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### Authors

Hie, Liana  
Fine Nathel, Noah F  
Shah, Tejas K  
[et al.](#)

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## Conversion of Amides to Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

Liana Hie<sup>1</sup>, Noah F. Fine Nathel<sup>1</sup>, Tejas K. Shah<sup>1</sup>, Emma L. Baker<sup>1</sup>, Xin Hong<sup>1</sup>, Yun-Fang Yang<sup>1</sup>, Peng Liu<sup>1</sup>, K. N. Houk<sup>1</sup>, and Neil K. Garg<sup>1</sup>

<sup>1</sup>Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, United States

### Abstract

Amides are common functional groups that have been well studied for more than a century.<sup>1</sup> They serve as the key building blocks of proteins and are present in a broad range of other natural and synthetic compounds. Amides are known to be poor electrophiles, which is typically attributed to resonance stability of the amide bond.<sup>1,2</sup> Whereas Nature can easily cleave amides through the action of enzymes, such as proteases,<sup>3</sup> the ability to selectively break the C–N bond of an amide using synthetic chemistry is quite difficult. In this manuscript, we demonstrate that amide C–N bonds can be activated and cleaved using nickel catalysts. We have used this methodology to convert amides to esters, which is a challenging and underdeveloped transformation. The reaction methodology proceeds under exceptionally mild reaction conditions, and avoids the use of a large excess of an alcohol nucleophile. Density functional theory (DFT) calculations provide insight into the thermodynamics and catalytic cycle of this unusual transformation. Our results provide a new strategy to harness amide functional groups as synthons and are expected to fuel the further use of amides for the construction of carbon–heteroatom or carbon–carbon bonds using non-precious metal catalysis.

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The ability to interconvert functional groups lies at the cornerstone of both synthetic chemistry and countless biological processes. As a result of decades of research, chemists have learned to strategically harness the reactivity of almost any functional group through the development of innovative methodologies.<sup>4,5</sup> Likewise, breakthroughs in biochemistry have allowed us to understand how Nature manipulates functional groups in order to regulate physiological processes.<sup>6</sup>

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Correspondence and requests for materials should be addressed to K.N.H. ([hok@chem.ucla.edu](mailto:hok@chem.ucla.edu)) and N.K.G. ([neilgarg@chem.ucla.edu](mailto:neilgarg@chem.ucla.edu)).

Supplementary Information is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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One particularly interesting dichotomy exists in considering the amide functional group,<sup>1</sup> which is the key component of all proteins and is therefore of tremendous importance (Figure 1a). Sparked by Schwann's initial discovery of pepsin in 1836, the first enzyme discovered, scientists have been intrigued by the remarkable ability of enzymes to break down amide linkages.<sup>6</sup> Such amide cleavage processes govern many cellular regulatory functions and are also responsible for the degradation of proteins to amino acids.<sup>1,3</sup> In contrast, the synthetic chemistry of amide bond cleavage has remained largely underdeveloped, despite that amides are well suited for use in multistep synthesis because of their pronounced stability to a variety of reaction conditions. The most commonly employed methods to break amide C–N bonds include the reductive conversion of amides to aldehydes using Schwartz's reagent<sup>7</sup> and the interception of Weinreb's *N*-OMe-*N*-Me amides with organometallic reagents en route to ketones.<sup>8</sup> Following Pauling's seminal postulate regarding amide planarity,<sup>2</sup> the poor reactivity of amides is now well understood by the strength of the resonance-stabilized amide C–N bond.<sup>1</sup>

To circumvent the long-standing problem involving the low reactivity of amides and their modest synthetic utility in C–N bond cleavage processes, we conceived of the general approach shown in Figure 1b. The C–N bond of amide **1** would undergo activation by a transition metal catalyst. Following oxidative addition, the resulting acyl metal species **2** would be trapped by an appropriate nucleophile to furnish product **3**, with the release of amine **4**. The success of this approach would allow for the breakdown of amides, and would also render amides useful synthetic building blocks. Although examples exist for the metal-catalyzed C–heteroatom bond activation of acid chlorides,<sup>9</sup> anhydrides,<sup>9</sup> and 2-pyridyl esters,<sup>10</sup> to our knowledge, the direct metal-catalyzed activation of C–N bonds of amides is unknown. This is notable given the rampant use of transition metal catalysis in organic synthesis, where there exist countless examples of catalytic transformations occurring smoothly in the presence of amide linkages.

