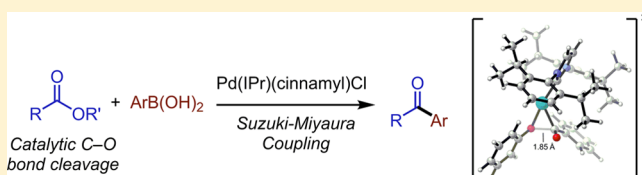


Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Esters

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Supporting Information

ABSTRACT: The Suzuki–Miyaura coupling is among the most important C–C bond-forming reactions available due to its reliability, chemoselectivity, and diversity. Aryl halides and pseudohalides such as iodides, bromides, and triflates are traditionally used as the electrophilic coupling partner. The expansion of the reaction scope to nontraditional electrophiles is an ongoing challenge to enable an even greater number of useful products to be made from simple starting materials. Herein, we present how an NHC-based Pd catalyst can enable Suzuki–Miyaura coupling where the C(acyl)–O bond of aryl esters takes on the role of electrophile, allowing the synthesis of various ketone-containing products. This contrasts known reactions of similar esters that provide biaryls via nickel catalysis. The underlying cause of this mechanistic divergence is investigated by DFT calculations, and the robustness of esters compared to more electrophilic acylative coupling partners is analyzed.



INTRODUCTION

The cross-coupling of organoboron nucleophiles with C–X bonds is among the most widely used reactions for reliable, selective C–C bond formation.¹ In traditional examples, the electrophilic coupling partner is an aryl halide. The extension of this reactivity mode to a broader range of starting materials and more diverse products is an ongoing goal in the field. For example, a range of carboxylic acid derivatives have been reported to act as cross-coupling electrophiles in Suzuki–Miyaura and related reactions, including acid chlorides,² thioesters,³ anhydrides,⁴ and select esters⁵ and amides.⁶ Multiple possible reaction pathways can be envisioned with these substrates depending on where oxidative addition occurs and whether or not possible acyl-bearing organometallic intermediates undergo decarbonylation (Scheme 1).

Among less activated acid derivatives, the utilization of simple ester starting materials was particularly notable first reported in 2008 by the groups of Garg^{5a} and Shi,^{5b,c} who reported that Nickel catalysis could be utilized to couple boronic acids with phenolic carboxylates.⁷ Despite the relative weakness of the C(acyl)–O bond, these pivalate and acetate derivatives react via cleavage of the C(aryl)–O bond to provide biaryl coupling products, reminiscent of the classical reactivity of aryl halides. Mechanistic studies later demonstrated that, particularly with monodentate phosphine ligands, selectivity for this pathway derives from a favorable C–O cleaving oxidative addition that proceeds via a 5-centered transition state.⁸

In 1976, the Yamamoto lab reported that aryl esters could react with stoichiometric Ni(0) via oxidative addition of the C(acyl)–O bond to produce a transient acyl Ni(II) species,

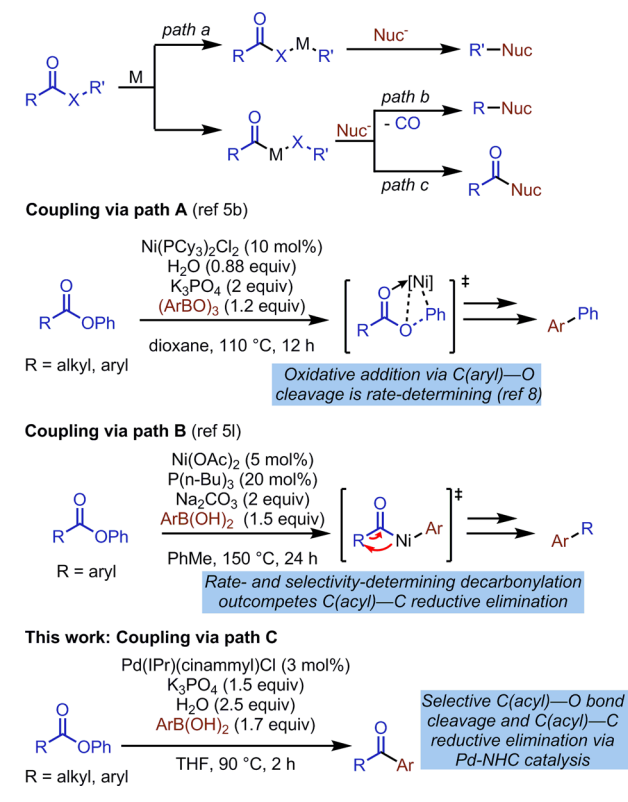
which underwent rapid decarbonylation.⁹ It was not until 2012 that this pathway was exploited in selective catalytic cross-couplings, when the Itami group reported that phenyl esters can be used in decarbonylative C–H activation with a Nickel catalyst bearing a bulky bidentate phosphine ligand.^{5d} Selectivity for the C–O bond cleavage originates from the inability of the bidentate Ni(0) to coordinate with the carbonyl oxygen during oxidative addition, and a rate-determining decarbonylation step that outcompetes C–C bond reductive elimination to preferentially form biaryls.^{5l,10} These aryl ester couplings have since proven to be quite diverse; decarbonylative Suzuki coupling,^{5l–n} silylation,^{5o,p} and borylation^{5p,q} have been recently reported. Notably, these reactions generally take place around 150 °C, a substantially elevated temperature which may facilitate decarbonylation. The substantial number of examples utilizing phenyl esters as couple partners via either C(aryl)–O cleavage (Scheme 1, path A) and C(acyl)–O cleavage with decarbonylation (path B) contrasts sharply with the large number of other carboxylic acid derivatives that are reported to under to C(acyl)–O cleavage with carbonyl retention (path C).¹¹

