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Methyl Esters as Cross-Coupling Electrophiles: Direct Synthesis of Amide Bonds

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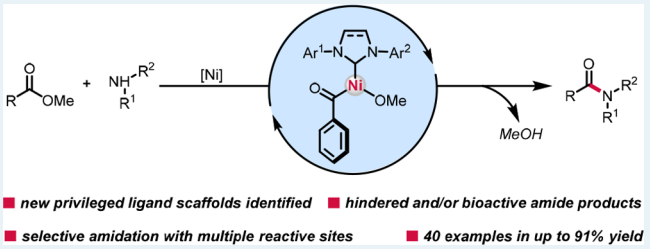
Supporting Information

ABSTRACT: Amide bond formation and transition metal-catalyzed cross-coupling are two of the most frequently used chemical reactions in organic synthesis. Recently, an overlap between these two reaction families was identified when Pd and Ni catalysts were demonstrated to cleave the strong C−O bond present in esters via oxidative addition. When simple methyl and ethyl esters are used, this transformation provides a powerful alternative to classical amide bond formations, which commonly feature stoichiometric activating agents. Thus far, few redox-active catalysts have been demonstrated to activate the C(acyl)−O bond of alkyl esters, which makes it difficult to perform informed screening when a challenging reaction needs optimization. We demonstrate that Ni catalysts bearing diverse NHC, phosphine, and nitrogen-containing ligands can all be used to activate methyl esters and enable their use in direct amide bond formation.



KEYWORDS: *nickel, amide bond formation, cross-coupling, esters*

INTRODUCTION

As one of the important functional groups of peptides, pharmaceuticals, agrochemicals, and synthetic materials, amides play a central role in the function of organic molecules.[1] As a consequence, the synthesis of amide bonds is one of the most frequently run chemical reactions, usually accomplished by uniting a carboxylic acid and free amine.[2] While progress has been made in enabling this reaction to be performed directly,[3] the majority of procedures first activate the carboxylic acid moiety as an acid chloride or by using coupling reagents such as EDC, HATU, and PyBOP (Scheme 1A),[4] rendering the carbonyl group sufficiently electrophilic for attack by the amine nucleophile. The high need for amide-containing molecules along with the high cost and waste generated using these common amide bond-forming procedures has led to numerous calls for more efficient methods.[5]

Esters can provide a promising alternative to carboxylic acids as reaction partners for amide bond formation. Simple methyl and ethyl esters are broadly available, stable, and capable of being carried through multistep synthesis. Alkyl groups are considered a protecting group for carboxylic acids. Further, esters are a useful functional group for α-functionalization and heterocycle syntheses. Due to their nonionizable nature, a different set of challenges is encountered when trying to use esters as electrophiles in amide bond formation. Existing methods primarily rely on activation of the ester by a Lewis acid[6] or activation of the amine with aggressive organometallic base,[7] with each strategy having significant scope limitations. As a consequence of these limitations, it is common for synthetic chemists to convert esters to amides by first hydrolyzing to the corresponding carboxylic acid and activation with, e.g., thionyl chloride or peptide coupling reagents prior to amide bond formation.[8]

In recent years, the development of transition-metal-catalyzed C−O bond activation methods has expanded the diversity and robustness of (pseudo)halide coupling partners that can participate in cross-coupling reactions.[9] For instance, esters can be used as a viable alternative to acid chlorides for the synthesis of diverse carbonyl-containing and decarbonylated coupling products.[10] This strategy, commonly accomplished with Pd and Ni catalysis, is facilitated by oxidative addition into the C(acyl)−O bond. Early reports in this area used easily activated species such as anhydrides, nitrophenyl esters, enol ether esters, and pyridyl esters.[11] More robust phenyl esters were first reported by Itami, Yamaguchi, and co-workers using Ni(0) to catalyze C−H functionalization reactions.[12] A number of powerful C−C and C−heteroatom-forming reactions were reported afterward using phenyl esters as aryl electrophiles via decarbonylative coupling[13] and as acyl electrophiles via a carbonyl-retention mechanistic pathway.[14]

