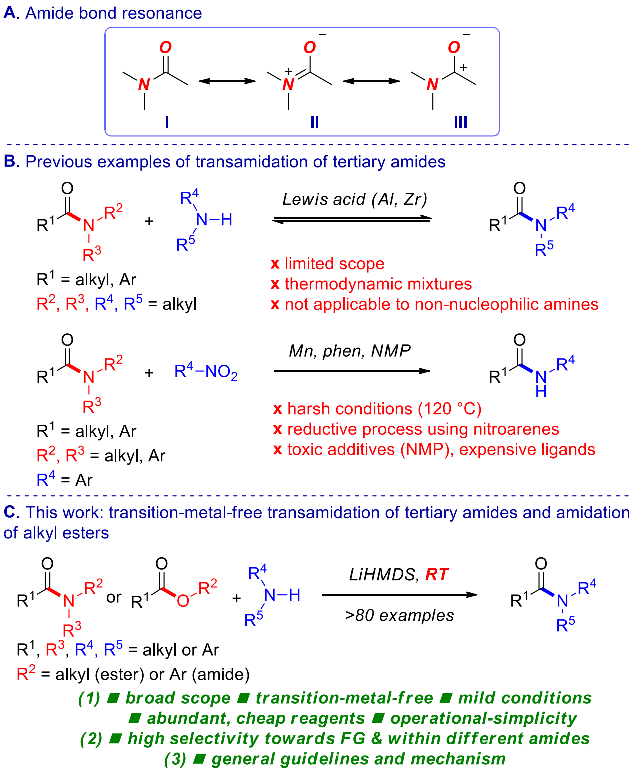


Figure 1. Recent progress in amidation reactions. A. Amide bond resonance prevents facile nucleophilic addition to amides. B. The challenge of transamidation of tertiary amides. C. This study: highly chemoselective, transition-metal-free transamidation of tertiary amides and amidation of alkyl esters.

$n_O \rightarrow \pi^*_{C=O}$ donation.[24] A general and practical approach to ester amidation would involve the use of abundant methyl esters in the more valuable from the environmental and operational standpoint transition-metal-free amidation process.[25,26]

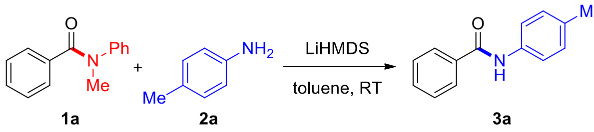
Herein, we report a major advance in the direct synthesis of amides from unactivated amides and esters and report the first general, mild and highly chemoselective method for transamidation of *unactivated* tertiary amides by a direct acyl N–C bond cleavage with non-nucleophilic amines and the direct amidation of abundant *alkyl* esters to afford amide bonds with exquisite selectivity by acyl C–O bond cleavage (Figure 1C). This operationally-simple method is performed in the absence of transition-metals and operates under extremely mild reaction conditions.

In principle, transamidation reactions represent a fundamental chemical process involving interconversion of one amide functional group into another.[1–3] The amide bond is one of the most prevalent functional groups in chemistry, biology and synthetic polymers.[1–5] As a consequence, there has been a major interest from the academic community in transamidation reactions as a mean to prepare amide bonds in synthetic contexts,[9] in functionalization of synthetic polyamides,[32] in dynamic amide exchange reactions[19,20] or in the development of methods for late-stage functionalization of pharmaceuticals.[21] Since the amide group is robust due to amidic resonance, and transamidations are hampered by thermodynamic factors, these reactions typically require harsh conditions or are limited in substrate scope. While the previous studies found that transamidation of tertiary amides requires harsh reaction conditions and is limited in scope, our report demonstrates that these reactions are feasible under much milder and general conditions. This represents a significant contribution to the progress of transamidation reactions of tertiary amides. In addition, our work realized cleavage of the C–O bond in esters to form new C–N amide bond. The classical amidation of esters is limited by substrate reactivity and also requires harsh conditions.[22] Our study reports general and mild conditions for both C–N transamidation and C–O amidation, and as such it supersedes the classical methods for transamidation and amidation reactions. The extensive selectivity and mechanistic studies suggest that it might be possible to execute transamidations with unprecedented selectivity within different classes of amides and develop processes with high group tolerance by transformations of the typically robust amide bond.

There are three features that distinguish our study: (1) unprecedented transamidation and amidation reactions of *unactivated* substrates that offer major practical advantages over existing methods that utilize transition-metals, non-benign additives and require harsh conditions;[15,17,19–21,27] (2) remarkable selectivity towards different functional groups and *within* different amide and ester electrophiles that is not feasible using existing methods;[28,29] (3) extensive studies on the mechanism that provide insight into the reaction mechanism and the origin of high selectivity and establish a set of broadly general *guidelines* for using unactivated amide and ester electrophiles in amidation reactions of key relevance to synthesis, drug discovery and synthetic polymers.[30–33]

Results and Discussion

Our interest in the design of new amide bond forming reactions stems from the premise that traditionally considered inert amide bonds provide a powerful opportunity in the synthesis of valuable molecules by discrete N–C functionalization.[1–3,12,34] Our laboratory has recently applied the amide bond activation paradigm to the design of several previously elusive bond forming reactions of *activated* amides by transition-metal-free and metal-catalyzed pathways.[16,17,35,36] For the outset, we realized that *unactivated* amides could undergo effective bond forming reactions with amine nucleophiles generated under mild conditions. Initial studies were conducted using *N*-methyl-*N*-phenyl benzamide **1a** (eq 1), a less reactive variant of *N*,*N*-diphenyl benzamide used in a recent study that required 120 °C to effect transamidation.[21]



(1)

To our delight, we found that the use of non-nucleophilic 4-toluidine (2.0 equiv) in the presence of LiHMDS (LiHMDS = lithium hexamethyldisilazane, 3.0 equiv) in toluene provided the desired transamidation product in 97% yield on gram scale at ambient conditions, without formation of any byproducts (see Table S3 in the SI for optimization data). The standard method involves charging a reaction vessel with amide, amine, and solvent, followed by a dropwise addition of LiHMDS. It is crucial to note that this reaction proceeds in the absence of toxic transition-metal-catalysts and using a practical bench-top set-up without the need for strict precautions to exclude air (*i.e.* glove-box set-up).[25,26] The use of inexpensive and readily available reagents that are much preferred from the pharmaceutical industry viewpoint[29,30] and the high selectivity for the N–C(O) bond cleavage[17,24] in unactivated tertiary amide confer further benefits on this mild amidation method. Control experiments established the importance of the base, as **2a** was not formed in its absence. Optimal reactivity was observed using LiHMDS with NaHMDS, *n*-BuLi and KHMDS providing inferior results in terms of reaction efficiency and selectivity. Kinetic studies established a remarkably facile transamidation processes at ambient conditions (5 min, >95% conversion), which compares very favorably with the previous limited examples of the direct transamidation of tertiary amides and is consistent with a facile and irreversible transamidation of **1a** (*vide infra*).

With optimal conditions in hand, we next explored the scope of this transamidation (Figure 2). As shown in Figure 2, a remarkably broad array of non-nucleophilic amines and amide electrophiles can serve as suitable substrates. A gamut of functional groups that serve as privileged motifs in medicinal chemistry,[4,5] including ethers, amines, unprotected alcohols, amides and sulfonamides, is tolerated. Furthermore, we found that sterically-hindered anilines leading to valuable N-*ortho*-substituted anilides are readily tolerated. It is noteworthy that ortho-substitution is typically not tolerated in the transition-metal-catalyzed approaches despite harsh reaction conditions, providing another clear benefit of this mild room temperature transamidation. Perhaps most important is the capacity of this method to enable facile transamidation with privileged heterocyclic motifs,[37] including both electron-rich heterocycles, such as carbazoles, and electron-deficient, such as quinolines and pyridines, as well as sensitive to 1,2-cleavage isoxazoles and electronically-deactivated aliphatic amines. It is worthwhile to note a tertiary amide to a tertiary amide interconversion (**3q**). We hypothesize that this reactivity is feasible through different kinetic barriers for the nucleophilic addition to these amides (*vide infra*). Moreover, a variety of amides were explored, including a thorough survey of aliphatic amides. Electronically-varied substitution, steric-hindrance, sensitive halides, polyfluorinated[38] and heterocyclic amides were all well-tolerated. Furthermore, it is important to note that aliphatic amides, including linear, α-branched and sterically-hindered tertiary amides all proved to be suitable substrates, even though metal-catalyzed methods often require time-consuming ligand optimization with aliphatic substrates;[15] note that α-branched aliphatic amides serve as models for radical polymerization/post-polymerization transamidation,[31,32] thus establishing a significant potential of unactivated amides to participate in this process.