Synthesis of ketones from carboxylic acid derivatives is a highly valuable transformation. Stoichiometric reaction of organometallic nucleophiles to carboxylic acid derivatives such as Weinreb amides or acid chlorides are well established, but issues of chemoselectivity and functional group tolerance limit applications. Catalytic strategies^{2–6} have mainly focused

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Scheme 1. Cross-Coupling of Carboxylate Derivatives



on utilizing carboxylic acid derivatives with very weak C(acyl)–X bonds that may be easily cleaved by oxidative addition, but may also be prone to other side reactions such as hydrolysis. This limits applications in multistep synthesis, where lengthy protection, deprotection, and activation of the carboxylic acid must be carried out.^{12,13} An efficient catalytic cross-coupling of aryl esters would fill a valuable role that begins blurring the line between a protecting and an activated group for carboxylic acids.

With this motivation in mind, we sought to determine if the acyl-metal species generated by oxidative addition to phenyl esters could be efficiently utilized in Suzuki–Miyaura coupling without loss of the carbonyl group. Additionally, we desired to gain some fundamental understanding of the underlying rules that dictate selectivity for the three plausible coupling pathways that aryl esters may undergo. In this manuscript, we demonstrate that the use of a bulky, NHC-bearing Pd catalysts enables this transformation via blocking potential C(aryl)–O oxidative addition and decarbonylation reaction pathways, leaving only the acylative coupling pathway active. Mechanistic studies elucidate how different catalysts are able to control whether C(aryl)–O or C(acyl)–O cleavage occurs, and whether or not acyl metal intermediates undergo decarbonylation.

RESULTS AND DISCUSSION

Reaction Discovery and Optimization. The transformation of phenyl benzoate and phenylboronic acid to benzophenone using palladium catalysts was chosen as the test reaction, and discovery/optimization is outlined in Table 1. Using 5 mol% Pd(OAc)₂, 1.5 equiv K₃PO₄, and 2.5 equiv H₂O in THF at 100 °C for 16 h provides no desired product when utilizing many of the most common phosphine ligands for

