Decarbonylative Sonogashira Cross-Coupling: Fruitful Marriage of Alkynes with Carboxylic Acid Electrophiles

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HIGHLIGHT

Decarbonylative Sonogashira Cross-Coupling: Fruitful Marriage of Alkynes with Carboxylic Acid Electrophiles

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The Sonogashira cross-coupling is one of the most fundamental C–C bond forming reactions, wherein the strategic value of the alkyne moiety has found widespread application at the frontiers of organic chemistry, materials science and drug discovery as the cornerstone building block of chemical synthesis. Although traditional variants of Sonogashira cross-coupling involve aryl halides and pseudohalides as electrophiles, recently, tremendous advances have been made in the unconventional disconnection exploiting common carboxylic acids by decarbonylation/transmetalation pathway. This manifold (1) permits to take advantage of carboxylic acids as a ubiquitous class of substrates in organic synthesis that are derived from an orthogonal pool of precursors to aryl halides and pseudohalides, (2) combines the benefits of the palladium catalyzed C(sp^2)–C(sp) coupling of terminal alkynes with the inherent presence of the carboxylic acid moiety in pharmaceuticals, natural products and organic materials. In this highlight article, we summarize recent progress generated by the decarbonylative Sonogashira cross-coupling of carboxylic acid electrophiles to produce arylalkynes and conjugated enynes as a novel avenue for chemical synthesis, whereby a large number of chemical reactions critically rely on transformations of alkynes.

The cross-coupling reactions represent the most powerful and most widely utilized class of organic reactions for the synthesis of C–C bonds.[1,2] In this respect, the Nobel Prize winning Suzuki cross-coupling and Heck olefination are predicated on the capacity of preformed organometallic reagents and alkenes as nucleophilic coupling partners (pK_a of aliphatic or C(sp^2)–H bonds of 43-50). In this avenue, the facility of terminal alkynes to form copper(I) and palladium(II) acetylides by direct deprotonation (pK_a of terminal alkynes of 25, Figure 1) has enabled broadly useful C(sp^2)–C(sp) carbon–carbon bond formation[3] in a mild, highly predictable and broadly useful manner since its first discovery in 1975 by the groups of Sonogashira, Heck and Cassar.[4]

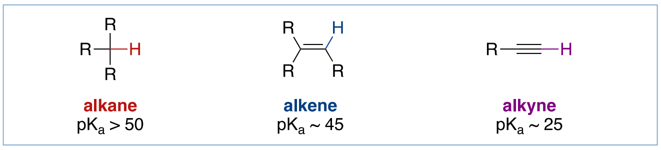

Figure 1 Acid dissociation constants of C–H bonds.

One of the major benefits of the Sonogashira cross-coupling is that alkynes are widely used as fundamental substrates to forge various organic molecules in a plethora of academic and industrial applications in the synthesis of pharmaceuticals, natural products, and functional materials.[1–3,5] In addition, the Sonogashira cross-coupling generates the substituted arylalkyne and conjugated enyne motifs that on their own represent synthetically important products.[3]

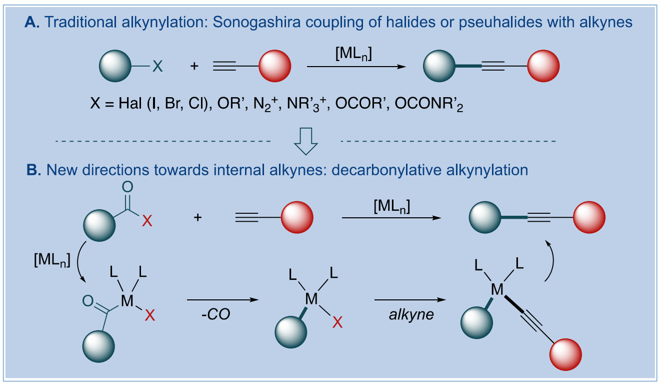

Figure 2 General methods for the synthesis of arylalkynes.

