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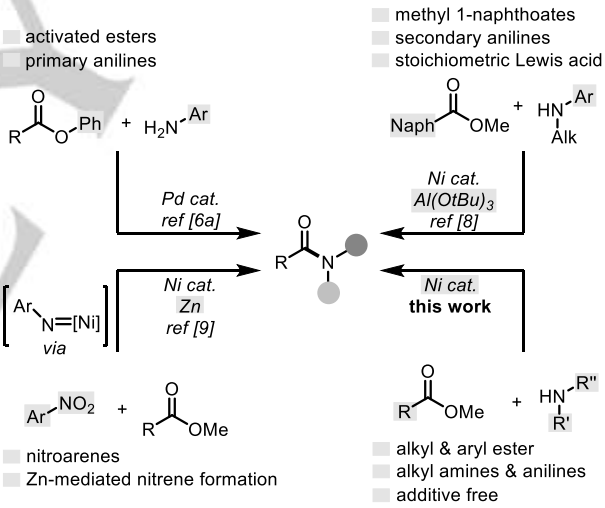
Nickel-Catalyzed Amide Bond Formation from Methyl Esters

Taoufik Ben Halima, Jeanne Masson-Makdissi, Stephen G. Newman *

Abstract: Despite being one of the most important and frequently run chemical reactions, the synthesis of amide bonds is accomplished primarily by wasteful methods that proceed by stoichiometric activation of one of the starting materials. We report a nickel-catalyzed procedure that can enable diverse amides to be synthesized from abundant methyl ester starting materials, producing only volatile alcohol as a stoichiometric waste product. In contrast to acid- and base-mediated amidations, the reaction is proposed to proceed by a neutral cross coupling-type mechanism, opening up new opportunities for direct, efficient, chemoselective synthesis.

Amides serve as the backbone of peptides, the key functional group that gives many lifesaving medicines their activity, and the linking functionality in some of the world's most important materials. Recent estimates from the U.S. patent literature suggest amidations represent ~15% of all transformations, the majority of which proceeds by reaction of an amine with an activated carboxylic acid.[1],[2] In contrast, direct amide bond formation from amines and unactivated esters are seldom utilized due to the need to deprotonate the amine with an aggressive organometallic reagents such as $AlMe_3$.[3] While some milder variants have been recently developed,[4] issues with epimerizable stereocenters, sensitive functional groups, or the need for excess reactant limit general utility. Essentially all established pathways rely on nucleophilic attack of the amine onto the ester carbonyl group, and as such, use of weak nucleophiles such as anilines is seldom achieved. These limitations are unfortunate because carboxylic acids are frequently protected as esters and later hydrolyzed in preparation for subsequent amidation. Better methods that make direct use of methyl esters as coupling partners would not only allow chemists to prepare amides with improved atom economy but, in many cases, improved step economy as well.

Recently, the use of transition metal catalysts to activate strong C–O bonds by oxidative addition has been identified as a viable pathway for ester derivatization, unique from traditional acid/base strategies.[5] For instance, our lab and others recently showed that phenyl esters can be used to make amides (Scheme 1), ketones, biaryls, and more with Pd and Ni catalysis.[6] While conceptually interesting, these phenol-derived substrates are considerably activated relative to abundant methyl and ethyl esters, and do not represent a major practical advance over traditional methods proceeding by stoichiometric ester activation. The development of coupling reactions with unactivated esters is needed to make this strategy practical.[7] Towards methyl ester activation, Garg et al. recently demonstrated the use of a Ni catalyst with stoichiometric $Al(O\textit{t}\text{-}Bu)_3$ to enable direct amide bond formation,[8] though the substrate scope was limited to methyl 1-naphthoate esters and N-alkyl aniline derivatives. These transformations were noted to be energetically unfavorable, and the aluminum additive was noted to both facilitate C–O bond activation and make the reaction more thermodynamically feasible. Hu et al. accomplished a similar transformation with more diverse ester starting materials but required in situ generated azobenzene nucleophiles by reduction of aniline derivatives with stoichiometric Zn.[9] Here-in, we present how transition metal-catalyzed ester activation can be exploited to couple a very broad range of methyl esters with amines, avoiding the substantial scope limitations of existing systems. A simple Ni(0) catalyst is used, providing high functional group tolerance and producing methanol as the only stoichiometric by-product.[10] This represents the first general cross-coupling of methyl esters to form carbonyl-containing products in the absence of stoichiometric activating agents, and is a unique demonstration of direct amidation of esters that doesn't rely on acid or base catalysis. As a consequence, these conditions are applicable even when using weakly nucleophilic coupling partners such as aniline derivatives, which render the net process thermodynamically uphill.



