ORGANOMETALLICS

pubs.acs.org/Organometallics Article

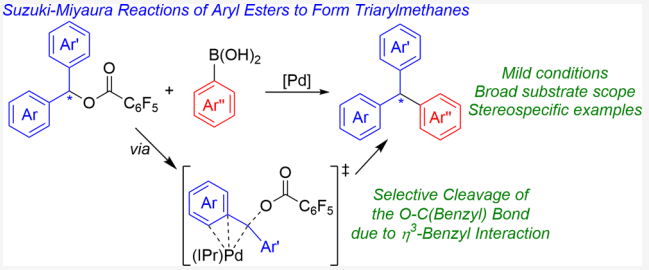
Synthesis of Triarylmethanes via Palladium-Catalyzed Suzuki–Miyaura Reactions of Diarylmethyl Esters

Amira H. Dardir, Irene Casademont-Reig, David Balcells,* Jonathan D. Ellefsen, Matthew R. Espinosa, Nilay Hazari,* and Nicholas E. Smith

Cite This: *Organometallics* 2021, 40, 2332–2344 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The synthesis of triarylmethanes via Pd-catalyzed Suzuki–Miyaura reactions between diarylmethyl 2,3,4,5,6-pentafluorobenzoates and aryl boronic acids is described. The system operates under mild conditions and has a broad substrate scope, including the coupling of diphenylmethanol derivatives that do not contain extended aromatic substituents. This is significant as these substrates, which result in the types of triarylmethane products that are prevalent in pharmaceuticals, have not previously been compatible with systems for diarylmethyl ester coupling. Furthermore, the reaction can be performed stereospecifically to generate stereoinverted products. On the basis of DFT calculations, it is proposed that the oxidative addition of the diarylmethyl 2,3,4,5,6-pentafluorobenzoate substrate occurs via an S_N2 pathway, which results in the inverted products. Mechanistic studies indicate that oxidative addition of the diarylmethyl 2,3,4,5,6-pentafluorobenzoate substrates to (IPr)Pd(0) results in the selective cleavage of the O–C(benzyl) bond in part because of a stabilizing η^3-interaction between the benzyl ligand and Pd. This is in contrast to previously described Pd-catalyzed Suzuki–Miyaura reactions involving phenyl esters, which involve selective cleavage of the C(acyl)–O bond, because there is no stabilizing η^3-interaction. It is anticipated that this fundamental knowledge will aid the development of new catalytic systems, which use esters as electrophiles in cross-coupling reactions.



INTRODUCTION

Triarylmethanes are common motifs in natural products,[1] fluorescent probes,[2] organic dyes,[3] metal ion sensors,[4] and active pharmaceutical ingredients.[5] For example, triarylmethanes have antiviral,[6] antituberculosis,[7] and antibreast cancer[8] properties (Figure 1). The most common method to synthesize triarylmethanes is through Lewis or Brønsted acid catalyzed Friedel–Crafts reactions of diarylmethanols or their derivatives with arenes; however, these reactions often have limited substrate scopes and poor selectivity.[5b] In recent years, a number of transition metal catalyzed $C(sp^2)–C(sp^3)$ cross-coupling reactions have been developed for the synthesis of triarylmethanes. These methods typically utilize nonclassical electrophiles, such as diarylmethyl ammonium salts,[9] sulfones,[10] and alcohol derivatives.[11] In particular, alcohol derivatives, for example, esters, are attractive as electrophiles for the synthesis of triarylmethanes because alcohols are abundant, stable, and diverse building blocks, which can easily be derivatized.[12]

In 2005, Kuwano et al. demonstrated that benzyl acetates can be used in Pd-catalyzed Suzuki–Miyaura reactions to generate diarylmethanes (Figure 2a).[13] Although this work was not extended to diarylmethyl esters, subsequent studies by Watson et al. and Jarvo et al. showed that diarylmethyl esters can be used in Ni-catalyzed Suzuki–Miyaura reactions to generate triarylmethanes stereospecifically (Figure 2b).[11,14] The later reactions are currently limited to electrophiles with extended aromatic systems, such as naphthyls and biaryls, and are not compatible with diphenylmethanol derivatives, which are prevalent in natural products and pharmaceuticals.[7,8b] Nevertheless, they are the first examples of a synthetically valuable transformation and are fundamentally interesting because of their selectivity. Specifically, the high yields of triarylmethane products suggest that the diarylmethyl esters undergo oxidative addition exclusively across the O–C(benzyl) bond (Figure 3a).[11,13,15] In contrast, depending on the catalyst and exact nature of the substrate some aryl esters can undergo oxidative addition across either the O–C(aryl) (Figure 3a)[16] or C(acyl)–O bond (Figure 3b),[17] to give either biaryl or ketone products, respectively, after transmetalation and reductive elimination. Furthermore, in some cases following C(acyl)–O bond cleavage a decarbonylative step can occur, which ultimately leads to biaryl products (Figure 3c).[18] At this stage, the exact reasons for the differences in selectivity are not clear, especially with regard to why the O–

Special Issue: Organometallic Solutions to Challenges in Cross-Coupling

Received: February 10, 2021
Published: May 27, 2021

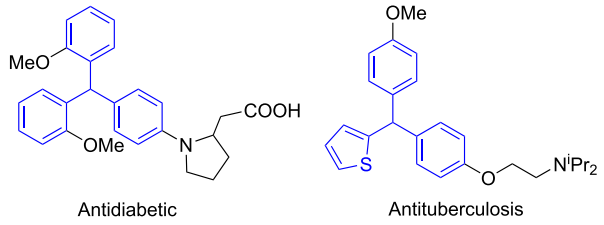


Figure 1. Examples of medicinally relevant triarylmethanes.

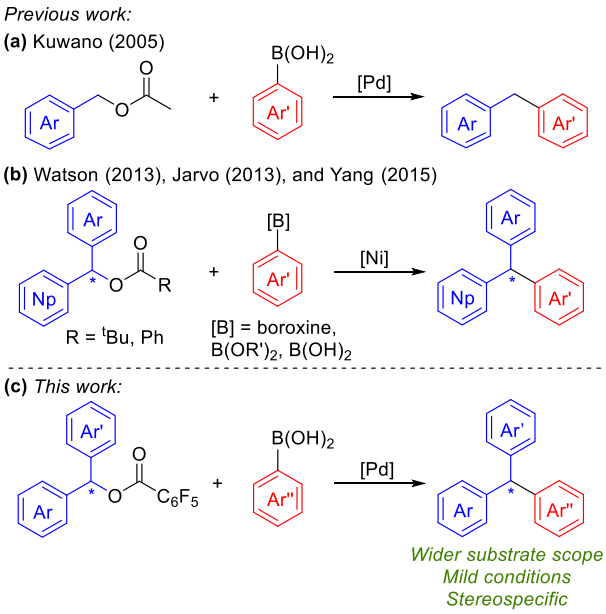


Figure 2. Summary of previous work on Suzuki−Miyaura reactions of diarylmethyl esters (a, b) and comparison to this work (c).[11,13,15d]

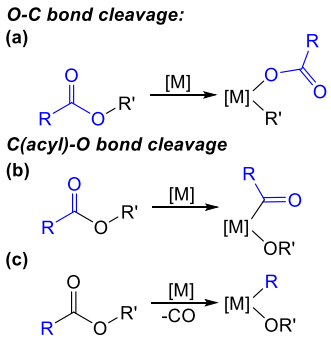


Figure 3. Bonds that can be cleaved in oxidative addition reactions involving esters.

C(benzyl) bonds of diarylmethyl esters are cleaved and not the C(acyl)−O bonds.

Recently, our group and others have reported Pd-catalyzed Suzuki−Miyaura reactions of phenyl esters in which the C(acyl)−O bond is selectively cleaved to generate ketones in high yields.[18c,19] Based in part on Kuwano et al.'s work with benzyl acetates,[13] we hypothesized that if the substrate was changed to a diarylmethyl ester then we could instead selectively cleave the O−C(benzyl) bond, which would ultimately lead to the formation of triarylmethanes. Herein, we report the first examples of Pd-catalyzed Suzuki−Miyaura reactions of diarylmethyl-2,3,4,5,6-pentafluorobenzoates to selectively generate triarylmethanes (Figure 2c). Importantly, the reaction is compatible with diphenylmethanol derivatives that do not contain extended aromatic substituents and enantioenriched diarylmethyl-2,3,4,5,6-pentafluorobenzoates can be coupled with high stereospecificity to give stereoinverted products. The latter observation, supported by DFT calculations, suggests that oxidative addition of the substrate to the (IPr)Pd(0) active catalyst occurs via an S_N2-type mechanism, and we were able to isolate the oxidative addition product from the reaction of a diarylmethyl-2,3,4,5,6-pentafluorobenzoate to an (IPr)Pd(0) complex. Additional DFT calculations demonstrate it is kinetically and thermodynamically more favorable to cleave the O−C(benzyl) bond of benzyl benzoate during oxidative addition to (IPr)Pd(0) in part due to an η^3-interaction between the benzyl group and the Pd. In contrast, it is kinetically and thermodynamically more favorable to cleave the C(acyl)−O bond of phenyl benzoate during oxidative addition to (IPr)Pd(0), which proceeds via a concerted mechanism. Overall, this work provides a notable synthetic advance due to the improved substrate scope for the formation of triarylmethanes and valuable fundamental information about selectivity in the cleavage of benzoates.

RESULTS AND DISCUSSION

Reaction Discovery and Development. In our preliminary work, we demonstrated that we could couple benzyl benzoate with phenyl boronic acid to selectively generate a diarylmethane product using (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl) (IPr = 1,3-bis(2,6-diisopropyl-phenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene) as a precatalyst (Figure 4). This is in agreement with Kuwano et al.'s results[13] and is indicative of selective cleavage of the O−C(R) (R = benzyl) bond. It is notable that when benzyl benzoate is replaced with phenyl benzoate under the same reaction conditions that we selectively form benzophenone, which is consistent with selective cleavage of the C(acyl)−O bond (Figure 4). Our results with benzyl benzoate suggested that we could leverage the observed cleavage of the O−C(R) (R = benzyl) bond to develop a selective

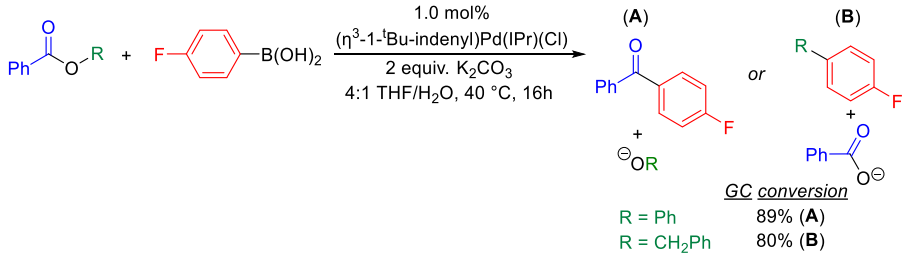


Figure 4. Comparison of Pd-catalyzed Suzuki−Miyaura reactions of phenyl and benzyl benzoate using (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl) as the precatalyst under identical conditions.