At present, the most common strategy for the synthesis of arylalkynes relies on transition-metal-catalyzed Sonogashira cross-coupling of aryl halides and pseudohalides as electrophiles.[3] Established electrophiles include aryl iodides, bromides and chlorides as well as pseudohalides, such as triflates, tosylates, mesylates, diazonium salts, sulfonium salts, ammonium salts, iodonium salts, phosphonium salts, and carbamates and nitriles engaging C–X, C–O, C–N, C–S and C–P cleavage by direct metal insertion into the electrophilic bond (Figure 2A).[6] The catalytic systems typically involve Pd(0)/Cu(I)

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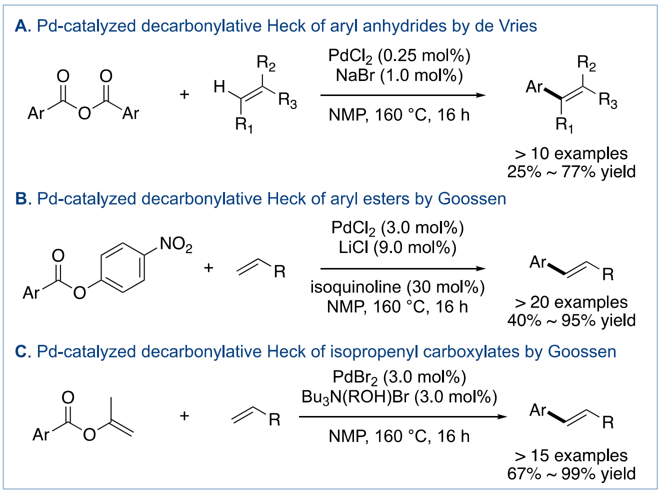

Figure 3 First examples of Pd-catalyzed decarbonylative cross-coupling of carboxylic acid derivatives with π-systems.

catalysis and Pd(0) copper-free catalysis.[1–6] The participation of copper can effectively accelerate the Sonogashira cross-coupling by forming Cu(I)-acetylides; however, at the same time, the addition of copper has its own shortcomings in that the in situ formed copper acetylides usually tend to lead to the formation of homo-coupling products of terminal alkynes. This side-reaction not only wastes raw starting materials, but also creates separation problems in isolating arylalkyne products.

An alternative catalytic system for Sonogashira cross-coupling that has received increased attention is copper-free variant.[1–6] Recent studies suggest that this catalysis involves a tandem Pd/Pd cycle with rate limiting transmetalation.[7] However, these copper-free Sonogashira reactions typically require excess of bases and tend to be more limited in scope than Cu-co-catalyzed variants, which leads to environment impact and reduces the applicability of these methods.

In consideration of the tremendous utility of alkynes as fundamental building blocks in organic synthesis, recent efforts have been focused on the development of new variants of Sonogashira cross-coupling.[8] In particular, major advances have been made in the unconventional disconnection exploiting common carboxylic acids as electrophiles in Sonogashira cross-coupling by decarbonylation/ transmetalation pathway in the absence of external oxidants (Figure 2B). This manifold (1) permits to take advantage of carboxylic acids as a ubiquitous class of substrates in organic synthesis that are derived from an orthogonal pool of precursors to aryl halides and pseudohalides,[9,10] (2) combines the benefits of the palladium catalyzed C(sp^2)–C(sp) coupling of terminal alkynes[1–6] with the inherent presence of the carboxylic acid moiety in pharmaceuticals, natural products and organic materials. Furthermore, carboxylic acids as a class of substrates are stable, non-toxic, easy-to-handle solids, and, as needed, easy to be synthesized by various methods. Thereby, merging with their ubiquitous presence in late-stage intermediates and orthogonal reactivity, carboxylic acids are often regarded as ideal substrates for organic synthesis and catalysis.[9,10]

