Transition-Metal-Free Esterification of Amides via Selective N–C Cleavage under Mild Conditions

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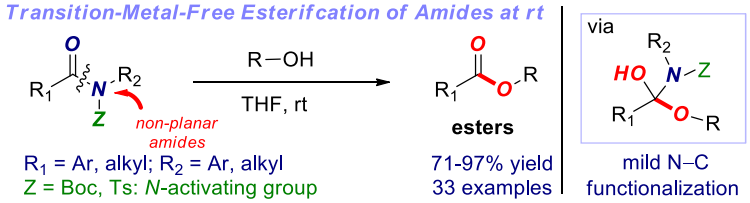
Supporting Information



ABSTRACT: A general, transition-metal-free and operationally-simple method for esterification of amides by a highly selective cleavage of N–C(O) bonds under exceedingly mild conditions is reported. The reaction is characterized by broad substrate scope and excellent functional group tolerance. The potential of this mild esterification is highlighted by late-stage diversification of natural products and pharmaceuticals. Conceptually, the metal-free acyl-functionalization of amides represents a significant step forward as a practical alternative to ligand exchange in acyl-metal intermediates.

The direct functionalization of amides represents a highly attractive strategy in organic synthesis.[1–5] Given that amides are among the most ubiquitous functional groups in pharmaceuticals,[6] natural products,[7] and polymers[8] as well as constitute the key linkage in peptides and proteins,[9] the development of new strategies for the conversion of amides into other functional groups provides powerful transformations for practitioners of organic synthesis.[10] The major challenge in the functional group interconversion of amides stems from amidic resonance (15-20 kcal/mol, $n_N \rightarrow \pi^*_{CO}$ conjugation),[11–13] which prohibits functionalization of the N–C(O) bond under mild, functional group tolerant and operationally-practical conditions.[14] In particular, the direct conversion of amides to esters represents a synthetic challenge that has been met with limited success to date owing to the high reactivity of the ester group under the conditions required to directly break the amide bond.

In 2015, a breakthrough study by Garg and co-workers reported the amide to ester interconversion[15] using Ni-catalyzed activation of the amide bond to produce versatile acyl-Ni intermediate (Figure 1A).[16] Later, Danoun and co-workers demonstrated Co-catalyzed esterification of amides,[17] thus introducing cobalt catalysis into field of amide bond activation (Figure 1A). Recently, a fluoride-catalyzed method[18] for esterification of amides at high temperature has been reported.[19,20] All of these elegant methods rely on the intrinsic properties of the amide bond to undergo controlled twisting and resonance destabilization from planarity to enable previously elusive synthetic transformations.[12]

Meanwhile, we have been interested in metal-catalyzed[21] and metal-free[22] activation of amides. We recognized that implementation of common acyclic amides, after a suitable N-activation[12d] in a fashion similar to the previous methods,[15–20] should enable a mild, transition-metal-free esterification of amides with broad substrate scope by exploiting amide bond destabilization platform (Figure 1B). In this context, N-acyl-Boc-carbamates (e.g., Ar = Ph, R = Ph, RE = 7.2 kcal/mol; τ = 29.1°; χ_N = 8.4°)[12a] and N-acyl-tosylamides (e.g., Ar = Ph, R = Ph, RE = 9.7 kcal/mol; τ = 18.8°; χ_N = 18.9°)[12a] have emerged as broadly useful resonance destabilized amides that have significantly improved the utility of amide bond interconversion tactics in transition-metal-catalysis.[5,15–20,21] We recognized that if a direct, transition-metal-free esterification manifold could be realized,[23] the reaction would represent a valuable addition to the synthetic toolbox available for interconversion of the ubiquitous amide bond endowed with all the advantages inherent to transition-metal-free reactions[24] and could stimulate the development of new methods for acyl-functionalization[5,16] of amides under attractive transition-metal-free conditions.

