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Nickel-catalyzed decarbonylative amination of carboxylic acid esters

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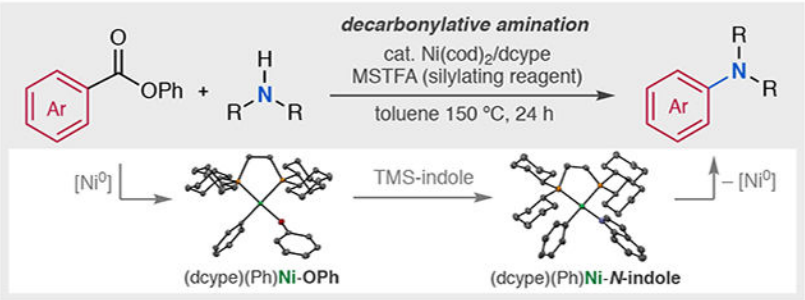
Abstract

The reaction of carboxylic acid derivatives with amines to form amide bonds has been the most widely used transformation in organic synthesis over the past century. Its utility is driven by the broad availability of the starting materials as well as the kinetic and thermodynamic driving force for amide bond formation. As such, the invention of new reactions between carboxylic acid derivatives and amines that strategically deviate from amide bond formation remains both a challenge and an opportunity for synthetic chemists. This report describes the development of a nickel-catalyzed decarbonylative reaction that couples (hetero)aromatic esters with a broad scope of amines to form (hetero)aryl amine products. The successful realization of this transformation was predicated on strategic design of the cross-coupling partners (phenol esters and silyl amines) to preclude conventional reactivity that forms inert amide by-products.

Graphical Abstract



Carboxylic acids are abundant, inexpensive, and stable compounds, and these properties render them attractive building blocks for organic synthesis. As such, metal-catalyzed decarbonylative or decarboxylative reactions that employ aryl carboxylic acid derivatives

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Supporting Information
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Experimental details, characterization data, and NMR spectra of compounds (PDF)
X-ray crystal structure files (CIF)

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[ArC(O)X] as coupling partners have gained tremendous attention over the past two decades.[1,2] A variety of (hetero)aryl carbon–carbon, carbon–sulfur, carbon–boron, carbon–silicon, carbon–halogen, and other carbon–heteroatom linkages can be formed using this approach.[1] However, methods for the decarbonylative or decarboxylative coupling of ArC(O)X (Ar = aryl) with amines to afford aryl C(sp^2)–N bonds (Figure 1A) remain limited. While a few such transformations have been reported, they often have a very narrow scope with respect to the carboxylic acid and/or amine coupling partner.[3–6] For example, most decarboxylative methods require strong electron withdrawing groups on the arene ring, or weakly nucleophilic *N*-group to form carbamates.[5–6] In decarbonylative reactions, couplings involving non-stabilized 1° or 2° amines remain challenging, largely due to the competing amide formation with these strongly nucleophilic partners (Figure 1A, conventional reactivity).[3] This is exemplified by Rueping's recent report of Ni-catalyzed decarbonylative amination of phenyl esters. As shown in Figure 1B, this transformation is effective for weakly nucleophilic benzophenone imine. In contrast, the use of more nucleophilic amines such as morpholine,[3] aniline, and indole results in exclusive formation of the amide product.

The paucity of methods to convert carboxylic acid derivatives to amines is particularly noteworthy because the products are of high value in medicinal chemistry.[7] As such, new, general, and practical approaches to forge (hetero)aryl C(sp^2)–N bonds from abundant starting materials have the potential for widespread application.

We hypothesized that undesired background amide formation could be mitigated by masking the amine with a main group element (M). Appropriate selection of M would provide an amine nucleophile, M–NR_2, that is inert to background acyl transfer but can selectively engage a metal catalyst via transmetalation.[8] A catalytic cycle that leverages this approach is shown in Figure 1B. First, ArC(O)X reacts with a low valent metal catalyst via oxidative addition and carbonyl deinsertion to afford an arylmetal intermediate (**B**).[9] Intermediate **B** then undergoes transmetalation with M–NR_2 and subsequent C(sp^2)–NR_2 coupling to release the targeted aryl amine product. The success of this cycle relies on strategic design of M–NR_2, ArC(O)X, and the metal catalyst such that: (i) background acyl transfer between M–NR_2 and ArC(O)X is slow; (ii) **B** undergoes facile transmetalation with M–NR_2; (iii) carbonyl deinsertion is fast relative to transmetalation (since reaction between M–NR_2 and metal acyl intermediate **A** would afford the undesired amide by-product; Figure 1B);[10] and (iv) other key steps of the catalytic cycle (oxidative addition, C(sp^2)–N coupling) are energetically feasible. This report describes the successful realization of this transformation, using a nickel phosphine catalyst to couple aromatic ester electrophiles with *in situ*-generated silyl amines.

