

The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C–N Cross-Coupling

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ABSTRACT: Palladium-catalyzed amination reactions using soluble organic bases have provided a solution to the many issues associated with heterogeneous reaction conditions. Still, homogeneous C–N cross-coupling approaches cannot yet employ bases as weak and economical as trialkylamines. Furthermore, organic base-mediated methods have not been developed for Ni(0/II) catalysis, despite some advantages of such systems over analogous Pd-based catalysts. We designed a new air-stable and easily prepared Ni(II) precatalyst bearing an electron-deficient bidentate phosphine ligand that enables the cross-coupling of aryl triflates with aryl amines using triethylamine (TEA) as base. The method is tolerant of sterically-congested coupling partners, as well as those bearing base- and nucleophile-sensitive functional groups. With the aid of density functional theory (DFT) calculations, we determined that the electron-deficient auxiliary ligands decrease both the pK_a of the Ni-bound amine and the barrier to reductive elimination from the resultant Ni(II)–amido complex. Moreover, we determined that precluding Lewis acid–base complexation between the Ni catalyst and the base, due to steric factors, is important for avoiding catalyst inhibition.

INTRODUCTION

The development of metal-catalyzed carbon–nitrogen (C–N) bond-forming reactions has had a transformative impact on the synthesis of pharmaceuticals, agrochemicals, organic materials and fine chemicals.¹ Catalysts based on palladium and copper have been broadly employed to facilitate the cross-coupling of aryl (pseudo)halides with amine nucleophiles, but these reactions have traditionally required the addition of inorganic bases.² In recent years, however, there has been increased interest in the use of soluble organic bases in place of these commonly used inorganic reagents.³ These single-phase reactions are easily transferrable to high-throughput reaction screening settings, continuous flow chemistry, and microfluidic screening platforms.⁴ Moreover, the use of weak organic bases avoids functional group incompatibility issues associated with nucleophilic alkoxide and metal amide bases, especially in combination with amines.⁵ Previously, several phosphazene,⁶ guanidine,⁷ and alkyl amine⁸ bases have been shown to facilitate Pd- and Cu-catalyzed⁹ C–N bond formation. The weakest among these, alkyl amine bases stand out as an attractive class of reagents, particularly since their steric properties, nucleophilicity, and basicity can be precisely tuned.¹⁰ Furthermore, many trialkylamine reagents, including triethylamine (TEA), are produced on large scale directly from alcohols and ammonia,¹¹ making them as inexpensive as common organic solvents.

Previously, our research group demonstrated that a bulky, electron-deficient Pd catalyst can facilitate C–N bond formation in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).¹² Mechanistic investigations¹³ and in-depth reaction optimization studies¹⁴ suggested that other organic bases, including TEA and diisopropylethylamine (DIPEA, Hünig's base) could facilitate the cross-coupling of aryl triflates and anilines, albeit with

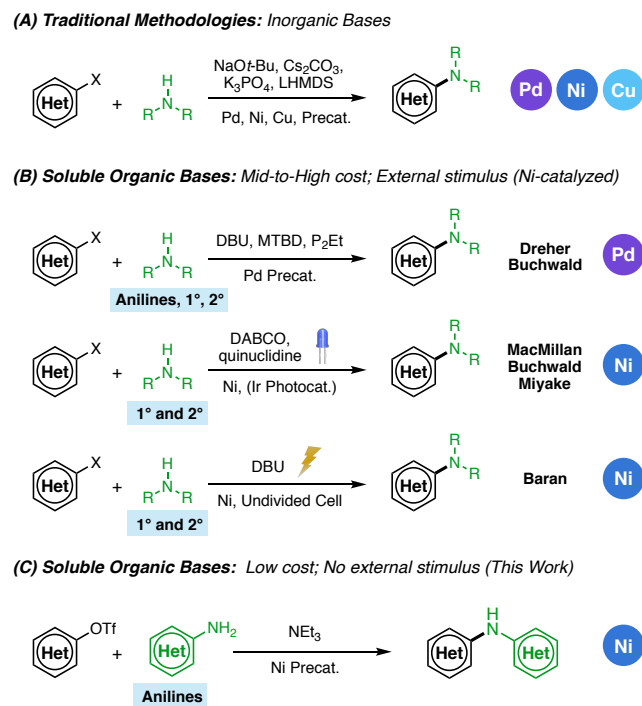


Figure 1. (A) Inorganic bases used in traditional Pd-, Ni-, and Cu-catalyzed C–N cross-coupling methodologies. (B) Amidine, guanidine, and phosphazene bases used in Pd-catalyzed amination and Ni-catalyzed photo- or electrocatalysis. (C) Nickel-catalyzed C–N cross coupling of aryl triflates and amines facilitated by triethylamine.