Perhaps most remarkable is the potential of this method to transamidate a broad variety of amides, irrespective of the N-substitution (Figure 3). In general, transamidation reactions involving transition metals are limited to a single subset of N-substitution,[15,17] which represents a major synthetic drawback. We were delighted to find that the present method is amenable to a broad range of acyclic amides to afford the transamidation products in high yields. *N*-Alkyl anilides, *N*,*N*-diphenyl amides as well as unactivated *N*,*N*-dialkyl amides resulted in high transamidation selectivity, albeit in latter cases slightly elevated temperatures were required. This selectivity observed in the optimization processes provides a segue to the remarkable chemoselectivity *within* different amides in present transamidation (*vide infra*). Furthermore, alicyclic amides including strained aziridine and azetidine amides as well as five- and six-membered pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, indolinyl and tetrahydroquinolinyl resulted in high selectivity for transamidation. Finally, we note, that *N*,*N*-di-isopropyl benzamide (PhCON*i*-Pr$_2$) was unreactive under our reaction conditions. Complete recovery was observed, which may prove useful in selective transamidations in the presence of this class of amides. Furthermore, alkanamides featuring two *N*-alkyl substituents perform well under our conditions. For example, transamidation of *N*,*N*-dimethyldecanamide with aniline proceeds in 95% yield.

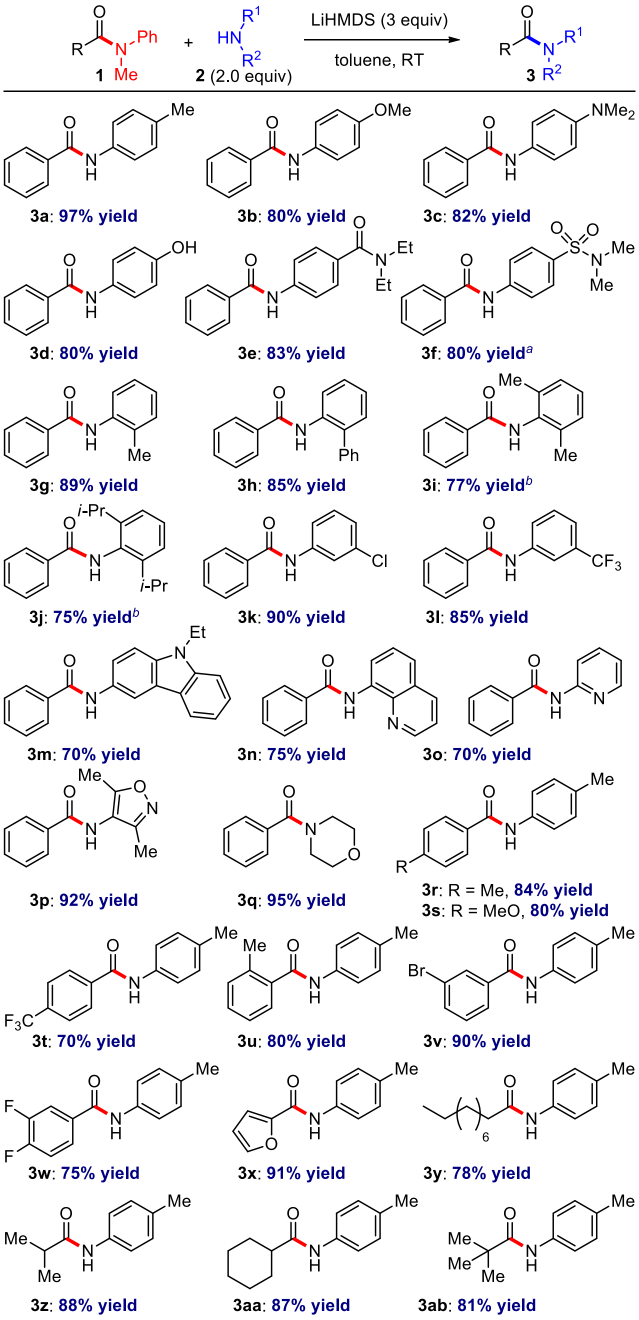


Figure 2. Transition-metal-free transamidation of *N*-alkyl-*N*-aryl amides: reaction scope. Amide (1.0 equiv), 2 (2.0 equiv), LiHMDS (3.0 equiv), toluene (0.25 M), 23 °C, 15 h. Isolated yields. [a]60 °C. [b]2 (3.0 equiv), LiHMDS (4.0 equiv). See SI for details.

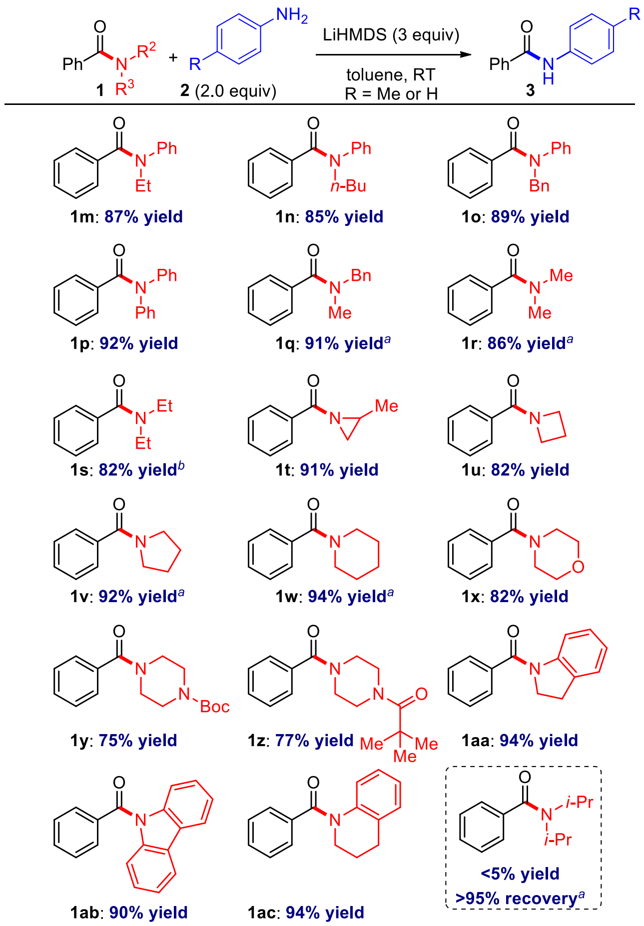


Figure 3. Transition-metal-free transamidation of tertiary amides: amide scope. Amide (1.0 equiv), 2 (2.0 equiv), LiHMDS (3.0 equiv), toluene (0.25 M), 23 °C, 15 h. Isolated yields. [a]60 °C. [b]2 (3.0 equiv), LiHMDS (4.0 equiv), 110 °C. See SI for details.

Overall, the presented examples show the utility of the present transamidation method and illustrate the fact that similar amides are inaccessible by the direct transamidation using other methods. Adding the fact that the method is transition-metal-free, operationally-simple and uses readily-available, non-toxic reagents brings about the environmental and practical benefits that may enable broad application in organic synthesis to produce valuable amides averting potential scale-up or contamination issues.[25,26,29]

Direct amidation of esters. To further enhance the utility of the developed amidation method, we examined the direct amidation of *unactivated* esters (Figure 4). Over the past years, fundamental studies have described the utility of activated aryl esters as electrophiles in selective acyl C–O cleavage mediated by transition-metals.[39] However, the direct amidation of common unactivated *alkyl* esters remains a formidable challenge due to much higher $n_O \rightarrow \pi^*_{C=O}$ isomerization than their aryl counterparts.[18] The application of abundant alkyl esters allows the particularly attractive direct amide bond formation from common ester moieties.[40] We were delighted to find that the proposed amidation of methyl benzoate proceeded in 93% yield on gram scale using aniline (1.2 equiv) and LiHMDS (LiHMDS = lithium hexamethyldisilazane, 2.0 equiv) in toluene at ambient conditions (Figure 4). This process provides the first example of an efficient transition-metal-free approach to amide bond construction from unactivated alkyl esters using non-nucleophilic amines. This result supersedes analogous reactions that require transition-metals, expensive and non-benign additives and harsh reaction temperatures.[22,23]