Based on the criteria outlined above, trimethylsilyl (TMS)-substituted amines as the M–NR_2 nucleophile are expected to slow background acyl transfer, while facilitating base-free transmetalation[8] between TMS–NR_2 and **B**. To identify a suitable ArC(O)X coupling partner, we evaluated the background reaction of TMS–morpholine with three carboxylic acid derivatives: acid chloride **1-Cl**, acid fluoride **1-F**, and aryl ester **1-OPh**. Heating TMS–morpholine with **1-Cl** or **1-F** at 100 °C for 1 h resulted in undesired acyl transfer to afford amide **3** in high yield (Figure 2A, [M] = TMS). In contrast, the less electrophilic **1-OPh** showed <5% amide formation under analogous conditions. Notably, as expected, the use of

free morpholine as the nucleophile led to a high yield of the amide product with all three electrophiles (Figure 2A, [M] = H).

We next examined the coupling of TMS–morpholine with **1-F** and **1-OPh** in the presence of Ni-bisphosphine catalysts (Figure 2B). Importantly, Ni phosphine complexes are known to participate in oxidative addition and carbonyl deinsertion with diverse ArC(O)X electrophiles.[1] Bisphosphine supporting ligands were chosen based on their ability to effect C(sp^2)–N coupling at Ni^{II} centers.[11] Representative results with dppf and dcype are shown in Figure 2 (see SI for larger ligand screen). Consistent with the fast background reaction, amide formation dominated with **1-Cl** and **1-F** under catalytic conditions. In contrast, with **1-OPh**, decarbonylative coupling to afford aryl amine **4** proceeded in modest to high yield with dppf and dcype, respectively. Under the optimized conditions (10 mol % Ni/dcype in toluene at 150 °C), **1-OPh** reacted with TMS–morpholine to afford **4** in 90% yield with >19:1 selectivity for amine **4** versus amide **3**.

We next explored the scope of this transformation and found that it is general for a variety of electron-deficient and electron-neutral carboxylic acid esters (Figure 3A).[12] Substituents such as trifluoromethyl, methyl ester, nitrile, ketone, and phenyl ether (**4**-**9**) are well tolerated. Competing cross-coupling is not observed at methyl ester (**5**) or boronate ester (**10**) sites. Various *N*-containing heteroaryl carboxylic acid esters such as pyridine, quinoline, and quinoxaline derivatives are converted to *N*-heteroaryl amines (**12**-**14**) in moderate to excellent yields. *S*- and *O*-containing heteroaryl esters such as benzothiophene (**15**), benzofuran (**16**), chromone (**17**), and thiazoles (**20**) are also converted to the desired amine products. Esters derived from carboxylic acid-containing drugs such as probenecid (**18**), bexarotene (**19**) and febuxostat (**20**) afford good to excellent yields. This transformation is also general with respect to the amine coupling partner (Figure 3B). Utilizing the probenecid ester **18-OPh** as the electrophile, various TMS-amines react smoothly to yield **18**, **25**, **27**, and **28**. More stable triethylsilyl (TES)- and triisopropylsilyl (TIPPS)-protected amines are effective coupling partners but provide lower yields of **25**.

While TMS–amines are straightforward to synthesize, their commercial availability is limited. In addition, some derivatives are susceptible to hydrolysis. Thus, the *in situ* formation of these species from readily available amine starting materials would significantly enhance the practicality of this method. After some optimization, we identified the commercial silyl transfer reagent *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) as effective for the rapid, room temperature conversion of diverse HNR_2 to TMS–NR_2. Indeed, the direct addition of HNR_2 and MSTFA to the standard coupling conditions resulted in effective Ni-catalyzed decarbonylative coupling (Figure 3B). Secondary dialkyl and diaryl *N*-heterocycles[13] such as morpholines (**18**), piperidines (**21**, **22**), piperazines (**23**), pyrrolidines (**24**), indoles (**25**), and carbazoles (**26**) underwent coupling in good to excellent yields under these conditions. Furthermore, both primary aryl (**28**-**30**), and alkyl amines (**31**-**34**) afforded secondary aryl amines products in good yields. In the few cases where background acyl transfer reactivity was observed (**31**-**34**), prestirring of HNR_2 with MSTFA for 1 h prior to catalysis resulted in selective generation of the desired aryl amine.