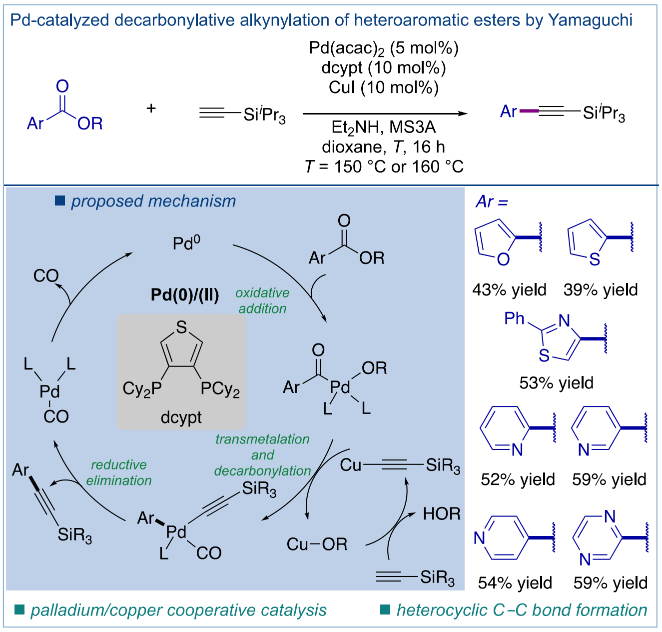

Figure 4 Pd/Cu-co-catalyzed decarbonylative Sonogashira cross-coupling of esters.

In this article, we summarize recent progress in the decarbonylative Sonogashira cross-coupling of carboxylic acid electrophiles to produce arylalkynes and conjugated enynes as a novel avenue for chemical synthesis. These reactions exploit readily-accessible carboxylic acid derivatives, such as anhydrides (R–C(O)–O)$_2$), esters (R–C(O)–OR’) and amides (R–C(O)–NR’R’’), including in situ protocols directly deploying carboxylic acids (R–C(O)–OH), enabling mild, reagent and substrate controlled oxidative addition of the C$_{(acyl)}$–X bond (X = OCOR, OR’, NR’R’’) to a transition metal, followed by decarbonylation under redox neutral conditions.

The pioneering study on decarbonylative cross-coupling of carboxylic acid derivatives with π-systems was reported in 1998 by de Vries and co-workers,[11] in a study that could be regarded as a precedent to decarbonylative manifold of carboxylic acid derivatives (Figure 3A).[12] This Pd-catalyzed methodology achieved coupling of aromatic carboxylic acid anhydrides with alkenes at 0.25% Pd loading to deliver the corresponding arylalkenes. In 2002, Goossen and co-workers followed up on the study by de Vries and developed a highly selective Pd-catalyzed decarbonylative olefination of aryl esters using 4-nitro-activating group on the ester component to facilitate oxidative addition (Figure 3B).[13a] The same group also reported Pd-catalyzed decarbonylative olefination of enol esters (Figure 3C).[13b] While these early studies set the stage for efficient decarbonylative C–C bond forming methodologies from esters[14] and amides,[15] including reactions with π-systems,[16] on the contrary, the Sonogashira coupling for the synthesis of C(sp^2)–C(sp) bonds from carboxylic acid derivatives represented an attractive goal. Compared with the traditional cross-coupling of aryl halides, the advantage of decarbonylative cross-coupling manifold is that it adopts well-established two electron mechanism,[17,18] while using ubiquitous carboxylic acids as coupling partners.

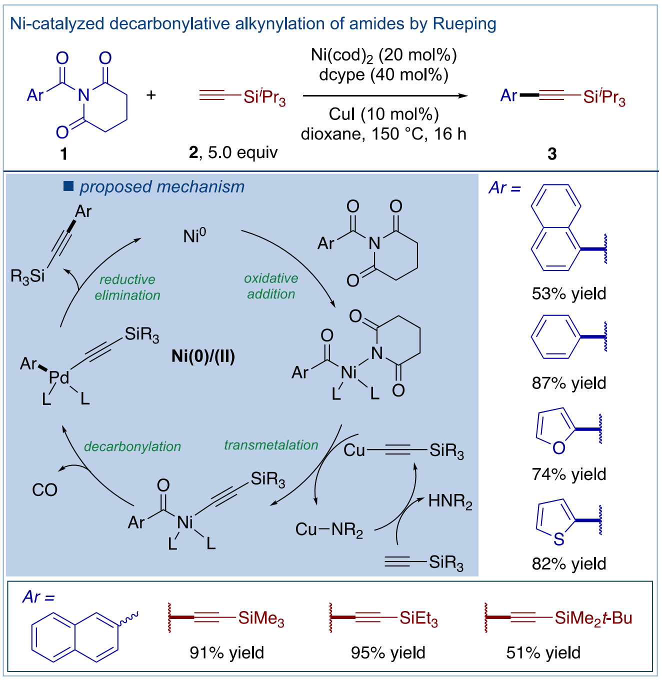

Figure 5 Ni/Cu-catalyzed decarbonylative Sonogashira cross-coupling of amides.