This manuscript describes the validation of the strategy outlined in Figure 1b through the conversion of amides to esters (Figure 1c). Amide to ester conversion, much like transamidation,<sup>11,12</sup> has remained a challenging and underdeveloped synthetic transformation. It is often the case that amides are sufficiently stable such that esterification is difficult and requires the use of harsh acidic or basic conditions, while employing a large excess of nucleophile (e.g., using the alcohol nucleophile as solvent).<sup>1</sup> Perhaps the most promising protocol to achieve amide to ester conversions is Keck's methylation/hydrolysis sequence,<sup>13</sup> although this methodology is limited to the synthesis of methyl esters. Esterifications using acyl aziridines<sup>14</sup> and *N*-methylamides (albeit with activation by nitrosation)<sup>15</sup> have also been reported. Here, we demonstrate the Ni-catalyzed conversion of amides to esters, which proceeds under exceptionally mild reaction conditions. In addition to establishing the scope of this methodology, we use DFT calculations to predict whether the amide to ester conversion, or the reverse, is thermodynamically favored. DFT calculations are also used to predict a full catalytic cycle. These experimental and computational studies not only substantiate the notion of utilizing non-precious metal catalysis for the activation of amide C–N bonds, but also lay the foundation for further studies aimed at the strategic manipulation of amides as synthetic building blocks using catalysis.

To initiate our studies, we examined the conversion of benzamides **7** to methyl benzoate **8a** using both computations and experiments (Figure 2). As amides are well known for their pronounced stability, we assessed if the amide to ester conversion could be rendered thermodynamically favorable by the judicious choice of amide *N*-substituents. Using DFT methods, the  $\Delta G$  for the reaction of amides **7** with methanol to give esters **8a** and amines **4** was calculated. Whether this transformation is favorable or not indeed depends on the nature of the *N*-substituents (entries 1–8). Methanolysis of Weinreb amide **7d** (entry 4) and *N*-arylated substrates **7f** and **7g** (entries 6–8) were found to be the most favorable energetically. In contrast, esterifications of *N*-alkyl amides **7a**, **7b**, and **7e** were deemed thermodynamically unfavorable. This is in line with the experimentally measured equilibrium constant for the reaction of *N,N*-dimethylbenzamide **7b** and methanol (entry 2), in which the reverse reaction is thermodynamically favored (see Supplementary Information for further discussion).<sup>16</sup> Encouraged by the unique ability of Ni to catalyze the activation of strong *aryl*-heteroatom bonds,<sup>17,18,19</sup> particularly those in phenol-,<sup>19</sup> aniline-,<sup>20,21,22</sup> and phthalimide derivatives,<sup>23</sup> we also calculated the activation energies for *acyl* C–N bond oxidative addition of each amide substrate using Ni catalysis. The calculated barriers using the commercially available *N*-heterocyclic carbene (NHC) ligand SIPr (entries 1–8) reveal that the oxidative addition barriers are reasonable in most cases. Simultaneously, we studied these reactions experimentally using 10 mol% Ni(cod)<sub>2</sub>, 10 mol% SIPr, 2.0 equivalents of methanol, and toluene as solvent at 110 °C for 12 h, and established strong correlations between our observations and computational predictions. No reaction or low yields were seen for substrates **7a–7e** (entries 1–5). However, in cases where the calculated  $\Delta G$  and the oxidative addition barrier were favorable, significant formation of product **8a** was observed (entries 6 and 7). Coupling of substrate **7g** gave a quantitative yield of product (entry 7), and further optimization showed that even with only 1.2 equivalents of methanol and a temperature of 80 °C, product formation occurred smoothly (entry 8) to give complete conversion to **8a**. Importantly, no reaction takes place if either the precatalyst or ligand are omitted, while the use of alternate NHC or phosphine ligands typically leads to lower yields or no reaction. We conclude that nickel catalysis is indeed operative in the amide activation/esterification process.

