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Decarbonylative Phosphorylation of Carboxylic Acids via Redox-Neutral Palladium Catalysis

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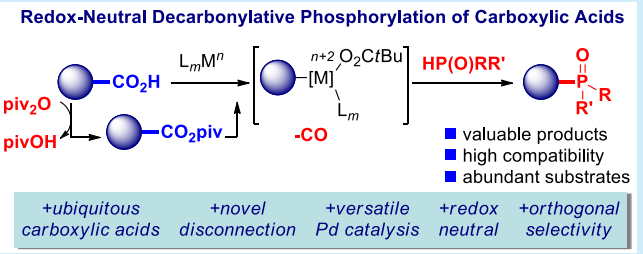
Supporting Information

ABSTRACT: We describe the direct synthesis of organophosphorus compounds from ubiquitous aryl and vinyl carboxylic acids via decarbonylative palladium catalysis. The catalytic system shows excellent scope and tolerates a wide range of functional groups (>50 examples). The utility of this powerful methodology is highlighted in the late-stage derivatization directly exploiting the presence of the prevalent carboxylic acid functional group. DFT studies provided insight into the origin of high bond activation selectivity and P(O)−H isomerization pathway.



The broad prevalence of organophosphorus compounds within bioactive products, coordination complexes, synthetic intermediates, and functional materials renders the preparation of this class of compounds a critical area of chemical research.[1−3] The C−P bond is typically installed by a classical nucleophilic addition of Grignard or organolithium reagents to phosphorus halides or by Michaelis−Arbuzov reaction; however, these methods suffer from harsh conditions, toxicity of reagents, and major scope limitations.[4,5] The development of transition-metal-catalyzed C−P bond formation opened up new avenues for exploration of organophosphorus compounds (Figure 1A).[6,7] This catalytic mechanism is now utilized to great effect to access key industrial substrates containing C−P bonds.[8] A variety of cross-coupling partners other than aryl halides have been successfully deployed, including aryl sulfonates,[9] diazonium salts,[10] boronic acids,[11] silanes,[12] organobismuth compounds,[13] pivalates,[14] and sulfides[15] involving C−X, C−O, C−N, C−B, C−Bi, C−Si, and C−S bond activation.[8−18] With these reactions, the most common mechanism involves oxidative addition of a low-valent metal to the C−X or equivalent bond, followed by ligand exchange with an electron-rich P−H nucleophile;[5,8] however, oxidative,[17] C−H activation,[19] and photoredox[20] pathways have also emerged. More recently, challenging C−P bond-forming reactions of amide derivatives[21] and phenolic esters[22] have been achieved. In contrast, to the best of our knowledge, no general catalytic method for the formation of organophosphorus compounds directly from ubiquitous carboxylic acids is currently available.[23]

Carboxylic acids represent quintessential substrates for chemical synthesis.[24] The intrinsic presence of carboxylic acids in a plethora biologically active molecules offers the unprecedented opportunity to directly produce novel three-dimensional architectures by late-stage modification. Notably, carboxylic acids are ubiquitous in every facet of chemistry, including agrochemicals, ligands, medicines, bioconjugates, and