In 2017, Yamaguchi and co-workers reported the first study on decarbonylative Sonogashira coupling of carboxylic acid derivatives using aromatic esters as electrophiles (Figure 4).[19] They established a catalyst system of $Pd(acac)_2$ (5 mol%) and dcypt (10 mol%) as bidentate thiophene-based phosphine ligand in the presence of CuI (10 mol%) as effective catalyst. The proposed mechanism involves oxidative addition of $C_{(acyl)}$–O bond to Pd(0), transmetalation with copper(I) acetylide, decarbonylation, and reductive elimination. Intriguingly, the thiophene-based phosphine proved to be significantly more effective than related dcype, indicating that a bite angle might play an important role in promoting decarbonylation in this process.[18a] Since carboxylic acids are widely present in pharmaceuticals and natural products, and orthogonal cross-couplings with conventional electrophiles are feasible, this first decarbonylative Sonogashira coupling set the stage for new vistas in alkyne synthesis.

Subsequently, Rueping and co-workers developed decarbonylative Sonogashira cross-coupling of amides using twisted N-acyl-glutarimides introduced by our group as highly effective substrates for this transformation (Figure 5).[20] The reactions were optimally accomplished using a Ni/Cu-co-catalyst system in the presence of $Ni(cod)_2$ (20 mol%), dcype (40 mol%) and CuI (10 mol%). Importantly, the transmetalation step was proposed to occur prior to the decarbonylation step, which is a more established pathway for decarbonylative cross-couplings. Intriguingly, this system also permitted for the synthesis of conjugated enynes, thus demonstrating for the first time that decarbonylative Sonogashira cross-couplings could be used for the synthesis of more sensitive π-conjugated systems. The method represents a rare example of Ni-catalyzed Sonogashira cross-coupling pioneered by Hu and co-workers.[21] The high stability and perpendicular N–C(O) twist of N-acyl-glutarimides[22] clearly expedites this challenging coupling.

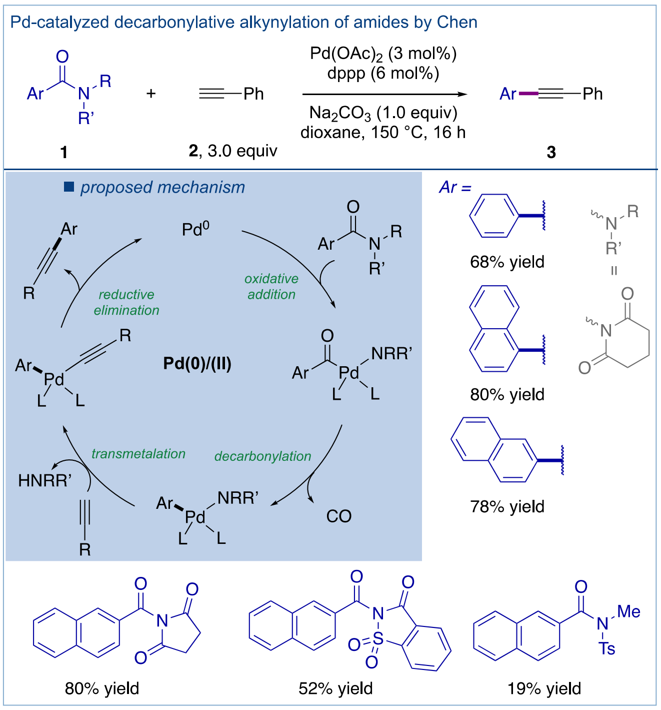

Figure 6 Pd-catalyzed decarbonylative Sonogashira cross-coupling of amides.