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

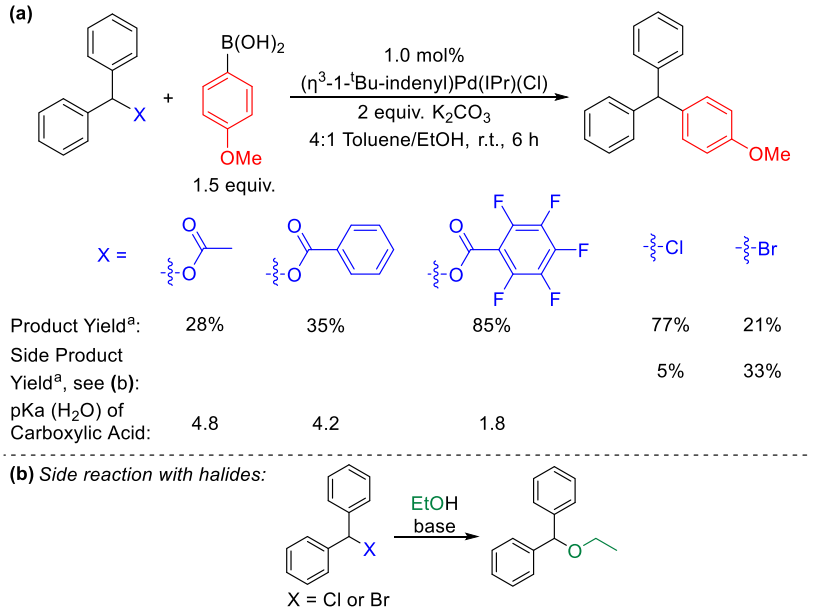
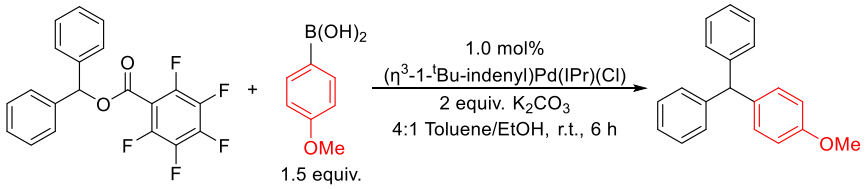


Figure 5. (a) Pd-catalyzed Suzuki−Miyaura reactions of diphenylmethyl esters and halides and (b) side reaction observed with aryl halides. [a]Conditions: diphenylmethyl−X (0.05 mmol), 4-methoxyphenylboronic acid (0.075 mmol), K_2CO_3 (0.1 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl) (0.0005 mmol), toluene (0.4 mL), and EtOH (0.1 mL). Yields are an average of two runs determined by GC-FID using the conversion of starting material to product.

Table 1. Optimization Table for the Pd-Catalyzed Suzuki−Miyaura Reaction of Diarylmethyl 2,3,4,5,6-Pentafluorobenzoate with 4-Methoxyphenylboronic Acid



entry	deviation from optimized conditions	GC yield[a]
1	no change	85%
2	no precatalyst	0%[b]
3	24 h instead of 6 h	>99%
4	40 °C instead of r.t. and 4 h instead of 6 h	>99%
5	(η^3-cinnamyl)Pd(IPr)Cl instead of (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl	73%
6	PEPPSI-IPr instead of (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl	64%
7	0.5 mol % [Pd(IPr)(μ-Cl)Cl]$_2$ instead of (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl	86%
8	SIPr instead of IPr	62%
9	IMes instead of IPr	16%
10	IPr*^{OMe} instead of IPr	40%
11	PCy_3 instead of IPr	2%[c]
12	XPhos instead of IPr	3%
13	SPhos instead of IPr	46%[d]
14	toluene only	<1%
15	H_2O instead of EtOH	69%
16	MeOH instead of EtOH	89%[e]
17	^{i}PrOH instead of EtOH	56%

[a]Conditions: diphenylmethyl ester (0.05 mmol), 4-methoxyphenylboronic acid (0.075 mmol), base (0.1 mmol), precatalyst (0.0005 mmol), solvent (0.5 mL). Yields are an average of two runs determined by GC-FID using the conversion of starting material to product. [b]Reached 64% conversion to $F_5C_6COOC_2H_5$ and 36% starting material remaining. [c]Reached 67% conversion to $F_5C_6COOC_2H_5$. [d]Reached 32% conversion to $F_5C_6COOC_2H_5$. [e]Reached 9% conversion to $F_5C_6COOCH_3$.

method for the synthesis of synthetically valuable triarylmethanes from diphenylmethyl esters through the careful selection of the leaving group on the ester and the optimization of the reaction conditions.

We initially synthesized diphenylmethyl-acetate, -benzoate, and -2,3,4,5,6-pentafluorobenzoate via a straightforward reaction between diarylmethanol and the appropriate carboxylic acid (see the Supporting Information).[17a] Subsequently, using 1 mol

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

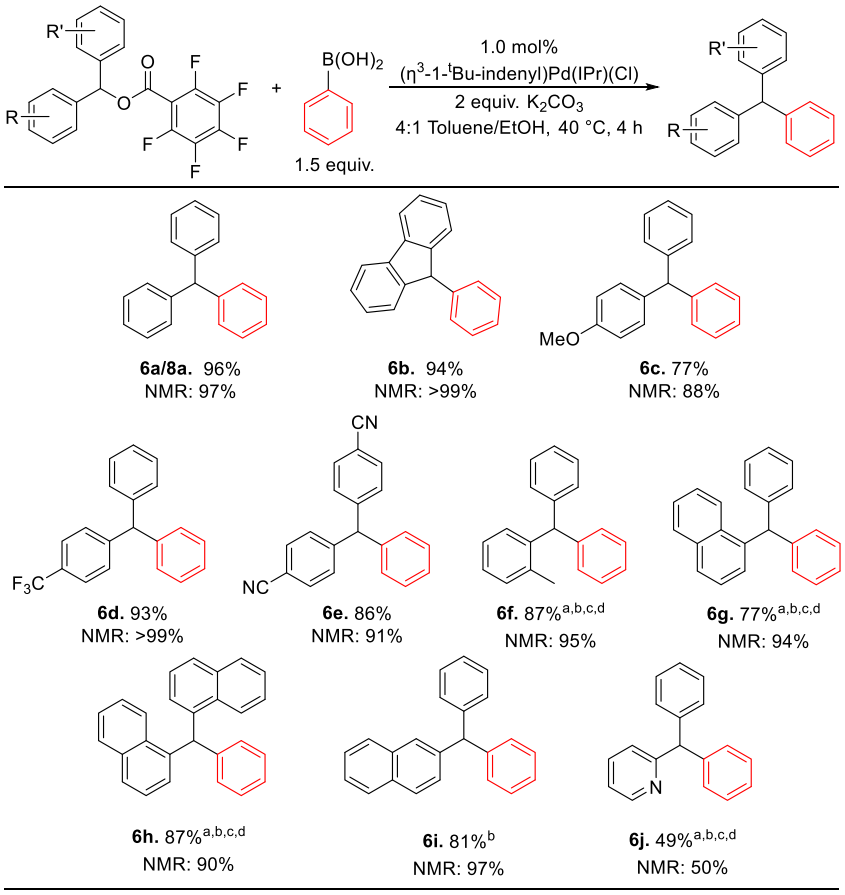


Figure 6. Isolated and NMR yields for Pd-catalyzed Suzuki−Miyaura reactions of diarylmethyl 2,3,4,5,6-pentafluorobenzoates with (4-methoxyphenyl)boronic acid. Conditions for isolated yields: ester (0.2 mmol), phenylboronic acid (0.3 mmol), K_2CO_3 (0.4 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl (0.0002 mmol), toluene (1.6 mL), and ethanol (0.4 mL). Conditions for NMR yields: ester (0.05 mmol), phenylboronic acid (0.075 mmol), K_2CO_3 (0.1 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl (0.0005 mmol), toluene (0.4 mL), and ethanol (0.1 mL). NMR yields were determined using 1,2,4,5-tetramethylbenzene as an internal standard. [a]Using 4 mol % (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl instead of 1 mol %. [b]Reacted for 16 h instead of 4 h. [c]Reacted at 80 °C instead of 40 °C. [d]Using water instead of ethanol.

% of (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl) as the precatalyst, a 4:1 mixture of toluene/ethanol as the solvent, and 2 equiv of K_2CO_3 as the base, we assessed these esters as substrates in Suzuki−Miyaura reactions with 4-methoxyphenylboronic acid at room temperature (Figure 5a). After 6 h, Suzuki−Miyaura reactions with diphenylmethyl-acetate and -benzoate give 28 and 35% of (diphenyl)(4-methoxyphenyl) methane, respectively, while the reaction with diphenylmethyl-2,3,4,5,6-pentafluorobenzoate yields 85% of the desired product. The observed trend in reactivity of the diphenylmethyl esters correlates with the pK_a's of the corresponding carboxylic acids, with acetic acid and benzoic acid having similar pK_a values and 2,3,4,5,6-pentafluorobenzoic acid having a much lower pK_a value.[20] We suggest that the pK_a values are reflective of the substrates relative ability to be activated by the Pd center via an S_N2-type mechanism, as well as the strength of the interaction between Pd and the anion (*vide infra*).[15i] These reactions are some of the first examples of Suzuki−Miyaura reactions of diphenylmethanol derivatives that do not contain extended aromatic substituents.[15k,21] We also compared the reactions using esters as electrophiles to those using diphenylmethyl chloride and diphenylmethyl bromide as substrates (Figure 5a). Although diphenylmethyl chloride gives a high yield (77%), the reaction results in the formation of (ethyl)(diphenylmethyl)ether as a side product (~5%) (Figure 5b), presumably as a result of base-mediated nucleophilic substitution of the alcohol solvent on the halide. In agreement with this proposal, the more reactive diphenylmethyl bromide gives an even lower yield (21%) and an increased quantity of the ether side product (~33%).

We performed a series of Suzuki−Miyaura reactions between diphenylmethyl 2,3,4,5,6-pentafluorobenzoate and 4-methoxyphenylboronic acid to evaluate the factors that are important in obtaining high yields. In the absence of precatalyst no product is observed, and the majority of the starting material is converted to ethyl 2,3,4,5,6-pentafluorobenzoate, indicating that the diphenylmethyl 2,3,4,5,6-pentafluorobenzoate is not stable under the reaction conditions (Table 1, entry 2). In the presence of (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl), the desired coupling outcompetes the side reaction and quantitative conversion occurs in 24 h (entry 3). Increasing the temperature to 40 °C, results in a quantitative yield after 4 h (entry 4). Other common precatalysts, such as (η^3-cinnamyl)Pd(IPr)Cl and PEPPSI-IPr, give moderate but reduced yields relative to that with (η^3-1-^{t}Bu-indenyl)Pd(IPr)(Cl) likely due to their slower rates of activation under our reaction conditions (entries 5 and 6).[22] A similar yield was obtained when (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl was replaced with [Pd(IPr)(μ-Cl)Cl]$_2$, but this precatalyst was not pursued further, as it lacks a precursor that can be readily used for ligand screening (entry 7).[23] Changing the ancillary ligand to other frequently utilized NHC ligands, such as SIPr, IMes, and

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

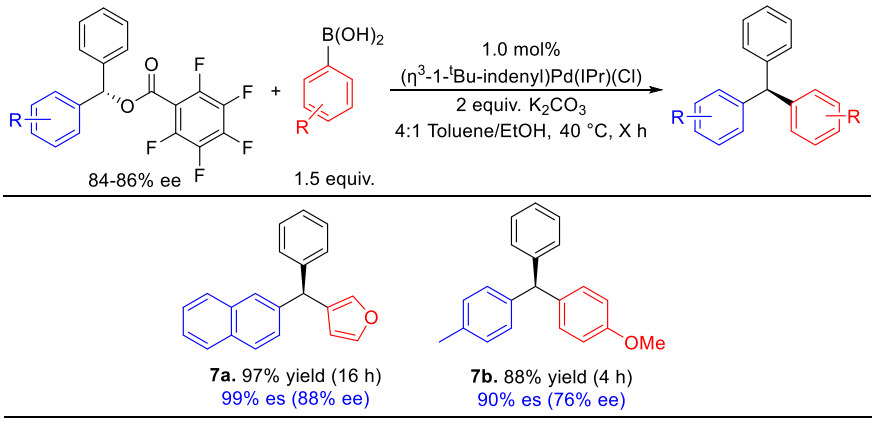


Figure 7. Isolated yields and enantioselectivity for Pd-catalyzed stereospecific Suzuki−Miyaura reactions of diarylmethyl 2,3,4,5,6-pentafluorobenzoates. Conditions for isolated yields enantioenriched ester (0.05 mmol), arylboronic acid (0.075 mmol), K_2CO_3 (0.1 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl (0.0005 mmol), toluene (0.4 mL), and ethanol (0.1 mL).