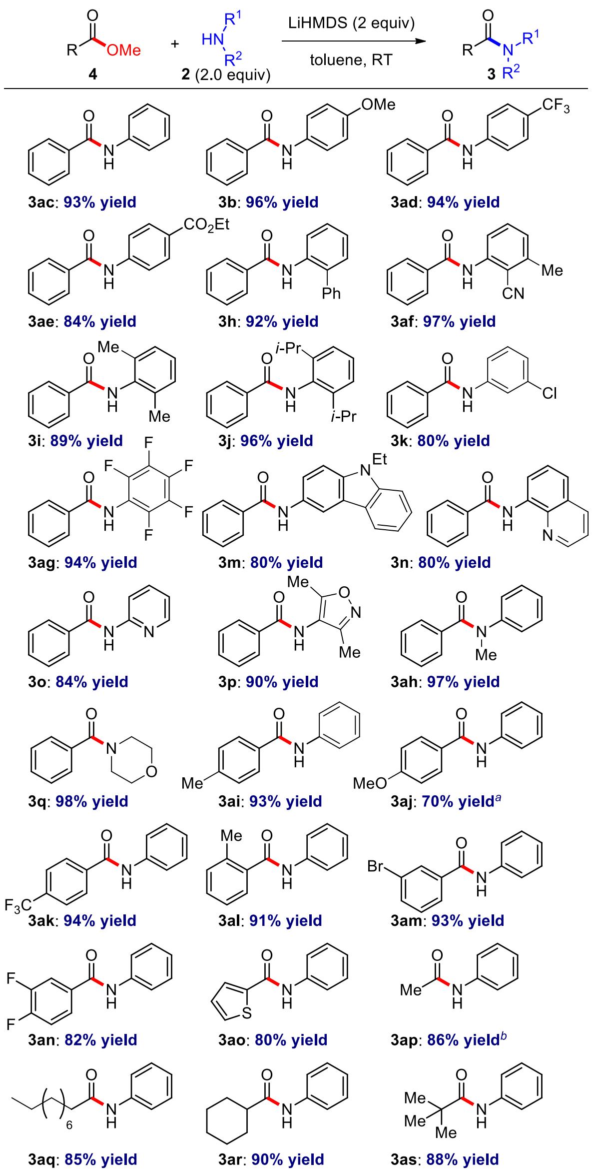


Figure 4. Transition-metal-free transamidation of methyl esters: reaction scope. Ester (1.0 equiv), 2 (1.2 equiv), LiHMDS (2.0 equiv), toluene (0.25 M), 23 °C, 15 h. Isolated yields. [a]2 (3.0 equiv), LiHMDS (3.0 equiv). [b]Using ethyl acetate. See SI for details.

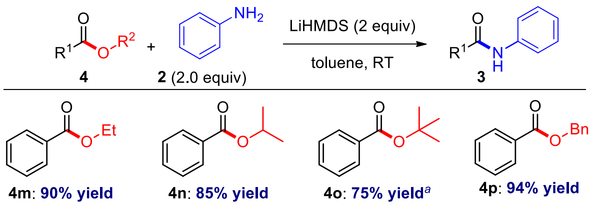


Figure 5. Transition-metal-free transamidation of alkyl esters: ester scope. Ester (1.0 equiv), 2 (1.2 equiv), LiHMDS (2.0 equiv), toluene (0.25 M), 23 °C, 15 h. Isolated yields. [a]2 (3.0 equiv), LiHMDS (3.0 equiv). See SI for details.

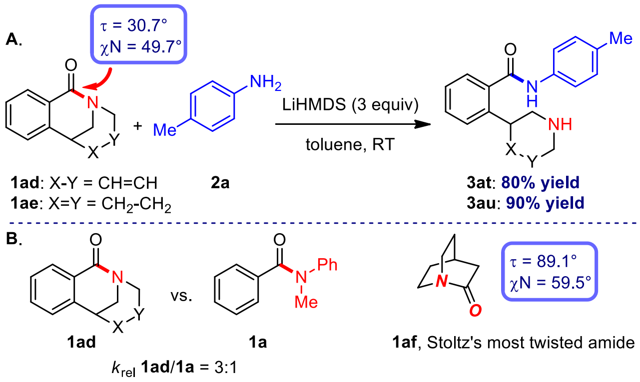


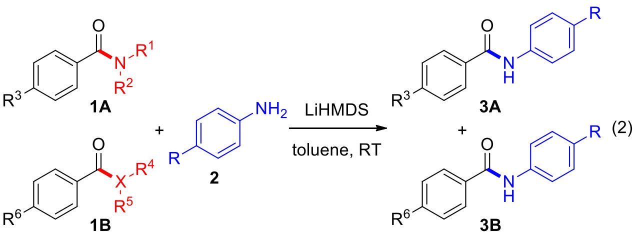
Figure 6. Transition-metal-free transamidation of twisted amides. Amide (1.0 equiv), 2 (2.0 equiv), LiHMDS (3.0 equiv), toluene (0.25 M), 23 °C, 15 h. Isolated yields. See SI for details.

We determined that this transition-metal-free amidation method is remarkably broad in scope and tolerates a wide palette of functionalities, including electronically-differentiated anilines, sensitive electrophilic functional groups, such as esters and nitriles, sterically-hindered anilines, halides, deactivated anilines, medicinally-relevant amines, tertiary amines, deactivated alkyl amines as well as a broad range of alkyl esters, including challenging α-branched and sterically-hindered esters (Figure 4). Perhaps most remarkable is the compatibility with different ester precursors (Figure 5), including prone to the O–C(sp^3) cleavage OBn esters and sterically-hindered *i*-Pr and *t*-Bu esters. Note that these esters are not compatible with related transition-metal-catalyzed approaches,[22] highlighting the unique capacity of the present method to effect amidation reactions under ambient conditions.

Overall, the direct amidation of esters demonstrates that (1) abundant *alkyl* esters can be routinely employed along amides to enable highly chemoselective construction of the amide bond by acyl C–O bond cleavage superseding transition-metal-catalyzed approaches on several levels; (2) the study delineates the concept of reactivity of common *unactivated* amides and esters by kinetically-controlled N–C and O–C cleavage of the acyl group (*vide infra*).

Transamidation of twisted amides. Twisted bridged lactams have attracted intense interest over the decades as the perfect transition-state models of non-planar amide bonds.[1,2,41] Considering the unique capacity of the transition-metal-free transamidation of unactivated amides, we were intrigued to examine the reactivity of model twisted bridged lactams under the reaction conditions (Figure 6). We selected the twisted amide embedded in a 1-azabicyclo[3.3.1]nonan-2-one scaffold, which is well-established in the literature as a model for half-twisted amide bond (τ = 30.7°, χ_N = 49.7°; $\Sigma(\tau+\chi_N)$ = 80.4°).[42] When twisted amide **1ad** was used in the transamidation reaction, the acyclic product corresponding to the selective acyl N–C cleavage was formed in high yield, with products corresponding to the non-selective σ C–N bond cleavage not observed (Figure 6). More importantly, intramolecular competition experiments established that transamidation of the twisted amide **1af** proceeds with a relative rate of 3:1 vs. anilide **1a**. An additional mechanistic probe using the most-twisted Stoltz's amide[2] (τ = 89.1°, χ_N = 59.5°; $\Sigma(\tau+\chi_N)$ = 148.6°) was selected to compare the barriers for nucleophilic addition (*vide infra*). Thus, the study allows to correlate and quantify for the first time the relative reactivity of classic twisted bridged lactams[1,2,41,42] with acyclic non-activated amides[11,12,17] in the extremely valuable acyl addition reactions under transition-metal-free regimen.

Selectivity studies. The transition-metal-free amide exchange reactions of unactivated amides and amidation reactions of esters permit for a remarkable reaction selectivity *within* different classes of amide and ester electrophiles that is not feasible using existing methods. To understand the selectivity difference observed in transition-metal-free amidation reactions, extensive competition studies were conducted between various amides and esters with kinetic differences in N–C and O–C bond cleavage (see SI for details, Table S5). In a typical experiment, two amide, ester or amide/ester electrophiles were reacted with a limiting amount of aniline in the presence of LiHMDS (eq 2).