Scheme 1*:* Recent Approaches to Metal-Catalyzed Amide Bond Formation.

We began by investigating the reaction of methyl benzoate with a selection of metals, ligands, and nucleophiles that had proven effective in previous catalytic coupling reactions that require cleavage of strong C–O bonds (Fig. S1). After an initial hit with a Ni/NHC catalyst system, optimization was carried out that revealed $Ni(cod)_2$ with 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) as a ligand could enable the coupling of esters with amines at 140 °C, and a range of control experiments revealed no background reaction in the absence of catalyst (Table S1). With this catalyst confirmed to be uniquely effective at enabling the reaction, a wide range of amides were formed. Using simple ester starting materials, amides derived from secondary aliphatic amines (**1**–**6**) and primary amines (**7**–**12**) could all be synthesized in good yields (Scheme 2). A competition experiment between

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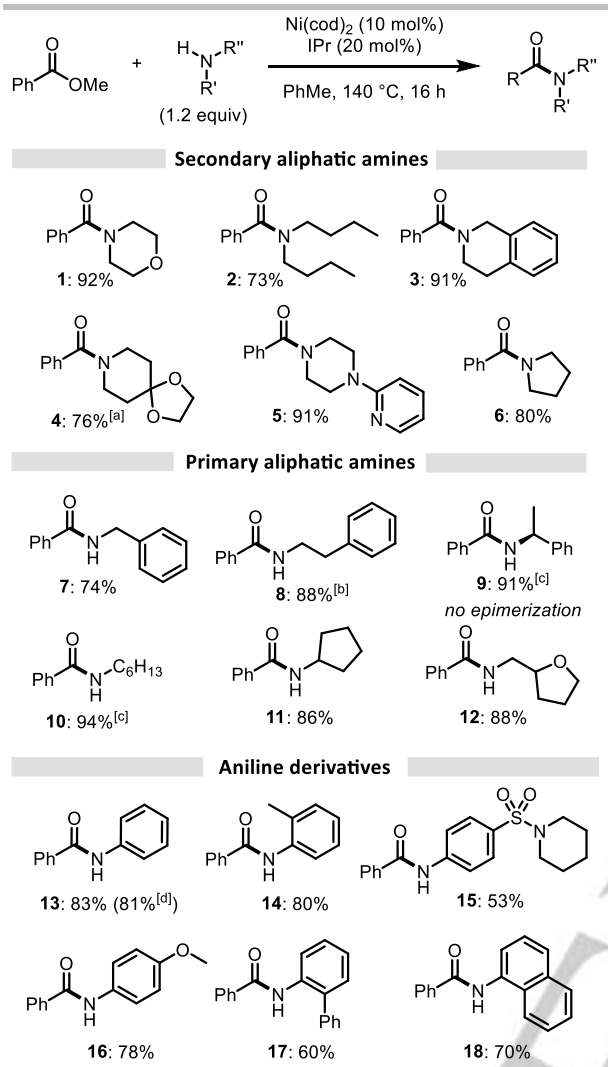
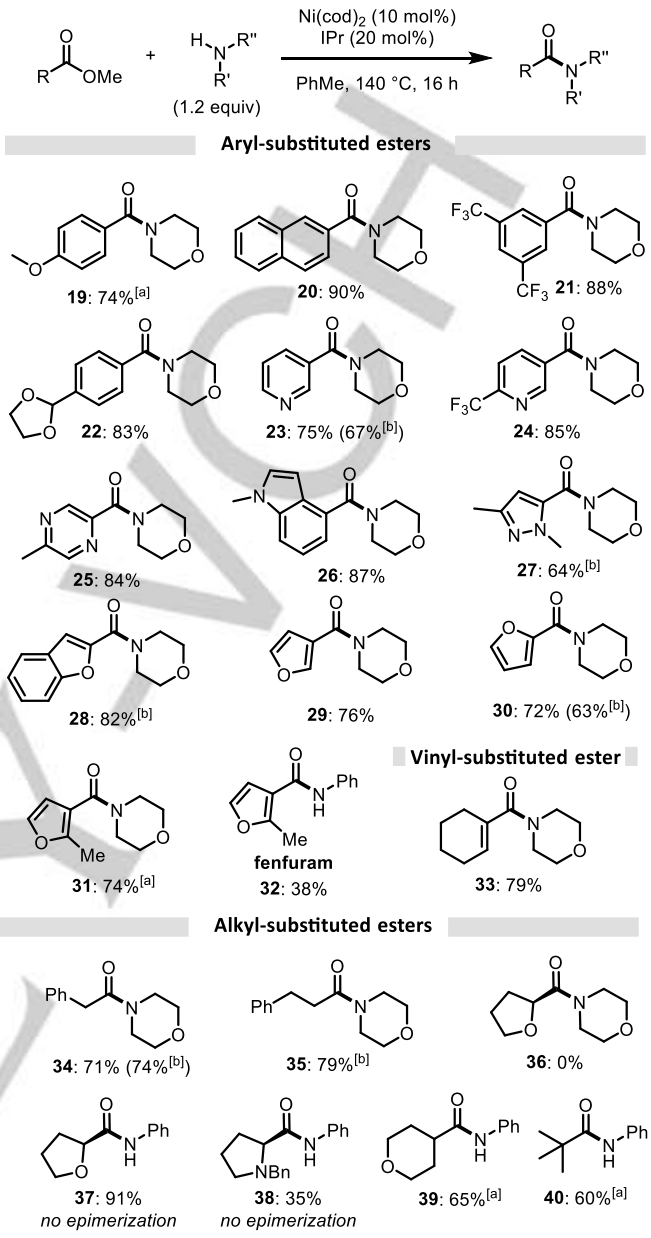