In an independent report, Chen and co-workers disclosed a palladium-catalyzed copper-free decarbonylative Sonogashira cross-coupling of amides (Figure 6).[23] As an alternative to the Ni/Cu-catalyzed variant, this method also uses N-acyl-glutarimides as the privileged class of amide N–C(O) electrophiles for the pivotal cross-coupling. The reaction conditions are operationally-simple and involve $Pd(OAc)_2$ (3 mol%) and dppp (6 mol%) in the presence of Na_2CO_3 (1.0 equiv). It is noteworthy that several other acyclic twisted amides are compatible in this method, including N-acyl-glutarimides, N-acyl-succinimides and N-acyl-saccharins. Mechanistically, the decarbonylation step was proposed prior to the transmetalation step, and the complete reaction mechanism involves oxidative addition of the C–N bond, decarbonylation, transmetalation and reductive elimination.

Most recently, two independent reports on direct decarbonylative Sonogashira coupling of carboxylic acids by in situ conversion to the corresponding mixed anhydrides (cf. de Vries, Figure 3) were accomplished by Chen group (Figure 7)[24] and our group (Figure 8).[25] These two catalytic systems are complementary involving $Pd_2(dba)_3$ (2.5 mol%) and Xantphos (10 mol%) in the presence of Ac_2O activator (Figure 7) and $Pd(OAc)_2$ (5 mol%) and Xantphos (10 mol%) in the presence of piv_2O activator (Figure 8). The most important feature of these complementary methods is that they directly use carboxylic acids as aryl electrophiles, thus prior conversion to the activated carboxylic acid derivatives is not required. This in turn enables to perform direct synthesis of complex alkynes from pharmaceuticals and natural products. At the same time, the establishment of copper-free system is intriguing and

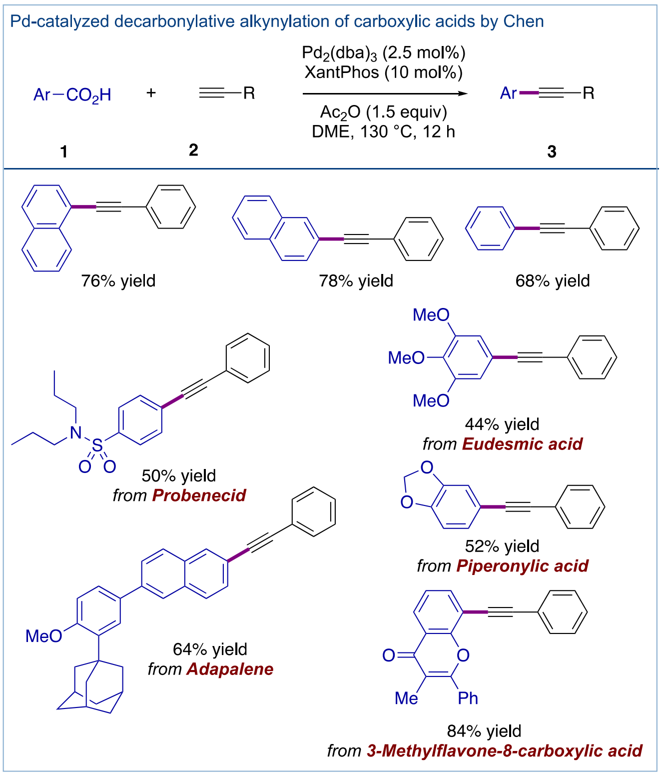

Figure 7 Decarbonylative Sonogashira cross-coupling of carboxylic acids by Chen.

