LETTER

doi:10.1038/nature14615

Conversion of amides to esters by the nickel–catalysed activation of amide C–N bonds

Liana Hie[1], Noah F. Fine Nathel[1], Tejas K. Shah[1], Emma L. Baker[1], Xin Hong[1], Yun-Fang Yang[1], Peng Liu[1], K. N. Houk[1] & Neil K. Garg[1]

Amides are common functional groups that have been studied for more than a century[1]. They are 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 the resonance stability of the amide bond[1,2]. Although amides can readily be cleaved by enzymes such as proteases[3], it is difficult to selectively break the carbon–nitrogen bond of an amide using synthetic chemistry. Here we demonstrate that amide carbon–nitrogen bonds can be activated and cleaved using nickel catalysts. We use 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 calculations provide insight into the thermodynamics and catalytic cycle of the amide-to-ester transformation. Our results provide a way to harness amide functional groups as synthetic building blocks and are expected to lead to the further use of amides in the construction of carbon–heteroatom or carbon–carbon bonds using non-precious-metal catalysis.

The ability to interconvert functional groups is important in synthetic chemistry and many biological processes. Methodologies[4,5] have been developed that enable chemists to strategically harness the reactivity of most functional groups. Likewise, breakthroughs in biochemistry have led to an understanding of how changes in functional groups regulate physiological processes[6].

One particularly interesting dichotomy exists in considering the amide functional group[1], which is the key component of all proteins (Fig. 1a). Since Schwann's initial discovery of pepsin—the first enzyme to be discovered—in 1836, scientists have been intrigued by the ability of enzymes to break amide linkages[3,6]. Such amide cleavage processes govern many cellular regulatory functions and are responsible for the degradation of proteins to amino acids[1,3]. In contrast, the synthetic chemistry of amide-bond cleavage has remained underdeveloped, even though amides are well suited for use in multistep synthesis because of their stability under a variety of reaction conditions. Commonly used methods to break amide carbon–nitrogen (C–N) bonds include the reductive conversion of amides to aldehydes using Schwartz's reagent[7] and the displacement of Weinreb's *N*-OMe-*N*-Me amides with organometallic reagents en route to ketones[8]. Following Pauling's seminal postulate regarding amide planarity[2], the poor reactivity of amides is now well understood as being a result of the strength of the resonance-stabilized amide C–N bond[1].

To circumvent the long-standing problem involving the low reactivity of amides and their modest synthetic use in C–N bond cleavage processes, we designed the general approach shown in Fig. 1b. The C–N bond of amide **1** undergoes activation by a transition-metal catalyst. Following oxidative addition, the resultant acyl metal species **2** is trapped by an appropriate nucleophile to furnish product **3**, with the release of amine **4**. This approach allows for the breakdown of amides, and renders amides useful synthetic building blocks. Although examples exist for the metal-catalysed C–heteroatom bond activation of acid chlorides[9], anhydrides[9], and 2-pyridyl esters[10], to our knowledge, the direct metal-catalysed activation of C–N bonds of amides is unknown. This is notable given the widespread use of

