21.19 Synthesis of Amides by Transamidation and Amidation of Activated Amides and Esters

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General Introduction

The amide bond is one of the most important functional groups in chemistry and biology.[1-10] Amides are ubiquitous as key linkages in natural products, pharmaceuticals, and fine chemicals, but even more important is the prevalence of amides in peptides and proteins.[1-4] Considering the importance of amides, the development of new methods for the construction of amide bonds has always represented an attractive undertaking in the field of organic synthesis.[5-7] In this context, the direct transamidation and amidation of bench-stable amides and esters via selective C(acyl)–N and C(acyl)–O cleavage has been particularly appealing due to the universal presence of amides and esters in common synthetic routes.[8-10] However, the main challenge in direct transamidation and amidation reactions of bench-stable amides and esters is that the classical $n_N \rightarrow \pi^*_{C=O}$[11-12] and $n_O \rightarrow \pi^*_{C=O}$ conjugation[13] results in the high stability of typical amides and esters to direct nucleophilic addition conditions.[14-15] In 2015, the concept of ground-state-destabilization of amides relying on the decrease of amidic resonance through steric and/or electronic substitution of the amide bond was introduced for transition-metal-catalyzed cross-coupling reactions of amides, enabling facile access to acyl- and aryl-metals from amides by oxidative insertion to N–C(O) amide bonds.[16] Subsequently, this concept was further expanded to transition-metal-free transformations of amides via selective formation of tetrahedral intermediates under mild and synthetically useful reaction conditions.[17-18] This chapter provides a summary of the recent advances in direct transamidation and amidation reactions of activated amides and esters via transition-metal-catalyzed and transition-metal-free C(acyl)–N and C(acyl)–O bond cleavage as a new disconnection for the synthesis of amide bonds.

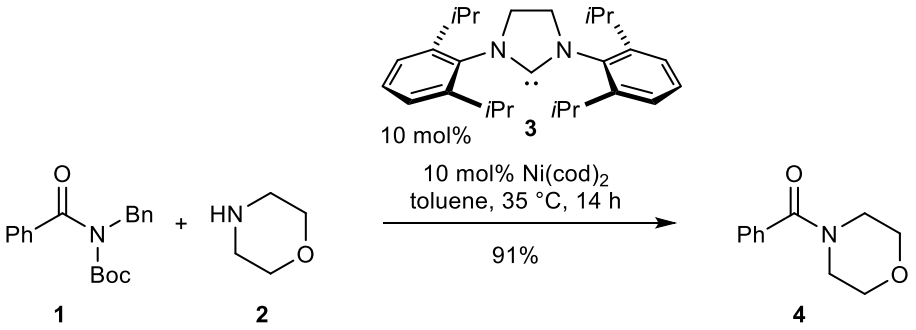
21.19.1 Method 1: Metal-Catalyzed Transamidation of Activated Amides (Acyl Buchwald-Hartwig Reaction)

Transition-metal-catalyzed transamidation of N-activated secondary amides represents one of the most powerful methods in this emerging area.[19-20] This strategy relies on two steps: (1) introducing sterically- and/or electronically-activating group, such as Boc or Ts, at the amide nitrogen atom of secondary amides to afford N-activated amides; (2) selective oxidative insertion of a transition-metal-catalyst to the C(acyl)–N bond to form acyl-metal intermediates that are further converted to the final amide products via ligand exchange and reductive elimination according to the Buchwald-Hartwig amination mechanism. To date, the most powerful catalytic system for this class of reactions is the combination of Ni or Pd with NHC (NHC = N-heterocyclic carbene) ancillary ligands, which benefits from the electron-rich N-heterocyclic carbene ligands facilitating oxidative addition of the amide C(acyl)–N bond to Ni or Pd.[21] It is further important to point out the advantageous properties of bench-stable, moisture- and air-stable and commercially-available Pd(II)–NHC precatalysts that are converted in situ to the catalytically-active monoligated Pd(0)–NHC species, while Ni(0) typically requires careful exclusion of air- and the use of glove-boxes.[21]

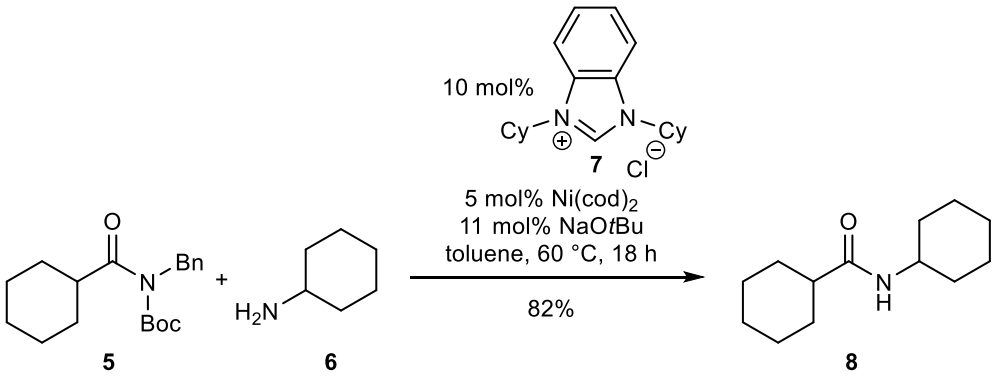
In 2016, Garg and co-workers reported the first example of a two-step transamidation of secondary amides by transition-metal-catalysis (Scheme 1).[22] This method involves N-Boc-activation of secondary amides to afford N-activated twisted tertiary amides[11] such as **1**, followed by Ni–NHC-catalyzed transamidation with amines such as **2** to furnish amide products such as **4** in 91% yield. The sterically-demanding, saturated imidazolidinylidene NHC ligand such as **3** was found to be optimal for this transformation.

The same group later reported Ni–NHC-catalyzed transamidation of aliphatic amide derivatives exploiting the same two-step approach (Scheme 2).[23] For example, aliphatic amides such as **5** reacted with amines such as **6** by using 5 mol% $Ni(cod)_2$ as a catalyst and 10 mol% of benzimidazolylidene-type NHC ligand such as **7** in the presence of 11 mol% NaO*t*Bu as a base to afford amide products such as **8** in 82% yield.