While phenyl esters are significantly more robust than traditional activated acyl electrophiles such as acid chlorides and anhydrides, they are still nonabundant functional groups that must first by synthesized prior to application. More useful catalytic methods would be able to directly use abundant methyl and ethyl ester starting materials, though the strength

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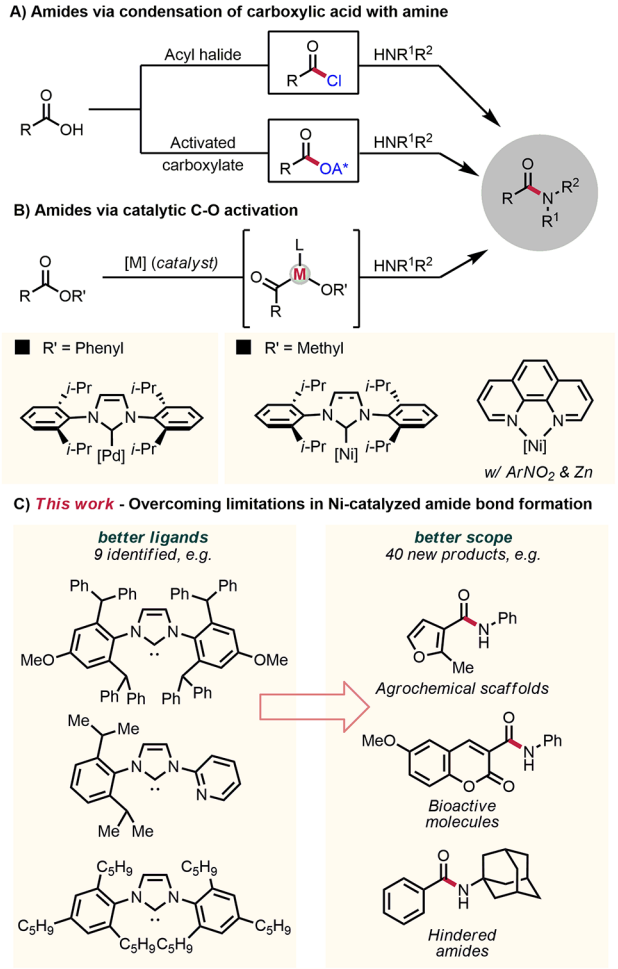
Scheme 1. Example Methods for Amide Bond formation



of the corresponding C−O bond makes them more challenging to activate.[15] In 2016, Garg and co-workers reported the first amide bond-forming reaction of methyl esters using a Ni(0) catalyst and Al(O*t*-Bu)$_3$ as an activating agent (Scheme 1B).[16] This seminal report was unfortunately limited to use of methyl 1-naphtholate esters and *N*-alkyl anilines. Computational studies and control experiments supported a cross-coupling-type mechanism with the Ni catalyst oxidatively adding to the ester C−O bond. Further progress was made toward nontraditional amide bond formation pathways from esters by our group on the use of Pd catalysis[17] and by Hu and co-workers in 2017, who reported a nickel-catalyzed coupling of nitroarenes mediated by stoichiometric zinc.[18] Their reaction was proposed to proceed by insertion to the C−O bond with an Ni(II) nitrene intermediate. Notably, a large portion of anilines is derived from nitroarenes, making this method highly step economical.

Very recently, our group reported that a Ni−NHC catalyst system could enable direct, additive-free synthesis of amides from simple alkyl esters.[19] The reaction worked with esters bearing both sp^2-(arene)- and sp^3-(alkyl)-hybridized carbons at the α position. Furthermore, both aliphatic amines and anilines derivatives could be used. Mechanistically, a cross-coupling-type pathway was proposed and later supported by mechanistic studies by Hong and co-workers, who showed that all three key steps—oxidative addition, proton transfer, and reductive elimination—have similar transition state energies.[20] Since the transformation does not rely on traditional nucleophile−electrophile pairing, both electron-donating and electron-withdrawing functional groups were tolerated on either reaction partner. Similarly, the absence of any basic or acidic additives in the reaction conditions enabled epimerizable stereocenters, acetals, ketals, Michael acceptors, and sites susceptible to attack via S$_N$Ar reactions to be untouched.