IPr*^{OMe} (entries 8−10), or phosphine ligands, such as PCy_3, XPhos, or SPhos (entries 11−13), gives reduced yields compared to IPr. We have observed similar trends in related Suzuki−Miyaura reactions involving phenyl benzoates.[19f] The choice of base is also crucial, and although high yields are obtained with K_2CO_3, lower yields are observed with other common inorganic bases, such as K_3PO_4 or Na_2CO_3 (see the Supporting Information). In the absence of a protic cosolvent, no product is observed (entry 14). Although the reaction worked comparably in the presence of methanol or ethanol (entries 16 and 1), faster transesterification occurs in methanol to generate the methyl 2,3,4,5,6-pentafluorobenzoate by-product, which unnecessarily consumes starting material. Furthermore, the yield suffered when water or isopropanol is used instead of ethanol (entries 15 and 17). The role of the alcohol cosolvent may be in solubilizing the reagents, assisting in precatalyst activation,[22b] or facilitating transmetalation by displacing the carboxylate with an alkoxy ligand.[13]

Substrate Scope. Given the success of Suzuki−Miyaura reactions involving diphenylmethyl 2,3,4,5,6-pentafluorobenzoate, we explored the substrate scope for the coupling of a range of diarylmethyl 2,3,4,5,6-pentafluorobenzoates with phenylboronic acid under our optimized conditions (Figure 6). Electron-neutral diarylmethyl esters (**6a** and **6b**), including fluorene-9-ester (**6b**), result in high yields of the desired product, 96 and 94%, respectively. The latter result is notable because fluorenes are important motifs in biologically active molecules,[24] as monomers in polymer chemistry,[25] and as dyes for solar cell applications, and our system provides a facile method for functionalization.[26] Additionally we were able to generate **6a** on a 1 mmol scale in 95% isolated yield (see the Supporting Information), which demonstrates that our method is scalable. The reaction is also compatible with esters containing electron-donating (**6c**) and -withdrawing (**6d** and **6e**) substituents. This includes the doubly cyano-substituted ester (**6e**) which is coupled in 86% yield. This is significant because cyano groups often coordinate to Pd and inhibit catalysis. It is more difficult to couple substrates with ortho-substitution on an aryl group of the diarylmethyl ester, such as **6f**. Even with higher precatalyst loading (4 mol %) and longer reactions times (16 h), when ethanol is used as the cosolvent, transesterification to generate the ethyl 2,3,4,5,6-pentafluorobenzoate competes with the desired cross-coupling reaction, and only a 40% NMR yield of cross-coupled product is observed. However, an 87% yield is obtained by increasing the precatalyst loading to 4 mol %, the temperature to 80 °C, the time to 16 h, and switching to water as the cosolvent to prevent transesterification. Consistent with the challenges in coupling ortho-substituted substrates, (1-naphthyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate (**6g**) gives minimal yield under the optimized conditions (6% NMR yield). When more forcing conditions are utilized, with the use of water in place of ethanol as a cosolvent, a yield of 77% is obtained. Under the same conditions, the even more sterically bulky bis(1-naphthyl)methyl 2,3,4,5,6-pentafluorobenzoate (**6h**) gives an 87% yield. In contrast, we are able to couple the less sterically bulky substrate (2-naphthyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate (**6i**) without major modification to our optimized conditions (16 h instead of 4 h). Pyridyl groups are common in pharmaceuticals but are often difficult substrates for cross-coupling reactions due to coordination of the heterocycle to Pd.[27] Using our more forcing conditions, including the replacement of ethanol with water as a cosolvent, we can couple a 2-pyridyl containing electrophile (**6j**) in 49%.

Enantiomers of chiral molecules often have different biological activity due to variations in their binding affinity with chiral targets.[28] Therefore, there are advantages to accessing single enantiomers of triarylmethanes.[1] We hypothesized that our method could be compatible with producing single enantiomers of triarylmethanes if enantioenriched diarylmethyl 2,3,4,5,6-pentafluorobenzoates esters were utilized as substrates. The enantioenriched substrates, (*S*)-(2-naphthyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate and (*S*)-(4-methylphenyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate, were readily synthesized from the appropriate (*S*)-diarylmethanol by following a literature procedure involving the reaction of an *in situ* generated phenylzinc species and an aldehyde catalyzed by a chiral pyrrolidine ligand (see the Supporting Information).[29] The subsequent coupling of (*S*)-(2-naphthyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate with 3-furylboronic acid under our optimized conditions results in the formation of triarylmethane **7a** in 97% yield and 99% es, indicating that the reaction proceeds with high enantiospecificity (Figure 7). Comparison of the polarimetry data of isolated **7a** ($[\alpha]_D^{20}$ −23.25 (*c* 0.400, $CDCl_3$)) with literature data ($[\alpha]_D^{29}$ −22.0 (*c* 1.00, $CDCl_3$))[11a] suggests the formation of the (*R*)-isomer, which is consistent with a pathway involving inversion. Similarly, the reaction of (*S*)-(4-methylphenyl)(phenyl)methyl 2,3,4,5,6-pentafluorobenzoate with (4-methoxy)phenylboronic

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

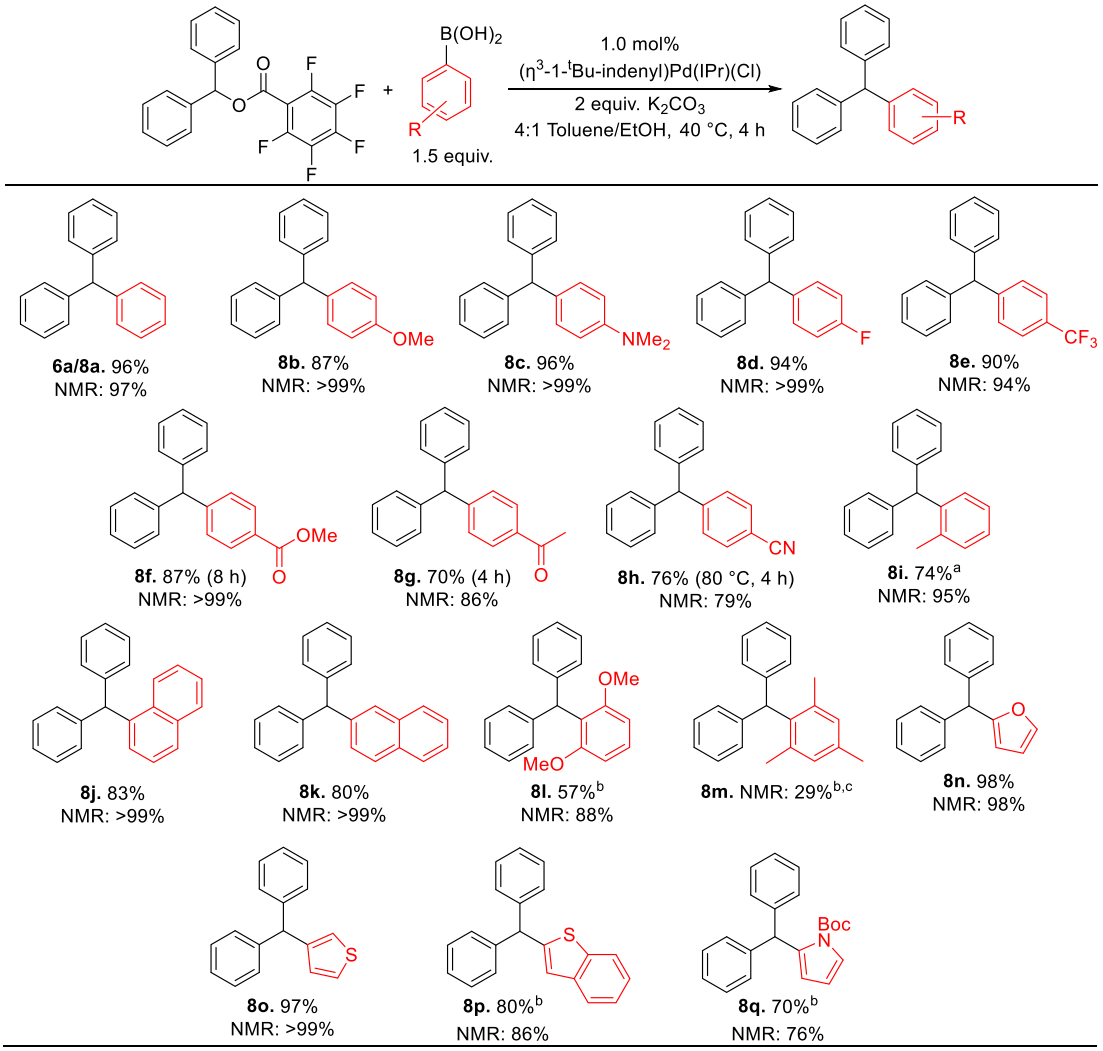


Figure 8. Isolated and NMR yields for Pd-catalyzed Suzuki−Miyaura reactions of diphenylmethyl 2,3,4,5,6-pentafluorobenzoate with boronic acids. Conditions for isolated yields: ester (0.2 mmol), boronic acid (0.3 mmol), K_2CO_3 (0.4 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl (0.0002 mmol), toluene (1.6 mL), and ethanol (0.4 mL). Conditions for NMR yields: diphenylmethyl 2,3,4,5,6-pentafluorobenzoate ester (0.05 mmol), (4-methoxyphenyl)boronic acid (0.075 mmol), K_2CO_3 (0.1 mmol), (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl (0.0005 mmol), toluene (0.4 mL), and ethanol (0.1 mL). NMR yields were determined using 1,2,4,5-tetramethylbenzene as an internal standard. [a]Reacted for 8 h instead of 4 h. [b]Reacted for 16 h instead of 4 h. [c]Using 4 mol % (η^3-1-^{t}Bu-indenyl)Pd(IPr)Cl instead of 1 mol %.

