

Decarbonylative Phosphorylation of Amides by Palladium and Nickel Catalysis: The Hirao Cross-Coupling of Amide Derivatives

Chengwei Liu and Michal Szostak*

Abstract: Considering the ubiquity of organophosphorus compounds in organic synthesis, pharmaceutical discovery, agrochemical crop protection and materials chemistry, new methods for their construction hold particular significance. A conventional method for the synthesis of C–P bonds involves cross-coupling of aryl halides and dialkyl phosphites (the Hirao reaction). We report a catalytic deamidative phosphorylation of a wide range of amides using a palladium or nickel catalyst giving aryl phosphonates in good to excellent yields. The present method tolerates a wide range of functional groups. The reaction constitutes the first example of a transition-metal-catalyzed generation of C–P bonds from amides. This redox-neutral protocol can be combined with site-selective conventional cross-coupling for the regioselective synthesis of potential pharmacophores. Mechanistic studies suggest an oxidative addition/transmetalation pathway. In light of the importance of amides and phosphonates as synthetic intermediates, we envision that this Pd and Ni-catalyzed C–P bond forming method will find broad application.

Organophosphorus compounds are essential structures in chemical synthesis, and have seen key applications as drug pharmacophores, agrochemicals and flame retardants (Figure 1A).^[1,2] The capacity of phosphorus to coordinate to transition metals and biological receptors has enabled design of novel reaction mechanisms and control of numerous biological functions.^[3,4] Considering the importance of organophosphorus compounds in modern chemistry, the development of new methods for their synthesis holds particular significance.

Since its discovery in 1981, the Hirao cross-coupling has become a central C–P bond forming reaction in organic synthesis (Figure 1B).^[5,6] In this context, aryl halides,^[7] sulfonates,^[8] diazonium salts,^[9] boronic acids,^[10] silanes,^[11] organobismuth compounds,^[12] pivalates,^[13] and sulfides^[14] via C–X, C–O, C–N, C–B, C–Bi, C–Si and C–S bond cleavage have found wide application in organic synthesis using Pd,^[7–12] Ni^[13–15] and Cu^[16] catalysis.^[7–9] These methods have significantly expanded a range of organic coupling partners to participate in the construction of C–P bonds. Additionally, chemical methods for the synthesis of C–P bonds using conventional Grignard or organolithium reagents and the Michaelis–Arbuzov reaction have been established; however, these protocols suffer from toxicity, substrate and efficiency limitations.^[17,18] New complementary methods for the construction of C–P bonds by C–H activation^[19] and photoredox pathways^[20] continue to evolve.

Amide bond cross-coupling has recently emerged as a powerful tool for the construction of organic molecules.^[21–24] As

amply demonstrated^[25–33] a unique amide bond activation mode utilizing amide bond n_N to $\pi_{C=O}$ resonance destabilization^[34] can be successfully deployed to accomplish direct metal insertion into the typically inert N–C(O) moiety.^[21] To date, the ability to utilize amides as precursors to form C–O, C–N, C–C, C–B, and C–H bonds with high predictability and chemoselectivity via acyl and decarbonylative pathways has been demonstrated.^[35] Such bond forming reactions of readily accessible, bench-stable amides^[22] significantly expand the portfolio of electrophiles available for cross-coupling under synthetically attractive redox-neutral conditions, wherein the reactivity is controlled by geometry and N-substitution of the amide bond.^[26,29] Moreover, the versatile amide electrophiles (i) are traditionally derived from different precursors than halides, phenols and anilines, (ii) are easy to prepare, and (iii) are inert to a variety of conditions allowing for ring prefunctionalization. Despite the significant progress, the intrinsic limitation is the reactivity of the N–C(O) amide bond for oxidative insertion and control of the relative reactivity of the acyl-metal intermediate towards decarbonylation.^[36] In light of the importance of amides as key building blocks in peptides and versatile bench-stable intermediates in organic synthesis,^[22] it is surprising that amides are yet to be employed as coupling partners in the synthesis of C–P bonds.

