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Research Article

Tungsten-Catalyzed Transamidation of Tertiary Alkyl Amides

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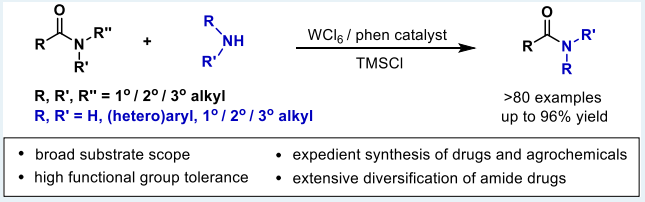
ABSTRACT: Transamidation has recently emerged as a straightforward and convenient means to diversify amides. However, the kinetically and thermodynamically demanding transamidation of notoriously robust, fully alkyl-substituted tertiary amides still remains a longstanding challenge. Here, we describe a method for the activation of tertiary alkyl amides to streamline transamidation using simple tungsten(VI) chloride as a catalyst and chlorotrimethylsilane as an additive. The highly electrophilic and oxophilic tungsten catalyst enables the selective scission of a C−N bond of tertiary alkyl amides to effect transamidation of a myriad of structurally and electronically diverse tertiary alkyl amides and amines. Mechanistic study implies that the synergistic effect of the catalyst and the additive could pronouncedly induce the nucleophilic acyl substitution of tertiary alkyl amide with amine to realize transamidation.



KEYWORDS: *transamidation, C−N activation, tertiary alkyl amide, amide, tungsten catalysis*

1. INTRODUCTION

Amides,[1] including fully alkyl-substituted tertiary amides (i.e., tertiary alkyl amides[2] (Scheme 1a)), are prevalent chemical feedstocks and omnipresent structural motifs in natural products, pharmaceuticals, and agrochemicals. Notwithstanding the exceeding robustness of an amide C−N bond,[3−5] amides are attractive compounds for chemical transformations owing to their abundance, versatility, and stability. Over the past decade, the amide C−N bond cleavage has been efficiently achieved by harnessing suitable catalysts and activation protocols, offering a valuable synthetic disconnection for chemical transformations.[6] Among these, a transamidation reaction has emerged as a reliable route for amide diversification.[4,6g,h] Whereas amides are most commonly accessed via the amidation of carboxylic acids, transamidation could be a more striking synthetic alternative in chemical and industrial settings: (1) transamidation is a more straightforward and telescoped strategy to diversify amides, obviating the multistep practice via amide hydrolysis, activation, and coupling steps that can be incompatible with sensitive functional groups; (2) when amide feedstocks are achievable or more economic than the acid counterparts, transamidation is more expedient or cost effective for amide production; and (3) transamidation represents a valuable synthetic handle to upcycle the less potent or unused amides to other variety of amides of interest in drug and agrochemical discoveries.

Transamidation has been inherently challenging owing to the kinetically unfavorable and typically thermoneutral transformation governed by the stability and robustness of an amide C−N bond.[3−5,7] While the general transamidation of primary[8] and secondary[9] amides could be driven by the formation of ammonia gas or by preactivation of the amide C−N bonds, the transamidation of tertiary amides is most challenging owing to their steric bulkiness around the C−N bond and the lack of an activation site on the nitrogen atom.[10] Current transamidation strategies rely on the use of electronically or sterically biased tertiary amides, including small-sized dimethylformamide and dimethylacetamide[11] (Scheme 1b-i), activated benzamides and *N*-aryl amides[10,12] (Scheme 1b-ii), and unconventional twisted amides[6h,13] (Scheme 1b-iii), which either reduce the activation barriers or destabilize ground-state energies to enable transamidation. Fully alkyl-substituted tertiary amide, however, is deemed to be the most robust and chemically stable amide, as dictated by its formally planar architecture, highest C(acyl)−N rotation energy, and lowest carbonyl electrophilicity.[14] The electron-donating nature of the three alkyl moieties probably further mitigate the reactivity of tertiary alkyl amides toward oxidative addition or nucleophilic acyl substitution, the two characteristic amide C−N cleavage patterns in transamidation. Whereas Stahl, Gellman, and co-workers engaged Al-amido[7c] and Zr-amido[7d] complexes to catalyze the transamidation of tertiary alkyl amides (Scheme 1b-iv, top), the formation of an equilibrium mixture of amides and limited substrate scope remain unaddressed. Furthermore, transamidation of tertiary alkyl amides with less nucleophilic aromatic amines is an uphill reaction,[5] further hampering the general utility of transamidation of tertiary amides in organic synthesis.

