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

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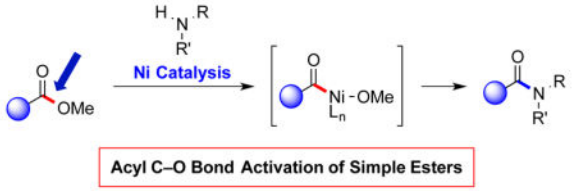
Abstract

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, understand why decarbonylation does not occur competitively, and to elucidate the beneficial role of the substrate structure and $Al(OtBu)_3$ additive on the kinetics and thermodynamics of the reaction.

Graphical Abstract



Keywords

nickel catalysis; acyl C–O bond activation; methyl esters

Catalytic methodologies that rely on the activation of C–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, which 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 proceed with loss of the carbonyl in the form of CO,[5] and Chatani's Suzuki–

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Supporting information for this article is available on the WWW under http://www.angewandte.org.

Miyaura coupling of activated pyridyl esters.[6] To 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 CO 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. In this manuscript, we report the validation of this approach, as demonstrated by the nickel-catalyzed conversion of aryl methyl esters to anilides,[7,8,9] in addition to computational insights.

Our decision to pursue ester to anilide conversion was in part driven by this transformation being the reverse of one that we recently reported[10] and 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. By using *N*-methylaniline (**6**) 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 $Al(O\mathit{t}Bu)_3$ was found to have a critical beneficial effect and led to the formation of amide **7** in 89% yield.[12] As described in the latter part of the manuscript, we propose that $Al(O\mathit{t}Bu)_3$ benefits the 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 that the methoxy group did not undergo activation by nickel under these reaction conditions. The methodology 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*-Bn and *N*-Bu substituted anilines could be coupled, as shown by the formation of amides **15** and **16**, respectively. Substitution on the arene of the aniline 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. Although this first-generation variation of this methodology requires the use of aryl esters and aniline coupling partners, as noted earlier, no reaction occurs in the absence of $Ni(cod)_2$, SIPr, or $Al(O\mathit{t}Bu_3)$.

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 to 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 relative to oxidative addition intermediate **22**. In contrast, the barrier for decarbonylation of **22** to give **25** is calculated to be 17.0 kcal/mol relative to **22**. Additionally, 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 more favorable compared to 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 SI for the full computed catalytic cycle).

DFT calculations were also used to probe the beneficial influence of the $Al(O\mathit{t}Bu)_3$ additive on the Ni-catalyzed ester to amide conversion (Figure 5). Without the additive, the amidation of ester **5** with aniline **6** is endergonic by 4.9 kcal/mol. However, with the addition of the aluminum additive, the amidation becomes almost thermoneutral.[20] This arises because of the greater Lewis basicity of the carbonyl oxygen of the amide compared to that of 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 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.[23]

With insight into the beneficial role of the $Al(O\mathit{t}Bu)_3$ additive, we questioned why certain substrates performed, while 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 compared to methyl 2-naphthoate and methyl benzoate (89% yield, versus 53% or 15% yield, respectively). This agrees with the computed trends in the Gibbs free energy for the amidation of each substrate. Calculations reveal that the 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 are nearly co-planar in all cases (13° or 2°) to maintain conjugation. In the case of methyl 1-naphthoate, the steric repulsions between the naphthyl group and the acyl moiety distort 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 because of lesser arene-carbonyl conjugation; amide conjugation prevails and the arenes and attached carbonyls are easily twisted out of planarity to minimize steric effects. Therefore, the stability of the amide–$Al(OR)_3$ complex is

minimally effected by the identity of the arene attached to the carbonyl.[25] The steric repulsion seen in the ester–$Al(OR)_3$ complex of methyl 1-naphthoate makes reactions of these substrates most thermodynamically favorable. This insight into ester destabilization is expected to guide future reaction discovery efforts.

An attractive aspect of employing simple methyl esters in this methodology 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** using 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 *t*-butyl ester cleavage to give **32**. This set the stage for sequential amide bond forming reactions. The first involved a conventional DCC coupling with valine-derived amino ester **33**, and furnished peptide **34**. With the methyl ester again remaining intact, a nickel-catalyzed amidation was performed to deliver dipeptide **35**. The *t*-butyl ester was not disturbed in this process, and the stereochemical integrity was preserved at both epimerizable centers. In addition to 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 methodologies can be strategically merged to build linkages in a predictable and chemoselective manner.