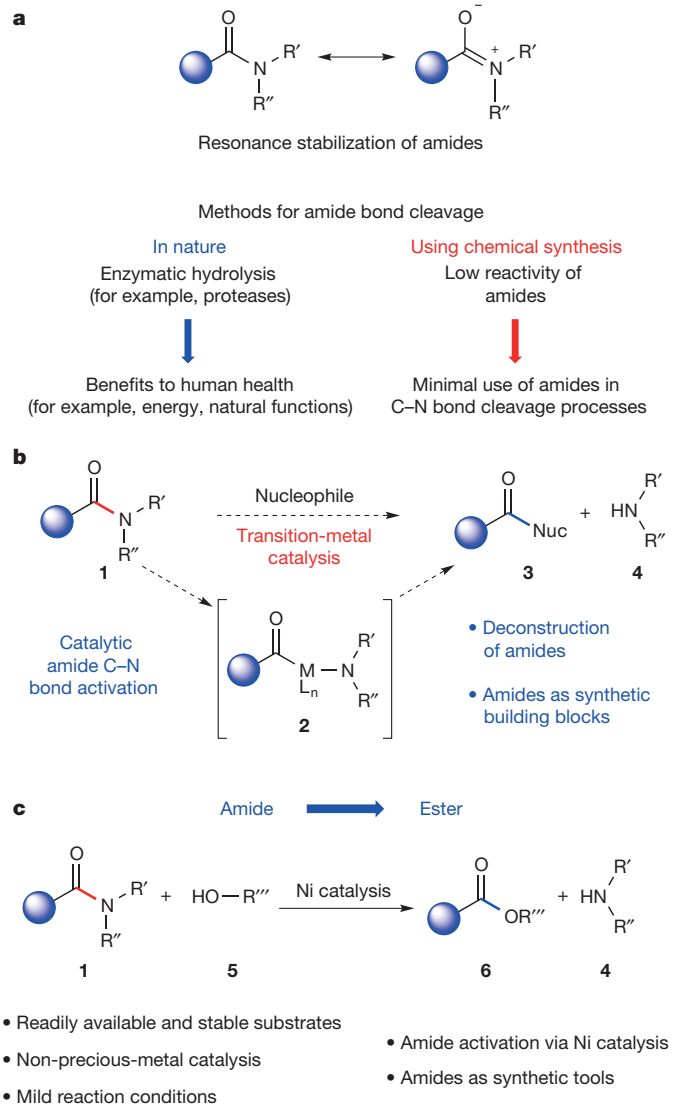
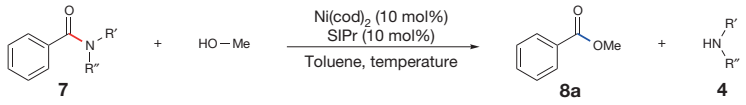


Figure 1 | Amide-bond cleavage using transition-metal catalysis. **a**, An illustration of the stability of amides and the contrast between how amides are used in nature and in chemical synthesis. **b**, Design of amide C–N bond activation to deconstruct amides and exploit them as synthetic building blocks (nuc, nucleophile; L_n, ligands coordinated to transition metal; blue spheres, R′, R″, R‴, any carbon-based functional groups). **c**, Strategy for the conversion of amides to esters.

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, USA.

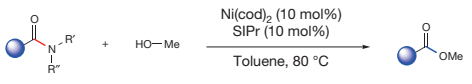


7 8a 4

Entry		Calculated ΔG (kcal mol^{-1})	Calculated oxidative addition barrier with Ni/SIPr (kcal mol^{-1})	Temperature (°C)	Equivalents of MeOH	Yield of ester
1	**7a**	+2.4	36.8	110	2.0	0%
2	**7b**	0.0	36.2	110	2.0	0%
3	**7c**	–1.1	34.0	110	2.0	23%
4	**7d**	–6.1	31.9	110	2.0	22%
5	**7e**	+3.1	39.0	110	2.0	0%
6	**7f**	–4.3	30.6	110	2.0	55%
7	**7g**	–6.8	26.0	110	2.0	>99%
8				80	1.2	>99%

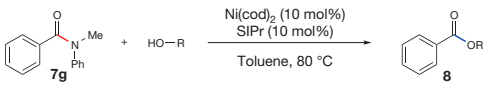
Figure 2 | Experimental and computational study of amide-bond activation during the conversion of benzamides 7 to methyl benzoate 8a. The ΔG values for the overall reactions were obtained using DFT calculations (assuming a temperature of 298 K). DFT methods were used to calculate oxidative addition barriers using Ni/SIPr as the metal/ligand combination. Reactions were carried out with bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$, 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 at the specified temperatures. Yields were determined by ^{1}H nuclear magnetic resonance (NMR) analysis using hexamethylbenzene as an internal standard. Me, methyl; OMe, methoxy; Ph, phenyl.