Scheme 2: Scope of Amines in Ni-Catalyzed Amidation. General reaction conditions: methyl benzoate (0.20 mmol), amine (0.24 mmol), $Ni(cod)_2$ (10 mol%), IPr (20 mol%), toluene (1 mL), 140 °C for 16 h. [a] dioxane instead of toluene. [b] competition experiment with 1 equiv. phenethylamine and 1 equiv. dibutylamine. [c] 150 °C instead of 140 °C. [d] Et ester used instead of Me ester.

phenylethylamine and dibutylamine demonstrated high chemoselecitivity, providing the secondary amide **8** in 88% yield. Most importantly, non-nucleophilic aniline derivatives, which typically require pre-treatment with aggressive base prior to reaction with esters, could be used without any modification of the conditions (**13**–**18**). Furthermore, ethyl benzoate could also be used to make benzanilide **13**, demonstrating that the reaction is not limited to methyl esters.

The reaction was also possible with a variety of ester coupling partners to prepare morpholine-derived amides with aromatic (**19**–**22**) and heteroaromatic (**23**–**31**) rings (Scheme 3). Fenfuram (**32**) could also be made, albeit in moderate yield, providing a potentially valuable route to this agrochemical that is industrially prepared by stoichiometric activation of the aniline with aluminum.[11] An α,β- unsaturated amide (**33**) could be prepared without any competitive Michael addition occurring. While primary aliphatic ester starting materials could be used to provide good yields with morpholine as a nucleophile (**34**, **35**), more hindered esters were problematic (**36**). Fortunately, aniline proved to be effective nucleophile for this substrate class (**37**–**40**). The tolerance of weakly nucleophilic anilines, hindered nucleophiles,