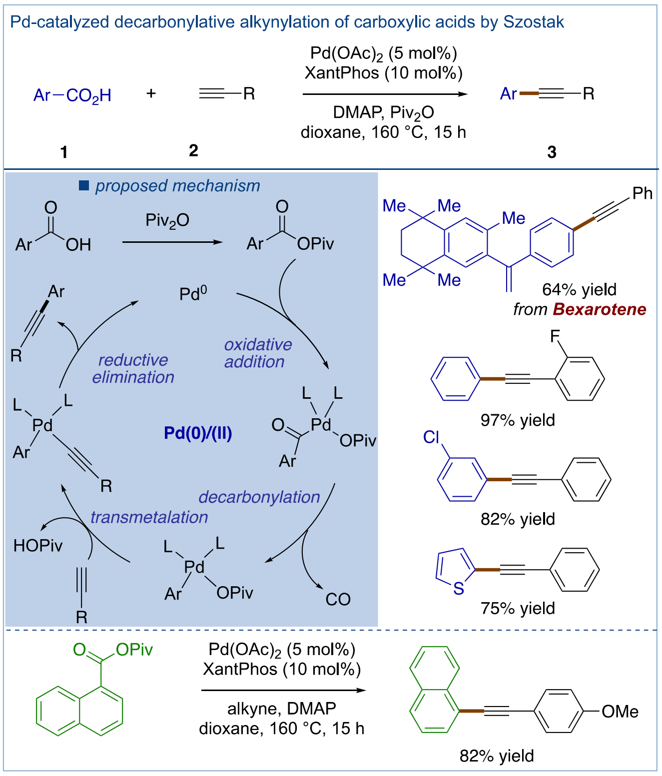

Figure 8 Pd-catalyzed decarbonylative Sonogashira of carboxylic acids by Szostak.

bodes well for future application of these methods for the functionalization of complex APIs.

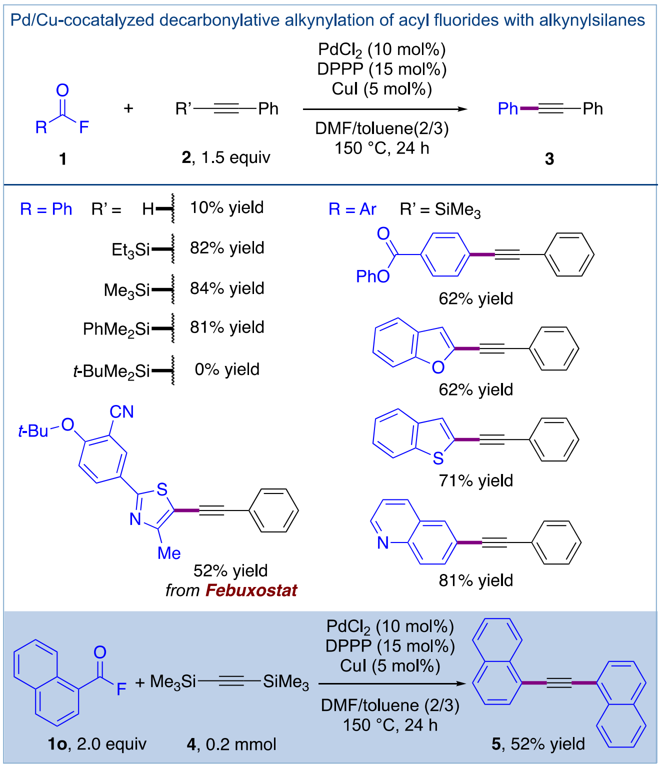

Figure 9 Pd/Cu-cocatalyzed decarbonylative alkynylation of acyl fluorides with alkynylsilanes by Nishihara.

In the realm of decarbonylative Sonogashira cross-coupling reactions, the first catalytic system for engaging acid halides was reported by Nishihara and co-workers using aroyl fluorides as electrophiles (Figure 9).[26] The use of less stable acid halides (cf. esters, amides, anhydrides, Figures 4-8) requires alkynylsilanes as nucleophiles with $PdCl_2$ (10 mol%), dppp (15 mol%) and CuI (5 mol%) catalyst system.[26a] This study represents an important scope extension that is attainable from yet another complementary class of carboxylic acid derivatives. Recently, this aroyl fluoride decarbonylative Sonogashira methodology was advanced to Ni-catalyzed/copper-free system of $Ni(cod)_2$ (10 mol%) and dppp (15 mol%),[26b] which permitted the use of simple alkynes with a comparatively more limited scope (not shown).