a



Entry	Amide substrate	Yield of methyl ester
1		88% (R = H)
2		80% (R = *p*-CF_3)
3		92% (R = *p*-F)
4		90% (R = *p*-OMe)
5		90% (R = *p*-Me)
6		83% (R = *m*-Me)
7		89% (R = *o*-Me)
8		94%
9		94%
10		91%
11		84%
12		56%
13		92%
14		78%
15		58%
16		49%
17		84% (R = Me)
18		89% (R = Bn)

b



Entry	Ester product	Yield of ester
19		82%
20		64%
21		67%
22		90%
23		49%
24		88%
25		67%
26		65%
27		91%
28		74%

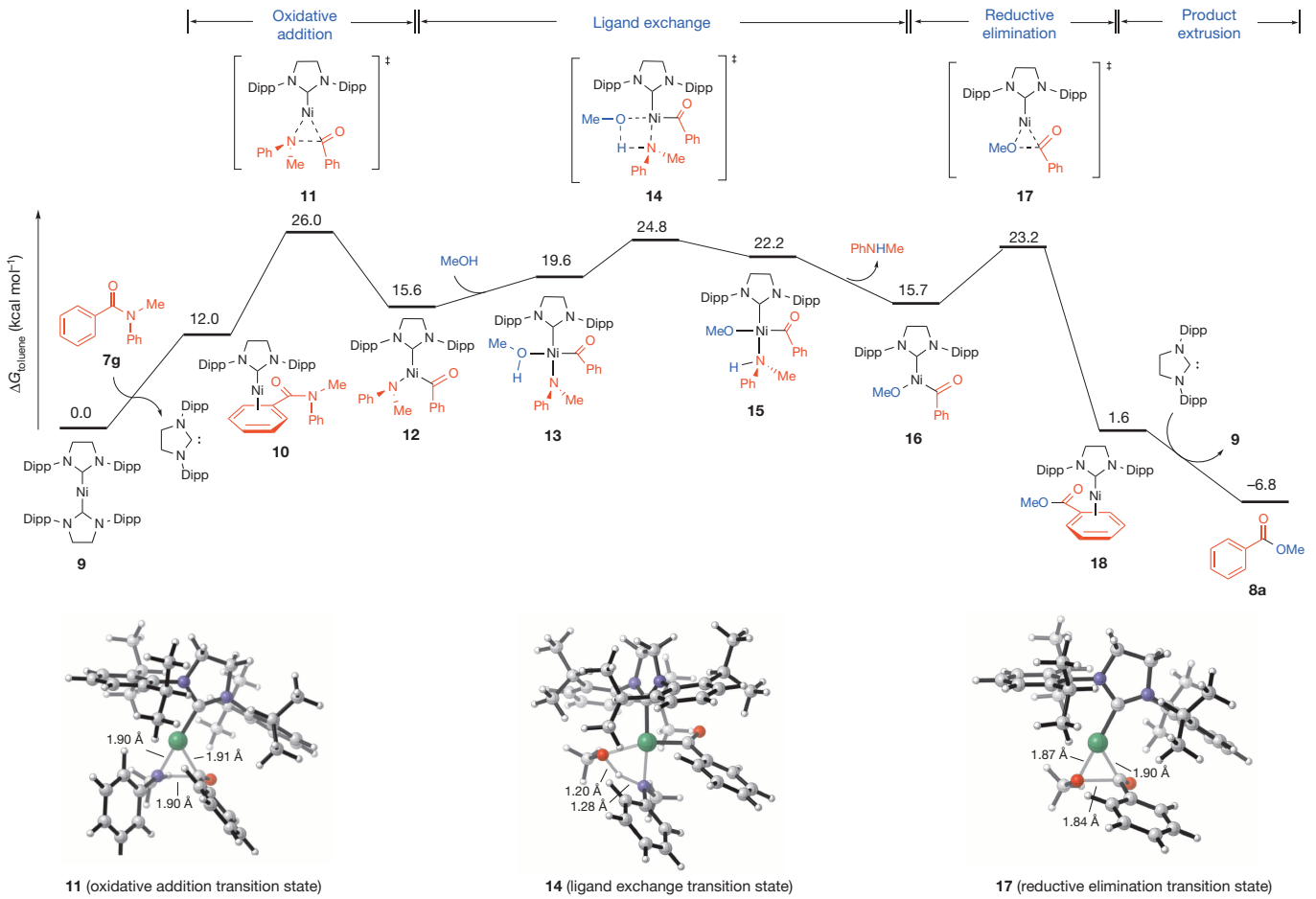
Figure 3 | Scope of our methodology. a, **b**, The scope of the amide-to-ester transformation was evaluated with respect to the amide substrate (**a**), and with respect to the alcohol nucleophile, using **7g** as the amide substrate (**b**). Reactions were carried out with $Ni(cod)_2$ (10 mol%), SIPr (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 isolated experiments, except for entry 10; the yield for entry 10 was determined by ^{1}H NMR analysis using hexamethylbenzene as an internal standard, owing to the volatility of the ester product. *t*-Bu, *tert*-butyl; *p*, *para*; *m*, *meta*; *o*, *ortho*.