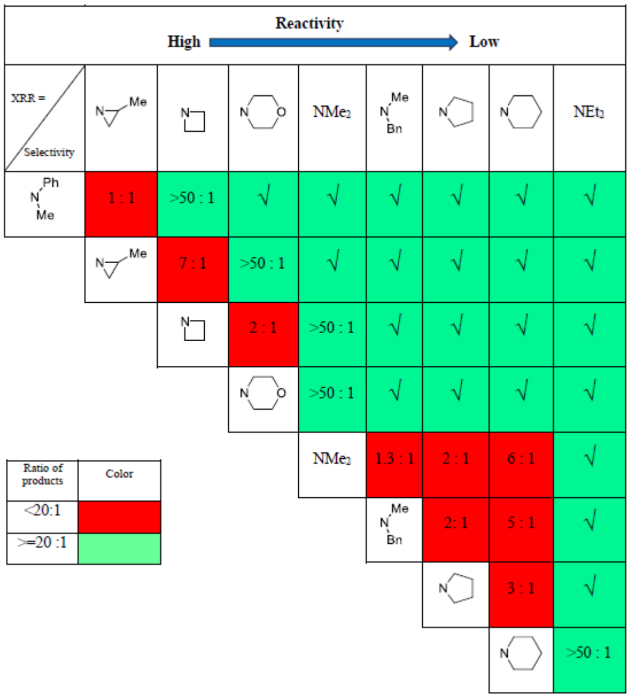


A summary of the chemoselectivity studies is presented in Charts 1-3. Several features of this class of reactions should be noted:

(1) Remarkable selectivity in reactions of unactivated amides (Chart 1). This includes, but is not limited to, (i) full selectivity in reactions of *N*-Ph/Me amides vs. N-morpholinyl amides as well as *N*-Ph/Me amides vs. NMe$_2$ amides; (ii) further, full selectivity is observed in reactions of *N*-morpholinyl amides vs. NMe$_2$ amides; (iii) further, full selectivity is observed in reactions of NMe$_2$ amides vs. NEt$_2$ amides. Collectively, this leads to unprecedented levels of selectivity *within* different amide classes and these experimental findings are supported by energy barriers in the nucleophilic addition reactions to the amide N–C acyl bond (*vide infra*).

(2) High selectivity in reactions of activated secondary amides (i.e. amides in which the nitrogen atom is connected to an electron withdrawing sulfonyl or acyl group)[15,16] versus unactivated esters increasing with an increased steric hindrance of the ester bond (Chart 2). Note that an excellent linear correlation in the reactivity of unactivated esters with the Charton steric parameter has been observed ($Y = 2.2027X + 1.05$, $R^2 = 0.996$, see SI, Figure S1).[43] For comparison, full selectivity is also observed in reactions of activated secondary amides vs. the most reactive unactivated amide, namely, indolinyl amide, favoring the activated counterparts (*vide infra*).

(3) Remarkable selectivity in reactions of activated amides and esters versus unactivated amides (Chart 3). In these cases, exclusive reactivity of the activated amide bond is observed, which is consistent with the nucleophilic addition to the N–C acyl bond *(vide infra)*.



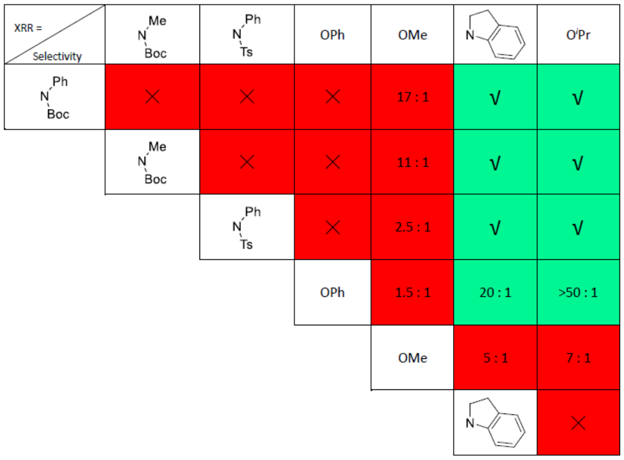
Reactivity

High → Low

XRR = / Selectivity	N Me	N	N O	NMe$_2$	Me N Bn	N	N	NEt$_2$
Ph N Me	1 : 1	>50 : 1	√	√	√	√	√	√
N Me		7 : 1	>50 : 1	√	√	√	√	√
N			2 : 1	>50 : 1	√	√	√	√
N O				>50 : 1	√	√	√	√
NMe$_2$					1.3 : 1	2 : 1	6 : 1	√
Me N Bn						2 : 1	5 : 1	√
N							3 : 1	√
N								>50 : 1

Ratio of products	Color
<20:1	🟥
>=20 :1	🟩

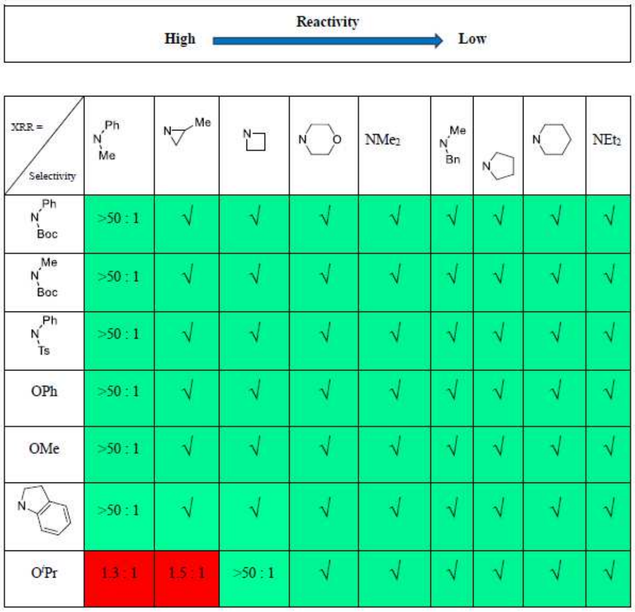
Chart 1. Selectivity in transition-metal-free transamidation of unactivated amides. Note that the selectivity ratios are presented from smallest to largest (i.e. the most reactive amides are shown in the top-left corner).



XRR = / Selectivity	Me N Boc	Ph N Ts	OPh	OMe	N	O^{i}Pr
Ph N Boc	×	×	×	17 : 1	√	√
Me N Boc		×	×	11 : 1	√	√
Ph N Ts			×	2.5 : 1	√	√
OPh				1.5 : 1	20 : 1	>50 : 1
OMe					5 : 1	7 : 1
N						×

Chart 2. Selectivity in transition-metal-free transamidation of activated secondary amides vs. unactivated esters. Note that the selectivity ratios are presented from smallest to largest (i.e. the most reactive amides/esters are shown in the top-left corner).

It should be noted that in addition to the unique selectivity *within* different amide classes, these reactions also show broad functional group tolerance, including moieties that are typically not tolerated under transition-metal-catalyzed conditions, which collectively holds great appeal for the preparation of valuable amide bonds in organic synthesis. Ultimately, the observed reactivity *between* different amides is highly chemoselective[44] and well-poised to find numerous applications in chemical contexts, including sequential and orthogonal amide bond forming processes. The vertical and horizontal axes Charts 1-3 present a comparative summary of the relative reactivity of amide and ester electrophiles in this transformation (*vide infra*).



Reactivity

High → Low

XRR = / Selectivity	Ph N Me	N Me	N	N O	NMe$_2$	Me N Bn	N	N	NEt$_2$
Ph N Boc	>50 : 1	√	√	√	√	√	√	√	√
Me N Boc	>50 : 1	√	√	√	√	√	√	√	√
Ph N Ts	>50 : 1	√	√	√	√	√	√	√	√
OPh	>50 : 1	√	√	√	√	√	√	√	√
OMe	>50 : 1	√	√	√	√	√	√	√	√
N	>50 : 1	√	√	√	√	√	√	√	√
O^{i}Pr	1.3 : 1	1.5 : 1	>50 : 1	√	√	√	√	√	√

Chart 3. Selectivity in transition-metal-free transamidation of activated amides and esters vs. unactivated amides. Note that the selectivity ratios are presented from smallest to largest (i.e. the most reactive amides/esters are shown in the top-left corner).

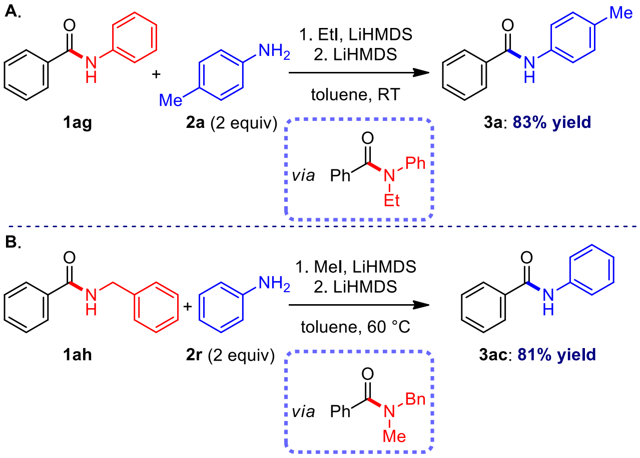


Figure 7. One-pot *N*-activation/transamidation via stable tertiary amides.