Given the high demand for more efficient amide bond-forming reactions and the traditional reliance on acid/base chemistry to functionalize esters, we wished to expand the boundaries of our Ni-catalyzed process. Although our initially reported substrate scope showed over 50 examples of diverse ester and amine reaction partners, many substrates could not be prepared in synthetically useful yields. For example, sterically hindered substrates (e.g., ortho-substituted anilines, benzoates), certain heterocycles (e.g., furans, coumarins), and dialkylamines were found to be problematic. Given that any of the elementary steps of the catalytic cycle could feasibly be turnover limiting, we proposed that different ester−amine pairs may have different optimal conditions. Herein, we describe our efforts in identifying a more diverse subset of ligands that can be used to catalytically activate esters and apply these privileged ligand scaffolds to improve the yields of many challenging amide bond-forming reactions.

RESULTS AND DISCUSSION

Our originally developed conditions for direct formation of amide bonds from esters and amines used a catalyst formed from mixing Ni(cod)$_2$ with the free N-heterocyclic carbene 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr). With this mixture, methyl benzoate **1** and aniline **2** react to form benzanilide **3** in 83% yield in toluene at 140 °C (Table 1, entry 1). No product is observed in the absence of the Ni (entry 2) or ligand (entry 3), even with stoichiometric base present (entry 4). While this catalyst is promising, both the metal and the ligand are air sensitive and must be weighed inside a glovebox, hindering adoption of the methodology. The air-stable, commercially available salt IPr·HCl was found to give a comparable yield to IPr if potassium *tert*-butoxide (entry 5) or potassium phosphate (entry 6) is used to release the NHC ligand in situ. Moving away from oxygen-sensitive Ni(cod)$_2$ was less successful. In situ reduction of Ni(OAc)$_2$ by stoichiometric Zn[10a] was inefficient (entry 7), as was the air-stable Ni(0) precatalyst Ni[P(OPh)$_3$]$_4$ (entry 8).[21] The Ni(II) precatalyst Ni(TMEDA)(*o*-Tol)Cl **4**[22] provided only 43% yield of product (entry 9). Preformed Ni-NHC complexes[23] were similarly inefficient, including the commercial Ni(II) catalysts **5** (entry 10) and **6** (entries 11 and 12), and styrenyl complex **7** (entries 13 and 14).[24] These results point to a clear need for more active and more stable alternatives to Ni(cod)$_2$ if methodologies based on this catalyst are to be of broad use.[25]

Continuing with Ni(cod)$_2$ as the metal source and with the knowledge that NHC salts can be effectively deprotonated in situ, we sought to uncover more viable ligands. While our originally identified ligand IPr (**L1**) was found to be quite general, there were numerous transformations that gave unsatisfactory yields that we hoped to solve by ligand screening. Using the synthesis of benzanilide **3** as a test reaction, over 60 different ligands were screened (Table S1−S3, Supporting Information)—a subset of these are provided in Scheme 2 using 10 mol % ligand if bidentate and 20 mol % ligand if monodentate.[26] Most phosphine ligands were entirely ineffective, including XantPhos (**L2**), CyPAd-Dalphos (**L3**),

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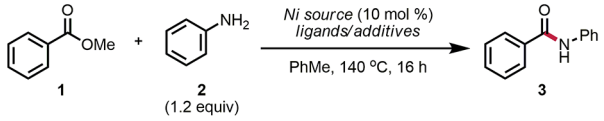
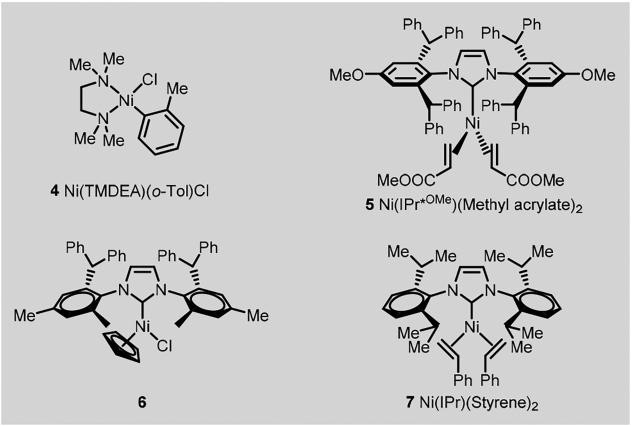
Table 1. Conditions for Direct Amide Bond Formation[a]