<Scheme 1> Nickel(0)-catalyzed transamidation of N-activated secondary amides[22]

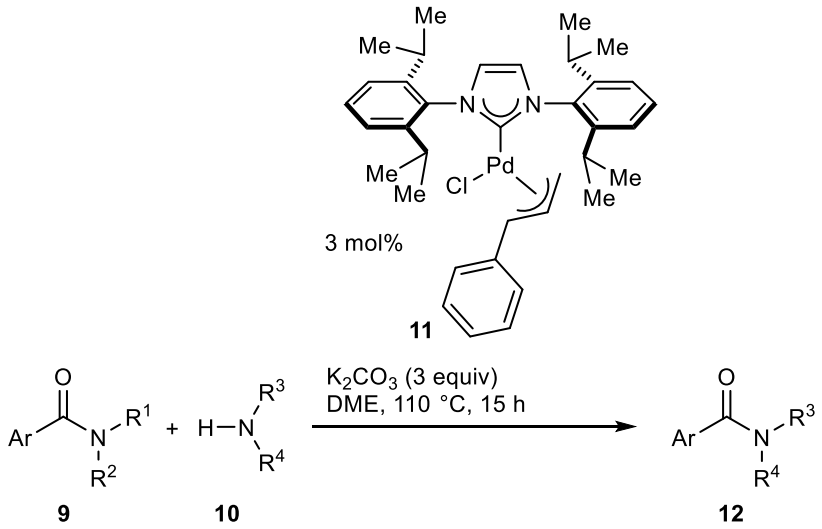


<Scheme 2> Nickel(0)-catalyzed transamidation of aliphatic amide derivatives[23]



In 2017, Szostak and co-workers reported a two-step transamidation of secondary carboxamides for the first time using air- and moisture-stable Pd(II)–NHC precatalysts (Scheme 3).[24] As such, N-activated amides **9** could be prepared by a direct chemoselective N-activation of secondary amides (R^2 = Boc or Ts) in one step. Next, the use of 3 mol% of Pd(II)–NHC catalyst such as **11** enabled transamidation of amides **9** with non-nucleophilic amines **10** at 110 °C to afford amide products **12** in good to excellent yields. In an extended substrate scope, [Pd(IPr)(cin)Cl] and [Pd(IPr)(allyl)Cl] are most effective for transamidations, enabling amide bond formation with non-nucleophilic amines using mild carbonate bases.[25]

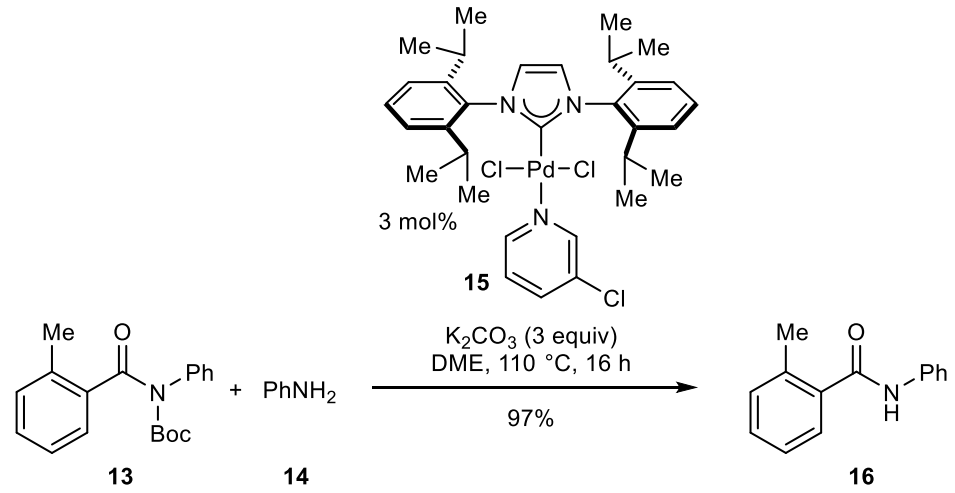
<Scheme 3> Palladium–NHC-catalyzed transamidation of N-activated secondary amides[24]



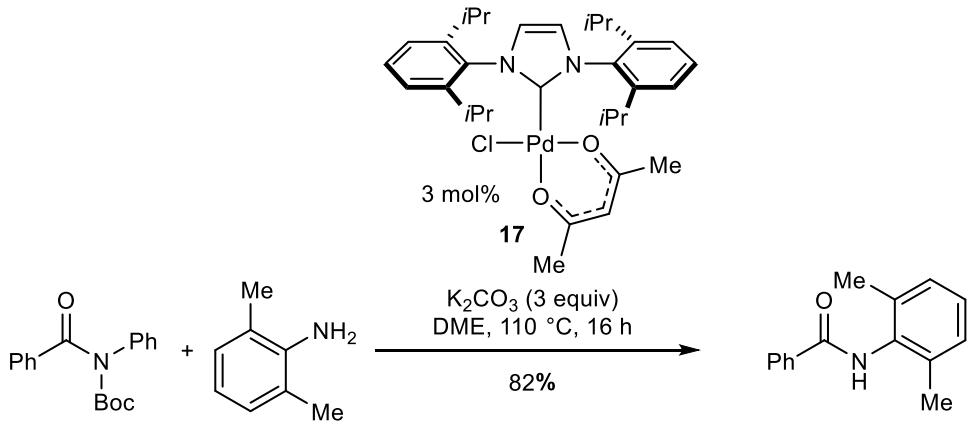
Ar	R^1	R^2	R^3	R^4	Yield (%)	Ref
Ph	Ph	Boc	H	2,6-$Me_2C_6H_3$	98	[24]
Ph	Ph	Boc	H	*t*Bu	80	[24]
4-$MeO_2CC_6H_4$	Ph	Boc	H	2,6-$Me_2C_6H_3$	77	[24]
Ph	Ph	Boc	Me	Ph	77	[24]
Ph	Me	Boc	H	4-$MeOC_6H_4$	96	[24]
Ph	Me	Ts	H	2,6-$Me_2C_6H_3$	83	[24]

In the same year, Szostak and co-workers reported Pd–PEPPSI-catalyzed transamidation of N-activated amides such as **13** with amines such as **14** to furnish amide product such as **16** in high yields (Scheme 4).[26] The ease of preparation of Pd–PEPPSI precatalysts offers a clear advantage of this protocol.[21] Later, the same group developed another class of Pd(II)–NHC precatalysts, [Pd(NHC)(acac)Cl] **17**, which (1) show excellent activity in transamidation of N-activated amides (Scheme 5), and (2) enable in situ screening of NHC salts for amide transamidation owing to the facile synthesis of [Pd(NHC)(acac)Cl] catalysts from $Pd(acac)_2$ and NHC salts.[27]

<Scheme 4> Palladium–PEPPSI-catalyzed catalyzed transamidation of N-activated secondary amides[26]



<Scheme 5> [Pd(NHC)(acac)Cl]-catalyzed transamidation of N-activated secondary amides[27]



Amides, e.g. 12; General Procedure:[24]

An oven-dried vial equipped with a stir bar was charged with an amide substrate **9** (0.10 mmol), potassium carbonate (0.30 mmol), amine **10** (0.20 mmol), Pd–NHC catalyst **11** (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. DME (0.40 mL) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil

bath and stirred for 15 h. After the indicated time, the reaction mixture was cooled down, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The crude product was purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes.