Herein, we report a catalytic deamidative phosphorylation of a wide range of amides using a palladium or nickel catalyst giving aryl phosphonates in good to excellent yields (Figure 1C). The reaction constitutes the first example of a transition-metal-catalyzed generation of C–P bonds from amides. The method tolerates a wide range of functional groups. Given the importance of amides and phosphonates as synthetic intermediates, we envision that this Pd and Ni-catalyzed C–P bond forming method will find broad utility in the construction of organic molecules. *Globally, the method represents a two-step approach to aryl phosphorus compounds from naturally abundant carboxylic acids^[35a] – a high value transformation that at present cannot be readily accomplished by other methods.*

Redox-neutral phosphorylation of ubiquitous carboxylic acid derivatives remains an important goal.^[35] In an effort to demonstrate the utility of the amide bond activation platform, we elected to explore a practical palladium-catalyzed^[23] decarbonylative coupling between N–C(O) electrophiles and dialkyl phosphites. We reasoned that the nucleophilic character of the phosphorus anion might render these couplings susceptible to decarbonylation with the appropriate ligand framework.^[6b] The phosphorylation of amide **1** with diethylphosphite was evaluated using palladium catalysts under various conditions (see SI). After very extensive investigation, we were delighted to find that the proposed deamidative coupling of **1** in the presence of H–P(O)(OEt)₂, Pd(OAc)₂ (5 mol%), Xantphos or DPPB (10 mol%) and Et₃N (1.5 equiv) in dioxane at 160 °C, provided the desired aryl phosphonate product in quantitative yield.

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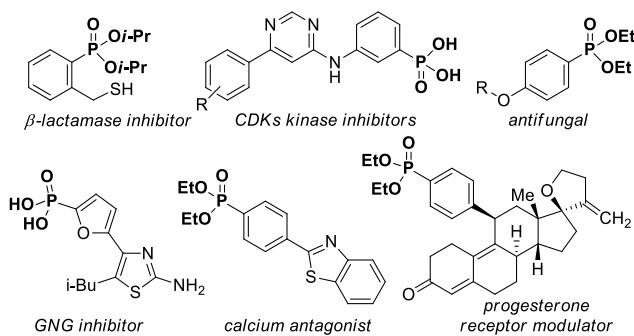
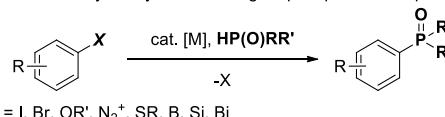
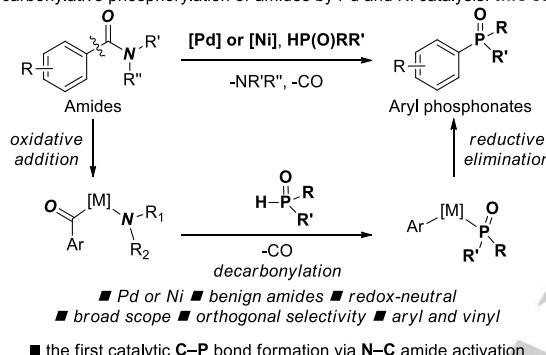
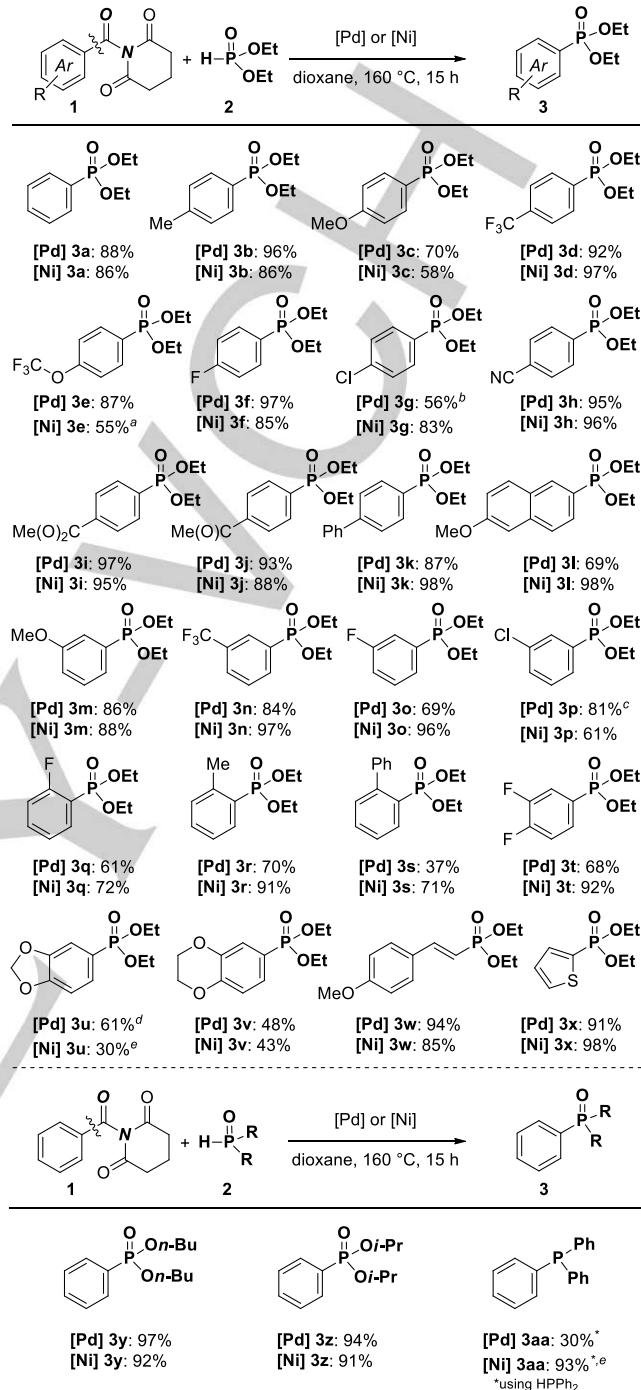
A. Examples of pharmaceutically-relevant organophosphorus compounds**B. Traditional metal-catalyzed synthesis of organophosphorus compounds****C. Decarbonylative phosphorylation of amides by Pd and Ni catalysis: *this study***