With optimized conditions in hand, we examined the scope of the transformation with regard to the amide substrate (Figure 3a). In addition to the parent benzamide (entry 1), substrates containing the electron-withdrawing trifluoromethyl or fluoride substituents (entries 2 and 3) or the electron-donating methoxy or methyl substituents (entries 4 and 5) were well tolerated. In addition, the transformation proceeded smoothly using *meta*- and *ortho*-methyl-substituted substrates to give the desired esters in excellent yields (entries 6 and 7). Beyond the use of phenyl derivatives, we examined naphthyl and heterocyclic substrates. Indeed, naphthyl compounds readily coupled (entries 8 and 9), as did furan, quinoline, and isoquinoline substrates (entries 10–12, respectively). It should be noted, however, that amides derived from alkyl carboxylic acids do not undergo the nickel-catalyzed esterification under our reaction conditions. As shown later in this manuscript (see Figure 5b), this attribute provides opportunities to realize selective amide C–N bond cleavages in more complex substrates.

A variety of *N*-substituents were also surveyed, as shown in Figure 3a. In addition to the longer *N*-Bu and the branched *N*-*i*Pr alkyl chains (entries 13 and 14, respectively), we found that a cyclic amide derived from indoline was tolerated by the methodology (entry 15). Lastly, protected *N*-alkyl benzamides were tested. Although use of the *N*-Ts derivative gave the corresponding ester in modest yield (entry 16), the corresponding *N*-Boc substrate more efficiently underwent conversion to ester **8a** (entry 17). The analogous *N*-Bn,Boc substrate was also evaluated and gave the desired ester in 89% yield (entry 18). These latter results show that the methodology is not restricted to anilide substrates, as long as the overall reaction energetics are thermodynamically favorable (see Supplementary Information for energetics involving *N*-Boc,Me substrate). Moreover, one can strategically employ secondary benzamides as substrates for esterification, following a straightforward activation step (i.e., Boc-protection).

Using amide **7g** as the substrate, we also evaluated the scope of the methodology with respect to the alcohol nucleophile (Figure 3b). As shown, synthetically useful yields of product were obtained using only 1.2 equivalents of the alcohol, even when significantly complex and hindered alcohols were utilized. Cyclohexanol, *t*-butanol, and 1-adamantol coupled smoothly to give the corresponding esters (entries 19–21, respectively). It should be noted that *t*-butyl esters can readily be hydrolyzed to carboxylic acids under acidic conditions. Similarly, we found that cyclopropyl carbinol and an oxetane-derived alcohol could be employed in the esterification reaction (entries 22 and 23, respectively). The use of the hindered secondary alcohol (–)-menthol was also tested. To our delight, the desired ester was obtained in 88% yield (entry 24). Furthermore, we found that Boc-L-prolinol was tolerated in the methodology (entry 25), in addition to an indole-containing alcohol (entry 26), thus further demonstrating the promise our methodology holds for reactions of heterocyclic substrates. As shown in entries 27 and 28, respectively, a complex sugar-containing alcohol bearing two acetals and an estrone-derived steroidal alcohol also underwent the desired esterification reaction.

Although nickel-catalyzed aryl and acyl C–O bond activation processes have been previously studied computationally,<sup>24,25,26,27,28</sup> no analogous studies involving C–N bond activation have been reported. Thus, to shed light on the mechanism of the facile amide to ester conversion, the catalytic cycle was computed using DFT calculations. Figure 4 provides the free energy profile using amide substrate **7g**. The [Ni(SIPr)<sub>2</sub>] complex, **9**, is believed to be the resting state of the catalytic cycle. Dissociation of one carbene ligand from complex **9** provides a coordination site for amide **7g**. Following coordination to give intermediate **10**, oxidative addition occurs via transition state **11**. This key event cleaves the amide C–N bond and produces acyl nickel species **12**. The next step of the catalytic cycle is ligand exchange, which proceeds by coordination of methanol to give intermediate **13**. Subsequent ligand exchange via transition state **14** facilitates the deprotonation of methanol, giving nickel complex **15**. Dissociation of *N*-Me-aniline produces acyl nickel species **16**, which in turn, undergoes reductive elimination via transition state **17** to deliver the ester-coordinated complex **18**. Finally, the ester product **8a** is released to regenerate catalyst **9**. The rate-determining step in the catalytic cycle is the oxidative addition (transition state **11**) with an overall barrier of 26.0 kcal/mol relative to the resting state **9**. The overall reaction is

thermodynamically favored by  $-6.8$  kcal/mol. As decarbonylation of acyl nickel species has been observed,<sup>29,30</sup> we also calculated the kinetic barrier for decarbonylation events (see Supplementary Information). Consistent with experiments, decarbonylation pathways from acyl nickel species **12** or **16** were found to be less favorable compared to product formation pathways.