Applicability of the direct transamidation and amidation reactions. The immense commercial value of amides stems from their utility as key building blocks throughout organic, medicinal and materials chemistry.[1–3] The present amidation process exploits amide exchange and amidation reactions under exceedingly mild conditions. The common presence of tertiary amides and simple alkyl esters throughout organic synthesis gives them intrinsic advantages as acylating reagents.[4–8] For example, one-pot *N*-activation /amidation is readily feasible (Figure 7). This highly-selective, one-pot process advances simple secondary *N*-alkyl and *N*-aryl carboxamides to amide exchange reactions[19,20] using stable *N*-alkyl linkage; however, note that in these examples, the secondary amide bond still needs to be prepared by established methods. Likewise, the facile amidation of esters permits the use of an alternative disconnection in organic synthesis (Figure 8). Since alkyl esters are obtained from acid-catalyzed esterification or O-alkylation reactions,[40] the present approach circumvents the use of classic acylating reagents or less sustainable coupling partners.

The utility of this process is further highlighted in the rapid diversification of biologically-active products. A pertinent example involves the modification of amide **1ai**, a novel tubulin inhibitor (Figure 9).[45] For comparison, transamidation of **1ai** under previous conditions occurred in 42% yield at 120 °C,[21] clearly demonstrating the practicality and potential of the present method in the production of biologically-active building blocks by amide exchange. It could be readily assumed that this approach might be used for the diversification of libraries of amides for testing biological activity. Likewise, the ester bond is often inherent as a synthetic handle in the preparation of heterocyclic motifs that serve as privileged synthons in drug discovery.[46] The versatility of the present method is illustrated by a rapid preparation of amide analogues from five-membered benzofused heterocycles that rely on α-keto-ester moiety for their synthesis (Figure 10); note that the method is compatible with both acidic NH and extremely sterically-bulky anilines, comparing very favorably with existing amidation methods. It is worthwhile to note that the examples in Figure 10 illustrate the complementary utility of the reaction, wherein esters naturally arise in a synthesis.

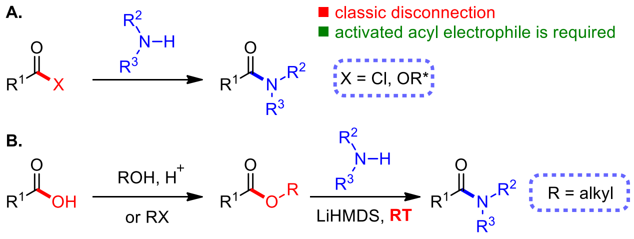


Figure 8. (A) Well-established methods for amidation in organic synthesis. (B) Orthogonal disconnection in amide synthesis.

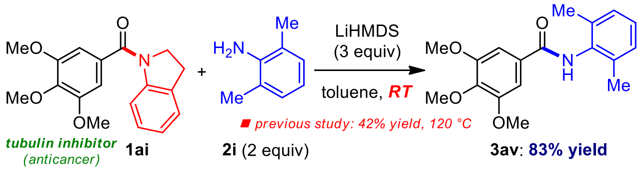


Figure 9. Application in medicinal chemistry: synthesis of tubulin inhibitors by diversification.

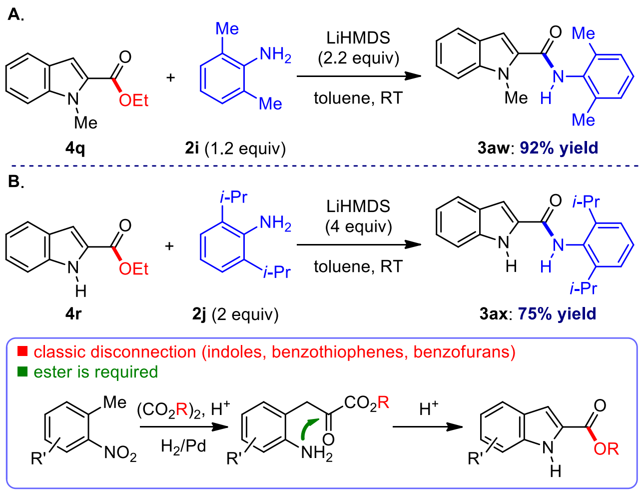


Figure 10. Application in heterocyclic chemistry: esters as a synthetic handle in the synthesis of privileged heterocycles.

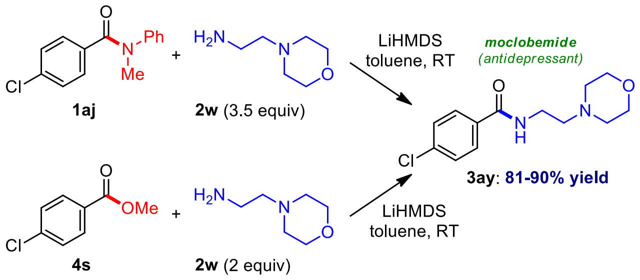


Figure 11. Application in medicinal chemistry: synthesis of moclobemide (antidepressant) from stable tertiary amide and alkyl ester electrophiles.

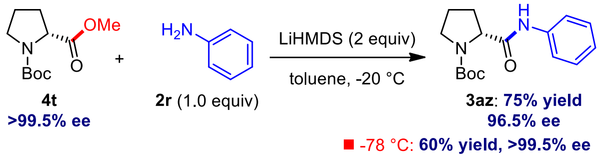


Figure 12. Direct amidation of enantiopure amino acid derivative.

This methodology can also be applied to the synthesis of amide-containing drugs as illustrated by the synthesis of moclobemide, a powerful antidepressant,[30] from either the tertiary unactivated amide or alkyl ester (Figure 11). In this case, the approach avoids the use of wasteful activating reagents, while the high stability of amide and ester linkages could permit for further transformations prior to the amidation step. Pleasingly, we found that these very mild amidation conditions are also well-compatible with direct amidation without significant loss of enantiopurity (Figure 12). It is noteworthy that the present transition-metal-catalyzed approaches require temperatures as high as 140 °C[22], thus clearly showing the inherent benefits of this process. Amidation and alpha-deprotonation represent two competitive reactions. In case of esters, amidation is faster than alpha-deprotonation, thus alpha-deprotonation does not occur to a significant extent under the reaction conditions (Figure 12). In case of amides, alpha-deprotonation is faster than transamidation; in which case racemization occurs under the reaction conditions (*i.e.* the analogous reaction using *N*-methylanilide proceeds with full racemization). An intriguing scenario would involve a ketene intermediate. Indeed, these intermediates have been suggested in hydrolysis of twisted amides.[41] To address this point, we have explored the feasibility of forming a ketene by computations. We found that the formation of ketene is thermodynamically unlikely (*vide infra*). Work is currently in progress to develop transamidations with tolerance for alpha-chiral substrates.

Mechanism studies. We next explored the reaction mechanism and origins of reactivity with density functional theory (DFT) calculations. The DFT-computed free energy profile is shown in Figure 13, using the experimental *N*-Ph/Me amide substrate as model. We found that the dimer **5d** and trimer **5t** of LiHMDS have comparable stabilities, which is consistent with previous literature.[47-50] Therefore, both LiHMDS dimer (blue pathway) and trimer (black pathway) were considered in the reaction mechanism. LiHMDS first deprotonates aniline, leading to the complex with deprotonated aniline anion (**6d** and **6t**). Subsequent complexation with amide generates the intermediates **7d** and **7t**, in which the lithium cation activates amide as a Lewis acid. From **7d** and **7t**, the intramolecular nucleophilic addition is