Traditional metal-catalyzed couplings between aryl electrophiles and amines require typically stoichiometric quantities of an exogenous inorganic base to promote metalation of the amine coupling partner.[14] This is a key limitation of the Buchwald-Hartwig amination of aryl halides, and significant recent effort has focused on identifying milder bases for these transformations.[15] In contrast, the current method eliminates the need for an exogenous base for C(sp^2)–N coupling. As such, base-sensitive amine substrates[16] are well tolerated and deliver aryl amine products (**24**, **33**, **34**) in good yields.

We then set out studies focused on eliminating the need for air-sensitive $Ni(cod)_2$ as the nickel source. These investigations revealed that the use of $Ni(CO)_2(PPh_3)_2$, an air-stable and commercial reagent, as Ni(0) source affords aryl amine **28** in good yield (Figure 3C). All of the catalysts and reagents were weighed on the benchtop without the requirement of an inert glovebox.

Finally, we conducted stoichiometric studies to interrogate the proposed reaction mechanism. The reaction of phenyl ester **8-OPh** with $Ni(cod)_2$/dcype in toluene at 80 °C for 3 h resulted in oxidative addition/carbonyl deinsertion to afford (dcype)Ni(Ph)(OPh) (**B**) in 60% yield (Figure 4A).[17] A Ni^{II} acyl intermediate (**A** in Figure 1B) was not detected by ^{31}P NMR spectroscopy during this reaction, suggesting that carbonyl deinsertion is fast under these conditions. Notably, reactions performed at 60 °C or lower did not afford observable conversion of **8-OPh** due to slow oxidative addition. The treatment of **B** with TMS–indole in toluene at room temperature for 1 h resulted in transmetalation to form Ni^{II} complex **C** in quantitative yield (Figure 4B). Complex **C** is stable and isolable at room temperature. Aryl C(sp^2)–N bond-forming reductive elimination was only observed upon heating at 120 °C, which afforded aryl amine product **35** in 65% yield after 16 h. These studies show the feasibility of each proposed step of the proposed catalytic cycle. Furthermore, they demonstrate that in this stoichiometric system, C(sp^2)–N bond formation is the most challenging step of the sequence.

In conclusion, we developed a Ni-catalyzed decarbonylative conversion of esters to aryl amines. The generality, selectivity, and base-free nature of this transformation render it complementary to existing Pd/Ni-catalyzed methods for the construction of (hetero)aryl amines. Current limitations, including low reactivity of electron rich and sterically hindered aryl esters (see SI), and the requirement of high temperatures and catalyst loading, will be addressed by future mechanistic and catalysis development studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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17. Complex **B** does not undergo C(sp^2)–O bond-forming reductive elimination even upon heating at 150 °C for 24 h. This is consistent with the observation that diaryl ether side products are not detected during catalysis.