21.19.2 Method 2: Transition-Metal-Free Transamidation of Amides

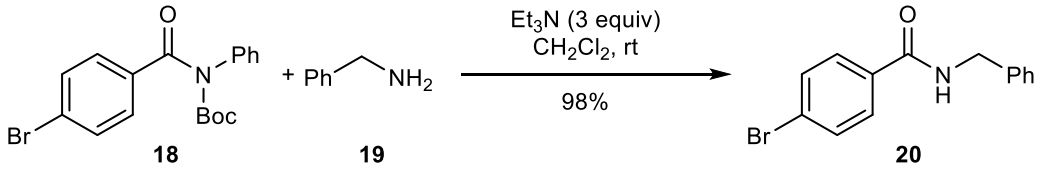
In addition to direct transition-metal insertion into C(acyl)–N amide bonds, selective metal-free or transition-metal-free activation of amides can be achieved via tetrahedral intermediates instead of acyl-metals.[28-32] This reaction manifold features several advantages over the use of transition-metals, such as (1) absence of expensive and potentially toxic transition-metal-catalysts; (2) operational simplicity; (3) exceedingly mild reaction conditions; (4) high selectivity in nucleophilic addition to the amide N–C(O) bond. Recent studies demonstrate that transition-metal-free activation of amides supersedes reactions via acyl-metal intermediates.[12]

In 2017, Szostak and co-workers reported a metal-free transamidation of N-activated secondary amides with aliphatic amines under very mild room temperature conditions (Scheme 6).[28] In this protocol, 3 equiv of triethylamine is used as a base to promote transamidation of N-activated amides such as **18** with aliphatic amines such as **19** in CH_2Cl_2 to afford amides product such as **20** in excellent yields. This transamidation involves nucleophilic addition of an amine to the amide N–C=O bond to afford the tetrahedral intermediate, followed by thermodynamic collapse to the final amide product. Recently, an improved protocol for metal-free, room temperature transamidation of N-activated secondary amides using CH_3CN as a solvent was published.[29]

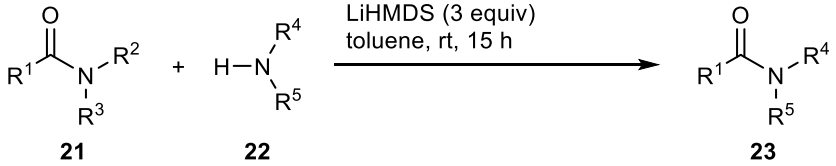
In 2018, Li and Szostak reported an operationally-simple, transition-metal-free method for transamidation of N-activated primary and secondary amides with non-nucleophilic amines (Scheme 7).[30] In this protocol, N-activated amides **21** (R^2, R^3 = Ar or alkyl, Boc, Ts, or Boc_2) undergo transamidation with aromatic or aliphatic amines **22**

in the presence of 3 equiv LiHMDS to afford amides **23** at room temperature in good to excellent yields via a remarkably mild transamidation process.

<Scheme 6> Metal-free transamidation of N-activated secondary amides with aliphatic amines[28]



<Scheme 7> Selective transition-metal-free transamidation of N-activated primary and secondary amides[30]

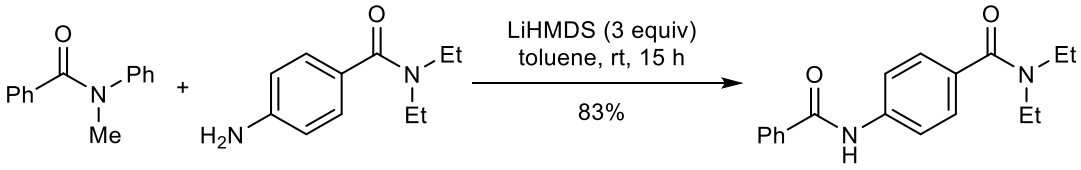


R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref
Ph	Ph	Boc	H	4-$MeOC_6H_4$	94	[30]
Ph	Ph	Boc	H	4-$EtO_2CC_6H_4$	78	[30]
Ph	Ph	Boc	H	2,6-iPr$_2C_6H_3$	98	[30]
Ph	Ph	Boc	Me	Ph	96	[30]
tBu	Ph	Boc	H	2,6-$Me_2C_6H_3$	87	[30]
Ph	Boc	Boc	H	2,3,4,5,6-F_5C_6	88	[30]
4-BrC_6H_4	Me	Boc	H	Ph	98	[30]
Ph	Me	Ts	H	Ph	97	[30]

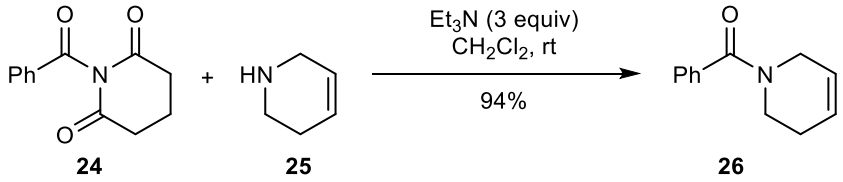
More recently, Szostak and co-workers developed the first general method for mild and highly chemoselective transamidation of unactivated N,N-dialkyl and N,N-aryl-alkyl tertiary amides (Scheme 8).[31] Importantly from the synthetic standpoint, this protocol shows excellent chemoselectivity (1) with respect to different functional groups and (2) between different amide and ester electrophiles.

Another approach to amide transamidation reactions involves the use of preformed N-acyl-transfer reagents. In 2018, Szostak and co-workers reported mild, metal-free transamidation of N-acyl-glutarimides such as **24** with aliphatic amines such as **25** to furnish amides such as **26** at room temperature in the presence of 3 equiv of triethylamine (Scheme 9).[32] The weakened amidic resonance in a twisted amide bond scaffold of N-acyl-glutarimides ($\tau = 88.6°$) renders this transamidation feasible.