Table 1. Reaction Discovery and Optimization

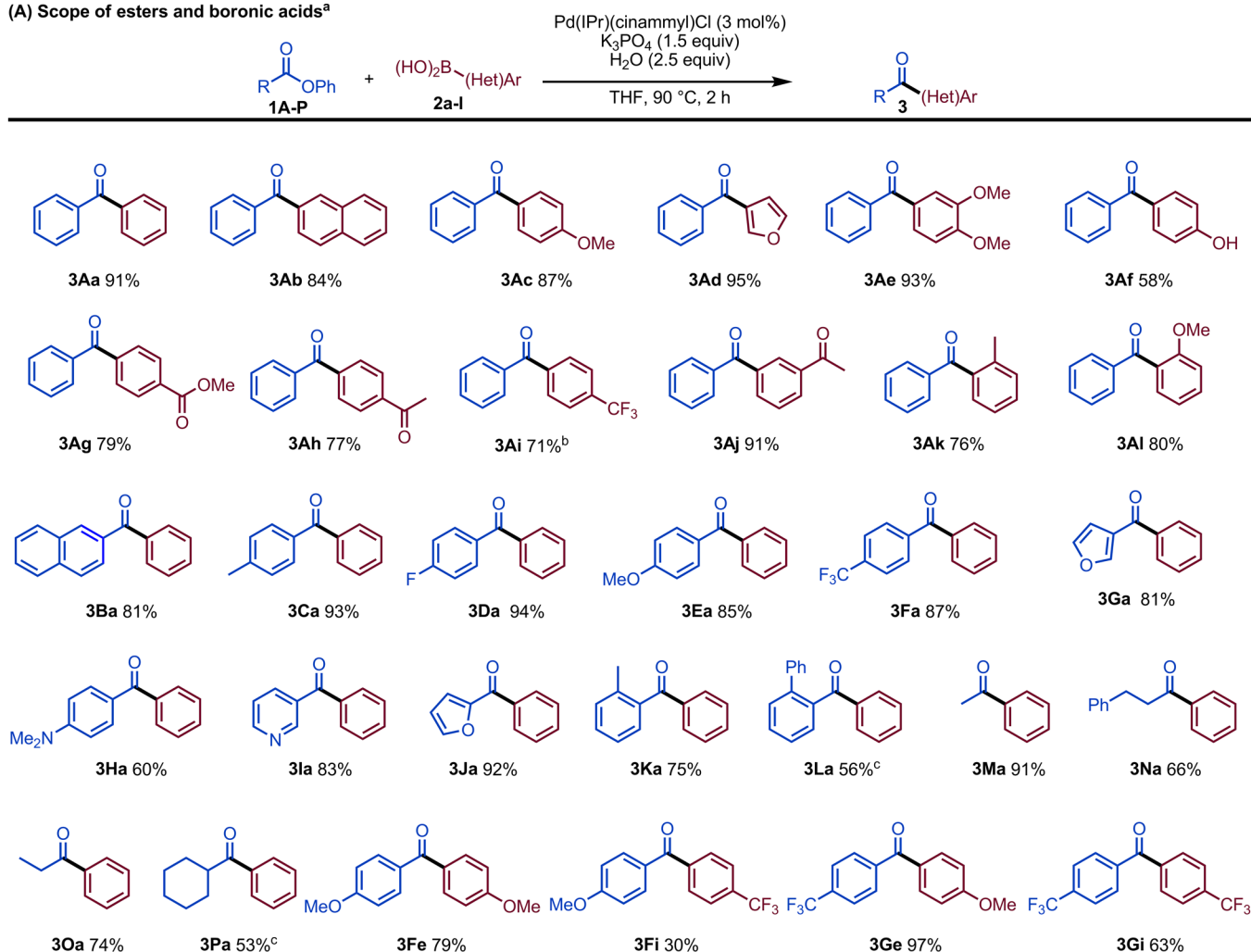
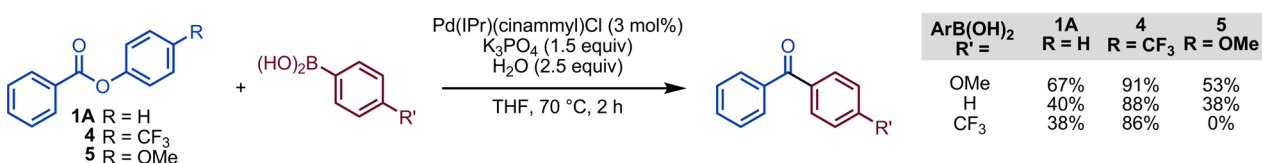
Entry	Pd source	x	Ligand	y	Yield (%) ^a
1	Pd(OAc) ₂	5	PPh ₃	10	<5
2	Pd(OAc) ₂	5	PtBu ₃	10	<5
3	Pd(OAc) ₂	5	P(o-tol) ₃	10	<5
4	Pd(OAc) ₂	5	dppf	10	<5
5	Pd(OAc) ₂	5	SPhos	10	<5
6	Pd(OAc) ₂	5	BINAP	10	<5
7	Pd(OAc) ₂	5	IPr+HCl	10	11
8	Pd ₂ (dba) ₃	5	IPr+HCl	10	16
9	[Pd(allyl)Cl] ₂	5	IPr+HCl	10	19
10	[Pd(cinammyl)Cl] ₂	5	IPr+HCl	10	21
11	[Pd(cinammyl)Cl] ₂	5	IPr+HCl	5	59
12	none	-	IPr+HCl	5	<5
13	Pd(IPr)(cinammyl)Cl	5	-	-	95
14	Pd(IPr)(cinammyl)Cl	3	-	-	94
15	Pd(IPr)(cinammyl)Cl	3	-	-	91 ^b

General reaction conditions: ester (0.1 mmol), boronic acid (0.17 mmol), Pd catalyst, ligand, K₃PO₄ (0.15 mmol), H₂O (0.25 mmol), THF (0.5 mL) at 100 °C for 16 h under argon atmosphere. ^aYield determined by GC with 1,3,5-trimethoxybenzene as internal standard. ^bReaction run for 2 h at 90 °C. Isolated yield.

Suzuki–Miyaura and other cross-couplings, including PPh₃ (entry 1), PtBu₃ (entry 2), P(o-tol)₃ (entry 3), dppf (entry 4), SPhos (entry 5), and BINAP (entry 6). In contrast, utilization of the N-heterocyclic carbene (NHC) ligand IPr (entry 6) gave a promising 11% yield. The combination of Pd(OAc)₂ and IPr are known to inefficiently form active Pd(0) catalyst,¹⁴ so different Pd sources were screened. The use of Pd₂(dba)₃, [Pd(allyl)Cl]₂, or [Pd(cinammyl)Cl]₂ gave only slight improvements (entries 8–10), while the use of a 1:1 ratio of metal to ligand (entry 11) provided a substantial increase to 59% yield. No significant product was observed under these conditions in the absence of Pd (entry 12). Further improvement was realized when the preformed catalyst Pd(IPr)(cinammyl)Cl was used, which gives an excellent 95% yield (entry 13). With these conditions, the catalyst loading could be decreased to 3 mol% (entry 14) and the temperature reduced to 90 °C (entry 15) without impacting on the reaction outcome.¹⁵ Low-yielding reactions during optimization general showed high recovery of starting materials, and no evidence of C(aryl)–O cleavage or decarbonylation pathways was observed. A thorough listing of variable screening and control experiments is given in the Supporting Information (Tables S1–S6).