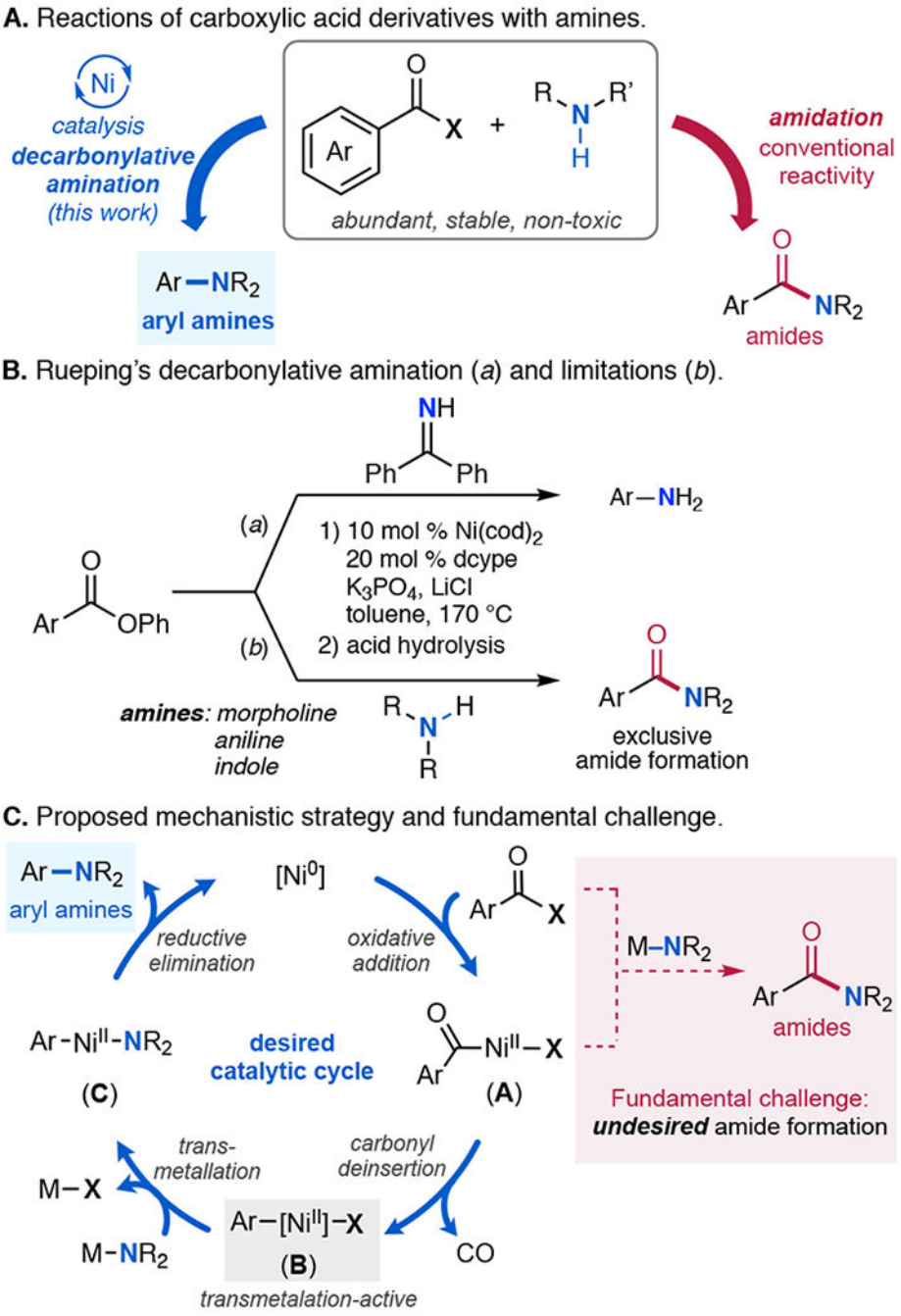

Figure 1.

Proposed strategy for the catalytic decarbonylation of carboxylic acid derivatives to aryl amines.

