Nickel Catalysis

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Nickel-Catalyzed Activation of Acyl C–O Bonds of Methyl Esters

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Abstract: *We report the first catalytic method for activating the acyl C–O bonds of methyl esters through an oxidative-addition process. The oxidative-addition adducts, formed using nickel catalysis, undergo in situ trapping to provide anilide products. DFT calculations are used to support the proposed reaction mechanism, to understand why decarbonylation does not occur competitively, and to elucidate the beneficial role of the substrate structure and the Al(OtBu)$_3$ additive on the kinetics and thermodynamics of the reaction.*

Catalytic methods that rely on the activation of carbon–heteroatom bonds have transformed the way chemists build molecules of importance.[1] Although decades of research have mainly focused on the coupling of halide and sulfonate derivatives, particularly on aryl systems, recent efforts have been put forth to catalytically activate functional groups that have traditionally been considered inert in cross-coupling reactions.[2] One such endeavor involves couplings of pivalate esters that proceed by the nickel-mediated activation of aryl C–O bonds (Figure 1).[3] In contrast, the cleavage of the acyl C–O bond of esters remains underdeveloped. Seminal efforts in ester acyl C–O bond cleavage include Yamamoto's stoichiometric studies of ester reactivity,[4] Itami's coupling of phenolic esters, which proceeds with loss of the carbonyl moiety in the form of CO,[5] and Chatani's Suzuki–Miyaura coupling of activated pyridyl esters.[6] To the best of our knowledge, no transition-metal-catalyzed couplings of simple esters, such as readily available methyl esters, have been reported.

With the aim of developing non-decarbonylative couplings of simple esters using non-precious-metal catalysis, we considered the sequence outlined in Figure 1. Ni-catalyzed activation of the acyl C–O bond of ester **1** would furnish oxidative-addition adduct **3**. Subsequent ligand exchange by trapping with a nucleophile would provide acyl nickel species **4**. Finally, reductive elimination would furnish product **2** and regenerate the requisite Ni^0 catalyst. Despite the simplicity of this strategy and the abundance of methyl esters, no such process has been discovered. Herein, we report the validation of this approach, as demonstrated by the nickel-catalyzed conversion of aryl methyl esters into anilides,[7–9] in addition to computational insights.

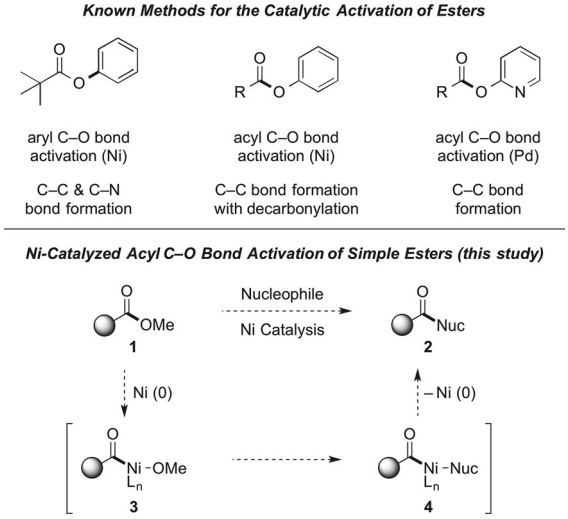

Figure 1. Known methods for the catalytic activation of esters and our approach for the activation of methyl esters (without decarbonylation).

Our decision to pursue ester into anilide conversion was in part driven by this transformation being the reverse of one that we recently reported,[10] and it was therefore considered to be both challenging and conceptually interesting. Methyl 1-naphthoate (**5**) was selected as the substrate for our initial studies (Figure 2).[11] We surveyed a range of reaction parameters, including the choice of amine coupling partner, ligand, solvent, temperature, concentration, and additives. When *N*-methylaniline (**6**) was used as the coupling partner, in conjunction with Ni/SIPr in toluene at 60 °C, only trace amounts of amide product **7** was observed. This finding is consistent with the overall reaction (i.e., ester **5**+amine **6**→amide **7**+methanol) being energetically uphill, which would be expected based on our recent studies.[10] However, the addition of Al(O*t*Bu)$_3$ was found to have a critical beneficial effect and led to the formation of amide **7** in 89 % yield.[12] As described below, we propose that Al(O*t*Bu)$_3$ benefits the

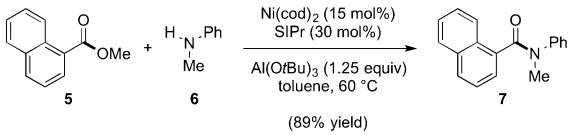

Figure 2. Conversion of ester **5** into amide **7**. Ni(cod)$_2$ = bis(1,5-cycloactadiene)nickel(0), SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene.