As highlighted by the experiments shown in Figure 5, the nickel-catalyzed conversion of amides to esters can be used to achieve selective and mild amide bond cleavages. In the first example, guided by our earlier computational and experimental observations (see Figure 2), we performed the esterification of bis(amide) substrate **19** using the hindered alcohol (–)-menthol (Figure 5a). Although both amides are *N*-arylated benzamides, only the tertiary amide was cleaved to give ester **21**, while also releasing aminoamide **22**. Additionally, bis(amide) **23**, which possesses two tertiary amides was studied in the nickel-catalyzed esterification reaction (Figure 5b). In this case, the tertiary L-proline-derived alkyl amide was not disturbed, while the tertiary benzamide underwent cleavage to give ester **21** and aminoamide **24** in good yields. Lastly, we prepared L-valine derivative **25**, which also bears an ester (Figure 5c). Upon exposure of **25** to 1.2 equiv of (–)-menthol and the nickel-catalyzed conditions, ester **21** and aminoester **26** were obtained in 70% and 79% yields, respectively. It is believed that the ester functionality withstands the reaction conditions because it is not attached to an arene, analogous to the lack of reactivity seen in our attempts to esterify amides derived from alkyl carboxylic acids (e.g., **23**). It should be noted that **24** and **26** were obtained in high enantiomeric excess, thus highlighting the mild nature of the reaction conditions, which avoid any significant epimerization of the  $\alpha$  stereocenters.

We have discovered an efficient means to achieve the conversion of amides to esters. The methodology circumvents the classic problem of amides being poorly reactive functional groups by using nickel catalysis to achieve the previously unknown catalytic activation of amide C–N bonds. DFT calculations support a catalytic cycle that involves a rate-determining oxidative addition step, followed by ligand exchange and reductive elimination. The methodology is broad in scope, particularly with respect to the alcohol nucleophiles, and proceeds under exceptionally mild reaction conditions using just 1.2 equivalents of the alcohol nucleophile. Moreover, selective amide bond cleavage can be achieved in the presence of other functional groups, including less reactive amides and esters, without the epimerization of  $\alpha$  stereocenters. Many future advances pertaining to this methodology can be envisioned, such as the catalytic esterification of primary amides, additional *N,N*-disubstituted amides, amides derived from alkyl or vinyl carboxylic acids, and perhaps even polyamide substrates bearing multiple stereocenters. We hope this study will also fuel the further harnessing of amides as valuable building blocks for the construction of C–heteroatom or C–C bonds using non-precious metal catalysis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