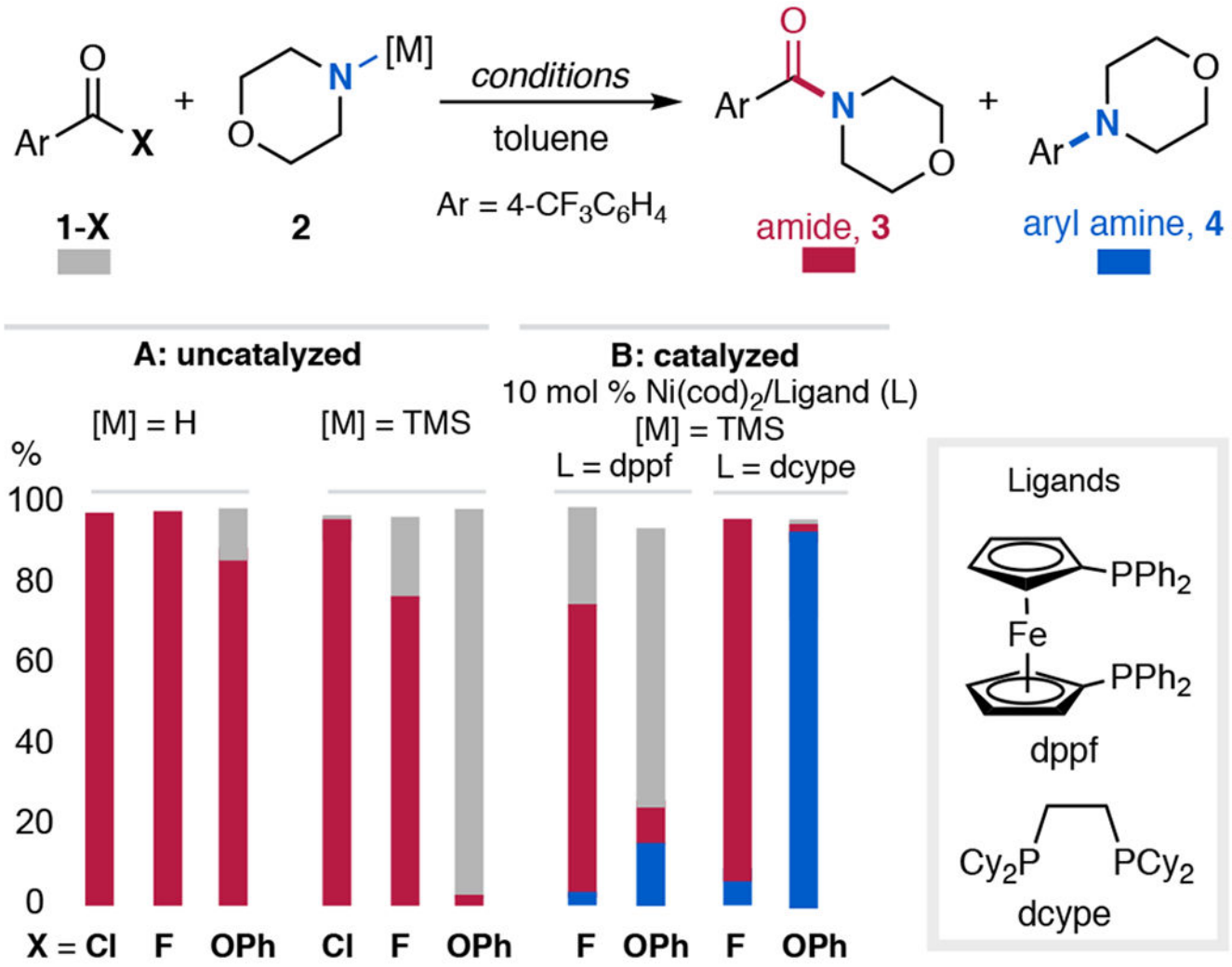

Figure 2.

(A) Uncatalyzed reaction of **1-X** with morpholine and TMS–morpholine at 100 °C for 1 h. (B) Ni-catalyzed reaction of **1-X** with TMS–morpholine at 150 °C for 24 h. Yields determined via ^{19}F NMR spectroscopy.