entry	Ni source	ligands/additives	% yield
1	$Ni(cod)_2$	IPr (20 mol %)	83
2	$Ni(cod)_2$	none	0
3	none	IPr (20 mol %)	0
4	none	KO*t*Bu (20 mol %)	trace
5	$Ni(cod)_2$	IPr·HCl + KOtBu (20 mol %)	83
6	$Ni(cod)_2$	IPr·HCl (20 mol %) + K_3PO_4 (1 equiv)	73
7	$Ni(OAc)_2$	IPr (20 mol %) and Zn (1 equiv)	trace
8	$Ni[P(OPh)_3]_4$	IPr (20 mol %)	0
9	**4**	IPr·HCl + KOtBu (20 mol %)	43
10	**5**	none	8
11	**6**	none	0
12	**6**	IPr·HCl + KOtBu (10 mol %)	12
13	**7**	none	53
14	**7**	IPr (10 mol %)	53

[a]Reactions run at 0.2 M concentration on 0.2 mmol scale. Yield determined by GC-FID of the crude mixture with 1,3,5-trimethoxybenzene as an internal standard.



dppp analog **L4**, P(*o*-Tol)$_3$ (**L5**), SPhos (**L6**), and PCy$_3$ (**L7**). Bidentate ligands (**L8**−**L10**) showed significant product formation, and dcype (**L11**) and dcypp (**L12**) were comparable to **L1**. One bidentate nitrogen species, **L13**, also proved to be a viable alternative, demonstrating that three different ligand classes can be used. Next, we focused on varying the steric and electronic environment around the heterocyclic ring and aryl substitutions of **L1**. Well-known ligands **L14**−**L19** gave low yields of product. In contrast, ligands **L20**−**L25** proved to be viable alternatives to IPr. Notably, several of these ligands are not known to be particularly effective for Ni-catalyzed C−N bond formation. For instance, 2,4,6-tricyclopentylaniline-derived **L24** was first synthesized by Plenio in 2014 but has never been reported in any catalytic reactions.[27] Pyridine-containing **L25**, recently reported by Michaelis and co-workers to enable Ni-catalyzed allylation reactions,[28] was particularly promising. This ligand has been observed to be bidentate when ligated to many metals,[29] making it unique among the other promising NHC ligands identified.

With a variety of promising ligands identified as viable in the catalytic synthesis of benzanilide, we explored whether this knowledge could be used to improve previously attempted low-yielding reactions. Challenging ester reactants were first targeted. For each ester + amine pair, all of the new ligands (**L11**−**L13** and **L20**−**L25**) were tested and compared to **L1**. The most efficient ligand was identified for each product, and the isolated yield is provided in Scheme 3. For instance, sterically hindered methyl 3-methyl-2-furoate provided amide **8** in 43% yield by ^{1}H NMR under the standard reaction conditions when using **IPr** as the ligand. Using **L22** instead provides **8** in 79% yield (75% after isolation). The Ni/**L22** catalyst could be used to make derivatives **9**−**11** with similar efficiency. A similar observation was found for the synthesis of the isomeric furan derivative fenfuram (**12**). This fungicide can be manufactured from the corresponding methyl ester using aniline as solvent in the presence of stoichiometric Al as an activating agent.[30] With Ni catalysis under our previous standard conditions, only 8% yield was observed. Use of **L22** provided 50% isolated yield, and analog **13** could be synthesized in a similarly improved 64% isolated yield. Various *ortho*-methoxy benzamides have been demonstrated to be inhibitors of cyclooxygenases.[31] These electron-rich and sterically hindered amides (**14**−**16**) were most efficiently prepared using SIPr **L20** as the ligand. The saturated backbone of SIPr gives a slightly increased buried volume relative to IPr,[32] which could potentially facilitate a more challenging reductive elimination step. Other ortho-substituted products bearing a fluorine (**17**) or phenyl (**18**) group were similarly enabled by the presence of **L20**.