In summary, this study establishes 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. As shown in Figure 6, theory predicts that substrate **5** should prove most fruitful.
12. On gram-scale, this coupling could be performed with 2.5 mol% of Ni to give amide **7** in 50% yield; see the SI 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. IPr, however, can be used in place of SIPr to give comparable yields of products.
14. The mass balance in most reactions is unreacted starting material.
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16. The favorable reactivity seen in π-extended systems may be related to pre-complexation of the nickel catalyst, as well as to the thermodynamic factors discussed here.
17. The non-catalyzed reaction of anilines with ester **5** is sluggish and is not observed under our reaction conditions.
18. For computational studies of nickel-catalyzed decarbonylative couplings of esters, see refs 5b,c and the following: Hong X, Liang Y, Houk KN. J Am Chem Soc. 2014; 136:2017–2025. [PubMed: 24428154] Li Z, Zhang SL, Fu Y, Guo QX, Liu L. J Am Chem Soc. 2009; 131:8815–8823. [PubMed: 19505075] Lu Q, Yu H, Fu Y. J Am Chem Soc. 2014; 136:8252–8260. [PubMed: 24823646]
19. Related ligand exchange processes presumably take place in the nickel-catalyzed amination of methyl ethers; see: Tobisu M, Yasutome A, Yamaka K, Shimasaki T, Chatani N. Tetrahedron. 2012; 68:5157–5161.

20. The variation between the calculated thermoneutral reaction free energy and the observed yields may partially be attributed to differences between the actual experimental conditions and the DFT calculations.
21. $Al(O\mathit{t}Bu)_3$ may also serve to absorb the methanol being generated, thus promoting the forward reaction. The complexation between $Al(OMe)_3$ and methanol was calculated to be exergonic by 11.0 kcal/mol.
22. Ni-toluene/NHC complex can also be considered as the resting stage of the catalyst; see: Hoshimoto Y, Hayashi Y, Suzuki H, Ohashi N, Ogoshi S. Organometallics. 2014; 33:1276–1282.
23. For further discussion, see the SI.
24. Distortion of bond lengths was also examined, but found to be insignificant in all cases.
25. The twisting out of planarity has a minimal effect on the amide–$Al(OR)_3$ stability; rather, electron donation from the amide nitrogen is the primary stabilizing factor.
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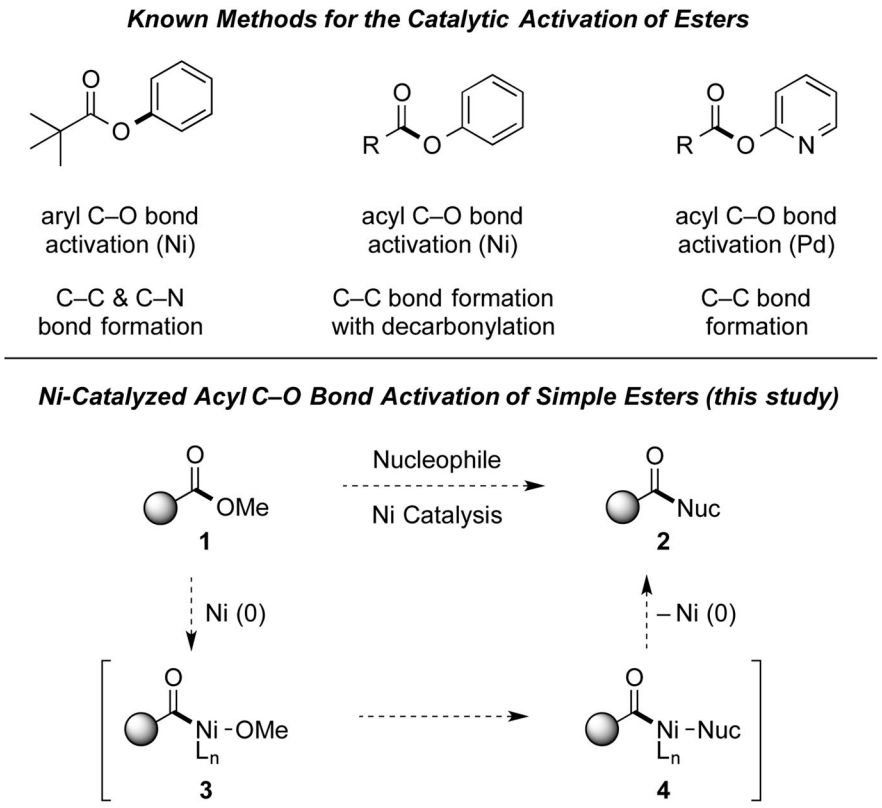


Figure 1.