transition-metal catalysis in organic synthesis, where there exist many examples of catalytic transformations occurring smoothly in the presence of amide linkages.

We validate the strategy outlined in Fig. 1b through the conversion of amides to esters (Fig. 1c). Amide to ester conversion, much like transamidation[11,12], remains a challenging and underdeveloped synthetic transformation. Amides are often stable enough that esterification is difficult and requires the use of harsh acidic or basic conditions, while employing a large excess of nucleophile (for example, using the alcohol nucleophile as a solvent)[1]. Perhaps the most promising protocol to achieve amide-to-ester conversions is Keck's methylation/hydrolysis sequence[13], although this methodology is limited to the synthesis of methyl esters. Esterifications using acyl aziridines[14] and *N*-methylamides (albeit with activation by nitrosation)[15] have also been reported. Here we demonstrate the nickel-catalysed conversion of amides to esters, which proceeds under exceptionally mild reaction conditions. In addition to establishing the scope of this methodology, we use density functional theory (DFT) calculations to predict whether the amide-to-ester conversion, or the reverse, is thermodynamically favoured. DFT calculations are also used to predict a plausible catalytic cycle. These experimental and computational studies not only substantiate the notion of using 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.

We examined the conversion of benzamides **7** to methyl benzoate **8a** both computationally (using the 'Gaussian 09' software; see Supplementary Information) and experimentally (Fig. 2). Because amides are known for their stability, we assessed whether the amide-to-ester conversion could be rendered thermodynamically favourable by the judicious choice of amide *N*-substituents. Using DFT methods, we calculated the change in Gibbs free energy ΔG for the reaction of amides **7** with methanol to give esters **8a** and amines **4**. Whether this transformation is favourable or not 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 energetically favourable. In contrast, esterifications of *N*-alkyl amides **7a**, **7b**, and **7e** were deemed thermodynamically unfavourable. 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 favoured (see Supplementary Information for further discussion)[16].