<Scheme 8> Selective transition-metal-free transamidation of unactivated tertiary amides[31]



<Scheme 9> Metal-free transamidation of N-acyl-glutarimides[32]



Amides, e.g. 23; General Procedure:[30]

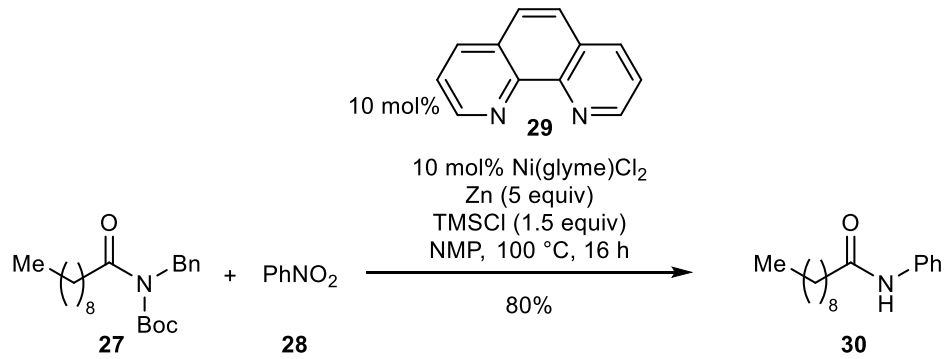
An oven-dried vial equipped with a stir bar was charged with amide **21** (0.10 mmol), amine **22** (0.20 mmol), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles. Toluene (0.40 mL) and LiHMDS (1.0 M in THF, 0.30 mmol) were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with NH_4Cl (aq., 1.0 M, 1 mL), diluted with CH_2Cl_2 (10 mL), the organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. The crude product was purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes.

21.19.3 Method 3: Transamidation of Amides under Reductive Conditions

Nitroarenes represent an alternative nitrogen source to anilines, offering several benefits in organic synthesis. First, nitroarenes are obtained directly from arenes by nitration and, as a consequence, more nitroarenes than anilines are commercially available. Second, nitroarenes are more stable than anilines as the oxidative decomposition is avoided. Third, nitroarenes are typically less expensive than the corresponding anilines.[33] In the past few years, reductive transamidations of amides utilizing nitroarenes as nitrogen source instead of anilines have been developed. This strategy involves a two-step, one-pot mechanism beginning with the reduction of a nitroarene substrate with Mn or Zn to give nitrosoarene or azobenzene intermediate, which then participates in the transamidation with the amide N–C(O) bond.

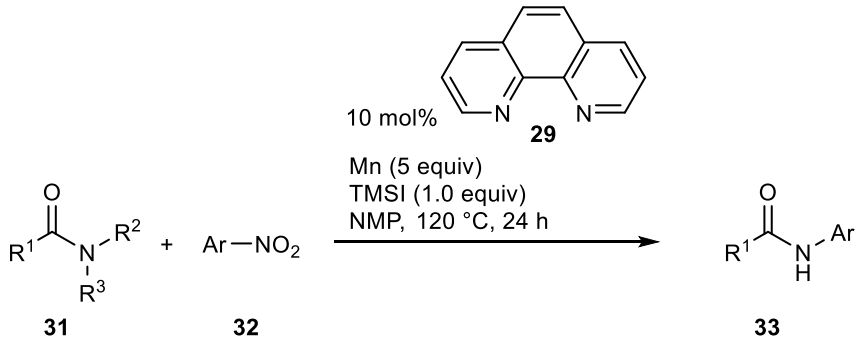
In 2017, Hu and co-workers have reported a reductive transamidation of N-Boc-activated secondary amides such as **27** with nitroarenes such as **28** to afford amide products such as **30** by using 5 equiv of zinc as a reductant, 10 mol% of Ni(glyme)Cl_2 as a catalyst and 10 mol% of 1,10-phenanthroline **29** as a ligand (Scheme 10). [34] The main advantage of this method is the direct use of nitroarenes instead of anilines, which improves the reaction cost, step-economy and permits for orthogonal reactivity in the presence of stable nitro groups.

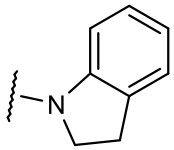
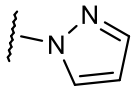
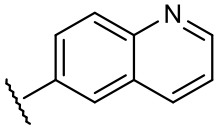
<Scheme 10> Transamidation of N-Boc-activated secondary amides with nitroarenes[34]



Subsequently, Hu and co-workers reported a related manganese-mediated reductive transamidation of tertiary amides **31** with nitroarenes **32** to furnish amide products **33** in typically good yields (Scheme 11).[35] This protocol employs 5 equiv of manganese as a reductant and promoter, 10 mol% of terpyridine **29** as a ligand and 1.0 equiv of iodotrimethylsilane as an additive. The method enables the use of manganese without additional metal co-catalysts.

<Scheme 11> Transamidation of unactivated tertiary amides with nitroarenes[35]



R^1	R^2	R^3	Ar	Yield (%)	Ref
Ph	Ph	Ph	Ph	80	[35]
Ph	Ph	Ph	4-$Et_2NO_2SC_6H_4$	67	[35]
Ph	Ph	$HOCH_2CH_2$	4-$MeOC_6H_4$	66	[35]
C_4H_7	Ph	Ph	4-*t*BuC_6H_4	77	[35]
2-naphthyl			4-$PhNHC_6H_4$	85	[35]
$CH_3(CH_2)_8$				42	[35]
4-$CF_3C_6H_4$	Me	Me	4-$OMeC_6H_4$	47	[35]
4-$CF_3C_6H_4$		$(CH_2)_4$	4-Tol	61	[35]

Amides, e.g. 33; General Procedure:[35]

An oven-dried 20 mL Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with manganese powder (2.5 mmol), amide **31** (0.50 mmol), nitroarene **32** (0.75 mmol) and 1,10-phenanthroline **29** (10 mol%). The tube was subjected to three evacuation/backfilling cycles under argon. N-methylpyrrolidone (NMP, 1.0 mL) and iodotrimethylsilane (TMSI, 0.50 mmol) were added. The resulting reaction mixture was placed in a preheated oil bath at 120 °C and stirred for 24 h. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (50 mL), the organic layer was acidified with HCl (aq., 1.0 *N*, 10 mL), neutralized with KOH (aq., 1.0 *N*, 30 mL), washed with saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes/Et_3N.