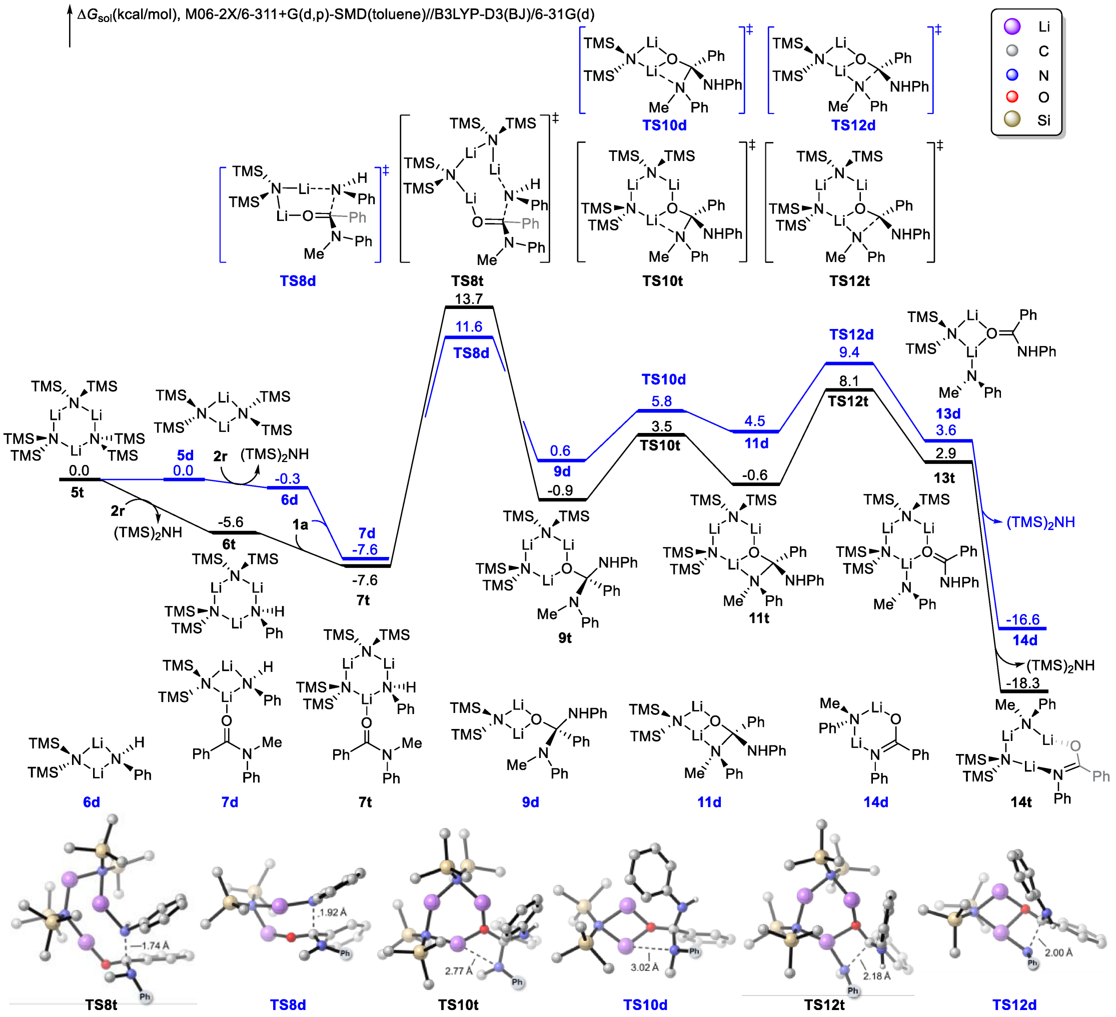


Figure 13. Computed free energy profile of LiHMDS-mediated transamidation. All C–H bonds are hidden for simplicity.

more favorable in the dimer pathway **(TS8d vs. TS8t)**, leading to the C–N bond formation in intermediate **9d**. Subsequent transformations are more favorable in the trimer pathway, which is probably related to the ring strain in the four-membered ring species in the dimer pathway (**9d** to **TS12d**). Thus, **9d** complexes with an additional LiHMDS to the corresponding intermediate **9t**. **9t** isomerizes to **11t**, and subsequent C–N bond cleavage through **TS12t** generates the product-coordinated complex **13t**. **13t** then undergoes a proton exchange to liberate the $(TMS)_2NH$ and form the more stable complex **14t** with amidate anion. We want to emphasize that the formation of the stable amidate anion provides a strong thermodynamic driving force for the overall transformation since the tertiary amide substrate does not contain acidic N-H. Indeed, in some cases we have noticed precipitation of lithium amides from the solution. Based on the computed free energy changes of the overall transformation, the nucleophilic addition via **TS8d** is the rate-limiting step, with a 19.2 kcal/mol barrier (**7d** to **TS8d**). We have also considered the possible pathway involving ketene intermediate for the amides containing α-proton, which is unlikely due to the unfavorable thermodynamics (Scheme S2).

This mechanistic model provides a molecular basis to understand the amide reactivities (Charts 1-3). Figure 14A shows the free energy changes of the rate-determining nucleophilic addition step for the twisted amides **1ad** and **1af**, and the optimized geometries of transition states are included in Figure 14B. The computed barriers indeed corroborate the high reactivities observed in experiments (Figure 6). Comparing the geometric features of the X-ray crystal structures of the two twisted amides,[2,42,51] **1af** is more twisted than **1ad** (τ and χ_N). This leads to the different elongation of the amide C–N bond and the change of resonance stabilization energy (E_R),[52] which explains the higher reactivity of the fully twisted amide **1af** as compared to that of the half-twisted amide **1ad**. These results highlight the important role of geometric twisting on the amide reactivities in the transamidation reaction.

Based on the rate-determining nucleophilic addition step, we further studied the reactivities of a wide array of amides (Figure 14C). The amide reactivities are ranked from the same LiHMDS dimer intermediate **5d**. Both LiHMDS dimer- and trimer-mediated C–N bond formations were considered, and the barrier details are included in the Supporting Information (Table S1). We chose the same intermediate **5d** as the reference to rank the amide reactivities instead of using a distinctive resting state for each amide, because this reactivity ranking reflects the Curtin-Hammett scenario in the experimental measurements. The amide reactivities were determined by the competitions in the same reaction mixture

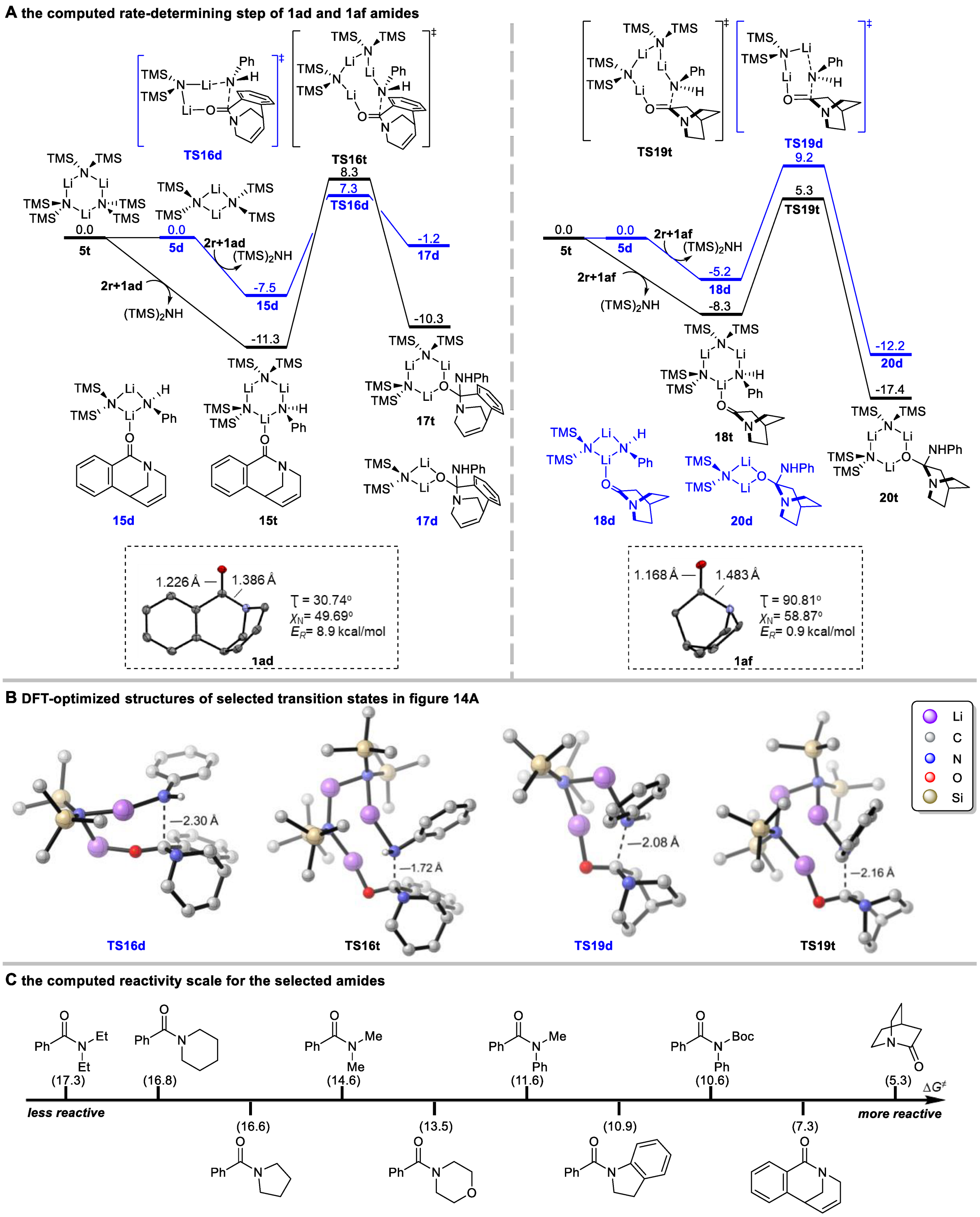


Figure 14. Computed reactivities of selected amides. All free energies in kcal/mol are compared with intermediate **5**. All C–H bonds are hidden for simplicity.