Reaction Scope. With optimized conditions in hand, we next turned our attention toward the reaction scope (Scheme 2A). Using phenyl benzoate 1A, a variety of boronic acids were analyzed. Beyond the synthesis of the parent benzophenone 3Aa in 91% yield, products arising from the coupling of

Scheme 2. Scope of Pd-Catalyzed Suzuki–Miyaura Cross-Coupling of Esters

(A) Scope of esters and boronic acids^a(B) Electronic influence at reduced temperature^d

^aGeneral reaction conditions: ester (0.2 mmol), boronic acid (0.34 mmol), Pd(IPr)(cinammyl)Cl (0.0067 mmol), K₃PO₄ (0.3 mmol), H₂O (0.5 mmol), THF (1 mL) at 90 °C for 2 h under argon atmosphere. Isolated yield. ^b0.01 mmol Pd(IPr)(cinammyl)Cl used. Reaction stirred for 16 h. ^cReaction run for 16 h at 100 °C in dioxane. ^dReactions run for 2 h at 70 °C. Yield determined by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard.

electron neutral (3Ab) and electron rich (3Ac–3Ae) boronic acids were prepared in >80% yield. The use of an unprotected phenol-containing boronic acid was also tolerated, providing 3Af in 58% yield. Products derived from electron-deficient (3Ag–3Aj) and sterically hindered (3Ak and 3Al) boronic acids generally provided lower yields, though still >70%.

Satisfied with the breadth of organoboron species that could be utilized, we next sought to explore a variety of ester starting materials. Several relatively electron-neutral ketones (3Ba–3Ea) were prepared in good yields. Electron-rich 3Fa, electron-poor 3Ga, and furanyl-containing 3Ha could all be prepared in similarly good yields. These products are identical in structure to 3Ac, 3Ai, and 3Ad, respectively, as are 3Ab and 3Ba, but

with the functionality placed on the ester starting material rather than the boronic acid. Comparing yields of these identical products prepared using different starting material illustrates that the outcome of the reaction is more sensitive to the electronics of the boronic acid than the starting ester. While efficient reactions can be obtained with an electron-donating group on either coupling partner, an electron-withdrawing CF₃ group only provides high yield when on the ester (3Fa, 87%), but not on the boronic acid (3Ai, 71% with increased catalyst loading and reaction time).

Ketones derived from highly electron-rich (3Ha), heterocyclic (3Ia, 3Ja) and sterically hindered (3Ka, 3La) esters could also be prepared. Alkyl aryl ketones 3Ma–3Oa could be

prepared from aliphatic esters, though yields decreased with increased bulk of the electrophiles. Attempts to use 2,6-disubstituted benzoic acid derivatives and aliphatic α -tertiary acids were unsuccessful, furthering this point. Nonetheless, these examples are notable since the use of alkyl halides and arylboronic acids to make alkyl aryl ketones via carbonylative coupling is rare.¹⁶ Finally, having both components contain an electron-donating group (3Fe), an electron-rich and electron-withdrawing group (3Fi, 3Ge), or electron-withdrawing groups (3Gi) were all tolerated, with the best yields arising from the CF₃-containing ester and OMe-containing boronic acid.

Electronic Influence. In the interest of getting further understanding about the electronic influence of substituents on the outcome of the reaction, the phenolic leaving group component of the ester was varied and the temperature reduced to 70 °C to accentuate differences in reactivity (Scheme 2B). Under these conditions, phenyl benzoate 1A provided the same trend observed at 90 °C with electron-rich boronic acids providing higher yields than electron-poor. Interestingly, when CF₃-containing benzoate 4 was used as a starting material, the same products were obtained in significantly higher yields. In contrast, the use of OMe-containing benzoate 5 was used, very low yields were obtained. The drastic changes in reactivity observed with electronic variation of both the ester and boronic acid coupling partner suggests that the rate-determining step of the reaction may change depending on the choice of substrate.