21.19.4 Method 4: Metal-Catalyzed Amidation of Esters

In recent years, Ni– and Pd–NHC catalyst systems have been identified as a powerful tool for transition-metal-catalyzed activation of C(acyl)–O bonds of esters.[21] While the mechanism of several of these transformations remains unclear, Ni– and Pd–NHCs have been shown as versatile catalysts in the direct amidation of aryl and alkyl esters.

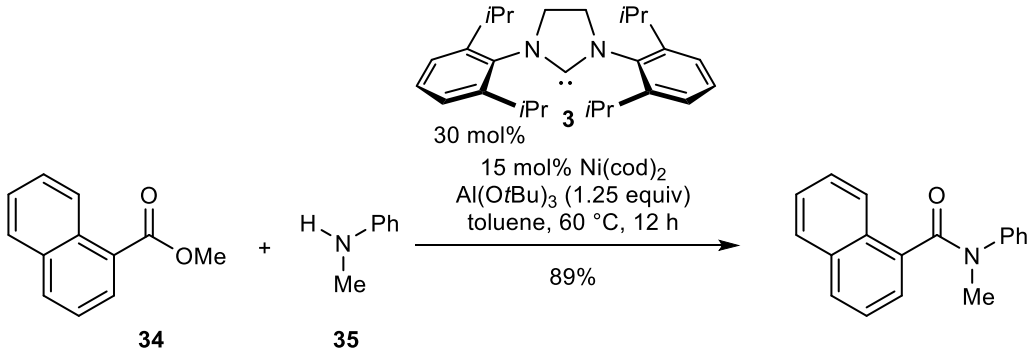
In 2016, Garg and co-workers reported a catalytic method for amidation of methyl esters such as **34** with amines such as **35** by Ni–NHC catalysis using 15 mol% of $Ni(cod)_2$, 30 mol% of imidazolidinylidene NHC ligand **3** and 1.25 equiv $Al(O\textit{t}Bu)_3$ as an additive at 60 °C (Scheme 12).[36] On the basis of DFT studies, the authors proposed that the reaction proceeds via oxidative addition of the C(acyl)–O bond. $Al(O\textit{t}Bu)_3$ is a critical additive that changes the amidation process to become close to thermoneutral, but also reduces the kinetic barrier for oxidative addition.

In 2018, Newman and co-workers reported a related Ni–NHC-catalyzed amide bond formation from methyl esters **36** and amines **37** to furnish amide products **39** in

good to excellent yields (Scheme 13).[37] This reaction is accomplished with 10 mol% of $Ni(cod)_2$ as a catalyst and 20 mol% of imidazolylidene **38** as a ligand without additional additives at 140 °C in toluene.

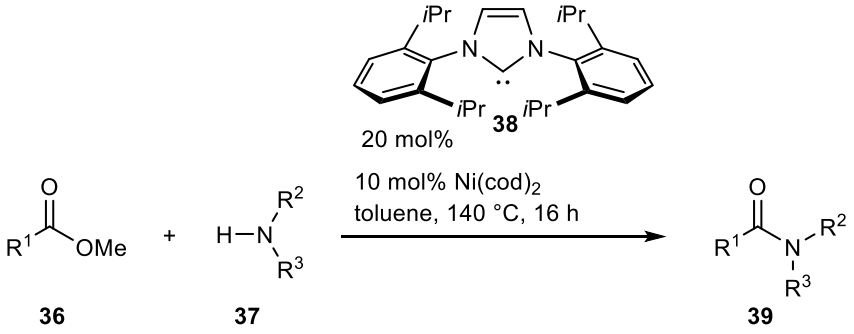
Later, the same group identified several classes of NHC ligands such as **40** to further expand the scope of the amide bond formation from methyl esters by Ni–NHC catalysis (Scheme 14).[38]

<Scheme 12> Nickel(0)-catalyzed amidation of methyl esters[36]



34 **35**

<Scheme 13> Nickel(0)-catalyzed amidation of methyl esters at high temperature[37]

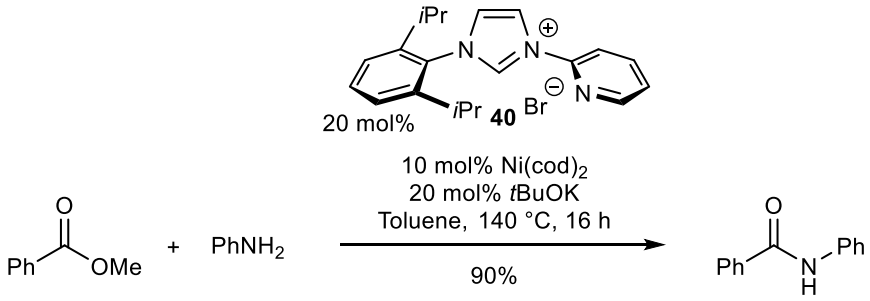


36 **37** **39**

R^1	R^2	R^3	Yield (%)	Ref
Ph	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$	73	[37]
Ph	$(CH_2)_4$		80	[37]
Ph	H	Bn	74	[37]

Ph	H	2-Tol	80	[37]
2-naphthyl		$(CH_2)_2O(CH_2)_2$	90	[37]
3,5-$(CF_3)_2C_6H_3$		$(CH_2)_2O(CH_2)_2$	88	[37]
Bn		$(CH_2)_2O(CH_2)_2$	71	[37]
*t*Bu	H	Ph	60	[37]

<Scheme 14> Nickel(0)-catalyzed amidation of methyl esters using NHC salts[38]