(Charts 1-3). The DFT computed trend agrees well with the experimental observations, which provides a useful guide to rationally utilize the amides in this transformation.[53,54] To provide the information of the intrinsic reactivities of amides, the reactivity ranking using the resting state reference are also included in the Supporting Information (Scheme S4).

In addition to amide, the same reaction mechanism also applies to ester. The DFT-computed free energy changes of the amidation of ester is included in Figure 15, using methyl benzoate as the model substrate. The C–N bond formation between ester and the deprotonated aniline proceeds via the dimer pathway (**TS22d**), leading to the four-membered ring intermediate **23d**. Subsequent transformations proceed via the trimer pathway, eventually generating the complex with amidate anion **28t**. The rate-limiting step is the nucleophilic

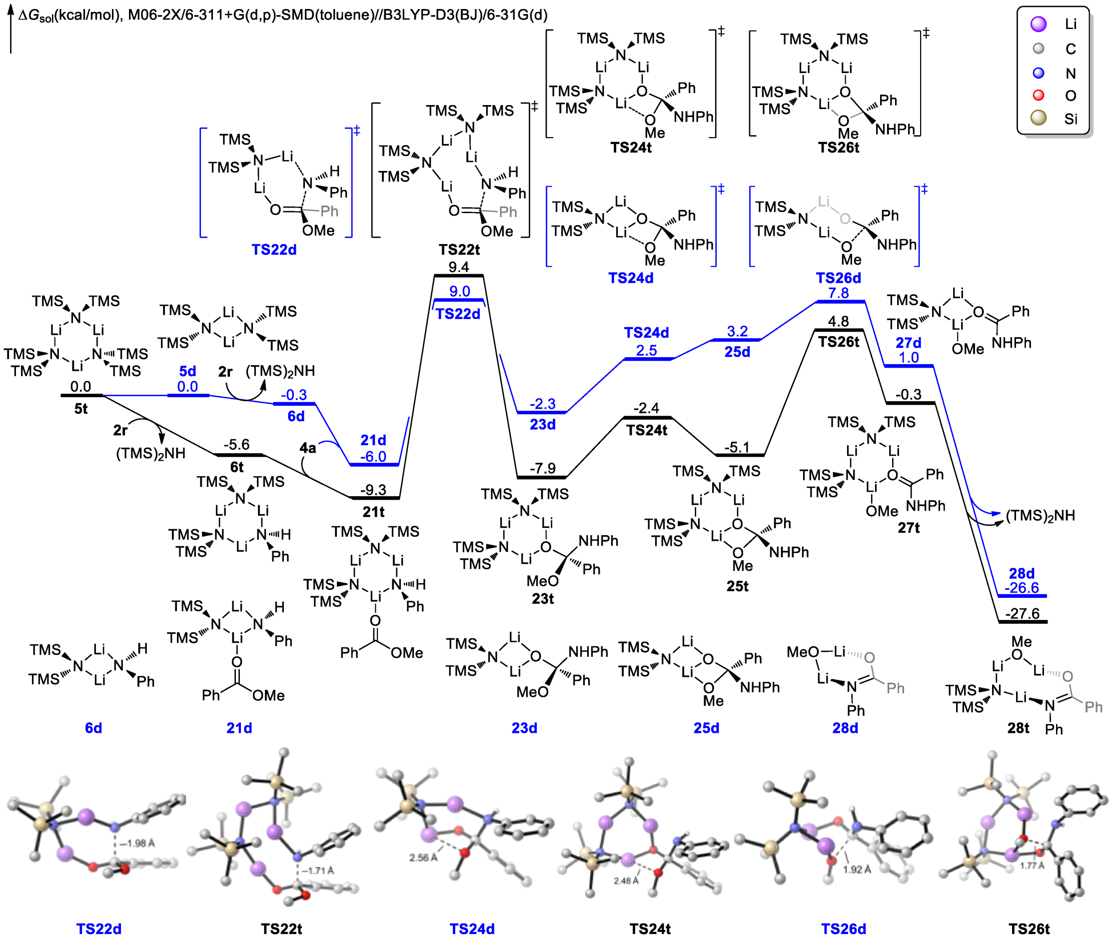


Figure 15. Computed free energy profile of LiHMDS-mediated amidation of ester. All C–H bonds are hidden for simplicity.

addition via **TS22d**, with an overall barrier of 18.3 kcal/mol (**21t** to **TRS22d**).

Conclusion

In summary, we have developed the first general, mild and highly chemoselective method for transamidation of *unactivated* tertiary amides and the direct amidation of abundant *alkyl* esters to afford amide bonds with exquisite selectivity by C–N and C–O bond cleavage. Kinetic control of the amidation process permits for the exceptional chemoselectivity *within* different amide and ester electrophiles that is not feasible using existing methods. The broad utility of this method is illustrated by remarkable functional group tolerance, the synthesis of bioactive agents, late stage diversification and compatibility with chiral amino acid. This amidation process is operationally-simple, obviates the use of transition-metals and operates under exceedingly mild reaction conditions. Extensive computational studies were conducted to provide insight into the reaction mechanism and investigate the origin of the high reaction selectivity. We found that the LiHMDS-mediated nucleophilic addition is the rate-determining step, which differentiates the amide reactivities. Based on the extensive experimental and computational studies, we have provided a set of guidelines to predict the reactivity of amides and esters in the synthesis of valuable amides. Considering the fundamental role of the amide bond in organic synthesis, biochemistry and polymer synthesis, we anticipate that this user-friendly process will be of broad interest in various facets of chemical science. It is anticipated that the powerful roadmap outlined in this study will be applicable to the development of novel resonance-guided transformations of unactivated amide and ester electrophiles.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational results, coordinates, energies of DFT-computed stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

hxchem@zju.edu.cn
michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Rutgers University (M.S.), the NSF (CAREER CHE-1650766, M.S.), NSFC (21702182 and 21873081, X.H.), the Chinese “Thousand Youth Talents Plan” (X.H.), and Zhejiang University (X.H.) for generous financial support. The Bruker 500 MHz spectrometer used in this study was supported by the NSF-MRI grant (CHE-1229030). Calculations were performed on the high-performance computing system at the

Department of Chemistry, Zhejiang University. We thank Mr. Guang Hu, Ms. Melanie Rodriguez and Prof. Stacey Brenner-Moyer (Rutgers University) for assistance with HPLC measurements.

REFERENCES

(1) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, 2003.

(2) Tani, K.; Stoltz, B. M. Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate. *Nature* **2006**, *441*, 731–734.

(3) Pattabiraman, V. R.; Bode, J. W. Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471–479.

(4) Roughley, S. D.; Jordan, A. M. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **2011**, 54, 3451–3479.

(5) Brown, D. G.; Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? *J. Med. Chem.* **2016**, 59, 4443–4458.

(6) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley–VCH: Weinheim, 2011.

(7) Marchildon, K. Polyamides: still strong after seventy years. *Macromol. React. Eng.* **2011**, 5, 22–54.

(8) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991.

(9) Marcia de Figueiredo, R.; Suppo, J. S.; Campagne, J. M. Nonclassical routes for amide bond formation. *Chem. Rev.* **2016**, *116*, 12029–12122.

(10) Loomis, W. D.; Stumpf, P. K. In *Transamination and Transamidation* (*Nitrogen Metabolism*); Allen, E. K., Ed.; Springer: Berlin, 1958.

(11) Pauling, L. *The Nature of the Chemical Bond*; Oxford University Press: London, 1940.

(12) Ruider, S. A.; Maulide, N. Strong bonds made weak: towards the general utility of amides as synthetic modules. *Angew. Chem. Int. Ed.* **2015**, 54, 13856–13858.