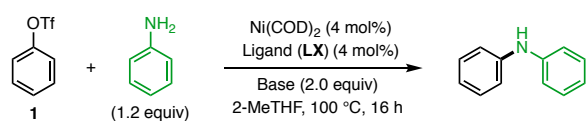
slower reaction rates. We considered whether an electron-deficient catalyst based on nickel might allow for these very mild and inexpensive trialkylamine bases to be used more effectively in C–N cross-coupling.

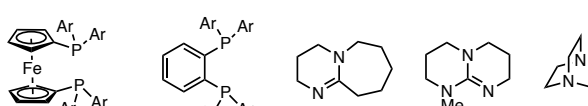
The use of Ni was of particular interest to us because the use of weak, soluble organic bases in Ni-catalyzed aryl amination has not yet been systematically explored. Since the first reports of Ni-catalyzed amination,¹⁵ the transformation has been significantly improved in terms of scope and efficiency through rational ligand design,¹⁶ the development of photocatalytic variants,¹⁷ and using electrochemistry.¹⁸ While these efforts have greatly expanded the number and type of electrophiles¹⁹ and nucleophiles²⁰ that can be cross-coupled under practical conditions, the majority of Ni-catalyzed methods remain predominantly reliant on inorganic bases such as metal *tert*-butoxides and phosphates to facilitate C–N formation (Figure 1A). Many useful solutions that are compatible with organic bases take advantage of energy input through either photo- or electrocatalysis. These protocols are primarily limited to the coupling of strongly coordinating nucleophiles such as aliphatic amines (Figure 1, B).^{17,18} Providing a complementary approach, we herein describe the rational discovery of a Ni (pre)catalyst capable of effecting arylation of weakly binding aniline nucleophiles using a trialkylamine base.

RESULTS AND DISCUSSION

Our studies began with an evaluation of commercially available bidentate phosphine ligands and organic bases in a model transformation, the Ni-catalyzed cross-coupling of phenyl triflate (**1**) and aniline. Selected results from these studies are summarized in Table 1 (see Supporting Information for further experimental details). When we used Ni(COD)₂ (4 mol%) and 1,1'-bis(diphenylphosphino)ferrocene (**L1**, DPPF) as precatalysts and triethylamine (TEA) as base, a 6% yield of the desired product was observed, with unreacted **1** making up the remainder of the mass balance. As in our previous work on Pd-catalyzed amination, we predicted that a more electron-deficient metal center would better facilitate the deprotonation of an amine-bound Ni complex by a base as weak as TEA.^{12a} Accordingly, we prepared several DPPF derivatives bearing electron-withdrawing trifluoromethyl (–CF₃) substituents on the *P*-aryl groups.²¹ Indeed, use of the fourfold trifluoromethylated ligand **L2** ([CF₃]₄-DPPF) resulted in 32% yield of the desired product. The yield was further increased to 94% by employing the further trifluoromethylated ligand **L3** ([CF₃]₈-DPPF).²² The ferrocene backbone was also found to be important to the success of these reactions: other ligands containing similar trifluoromethylated aryl groups, such as a 1,2-bis(diphenylphosphino)benzene (DPPBz) derivative (**L5**, [CF₃]₈-DPPBz) were less effective in promoting the C–N coupling reaction. TEA, besides being advantageous in terms of cost and mildness, was also uniquely efficacious as a base. Several stronger bases that had been reported to facilitate Pd-catalyzed amination reactions, including DBU and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), were essentially unable to promote our Ni-catalyzed transformation. Other alkylamine bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and DIPEA, could be used instead of TEA, but with lower reaction yields.

Table 1. Comparison of ligands and bases in the Ni-catalyzed cross-coupling of phenyl triflate (**1**) and aniline.