Herein, we describe the successful development of this process and report a general, transition-metal-free and operationally-simple method for esterification of amides by a highly selective N–C(O) bond cleavage under exceedingly mild room temperature conditions (Figure 1B). The reaction is characterized by broad substrate scope and excellent functional group tolerance enabled by mild activation of the amide bond. Notably, in contrast to transition-metal-catalyzed approaches,[15–20]

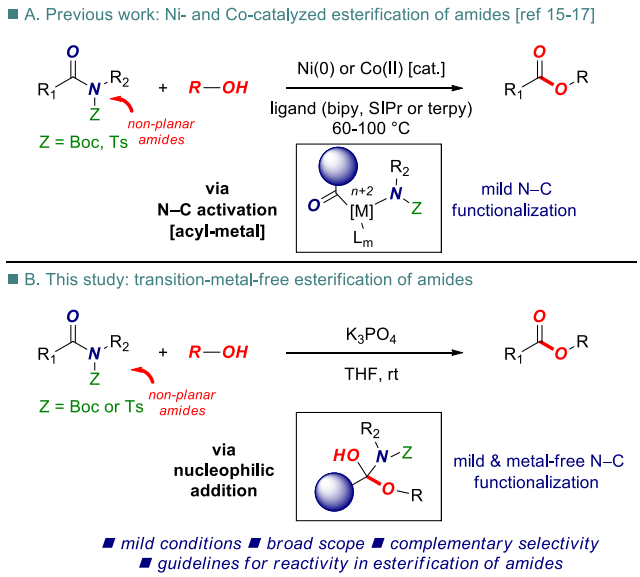


Figure 1. (a) Metal-catalyzed esterification of amides (previous work). (b) Transition-metal-free esterification of amides (this study).

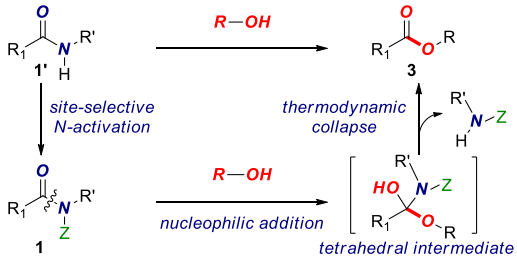


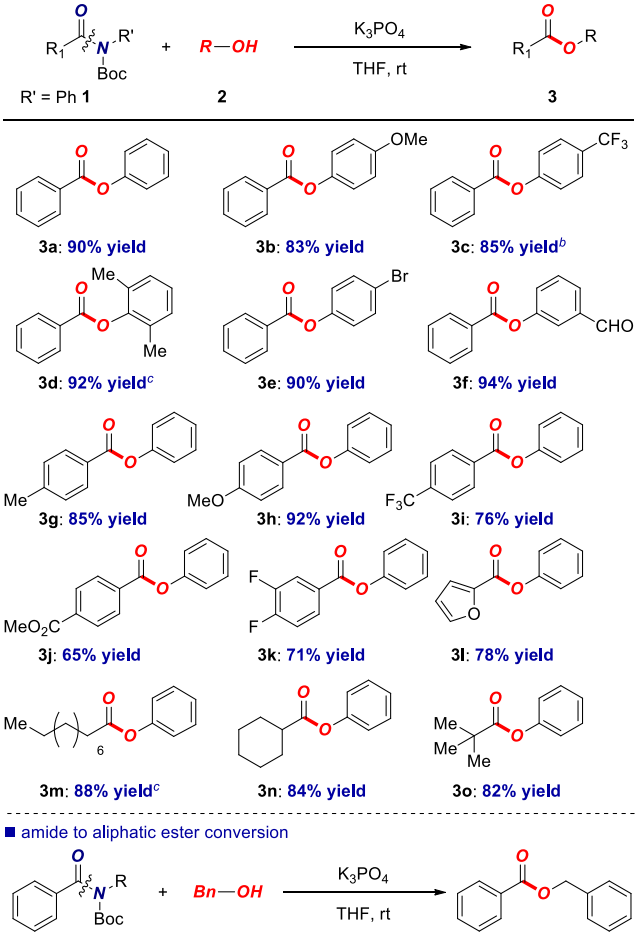
Figure 2. Proposed mechanism for metal-free esterification of amides.