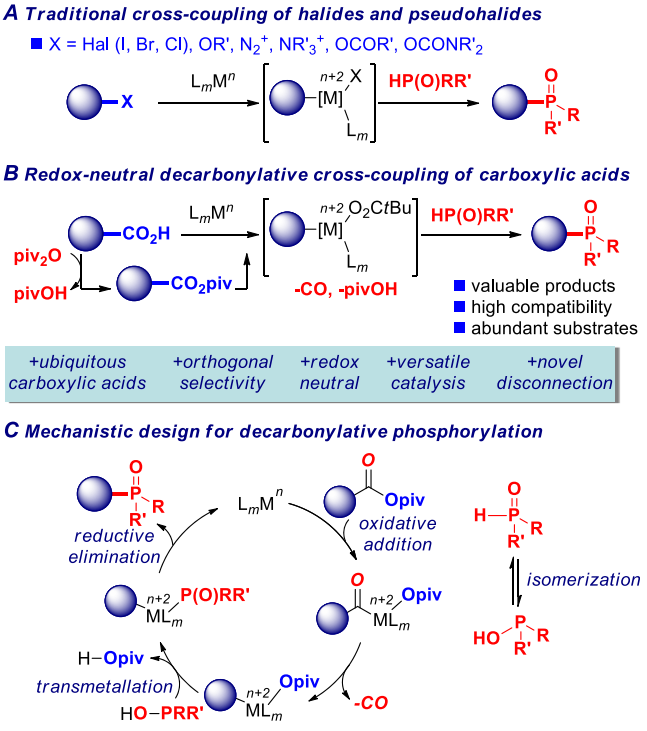


Figure 1. (A) Conventional synthesis of organophosphorus compounds. (B) Present work. (C) Mechanistic design of decarbonylative phosphorylation.

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advanced materials.[25] Carboxylic acids are cheaper, less toxic, and chemically orthogonal to the classical aryl halides.[26]

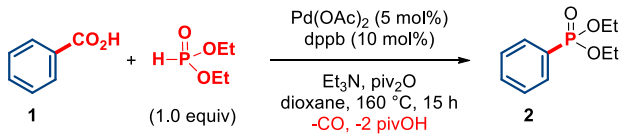
Herein, we report the first catalytic method for the direct synthesis of organophosphorus compounds from carboxylic acids via redox-neutral decarbonylative palladium catalysis (Figure 1B).

We hypothesized that critical advantages of the in situ activation of the carboxylic acid to form a mixed anhydride (piv = C(O)*t*-Bu) (Figure 1C) are that (1) carboxylic acids are exploited directly without separate or additional preactivation steps utilizing expensive reagents and (2) this mechanistic approach allows access a range of high-value organophosphorus compounds[1,3] that are impossible to synthesize from other derivatives.

While decarboxylative strategies (loss of carbon dioxide) have been an area of extensive study,[25,26] this catalytic mechanism is typically limited by specific substitution of the aromatic substrate, requires the use of expensive and less practical inorganic oxidants, and is plagued by a high energy decarboxylation step. We devised a strategy based on selective metal insertion into the C−O acyl bond of the carboxylic acid after in situ activation to afford a mixed anhydride, a process that is reminiscent to the classic activation of carboxylic acids for nucleophilic acyl addition reactions.[27−31] This approach renders decarbonylative mechanism of carboxylic acids a general method to access aryl electrophiles.[32,33] This process is operationally simple in that all reactions are executed in a one-pot fashion, while the byproducts are a mild organic acid PivOH (pK_a ca. 5) and carbon monoxide.

The proposed coupling was examined using benzoic acid and diethyl phosphite as model substrates (Table 1 and SI).

Table 1. Summary of Optimization Studies[a]



1 2

entry	variation from standard conditions	yield[b] (%)
1	no change	98
2	no piv_2O	<2
3	pivCl instead of piv_2O	51
4	Boc_2O instead of piv_2O	17
5	pyridine instead of Et_3N	84
6	Na_2CO_3 instead of Et_3N	<2
7	PPh_3 instead of dppb	48
8	dppf instead of dppb	54
9	dppp instead of dppb	83
10	dppPent instead of dppb	63

[a]Standard conditions: $PhCO_2H$ (0.20 mmol), $Pd(OAc)_2$ (5 mol %), dppb (10 mol %), $HP(O)(OEt)_2$ (1.0 equiv), Et_3N (1.0 equiv), piv_2O (1.0 equiv), dioxane, 160 °C, 15 h. [b]Determined by GC/^{1}H NMR. See the SI for details. Dppb = 1,4-bis(diphenylphosphino)butane. piv = pivaloyl.

After extensive optimization, we were delighted to find that excellent yields could be obtained by reacting benzoic acid (1.0 equiv) with $Pd(OAc)_2$ (5 mol %) as a catalyst, dppb (10 mol %) as a ligand in the presence of Et_3N (1.0 equiv) and piv_2O (1.0 equiv) additives, and an equivalent amount of $HP(O)(OEt)_2$ (1.0 equiv), delivering the desired aryl phosphonate product in 94% yield on a gram scale (Figure 2, **2a**). Control experiments established that all reaction components were required in accord with our design. Notably, the cross-coupling proceeds in the absence of activating groups on the aromatic carboxylic acid coupling partner and utilize cheap and nontoxic organic additives.