		
Ligand	Base	Yield (%)
L1 , DPPF	NEt ₃	6
L2 , [CF ₃] ₄ -DPPF	NEt ₃	32
L3 , [CF ₃] ₈ -DPPF	NEt ₃	94
L4 , DPPBz	NEt ₃	Trace
L5 , [CF ₃] ₈ -DPPBz	NEt ₃	23
L3 , [CF ₃] ₈ -DPPF	<i>i</i> -Pr ₂ NEt	87
L3 , [CF ₃] ₈ -DPPF	DABCO	17
L3 , [CF ₃] ₈ -DPPF	DBU	Trace
L3 , [CF ₃] ₈ -DPPF	MTBD	Trace

				
L1 : Ar = Ph L2 : Ar = 4-CF ₃ L3 : Ar = 3,5-CF ₃	L4 : Ar = Ph L5 : Ar = 3,5-CF ₃	DBU	MTBD	DABCO

^aGC yields were determined relative to hexamethylbenzene internal standard and are reported as a single run. Reaction conditions: phenyl triflate (0.20 mmol), aniline (0.24 mmol), base (0.40 mmol), Ni(COD)₂ (0.016 mmol, 4 mol% Ni), ligand (0.016 mmol, 4 mol%), and 2-MeTHF (0.40 mL, 0.50 M). 2-MeTHF = 2-methyltetrahydrofuran.

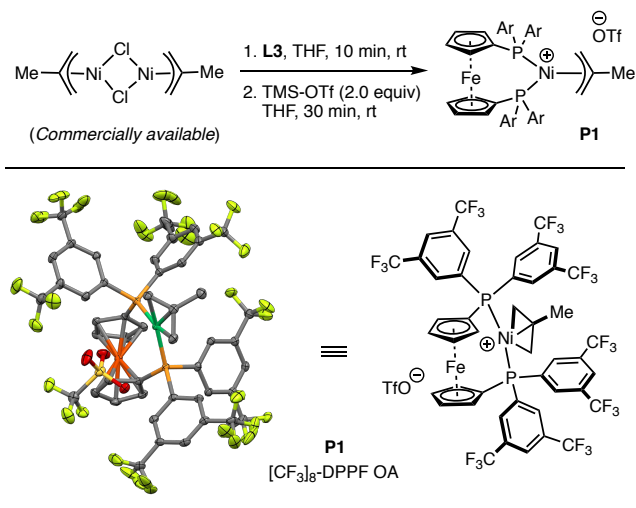
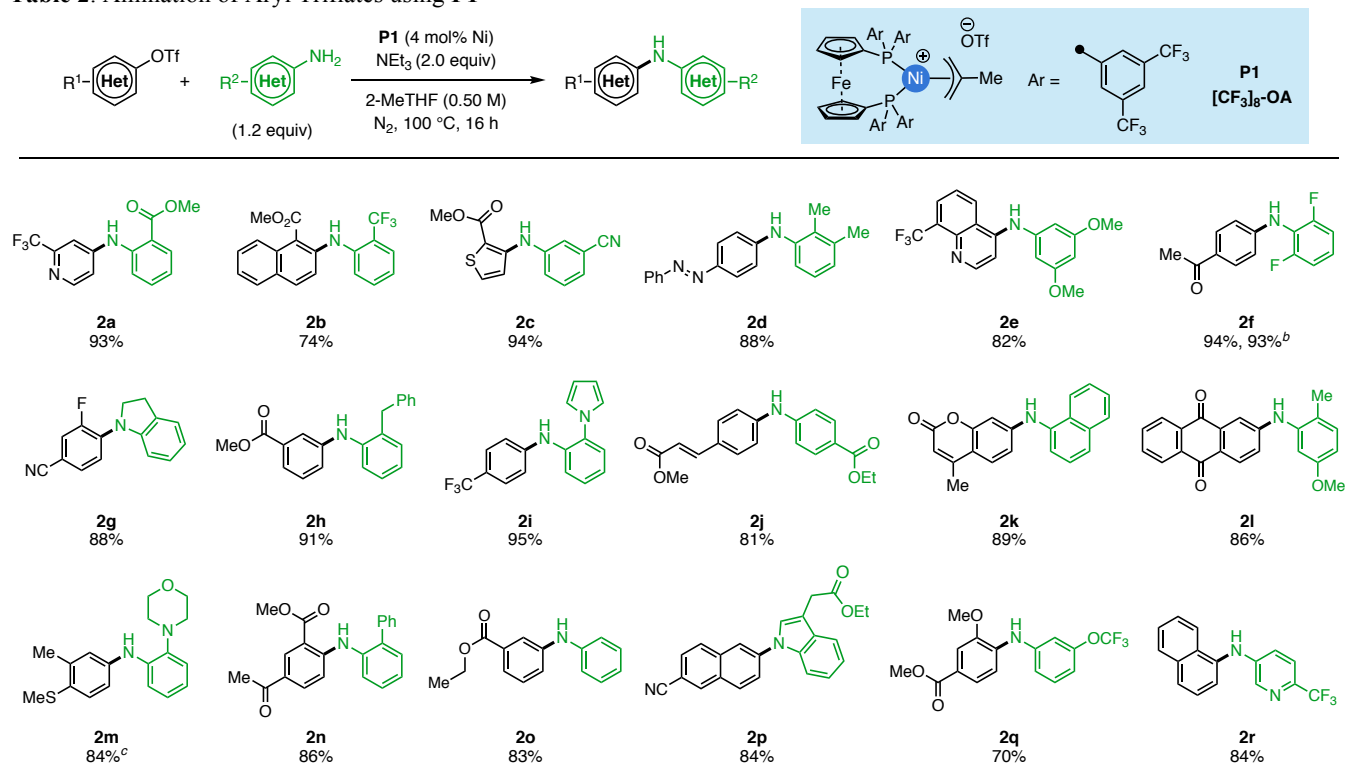