Scheme 3: Scope of Esters in Ni-Catalyzed Amidation. General reaction conditions: ester (0.20 mmol), amine (0.24 mmol), $Ni(cod)_2$ (10 mol%), IPr (20 mol%), toluene (1 mL), 140 °C for 16 h. [a] 150 °C instead of 140 °C. [b] Et ester used instead of Me ester.

diverse heterocycles, acid-sensitive acetals, and a range of substitution-patterns on both coupling partners highlights the strength of this pathway for ester activation, particularly in contrast to acid- or base-mediated transformations. Furthermore, no epimerization was observed when using enantiopure amine (Scheme 2, **9**) or ester (Scheme 3, **37**, **38**) starting materials. Notable limitations include the use of tertiary amine nucleophiles, unhindered acrylate derivatives, relatively acidic protons, and certain sterically hindered substrates (Fig. S3).

To further evaluate the advantages of this amide bond-forming method, synthetic applications were explored. The orthogonality of using a metal to activate esters was investigated via reactions with methyl 4-fluorobenzoate **41**. Traditional S_NAr reactions were achieved when using DMSO as a solvent (**42**, **43**), while amide

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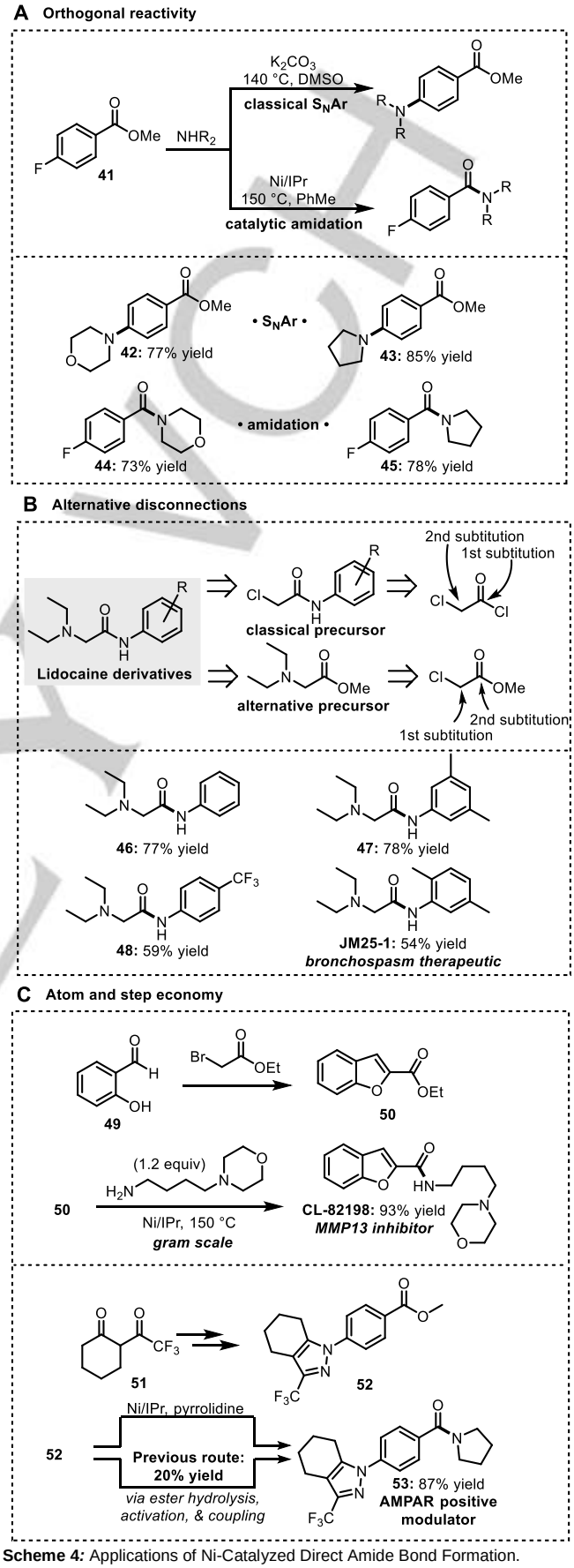
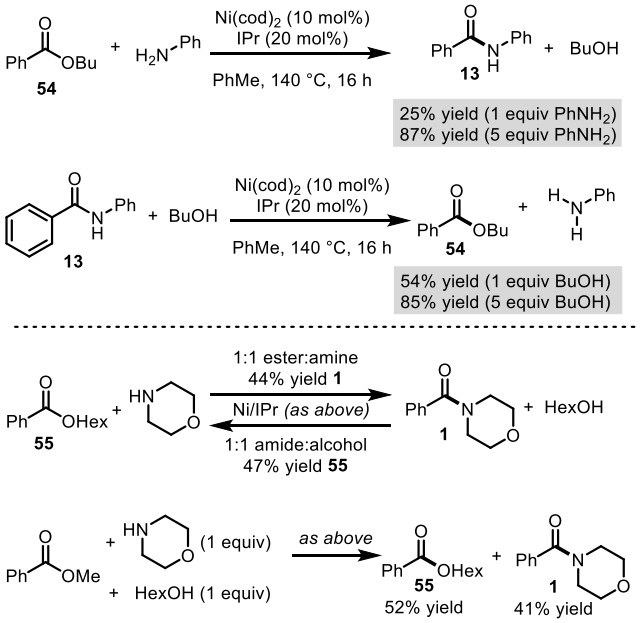
bond formation occurred selectively in toluene with the Ni catalyst (**44**, **45**) (Scheme 4a). Use of esters rather than carboxylic acids or acid chlorides as coupling partners also enables useful synthetic disconnections for medicinal chemistry. For instance, variation of the amide-component of lidocaine is typically accomplished by subsequent substitutions of chloroacetyl chloride, with each new derivative requiring a two-step process to be carried out. With ester activation, methyl chloroacetate can instead be used to first substitute at the α-carbon and then diversify the amide component by Ni-catalyzed coupling. This strategy was used to more efficiently access lidocaine derivatives **46**–**48**[12] and **JM25-**1,[13] a recently discovered potential bronchospasm therapeutic (Scheme 4b). Lastly, the value of directly coupling esters with amines was demonstrated through the synthesis of bioactive molecules with improved step and atom economy over established routes (Scheme 4c). For instance, benzofuran ester **50** can be directly converted into over 1 gram of the commercially available MMP13 inhibitor **CL-82198**, avoiding the wasteful EDC-mediated couplings used to make analogous amides.