Comparison of Acylative Coupling Partners. The synthesis of ketones by catalytic cross-coupling of carboxylic acid derivatives is well established with a variety of substrate, catalyst, and nucleophile combinations.^{2–6} Alternatively, carboxylic acids can be used directly by in situ derivatization to a more electrophilic intermediate.¹⁷ It is thus important to consider the relative merits of this new method. Functional groups that are tolerant to a range of reaction conditions but can be selectively cleaved when desired are ideal in multistep synthesis. For example, in polymer synthesis, free acid monomers are often simultaneously activated and protected as an aryl ester derivative, polymerization is carried out, then the ester is utilized for chemoselective derivatization.¹⁸ To compare robustness of many of the acid derivatives that undergo acylative cross-coupling, a set of experiments were carried out with a thioester,³ anhydride,⁴ pyridyl ester,^{5e} twisted amide,^{6f} and phenyl ester as representative acylative coupling precursors (Table 2). To determine their stability to cleavage via substitution, the five substrates were dissolved together in DMF/MeOH in the presence of K₂CO₃, and consumption was monitored over time. Within 24 h, all molecules had completely converted to the corresponding methyl ester except phenyl benzoate, which required 96 h. To test stability in nonpolar solvents, each substrate was treated with 1.1 equiv of morpholine in toluene at 40 °C and conversion to the corresponding amide was monitored over time. An identical trend was observed, with the anhydride being consumed fastest and the phenyl ester being the most stable. Together, these data provide evidence that, among chosen substrates, phenyl esters are least susceptible to undesirable side reactions that may occur in multistep synthesis.¹⁹ It is also consistent with the catalyst requirements for coupling: While relatively simple Pd(OAc)₂/PR₃ catalyst systems are sufficient for activation of these established acylative coupling partners, we found only a highly specific Pd-NHC precatalyst was able to achieve efficient C–O bond activation of phenyl esters. Coupling of even more

Table 2. Stability Study of Select Acylative Cross-Coupling Electrophiles

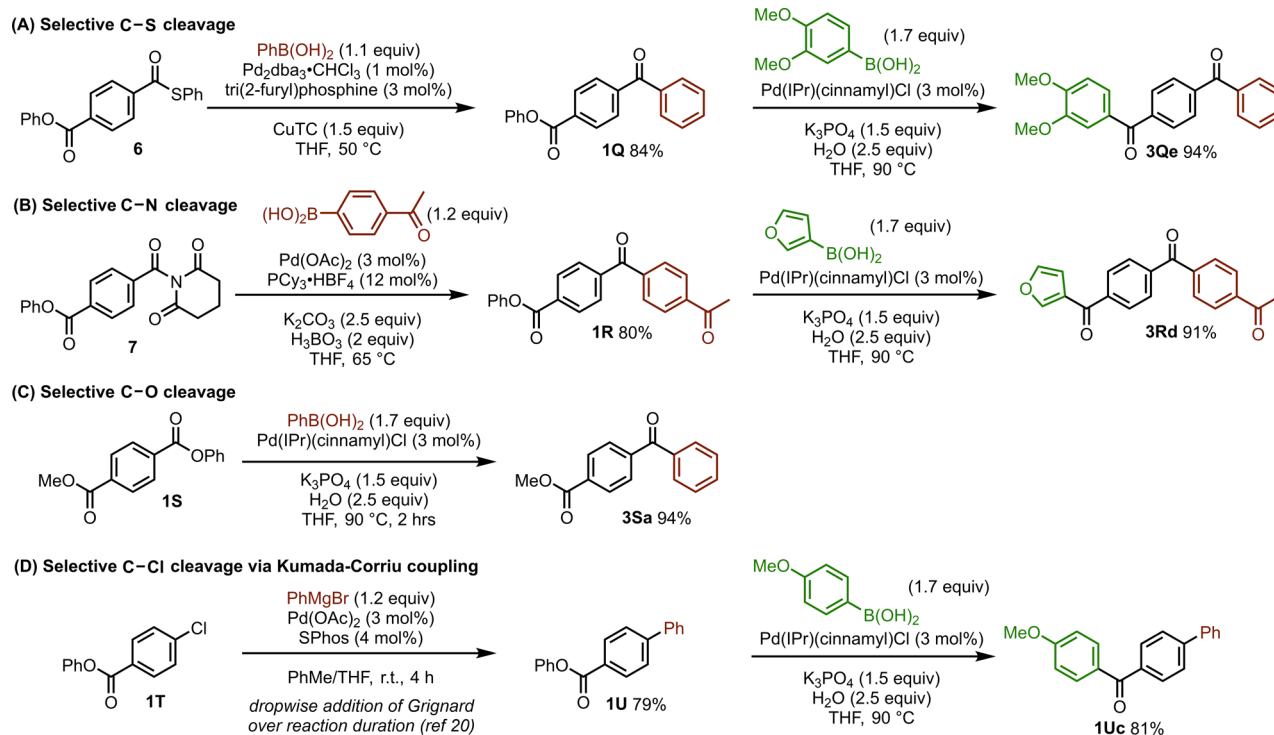
X =	Stability to methanolysis	Stability to amidation
	consumed within 10 minutes	consumed within 10 minutes
	consumed within 1 hour	consumed within 30 min
	consumed within 4 hours	consumed within 6 hours
	consumed within 24 hours	trace remained after 96 hours
	consumed within 96 hours	69% remained after 96 hours

robust substrates such as methyl esters^{5h} may be achievable with further mechanistic and ligand design research.