The scope of our protocol is outlined in Figure 2. We were pleased to find that the reaction exhibits remarkably broad scope, including a vast array of sensitive functional groups that could be utilized for orthogonal cross-coupling strategies or conventional nucleophilic manipulation. The effectiveness of our method is highlighted by the fact that simple (**2a−c**) as well as sterically demanding carboxylic acids (**2d−g**, **2w**) are readily accommodated by this process. Moreover, this transformation appears to be compatible with substrates bearing diverse electronic substitution, including neutral, electron-donating, and electron-withdrawing substituents (**2c−v**), which is uncommon in decarboxylative manifolds[24] and clearly distinguishes the present mechanism from alternative methods, including Ni-catalysis.[33] Perhaps most notably, a broad range of functional groups is compatible, such as halides (**2k**, **2u−v**), nitriles (**2l**, **2p**), esters (**2m**, **2q**, **2ao**), ketones (**2n**, **2r**), aldehydes (**2o**, **2s**), amides (**2am**, **2an**), phenols (**2ak**), anilines (**2t**, **2aj**, **2ap**), nitrogen (**2x**, **2z**, **2aa**, **2ab**, **2ar**), sulfur (**2y**, **2ac**, **2ae**) and oxygen heterocycles (**2ad**, **2as**), amines (**2t**, **2ap**), lactams (**2aq**), sulfonate esters (**2ah**), sulfonamides (**2ai**), and trifluoromethyl ethers (**2al**). The scope of the reaction supersedes other methods for the synthesis of $C(sp^2)$−P bonds by the decarbonylative pathway.[21,22]

Furthermore, this new phosphorylation method can be applied to a direct derivatization of drugs (probenecid, **2ai**, flufenamic acid, **2aj**), pesticides (diflufenican, **2ar**), and natural products (tocopherol, **2as**), clearly benefiting from the direct deployment of the ubiquitous carboxylic acid moiety. With respect to the phosphite, sterically hindered diisopropyl phosphite (**2at**) and dibutyl phosphite (**2au**) are competent coupling partners for phosphorylation. Notably, this protocol could also be used to form phosphines as indicated in the cross-coupling using diphenylphosphine (**2av**). To underline the synthetic utility, we showed that this method can be used to engage carboxylic acids by exploiting orthogonal directing properties of this functional group.[24] Thus, C−H arylation[34]/C−P formation (**2aw**), Suzuki−Miyaura cross-coupling[35]/C−P formation (**2x**), and Buchwald−Hartwig amination[36]/C−P formation (**2ay**) demonstrate how this coupling can be used to streamline the synthesis of functionalized organophosphorus compounds.

Next, DFT calculations were performed to provide key insight into the reaction mechanism and identify the origins of high chemoselectivity of bond activation (Figure 3).[37] The computed free energy profile of decarbonylative phosphorylation is shown in Figure 3A. From the substrate-coordinated complex **3**, the C−O bond activation of anhydride via **TS4** is reversible,[27,38] leading to the fast equilibrium between LPd(acyl)(OPiv) **5** and **3**. Subsequent decarbonylation occurs via **TS6** to generate the arylpalladium intermediate **8**.[39] Isomerization of phosphite[40] from $HP(O)(OEt)_2$ to $HOP(OEt)_2$ is necessary to allow the facile proton transfer[41] via **TS10**, generating intermediate **11**. Intermediate **11** then undergoes the C−P reductive elimination[42] through **TS12** to produce the phosphorylation product **14** and regenerates the active palladium(0) catalyst. The computations suggest that the acylpalladium intermediate **5** is the on-cycle resting state,