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reaction both kinetically and thermodynamically. Also, it should be emphasized that the reaction does not proceed in the absence of Ni/SIPr.[13]

We next examined variations in both coupling partners (Figure 3).[14] 1- And 2-naphthyl substrates bearing fluoride, methoxy, and morpholino substituents were tolerated, as shown by the formation of anilides **8**–**11**, respectively. It is notable that *ortho* substitution did not hinder reactivity and

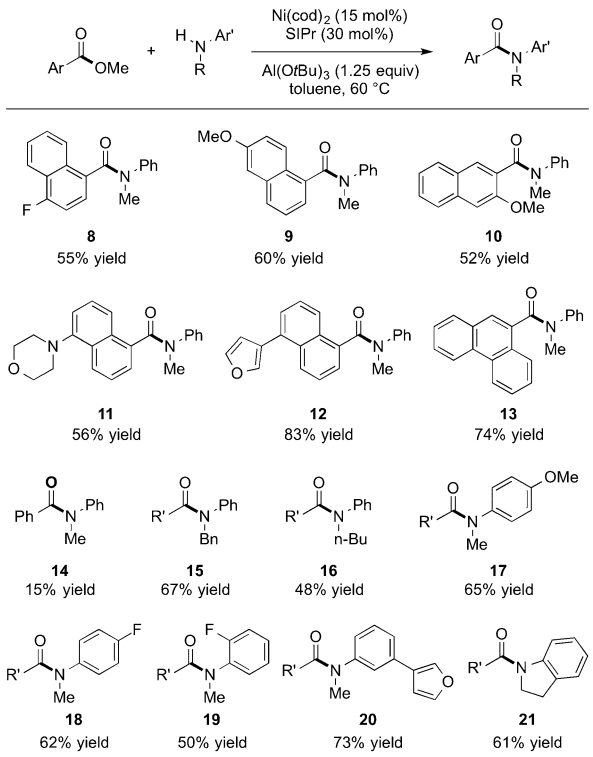


Figure 3. Scope of methodology (R′ = 1-naphthyl). Bn = benzyl.

that the methoxy group did not undergo activation by nickel under these reaction conditions. The reaction could also be performed in the presence of a furan heterocycle to give anilide **12**. The coupling of a phenanthrene derivative proceeded smoothly to furnish **13** in 74% yield. In contrast, attempts to employ non-extended aromatic substrates were less successful, as shown by the formation of **14** in only modest yield. Extended aromatic substrates are frequently necessary to enable nickel-mediated C–O bond cleavage,[2,15] although this effect is still not well understood.[16] With regard to the aniline coupling partner,[17] *N*-benzyl- and *N*-butyl-substituted anilines could be coupled, as shown by the formation of amides **15** and **16**, respectively. Substitution on the arene of the aniline coupling partner was also well tolerated. For example, methoxy- and fluoride-containing substrates underwent the coupling reaction to give amides **17**–**19**. An aniline bearing a furan moiety could also be used, as demonstrated by the formation of **20**. Finally, the use of the cyclic aniline derivative indoline gave the corresponding amide product **21** in 61% yield. Whereas this first-generation variation of our new method requires the use of aryl esters and aniline coupling partners, as noted earlier, no reaction occurred in the absence of $Ni(cod)_2$, SIPr, or $Al(OtBu_3)$. Therefore, these results support the notion that nickel catalysis is indeed operative in the methyl ester acyl C–O bond-cleavage process.