3-Carboxamido coumarin derivatives such as **19** have been shown as efficient inhibitors against human monoamine oxidases.[33] During medicinal chemistry synthesis, they were prepared from the corresponding ester and aniline derivatives by first hydrolyzing the ester in aqueous base and then activating the corresponding acid as an acid chloride or with a diimide coupling reagent. Using **L25** as the ligand, carboxamides **19**−**25** could be directly prepared in 70−90% isolated yields. Notably, even anilines with electron-withdrawing groups could be used, including selective intermolecular coupling with the coumarin ester over potential polymerization to prepare **25**. **IPr** as a ligand was also observed to be poor for performing coupling reactions with α-secondary esters, such as for the formation of proline derivative **26**. Here, **L20** was observed to give synthetically useful 65% yield, and more nucleophilic anilines with dimethyl (**27**) and OMe (**28**) group as well as less nucleophilic anilines with acetyl (**29**) and COOMe (**30**) are tolerated. Lastly, pyrrazole-bearing amides such as **32** are privileged structures in a number of commercial fungicides. Given the large scale generally required for agrochemical manufacturing, routes to these molecules generally avoid the use of coupling reagents and instead proceed by multistep procedures involving acid chloride intermediates.[34] While no ligand could be identified that provided exceptional yields, **L24** was found to be superior to IPr, providing **31** and **32** in 40% and 39% yield, respectively.

Next, we turned our attention to amine-coupling partners that proved to be challenging using the Ni/IPr catalyst (Scheme 4). Cyclic amines such as morpholine and pyrrolidine are excellent reactants; however, bulky primary amines and noncyclic secondary amines are challenging to couple. For example, adamantan-1-amine provided amide **33** in just 18% yield using **L1**. Screening of the newly identified ligands enabled the yield to be improved to 91% by the application of **L24**. This ligand also provided improved yields when using *N*-methyl benzylamine and dibenzylamine, giving **34** and **35** in