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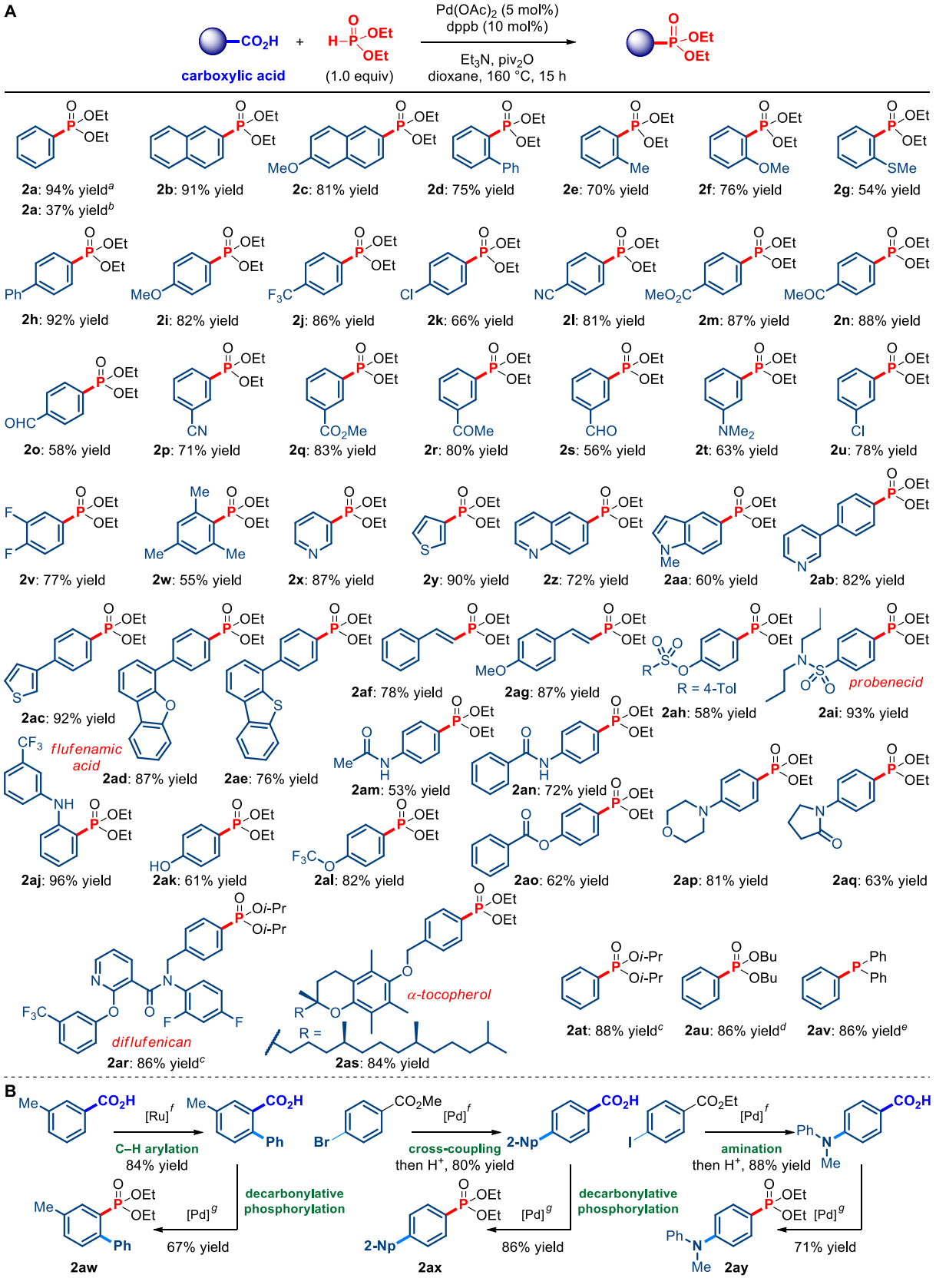