Given that decarbonylation is not observed in the nickel-catalyzed conversion of esters into amides, we examined the competing pathways that would stem from the putative oxidative-addition intermediate **22** using DFT methods (Figure 4).[18] Ligand exchange[19] to give **23** is thought to occur through a two-step process, with a small barrier of 4.9 kcal mol^{-1} relative to oxidative-addition intermediate **22**. In contrast, the barrier for decarbonylation of **22** to give **25**

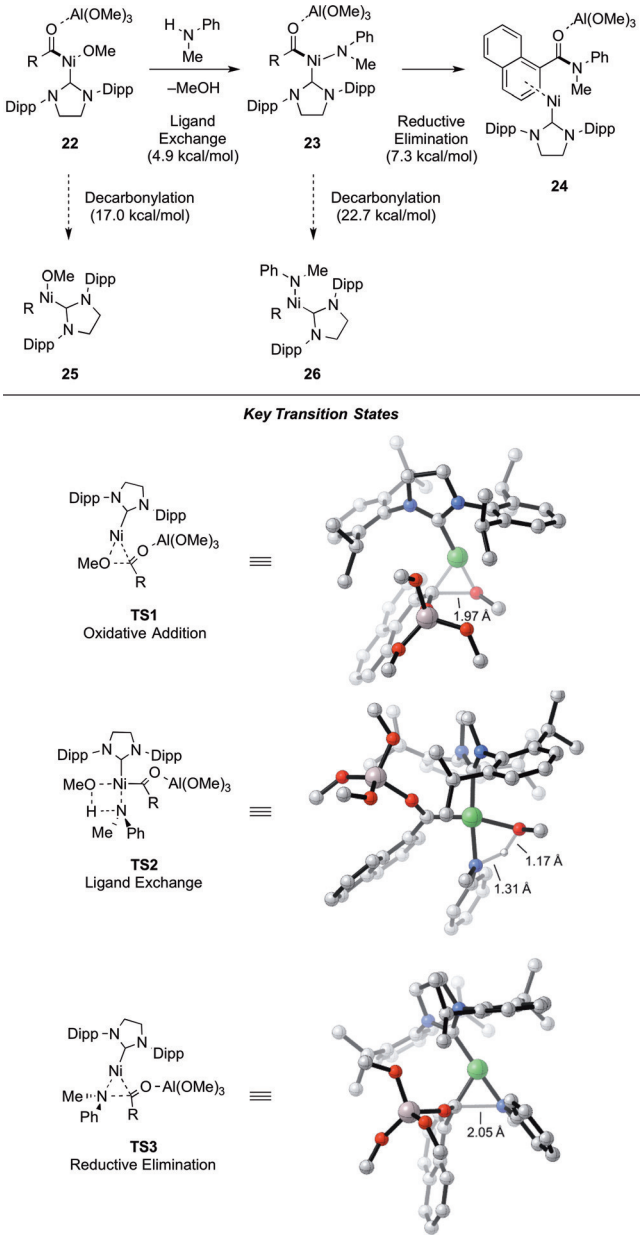


Figure 4. DFT calculations show the relative ease of ligand exchange and reductive elimination compared to disfavorable decarbonylation pathways. $Al(OMe)_3$ is used as a model for $Al(OtBu)_3$ and R = 1-naphthyl. Dipp = 2,6-diisopropylphenyl.

was calculated to be 17.0 kcal mol^{-1} relative to **22**. Furthermore, we examined the activation barriers for reductive elimination and decarbonylation of **23**. The barrier for reductive elimination to give **24** is 15.4 kcal mol^{-1} more favorable than decarbonylation to give **26**, which is consistent with amide bond formation taking place. Moreover, the high barriers for decarbonylation are consistent with prior computational studies.[18c] The transition states for oxidative addition (**TS1**), ligand exchange (**TS2**), and reductive elimination (**TS3**) are depicted in Figure 4 (see the Supporting Information for the full computed catalytic cycle).