[14] Similarly, lead AMPAR positive modulator **53** could be made by direct coupling, rather than requiring low yielding hydrolysis, CDI-activation, and coupling process.[15] Notably, the corresponding esters **50** and **52** are readily accessible from building blocks **49** and **51**, making them more desirable starting materials than the corresponding carboxylic acids.

Mechanistically, the reaction likely begins via insertion of the catalyst into the strong ester C–O bond as has been previously demonstrated, primarily with activated esters.[16] The NHC ligand on the resultant acyl-Ni species is believed to be sufficiently bulky to prevent decarbonylation, as was observed for analogous Pd complexes.[8b] Unlike more traditional catalytic amination reactions, which require a strong external base to facilitate deprotonation of the amine nucleophile, an intramolecular proton exchange with the methoxide can occur to provide a Ni(II) amido complex that can then undergo reductive elimination. This pathway is analogous to that proposed for the reverse reaction – Ni-catalyzed conversion of amides to esters – first developed by Garg, Houk, and co-workers.[17] In this pioneering work, reductive elimination of a proposed acyl Ni(II) methoxide intermediate was calculated to be 22.5 kcal/mol downhill with an activation energy of 7.5 kcal/mol. By the principle of microscopic reversibility, the activation energy for the oxidative addition of this Ni(0)-NHC catalyst into the C–O bond of a methyl ester can be predicted to be a kinetically reasonable 30.0 kcal/mol. The amide to ester transformation was calculated to be thermodynamically downhill with aniline and morpholine as the amine leaving groups, and thermodynamically uphill with pyrrolidine, raising the question of how the current ester to amide conversion can be accomplished even with aniline derivatives.

