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A General and Efficient Suzuki–Miyaura Cross-Coupling Protocol Using Weak Base and No Water: The Essential Role of Acetate

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A weak base, CsOAc, promotes Suzuki–Miyaura cross-coupling and related Pd-catalyzed reactions under anhydrous conditions as effectively as stronger bases. Aryl triflates exhibit unusual reaction rates, which are comparable to that of bromoarenes. A neglected six-membered transition-state model was proposed to give alternative insight into the key process of transmetalation.

Introduction

Suzuki–Miyaura cross-coupling is dubbed as the “Grignard reaction of the 21st century”, thanks to its versatility in constructing various types of C–C bonds.[1] Important advances in effecting the coupling of unreactive substrates[2] as well as novel nucleophiles[3] have greatly expanded the scope of this reaction. In particular, the *B*-alkyl coupling,[4] an important variation, has attracted much recent attention and considerable breakthroughs have been made by Fu and co-workers.[5] Much emphasis was placed on facilitating the process of oxidative addition and reductive elimination, however, studies on the base were less prevalent.[6]

Suzuki and Miyaura rationalized the role of bases, usually hydroxide or alkoxide, in the key process of transmetalation within the catalytic cycle.[7] Soderquist[8a] and Woerpel[8b] demonstrated that this step proceeded with retention of configuration for alkylboranes. So far, a four-membered μ_2-hydroxo-bridged transition-state model[8a] has been put forward and has since become the textbook mechanism for transmetalation. As a base is an indispensable component in normal Suzuki coupling, with the exception of that of diazonium salts, the improvement of our understanding of its role may have a twofold benefit. First, the scope of the reaction could be broadened by optimizing this critical parameter, for conventional aqueous strong bases are incompatible with many base- and moisture-sensitive substrates.More importantly, it could provide more insight into the transmetalation process, which to some extent is still a “mechanistic black box”.[9]

Results and Discussion

We have recently developed a protocol for the direct *B*-alkyl Suzuki coupling of bromoarenes in the presence of unmasked acidic or basic functional groups.[10] During the course of that study, we came across a notable observation; with K_2CO_3 as a base, only a trace (<3%) reaction was detected for 4-bromobenzoic acid **1a**, while the coupling of its sodium salt **1b** realized an appreciable (21%) conversion in 3 h (Table 1, Entries 1 and 2). Presumably, solubility of the base may not be the major cause for this result, because relative to the free acid **1a**, its sodium salt is far less soluble in THF, but exhibits a much higher reaction rate. Instead, it pointed towards the fact that *B*-alkyl Suzuki coupling could be promoted by the carboxylate anion. Stimulated by this finding, and coupled with our interest in Lewis base catalysis,[11] we screened a series of carboxylate salts as the base. Gratifyingly, CsOAc stood out as the most effective base, affording a 92% yield and full conversion (Entry 5). Other carboxylic salts gave inferior conversions and yields, for example, the sodium and silver salts afforded only trace amounts of the coupling product. Here, the normal qualitative correlation of reaction rate with the strength of base in Suzuki coupling was not observed; the reaction with KOAc worked, while that with much more basic K_2CO_3 failed. To the best of our knowledge, this is the first example in which a base as weak as acetate effectively promotes *B*-alkyl Suzuki coupling. THF was the solvent of choice, although dioxane and polar aprotic solvents such as DMF and NMP are also suitable. Subsequently, we tested the new protocol on the reaction using triflate substrate **1c**. A near quantita-

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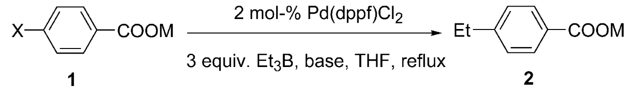
tive yield was obtained, and the reaction rate was surprisingly high: the ethylation was complete within 0.5 h under reflux, or 2 h at room temperature.