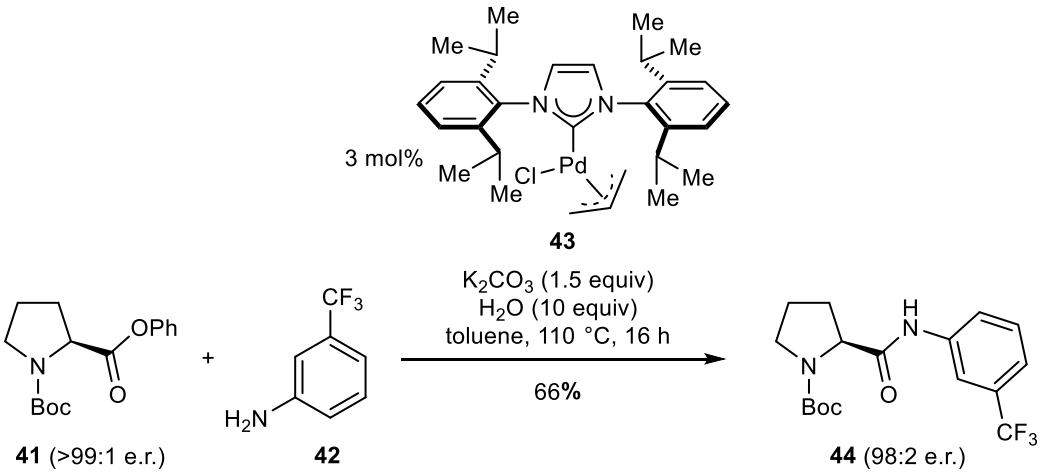
In addition to Ni–NHC catalysis, significant recent progress in direct amidation reactions of esters has been achieved with Pd–NHCs. In 2017, Newman and co-workers reported a direct amidation of aryl esters such as **41** with anilines such as **42** catalyzed by Pd(II)–NHC complex **43** to afford diverse amide products such as **44** in good to excellent yields (Scheme 15).[39] It is particularly noteworthy that this method could be applied to the synthesis of chiral proline derivatives without erosion of the α-stereocenter.

In 2017, Szostak and co-workers reported Pd–PEPPSI-catalyzed amidation of aryl esters such as **45** with anilines to afford amide products such as **46** in good to excellent yields (Scheme 16).[26] Later, the same group identified [Pd(NHC)(acac)Cl] catalysts **17** as an efficient catalyst system for the direct amidation of aryl esters with anilines (Scheme 17).[27] These Pd(II)–NHCs are highly attractive due to their air- and moisture-stability, ease of synthesis and the potential to engage in an in situ NHC salt screening in amidation reactions of aryl esters.

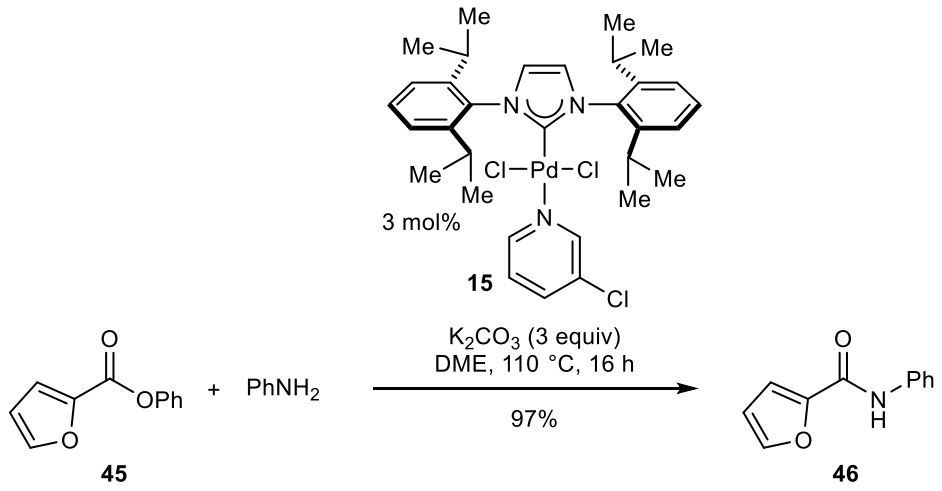
Independently, Hazari and co-workers developed their [Pd(NHC)(1-*t*-Bu-ind)(Cl)] precatalysts such as **49** for amidation of aryl esters such as **47** with anilines such as

48 at 40 °C (Scheme 18).[40] The authors proposed that water as a co-solvent facilitates the reaction by improving the solubility of a base and increasing the rate of precatalyst activation.

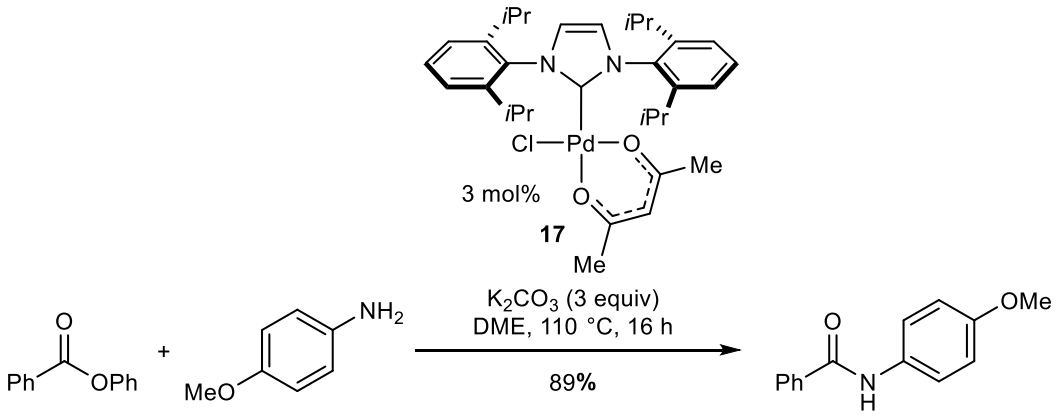
<Scheme 15> Palladium–NHC-catalyzed amidation of aryl esters[39]



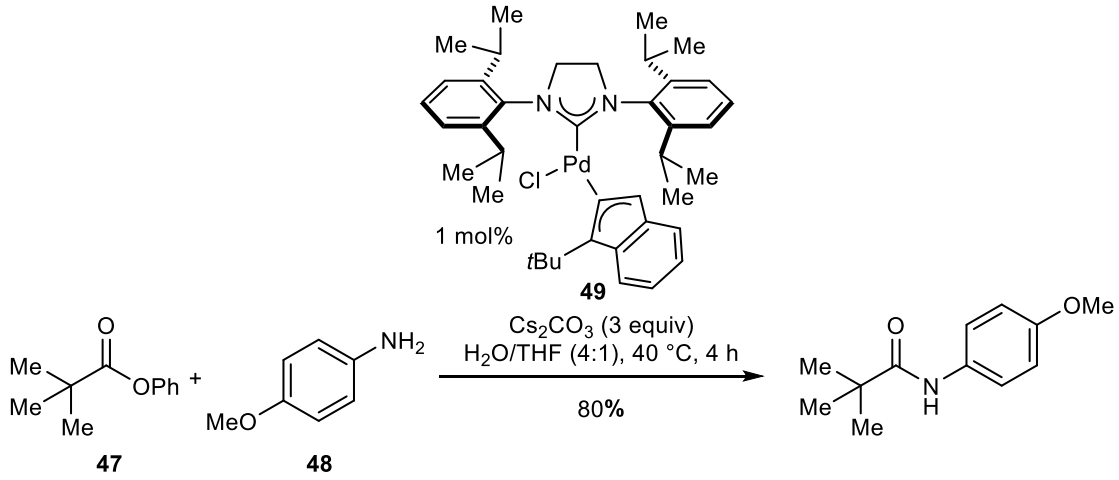
<Scheme 16> Palladium–PEPPSI-catalyzed amidation of aryl esters[26]