Figure 2. Synthesis and crystal structure of an **L3**-bound methallyl triflate nickel oxidative addition complex. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms are omitted for clarity.

Although Ni(COD)₂ is a convenient source of Ni(0) for reaction discovery and mechanistic studies, the complex is highly sensitive to air and moisture, generally requiring the use of an inert atmosphere glovebox to handle.²³ To alleviate the associated operational complications, we aimed to develop an air-stable Ni precatalyst bearing **L3**, the most effective ligand.²⁴

Table 2. Amination of Aryl Triflates using **P1**^a

^aIsolated yields are reported as the average of two runs. Unless noted, standard reaction conditions: aryl triflate (1.0 mmol), aryl amine (1.2 mmol), triethylamine (2.0 mmol), **P1** (0.04 mmol, 4% Ni), 2-MeTHF (2.0 mL, 0.5 M), 100 °C for 16 h. ^bSingle reaction performed without stirring. ^c1.5 equiv of aryl amine was used.

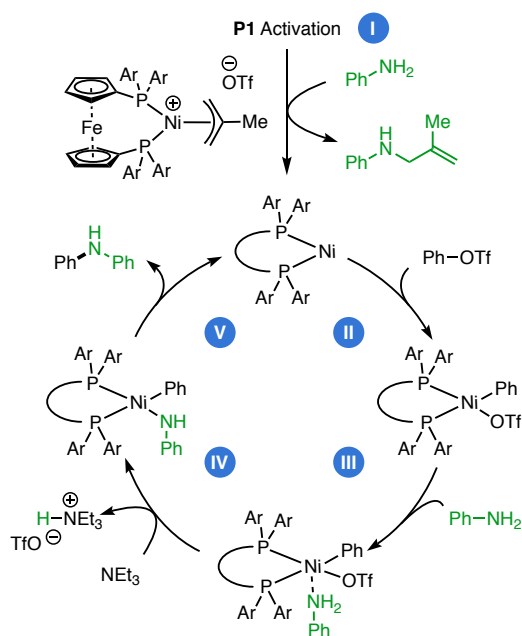


Figure 3. The proposed catalytic cycle for the nickel-catalyzed cross-coupling of aryl triflates with anilines: **I**, activation of **P1**; **II**, oxidative addition of an aryl triflate; **III**, aniline binding to OA complex; **IV**, deprotonation of an amine-bound OA complex; **V**, reductive elimination of an amido complex.