Although the main topic of the present highlight is decarbonylative Sonogashira cross-coupling (loss of CO), a related method for decarboxylative Sonogashira cross-coupling (loss of CO_2) of carboxylic acids via Pd-catalyzed decarboxylative bromination was recently reported by the Su group (Figure 10).[27] The reaction mechanism involves decarboxylative bromination of carboxylic acids to produce aryl bromides, which then react with terminal alkynes under conventional Pd(0)/(II) cycle using $Pd(PPh_3)_4$ (10 mol%) and PCy_3 (20 mol%) in the absence of copper to deliver a range of functionalized diaryl alkynes. This useful methodology bears all the hallmarks of decarboxylative processes,[28] requiring ortho-substitution for decarboxylation. This contrasts with decarbonylative processes,[12,14–18] which have no or very little limitations in terms of substrate scope.

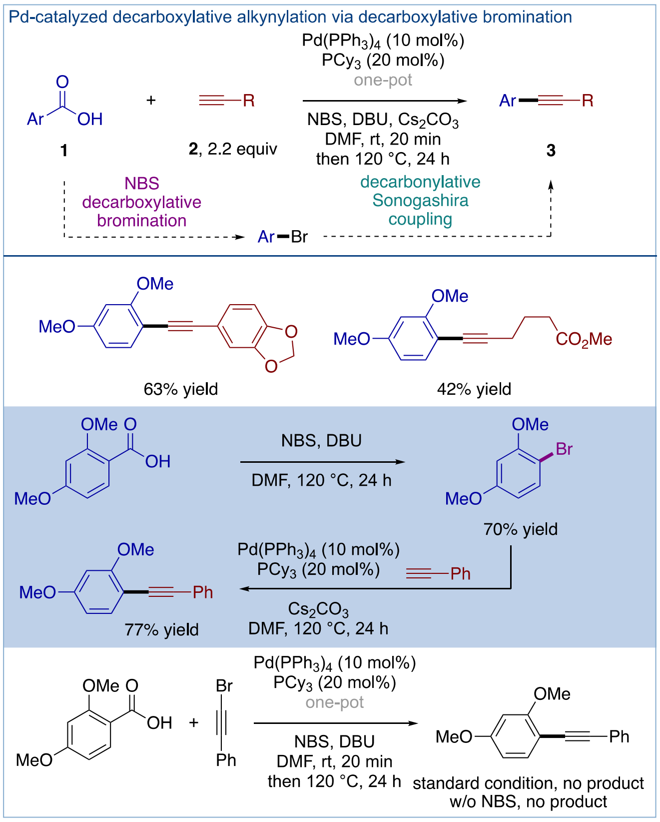

Figure 10 Pd-catalyzed decarboxylative alkynylation via decarboxylative bromination by Su.

Conclusions

In summary, decarbonylative Sonogashira cross-coupling of carboxylic acid derivatives as electrophiles has been accomplished through oxidative addition of the $C_{(acyl)}$–X bond and decarbonylation using a broad variety of substrates and catalyst systems. The most important advance is that carboxylic acids as electrophiles enable to translate the traditional Sonogashira cross-coupling manifold of aryl halides and pseudohalides to ubiquitous carboxylic acids that are inherently present in complex pharmaceuticals, natural products and organic materials. Thus, the development of decarbonylative Sonogashira cross-couplings merge the potential of diversity in alkyne functionalization with carboxylic acid substrates. Moreover, these studies address several previous major limitations, including (1) addition of acyl electrophiles across π-systems rather than cross-coupling, and (2) alkyne dimerization (Glaser-Hay coupling), by inventing new highly reactive yet stable acyl precursors (phenolic esters, N-acyl-glutarimides, mixed anhydrides, acyl fluorides) together with precise tuning of catalytic systems (Pd/Cu, Ni/Cu, Pd, Ni) that permit to match the rate of oxidative addition and decarbonylation with the class of acyl precursors preventing side reactions. Considering the importance of alkynes and carboxylic acids as fundamental substrates in organic synthesis, many exciting developments are expected in this area.

Acknowledgements

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