<Scheme 17> [Pd(NHC)(acac)Cl]-catalyzed amidation of aryl esters[27]



<Scheme 18> [Pd(NHC)(1-t-Bu-ind)Cl]-catalyzed amidation of aryl esters[40]



Amides, e.g. 39; General Procedure:[37]

In a glovebox, an oven dried screw-capped vial was charged with a magnetic stir bar, $Ni(cod)_2$ (10 mol%), and NHC ligand **38** (20 mol%). Thoroughly degassed toluene (1.0 mL) was then added. To a vigorously shaken reaction mixture, ester **36** (0.20 mmol) and amine **37** (0.24 mmol) were added. The vial was sealed with a Teflon-lined screw cap, placed outside of the glovebox, and stirred vigorously in an oil bath at 140 °C for 16 h. After the indicated time, the reaction mixture was cooled down to room temperature, quenched with NH_4Cl (aq.), diluted with EtOAc, and filtered through a plug of silica gel

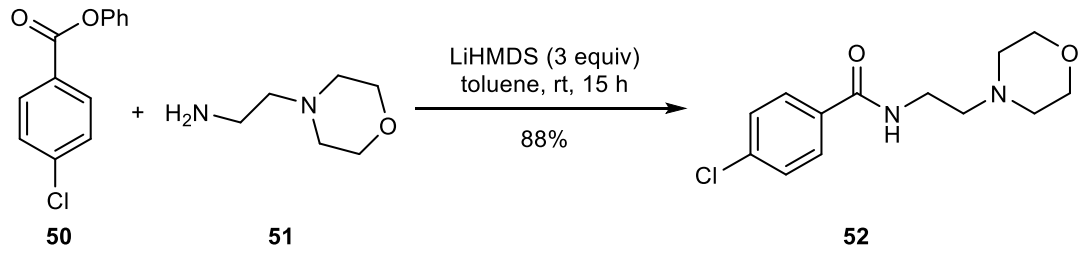
eluting with EtOAc. The crude mixture was then concentrated in vacuo and purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes.

21.19.5 Method 5: Transition-Metal-Free Amidation of Esters

Amidation of esters represents one the classic methods in organic synthesis;[41,42] however, transition-metal-free direct amidation with non-nucleophilic amines has been a challenge due to the low reactivity of non-nucleophilic amines.[43] Considering that esters are some of the most common derivatives of carboxylic acids and broadly present in strategic routes, direct amide bond formation from esters is synthetically appealing.[44]

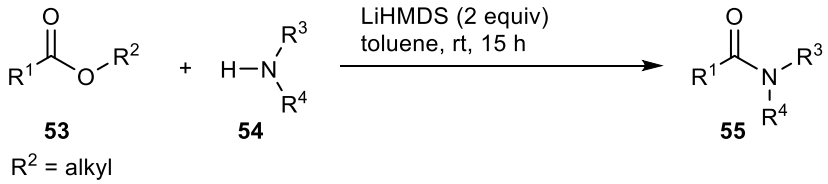
Recently, significant progress has been made in transition-metal-free, chemoselective amidation of aryl and alkyl esters with non-nucleophilic amines. In 2018, Li and Szostak reported a general LiHMDS-mediated protocol for transition-metal-free amidation of aryl esters such as **50** by a selective C(acyl)–O bond cleavage with non-nucleophilic amines such as **51** to afford amide products such as **52** in excellent yields (Scheme 19).[29] Later, the same group further extended this protocol to the direct amidation of alkyl esters **53** by C(acyl)–O bond cleavage under exceedingly mild reaction conditions (Scheme 20). [31] This method is characterized by operational-simplicity and broad substrate scope, including sterically-hindered O*i*Pr and O*t*-Bu esters, which are incompatible with transition-metal-catalyzed amidations at high temperatures.

<Scheme 19> Selective metal-free amidation of aryl esters[30]



50 **51** **52**

<Scheme 20> Selective metal-free amidation of alkyl esters[31]



53 **54** **55**

R^2 = alkyl

R^1	R^2	R^3	R^4	Yield (%)	Ref
Ph	Me	H	Ph	93	[31]
Ph	Me	H	4-$EtO_2CC_6H_4$	84	[31]
Ph	Me	H	2,6-*i*PrC_6H_3	96	[31]
3-BrC_6H_4	Me	H	Ph	93	[31]
*t*Bu	Me	H	Ph	88	[31]
Ph	Me	Me	Ph	97	[31]
Ph	*i*Pr	H	Ph	85	[31]
Ph	*t*Bu	H	Ph	75	[31]

Amides, e.g. 55; General Procedure:[31]

An oven-dried vial equipped with a stir bar was charged with an ester substrate **53** (0.10 mmol), amine **54** (0.12 mmol), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles. Toluene (0.40 mL) and LiHMDS (1.0 M in THF, 0.2 mL) were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with NH4Cl (aq., 1.0 M, 1 mL), diluted with EtOAc (10 mL), the organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. The crude product was purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes.