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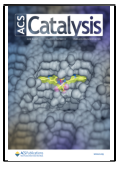
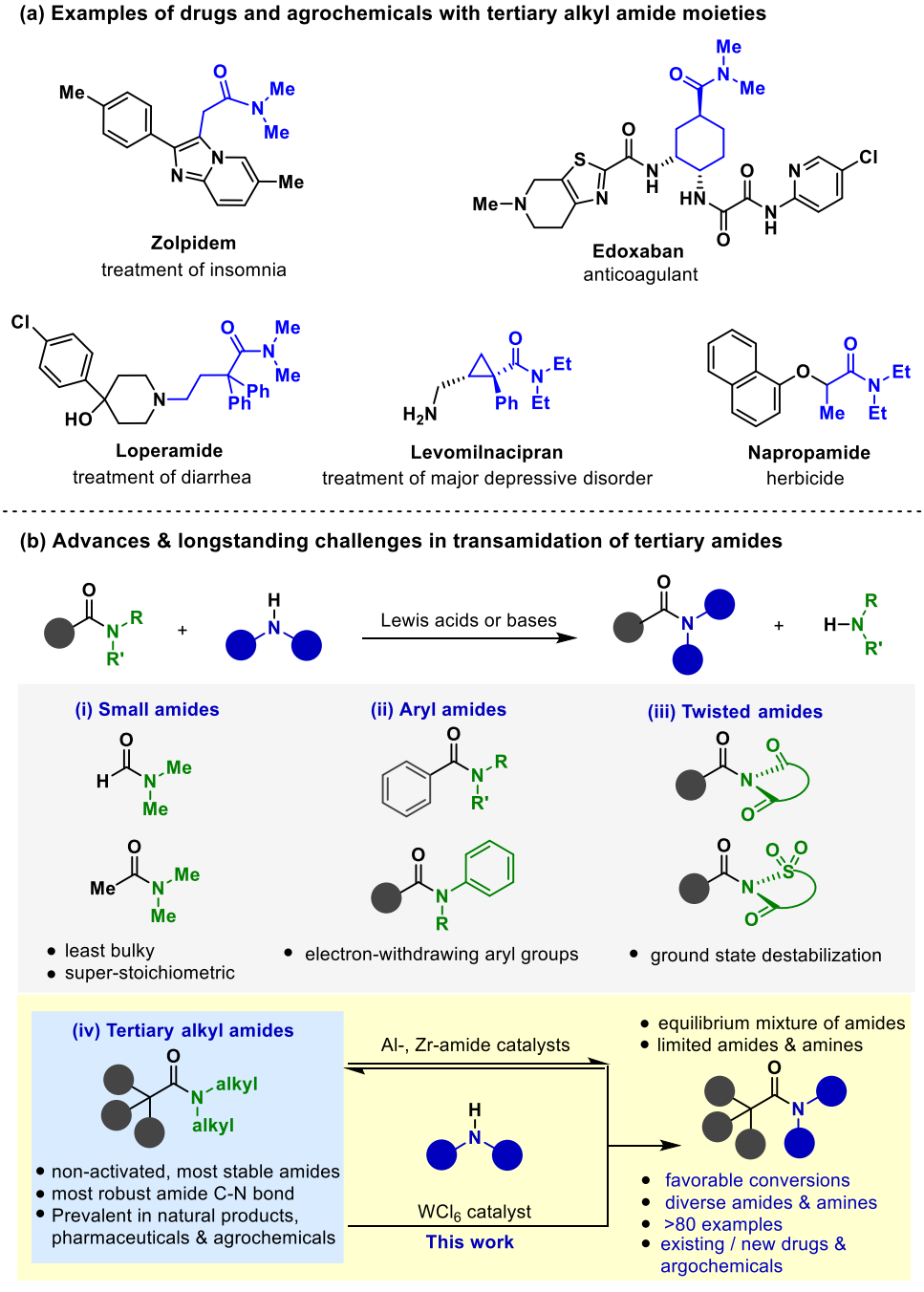


Scheme 1. Development of General Transamidation of Tertiary Alkyl Amides



Given the ubiquity of diversely functionalized tertiary alkyl amides and amines in chemical feedstocks, biologically active molecules, drugs, and agrochemicals, a unified transamidation method based on these two functionalities would offer an appealing and practical toolkit to expediently broaden the spectrum of amides. As inspired by the remarkable electrophilicity and oxophilicity of tungsten(VI) chloride (WCl_6) that is capable of facilely activating the carbonyl groups of carboxylic acids and their derivatives for chemical transformations,[15−17] we hypothesized that such a W-mediated activation strategy would be viable to activate the most robust tertiary alkyl amides to trigger transamidation. Herein, we describe the development of a modular transamidation method based on abundant tungsten[18] as a catalyst (Scheme 1b-iv), bottom). A wide range of variegated tertiary alkyl amides and amines, particularly aromatic amines, can be employed to offer new amides. The utility of this protocol is showcased by the shortened and upcycling routes to access existing or novel drugs and agrochemicals.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization. To testify the hypothesis, we employed *N*,*N*-diethyl 4-phenylbutanamide **A1** and aniline **B1** as model substrates to study the transamidation (Table 1). Chlorotrimethylsilane (TMSCl) was utilized as a Lewis acid additive to activate amides as well as for transformations.[19] The use of 20 mol % WCl_6 in association with a phenanthroline ligand (**L1**) as a catalytic system and TMSCl

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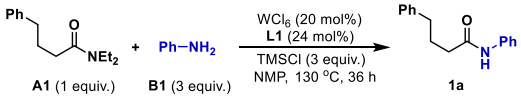
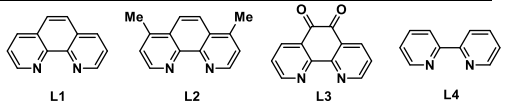
Table 1. Optimization of Catalytic Transamidation of Tertiary Alkyl Amide[a]



Entry	Deviation from above	Yield/%[b]
1	none	68
2	$AlCl_3$	12
3	$FeCl_3$	trace
4	$ZrCl_2$	10
5	$MoCl_5$	11
6	**L2 / L3 / L4**	59/51/48
7	no WCl_6	0
8	no **L1**	trace
9	no TMSCl	20
10	Optimal conditions[c]	90