Encouraged by the unique ability of nickel to catalyse the activation of strong aryl–heteroatom bonds[17–19], particularly those in phenol[19], aniline[20–22], and phthalimide[23] derivatives, we also calculated the activation free energies for acyl C–N bond oxidative addition of each amide substrate using nickel catalysis. The barriers calculated for commercially available *N*-heterocyclic carbene ligand SIPr (entries 1–8) reveal that the oxidative addition barriers are reasonable in some cases. We studied these reactions experimentally using 10 mol% $Ni(cod)_2$, 10 mol% SIPr, 2.0 equivalents of methanol, and toluene as solvent at 110 °C for 12 h. There was good agreement between our observations and computational predictions. No reaction or low yields were seen for substrates **7a**–**7e** (entries 1–5). However, when the calculated ΔG and the oxidative addition barrier were favourable, substantial formation of product **8a** was observed (entries 6 and 7). Coupling of substrate **7g**



11 (oxidative addition transition state) **14** (ligand exchange transition state) **17** (reductive elimination transition state)

Figure 4 | Computational study of catalytic cycle. DFT methods were used to calculate the full catalytic cycle for the amide-to-ester conversion (assuming a temperature of 298 K). We propose that the reaction occurs by oxidative addition, ligand exchange, and reductive elimination. Key transition state structures (**11**, **14**, and **17**) are shown at the bottom. Dipp, 2,6-diisopropylphenyl.

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 the ligand are omitted, whereas the use of alternative *N*-heterocyclic carbene 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.

Having determined the optimal reaction conditions, we examined the scope of the transformation with regard to the amide substrate (Fig. 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. The transformation also 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. Naphthyl compounds readily coupled (entries 8 and 9), as did furan, quinoline, and isoquinoline substrates (entries 10–12, respectively). However, amides derived from alkyl carboxylic acids did not undergo the nickel-catalysed esterification under our reaction conditions. This attribute provides opportunities to realize selective amide C–N bond cleavages in more complex substrates (see below).

A variety of *N*-substituents were also surveyed, as shown in Fig. 3a. In addition to the longer *N*-butyl (Bu) and the branched *N*-*iso*-propyl 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*-*p*-toluenesulfonyl (Ts) derivative gave the corresponding ester in modest yield (entry 16), the corresponding *N*-*tert*-butyloxycarbonyl (Boc) substrate more efficiently underwent conversion to ester **8a** (entry 17). The analogous *N*-benzyl, *N*-*tert*-butyloxycarbonyl (*N*-Bn,Boc) substrate was also evaluated and gave the desired ester in 89% yield (entry 18). These results show that the methodology is not restricted to anilide substrates, as long as the overall reaction energetics are thermodynamically favourable (see Supplementary Information for energetics involving the *N*-Boc,Me substrate). Moreover, secondary benzamides can be used strategically as substrates for esterification, following a straightforward activation step (Boc-protection).

Using amide **7g** as the substrate, we evaluated the scope of the methodology with respect to the alcohol nucleophile (Fig. 3b). As shown, synthetically useful yields of product were obtained using only 1.2 equivalents of the alcohol, even when complex and hindered alcohols were used. Cyclohexanol, *t*-butanol, and 1-adamantol coupled smoothly to give the corresponding esters (entries 19–21, respectively); *tert*-butyl esters can readily be hydrolysed to carboxylic acids under acidic conditions. Similarly, we found that cyclopropyl carbinol and an oxetane-derived alcohol could be used in the esterification reaction (entries 22 and 23, respectively). The use of the hindered secondary alcohol (–)-menthol was also tested and 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), which further demonstrates the promise our methodology holds for reactions of heterocyclic substrates. As shown in entries 27 and 28, a complex sugar-containing alcohol bearing two acetals and an estrone-derived steroidal alcohol, respectively, also underwent the desired esterification reaction.