Our initial efforts focused on the use of σ -aryl “oxidative addition” (OA) complexes of aryl bromides and chlorides.²⁵ However, OA complexes bearing **L3** and various aryl groups,²⁶ including *o*-tolyl and mesityl, were unable to facilitate the reaction, even when activated with reducing additives including phenylboronic acid and activated olefins. We hypothesized that the presence of strongly associating halide anions inhibits C–N coupling by outcompeting aniline for binding to Ni (see below for further mechanistic discussion).²⁷ Predicated on this lack of reactivity, we sought to prepare OA complexes bearing non-coordinating triflate anions.²⁸ However, due to the propensity of coordinatively unsaturated Ni(II) complexes to undergo bimetallic decomposition pathways, our attempts to isolate Ni(II) σ -aryl complexes bearing triflate anions were not successful. Based on the work of Nolan²⁹ and Hazari,³⁰ we hypothesized that the introduction of an η^3 -allyl group would saturate the Ni coordination sphere without introducing new strongly-coordinating ligands such as halides. Combining a commercially available methallyl nickel chloride dimer with **L3** in the presence of THF led to the formation of **L3**-Ni(Cl)(η^3 -methallyl).³¹ This complex was not purified, but immediately treated with trimethylsilyl triflate (TMS-OTf), upon which a methallyl nickel triflate complex was rapidly formed.³² The structure of this complex (**P1**) was unambiguously characterized using X-ray diffraction (Figure 2). Under optimized reaction conditions, this precatalyst (**P1**) facilitated the C–N coupling reaction and provided the desired product in