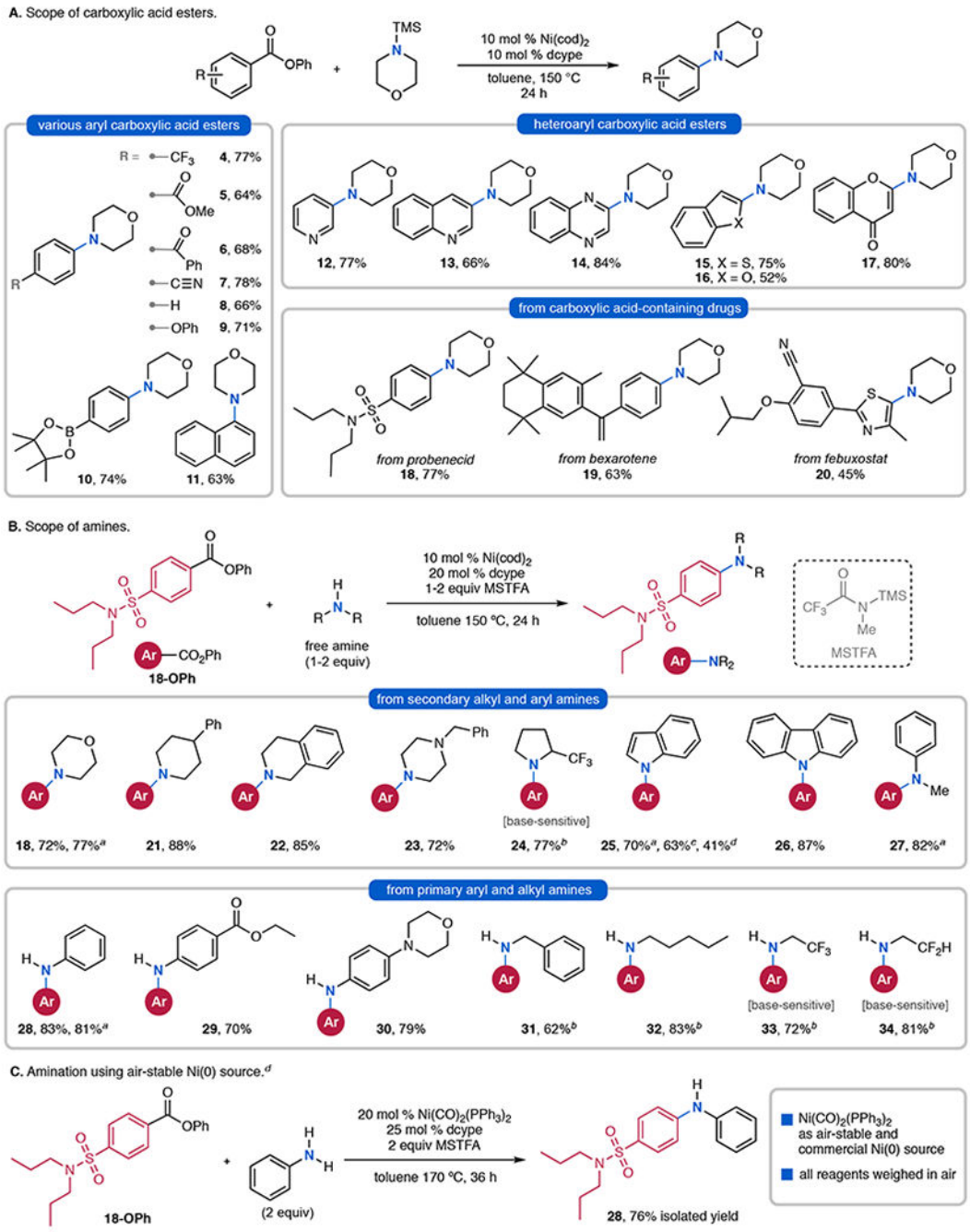

Figure 3.

Scope of Ni-catalyzed decarbonylative amination. [a]Using TMS–amine. [b]TMS–amine was generated *in situ* by premixing the amine with MSTFA. [c]Using TES–indole or [d]TIPPS–indole. [d]Reagents were weighed on benchtop. For additional substrates that were found to be challenging under the optimized conditions, see SI.

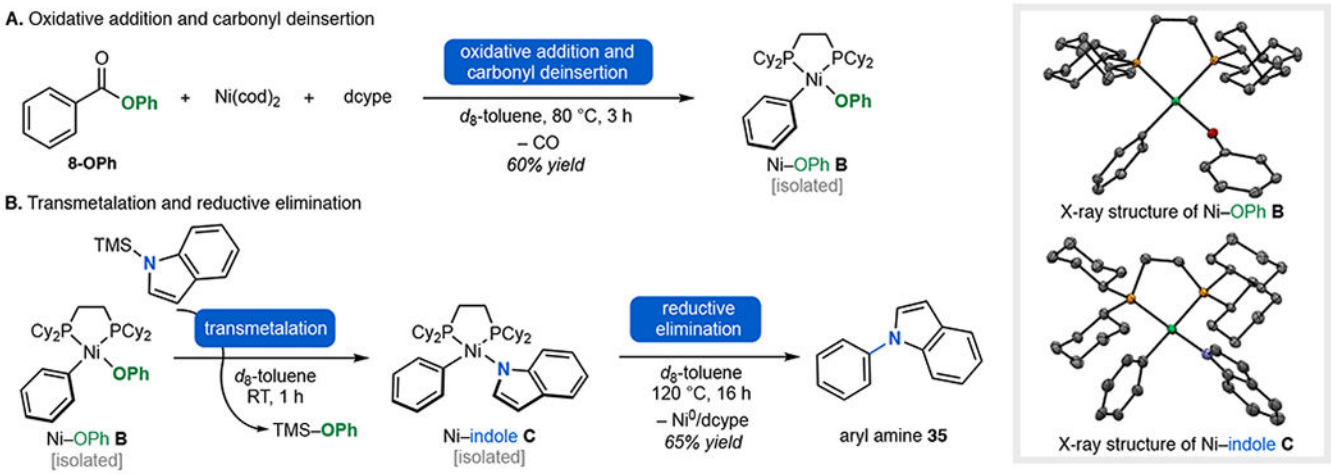

Figure 4.

Mechanistic studies: stoichiometric reactions for the fundamental steps in decarbonylative amination. See the SI for details on reaction conditions.