Although nickel-catalysed aryl and acyl C–O bond activation processes have been previously studied computationally[24–28], 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)$_2$] 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

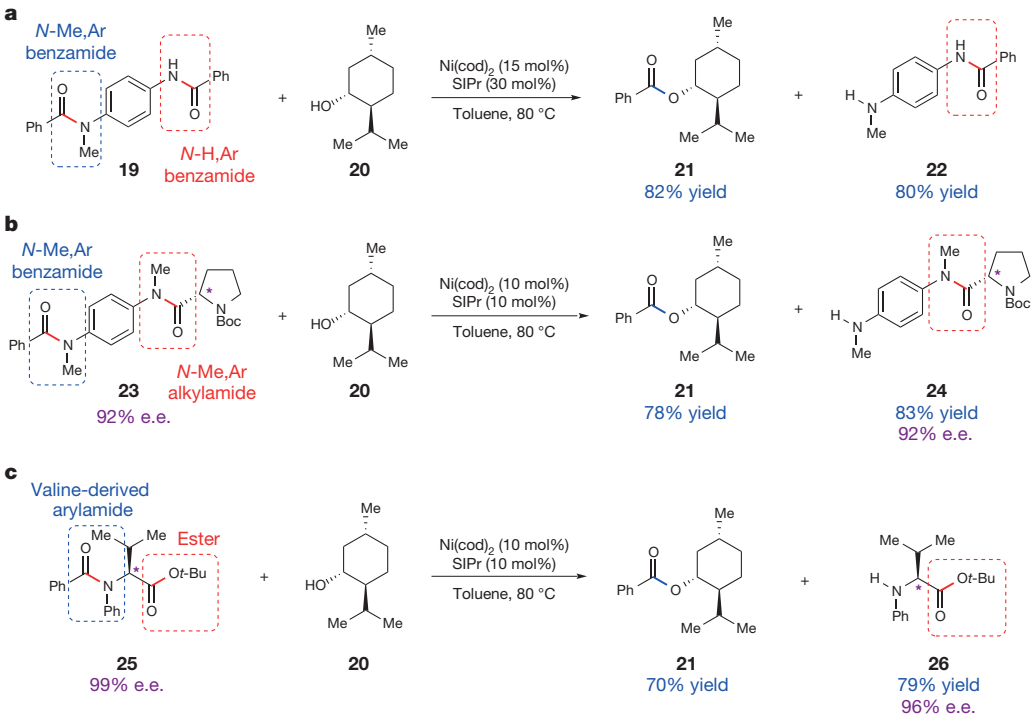


Figure 5 | Selective amide-bond cleavage processes. a, Cleavage of tertiary over secondary amide using menthol (1.2 equiv.). **b**, Cleavage of benzamide over an alkyl proline-derived amide using menthol (1.2 equiv.). **c**, Cleavage of valine-derived amide in the presence of an ester using menthol (1.2 equiv.). e.e., enantiomeric excess.

overall barrier of 26.0 kcal mol^{-1} relative to the resting state **9**. The overall reaction is thermodynamically favoured by −6.8 kcal mol^{-1}. Because decarbonylation of acyl nickel species have been observed[29,30], 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 favourable than the product formation pathways.

As highlighted by the experiments shown in Fig. 5, the nickel-catalysed conversion of amides to esters can be used to achieve selective and mild amide-bond cleavages. First, we performed the esterification of bis(amide) substrate **19** using (–)-menthol (Fig. 5a). Although both amides are *N*-arylated benzamides, only the tertiary amide was cleaved to give ester **21**, while also releasing aminoamide **22**. Second, bis(amide) **23**, which possesses two tertiary amides, was studied in the nickel-catalysed esterification reaction (Fig. 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 (Fig. 5c). Upon exposure of **25** to 1.2 equivalents of (–)-menthol and the nickel-catalysed conditions, ester **21** and aminoester **26** were obtained in 70% and 79% yields, respectively. We believe 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 (for example, **23**). Compounds **24** and **26** were obtained in high enantiomeric excess, highlighting the mild nature of the reaction conditions, which avoid any substantial epimerization of the α stereocentres.

We have presented an efficient way to convert 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 is achieved in the presence of other functional groups, including less reactive amides and esters, without the epimerization of α stereocentres. We envision that this methodology will lead to advances 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 stereocentres. This study should enable the further use of amides as valuable building blocks for the construction of C–heteroatom or C–C bonds using non-precious-metal catalysis.