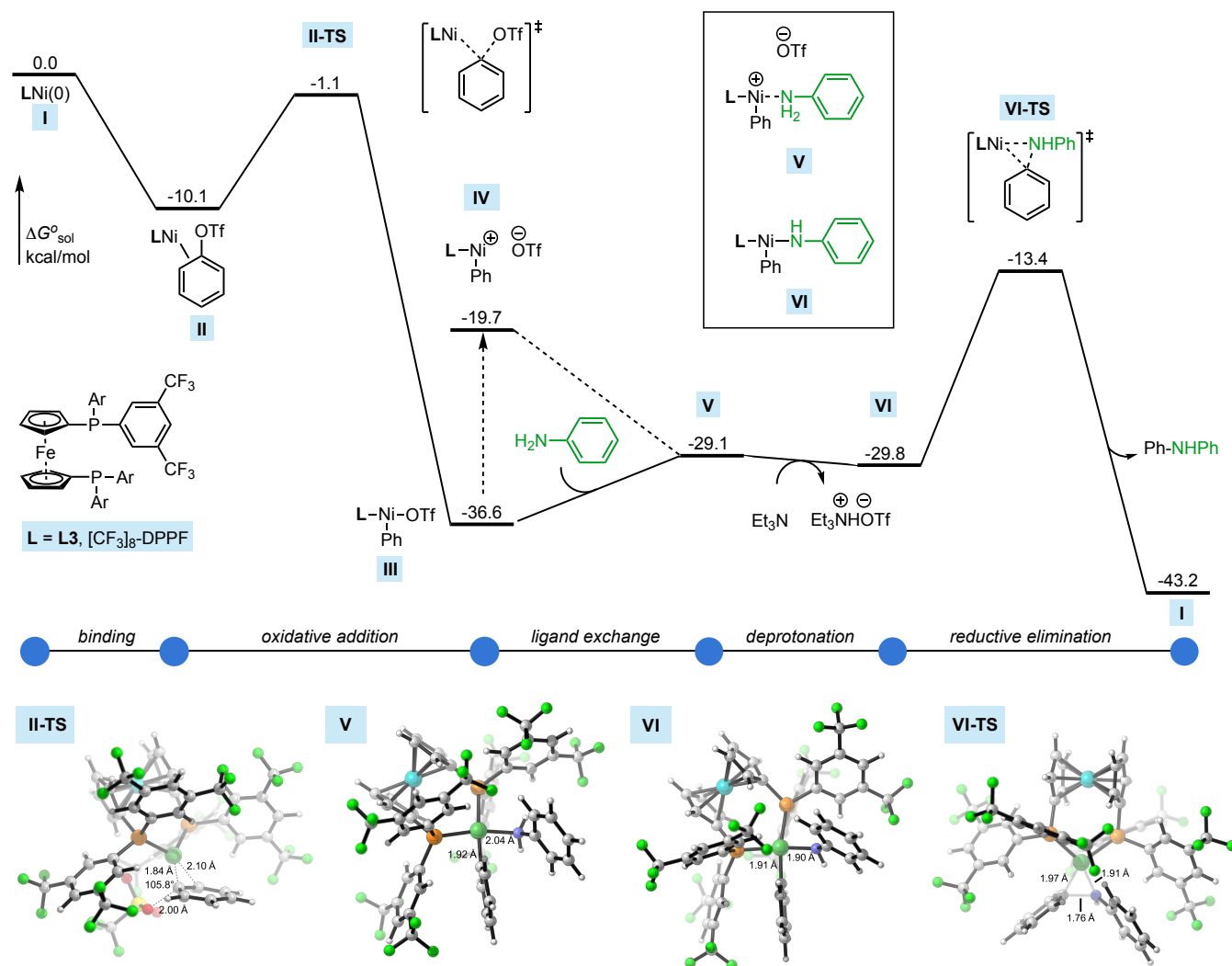


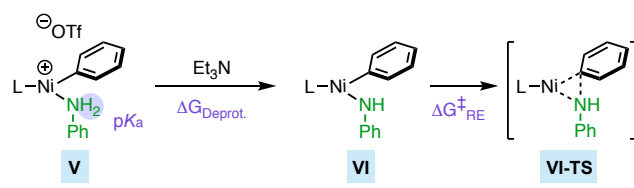
Figure 4. Computed energy profiles for the Ni-catalyzed cross-coupling of **1** and aniline. Gibbs free energy values calculated with M06/6-311+G(d,p)-SDD(Ni,Fe)/B3LYP/6-31G(d)-SDD(Ni,Fe).

98% yield in 2 h. Analysis of the crude reaction mixture (GC/MS) showed that *N*-methallyl aniline was formed during the reaction, consistent with activation of **P1** through outer-sphere nucleophilic attack by aniline at the methallyl ligand.³³

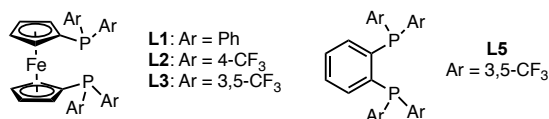
Using this new precatalyst, we explored the scope of the cross-coupling reaction by testing a variety of aryl triflate electrophiles and amine nucleophiles. In contrast to some Pd-catalyzed amination procedures, in particular those facilitated by soluble organic bases, this methodology is tolerant of sterically encumbered coupling partners. Specifically, aryl triflates and anilines bearing bulky *ortho*-substituents, such as trifluoromethyl (**2b**), benzyl (**2h**), morpholino (**2m**) and phenyl (**2n**), underwent coupling in high yields. In contrast to traditional Ni-catalyzed amination protocols that work well for strongly coordinating alkylamine nucleophiles, the current method is especially effective for weakly coordinating anilines, including those bearing cyano (**2c**), trifluoromethoxy (**2q**), and carbonyl substituents (**2a**, **2j**). Additionally, secondary aryl amines, including indoline (**2g**) and a 3-substituted indole (**2p**) could be arylated in high yields.²² We note, however, that aliphatic amines do not react under these conditions, likely due

to their decreased acidity compared to anilines.³⁴ Coupling partners containing heterocycles, including pyridines (**2a**, **2r**), a quinoline (**2e**), a thiophene (**2c**), and a pyrrole (**2i**) were tolerated well. Several electrophilic functional groups, including methyl esters (**2a-c**, **2h**, **2n**) and nitriles (**2c**, **2g**, **2p**), remained intact under the mildly basic reaction conditions. An α,β -unsaturated ester (**2j**), and a coumarin derivative (**2k**) could be cross-coupled under these reaction conditions, despite their potential to react with anilines in metal-catalyzed aza-Michael reactions.³⁵ Moreover, substrates bearing redox-sensitive functional groups, including an anthraquinone (**2l**) are tolerated.³⁶ Finally, because reproducibility issues associated with stirring rate can occur in amination protocols featuring inorganic bases³⁷ or electric potentials,^{18b} we wished to demonstrate that this method is not dependent on mixing efficiency. To show this, we prepared **2f** without using a stir bar or external agitation. The desired product was obtained in 93% yield, which is in line with that obtained when magnetic stirring was used. This result suggests that these single-phase reactions are less prone to reproducibility issues when varied stirring techniques are used.