Unique Advantages of Aryl Esters. Given this greatly differing reactivities of the studied acid derivatives, competition experiments were run to determine if selective coupling reactions could be performed on multifunctional substrates. Using a Pd/phosphine system with copper(I) thiophene-2-carboxylate (CuTC) activation (Liebeskind–Srogl coupling),^{3a} bifunctional 6 could be coupled first via selective C–S bond cleavage to provide 1Q in 84% yield, followed by C–O cleavage to prepare 3Qe in 94% yield (Scheme 3A). Similarly, coupling of twisted amide 7 using conditions developed by Szożak and co-workers^{6f} was also completely selective. This substrate coupled exclusively via C–N cleavage, providing 1R in 80% yield, which in turn couples via C–O cleavage to provide polyketone 1Rd in 91% yield (Scheme 3B). Attempts to selectively first couple the phenyl ester while leaving the thioester or 6 or twisted amide of 7 intact were unsuccessful. Next, bis-ester 1S was subjected to the cross-coupling reaction conditions to determine if C–O bond cleavage would occur at an aryl ester in the presence of a methyl ester (Scheme 3C). Indeed, selective coupling occurred, providing ketone 3Sa in 94% yield with no evidence of reactivity of the methyl ester. Finally, 1T, bearing an aryl chloride and phenyl ester, was studied (Scheme 3D). Using a slow addition strategy developed in our lab,²⁰ chemoselective Kumada–Corriu coupling could be performed provide 1U in 79% yield, followed by acylative Suzuki–Miyaura to give 1Uc in 81% yield. The selectivity of both the Pd catalyst and the Grignard reagent react at the C–Cl bond of 1T demonstrates that the ester functionality can tolerate even exceptionally harsh reaction conditions.

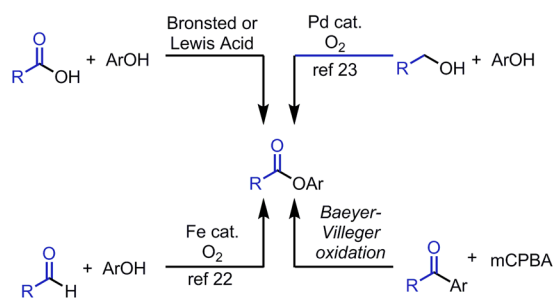
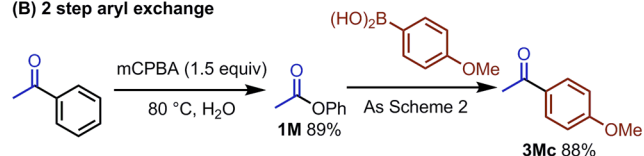
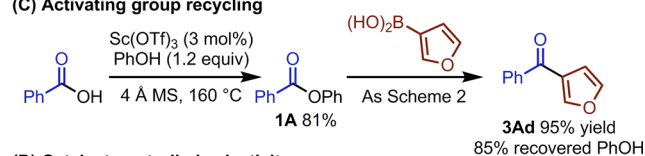
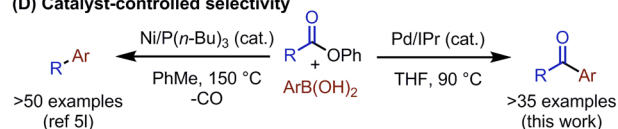
The common occurrence of esters as both starting materials and products of in many reactions gives them another distinct advantage over alternative acylative coupling partners. Aryl esters can be obtained from redox-neutral esterification of carboxylic acids,²¹ or oxidative coupling of phenol with

Scheme 3. Chemoselectivity Study in the Cross-Coupling of Multifunctional Substrates



aldehydes²² or alcohols (Scheme 4A).²³ Alternatively, aryl esters can be obtained from the corresponding aryl ketones via Baeyer–Villiger oxidation if the R group has a lower migratory

Scheme 4. Unique Aspects of Using Aryl Esters as Acylative Coupling Partners

(A) Aryl ester synthesis from diverse starting materials**(B) 2 step aryl exchange****(C) Activating group recycling****(D) Catalyst-controlled selectivity**

aptitude than the phenyl ring.²⁴ These diverse methods provide many unique possibilities for synthetic applications. For instance, treatment of acetophenone with mCPBA provides phenyl ester **1M** in 80% yield (Scheme 4B). Subsequent cross-coupling with 4-methoxyphenylboronic acid then provides ketone **3Mc** in 88% yield, representing an unusual two step “aryl exchange” process. Toward the goal of decreasing waste in acylative coupling procedures, esterification benzoic acid was carried out neat with catalytic Sc(OTf)_3 ,^{5k} providing phenyl benzoate **1A** in 81% yield with water as the only byproduct. In the subsequent coupling, 85% of phenol could be recovered, which enables efficient recycling for an overall atom economic process. Finally, the ability to form ketone-containing products by aryl ester cross-coupling is highly complementary to the high yielding decarbonylative couplings developed by Itami and co-workers,^{5l} allows highly efficient and selective formation of biaryls (Scheme 4D). The ability to convert one starting material into two different product classes by careful selection provides a powerful opportunity for diversification of interesting molecular scaffolds. To our knowledge, only twisted amides have been reported as being able to access both of these reaction modes.^{6c–f}