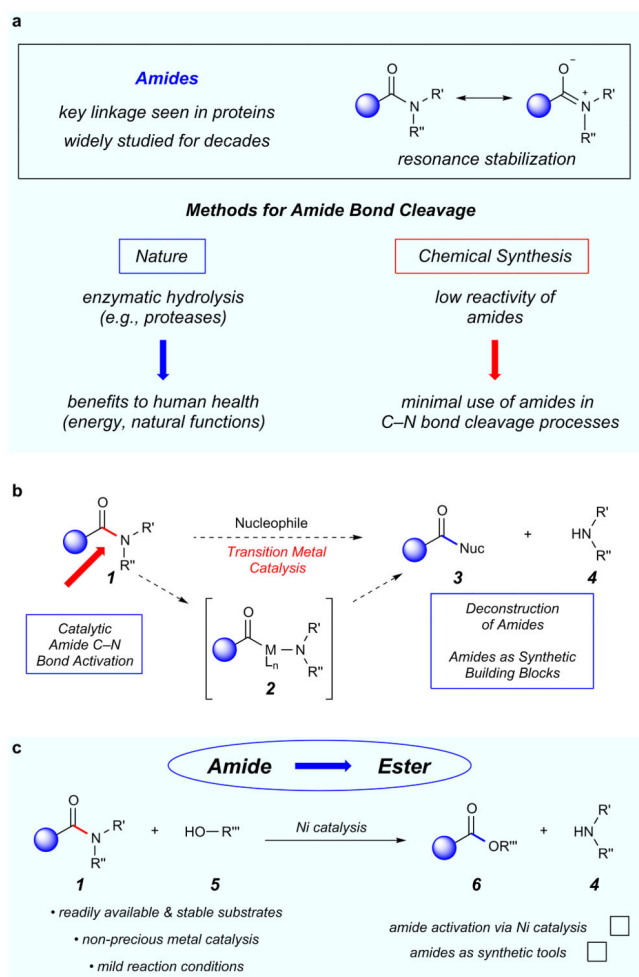
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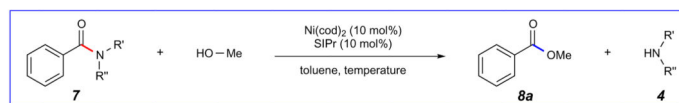
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**Figure 1. Amide bond cleavage overview and objectives of present study**

**a.** Stability of amides and contrast in how Nature and chemical synthesis are able to utilize amides. **b.** Design of amide C–N bond activation to deconstruct amides and exploit amides as synthetic building blocks. **c.** Strategy for the conversion of amides to esters.

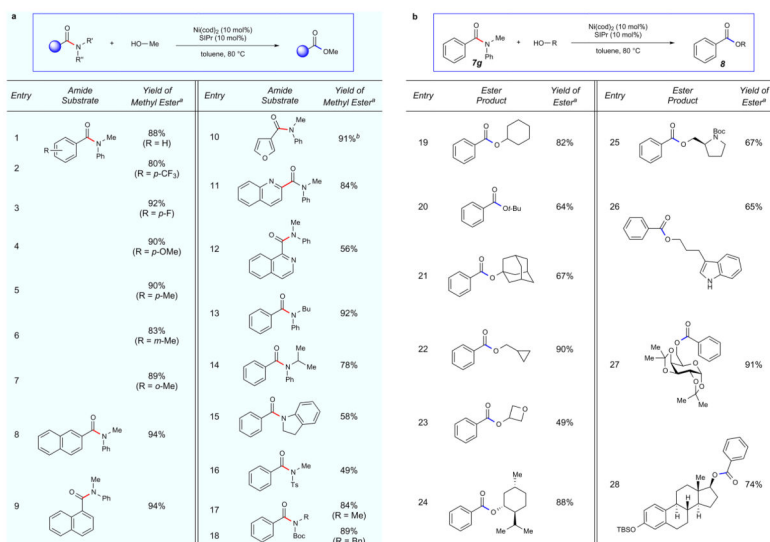


Entry		Calculated $\Delta G^a$ (kcal/mol)	Calculated oxidative addition barrier with Ni / SiPr (kcal/mol) <sup>b</sup>	Temp	Equivalents of MeOH	Yield of ester <sup>c</sup>
1		+2.4	36.8	110 °C	2.0	0%
2		0.0	36.2	110 °C	2.0	0%
3		-1.1	34.0	110 °C	2.0	23%
4		-6.1	31.9	110 °C	2.0	22%
5		+3.1	39.0	110 °C	2.0	0%
6		-4.3	30.6	110 °C	2.0	55%
7		-6.8	26.0	110 °C	2.0	>99%
8		-6.8	26.0	80 °C	1.2	>99%