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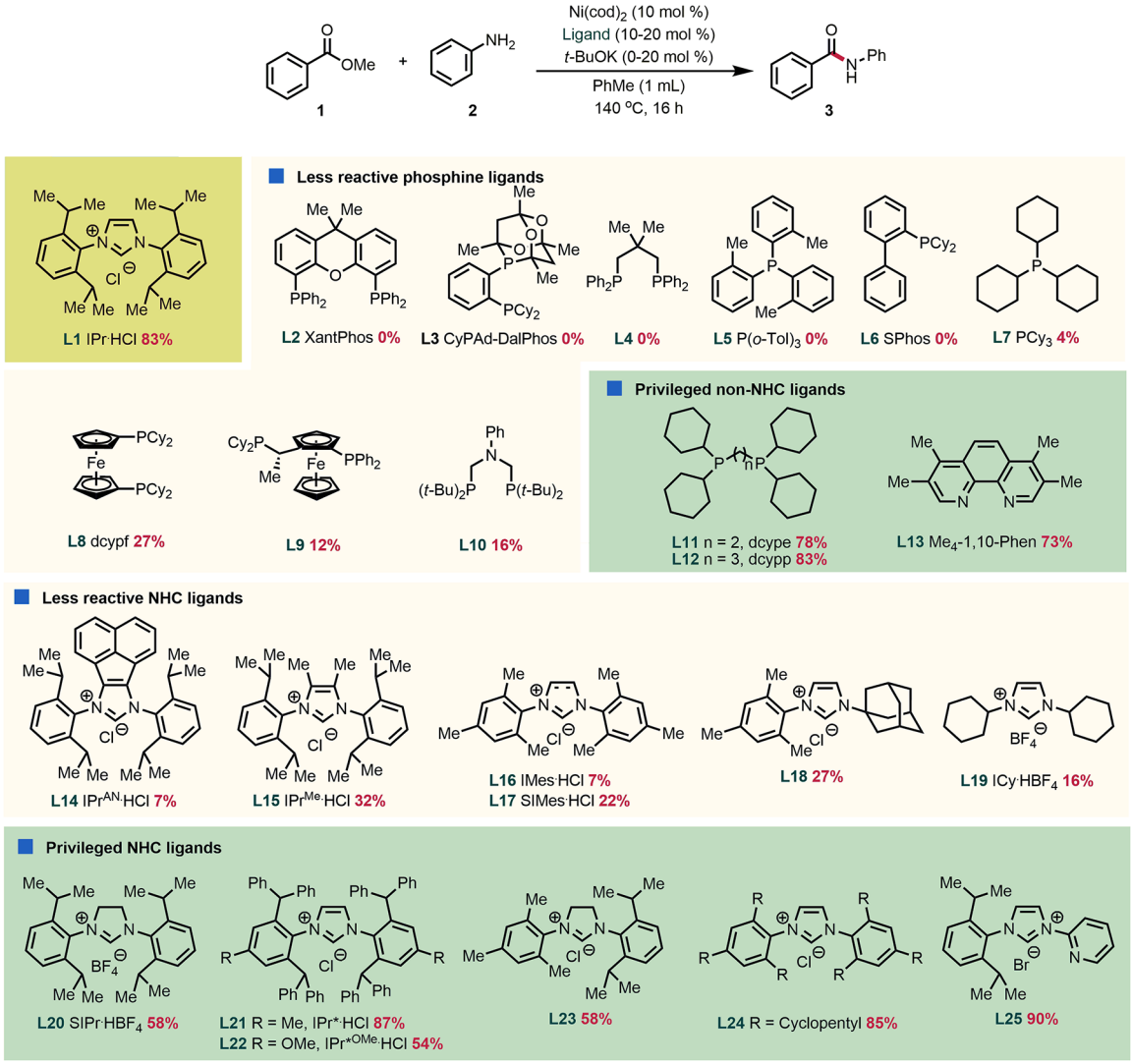
Scheme 2. Selected Ligand Evaluation



53% and 22% yield, respectively. Hindered nicotinamide derivatives were next studied, representing the core scaffold of the fungicide Boscalid. While SIPr (**L20**) and SIMes (**L17**) were poor ligands for preparing amide **36**, the unsymmetrical mixed analog **L23** gave a useful 50% yield. Similar moderate yields were obtained for the preparation of **37**−**39**, suggesting there is a subtle balance of steric factors required when using hindered aniline coupling partners. The most challenging family of amines thus far identified are *N*-alkyl aniline derivatives. Their reaction with esters is highly thermodynamically uphill, though success was achieved by Garg and coworkers when coupling with naphthalene esters in the presence of stoichiometric Lewis acids.[16] Unfortunately, attempts to synthesize *N*-methyl-*N*-phenylbenzamide were ineffective with all privileged ligands under additive-free conditions (Table S17, Supporting Information). In contrast, indoline was found to be a good coupling partner, providing amide **40** in near quantitative yield when using **L13**. Amide **41**, which has been demonstrated to inhibit growth human leukemia cells,[35] was prepared with similar efficiency. Lastly, amine nucleophiles with remote basic sites were studied, which can potentially compete with the ligand for coordination to the metal center during the catalytic cycle. With pyridylmethyl amine as a nucleophile, **L24** was most effective, enabling the synthesis of amides **42** and **43** in moderate yield. Synthesis of **44** was more challenging, but **L15** showed a drastic improvement over IPr to give a 32% yield.

Given the efficient synthesis of amides **25** and **30**, which involve selective coupling among two different esters, we next ran competition studies to understand selectivity between different esters (Figure S1). In general, methyl esters bearing α-aryl groups react favorably relative to those bearing α-alkyl groups with the exception of α-benzylic esters which are most reactive. To demonstrate this selectivity, amine **45** was selectively coupled with esters **46** and **47** using L24, affording ester-containing amides **48** and **49** in 79% and 43% yield, respectively (Scheme 5). Substrate **50** underwent a similarly efficient selective reaction at the α-benzyl ester site instead of the α-aryl ester.