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

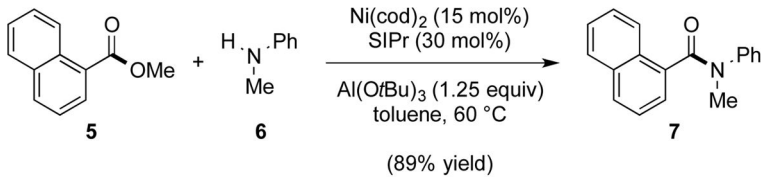


Figure 2.

Conversion of ester **5** to amide **7**; SIPr=1,3-bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene, cod=bis(1,5-cycloactadiene)nickel(0).

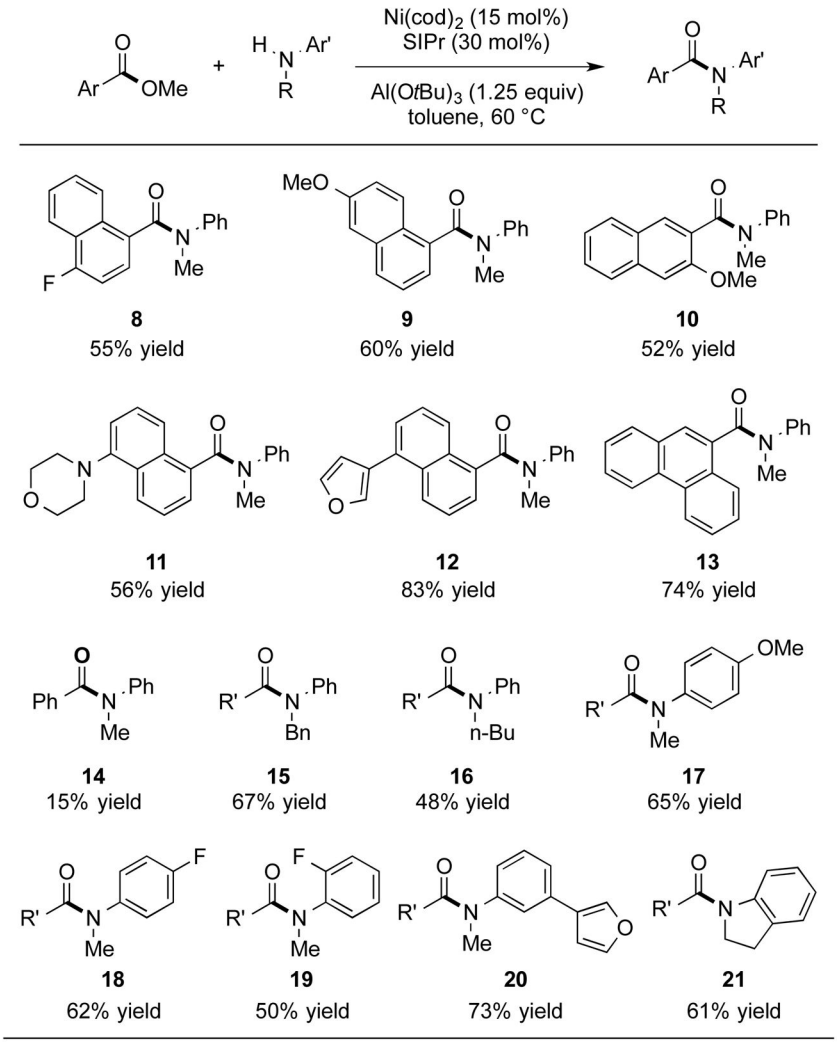


Figure 3.

Scope of methodology (R′=1-naphthyl); SIPr=1,3-bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene, cod=bis(1,5-cycloactadiene)nickel(0), Bn=benzyl.