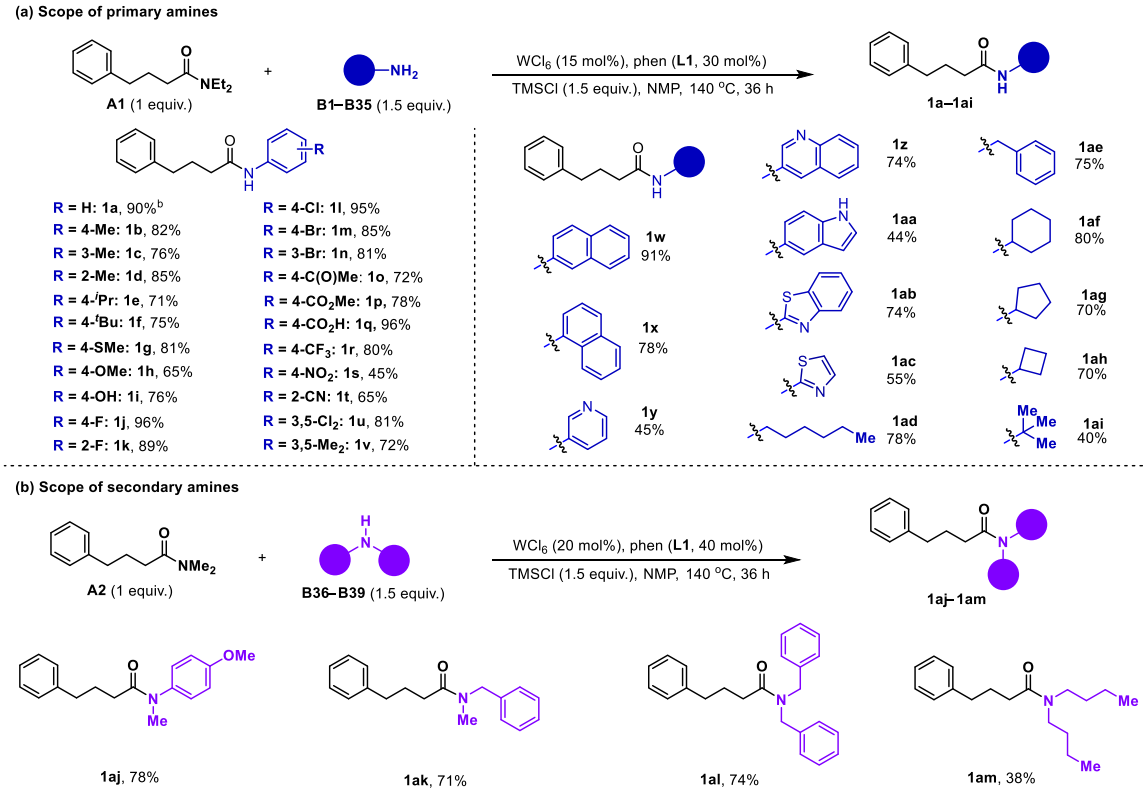


[a]Reaction conditions: **A1** (0.2 mmol, 1 equiv), **B1** (0.6 mmol, 3 equiv), WCl_6 (0.04 mmol), **L1** (0.048 mmol), TMSCl (0.6 mmol), NMP (2 mL), an argon atmosphere, 130 °C, and 36 h. [b]Isolated yield. [c]**A1** (1 equiv), **B1** (1.5 equiv), WCl_6 (15 mol %), **L1** (30 mol %), TMSCl (1.5 equiv), and 140 °C.

as an additive was feasible, effecting the transamidation in a *N*-methylpyrrolidone (NMP) solvent at 130 °C to give the transamidated product **1a** in a 68% yield (entry 1). Various Lewis acid metals previously employed in transamidation (e.g., Al, Fe, Zr) or alternative group VI metals (e.g., $MoCl_5$) did not catalyze this reaction (entries 2–5 and Table S1 in the Supporting Information (SI)). Likewise, lower yields were obtained when other nitrogen and phosphine ligands were used (entry 6 and Table S2 in the SI). When WCl_6 or **L1** was omitted, the product formations were negligible (entries 7 and 8), revealing that the **L1**-ligated W complex likely serves as a catalyst. In the absence of TMSCl, the transamidated product **1a** was formed in a 20% yield, suggesting that TMSCl is indeed requisite for amide activation (entry 9). The optimal transamidation conditions, upon meticulous screening, were identified to give amide **1a** in a 90% yield, involving the use of 1.5 equiv of aniline and TMSCl, 15 mol % WCl_6, 30 mol % **L1**, and reaction temperature of 140 °C (entry 10 and Table S3 in the SI).

2.2. Scope of Transamidation. The transamidation protocol proved to be general. A vast number of substituted and functionalized primary aromatic and aliphatic amines (**B1**–**B35**) could be employed to react with *N*,*N*-diethyl-4-phenylbutanamide **A1** to afford the corresponding amides **1a**–**1ai** (Scheme 2a), irrespective of the numbers, positions, and electronic and steric properties of the substituents. It is worth noting that anilines containing protic hydroxy (**1i**) and carboxylic acid (**1q**) groups and other functional groups prone to nucleophilic substitution or addition with amines [fluoro (**1j, 1k**), chloro (**1l**), bromo (**1m, 1n**), keto (**1o**), ester (**1p**), and nitrile (**1t**)] were all tolerated without noticeable diminishment in yields. Naphthyl (**1w, 1x**) and heterocyclic amines (**1y**–**1ac**) were also suitable reaction substrates. Interestingly, the aniline moiety reacted solely without engaging indolyl N–H (**1aa**), demonstrating the superior

Scheme 2. Scope of Amines in Transamidation of Tertiary Alkyl Amides[a,b]



[a]All reactions were conducted based on 0.5 mmol tertiary amide substrates **A**. [b]Reaction based on 0.2 mmol **A1**.