Given the relatively high reaction temperature used and the low boiling point of the methanol byproduct (63 °C), a series of experiments were run with esters bearing less volatile alcohol leaving groups (Scheme 5). While the reaction of aniline with both methyl and ethyl benzoate efficiently provides benzanilide **13**, the use of butyl benzoate **54** gives only 25% yield. Running the reaction in reverse by treating benzanilide **13** with 1 equivalent of butanol (BuOH) under the reaction conditions gives **54** in 54% yield, demonstrating that esterification is more efficient for these coupling partners. Both the amidation and esterification can be driven almost to completion when using an excess of the nucleophilic coupling component. Next, the use of morpholine



Scheme 4: Applications of Ni-Catalyzed Direct Amide Bond Formation.



Scheme 5*:* Controlling reaction equilibrium.

was tested with hexyl benzoate **55**. Running this reaction in the forward direction provided amide **1** in 44% yield. Operating in reverse by treating amide **1** with one equivalent of hexanol (HexOH) gave ester **55** in 47% yield. Lastly, a competition experiment between methyl benzoate, morpholine, and hexanol gave a mixture of the ester and amide products in 52% and 41% yield, respectively, with trace recovery of the starting material. Together, these experiments indicate that the reaction is under equilibrium control. In agreeance with calculations from the Garg and Houk groups, formation of benzanilide **13** being thermodynamically uphill and formation of benzoylmorpholine **1** is near thermoneutral. When methyl benzoate is used as a starting material, the high reaction temperature leads to removal of the methanol by-product from the liquid phase and allows reactions to be driven forward even with near equimolar stoichiometry. These amidations and esterifications are analogous to other transformations that can be controlled by Le Chatelier's Principle such as ketone hydrogenation and alcohol dehydrogenation, which can be driven in either direction by the same catalyst with the addition or removal of hydrogen.[18] Further studies on the importance of the alcohol leaving group are provided in Figures S4 and S5.

In summary, we have developed a catalytic amide bond forming reaction from methyl esters and a range of aliphatic amine and aniline coupling partners. The reaction is proposed to proceed by a cross-coupling pathway, making it mechanistically distinct from the majority of catalytic amidations that rely on acid-mediated activation of the ester or base-mediated activation of the amine. Consequently, the reaction is highly general, works with both aliphatic amines and anilines, tolerates diverse heterocycles and epimerizable stereocenters, and was shown to avoid side reactions with an acetal, ketal, Michael acceptor, and S_NAr electrophile. We anticipate that this procedure will be an appealing alternative to the commonly executed hydrolysis, acid chloride formation, and Schotten-Baumann sequence for accessing amides from esters, or other methods that require aggressive stoichiometric reagents. While it is remarkable that a simple and well-known Ni/NHC catalyst system can enable this transformation, relatively high catalyst loadings and reaction temperatures leave room for improvement. Further efforts in the design of tailored ligands will be needed to further establish cross-coupling as an important strategy for derivatization of common methyl esters.

Acknowledgements

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Keywords: cross-coupling • nickel catalysis • C–O activation • amides

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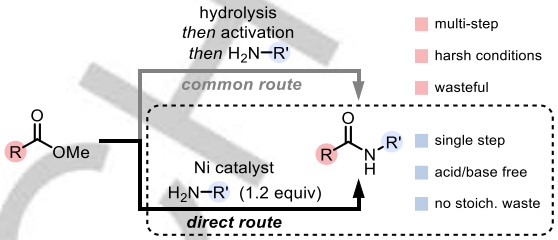

The cross-coupling between diverse esters and amines to form amides is enabled by the use of Ni catalysis. Unlike traditional approaches to amide bond formation, the reaction works in the absence of acidic or basic additives, and both aliphatic amines and aniline derivatives can be effectively utilized.

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