Table 1. *B*-Alkyl Suzuki coupling promoted by carboxylates.[a]



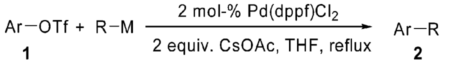
Entry	**1**, M, X	Base (equiv.)	Conv. [%]	**2** [%][b]
1	**1a**, H, Br	K_2CO_3 (3.0)	trace	**2a**, n.d.
2	**1b**, Na, Br	K_2CO_3 (3.0)	21	**2a**, 19[c]
3	**1a**	NaOAc (3.0)	trace	**2a**, n.d.
4	**1a**	KOAc (3.0)	58	**2a**, 51
5	***1a***	*CsOAc (3.0)*	*100*	***2a**, 92*
6	**1a**	AgOAc (2.0)	10	**2a**, 4
7	**1a**	NaOBz (3.0)	14	**2a**, 12
8[d]	***1c**, Et, OTf*	*CsOAc (2.0)*	*100*	***2c**, 99*

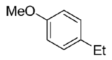
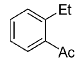
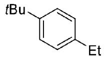
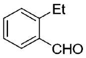
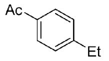
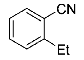
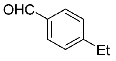
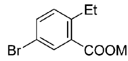
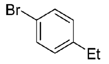
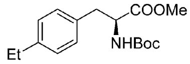
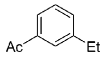
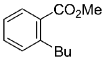
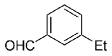
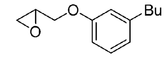
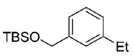
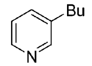
[a] Reaction conditions: 1.0 mmol substrate, 3.0 mmol Et_3B (1.0 M in THF, 3.0 mL), 2.0–3.0 mmol base, 5 mL THF, reflux, 3 h, except otherwise noted. [b] Isolated yields. [c] Isolated as the free acid **2a**. [d] 2.0 equiv. Et_3B, reflux, 0.5 h.

The scope of the substrate for the present protocol was then investigated under optimized conditions (Table 2). For aryl triflate substrates with electron-withdrawing or electron-donating groups in various substitution patterns, good to excellent yields were obtained. In general, the yields are comparable to those obtained by using strong bases. Carbonyl functional groups such as aldehydes, ketones, and esters were compatible, even if positioned *ortho* to the reaction site. For an α-amino acid derivative prone to base-induced racemization (Entry 11), the optical integrity was fully preserved, as judged by the chiral HPLC analysis of the product (see Supporting Information). Reactions run with tri-*n*-butylborane gave equally good results (Entries 14–16). It is noteworthy that a monosubstituted (terminal) epoxide remained intact (Entry15), and the nucleophilic pyridine heterocycle posed no problem. With regard to chemoselectivity, in contrast to the observations by Fu, and Brown and co-workers, certain aryl triflates reacted preferentially with respect to bromoarenes at both room temperature and at reflux (Entries 5, 12), and this may complement the usual order of reactivity manifested in most catalytic systems.[1a,12]

The potential of CsOAc in other mechanistically related reactions was then probed (Table 3). Aryl bromides underwent coupling in THF under reflux in excellent yields (Entries 1, 5, 6). Notably, it was demonstrated that CsOAc also promoted aryl–aryl coupling by using aryl boronic acids ($pK_a \approx 9$); generally, bases stronger than acetates are required (Entries 2–6).[13] The anhydrous conditions allowed the use of moisture-sensitive 2-formylphenylboronic acid, which is known to undergo protodeboronation under aqueous conditions.[14] It is also worth noting that highly base-labile phenolic acetyl protection was well tolerated (Entry 3).[15] Furthermore, Stille coupling between **1c** and a couple of stannanes, including one with a trisubstituted alkenyl moiety and a free hydroxyl (Entry 8), proceeded smoothly in good to excellent yields without the need of excess fluorides or lithium halides as stabilizing additives.[16] Finally, to our satisfaction, the present protocol can also be successfully applied to reactions with potassium trifluoroborates[3,17] as the coupling partner (Entries 9 and 10). With 5 vol.-% water, the coupling of **1c** with phenyl- and styryl trifluoroborate gave near quantitative yields. However, it should be mentioned that no reaction occurred in the absence of water. Again, the mildness of our protocol could also mitigate the problems associated with the strongly basic aqueous conditions usually required for coupling of organotrifluoroborates.

Table 2. *B*-Alkyl Suzuki coupling of aryl triflates promoted by CsOAc.