Mechanistic Studies. An unusual divergence in selectivity is seen in the cross-coupling of carboxylic acid derivatives. Use of highly activated species such as acid chlorides and anhydrides generally provides ketone products. In contrast, recent literature on the cross-coupling of esters has deviated from this trend, demonstrating C(aryl)–O bond cleavage^{7,8} or C(acyl)–O^{12–14} cleavage with decarbonylation. Thorough mechanistic studies^{10,12} have been done on these reactions, demonstrating the challenges in forming ketones from esters via cross-coupling. The success of the current method is thus curious, and we desired to further understand the mechanism and the key factors that control the divergent behavior of different catalysts toward the coupling of esters. Using phenyl

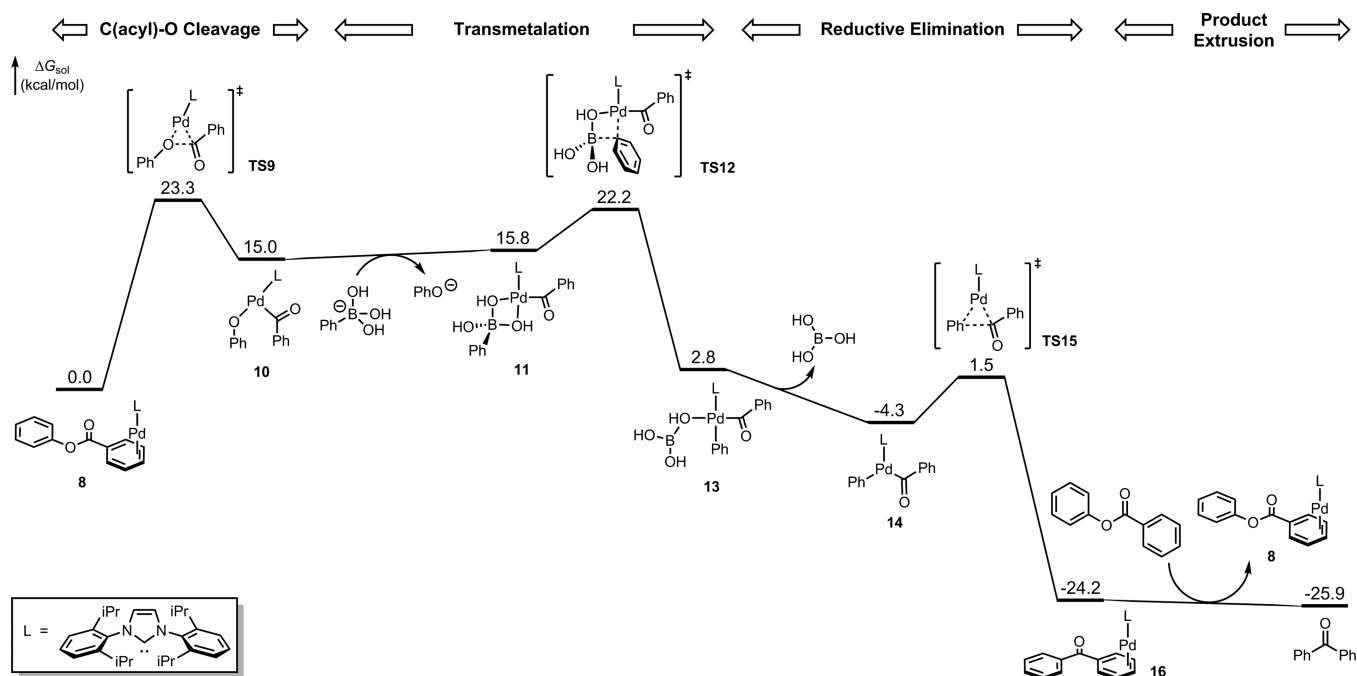


Figure 1. Gibbs free energy profile of the Pd-catalyzed Suzuki–Miyaura coupling reaction of phenyl benzoate.

benzoate as the model substrate, density functional theory (DFT) calculations were carried out toward this goal.

All DFT calculations were performed with Gaussian 09.²⁵ Geometry optimization of all the minima and transition states was carried out at the B3LYP level of theory²⁶ with the LANL2DZ basis set²⁷ for palladium and the 6-31G(d) basis set for the other atoms (keyword 5D was used in the calculations). The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum or a transition state and to evaluate its zero-point vibrational energy (ZPVE) and thermal corrections at 298 K. The single-point energies and solvent effects in THF were computed at the M06 level of theory²⁸ with the SDD basis set²⁹ for palladium and the 6-311+G(d,p) basis set for the other atoms, based on the gas-phase optimized structures. Solvation energies were evaluated by a self-consistent reaction field (SCRF) using the SMD model.³⁰ The calculated Gibbs free energies are determined by adding the thermal correction to Gibbs free energies, based on B3LYP level of theory, and single point energy with solvation energy correction, based on M06 level of theory. Extensive conformational searches for the intermediates and transition states have been conducted, and only the lowest energy conformers and isomers are shown in this work.