Figure 2. Palladium-catalyzed redox-neutral decarbonylative phosphorylation of carboxylic acids. Conditions: Ar−CO_2H (0.20 mmol), $Pd(OAc)_2$ (5 mol %), dppb (10 mol %), $HP(O)(OEt)_2$ (1.0 equiv), Et_3N (1.0 equiv), piv_2O (1.0 equiv), dioxane, 160 °C, 15 h. Isolated yields. (a) Gram scale. (b) Reaction using $PhCOCO_2H$. (c) $HP(O)(O\textit{i}\text{-}Pr)_2$. (d) $HP(O)(OBu)_2$. (e) $HPPh_2$. (f) See SI. (g) Standard conditions.

and the decarbonylation step is the rate-determining step with an overall barrier of 24.2 kcal/mol (**5** to **TS6**). The unfavorable pathway without the phosphite isomerization is included in the Supporting Information (Figure S1). We also

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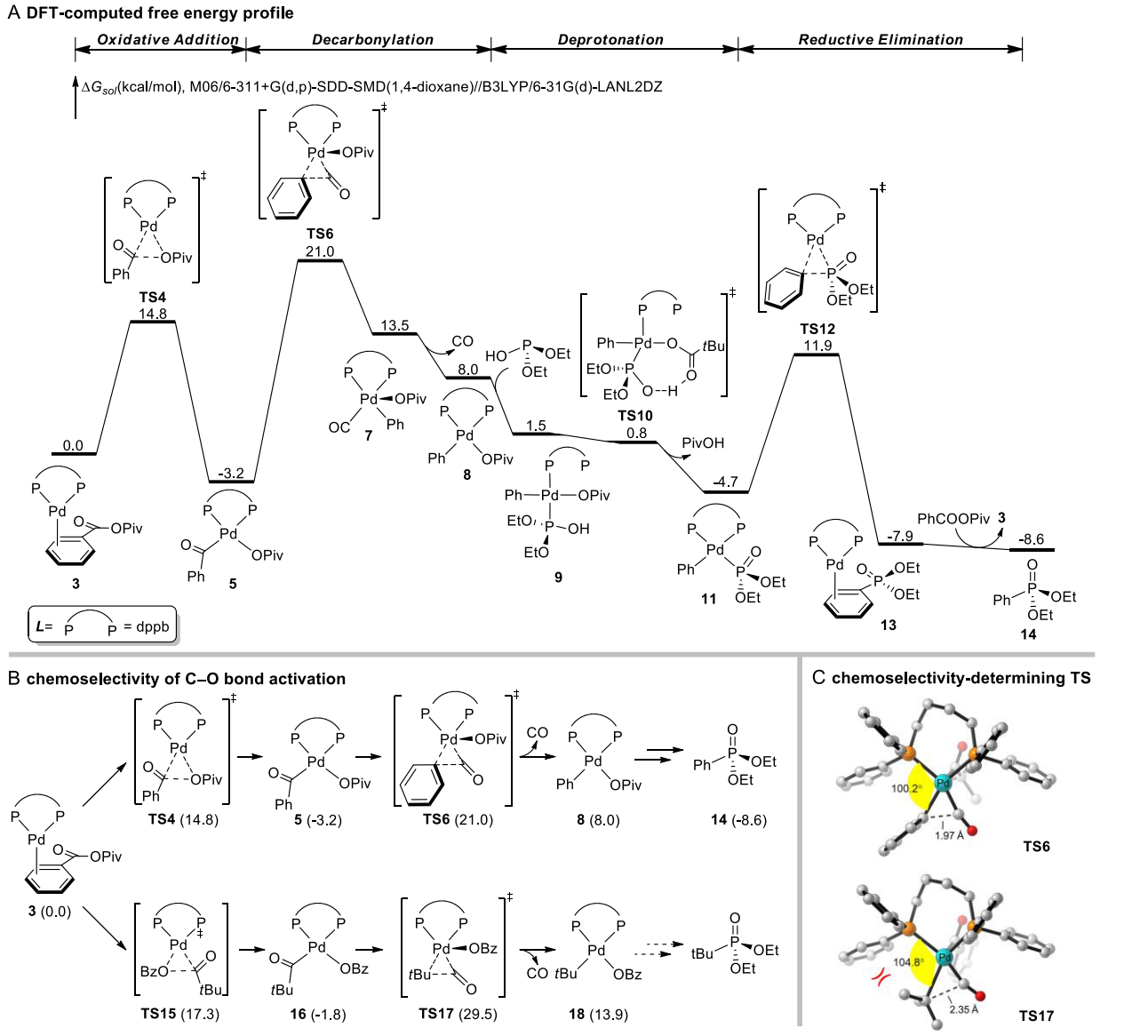