(13) Aubé, J. A new twist on amide solvolysis. *Angew. Chem. Int. Ed.* **2012**, *51*, 3063–3065.

(14) Gonzalez-Rosende, M. E.; Castillo, E.; Lasri, J.; Sepulveda-Arques, J. Intermolecular and intramolecular transamidation reactions. *Prog. React. Kinet. Mech.* **2004**, *29*, 311–332.

(15) Baker, E. L.; Yamano, M. M.; Zhou, Y.; Anthony, S. M.; Garg, N. K. A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. *Nat. Commun.* **2016**, *7*, 11554.

(16) Li, G.; Szostak, M. Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature. *Nat. Commun.* **2018**, *9*, 4165.

(17) Shi, S.; Nolan, S. P.; Szostak, M. Well-defined palladium(II)-NHC (NHC = N-heterocyclic carbene) precatalysts for cross-coupling reactions of amides and esters by selective acyl CO–X (X = N, O) cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589–2599.

(18) Liebman, J.; Greenberg, A. The origin of rotational barriers in amides and esters. *Biophys. Chem.* **1974**, *1*, 222–226.

(19) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. Discovery and mechanistic study of Al(III)-catalyzed transamidation of tertiary amides. *J. Am. Chem. Soc.* **2008**, *130*, 647–654.

(20) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. Catalytic transamidation reactions compatible with tertiary amide metathesis under ambient conditions. *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008.

(21) Cheung, C. W.; Ma, J. A.; Hu, X. Manganese-mediated Reductive Transamidation of tertiary amides with nitroarenes. *J. Am. Chem. Soc.* **2018**, *140*, 6789–6792.

(22) Halima, B. T.; Masson-Makdissi, J.; Newman, S. G. Nickel-catalyzed amide bond formation from methyl esters. *Angew. Chem. Int. Ed.* **2018**, 57, 12925–12929.

(23) Cheung, C. W.; Ploeger, M. L.; Hu, X. Direct amidation of esters with nitroarenes. *Nat. Commun.* **2017**, *8*, 14878.

(24) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Reversible twisting of primary amides via ground state N–C(O) destabilization: highly twisted rotationally inverted acyclic amides. *J. Am. Chem. Soc.* **2018**, *140*, 727–734.

(25) Summerton, L.; Sneddon, H. F.; Jones, L. C.; Clark, J. H. *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*; RSC: Cambridge, 2016.

(26) Li, C. J.; Trost, B. M. Green chemistry for chemical synthesis. *Proc. Natl. Acad. Sci.* **2008**, *105*, 13197–13202.

(27) *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Molander, G. A.; Wolfe, J. P.; Larhed, M., Eds.; Thieme: Stuttgart, 2013.

(28) Afagh, N. A.; Yudin, A. K. Chemoselectivity and the curious reactivity preferences of functional groups. *Angew. Chem. Int. Ed.* **2010**, *49*, 262–310.

(29) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Key green chemistry research areas – a perspective from pharmaceutical manufacturers. *Green Chem.* **2017**, *9*, 411–420.

(30) Brunton, L.; Chabner, B.; Knollman, B. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacGraw-Hill: New York, 2010.

(31) Larsen, M. B.; Herzog, S. E.; Quilter, H. C.; Hillmyer, M. A. Activated polyacrylamides as versatile substrates for postpolymerization modification. *ACS Macro Lett.* **2018**, *7*, 122–126.

(32) Larsen, M. B.; Wang, S. J.; Hillmyer, M. A. Poly(allyl alcohol) homo- and block polymers by postpolymerization reduction of an activated polyacrylamide. *J. Am. Chem. Soc.* **2018**, *140*, 11911–11915.

(33) Ramsden, E. *Comprehensive Organic Functional Group Transformations*; Elsevier: Oxford, 2005.

(34) Kaiser, D.; Maulide, N. Making the least reactive electrophile the first in class: domino electrophilic activation of amides. *J. Org. Chem.* **2016**, *81*, 4421–4428.

(35) Meng, G.; Szostak, M. General olefin synthesis by the palladium-catalyzed Heck reaction of amides: sterically-controlled chemoselective N–C activation. *Angew. Chem. Int. Ed.* **2015**, 54, 14518–14522.

(36) Shi, S.; Meng, G.; Szostak, M. Synthesis of biaryls via nickel catalyzed Suzuki–Miyaura coupling of amides by carbon–nitrogen cleavage. *Angew. Chem. Int. Ed.* **2016**, 55, 6959–6963.

(37) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in drugs. *J. Med. Chem.* **2014**, 57, 5845–5859.

(38) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.

(39) Halima, T. B.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Esters. *J. Am. Chem. Soc.* **2017**, 139, 1311-1318.

(40) Otera, J. *Esterification: methods, reactions, and applications*; Wiley: Weinheim, 2010.

(41) Szostak, M.; Aubé, J. Chemistry of bridged lactams and related heterocycles. *Chem. Rev.* **2013**, *113*, 5701–5765.

(42) Greenberg, A.; Venanzi, C. A. Structures and energetics of two bridgehead lactams and their N- and O-protonated forms: an ab initio molecular orbital study. *J. Am. Chem. Soc.* **1993**, *115*, 6951–6957.

(43) Charton, M. The upsilon steric parameter: definition and determination. *Top. Curr. Chem.* **1983**, *114*, 57–91.

(44) Dorr, B. M.; Fuerst, D. E. Enzymatic amidation for industrial applications. *Curr. Opin. Chem. Bio.* **2018**, *43*, 127–133.

(45) Kim, N. D.; Park, E. S.; Kim, Y. H.; Moon, S. K.; Lee, S. S.; Ahn, S. K.; Yu, D. Y.; No, K. T.; Kim, K. H. Structure-based virtual screening of novel tubulin inhibitors and their characterization as antimitotic agents. *Bioorg. Med. Chem.* **2010**, *18*, 7092–7100.

(46) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Wiley-Blackwell: Oxford, 2010.

(47) Rogers, R. D.; Atwood, J. L.; Grüning, R. The crystal structure of N-lithiohexamethyldisilazane. *J. Organomet. Chem.* **1978**, *157*, 229–237.

(48) Lucht, B. L.; Collum, D. B. Lithium ion salvation: amine and unsaturated hydrocarbon solvates of lithium hexamethyldisilazide (LiHMDS). *J. Am. Chem. Soc.* **1996**, *118*, 2217–2225.

(49) Pratt, L. M.; Streitwieser, A. A computational study of lithium enolate mixed aggregates. *J. Org. Chem.* **2003**, *68*, 2830–2838.

(50) Details of computed LiHMDS dimer/trimer equilibrium are included in the Supporting Information (Scheme S1)

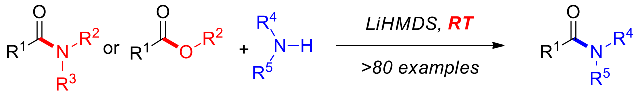
(51) Hu, F.; Lalancette, R.; Szostak, M. Structural characterization of N-alkylated twisted amides: consequences for amide bond resonance and N–C cleavage. *Angew. Chem. Int. Ed.* **2016**, 55, 5062–5066.

(52) The computational details of resonance stabilization energy are provided in the Supporting Information (Scheme S3).

(53) For additional studies on the mechanism, see the Supporting Information.

(54) For additional studies, see: (a) Noshita, M.; Shimizu, Y.; Morimoto, H.; Akai, S.; Hamashima, Y.; Ohneda, N.; Odajima, H.; Ohshima, T. Ammonium-Salt Accelerated Hydrazinolysis of Unactivated Amides: Mechanistic Investigation and Application to a Microwave Flow Process. *Org. Process Res. Dev.* **2019**, *23*, 588-594. (b) Yu, S.; Shin, T.; Zhang, M.; Xia, Y.; Kim, H.; Lee, S. Nickel/Briphos-Catalyzed Direct Transamidation of Unactivated Secondary Amides Using Trimethylsilyl Chloride. *Org. Lett.* **2018**, *20*, 7563-7566.

Highly chemoselective transamidation of 3° amides and amidation of alkyl esters



R^1 = alkyl, Ar; R^2, R^3 = alkyl, Ar (amide)

R^2 = alkyl (ester); R^4, R^5 = alkyl, Ar

(1) ■ broad scope ■ transition-metal-free ■ mild conditions
■ abundant, cheap reagents ■ operational-simplicity
(2) ■ high selectivity towards FG & within different amides
(3) ■ general guidelines and full mechanism