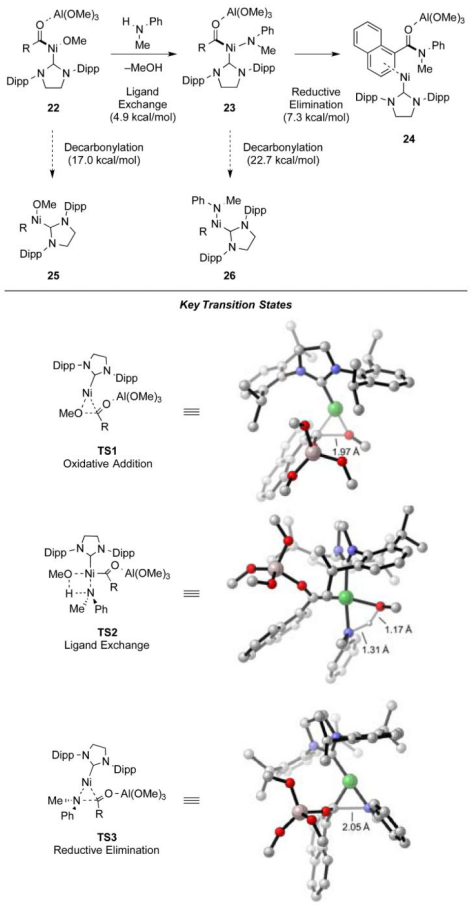


Figure 4.

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 $Al(O\mathit{t}Bu)_3$ and R = 1-naphthyl; Dipp=2,6-diisopropylphenyl.

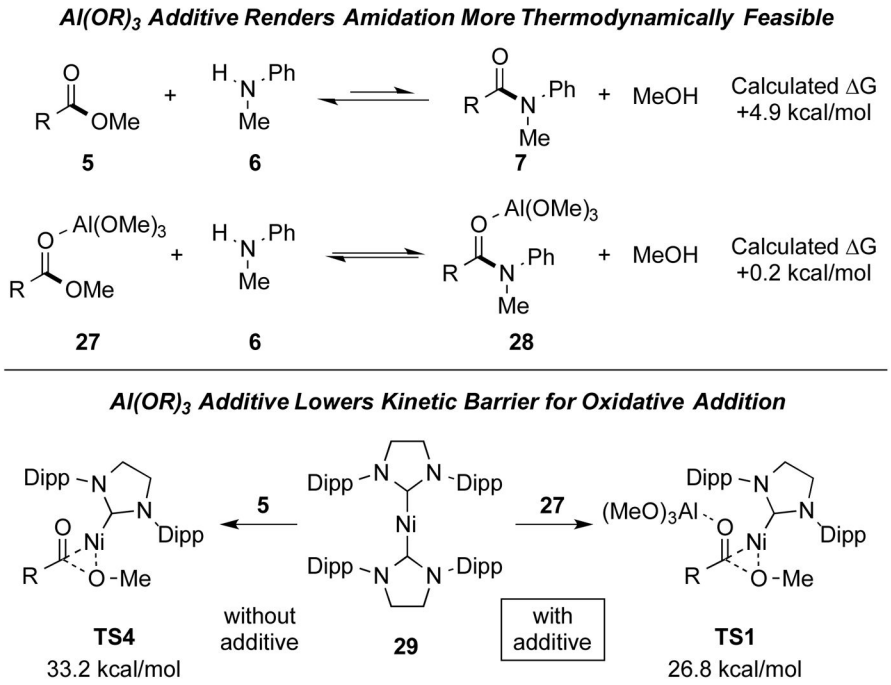


Figure 5.

Effect of the additive on the thermodynamics of amidation and kinetic barrier for oxidative addition using DFT calculations. $Al(OMe)_3$ is used as a model for $Al(O\mathit{t}Bu)_3$ and R = 1-naphthyl; Dipp=2,6-diisopropylphenyl.