Figure 3. DFT-calculated free energy profile and chemoselectivity of C−O bond activation of [Pd(dppb)]-catalyzed decarbonylative phosphorylation of benzoic pivalic anhydride. See the SI for details.

considered the possible dissociation of pivalate anion from intermediate **8**, this pathway is unlikely due to the high-energy cationic palladium species (Figure S2).

The steric effects of anhydride substituent determine the chemoselectivity of C−O bond activation and functionalization. Figure 3B shows the free energies of the key intermediates and transition states in the competing C−O bond activation pathways. The rate-determining decarbonylation transition states (**TS6** vs **TS16**) differentiates the competing pathways by 8.5 kcal/mol, leading to the strong preference for the C−O bond activation of benzoic acid. The two acyl C−O bond activations (**TS4** vs **TS15**) are both facile, leading to an equilibrium between the two acylpalladium species **5** and **16**. This confirms that the decarbonylation step differentiates the chemoselectivity of C−O bond activation. The computed chemoselectivity in Figure 3B indeed suggests that the formation of *t*Bu-Pd species is unlikely, which is consistent with the experimental observations. These calculations aim to understand the determining step that differentiates the chemoselectivity, providing a rational basis for future designs of anhydride for target transformation. The steric repulsions between the bulky *t*Bu group and dppb ligand are reflected in the highlighted C−Pd−P angle in both **TS16** and intermediate **TS17** (Figure 3C).[43] The high selectivity of bond activation bodes well for future catalyst design studies in this general activation platform.

To further demonstrate the potential value of this method, we performed additional direct derivatizations of pharmaceuticals (Figure 4). We were delighted to find that the direct decarbonylative phosphorylation of a topical retinod, adapalene (**2az**), antileukemic, tamibarotene (**2ba**), and antidiabetic, repaglinide (**2bb**) proceeded in high yields without modification of the reaction conditions. Clearly, this process benefits from directly using the ubiquitous carboxylic acid moiety to forge the C−P bonds.

In summary, we have developed a direct synthesis of organophosphorus compounds from ubiquitous carboxylic acids via redox-neutral decarbonylative palladium catalysis. This versatile C−P bond-forming method allows rapid access to organophosphorus compounds from readily available

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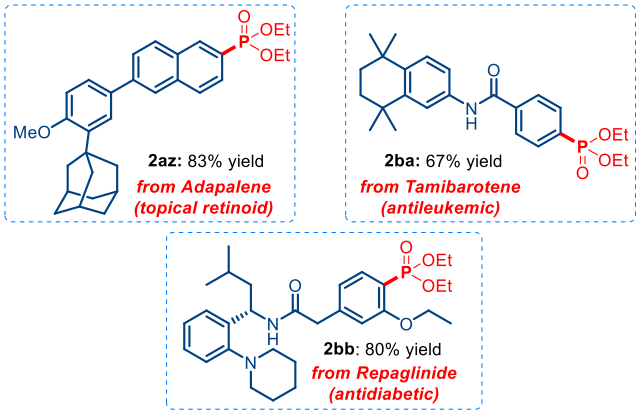

Figure 4. Decarbonylative phosphorylation of pharmaceuticals.

carboxylic acids, has a broad scope and tolerates a remarkable range of functional groups. DFT calculations were used to investigate the reaction mechanism and provide information into the origin of high reaction selectivity. This study highlights that the redox-neutral decarbonylative manifold of carboxylic acids provides a unique approach to controlling the cross-coupling reactivity of carboxylic acids and holds promise for being translated into a general cross-coupling platform on par with aryl halides and pseudohalides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03678.

Experimental procedures, characterization data, computational details, coordinates, and energies of DFT-computed stationary points (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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