CONCLUSION

In summary, we have greatly expanded the scope of the Ni-catalyzed amide bond formation from simple methyl esters and amines. This was accomplished by identifying new ligand families that can enable this transformation. Of the 60 ligands initially tested, 9 were identified as being comparable to our

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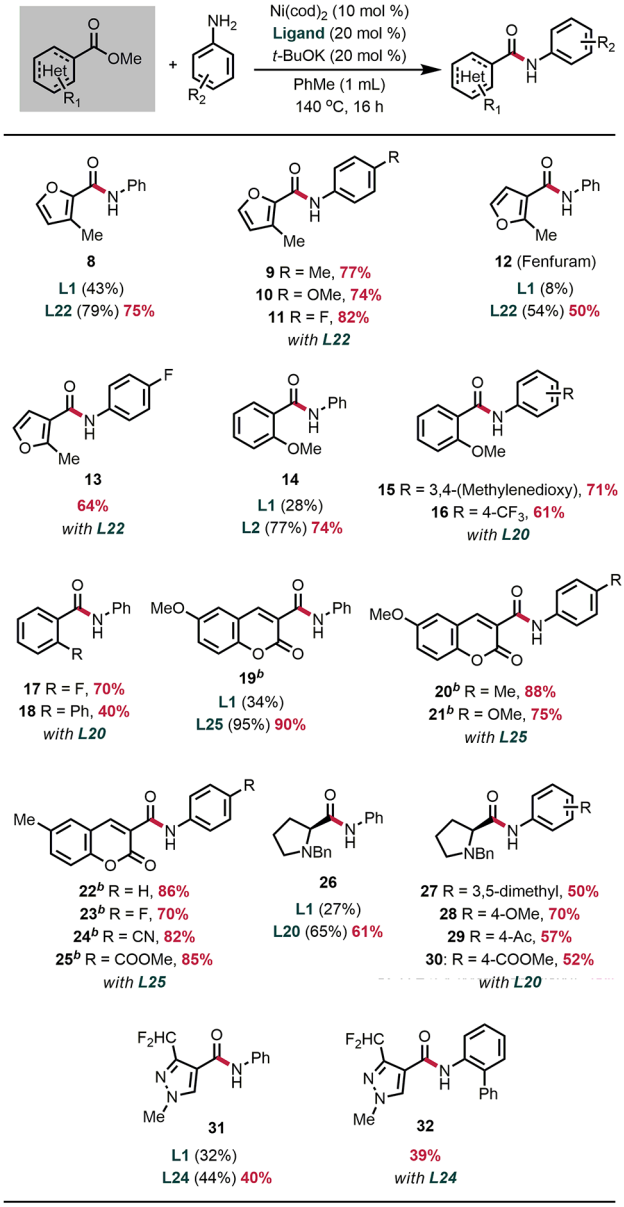
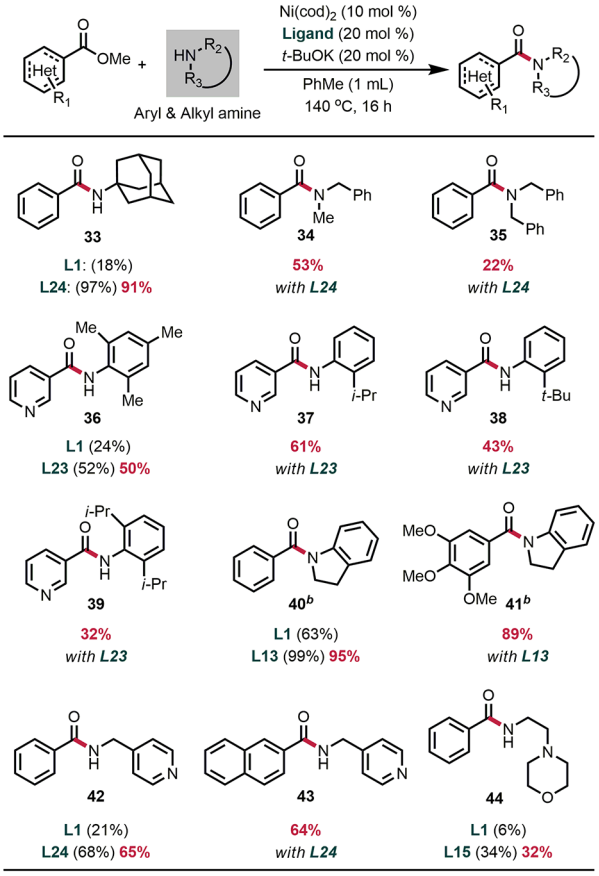
Scheme 3. Substrate Scope of Challenging Ester[a]