acid generates enantioenriched triarylmethanes **7b** in 88% yield and 90% es. Given that we propose the mechanism of the reaction involves oxidation addition, transmetalation, and reductive elimination (*vide infra*), the stereochemical inversion of the (*S*)-diarylmethyl 2,3,4,5,6-pentafluorobenzoates to the (*R*)-triarylmethanes suggests that oxidative addition proceeds via an S_N2 pathway. This is because transmetalation and reductive elimination typically occur with retention of configuration in Suzuki−Miyaura reactions;[30] therefore, the stereochemistry of the product is likely based on oxidative addition. Our work is consistent with previous studies utilizing NHC−Ni catalysts for the stereoselective coupling of naphthyl and biaryl diarylmethyl esters, which also proceed with inversion and propose that oxidative addition is responsible for the observed stereochemistry.[11a,15i]

The scope of the boronic acid coupling partner was evaluated using diphenylmethyl 2,3,4,5,6-pentafluorobenzoate as the electrophile (Figure 8). The reaction is compatible with electron-neutral, -donating, and -withdrawing aryl boronic acids (**8a−h**). In a noteworthy result, 4-methylester- (**8f**) and 4-acetyl-phenylboronic acids (**8g**) give yields of 87 and 70%, respectively, which are not only electron-withdrawing but can be further functionalized, for example, via nucleophilic addition reactions.[31] The reaction is tolerant of ortho-substituted aryl boronic acids (**8i−j**). However, while 2,6-dimethoxyphenyl boronic acid (**8l**) could be coupled in high yield (although difficulty in isolation resulted in a lower isolated yield), minimal product is observed with 2,4,6-trimethylphenyl boronic acid (**8m**) even with higher precatalyst loadings. The 1- and 2-naphthyl boronic acids (**8j** and **8k**) are coupled in yields of 83 and 80%, respectively. Heteroaryl-substituted triarylmethanes derivatives are common in pharmaceutical compounds,[7b,32] but cross-coupling reactions of diarylmethanol derivatives with heteroaryl boronic acids are limited,[11a,33] possibly due to the instability of heteroaryl nucleophiles.[34] Our system is able to couple 2-furyl (**8n**) and 3-thiophene (**8o**) boronic acids in yields of 98 and 97%, respectively, but 2-substituted thienyl boronic acid gives low conversion (see the Supporting Information). Benzo[*b*]thien-2-yl- (**8p**) and boc-protected pyrrole- (**8q**) boronic acids give yields of 80 and 70%, respectively, but

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

require longer reaction times. Unfortunately, pyridyl boronic acids could not be coupled (see the Supporting Information), likely due to protodeborylation or coordination of the nitrogen atom of the pyridine ring to the catalyst.

Overall, our substrate scope demonstrates that we have developed a mild and general method for the synthesis of triarylmethanes, containing both extended and nonextended aromatic groups, from readily available diarylmethyl esters. In particular, the ability of our system to couple diphenylmethyl esters that do not contain extended aromatic substrates is significant, as these substrates have not previously been utilized. Furthermore, our system is tolerant of a variety of different functional groups, is compatible with heterocyclic substrates and is stereospecific. As a result, we expect that it will be valuable for the synthesis of medicinally relevant triarylmethanes.

Mechanistic Studies. The high yields of triarylmethanes that are observed in Suzuki−Miyaura reactions involving diarylmethyl 2,3,4,5,6-pentafluorobenzoates indicate that the reaction must be proceeding with high selectivity, consistent with the selective cleavage of the O−C(benzyl) bond. Furthermore, there is no evidence for cleavage of the C(acyl)−O bond, which presumably occurs readily when a phenyl ester is utilized instead of a benzyl ester (Figure 4). Previous studies have hypothesized that oxidative addition to Pd(0) is responsible for the differences in selectivity between phenyl- and benzyl-esters, but there are few well-defined examples of the oxidative addition of these substrates and the reaction pathways (e.g., concerted versus S_N2) have not been probed.[35] In seminal work, Yamamoto et al. demonstrated differences in oxidative addition for aryl- and benzyl-trifluoroacetates to phosphine ligated Pd(0) complexes.[15b,35b,c] Specifically, aryl trifluoroacetates were shown to oxidatively add across the C(acyl)−O bond, while benzyl trifluoroacetates underwent oxidative addition across the O−C(benzyl) bond. However, the mechanistic origins for this difference were not elucidated and their applicability to our system, which features a different ester and ancillary ligand, was unclear. Therefore, we studied the oxidative addition of the type of esters used in this work, such as phenyl- and benzyl-benzoates, to the proposed active catalytic species (IPr)Pd(0).[36]

Initial evaluation of the oxidative addition of phenyl benzoate with the Pd(0) source (IPr)Pd(0)(styrene)$_2$ resulted in slow decomposition to Pd black and (IPr)$_2$Pd. The use of more electron-withdrawing electrophiles is known to result in more facile oxidative addition and also stabilize the resulting transition metal complexes.[37] In this case, treatment of phenyl 2,3,4,5,6-pentafluorobenzoate with (IPr)Pd(styrene)$_2$ at room temperature resulted in the slow formation of new product(s) as determined by NMR spectroscopy, but this was followed by decomposition, which prevented full characterization. We hypothesized that an ortho-coordinating ligand on the benzoate group, such as diphenylphosphine, would stabilize the putative three-coordinate oxidative addition complex by binding to the open coordination site on the metal center. The reaction of phenyl 2-(diphenylphosphino)benzoate with (IPr)Pd(styrene)$_2$ at room temperature resulted in the clean formation of a product, **1**, with a single resonance in the ^{31}P NMR spectrum at 50.4 ppm, which was isolated in 75% yield (Figure 9a). X-ray crystallography confirmed that **1** is the result of oxidative addition of the C(acyl)−O bond to (IPr)Pd(0) with coordination of the phosphine (Figure 9b). Interestingly, the crystal structure shows that the C(acyl) ligand is trans to the OPh ligand and that the phosphine ligand is trans to the IPr

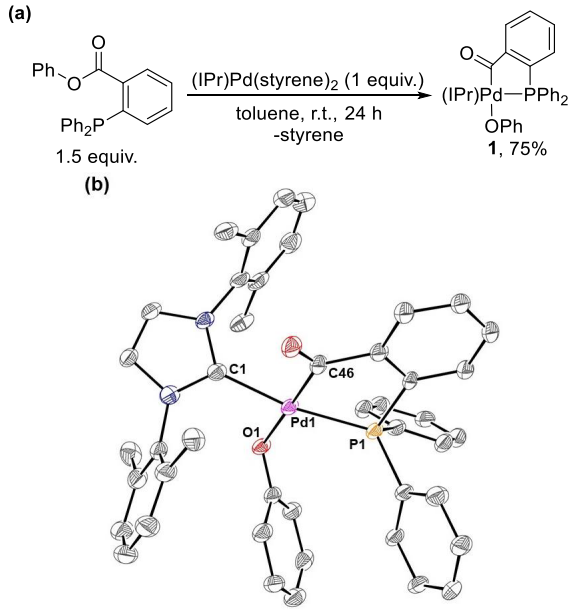


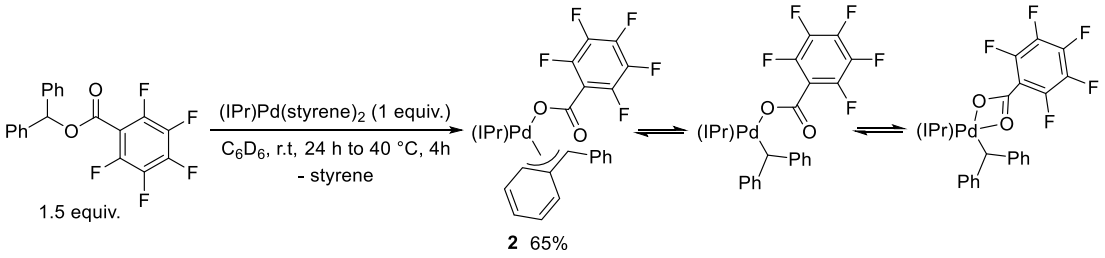
Figure 9. (a) Oxidative addition of phenyl 2-(diphenylphosphino)-benzoate to (IPr)Pd(0) to form **1**. (b) ORTEP (30% probability) of **1**. Hydrogen atoms and methyl groups associated with the isopropyl substituents of IPr omitted for clarity. Selected bond distances (Å) and angles (deg): Pd1−C1 1.971(9), Pd1−C46 1.975(7), Pd1−P1 2.287(2), Pd1−O1 2.107(6); C46−Pd1−O1 90.2(2), C1−Pd1−C46 89.5(3), P1−Pd1−O1 96.0(1), P1−Pd1−C1 84.0(2).

ligand. It would be expected, however, that after concerted oxidative addition the C(acyl) ligand and OPh ligand would be cis to one another, which suggests that the ligands can rearrange on the metal center either by decoordination of the phosphine or OPh ligands. Nevertheless, the formation of **1** indicates that (IPr)Pd(0) is capable of facile cleavage of the C(acyl)−O bond of a phenyl ester. Notably, this is the first example of a well-defined oxidative addition product from the addition of a phenyl ester to Pd(0) that does not undergo decarbonylation.

Next, we investigated the reaction of benzyl benzoate derivatives with (IPr)Pd(styrene)$_2$. In an analogous fashion to the reaction with the unsubstituted phenyl benzoate, the reaction of benzyl benzoate with (IPr)Pd(styrene)$_2$ resulted in slow decomposition to Pd black and (IPr)$_2$Pd. However, when we performed the reaction of (IPr)Pd(styrene)$_2$ with 2,3,4,5,6-pentafluorobenzoate, a substrate used in catalysis, one new product, **2**, is formed and isolated in a 65% yield (Scheme 1).[38] In the ^{1}H NMR spectrum of **2**, the resonance associated with the methine proton of the benzyl group is shifted upfield relative to that of the free ester (4.78 vs 7.19 ppm), consistent with the presence of a metal center in close proximity to the methine proton.[39] The ^{13}C NMR spectrum includes a resonance at 177.0 ppm and two new peaks are observed in the IR spectrum at 1633 and 1343 cm^{-1}. This is indicative of the presence of a carbonyl group. Overall, our NMR data suggests that **2** is the oxidative addition product from cleavage of the O−C(benzyl) bond of 2,3,4,5,6-pentafluorobenzoate. However, we were unable to identify the exact structure of **2** despite repeated unsuccessful attempts to obtain single crystals for X-ray diffraction. Possible structures of **2** include those with the diarylmethyl ligand binding in either an η^1- or η^3-fashion, and the 2,3,4,5,6-pentafluorobenzoate ligand binding in a κ^1- or κ^2-manner (Scheme 1). Furthermore, it is possible that the 2,3,4,5,6-pentafluorobenzoate anion is not coordinated to Pd and that an

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

Scheme 1. Formation of Oxidative Addition Complex (IPr)Pd(CHPh$_2$)(OOCC$_6$F$_5$) (2) and Possible Structures of 2



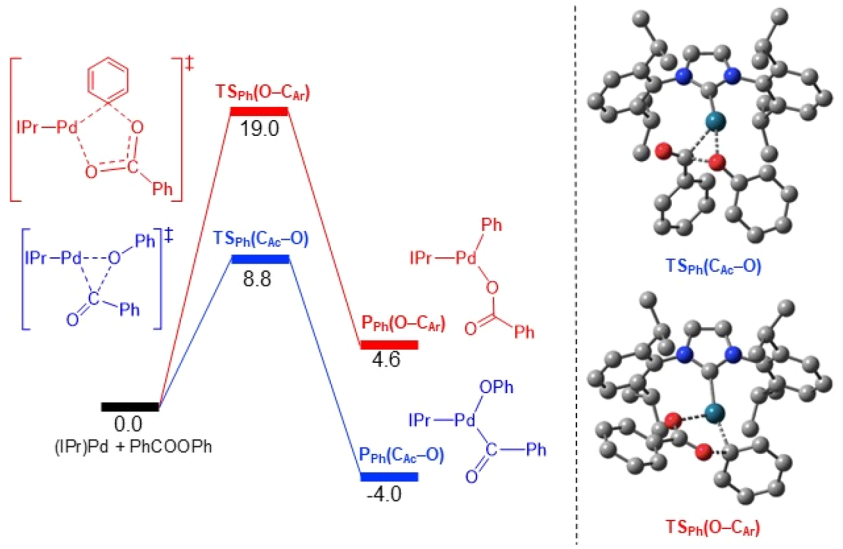


Figure 10. DFT calculations comparing the oxidative addition of phenyl benzoate via C(acyl)−O and O−C(aryl) bond cleavage. Relative energies in kcal/mol.