Figure 1. (A) Pharmaceutically important organophosphorus compounds. (B) Conventional synthesis of organophosphorus compounds (Hirao coupling). (C) Palladium- and nickel-catalyzed decarbonylative phosphorylation of amides (this study).

In consideration of the economic advantages offered by nickel catalysis,^[37] we questioned whether nickel might be employed catalytically to promote the C-P bond formation by the uncommon cleavage of the N-C amide bond. Thus far, limited success using both Pd and Ni to promote a single reaction of amides through N-C activation has been achieved. To our delight, after very extensive investigation we discovered that an inexpensive, bench-stable Ni(dppp)Cl₂ in the presence of Na₂CO₃ as a base promotes the desired coupling (see SI).

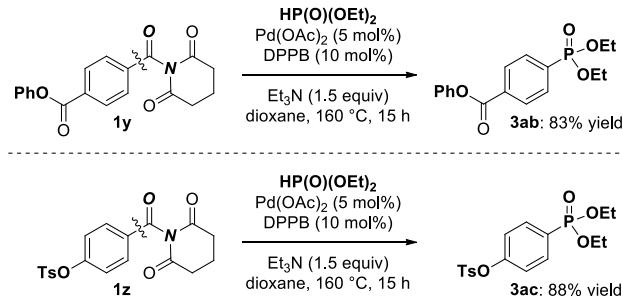
With the optimized conditions in hand, the scope of this new method for C-P bond construction was investigated. As shown in Scheme 1, the scope of the reaction is very broad and accommodates a wide range of functional groups. As shown, the reaction conditions are compatible with a wide range of electronically-and sterically-diverse substrates, bearing various functional groups and synthetic handles, including aryl halides, ethers, nitriles, esters, ketones, naphthalenes, biaryls, dioxolanes, dioxanes, vinyl amides, and thiophenes. Generally speaking, Ni-catalysis results in comparable yields in the vast majority of examples examined. However, the transformation is more efficient for conjugated and sterically-hindered substrates, consistent with higher nucleophilicity of Ni.^[37] Moreover, while with respect to the phosphite, dibutylphosphite and diisopropylphosphite also readily participate in this coupling,