Entry		**2**, Yield [%][a]	Entry		**2**, Yield [%][a]
1		**2d**, 57	9		**2l**, 62
2		**2e**, 90	10		**2m**, 75
3		**2f**, 86	11		**2n**, 75
4		**2g**, 78	12		**2o**, 67[b]
5		**2h**, 72	13		**2p**, 80
6		**2i**, 81	14		**2q**, 66
7		**2j**, 78	15		**2r**, 79
8		**2k**, 92	16		**2s**, 75

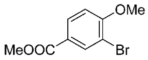
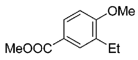
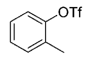
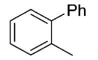
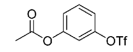
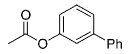
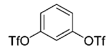
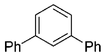
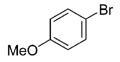
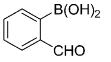
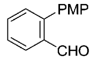
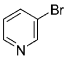
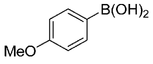
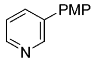
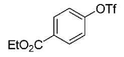
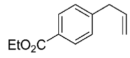
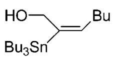
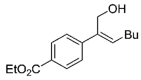
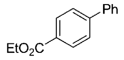
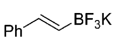
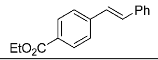
[a] Isolated yields. [b] Room temperature, 6 h, 10% diethylation product.

To verify the rate enhancement of aryl triflates, we carried out an intermolecular competition study using **1z** and **1aa** as substrates, to eliminate possible electronic interactions in the intramolecular examples (Scheme 1). By assuming the *para*-ethyl and -methyl ester possess virtually the same electronic and steric effects, these two substrates represent the true intrinsic reactivities of aryl triflates and bromides, respectively, in the present protocol. By measuring the ratio of Et/Me esters in the crude coupling products by GC-MS, a rough estimate of k_{OTf}/k_{Br} could thus be obtained. It turned out that at room temperature, the reactivity of triflate **1z** for *B*-alkyl coupling was indeed higher than that of bromide **1aa**, while in the analogous *B*-aryl coupling, the aryl bromide was slightly more reactive. On the other hand, elevated temperatures (70 °C) increased the reaction rate of the aryl bromide reaction by twice as much relative to that of the triflate reaction, and **1aa** is the preferred substrate in both types of coupling. Thus, in retrospect, the triflate-selective coupling of **1h** and **1o** do involve

Table 3. Applications of CsOAc in cross-coupling reactions.[a]

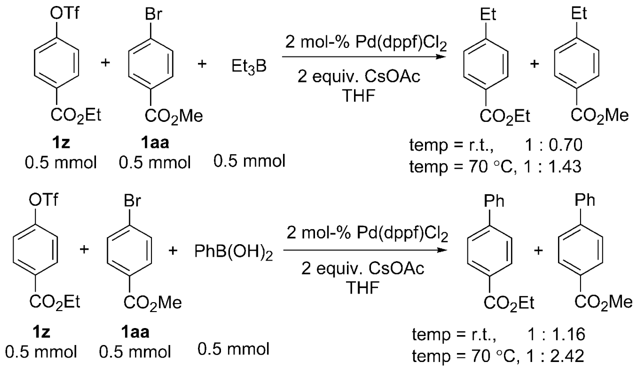
$$\underset{\mathbf{1}}{\text{Ar–X}} + \text{R–M} \xrightarrow[\text{2 equiv. CsOAc, THF, reflux}]{\text{2 mol-\% Pd(dppf)Cl}_2} \underset{\mathbf{2}}{\text{Ar–R}}$$

X = OTf, Br
R = alkyl, aryl, alkenyl
M = BR'$_2$, B(OH)$_2$, BF$_3$K, SnR'$_3$

Entry	1	R–M	2, Yield [%][b]
1	 **1t**	Et$_3$B	 **2t**, 90
2	 **1u**	PhB(OH)$_2$	 **2u**, 92
3	 **1v**	PhB(OH)$_2$	 **2v**, 90
4[c]	 **1w**	PhB(OH)$_2$	 **2w**, 94
5[d]	 **1x**		 **2x**, 66
6[d]	 **1y**		 **2y**, 95
7	 **1z**	Allyl–SnBu$_3$	 **2z**, 84
8	**1z**		 **2aa**, 63
9[e]	**1z**	PhBF$_3$K	 **2ab**, 99
10[e]	**1z**		 **2ac**, 95

[a] All reactions performed on a 0.50–1.0-mmol scale. [b] Isolated yields. [c] 3.0 equiv. PhB(OH)$_2$ and 4.0 equiv. CsOAc were used. [d] PMP = *p*-methoxyphenyl. [e] 5 vol.-% water was added.