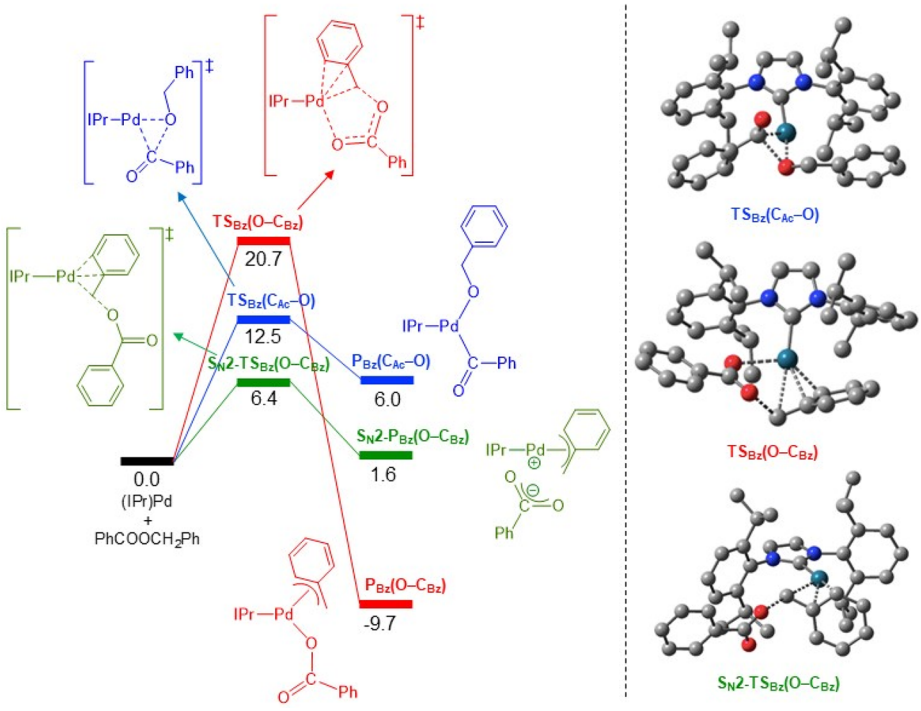
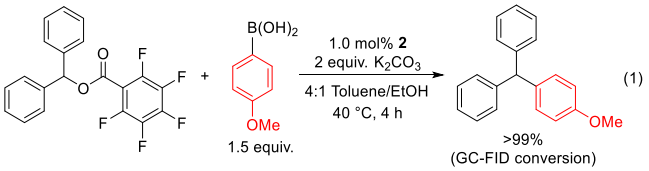


Figure 11. DFT calculations comparing the oxidative addition of benzyl benzoate via concerted C(acyl)−O and O−C(aryl) bond cleavage and also an S_N2 pathway. Relative energies in kcal/mol.

ion pair is generated. Nevertheless, our results indicate that oxidative addition of 2,3,4,5,6-pentafluorobenzoate with cleavage of the O−C(benzyl) bond is facile, and we suggest that this is the first step in catalysis. Consistent with this proposal, when **2** is

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

used as a catalyst in the coupling of diphenylmethyl 2,3,4,5,6-pentafluorobenzoate with (4-methoxy)phenylboronic acid under our optimized conditions (eq 1), complete conversion to (2- methoxyphenyl)(diphenyl)methane is observed, indicating that **2** is a kinetically competent catalyst.



(1)

DFT calculations were performed to help us understand the observed selectivity in the oxidative addition of phenyl- and benzyl-benzoates to (IPr)Pd(0).[40] Phenyl- and benzyl-benzoate were used as model substrates given our results in Figure 4, showing that they undergo selective cleavage of the C(acyl)−O bond and O−C(benzyl) bond, respectively. For both substrates, the concerted oxidative addition pathway was computed for the heterolytic cleavage of the C(acyl)−O and the O−C(aryl) bonds. In the case of benzyl benzoate, an S_N2 pathway was also calculated for the cleavage of the O−C(benzyl) bond.

The oxidative addition transition state for C(acyl)−O cleavage in phenyl benzoate, $\mathbf{TS_{Ph}(C_{Ac}–O)}$, is shown in Figure 10. In addition to the C(acyl)−O bond cleavage (1.71 Å), this transition state also involves the concerted formation of the Pd−C(acyl)Ph (2.08 Å) and Pd−OPh (2.16 Å) bonds. The three atoms involved in the bond rearrangement form a three-membered Pd−O−C metallacycle, consistent with literature precedent.[17a] In contrast, the transition state for O−C(aryl) bond cleavage, in phenyl benzoate $\mathbf{TS_{Ph}(O–C_{Ar})}$, has a five-membered metallacycle geometry, in which one of the two carboxylate O atoms breaks the bond with the Ph ring (2.04 Å), whereas the other forms a new bond with Pd (2.20 Å). The full relaxation of these two transition states to the oxidative addition products yields the complexes $\mathbf{P_{Ph}(C_{Ac}–O)}$ and $\mathbf{P_{Ph}(O–C_{Ar})}$ with the expected Ph(O)C−Pd−OPh and Ph(O)CO−Pd−Ph moieties, respectively (Figure 10).[41] Importantly, the cleavage of the C(acyl)−O bond in phenyl benzoate is both kinetically (8.8 vs 19.0 kcal/mol) and thermodynamically (−4.0 vs 4.6 kcal/mol) preferred compared with cleavage of the O−C(aryl) bond, consistent with our experimental results (Figure 4).

The concerted transition states associated with cleavage of the C(acyl)−O and O−C(benzyl) bond of benzyl benzoate are shown in Figure 11, along with the transition state associated with cleavage of the O−C(benzyl) bond via an S_N2 mechanism. The geometry of $\mathbf{TS_{Bz}(C_{Ac}–O)}$ is very similar to $\mathbf{TS_{Ph}(C_{Ac}–O)}$, with the cleavage and formation of the C(acyl)−O (1.96 Å), Pd−C(acyl)Ph (2.02 Å), and Pd−OBz (2.11 Å) bonds in a three-membered palladacycle. The transition state for O−C(aryl) bond cleavage, $\mathbf{TS_{Bz}(O–C_{Bz})}$, is also similar to $\mathbf{TS_{Ph}(O–C_{Ar})}$, involving both O atoms of the carboxylate group, one cleaving the bond to the benzyl (1.99 Å), and the other forming a new bond with Pd (2.41 Å). However, $\mathbf{TS_{Bz}(O–C_{Bz})}$ has a distinct feature. Specifically, there is an η^3-interaction between the metal center and the benzyl moiety, with Pd−C interatomic distances of 2.71, 2.34, and 2.17 Å for the C_{Bz}, C_{ipso}, and C_{ortho} atoms, respectively.[42] This interaction becomes a covalent η^3-bond in the $\mathbf{P_{Bz}(O–C_{Bz})}$ product, with distances shortened to 2.09, 2.27, and 2.39 Å, respectively. This is likely the main reason why the $\mathbf{P_{Bz}(O–C_{Bz})}$ product is lower in energy than the $\mathbf{P_{Bz}(C_{Ac}–O)}$ product (−9.7 vs 6.0 kcal/mol), although the transition state energy associated with $\mathbf{TS_{Bz}(C_{Ac}–O)}$ is still lower than that observed for $\mathbf{TS_{Bz}(O–C_{Bz})}$ (12.5 vs 20.7 kcal/mol).

The cleavage of the O−C(benzyl) bond can also occur via an S_N2 pathway. The S_N2 mechanism follows a lower energy pathway than either the concerted O−C(benzyl) or C(acyl)−O bond cleavage, as the barrier associated with the $\mathbf{S_N2\text{-}TS_{Bz}(O–C_{Bz})}$ transition state, 6.4 kcal/mol, is the lowest found for this substrate (Figure 11). The two main structural features of $\mathbf{S_N2\text{-}TS_{Bz}(O–C_{Bz})}$ are as follows: (1) The η^3-interaction between the metal center and the C_{Bz} (2.32 Å), C_{ipso} (2.29 Å), and C_{ortho} (2.25 Å) atoms is similar to that of the concerted $\mathbf{TS_{Bz}(O–C_{Bz})}$ transition state. (2) A linear arrangement exists between the forming Pd−C_{Bz} (2.32 Å) and the breaking C_{Bz}−O (2.08 Å) bonds, with a Pd−C_{Bz}−O angle of 173.6°, and C_{Bz} adopts a distorted trigonal bipyramid geometry. The preference for the S_N2 pathway is in agreement with the inversion of configuration observed in the Pd-catalyzed Suzuki−Miyaura reactions of enantioenriched (diaryl)methyl 2,3,4,5,6-pentafluorobenzoate (Figure 7), as well as that seen in the literature with (NHC)Ni catalysts.[11b,15i] The product of the S_N2 pathway, $\mathbf{S_N2\text{-}P_{Bz}(O–C_{Bz})}$, is an ion pair between the (IPr)Pd(η^3-Bz)$^+$ cation and the $PhCO_2^-$ anion (with a natural charge $q = \pm 0.78$ value). This ion pair is more stable than the $\mathbf{P_{Bz}(C_{Ac}–O)}$ complex (1.6 vs 6.0 kcal/mol) and can be further stabilized by rearranging into the $\mathbf{P_{Bz}(O–C_{Bz})}$ complex (1.6 vs −9.7 kcal/mol).[43] Thus, O−C(benzyl) cleavage is both kinetically and thermodynamically preferred over C(acyl)−O cleavage. Overall, the computational results explain the experimental observation that for phenyl benzoate the C(acyl)−O bond is cleaved, whereas for benzyl benzoate the O−C(benzyl) bond is cleaved.