21.19.6 Method 6: Amidation of Esters under Reductive Conditions

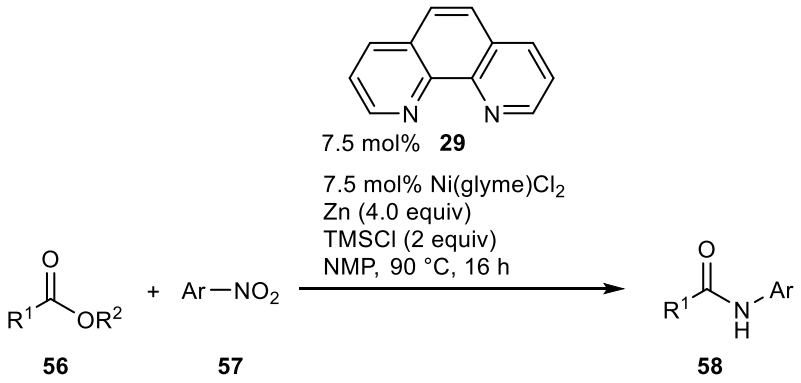
Another recent strategy for amide bond formation by direct amidation of esters involves the use of nitroarenes as nitrogen source instead of anilines. In this approach, nitroarenes are reduced by a metal such as Zn, Mn or Mg to azoarene or nitrosoarene intermediates, which then undergo amidation with esters to furnish amide products in the presence of a transition-metal and a Lewis acid.

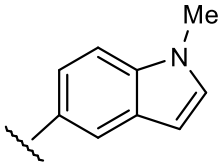
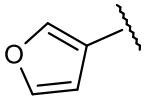
In 2017, Hu and co-workers reported a nickel-catalyzed reductive amidation of alkyl esters **56** with nitroarenes **57** to afford a wide range of amide products **58** in the presence of phenanthroline ligand **29** and zinc as a stoichiometric reductant in generally good yields (Scheme 21).[45] The proposed amidation mechanism involves the reaction of azobenzene with Ni(0) to form a Ni(II)-nitrene intermediate, which is more likely than the direct oxidative addition of the ester C(acyl)–O bond to Ni(0) to afford Ni(II)–acyl complex.

Recently, Cheung and co-workers reported a manganese-mediated reductive amidation of aryl and alkyl esters such as **59** with nitroarenes such as **60** to afford amides such as **61** in good to excellent yields (Scheme 22). [46] In this method, Mn firstly reduces nitrobenzene to nitrosobenzene intermediate, which then reacts with the C(acyl)–O ester bond in the presence of Mn and TMSCl to afford amide products. It is worth noting that the method does not require pyridine ligands to promote the reaction.

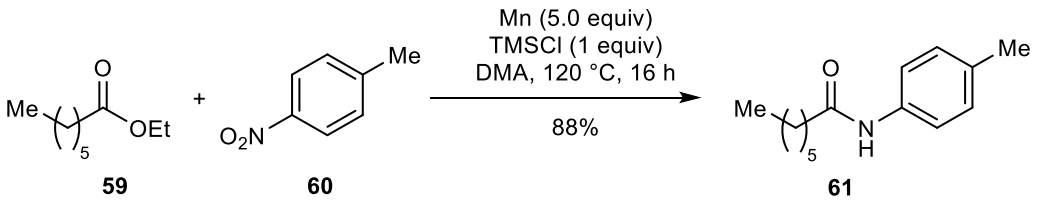
An interesting variation using catalytic Cr in the presence of stroichiometric Mg and TMSCl was recently reported by Zeng and co-workers (Scheme 23).[47] This low-cost method features an excellent scope and broad functional group tolerance to form amides from alkyl esters and nitroarenes, including the synthesis of pesticide Mepronil **65** from alkyl ester **62** and nitroarene **63** in the presence of bipyridine ligand **64**.

<Scheme 21> Nickel-catalyzed amidation of esters with nitroarenes[45]

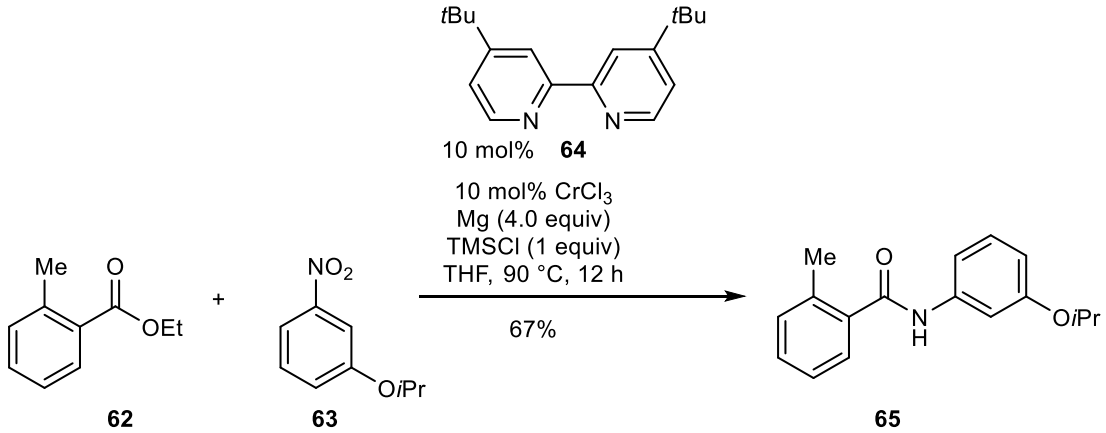


R^1	R^2	Ar	Yield (%)	Ref
$CH_3(CH_2)_8$	Me	4-$MeSC_6H_4$	72	[45]
$CH_3(CH_2)_8$	*t*Bu	4-$OMeC_6H_4$	68	[45]
$CH_3(CH_2)_8$	Me		59	[45]
$Cl(CH_2)_6$	Me	4-*t*BuC_6H_4	67	[45]
4-$NH_2C_6H_4$	Me	4-*t*BuC_6H_4	52	[45]
2-naphthyl	Me	3-$CF_3C_6H_4$	77	[45]
	Et	4-Tol	66	[45]
Ph	Bn	3-MeO-4-MeC_6H_3	87	[45]

<Scheme 22> Manganese-mediated amidation of esters with nitroarenes[46]



<Scheme 23> Chromium-catalyzed amidation of esters with nitroarenes[46]



Amides, e.g. 58; General Procedure:[45]

An oven-dried 30 mL screw-cap vial equipped with magnetic stir bar was charged with zinc powder (2.0 mmol), ester **56** (0.50 mmol), nitroarene **57** (0.60 mmol), 1,10-phenanthroline (7.5 mol%), Ni(glyme)Cl_2 (7.5 mol%), NMP (1.0 mL) and TMSCl (1.0 mmol). The resulting mixture was placed in a preheated oil bath (90 °C) and stirred for 16 h. After the indicated time, the reaction mixture was cooled down to room temperature, the crude product was acidified with NH_4Cl (aq., 5 mL), neutralized with $NaHCO_3$ (aq., 10 mL), and extracted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with a mixture of EtOAc/hexanes.

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