Table 3. Ligand effects on deprotonation and reductive elimination.^a



Ligand for V	pK _a (THF)	ΔG _{Deprot.} (kcal/mol)	ΔG _{RE} [‡] (kcal/mol)	ΔG _{RE} [‡] + ΔG _{Deprot.}	Yield (%)
L1	15.3	6.4	17.2	23.6	6%
L2	13.4	2.0	16.7	18.7	32%
L3	12.2	-0.6	16.4	15.8	94%
L5	13.0	1.3	17.9	19.2	23%
PhNH ₂	28.5				
Et ₃ N•HOTf	12.5 (experimental, see ref. 41)				



^aGibbs free energy values and acidities calculated with M06/6-311+G(d,p)-SDD(Ni,Fe)//B3LYP/6-31G(d)-SDD(Ni,Fe), except for the pK_a of Et₃NHOTf, used as a reference, which was obtained from the literature.⁴¹

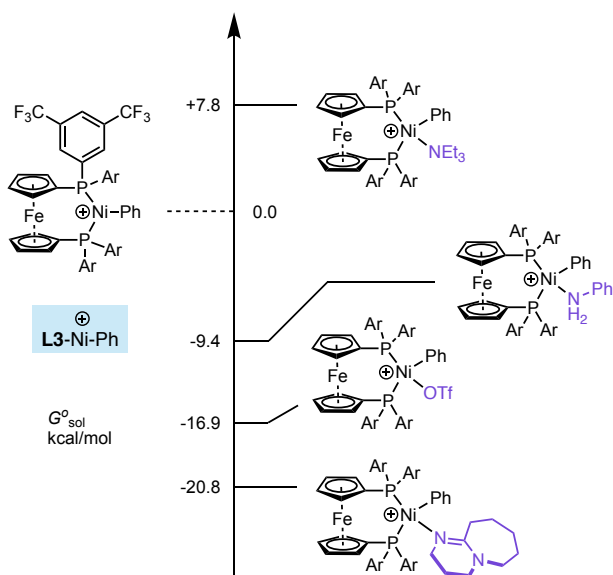


Figure 5. Relative binding energies of triethylamine, triflate anion, and DBU to an **L3**-supported, cationic nickel complex. Gibbs free energy values calculated with M06/6-311+G(d,p)-SDD(Ni,Fe)//B3LYP/6-31G(d)-SDD(Ni,Fe).

The proposed catalytic cycle of this Ni-catalyzed amination reaction is summarized in Figure 3.^{20b,38} First, activation of **P1** via nucleophilic attack of the aniline at the methallyl group provides a **L3**-supported Ni(0) catalyst. Next, Ni undergoes oxidative insertion into the aryl triflate. Then, the

amine binds to the Lewis acidic Ni(II) metal center, acidifying its hydrogens for deprotonation by TEA. Finally, reductive elimination from resultant Ni(II)–amido complex affords the desired product and regenerates the Ni(0) catalyst. Although this proposed mechanism is directly analogous to that of other Ni- and Pd- catalyzed C–N cross-coupling reactions,¹³ it was important to determine how the highly fluorinated ligand **L3** might affect the elementary steps, and importantly, how it is able to facilitate the catalytic transformation using such a weak base (TEA).

Using density functional theory (DFT) calculations we obtained a model of the catalytic mechanism using phenyl triflate (**1**) and aniline as substrates. The energy profile of this mechanism is illustrated in Figure 4. The binding of phenyl triflate to **L3**-Ni(0) (complex **I**) was found to be exergonic by 10.1 kcal/mol (**II**). From this π -complex, oxidative addition through an S_NAr-type mechanism³⁹ was predicted to be extremely rapid, with a barrier of only 9.0 kcal/mol (**II**-TS), and thermodynamically favorable, releasing 26.5 kcal/mol of free energy (**III**). In the ground state of the resultant Ni(II) complex **III**, the triflate anion was bound to Ni, although its dissociation appeared possible under the reaction conditions (+16.9 kcal/mol, **IV**). Regardless, the displacement of the triflate ligand by aniline is only slightly endergonic (+7.5 kcal/mol, **V**). Interestingly, deprotonation of this cationic Ni–aniline complex by TEA was predicted to be slightly favorable in free energy (-0.7 kcal/mol, **VI**). Reductive elimination from this amido complex through a three-membered transition state (+16.4 kcal/mol, **VI**-TS) would then provide the diphenylamine product.