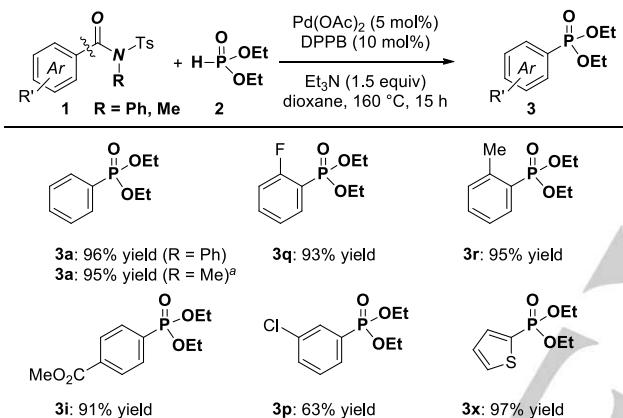
Scheme 1. Pd- and Ni-catalyzed decarbonylative phosphorylation of amides. Conditions: [Pd]: amide (1.0 equiv), HP(O)(OR)₂ (0.5 equiv), Pd(OAc)₂ (5 mol%), DPPB (10 mol%), Et₃N (1.5 equiv), dioxane (0.125 M), 160 °C, 15 h. Isolated yields. Conditions: [Ni]: amide (1.0 equiv), HP(O)(OR)₂ (1.5 equiv), Ni(dppp)Cl₂ (10 mol%), Na₂CO₃ (1.5 equiv), dioxane (0.25 M), 160 °C, 15 h. Isolated yields. ^aNi(dppp)Cl₂ (20 mol%). ^bN,N-Ph,Ms-amide. ^cDIPEA as base. ^dPd(OAc)₂ (10 mol%), DPPB (20 mol%). ^e48 h. See SI for full details.

diphenylphosphine can be employed to afford the corresponding phosphine. Overall, the developed process employs air-stable, inexpensive Ni catalyst, which is economically advantageous over Pd, with the complementary scope to the Pd-catalyzed C-P bond formation. A careful control of the reaction stoichiometry is

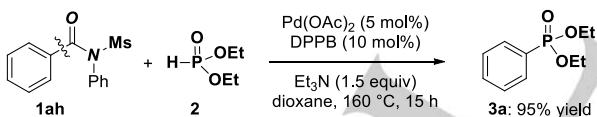
essential to harness reactivity of the acylmetal intermediate, in particular in the case of acylpalladium, which decarbonylates more slowly than acylnickel.^[28,29] The observed selectivity of the amide coupling in the presence of Ar-Cl or Ar-CN bonds is consistent with the facility of metal insertion into the resonance destabilized amides.^[26-33]



Scheme 2. Chemoselective deamidative phosphorylation in the presence of O-electrophiles.



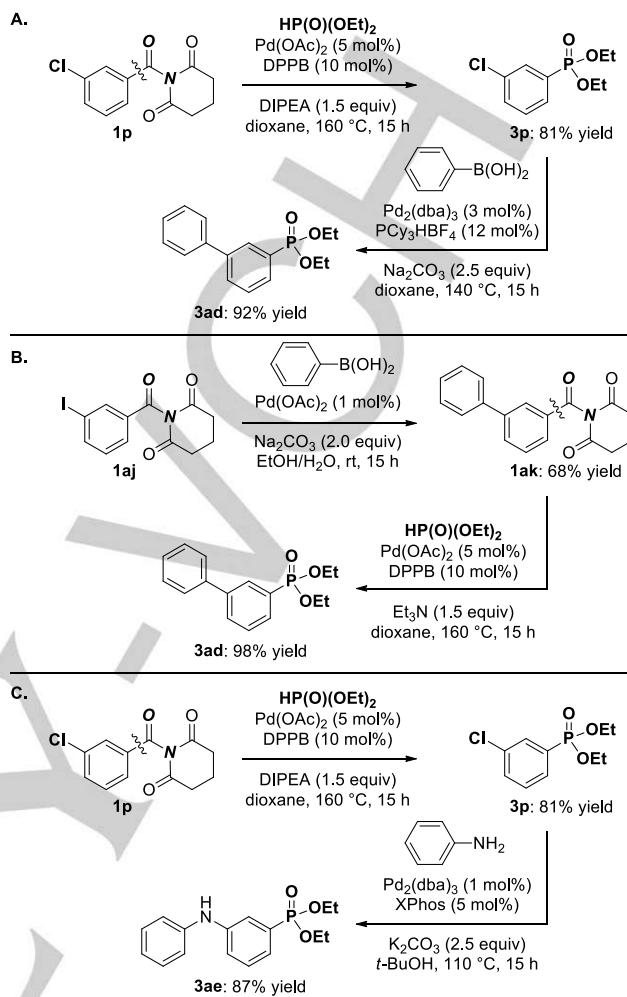
Scheme 3. Pd-catalyzed decarbonylative phosphorylation of *N*-Ts amides. Conditions: amide (1.0 equiv), $\text{HP}(\text{O})(\text{OEt})_2$ (0.5 equiv), $\text{Pd}(\text{OAc})_2$ (5 mol%), DPPB (10 mol%), dioxane (0.125 M), 160 °C, 15 h. Isolated yields. Entries 2-5, R = Ph. ^a $\text{Pd}(\text{OAc})_2$ (10 mol%), DPPB (20 mol%). See SI for full details.