Received 20 December 2014; accepted 20 May 2015.
Published online 22 July 2015.

1. Greenberg, A., Breneman, C. M. & Liebman, J. F. (eds) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science* (Wiley, 2003).
2. Pauling, L., Corey, R. B. & Branson, H. R. The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain. *Proc. Natl Acad. Sci. USA* **37,** 205–211 (1951).
3. Brix, K. & Stöcker, W. (eds) *Proteases: Structure and Function* (Springer, 2013).
4. Corey, E. J. & Cheng, X.-M. *The Logic of Chemical Synthesis* (Wiley, 1995).
5. Hudlicky, T. & Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products* (Wiley, 2007).
6. Van Vranken, D. L. & Weiss. G. A. *Introduction to Bioorganic Chemistry and Chemical Biology* (Garland Science, 2013).
7. Spletstoser, J. T., White, J. M., Tunoori, A. R. & Georg, G. I. Mild and selective hydrozirconation of amides to aldehydes using $Cp_2Zr(H)Cl$: scope and mechanistic insight. *J. Am. Chem. Soc.* **129,** 3408–3419 (2007).
8. Nahm, S. & Weinreb, S. M. *N*-methoxy-*N*-methylamides as effective acylating agents. *Tetrahedron Lett.* **22,** 3815–3818 (1981).
9. Blangetti, M., Rosso, H., Prandi, C., Deagostino, A. & Venturello, P. Suzuki–Miyaura cross-coupling in acylation reactions, scope and recent developments. *Molecules* **18,** 1188–1213 (2013).
10. Tatamidani, H., Kakiuchi, F. & Chatani, N. A new ketone synthesis by palladium-catalyzed cross-coupling reactions of esters with organoboron compounds. *Org. Lett.* **6,** 3597–3599 (2004).
11. Dineen, T. A., Zajac, M. A. & Myers, A. G. Efficient transamidation of primary carboxamides by in situ activation with *N,N*-dialkylformamide dimethyl acetals. *J. Am. Chem. Soc.* **128,** 16406–16409 (2006).
12. 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.* **131,** 10003–10008 (2009).
13. Keck, G. E., McLaws, M. D. & Wager, T. T. A direct and mild conversion of tertiary aryl amides to methyl esters using trimethyloxonium tetrafluoroborate: a very useful complement to directed metalation reactions. *Tetrahedron* **56,** 9875–9883 (2000).
14. Nishimoto, S.-i., Izukawa, T. & Kagiya, T. Photo-induced ring-opening reactions of 1-(2-naphthoyl)aziridine in various solvents. *Bull. Chem. Soc. Jpn* **55,** 1484–1488 (1982).
15. White, E. H. The chemistry of *N*-alkyl-*N*-nitrosoamides. II. A new method for the deamination of aliphatic amines. *J. Am. Chem. Soc.* **77,** 6011–6014 (1955).
16. Guthrie, J. P., Pike, D. C. & Lee, Y.-C. Equilibrium constants and heats of formation of methyl esters and *N,N*-dimethyl amides of substituted benzoic acids. *Can. J. Chem.* **70,** 1671–1683 (1992).
17. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **509,** 299–309 (2014).
18. Mesganaw, T. & Garg, N. K. Ni- and Fe-catalyzed cross-coupling reactions of phenol derivatives. *Org. Process Res. Dev.* **17,** 29–39 (2013).
19. Rosen, B. M. *et al.* Nickel-catalyzed cross-couplings involving carbon–oxygen bonds. *Chem. Rev.* **111,** 1346–1416 (2011).
20. Blakey, S. B. & MacMillan, D. W. C. The first Suzuki cross-couplings of aryltrimethylammonium salts. *J. Am. Chem. Soc.* **125,** 6046–6047 (2003).
21. Zhang, X.-Q. & Wang, Z.-X. Nickel-catalyzed cross-coupling of aryltrimethylammonium triflates and amines. *Org. Biomol. Chem.* **12,** 1448–1453 (2014).
22. Tobisu, M., Nakamura, K. & Chatani, N. Nickel-catalyzed reductive and borylative cleavage of aromatic carbon–nitrogen bonds in *N*-aryl amides and carbamates. *J. Am. Chem. Soc.* **136,** 5587–5590 (2014).
23. Shiba, T., Kurahashi, T. & Matsubara, S. Nickel-catalyzed decarbonylative alkylidenation of phthalimides with trimethylsilyl-substituted alkynes. *J. Am. Chem. Soc.* **135,** 13636–13639 (2013).
24. Quasdorf, K. W. *et al.* Suzuki–Miyaura cross-coupling of aryl carbamates and sulfamates: experimental and computational studies. *J. Am. Chem. Soc.* **133,** 6352–6363 (2011).
25. Mesganaw, T. *et al.* Nickel-catalyzed amination of aryl carbamates and sequential site-selective cross-couplings. *Chem. Sci.* **2,** 1766–1771 (2011).
26. Hong, X., Liang, Y. & Houk, K. N. Mechanisms and origins of switchable chemoselectivity of Ni-catalyzed C(aryl)–O and C(acyl)–O activation of aryl esters with phosphine ligands. *J. Am. Chem. Soc.* **136,** 2017–2025 (2014).
27. Lu, Q., Yu, H. & Fu, Y. Mechanistic study of chemoselectivity in Ni-catalyzed coupling reactions between azoles and aryl carboxylates. *J. Am. Chem. Soc.* **136,** 8252–8260 (2014).
28. Xu, H. *et al.* Key mechanistic features of Ni-catalyzed C–H/C–O biaryl coupling of azoles and naphthalene-2-yl pivalates. *J. Am. Chem. Soc.* **136,** 14834–14844 (2014).
29. Yamamoto, T., Ishizu, J., Kohara, T., Komiya, S. & Yamamoto, A. Oxidative addition of aryl carboxylates to nickel(0) complexes involving cleavage of the acyl–oxygen bond. *J. Am. Chem. Soc.* **102,** 3758–3764 (1980).
30. Amaike, K., Muto, K., Yamaguchi, J. & Itami, K. Decarbonylative C–H coupling of azoles and aryl esters: unprecedented nickel catalysis and application to the synthesis of muscoride A. *J. Am. Chem. Soc.* **134,** 13573–13576 (2012).