these mild conditions are particularly effective for esterification of amides with phenols, a previously elusive transformation in metal-catalyzed activation of the amide bond, thus enabling direct access to valuable aromatic esters from amides.[23] The potential of this mild esterification method is highlighted by late-stage diversification of natural products and pharmaceuticals. Conceptually, the transition-metal-free acyl-functionalizations of amides with ample substrate scope represent a significant step forward in the conversion of amides by N–C(O) bond activation as a practical alternative to ligand exchange in acyl-metal intermediates.

After extensive optimization, we determined that esterification of N-Boc activated amide **1a** proceeds in excellent 90% yield at room temperature using inexpensive K_3PO_4 as a base and THF as a solvent (Scheme 1, **3a**). The reaction requires only close to stoichiometric amount of PhOH (1.2 equiv), consistent with the efficient direct O-addition to the activated amide bond under these conditions. Optimization studies (see Supporting Information (SI)) revealed that other bases (K_2CO_3, KO*t*-Bu, KF, KOH, Cs_2CO_3) and solvents (DMF, CH_3CN, acetone, CH_2Cl_2) are less effective in promoting the reaction. The base is required for the reaction, with modest conversion observed with close to stoichiometric amount of the base (55%, K_3PO_4, 1.2 equiv). Importantly, under the optimized conditions, cleavage of the N-Boc group deactivating the amide was not observed.

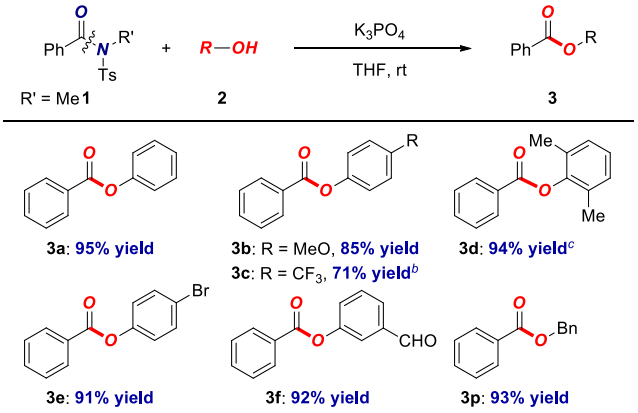
With optimal conditions in hand, the substrate scope was next examined (Scheme 1). Importantly, the reaction readily accommodates a broad range of phenols including simple (**3a**),

Scheme 1. Transition-Metal-Free Esterification of N-Boc-Activated 2° Amides[a]



[a]Conditions: amide (1.0 equiv), ROH (1.2 equiv), K_3PO_4 (3.0 equiv), THF (1.0 M), 23 °C, 15 h. Isolated yields. [b]ROH (3.0 equiv). [c]ROH (2.0 equiv).

Scheme 2. Transition-Metal-Free Esterification of N-Ts-Activated 2° Amides[a]

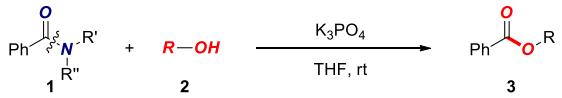


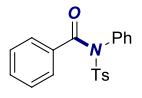
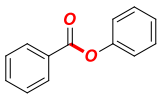
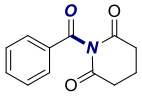
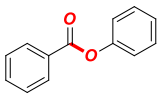
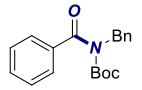
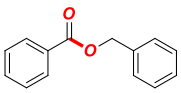
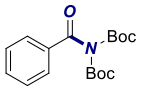
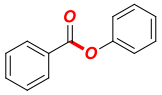
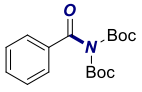
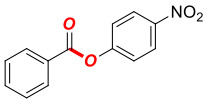
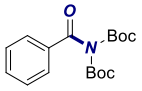
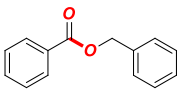
[a–c]See Scheme 1.

electron-rich (**3b**), electron-deficient (**3c**), sterically-hindered (**3d**) as well as those bearing sensitive functional groups such

as bromo (**3e**) and aldehyde (**3f**). Note that these substituents are often problematic in transition-metal-catalyzed protocols, showing the advantage of these mild conditions.