The free energy profile of the productive pathway is shown in Figure 1. Starting from the substrate-coordinated complex, **8**, the C(acyl)–O cleavage occurs through a three-centered transition state **TS9** to give the Pd(II) intermediate **10**. Subsequent ligand exchange with phenylboronate leads to Pd(II)-boronate intermediate **11**, which then undergoes the transmetalation via **TS12** to produce intermediate **13**. This contrasts the work on the analogous decarbonylative Suzuki–Miyaura coupling of aryl esters, which are performed under anhydrous conditions and require cluster formation of the oxidative addition complex with carbonate base prior to transmetalation.⁵¹ Notable, The subsequent Csp²–Csp² reductive elimination via **TS15** is facile, and the product-coordinated complex, **16**, eventually releases the product and regenerates

intermediate **8** for the next catalytic cycle. The rate-limiting step of the whole catalytic cycle is the C(acyl)–O cleavage step via **TS9**, with a 23.3 kcal/mol barrier. Consistent with the high electronic sensitivity observed (Scheme 2B), the barrier for transmetalation is only 1.1 kcal/mol smaller than the oxidative addition, and may thus become rate-limiting when using esters that undergo more facile oxidative addition, or nucleophiles that are less effective for transmetalation.

Based on the working mechanism, we also studied the chemoselectivity of the C–O bond cleavage step (Figure 2).

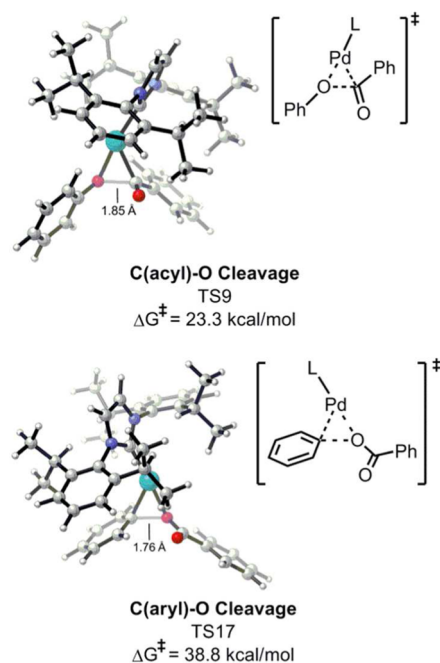


Figure 2. Optimized structures and free energies of competing C–O bond-cleaving transition states relative to complex **8**.

Our previous theoretical study on this cleavage with a Ni/PCy₃ catalyst showed that the distortion of substrate controls the barrier if both C–O bonds are cleaved through similar three-centered transition states.^{10a} In the case of metal-mediated bond cleavage, the distortion of substrate is mainly related to the strength of the cleaving bond. Therefore, the C(aryl)–O cleavage made a five-centered transition state possible and the cleavage of the stronger C–O bond more facile.^{10a} In the present system, the palladium catalyst cleaves both C(acyl)–O and C(aryl)–O bonds through three-centered transition states.³¹ Consistent with experiment, TS9, which leads to the C(acyl)–O bond cleavage, is 15.0 kcal/mol more favorable than the competing C(aryl)–O cleavage transition state, TS17.

In addition, we also studied the potential decarbonylation pathway as a comparison with the productive carbonyl-retention pathway. Previous computational studies with Ni/PBu₃ found the acyl intermediate to undergo decarbonylation with an 8 kcal/mol barrier. In contrast, a 23.2 kcal/mol barrier was calculated with the Pd/NHC system, which is much higher as compared to the 5.8 kcal/mol barrier for direct reductive elimination. The exceptional bulkiness of the ligand makes this step both thermodynamically and kinetically more challenging. Details are listed in the [Supporting Information](#).

CONCLUSION

The cleavage of relatively strong phenyl ester bonds by oxidative addition, first reported in 1976,⁹ has for the first time been utilized to catalytically prepare carbonyl-containing materials with high selectivity. The use of a Pd-NHC catalyst enables this reactivity, where previous systems based on Nickel catalysis have only provided selectivity for C(aryl)–O and decarbonylative C(acyl)–O coupling pathways with these substrates. Excellent yields of ketone-containing products were obtained with a broad range of ester and boronic acid starting materials. These starting materials are particularly robust in comparison to other carboxylic acid derivatives used in cross-coupling, suggesting they are applicable to the synthesis of complex molecules where chemoselectivity issues may occur. Calculations were performed to reveal the underlying mechanistic features that enable this reaction to selectively occur, illustrating unique differences in reactivity modes of Pd vs Ni. Specifically, the Pd/NHC combination allows kinetically feasible C(acyl)–O oxidative addition while preventing the 5-centered transition state which may favor C(aryl)–O cleavage. The bulky NHC then prevents decarbonylation of the acyl-Pd intermediate, allowing direct coupling. The ability to selectively obtain multiple different products based on catalyst choice is of broad applicability, and further studies are underway to extend this reaction scope beyond phenyl ester electrophiles and boronic acid nucleophiles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12329.

Experimental procedures, characterization of organic molecules, optimization tables, Cartesian coordinates, and Gibbs free energies of the calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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