**Figure 2.**

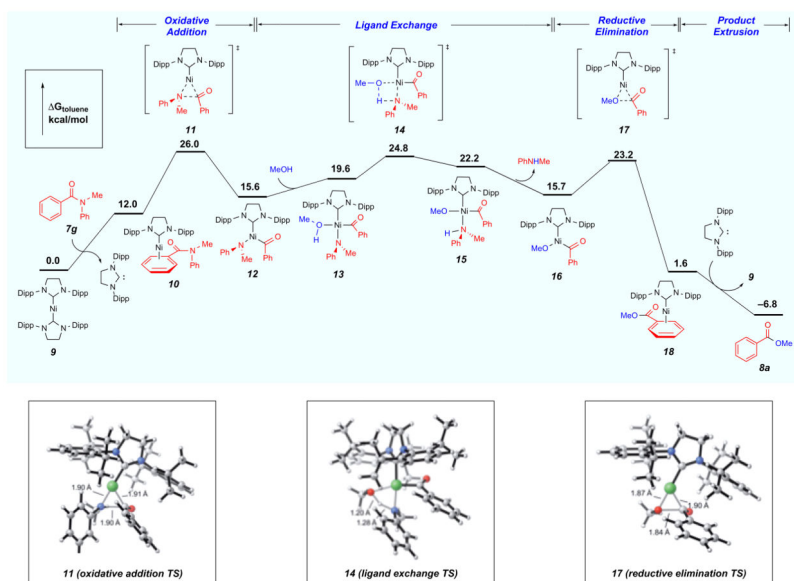
Experimental and computational study of amide bond activation

<sup>a</sup>The  $\Delta G$  values (kcal/mol) for the overall non-catalyzed reactions were obtained using DFT calculations (298 K). <sup>b</sup> DFT methods were used to calculate oxidative addition barriers (kcal/mol) using Ni/SiPr as the metal/ligand combination. <sup>c</sup> Reactions were carried out with Ni(cod)<sub>2</sub> (10 mol%), SiPr (10 mol%), substrate (50.0 mg, 1.0 equiv), methanol (1.2 or 2.0 equiv), and toluene (1.0 M), for 12 h; yields were determined by <sup>1</sup>H NMR analysis using hexamethylbenzene as an internal standard.



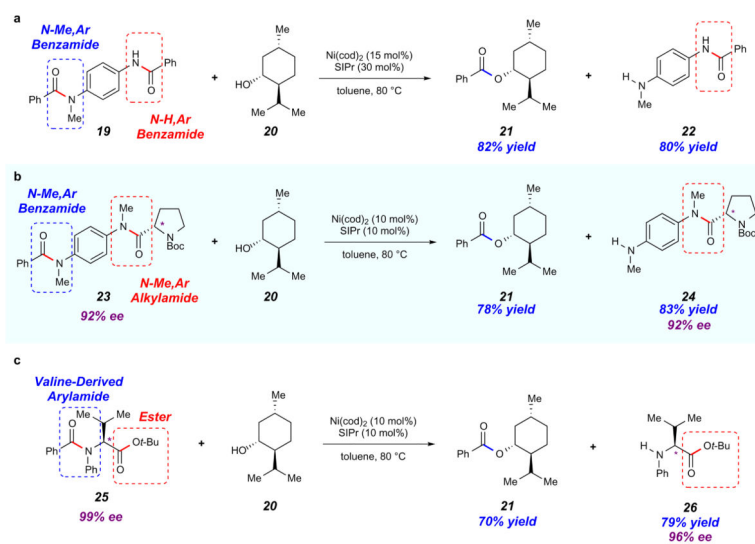
**Figure 3.**  
Scope of methodology

<sup>a</sup>Reactions were carried out with Ni(cod)<sub>2</sub> (10 mol%), SIPr (10 mol%), substrate (100.0 mg, 1.00 equiv), alcohol (1.2 equiv), and toluene (1.0 M) at 80 °C for 12 h. Yields shown reflect the average of two isolation experiments. <sup>b</sup>Yield was determined by <sup>1</sup>H NMR analysis using hexamethylbenzene as an internal standard due to the volatility of the ester product.



**Figure 4. Computational study of catalytic cycle**

DFT methods were used to calculate the full catalytic cycle for the amide to ester conversion (298 K). The reaction is proposed to occur by oxidative addition, ligand exchange, and reductive elimination. Key transition state structures are shown (i.e., **11**, **14**, and **17**).



**Figure 5. Selective amide bond cleavage processes**

**a.** Cleavage of tertiary over secondary amide using menthol (1.2 equiv). **b.** Cleavage of benzamide over an alkyl proline-derived amide using menthol (1.2 equiv). **c.** Cleavage of valine-derived amide in the presence of an ester using menthol (1.2 equiv).