Table 1. Transition-Metal-Free Esterification of Amides[a]



entry	**1** (R'/R'')	product	yield (%)
1			97
2			95[b]
3			80
4			92
5			72[c]
6			90

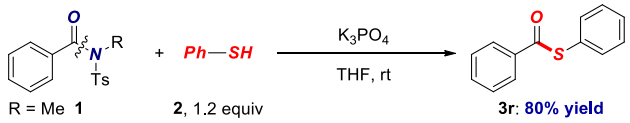
[a]See Scheme 1. [b]ROH (2.0 equiv). [c]ROH, K_3PO_4 (3.0 equiv), 110 °C.

The scope with respect to the amide substitution is also broad (Scheme 1) and accommodates amides bearing both electron-rich (**3g-h**) and electron-deficient (**3i-j**) substituents. Fluorine-containing amides relevant from a medicinal chemistry standpoint (**3k**) and heterocyclic amides bearing a deactivating heteroatom at the conjugating position (**3l**) are well-tolerated. Perhaps most notably, the reaction readily accommodates aliphatic amides with systematic variation of sterics at the α-position (**3m-o**). In contrast, transition-metal-catalyzed esterification typically requires extensive ligand optimization to provide reactivity of aliphatic amides.[15b] Finally, although we were primarily interested in the synthesis of aromatic esters because such method has been elusive using transition metals,[15–20] the present conditions can also be readily applied to esterification with aliphatic alcohols without modification of the reaction conditions (**3p**).

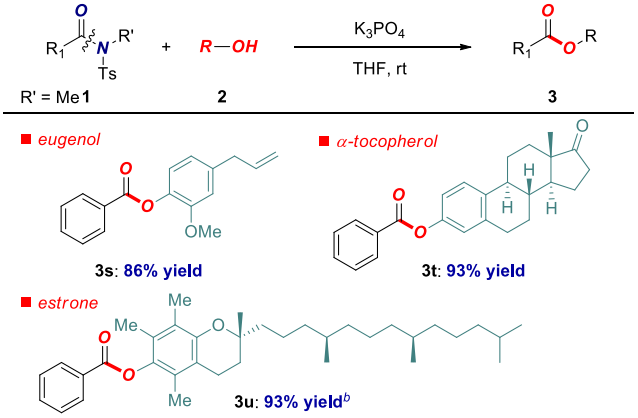
Pleasingly, this new method is also compatible with N-Ts activated amides to give the corresponding esterification products in high yields (Scheme 2). These examples include electronically-differentiated (**3a-c**), sterically-hindered (**3d**), halide (**3e**), aldehyde-containing (**3f**) and aliphatic alcohols (**3l**). Importantly, removal of the activating N–S group is not observed under these conditions. In this case, selective N-activation of secondary amides using TsCl offers a complementary activation method.[5,12,16]

Notably, the reaction could be extended to a variety of amide activating groups (Table 1). N-Ts-anilides (entry 1), N-acyl-glutarimides (entry 2), N-alkyl-carbamates (entry 3) as well as readily prepared from 1° carboxamides[12d,14] N,N-Boc_2 amides (entries 4-6) underwent smooth esterification to provide C–O interconversion products in high yields. It is particularly noteworthy that esterification using electron-deficient 4-