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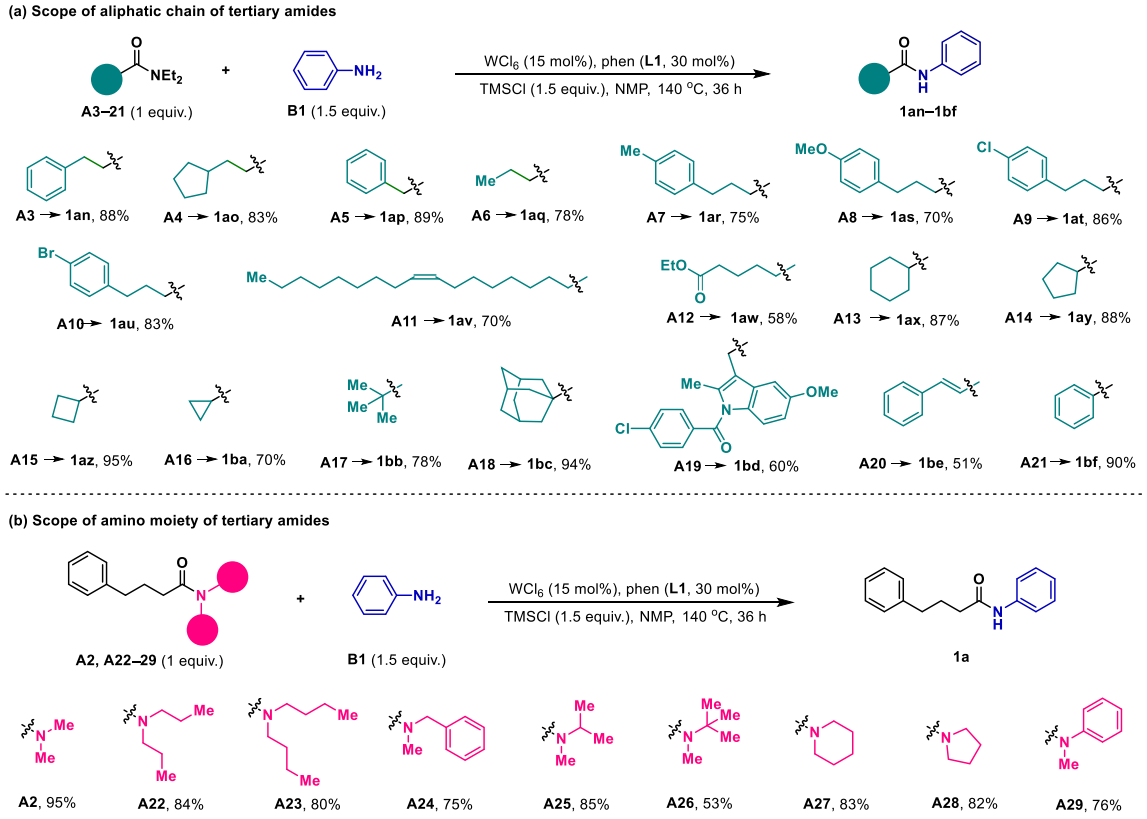
Scheme 3. Scope of Tertiary Alkyl Amides in Transamidation[a]



[a]All reactions were conducted based on 0.5 mmol tertiary amide substrates **A**.

chemoselectivity for transamidation. The results showcased the unprecedented broad scope of aniline derivatives in transamidation with tertiary alkyl amides. Additionally, acyclic and cyclic primary aliphatic amines could also be employed for transamidation to form the corresponding amides **1ad**−**1ai**, wherein the eminently bulky *tert*-butyl amine remained reactive to afford the product **1ai** in a 40% yield. The more bulky secondary amine substrates, such as *N*-methyl anilines and *N*,*N*-dialkyl amines (**B36**−**B39**, Scheme 2b), could participate in the transamidation with *N*,*N*-dimethyl 4-phenylbutanamide **A2** as well to give the corresponding amides **1aj**−**1am** in 38−78% yields.

Next, we studied the scope of tertiary alkyl amides. When the *C*-alkyl skeletons of amides (**A3**−**A18**, Scheme 3a) were substituted with primary, secondary, and tertiary alkyl groups, the transmidation proceeded smoothly to furnish amides **1an**−**1bc** in good to excellent yields. Likewise, the functional groups on amides, such as chloro (**A9**), bromo (**A10**), alkene (**A11**), and ester (**A12**), remained intact without reacting with amines. It is worth noting that tertiary amide derived from inflammatory drug indomethacin (**A19**) underwent the transamidation chemoselectively to give **1bd** without interfering with the more electron-deficient *N*-acyl indolyl amide linkage. Cinnamide and benzamide, a class of activated amides, were also suitable substrates in this manifold (**A20** and **A21**). Furthermore, the steric pattern of *N*-substitutions on tertiary amides displayed an unmeasurable effect on transamidation (Scheme 3b). Tertiary amides derived from symmetric or unsymmetric *N*-methyl (**A2**), -propyl (**A22**), -butyl (**A23**), -benzyl (**A24**), -isopropyl (**A25**), and -*tert*-butyl (**A26**) amines, as well as pyrrolidine (**A27**) and piperidine (**A28**), collectively reacted smoothly to afford the transamidated products in generally high yields. As expected, the activated *N*-aryl tertiary amide (**A29**) also transamidated equally well.

Taken together, this W-catalyzed transamidation protocol is general, tolerates wide-ranging tertiary alkyl amides and amines, and is insensitive to the electronics and sterics of the reaction substrates to achieve amide diversification.

2.3. Synthetic Utility. Transamidation is still an underrepresented reaction in pharmaceutical and agrochemical settings compared with the condensation reaction of carboxylic acids with amines. Thus, we sought to explore the potential utility of this transamidation for the synthesis of biologically active molecules. Piperine-derived amides have shown promising activities in medicinal chemistry, as exemplified by the free radical scavenger and α-glucosidase inhibitor **2a**[20] as well as the antianxiolysis agent **2b**[21] (Scheme 4a). Previously, they were prepared via the hydrolysis of piperine to piperic acid followed by the subsequent activation and coupling with amine, or alternatively, by subjecting the commercially more costly piperic acid to amidation. Our protocol directly harnessed the inexpensive piperine for transamidation to access **2a** and **2b** in 60% and 48% yields, respectively, providing a step-economical and cost-efficient route for drug synthesis.