Considering our original hypothesis that the electron-deficiency of the ligand had a favorable influence on the thermodynamics of the deprotonation step, we more closely examined the effect of varying the phosphine ligand on this process. Table 3 shows the pK_a of several amine-bound Ni(II) complexes analogous to **V** as well as triethylammonium triflate and aniline for comparison purposes. The free energy change associated with the proton transfer step can be calculated on the basis of pK_a differences. The deprotonation of weakly acidic aniline (pK_a = 28) by triethylamine (pK_{aH+} = 12.5)⁴¹ is thermodynamically highly disfavored. However, association of the aniline to cationic Ni(II) results in dramatic acidification, to the extent of roughly 13 pK_a units in THF when the ligand is DPPF (**L1**). With the addition of electron-withdrawing groups on the ligand, the amine is further acidified. Indeed, in the complex with **L3**, the aniline is sufficiently activated that it is predicted to be more acidic (pK_a = 12.2) than triethylammonium triflate. Thus, deprotonation by triethylamine is in this case slightly thermodynamically favorable.

We also found that the barrier to reductive elimination is also somewhat affected by the electronic properties of the phosphine ligand: as the number of trifluoromethyl substituents on the catalyst increase, the reductive elimination is increasingly facile. For comparison, we also evaluated an analogue derived of **L3** from DPPBz (**L4**). With the **L4**-ligated catalyst, the free energy of deprotonation and barrier to reductive elimination were both higher (+1.9 kcal/mol and +1.5 kcal/mol, respectively) than from the **L3**-bound complexes. Thus, not only the identity of the *P*-aryl groups, but the backbone structure of the chelating ligand significantly influences these steps. The combined barrier from deprotonation–reductive elimination sequence is also shown in

Table 3. The net activation energies are qualitatively consistent with the experimentally determined yields using these catalysts.

Finally, our model also explained the superior performance of triethylamine compared to other organic bases, even those that were significantly stronger bases. Previously, in experimental^{13a} and theoretical^{13b} mechanistic studies of Pd-catalyzed amination using DBU, we found that off-cycle binding of the base to Pd could have an inhibitory effect. We investigated the relative binding ability of TEA, DBU, and aniline to the cationic intermediate **IV** (Figure 5). As a reference, we had found earlier that the binding of triflate to **IV** is exergonic by 16.9 kcal/mol. Due presumably to steric interactions, the binding of TEA to **IV** is significantly disfavored ($\Delta G^\circ = +7.8$ kcal/mol), in a manner similar to well-known “frustrated” Lewis acid-base pairs.⁴⁰ Accordingly, aniline can outcompete the base for binding ($\Delta G^\circ = -9.4$ kcal/mol for aniline binding to **IV**), and the productive reaction can take place. In contrast, when DBU is present, we found that it tightly coordinates to **IV** ($\Delta G^\circ = -20.8$ kcal/mol), sequestering Ni in this off-cycle resting state and thus increasing the overall activation energy for cross-coupling. We believe that this effect explains the unique effectiveness of TEA compared to stronger, more nucleophilic organic bases.

CONCLUSION

In summary, we have developed a novel Ni(II) precatalyst bearing an electron-deficient DPPF-derived ligand (**L3**) that is able to facilitate the cross-coupling of aryl triflates with primary anilines, as well as indolines and indoles. The precatalyst is a rare example of a bench-stable cationic Ni(II) triflate complex and represents a new class of halide-free Ni precatalysts that might have general applicability to reactions currently requiring Ni(COD)₂. Using DFT calculations, relationships between ligand structure and the energetics of the key deprotonation and reductive elimination steps were elucidated. Moreover, we determined that the unique effectiveness of alkylamine bases can be attributed to their steric bulk, which prevents unwanted binding to cationic Ni intermediates. We anticipate that these mechanistic insights can assist in the development of new Ni-catalyzed cross-coupling methodologies that employ soluble organic bases.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; computational, spectral, and reaction optimization data; X-ray data.

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