Scheme 3. Amide to Thioester Conversion

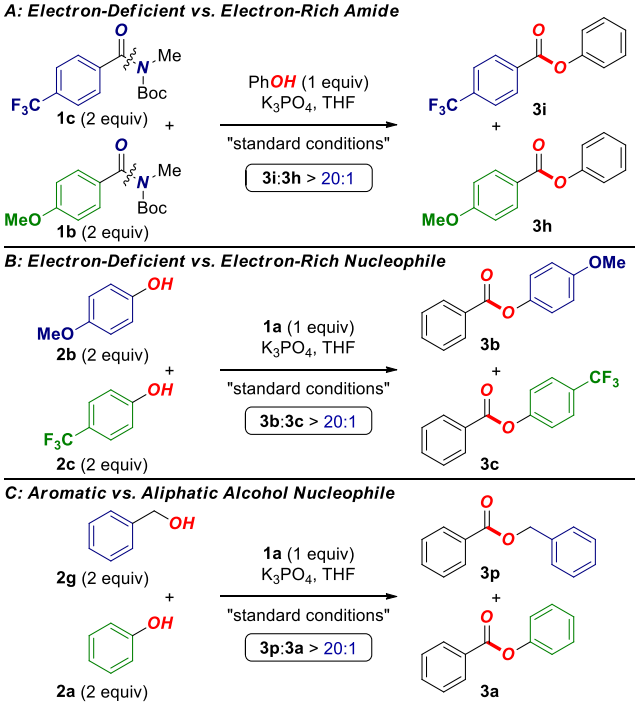


Scheme 4. Late-Stage Diversification[a]



[a]See Scheme 1. [b]ROH (1.5 equiv).

Scheme 5. Competition Experiments



nitro-phenol proceeded in high yield (**3q**), albeit at elevated temperature. This reaction establishes primary amide to activated 4-NO_2-ester interconversion.[25] Given the broad utility of such activated esters in cross-coupling reactions,[25] this protocol may find utility in sequential strategies for manipulation of common amide bonds.

Importantly, the present method can be applied directly to effect transition-metal-free amide to thioester [CO–N → CO–S] interconversion without modification of the reaction condi-

tions (Scheme 3). This protocol further expands the range of downstream transformations of amides enabled by a versatile thioester functional group handle.[26]

The broad synthetic utility of this process is further highlighted by the late-stage diversification of natural products and pharmaceuticals (Scheme 4). We were pleased to find that the direct esterification of eugenol (**3s**), a naturally-occurring guaiacol with a sensitive double bond, estrone (**3t**), an estrogen receptor agonist, and α-tocopherol (**3u**), an essential vitamin, delivered the esterification products in high to excellent yields, demonstrating a synthetic advantage of this protocol.

To gain preliminary insight into the reaction mechanism, we conducted competition experiments (Scheme 5). We found that electron-deficient amides are inherently more reactive, consistent with the relative electrophilicity of the amide bond (Scheme 5A). Furthermore, electron-rich alcohols were found to react preferentially (Scheme 5B). Finally, aliphatic alcohols are inherently more reactive than their aromatic counterparts (Scheme 5C). Overall, these results emphasize the challenge of selective nucleophilic addition of phenols to the amide bond and are consistent with alcohol nucleophilicity in the metal-free activation pathway (Figure 1B).

A summary of state-of-the-art methods in metal-catalyzed and transition-metal-free esterification of amides is presented in the SI (Table SI-1). The successful esterification of a broad range of amides establishes a unique approach to deploying amide bond functional group interconversion by complementary reaction mechanisms.

In summary, we have reported a transition-metal-free platform for esterification of amides by highly selective N–C(O) bond cleavage under exceedingly mild conditions. The reaction demonstrates a broad substrate scope and excellent functional group tolerance. This operationally-simple, mild and practical method establishes the first general interconversion of amides to aromatic esters that were previously elusive in transition-metal-catalyzed N–C amide bond activation. The potential of this method has been highlighted by late-stage diversification of natural products and pharmaceuticals. We fully expect that the transition-metal-free esterification will be of great interest for manipulation of amides in organic synthesis. In a broader context,[5,16,21] it becomes crystal clear that both metal-catalyzed and transition-metal-free approaches should be considered in acyl-conversion of the historically-inert amide bond with wide-ranging implications in chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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