Supplementary Information is available in the online version of the paper.

Acknowledgements We are grateful to Boehringer Ingelheim, DuPont, Bristol-Myers Squibb, the Camille and Henry Dreyfus Foundation, the A. P. Sloan Foundation, the S. T. Li Foundation, the University of California, Los Angeles (UCLA), and the NIH-NIGMS (grant number GM036700 to K.N.H.) for financial support. We are grateful to the NIH (grant number F31 GM101951-02 to N.F.F.N.), the NSF (grant number DGE-1144087 to E.L.B.), the Foote Family (L.H., T.K.S. and X.H.), and the ACS Division of Organic Chemistry (L.H.) for fellowship support. Computations were performed with resources made available by the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (grant number OCI-1053575), as well as the UCLA Institute of Digital Research and Education (IDRE). This work was also supported by shared instrumentation grants from the NSF (grant number CHE-1048804) and the National Center for Research Resources (grant number S10RR025631).

Author Contributions L.H., N.F.F.N., T.K.S., and E.L.B. designed and performed the experiments and analysed the experimental data; X.H., Y.-F.Y., and P.L. designed the computational studies and performed the analysis; K.N.H. and N.K.G. conceived and directed the investigations, and prepared the manuscript with contributions from all authors; all authors contributed to discussions.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to K.N.H. (houk@chem.ucla.edu) and N.K.G. (neilgarg@chem.ucla.edu).