Recently, Maulide and co-workers employed readily available tertiary alkyl amide **3** to access a fluorinated variant of an antidepressant drug citalopram[22] (Scheme 4b). Likewise, we were able to engage **3** in transamidation with various anilines and alkylamines to afford the citalopram variants **4a**−**4c**. Zolpodem, a hypnotic drug, could also be transformed to an aniline-derived variant **5** (Scheme 4c). These amide drug

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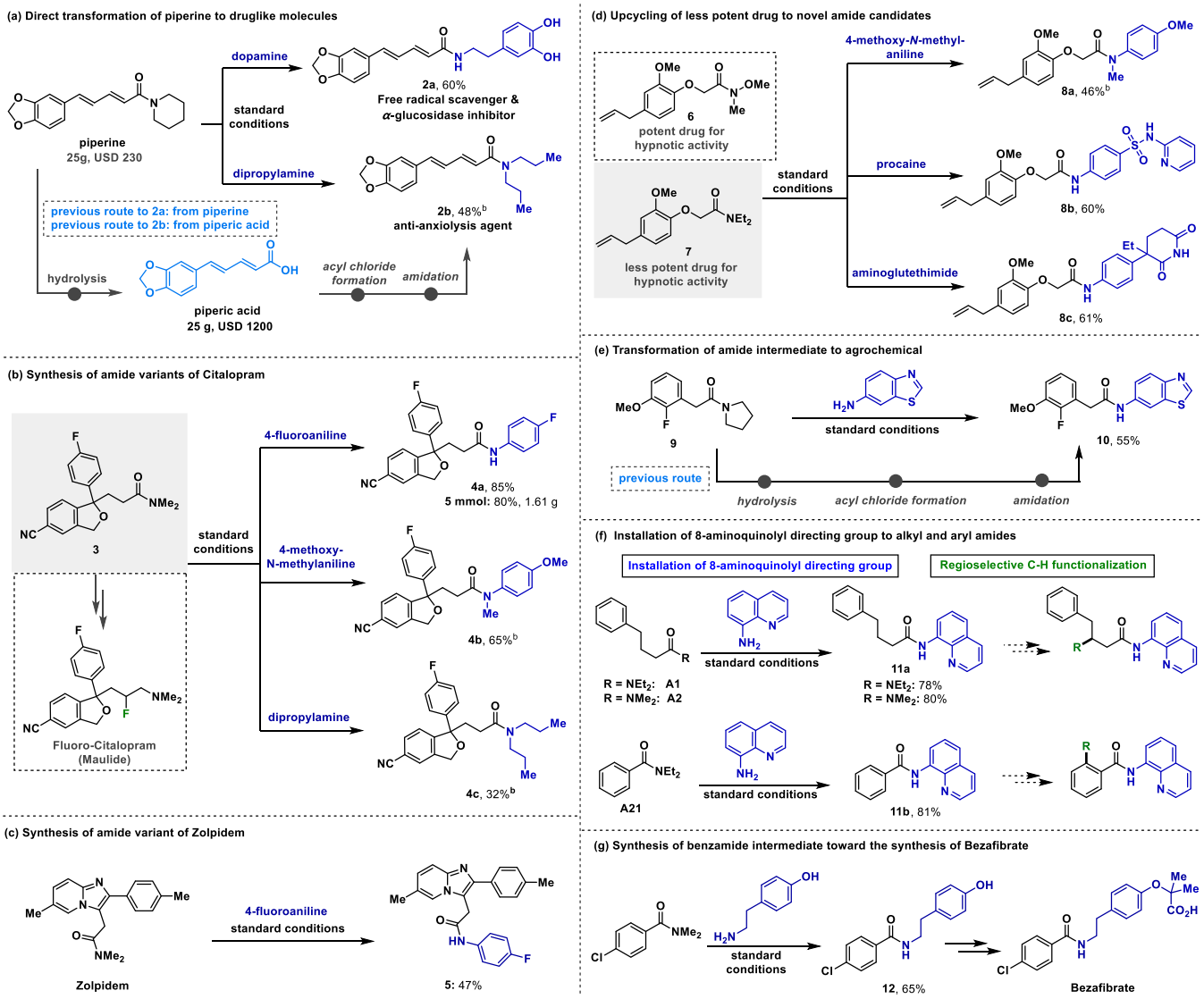
Scheme 4. Synthetic Utility of Tungsten-Catalyzed Transamidation[a,b]



[a]All reactions were conducted based on 0.5 mmol tertiary amide substrates. [b]WCl_6 (20 mol %) and **L1** (40 mol %) were used.

variants could be readily accessible for biological study. The transamidation was also amenable for gram-scale synthesis of **4a** in an 80% yield without remarkable erosion of the yield, implicating the possible utility in process chemistry.

In drug discovery, only several amides are eventually employed as the most potent drugs upon screening a vast number of structurally analogous amides. The one-step upcycling of less potent amides to other novel amide candidates would aid in speeding up the drug discovery process and minimizing the chemical waste generation, especially when the preparation of amide precursors is nontrivial. For instance, *N*-methoxy-*N*-methyl-2-phenoxyacetamide **6** is a potent drug-like molecule for treatment of hypnosis, whereas *N*,*N*-diethylacetamide **7** is a less potent congener[23] (Scheme 4d). Under our tranamidation protocol, **7** reacted with *N*-methyl-4-anisole to obtain an aryl amide analogue **8a**. Amine drugs, procaine and aminoglutethimide, could also be incorporated into **7** to form the drug variants **8b** and **8c**. The results demonstrated the potential utility of transamidation in industrial upcycling.

Furthermore, this transamidation could find use in the agrochemical industry, offering a straightforward route to convert the synthetic intermediate **9** to the herbicide **10**[24] in a 55% yield (Scheme 4e). Previously, **10** was obtained via hydrolysis, chlorination, and amidation of **9**. In transition-metal-catalyzed reactions, 8-aminoquinoline has emerged as a versatile ancillary to direct the chemo- and regioselective transformations of carboxylic acids.[25] This transamidation protocol permitted the direct installation of an 8-aminoquinolyl group into both tertiary alkyl (**A1** and **A2**) and aromatic (**A21**) amides to form **11a** and **11b**, respectively (Scheme 4f), offering an alternative potential disconnection strategy in oriented C−H functionalization. Such a disconnection approach also provided access to benzamide **12** based on *N*,*N*-dimethyl benzamide en route to the hyperlipidaemia drug bezafibrate[26] (Scheme 4g).