In our experimental work, we demonstrated that a Suzuki−Miyaura reaction with diphenylmethyl 2,3,4,5,6-pentafluorobenzoate is more efficient than the corresponding reaction with diphenylmethyl benzoate (Figure 5). To investigate this observation, the transition state for cleavage of O−C(benzyl) bond of benzyl 2,3,4,5,6-pentafluorobenzoate via an S_N2-type oxidative addition pathway was calculated using DFT. The barrier is 2.1 kcal/mol lower in energy than that of the benzyl benzoate consistent with our experimental results (Figure 12). However, in both cases the barrier for oxidative addition is very low (4.3 and 6.4 kcal/mol), suggesting that oxidative addition is facile. The S_N2 product of the oxidative addition of benzyl 2,3,4,5,6-pentafluorobenzoate to (IPr)Pd(0), $\mathbf{P_{FBz}(O–C_{Bz})}$, is

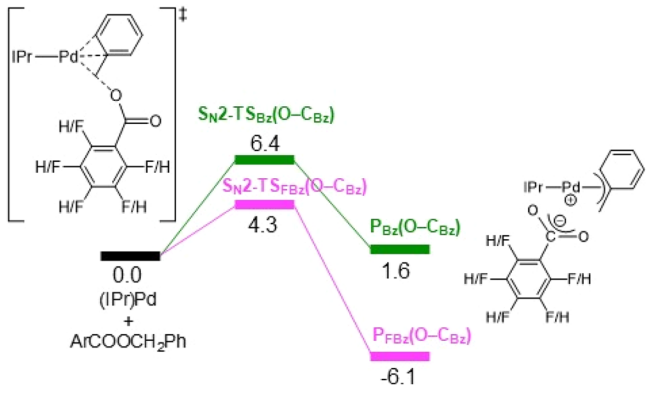


Figure 12. DFT calculations comparing the oxidative addition of the O−C(benzyl) bond in benzyl benzoate and benzyl 2,3,4,5,6-pentafluorobenzoate to (IPr)Pd(0). Relative energies are given in kcal/mol.

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

also an ion pair (i.e., (IPr)Pd(η^3-FBz)$^+$PhCO$_2^-$, with q = ±0.82e), which is significantly more stable than that formed by the nonfluorinated substrate (−6.1 vs 1.6 kcal/mol), likely due to the fluorides promoting charge separation.[44] We propose that the outersphere 2,3,4,5,6-pentafluorobenzoate anion in $\mathbf{P_{FBz}(O-C_{Bz})}$ may lead to faster transmetalation, the likely next elementary step in the mechanism after oxidative addition (Figure 13), in part because the formation of $\mathbf{P_{FBz}(O-C_{Bz})}$ is not as thermodynamically favorable as the formation of $\mathbf{P_{Bz}(O-C_{Bz})}$ (see the Supporting Information). Thus, utilizing the 2,3,4,5,6-pentafluorobenzoate as the leaving group may result in improvements to multiple elementary steps on the catalytic cycle. By analogy to other cross-coupling reactions,[45] we expect that the final step reductive elimination is facile, suggesting that transmetalation is the turnover-limiting step.

To further probe the nature of the turnover-limiting step in catalysis we investigated the oxidative addition of (diphenyl)-methyl-2,3,4,5,6-pentafluorobenzoate (**14a**) and (2-methylphenyl)(phenyl)methyl-2,3,4,5,6-pentafluorobenzoate (**14b**) to (IPr)Pd(styrene)$_2$. Our substrate scope showed that the use of diarylmethylesters with ortho-substitution, such as **14b**, on the aryl groups results in reduced yields under optimized conditions and necessitates the use of harsher reaction conditions to obtain satisfactory yields (Figure 6). However, the rates of oxidative addition of **14a** and **14b** are comparable (Figure 14), with both occurring at room temperature. This is not consistent with oxidative addition being the reason that harsher conditions are required for the coupling of **14b** and suggests that a subsequent step in the catalytic cycle is turnover-limiting. It also provides further evidence that oxidative addition is facile.

CONCLUSIONS

We have developed a broad method for synthesizing triarylmethanes under mild conditions via Pd-catalyzed Suzuki−Miyaura coupling reactions involving 2,3,4,5,6-pentafluorobenzoate electrophiles. Importantly, our method is not limited to electrophiles containing extended aromatic systems, such as naphthyl or biaryl groups, and as a result represents a significant advance over previous methods. Furthermore, the reaction is stereospecific and is able to generate chiral triarylmethanes with inversion of configuration. Intriguingly, while the Suzuki−Miyaura reaction of diarylmethyl esters involves the cleavage of the O−C(benzyl) bond, the reaction featuring closely related phenyl ester electrophiles involve selective cleavage of the C(acyl)−O bond. DFT calculations show that cleavage of the O−C(benzyl) bond in benzyl electrophiles is both kinetically and thermodynamically preferred. This is because oxidative addition of benzyl electrophiles to (IPr)Pd(0) via an S_N2 mechanism provides a low barrier pathway for cleavage of the O−C(benzyl) bond, while the formation of products with an η^3-benzyl interaction thermodynamically stabilizes the Pd(II) products. In fact, in our reactions the oxidative addition of the 2,3,4,5,6-pentafluorobenzoate electrophiles is so facile that transmellation is likely the turnover-limiting step in catalysis. Phenyl ester electrophiles cannot readily undergo oxidative addition via an S_N2 pathway or form products which are stabilized via chelation and as a result cleavage of the C(acyl)−O bond is kinetically and thermodynamically preferred. Overall, apart from the development of a more general method for the synthesis of triarylmethanes, our work provides fundamental information on the selectivity of oxidative addition of ester electrophiles. Given the currently high level of interest in using esters as electrophiles in cross-coupling, this is likely to be valuable for the design of new and improved synthetic methods.

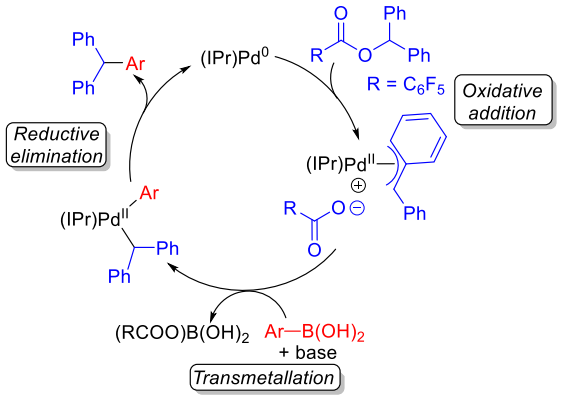


Figure 13. Proposed catalytic cycle for Pd-catalyzed Suzuki−Miyaura reactions of diphenylmethyl 2,3,4,5,6-pentafluorobenzoate.

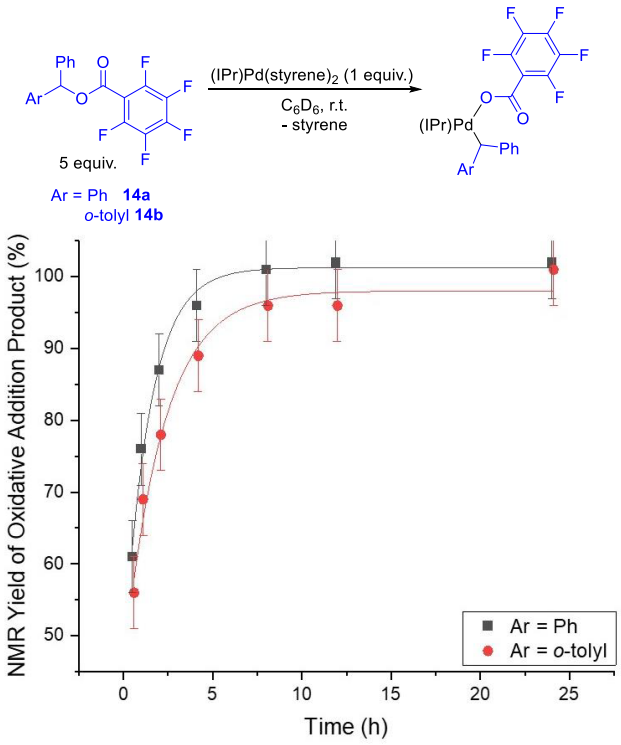


Figure 14. NMR yields of oxidative addition product over time for the reaction of diarylmethyl pentafluorobenzoate with (IPr)Pd(styrene)$_2$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00085.

Additional information about selected experiments and calculations, characterizing data including NMR spectra (PDF)

Cartesian coordinates (XYZ)

Accession Codes

CCDC 2045209 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

David Balcells − *Hylleraas Centre for Quantum Molecular Sciences, Department of Chemistry, University of Oslo, N-0315 Oslo, Norway;* orcid.org/0000-0002-3389-0543; Email: david.balcells@kjemi.uio.no

Nilay Hazari − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States;* orcid.org/0000-0001-8337-198X; Email: nilay.hazari@yale.edu

Authors

Amira H. Dardir − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States*

Irene Casademont-Reig − *Hylleraas Centre for Quantum Molecular Sciences, Department of Chemistry, University of Oslo, N-0315 Oslo, Norway; Donostia International Physics Center (DIPC), 20018 Donostia, Euskadi, Spain; Kimika Fakultatea, Euskal Herriko Unibertsitatea (UPV/EHU), 20080 Donostia, Euskadi, Spain*

Jonathan D. Ellefsen − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States*

Matthew R. Espinosa − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States*

Nicholas E. Smith − *Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States;* orcid.org/0000-0003-2504-0191

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.1c00085

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

N.H. acknowledges support from the NIHGMS under Award Number R01GM120162. I.C.R. acknowledges the Basque Government for funding through a predoctoral fellowship (PRE_2016_1_0159). D.B. acknowledges the support from the Research Council of Norway through its Centers of Excellence Scheme (project number 262695) and the Norwegian Supercomputing Program (NOTUR; project number NN4654K). We thank Dr. Scott J. Miller for access to his group's chiral HPLC and Orven Mallari for the synthesis of diphenylmethyl benzoate.

REFERENCES

(1) Zhou, B.; Liu, D. X.; Yuan, X. J.; Li, J. Y.; Xu, Y. C.; Li, J.; Li, Y.; Yue, J. M. (−)- and (+)-Securidanes A and B, Natural Triarylmethane Enantiomers: Structure and Bioinspired Total Synthesis. *AAAS Research* **2018**, *2018*, 1−9.

(2) (a) Miura, T.; Urano, Y.; Tanaka, K.; Nagano, T.; Ohkubo, K.; Fukuzumi, S. Rational Design Principle for Modulating Fluorescence Properties of Fluorescein-Based Probes by Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2003**, *125*, 8666−8671. (b) Urano, Y.; Kamiya, M.; Kanda, K.; Ueno, T.; Hirose, K.; Nagano, T. Evolution of Fluorescein as a Platform for Finely Tunable Fluorescence Probes. *J. Am. Chem. Soc.* **2005**, *127*, 4888−4894. (c) Beija, M.; Afonso, C. A. M.; Martinho, J. M. G. Synthesis and Applications of Rhodamine Derivatives as Fluorescent Probes. *Chem. Soc. Rev.* **2009**, *38*, 2410−2433.

(3) (a) Mason, C. D.; Nord, F. F. Studies on the Chemistry of Heterocycles. XIII. Triarylmethanes Dyes Containing a Thiophene Ring. *J. Org. Chem.* **1951**, *16*, 722−727. (b) Duxbury, D. F. The Photochemistry and Photophysics of Triphenylmethane Dyes in Solid and Liquid Media. *Chem. Rev.* **1993**, *93*, 381−433. (c) Muthyala, R.; Katritzky, A. R.; Lan, X. A Synthetic Study on the Preparation of Triarylmqthanes. *Dyes Pigm.* **1994**, *25*, 303−324.

(4) Nolan, E. M.; Lippard, S. J. Tools and Tactics for the Optical Detection of Mercuric Ion. *Chem. Rev.* **2008**, *108*, 3443−3480.

(5) (a) Nambo, M.; Crudden, C. M. Recent Advances in the Synthesis of Triarylmethanes by Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 4734−4742. (b) Kshatriya, R.; Jejurkar, V. P.; Saha, S. Advances in The Catalytic Synthesis of Triarylmethanes (TRAMs). *Eur. J. Org. Chem.* **2019**, *2019*, 3818−3841.