DFT calculations were also used to probe the beneficial influence of the Al(O*t*Bu)$_3$ additive on the Ni-catalyzed ester into amide conversion (Figure 5). Without the additive, the

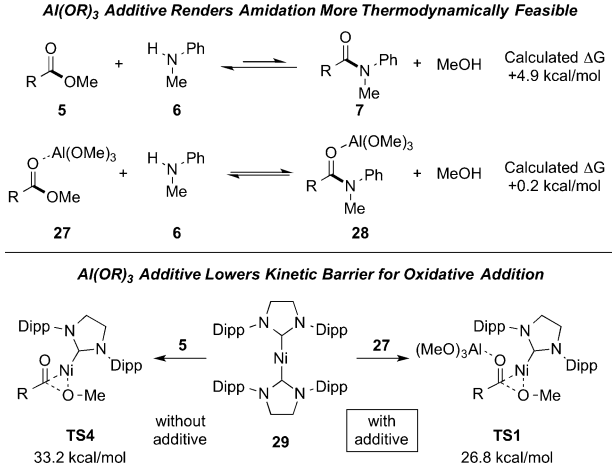


Figure 5. Effect of the additive on the thermodynamics of amidation and the kinetic barrier for oxidative addition as determined by DFT calculations. Al(OMe)$_3$ is used as a model for Al(O*t*Bu)$_3$ and R = 1-naphthyl.

amidation of ester **5** with aniline **6** is endergonic by 4.9 kcal mol^{-1}. However, upon addition of the aluminum additive, the amidation becomes almost thermoneutral.[20] This is due to the greater Lewis basicity of the carbonyl oxygen atom of the amide compared to that of the ester, which therefore drives the equilibrium towards amide complex **28**.[21] The additive is also thought to have a beneficial kinetic influence with regard to the rate-determining oxidative-addition step. In the absence of the additive, the kinetic barrier for oxidative addition is computed to be 33.2 kcal mol^{-1} relative to [Ni(SIPr)$_2$] **29**.[22] With the additive, however, the oxidative addition becomes significantly more facile, with a kinetic barrier of 26.8 kcal mol^{-1}.[23]

With insight into the beneficial role of the Al(O*t*Bu)$_3$ additive, we questioned why certain substrates performed, whereas others proved more challenging in the nickel-catalyzed amidation. Key results are shown in Figure 6. Experimentally, methyl 1-naphthoate undergoes amidation in higher yields than methyl 2-naphthoate and methyl benzoate (89 % vs. 53 % and 15 % yield, respectively). This agrees with the computed trends in the Gibbs free energy for the amidation of each substrate. Calculations reveal that the

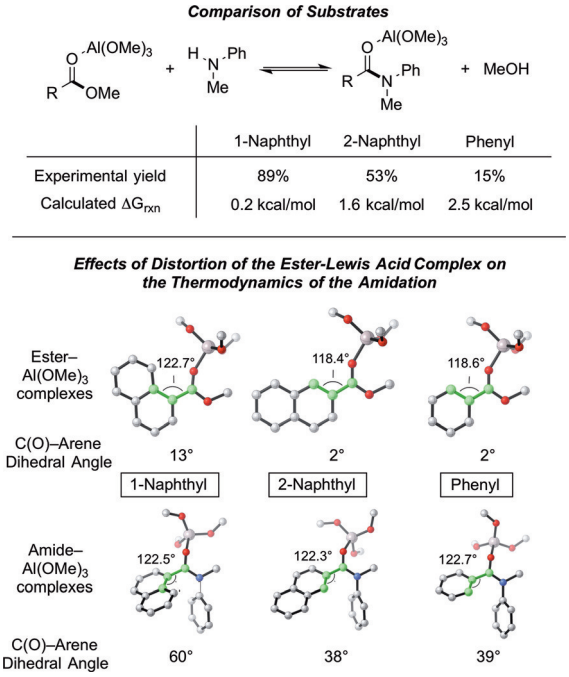
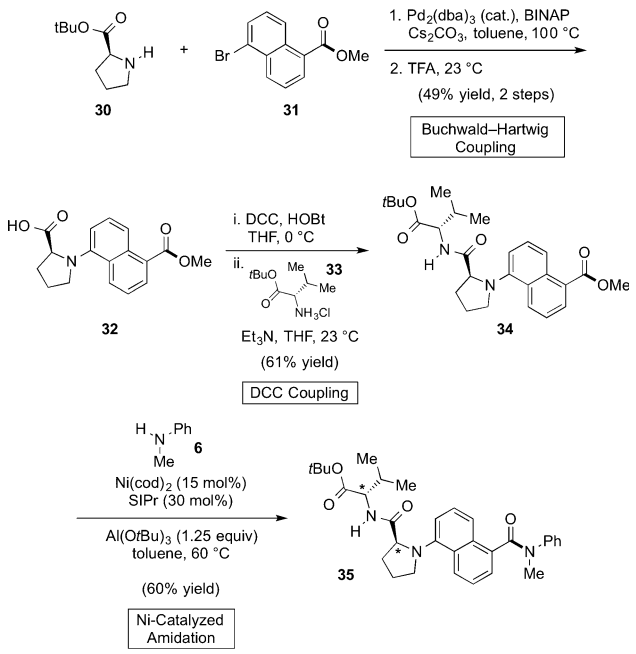