2.4. Mechanistic Investigation. Oxophilic WCl_6 could be successively hydrolyzed in the presence of residual water in a reaction system to form tungsten oxytetrachloride ($WOCl_4$), tungsten dichloride dioxide (WO_2Cl_2), and tungsten trioxide (WO_3);[27] meanwhile, electron-deficient WCl_6 can be reduced

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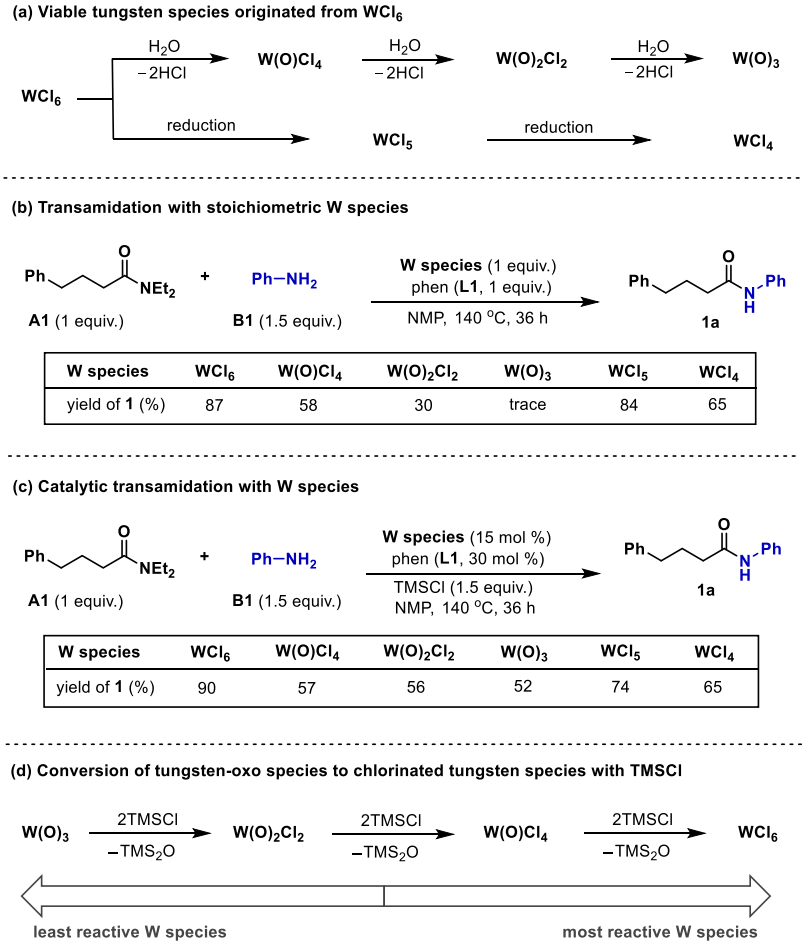
Scheme 5. Probing the Reactivity of Viable W Species for Transamidation



W species	WCl_6	$W(O)Cl_4$	$W(O)_2Cl_2$	$W(O)_3$	WCl_5	WCl_4
yield of **1** (%)	87	58	30	trace	84	65

W species	WCl_6	$W(O)Cl_4$	$W(O)_2Cl_2$	$W(O)_3$	WCl_5	WCl_4
yield of **1** (%)	90	57	56	52	74	65

by amides,[16,17,28] amines,[29] and/or ligand **L1**[27] to form tungsten(V) or tungsten(IV) species (Scheme 5a). To probe the formation of the proposed W species, we studied the stoichiometric reaction based on an equimolar ratio of WCl_6 and **L1** in dichloromethane under ambient conditions. In the presence of an equivalent of aniline, a $W^{VI}(phen)(O)_2Cl_2$ complex (**C1**) was formed (Figure S1 in the SI). In contrast, when an equivalent of tertiary amide **A1** was added, the W(VI) center was further reduced to give a $W^{V}(phen)(O)Cl_3$ complex (**C2**, Figure S2 in the SI). The formation of both **C1** and **C2** complexes were unambiguously identified by X-ray crystallographic analysis. The expected $W^{VI}(phen)Cl_6$ (**C1′**) and $W^{V}(phen)Cl_5$ (**C2′**) were not observed, indicating the propensity of W complexes toward hydrolysis.[27] The observed oxygenation and reduction of WCl_6 suggested that both hydrolysis and reduction WCl_6 are feasible in the course of transamidation.

Next, we examined the reactivity of the proposed W species based on their stoichiometric transamidation reaction with tertiary amide **A1** in the absence of TMSCl (Scheme 5b). Hinging on the yields of transamidation as the indicator of reactivity, the reactivity of transamidation is essentially consistent with the Lewis acidity of W species (WCl_6 > $W(O)Cl_4$ > WO_2Cl_2 > WO_3; WCl_6 > WCl_5 > WCl_4). A similar reactivity pattern was displayed as well when 25 mol % WCl_6, $W(O)Cl_4$, and WO_2Cl_2 was employed (Figure S3 in the SI). Subsequently, the catalytic reactivity of the W species under otherwise identical transamidation conditions was examined (Scheme 5c). All W species were able to catalyze the transmidation to give the desired product **1a** in 52−90% yields, again in line with the Lewis acidity of W species. It is worth noting that the least reactive tungesten-oxo complexes WO_2Cl_2 and WO_3 saliently promoted the reaction yields to over 50% in the presence of TMSCl. We surmised that one of the crucial roles of TMSCl is to act as an oxo scavenger of possibly formed tungsten-oxo complexes,[30] regenerating the more labile tungsten polychlorides to sustain the productive transamidation (Scheme 5d). Given the observed reactivity pattern of the W species, we speculated that WCl_6 is likely the predominant catalyst to mediate the transamidation, in association with limited $W(O)Cl_4$-, WCl_5-, and WCl_4-catalyzed transmidation.