(6) Bossche, H. V.; Willemsens, G.; Roels, I.; Bellens, D.; Moereels, H.; Coene, M.-C.; Jeune, L. L.; Lauwers, W.; Janssen, P. A. J. R 76713 and Enantiomers: Selective, Nonsteroidal Inhibitors of the Cytochrome P450-Dependent Oestrogen Synthesis. *Biochem. Pharmacol.* **1990**, *40*, 1707−1718.

(7) (a) Panda, G.; Shagufta; Mishra, J. K.; Chaturvedi, V.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. Diaryloxy Methano Phenanthrenes: a New Class of Antituberculosis Agents. *Bioorg. Med. Chem.* **2004**, *12*, 5269−5276. (b) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. Thiophene Containing Triarylmethanes as Antitubercular Agents. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289−292.

(8) (a) Bhatnagar, A. S.; Hausler, A.; Schieweck, K.; Lang, M.; Bowman, R. Highly Selective Inhibition of Estrogen Biosynthesis by CGS 20267, a New Non-steroidal Aromatase Inhibitor. *J. Steroid Biochem. Mol. Biol.* **1990**, *37*, 1021−1027. (b) Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. Substituted Phenanthrenes with Basic Amino Side Chains: a New Series of Anti-breast Cancer Agents. *Bioorg. Med. Chem.* **2006**, *14*, 1497−1505.

(9) (a) Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P. A General, Simple Catalyst for Enantiospecific Cross Couplings of Benzylic Ammonium Triflates and Boronic Acids: No Phosphine Ligand Required. *Tetrahedron* **2014**, *70*, 4257−4263. (b) Zhang, Z.; Wang, H.; Qiu, N.; Kong, Y.; Zeng, W.; Zhang, Y.; Zhao, J. Synthesis of Triarylmethanes via Palladium-Catalyzed Suzuki Coupling of Trimethylammonium Salts and Arylboronic Acids. *J. Org. Chem.* **2018**, *83*, 8710−8715.

(10) (a) Cao, L.-L.; Ye, Z. S.; Jiang, G.-F.; Zhou, Y.-G. Rhodium-Catalyzed Addition of Boronic Acids to Vinylogous Imines Generated in situ from Sulfonylindoles. *Adv. Synth. Catal.* **2011**, *353*, 3352−3356. (b) Cao, L.-L.; Li, X.-N.; Meng, F.-Y.; Jiang, G.-F. Pd-Catalyzed Addition of Boronic Acids to Vinylogous Imines: a Convenient Approach to 3-sec-Alkyl Substituted Indoles. *Tetrahedron Lett.* **2012**, *53*, 3873−3875. (c) Nambo, M.; Crudden, C. M. Modular Synthesis of Triarylmethanes through Palladium-Catalyzed Sequential Arylation of Methyl Phenyl Sulfone. *Angew. Chem., Int. Ed.* **2014**, *53*, 742−746.

(11) (a) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. Retention or Inversion in Stereospecific Nickel-Catalyzed Cross- Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst. *J. Am. Chem. Soc.* **2013**, *135*, 3303−3306. (b) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. Nickel-Catalyzed Cross-Couplings of Benzylic Pivalates with Arylboroxines: Stereospecific Formation of Diarylalkanes and Triarylmethanes. *J. Am. Chem. Soc.* **2013**, *135*, 3307−3310.

(12) Zarate, C.; van-Gemmeren, M.; Somerville, R. J.; Martin, R. Phenol Derivatives: Modern Electrophiles in Cross-Coupling Reactions. *Adv. Organomet. Chem.* **2016**, *66*, 143−222.

(13) Kuwano, R.; Yokogi, M. Cross-Coupling of Benzylic Acetates with Arylboronic Acids: One-pot Tansformation of Benzylic Alcohols to Diarylmethanes. *Chem. Commun.* **2005**, 5899−5901.

(14) In ref 11a, the primary focus is the coupling of benzylic carbamates with arylboronic esters. However, a number of examples of reactions with benzylic esters are also described.

(15) (a) Yokogi, M.; Kuwano, R. Use of Acetate as a Leaving Group in Palladium-Catalyzed Nucleophilic Substitution of Benzylic Esters. *Tetrahedron Lett.* **2007**, *48*, 6109−6112. (b) Narahashi, H.; Shimizu, I.; Yamamoto, A. Synthesis of Benzylpalladium Complexes Through C−O Bond Cleavage of Benzylic Carboxylates: Development of a Novel Palladium-Catalyzed Benzylation of Olefins. *J. Organomet. Chem.* **2008**, *693*, 283−296. (c) Mendis, S. N.; Tunge, J. A. Palladium-Catalyzed Stereospecific Decarboxylative Benzylation of Alkynes. *Org. Lett.* **2015**, *17*, 5164−5167. (d) Chen, Q.; Fan, X.-H.; Zhang, L.-P.; Yang, L.-M. Ni(II) Source as a Pre-Catalyst for the Cross-Coupling of Benzylic Pivalates with Arylboronic Acids: Facile Access to Tri- and Diarylmethanes. *RSC Adv.* **2015**, *5*, 15338−15340. (e) Stewart, G. W.; Maligres, P. E.; Baxter, C. A.; Junker, E. M.; Krska, S. W.; Scott, J. P. An Approach to Heterodiarylmethanes via sp^2−sp^3 Suzuki−Miyaura Cross-Coupling. *Tetrahedron* **2016**, *72*, 3701−3706. (f) Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P. Stereospecific Cross Couplings To Set Benzylic, All-Carbon Quaternary Stereocenters in High Enantiopurity. *J. Am. Chem. Soc.* **2016**, *138*, 12057−12060. (g) Makida, Y.; Matsumoto, Y.; Kuwano, R. Palladium-Catalyzed Decarboxylation of Benzyl Fluorobenzoates. *Synlett* **2017**, *28*, 2573−2576. (h) Ohsumi, M.; Nishiwaki, N. Selective Synthesis of (Benzyl)biphenyls by Successive Suzuki−Miyaura Coupling of Phenylboronic Acids with 4-Bromobenzyl Acetate under Air Atmosphere. *ACS Omega* **2017**, *2*, 7767−7771. (i) Zhang, S.-Q.; Taylor, B. L. H.; Ji, C.-L.; Gao, Y.; Harris, Y. R.; Hanna, L. E.; Jarvo, E. R.; Houk, K. N.; Hong, X. Mechanism and Origins of Ligand-Controlled Stereoselectivity of Ni-Catalyzed Suzuki−Miyaura Coupling with Benzylic Esters: A Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 12994−13005. (j) Ohsumi, M.; Ito, A.; Nishiwaki, N. Substrate Switchable Suzuki−Miyaura Coupling for Benzyl Ester vs. Benzyl Halide. *RSC Adv.* **2018**, *8*, 35056−35061. (k) Tsuji, H.; Hashimoto, K.; Kawatsura, M. Nickel-Catalyzed Benzylic Substitution of Benzyl Esters with Malonates as a Soft Carbon Nucleophile. *Org. Lett.* **2019**, *21*, 8837−8841.

(16) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. Cross-Coupling Reactions of Aryl Pivalates with Boronic Acids. *J. Am. Chem. Soc.* **2008**, *130*, 14422−14423. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. Biaryl Construction via Ni-Catalyzed C−O Activation of Phenolic Carboxylates. *J. Am. Chem. Soc.* **2008**, *130*, 14468−14470. (c) Li, B. J.; Li, Y. Z.; Lu, X. Y.; Liu, J.; Guan, B. T.; Shi, Z. J. Cross-Coupling of Aryl/Alkenyl Pivalates with Organozinc Reagents through Nickel-Catalyzed C-O Bond Activation under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124−10127. (d) Gooßen, L. J.; Gooßen, K.; Stanciu, C. C(aryl)-O Activation of Aryl Carboxylates in Nickel-Catalyzed Biaryl Syntheses. *Angew. Chem., Int. Ed.* **2009**, *48*, 3569−3571. (e) Shimasaki, T.; Tobisu, M.; Chatani, N. Nickel-Catalyzed Amination of Aryl Pivalates by the Cleavage of Aryl C-O Bonds. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929−2932. (f) Li, W.; Gao, J. J.; Zhang, Y.; Tang, W.; Lee, H.; Fandrick, K. R.; Lu, B.; Senanayake, C. H. A Mild Palladium-Catalyzed Suzuki Coupling Reaction of Quinoline Carboxylates with Boronic Acids. *Adv. Synth. Catal.* **2011**, *353*, 1671−1675. (g) Ehle, A. R.; Zhou, Q.; Watson, M. P. Nickel(0)-Catalyzed Heck Cross-Coupling via Activation of Aryl C−OPiv Bonds. *Org. Lett.* **2012**, *14*, 1202−1205. (h) Cornella, J.; Jackson, E. P.; Martin, R. Nickel-Catalyzed Enantioselective C-C Bond Formation through C-O Cleavage in Aryl Esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 4075−4078. (i) Guo, L.; Hsiao, C.-C.; Yue, H.; Liu, X.; Rueping, M. Nickel-Catalyzed Csp^2−Csp^3 Cross-Coupling via C−O Bond Activation. *ACS Catal.* **2016**, *6*, 4438−4442. (j) Liu, X.; Jia, J.; Rueping, M. Nickel-Catalyzed C-O Bond-Cleaving Alkylation of Esters: Direct Replacement of the Ester Moiety by Functionalized Alkyl Chains. *ACS Catal.* **2017**, *7*, 4491−4496. (k) Becica, J.; Gaube, G.; Sabbers, W. A.; Leitch, D. C. Oxidative Addition of Activated Aryl-Carboxylates to Pd(0): Divergent Reactivity Dependant on Temperature and Structure. *Dalton Trans.* **2020**, *49*, 16067−16071.

(17) (a) Ben-Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. Palladium-Catalyzed Suzuki−Miyaura Coupling of Aryl Esters. *J. Am. Chem. Soc.* **2017**, *139*, 1311−1318. (b) Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc. Rev.* **2017**, *46*, 5864−5888. (c) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)−NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N−C/O−C Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589−2599.

(18) (a) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. Decarbonylative Organoboron Cross-Coupling of Esters by Nickel Catalysis. *Nat. Commun.* **2015**, *6*, 7508. (b) LaBerge, N. A.; Love, J. A. Nickel-Catalyzed Decarbonylative Coupling of Aryl Esters and Arylboronic Acids. *Eur. J. Org. Chem.* **2015**, *2015*, 5546−5553. (c) Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. Switchable Selectivity in the Pd-Catalyzed Alkylative Cross-Coupling of Esters. *Org. Lett.* **2018**, *20*, 4094−4098.