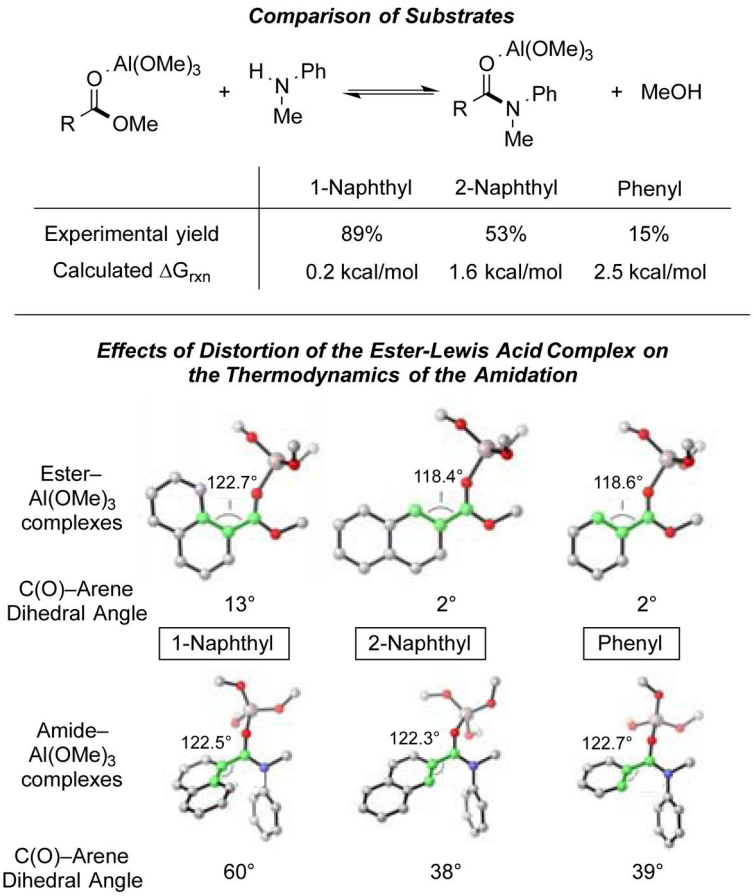
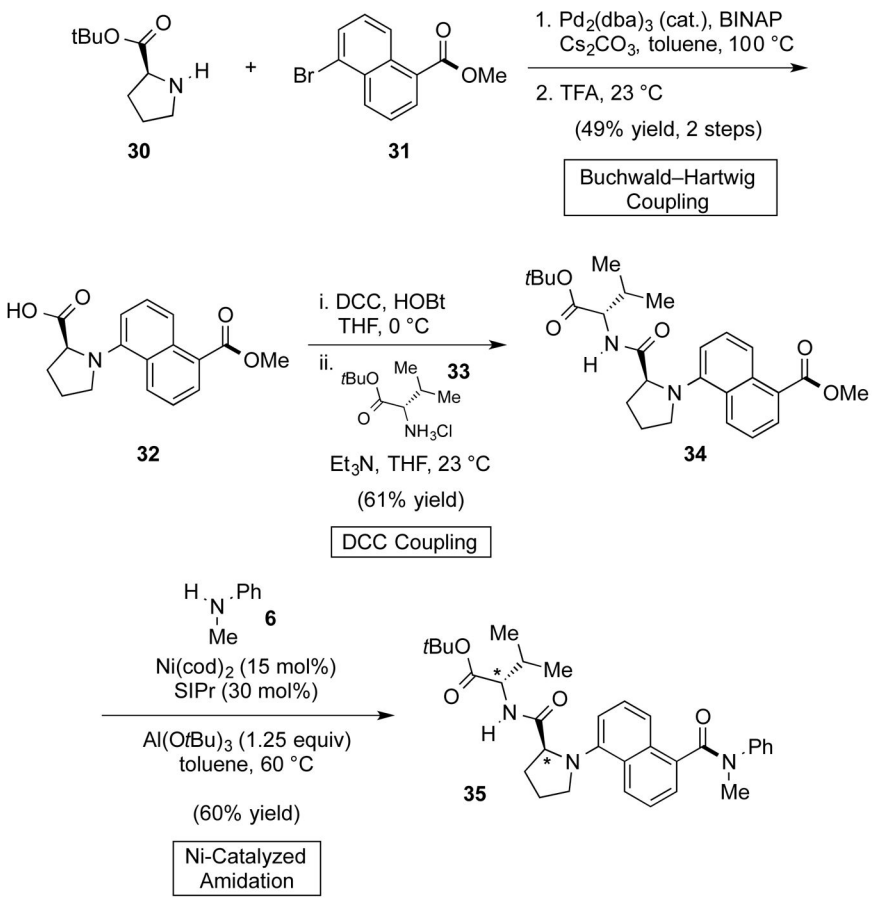


Figure 6.

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 $Al(O\mathit{t}Bu)_3$.



Scheme 1.

Multistep synthesis using mild catalytic ester activation and sequential site-selective C–N bond forming processes; dba= dibenzylideneacetone, BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, TFA= trifluoroacetic acid, DCC= *N,N′*-dicyclohexylcarbodiimide, HOBt=1-hydroxybenzotriazole, SIPr=1,3-bis(2,6-di-*i*-propylphenyl)imidazolidin-2-ylidene, cod=bis(1,5-cycloactadiene)nickel(0).