To identify whether the transamidation is driven by a radical mechanism, an equivalent of butylated hydroxytoluene (BHT) was added as a radical trap in the model reaction (Scheme 6a). The product **1a** was formed in a 70% yield without remarkable diminishment of the yield, while no radical-trapped organic species was detected. We speculated that radical organic intermediates are not involved in transamidation. Subsequently, the pattern of C−N activation of tertiary amide was evaluated. First, we proposed that amine initially reacts with TMSCl to give *N*,*N*-bis(trimethylsilyl)amine, which would react with WCl_6 to give a W-imido or W-amido complex[31] to mediate the transamidation (Figure S4 in the SI). Only a trace of **1a** was formed when *N*,*N*-bis(trimethylsilyl)aniline **13** was subjected to transamidation (Scheme 6b), revealing that *N*-

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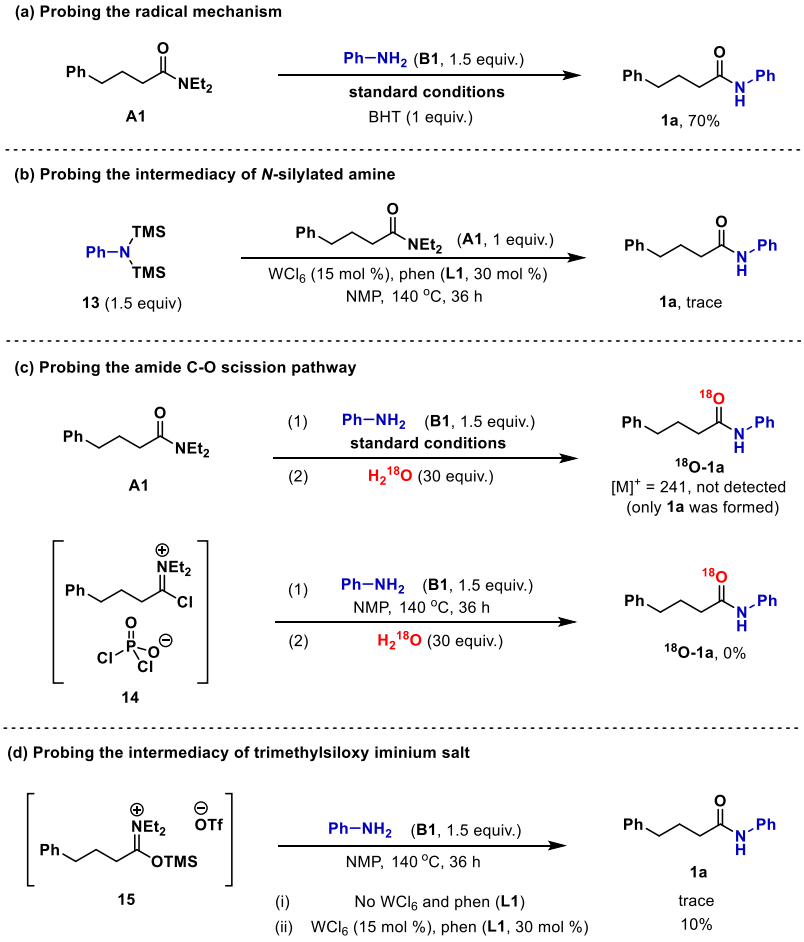
Scheme 6. Mechanistic Insights into Transamidation



silyl-substituted amine could not be involved in transamidation. Second, we proposed the transamidation via the W-mediated amide C═O scission[16] (Figure S5 in the SI), wherein the Vilsmeier salt (**Int-1**) may also be involved as an intermediate. This reaction pathway would afford the amino-substituted iminium salt (**Int-2**), which, upon hydrolysis in workup, furnishes the amide product. If this mechanism was involved, ^{18}O-enriched amide would be formed after hydrolysis with ^{18}O-water. A control experiment demonstrated that such an ^{18}O-labeled amide product (**^{18}O-1a**) was not formed but only unlabeled **1a** (Scheme 6c, top), indicating that the amide oxygen remains intact throughout transamidation. Furthermore, Vilsmeier salt **14** derived from **A1** did not react with aniline to give the amide product (Scheme 6c, bottom), precluding its formation for transamidation. Finally, we proposed the trimethylsiloxy-substituted iminium salt (**Int-3**) as the reaction intermediate, which could be generated via the *O*-trimethylsilylation of tertiary alkyl amide with TMSCl[32] (Figure S6 in the SI). The trimethylsiloxy iminium salt **15**, which was formed in situ from **A1** and trimethylsilyl trifluoromethanesulfonate (TMSOTf),[33] reacted with aniline to give only a trace of product **1a**, even when a WCl_6 catalyst was added (Scheme 6d). Transamidation via the intermediacy of **Int-3** is also unlikely.