(19) (a) Shi, S.; Lei, P.; Szostak, M. Pd-PEPPSI: A General Pd-NHC Precatalyst for Suzuki−Miyaura Cross-Coupling of Esters by C−O Cleavage. *Organometallics* **2017**, *36*, 3784−3789. (b) Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Suzuki−Miyaura Cross-Coupling of Amides and Esters at Room Temperature: Correlation with Barriers to Rotation Around C−N and C−O Bonds. *Chem. Sci.* **2017**, *8*, 6525−6530. (c) Shi, S.; Szostak, M. Pd−PEPPSI: A General Pd−NHC Precatalyst for Buchwald−Hartwig Cross-Coupling of Esters and Amides (transamidation) Under the Same Reaction Conditions. *Chem. Commun.* **2017**, *53*, 10584−10587. (d) Ben-Halima, T.; Vandavasi, J. K.; Shkoor, M.; Newman, S. G. A Cross-Coupling Approach to Amide Bond Formation from Esters. *ACS Catal.* **2017**, *7*, 2176−2180. (e) Li, G.; Shi, S.; Lei, P.; Szostak, M. Pd-PEPPSI: Water-Assisted Suzuki Miyaura Cross-Coupling of Aryl Esters at Room Temperature using a Practical Palladium- NHC (NHC = N-Heterocyclic Carbene) Precatalyst. *Adv. Synth. Catal.* **2018**, *360*, 1538−1543. (f) Dardir, A. H.; Melvin, P. R.; Davis, R. M.; Hazari, N.; Mohadjer-Beromi, M. Rapidly Activating Pd-Precatalyst for Suzuki−Miyaura and Buchwald−Hartwig Couplings of Aryl Esters. *J. Org. Chem.* **2018**, *83*, 469−477. (g) Dardir, A. H.; Hazari, N.; Miller, S. J.; Shugrue, C. R. Palladium-Catalyzed Suzuki−Miyaura Reactions of Aspartic Acid Derived Phenyl Esters. *Org. Lett.* **2019**, *21*, 5762−5766. (h) Zhou, T.; Li, G.; Nolan, S. P.; Szostak, M. [Pd(NHC)(acac)Cl]: Well-Defined, Air-Stable, and Readily Available Precatalysts for Suzuki and Buchwald−Hartwig Cross-coupling (Transamidation) of Amides and Esters by N−C/O−C Activation. *Org. Lett.* **2019**, *21*, 3304−3309. (i) Lei, P.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. 2-Methyltetrahydrofuran (2-MeTHF): A Green Solvent for Pd NHC-Catalyzed Amide and Ester Suzuki-Miyaura Cross- Coupling by N-C/O-C Cleavage. *Adv. Synth. Catal.* **2019**, *361*, 5654−5660.

(20) Dissociation Constants of Organic Acids and Bases. http://diverdi.colostate.edu/C477/miscellanea/CRC%20reference%20data/dissociation%20constants%20of%20organic%20acids%20and%20bases.pdf.

(21) Umeda, R.; Jikyo, T.; Toda, K.; Osaka, I.; Nishiyama, Y. Rhenium Complex-Catalyzed Carbon-Carbon Formation of Alcohols and Organosilicon Compounds. *Tetrahedron Lett.* **2018**, *59*, 1121−1124.

(22) (a) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: (η^3-1-^{t}Bu-indenyl)$_2$(μ-Cl)$_2$Pd$_2$. *ACS Catal.* **2015**, *5*, 3680−3688. (b) Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type (η^3-allyl)Pd(L)(Cl) and (η^3-indenyl)Pd(L)(Cl). *ACS Catal.* **2015**, *5*, 5596−5606.

(23) Zhou, T.; Ma, S.; Nahra, F.; Obled, A. M. C.; Poater, A.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; Szostak, M. [Pd(NHC)(μ-Cl)Cl]2: Versatile and Highly Reactive Complexes for Cross-Coupling Reactions that Avoid Formation of Inactive Pd(I) Off-Cycle Products. *iScience* **2020**, *23*, 101377.

(24) Hussein, E. M.; Alsantali, R. I.; Abd El-Galil, S. M.; Obaid, R. J.; Alharbi, A.; Abourehab, M. A. S.; Ahmed, S. A. Bioactivefluorenes. Part I. Synthesis, Pharmacological Study and Molecular Docking of Novel Dihydrofolate Reductase Inhibitors Based-2,7-dichlorofluorene. *Heliyon* **2019**, *5*, e01982.

(25) Leclerc, M. Polyfluorenes: Twenty Years of Progress. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2867−2873.

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344

(26) (a) Baheti, A.; Tyagi, P.; Thomas, K. R. J.; Hsu, Y.-C.; Lin, J. T. Simple Triarylamine-Based Dyes Containing Fluorene and Biphenyl Linkers for Efficient Dye-Sensitized Solar Cells. *J. Phys. Chem. C* **2009**, *113*, 8541−8547. (b) Shaya, J.; Fontaine-Vive, F.; Michel, B. Y.; Burger, A. Rational Design of Push−Pull Fluorene Dyes: Synthesis and Structure−Photophysics Relationship. *Chem. - Eur. J.* **2016**, *22*, 10627−10637.
(27) Kudo, K.; Miyazaki, C.; Kadoya, R.; Imamura, T.; Jitsufuchi, N.; Ikeda, N. Laxative Poisoning: Toxicological Analysis of Bisacodyl and Its Metabolite in Urine, Serum, and Stool. *J. Anal. Toxicol.* **1998**, *22*, 274−278.
(28) Brooks, W. H.; Guida, W. C.; Daniel, K. G. The Significance of Chirality in Drug Design and Development. *Curr. Top. Med. Chem.* **2011**, *11*, 760−770.
(29) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. Acceleration of Arylzinc Formation and Its Enantioselective Addition to Aldehydes by Microwave Irradiation and Aziridine-2-methanol Catalysts. *J. Org. Chem.* **2008**, *73*, 2879−2882.
(30) (a) Milstein, D.; Stille, J. K. Mechanism of Reductive Elimination. Reaction of Alkylpalladium(II) Complexes with Tetraorganotin, Organolithium, and Grignard Reagents. Evidence for Palladium(IV) Intermediacy. *J. Am. Chem. Soc.* **1979**, *101*, 4981−4991. (b) Ridgway, B. H.; Woerpel, K. A. Transmetalation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry. *J. Org. Chem.* **1998**, *63*, 458−460. (c) Rodríguez, N.; Ramírez de Arellano, C.; Asensio, G.; Medio-Simon, M. Palladium-Catalyzed Suzuki−Miyaura Reaction Involving a Secondary sp^3 Carbon: Studies of Stereochemistry and Scope of the Reaction. *Chem. - Eur. J.* **2007**, *13*, 4223−4229. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. Transmetalation in the Suzuki−Miyaura Coupling: The Fork in the Trail. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362−7370.
(31) Magano, J.; Dunetz, J. R. Large-Scale Carbonyl Reductions in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2012**, *16*, 1156−1184.
(32) Jaratjaroonphong, J.; Tuengpanya, S.; Saeeng, R.; Udompong, S.; Srisook, K. Green Synthesis and Anti-inflammatory Studies of a Series of 1,1-bis(heteroaryl)alkane Derivatives. *Eur. J. Med. Chem.* **2014**, *83*, 561−568.
(33) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. Synthesis of Enantioenriched Triarylmethanes by Stereospecific Cross- Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790−7793.
(34) Molander, G. A.; Biolatto, B. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions of Potassium Aryl- and Heteroaryltrifluoroborates. *J. Org. Chem.* **2003**, *68*, 4302−4314.
(35) (a) Yamamoto, T.; Ishizu, J.; Kohara, T.; Komiya, S.; Yamamoto, A. Oxidative Addition of Aryl Carboxylates to Ni(0) Complexes Involving Cleavage of the Acyl-O Bond. *J. Am. Chem. Soc.* **1980**, *102*, 3758−3764. (b) Nagayama, K.; Shimizu, I.; Yamamoto, A. Oxidative Addition of Aryl and Benzyl Trifluoroacetates to Zerovalent Palladium Complexes with Two Modes of C-O Bond Cleavage Processes. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799−803. (c) Kakino, R.; Shimizu, I.; Yamamoto, A. Synthesis of Trifluoromethyl Ketones by Palladium-Catalyzed Cross-Coupling Reaction of Phenyl Trifluoroacetate with Organoboron Compounds. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371−376. (d) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. Isolation, Structure, and Reactivity of an Arylnickel(II) Pivalate Complex in Catalytic C−H/C−O Biaryl Coupling. *J. Am. Chem. Soc.* **2013**, *135*, 16384−16387. (e) Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. Key Mechanistic Features of Ni-Catalyzed C−H/C−O Biaryl Coupling of Azoles and Naphthalen-2-yl Pivalates. *J. Am. Chem. Soc.* **2014**, *136*, 14834−14844. (f) Desnoyer, A. N.; Friese, F. W.; Chiu, W.; Drover, M. W.; Patrick, B. O.; Love, J. A. Exploring Regioselective Bond Cleavage and Cross-Coupling Reactions using a Low-Valent Nickel Complex. *Chem. - Eur. J.* **2016**, *22*, 4070−4077.
(36) In catalysis the Pd(II) precatalyst needs to be activated to form the (IPr)Pd(0) active species. Under our reaction conditions this is likely an efficient process, which occurs via the mechanism described in ref 22b.
(37) Kégl, T. R.; Kollár, L.; Kégl, T. DFT Study on the Oxidative Addition of 4-Substituted Iodobenzenes on Pd(0)-Phosphine Complexes. *Adv. Phys. Chem.* **2015**, *2015*, 1−6.
(38) The oxidative addition occurs at room temperature. However, the reaction mixture is heated to 40 °C when the reaction is essentially complete as this makes purification of the product easier because it causes the decomposition of any residual (IPr)Pd(styrene)$_2$.
(39) (a) Andrews, M. A.; Chang, T. C.-T.; Cheng, C.-W. F.; Emge, T. J.; Kelly, K. P.; Koetzle, T. F. Synthesis, Characterization, and Equilibria of Palladium(II) Nitrile, Alkene, and Heterometallacyclopentane Complexes Involved in Metal Nitro Catalyzed Alkene Oxidation Reactions. *J. Am. Chem. Soc.* **1984**, *106*, 5913−5920. (b) Herbert, D. E.; Lara, N. C.; Agapie, T. Arene C-H Amination at Nickel in Terphenyl−Diphosphine Complexes with Labile Metal−Arene Interactions. *Chem. - Eur. J.* **2013**, *19*, 16453−16460.
(40) For details about the computational methods utilized please refer to the Supporting Information. However, calculations were performed with solvent corrections due to the large influence of solvent on SN2 reactions.
(41) For the O−C(aryl) bond cleavage, one additional transition state was found on the potential energy surface, although at a higher energy level (Figure S2). A pre-reaction complex was also found.
(42) One additional transition state was also found in the O−C(aryl) bond cleavage pathway, although at a higher energy level (Figure S2). A pre-reaction complex was also found.
(43) Figure S3 provides a complete list of possible isomers of this complex with their relative energies.
(44) Figure S4 provides a complete list of possible isomers of this complex with their relative energies.
(45) (a) Barder, T. E.; Buchwald, S. L. Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Arylpalladium Amido Complexes via Density Functional Theory. *J. Am. Chem. Soc.* **2007**, *129*, 12003−12010. (b) Zhang, H.; Luo, X.; Wongkhan, K.; Duan, H.; Li, Q.; Zhu, L.; Wang, J.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. Acceleration of Reductive Elimination of [Ar-Pd-C] by a Phosphine/Electron-Deficient Olefin Ligand: A Kinetic Investigation. *Chem. - Eur. J.* **2009**, *15*, 3823−3829. (c) Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486−12493. (d) Melvin, P. R.; Nova, A.; Balcells, D.; Hazari, N.; Tilset, M. DFT Investigation of Suzuki−Miyaura Reactions with Aryl Sulfamates Using a Dialkylbiarylphosphine-Ligated Palladium Catalyst. *Organometallics* **2017**, *36*, 3664−3675.

https://doi.org/10.1021/acs.organomet.1c00085
Organometallics 2021, 40, 2332−2344