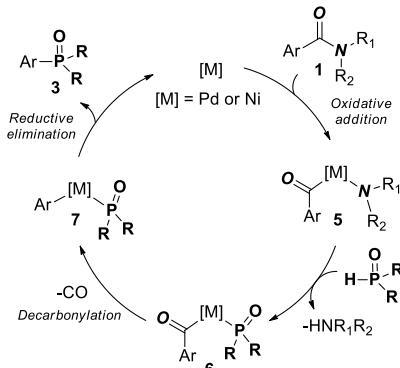
Scheme 4. Decarbonylative phosphorylation of *N*-Ms amide.

Notably, this transformation is tolerant to functional groups that are prone to metal-catalyzed C–O cleavage, such as aryl ester and aryl sulfonate (Scheme 2), highlighting the potential to achieve high selectivity using amide electrophiles under orthogonal cross-coupling conditions.

We were pleased to find that acyclic N-Ts amides serve as suitable cross-coupling partners in this new C–P bond forming protocol (Scheme 3). Notably, these amide precursors can be prepared directly from secondary amides,^[26] thus demonstrating the ability of the current protocol to generate C–P bonds from common acyclic amides. The coupling of atom-economic N-Ms amide **1ah** proceeded with excellent efficiency (Scheme 4). This result demonstrates the potential to engage different amide precursors in decarbonylative N–C coupling.



Scheme 5. Selective cross-coupling/deamidative phosphorylation.



Scheme 6. Proposed mechanism.

The utility of this new phosphorylation reaction to site-selectively construct C–P and C–C or C–N bonds was showcased in sequential orthogonal cross-couplings (Scheme 5).

Studies were performed to gain insight into the reaction mechanism and investigate factors controlling the Pd- and Ni-catalyzed deamidative phosphorylation protocol (see SI).^[38] The key step involves metal insertion into the amide N–C bond/transmetalation (Scheme 6).

In summary, we have developed the first deamidative phosphorylation of amides by palladium and nickel catalysis. The reaction constitutes the first example of a transition-metal-catalyzed generation of C–P bonds from amides. This new process provides an alternative to the classic Hirao reaction and uses carboxylic acid derived electrophiles. This versatile method tolerates a wide range of functional groups and accommodates cyclic and acyclic N-activating groups. Mechanistic studies have provided support for the oxidative addition/transmetalation pathway, in which transmetalation proceeds prior to decarbonylation under both Pd and Ni catalytic conditions. Considering the ubiquity of organophosphorus compounds in modern organic synthesis, we expect that this Pd and Ni-catalyzed C–P bond forming method will be of general interest.

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Keywords: amides • phosphonates • cross-coupling • N–C activation • carboxylic acids

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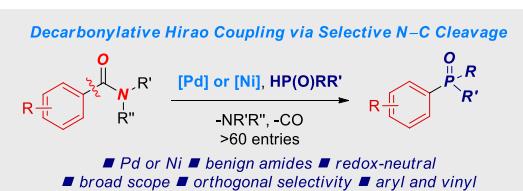
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Decarbonylative Phosphorylation of Amides by Palladium and Nickel Catalysis: The Hirao Cross-Coupling of Amide Derivatives

We report a general method for catalytic deamidative phosphorylation of a wide range of amides using a palladium or nickel catalyst giving aryl phosphonates in good to excellent yields. The reaction constitutes the first example of a transition-metal-catalyzed generation of C–P bonds from amides. In light of the importance of amides and phosphonates as synthetic intermediates, we envision that this Pd and Ni-catalyzed C–P bond forming method will find broad application.