Based on experimental evidence, we proposed a plausible transamidation mechanism (Scheme 7a). WCl_6 coordinates with **L1** to form ligated tungsten catalysts, which could be chlorinated W(VI), W(V), and W(IV)-based species. The tungsten catalyst activates the amide bond of tertiary alkyl amide **A** to form a cationic *O*-bound W-iminium species **Int-4**, wherein TMSCl could serve as a Lewis acid to expedite the process. **Int-4** is highly electron-deficient, thereby promoting the nucleophilic addition of amine **B** to form the tetrahedral intermediate **Int-5**. The proton is then shifted from **B** to the nitrogen of **A** to give the intermediate **Int-6**, which is particularly favorable when a more protic aromatic amine or primary alkylamine undergoes transamidation. Subsequently, TMSCl presumably aids in the elimination of more basic dialkyl amine to form **Int-8**, in concert with the formation of the W-iminium species **Int-7**. Eventually, **Int-7** splits to give the transamidated product and the W complex for a subsequent catalytic cycle. To gain further mechanistic insight, the competitive transamidation among tertiary (**A1**), secondary (**A30**), and primary (**A31**) alkyl amides was studied, indicating that tertiary amide underwent transamidation more readily than secondary and primary amides (Scheme 7b). We rationalized that the transamidation of tertiary amide involves the putative formation of cationic **Int-4** that strongly favors amine addition; on the contrary, the transamidation of secondary and primary amides presumably involves the neutral imine **Int-9** (Scheme 7a) that is less prone to amine attack. We postulated that the synergistic effect of the tungsten catalyst and TMSCl pronouncedly lowered the activation barrier of the transamidation reaction. Furthermore, the use of slightly excessive amine **B** (1.5 equiv) and the stronger dipole interaction between TMSCl and dialkyl amine in form of

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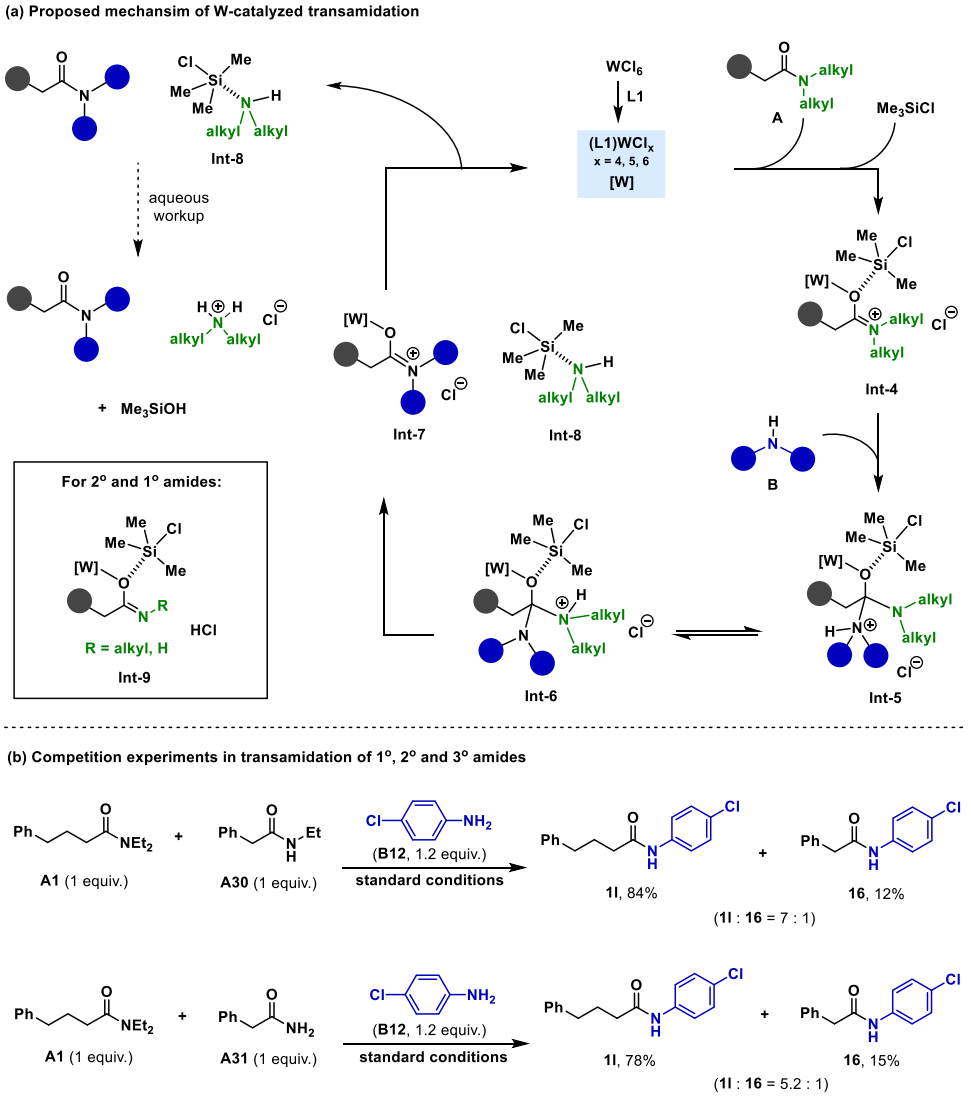
Scheme 7. Plausible Mechanism of W-Catalyzed Transamidation



Int-8[34] probably drive the reaction. Consequently, the overall reaction rate is promoted both kinetically and thermodynamically to furnish the transamidated products in generally good to high yields.

3. CONCLUSIONS

In summary, we have demonstrated that the use of tungsten-phenanthroline complexes and a chlorotrimethylsilane additive enable the catalytic transamidation of intrinsically robust tertiary alkyl amides, tolerating a diverse array of tertiary alkyl amides and amines for amide diversification. Furthermore, this method telescopes the access of amide drug and agrochemical molecules, provides handles for upcycling of tertiary amide drugs, and offers an alternative disconnection in chemical elaborations. Amide is a privileged structure in a broad spectrum of research fields. We anticipate that this transamidation manifold would be applicable in speeding up amide diversification for organic synthesis, particularly streamlining the drug discovery processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01840.

Experimental details, screening of catalyst and control experiments; screening of ligands; formation of $W^{VI}(phen)(O)_2Cl_2$ (**C1**); formation of $W^{V}(phen)(O)Cl_3$ (**C2**); transamidation via the intermediacy of trimethylsilyoxy imine species; competition experiments among tertiary, secondary and primary amides; probing the reactivity of viable W species; and spectral data of all compounds (PDF)

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This manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

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