Figure 6. Effects of distortion of the ester aluminum additive complex on the thermodynamics of the amidation based on substrate. Al(OMe)$_3$ is used as a model for Al(O*t*Bu)$_3$.

distortion of the ester–Al(OR)$_3$ complex from steric hindrance facilitates and controls the thermodynamics of the amidation. In the ester–Al(OR)$_3$ complexes, the carbonyl and arene moieties are nearly co-planar in all cases (13° or 2°) to maintain conjugation. In the case of methyl 1-naphthoate, steric repulsion between the naphthyl group and the acyl moiety distorts the highlighted angle to 122.7°, which is about 4° larger than the corresponding angles of the complexes with methyl 2-naphthoate and methyl benzoate. This renders the Al(OR)$_3$ complex with methyl 1-naphthoate less stable than the other two complexes.[24] The amide–Al(OR)$_3$ complexes are all relatively nonplanar, and each possesses a similar C-C-C(O) angle of 122.3–122.7°. This is due to reduced arene–carbonyl conjugation; amide conjugation prevails, and the arenes and attached carbonyl groups are easily twisted out of planarity to minimize steric effects. Therefore, the stability of the amide–Al(OR)$_3$ complex is minimally affected by the identity of the arene attached to the carbonyl group.[25] The steric repulsion seen in the ester–Al(OR)$_3$ complex of methyl 1-naphthoate makes reactions of these substrates thermodynamically most favorable. This insight into ester destabilization is expected to guide future reaction discovery efforts.

An attractive aspect of employing simple methyl esters in this method is that esters are generally stable to a variety of reaction conditions. As such, they are well suited for use in multistep synthesis. To probe this feature, we conducted the reaction sequence shown in Scheme 1. First, proline-derived ester **30** was united with **31** in a Buchwald–Hartwig coupling.[26] This C–N bond formation occurred smoothly without disturbing either of the ester motifs. Treatment of the coupled product with TFA led to selective *tert*-butyl ester cleavage to give **32**. This set the stage for sequential amide bond forming



Scheme 1. Multistep synthesis using mild catalytic ester activation and sequential site-selective C–N bond-forming processes. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, dba = dibenzylideneacetone, DCC = *N*,*N*′-dicyclohexylcarbodiimide, HOBt = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid.

reactions. The first involved a conventional DCC coupling with valine-derived amino ester **33** and furnished peptide **34**. With the methyl ester still intact, a nickel-catalyzed amidation was performed to deliver dipeptide **35**. The *tert*-butyl ester was not disturbed in this process, and the stereochemical integrity was preserved at both epimerizable centers. Aside from highlighting the mildness of the acyl C–O bond activation and illustrating the potential of esters as cross-coupling partners, this sequence demonstrates that conventional and new C–N bond-forming methods can be strategically merged to build linkages in a predictable and chemoselective manner.

In summary, this study has established that the acyl C–O bonds of simple esters may be activated using nickel catalysis. This finding is expected to prompt the further exploration of simple esters in non-decarbonylative cross-coupling processes that rely on non-precious-metal catalysis.

Acknowledgements

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[11] As shown in Figure 6, theory predicts that substrate **5** should prove most suitable.

[12] On gram scale, this coupling could be performed with 2.5 mol% of Ni to give amide **7** in 50% yield; see the Supporting Information for details.

[13] The use of other ligands (e.g., mono- and bidentate phosphines, bidentate pyridyl, pybox, and many other N-heterocyclic carbenes) in place of SIPr also led to no reaction or low conversions.

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[21] $Al(OtBu)_3$ may also serve to absorb the methanol that is generated, thus promoting the forward reaction. The complexation between $Al(OMe)_3$ and methanol was calculated to be exergonic by 11.0 kcal mol^{-1}.
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