[a]General reaction conditions: ester (0.20 mmol), amine (0.24−0.4 mmol), Ni(cod)$_2$ (10 mol %), ligand (20 mol %), *t*-BuOK (20 mol %), toluene (0.2 M), 140 °C for 16 h. Assay yields of the crude reaction mixture are given in parentheses; isolated yields are reported in bold. [b]Ligand (10 mol %) and *t*-BuOK (10 mol %) were used.

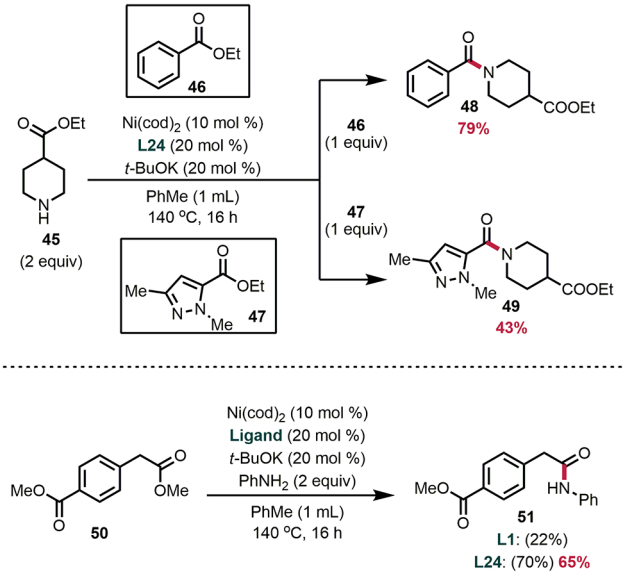
originally identified ligand, IPr, in the synthesis of benzanilide. Notably, these new ligands are highly diverse, including NHCs, phosphines, and a phenanthroline derivative. With these effective ligands, several challenging coupling reactions can be drastically improved, particularly when using more sterically hindered reactants. In particular, bioactive scaffolds were targeted and yields were improved to provide a synthetically viable alternative to more traditional multistep synthesis. Finally, selective coupling was demonstrated when multiple esters are present, again enabled by the expanded ligand scope. Further efforts are still required to identify a robust, air-stable catalyst. Moreover, the ligands identified still require the use of high reaction temperatures, hindering scale up. With these future developments in mind, the research outlined herein

Scheme 4. Substrate Scope of Challenging Amine[a]



[a]General reaction conditions: ester (0.20 mmol), amine (0.24−0.4 mmol), Ni(cod)$_2$ (10 mol %), ligand (20 mol %), *t*-BuOK (20 mol %), toluene (0.2 M), 140 °C for 16 h. Assay yields of the crude reaction mixture are given in parentheses; isolated yields are reported in bold. [b]10 mol % ligand.

Scheme 5. Selective Amidation of Esters and Amines



demonstrates that Ni catalysis has the potential to streamline the synthesis of important amides. Application of these new

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catalysts to more cross-coupling reactions featuring catalytic activation of methyl esters is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b00884.

Experimental procedures, characterization of organic molecules, and optimization tables (PDF)

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Notes

The authors declare no competing financial interest.

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