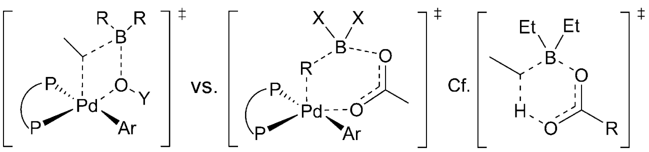
electronic interactions between the two substituents. Nevertheless, the enhanced reactivity of triflates is still noteworthy and useful.



Scheme 1. Kinetic study on electrophile reactivity.

The paradoxical high efficiency of the weak base CsOAc, the generality of the Pd-catalyzed couplings it promoted, and the unusual enhanced reactivity of aryl triflates suggest that a neglected mode of action could be present, probably within the transmetalation process.[18] As the TfO$^-$ anion is non-coordinating, the cationic Pd^{II} species formed upon oxidative addition would be rapidly trapped by CsOAc to irreversibly form an acetato complex L$_2$ArPdOAc,[19] and the subsequent transmetalation is most probably the rate-determining step. On the other hand, the displacement of Br$^-$ by AcO$^-$ from the covalent intermediate L$_2$ArPdBr is conceivably slower, and this may instead become part of the rate-determining step for the coupling of aryl bromides. The temperature dependence of the relative reactivity in the above kinetic study also supports this hypothesis.

Unlike Cs$_2$CO$_3$, the mixing of CsOAc with Et$_3$B showed no evidence of quaternization of boron, as indicated by ^{11}B NMR spectroscopy, hence borane must enter the catalytic cycle after the formation of L$_2$ArPdOAc. Thus, we conjecture that, in this protocol where monodentate strong bases such as HO$^-$ or RO$^-$ are precluded and the only nucleophile/base available is the acetoxy anion, it is the carbonyl oxygen of the acetatopalladium(II) intermediate, rather than the oxygen bonded to Pd, that coordinates with the electrophilic boron atom, thus activating the B–C bond.[20] Therefore, the transmetalation is likely to proceed via a six-membered S$_E$2 (cyclic) transition state (TS2, Figure 1), which is distinct from the conventional mechanism (TS1, Y = H, alkyl).[21]



TS**1** (Aqueous)
Suzuki–Miyaura
Soderquist

TS**2** (Nonaqueous)
X = alkyl, OH, F; R = alkyl, aryl
this work

TS **3**
Dessy

Figure 1. Comparison of transition-state models for Suzuki coupling and related reactions.

The high reaction rate suggests that TS2 is energetically favorable because of less strain in its geometry.[22] TS2 also finds analogy in the protolysis of alkylboranes in which weaker carboxylic acids are much more effective than mineral acids, for the former are unique in being able to adopt six-membered transition structures by coordination through the carbonyl group (TS3).[22,23] Moreover, important recent studies on topics as diverse as Pd-catalyzed direct arylation,[24] aerobic oxidation,[25] Ru-catalyzed C–H activation,[26] and Suzuki-type coupling[27] all suggest the intermediacy of carboxylato–metal species and the nucleophilic role of the carbonyl oxygen atom. Thus, the efficiency of the acetate-promoted Suzuki coupling fits logically in this context. Transition states analogous to TS2 could also be invoked for the coupling by using boronic acids (X = OH), organotrifluoroborates (X = F), and stannanes, as well as for Suzuki reactions employing cesium carbonate[10] or K$_3$PO$_4$ as the base, whose bidentate character resembles that of AcO$^-$.

Conclusions

In summary, the weak base CsOAc promotes Suzuki coupling and related Pd-catalyzed reactions as effectively as stronger bases. Its mildness offers an attractive option when base-sensitivity needs to be addressed. In addition, the reactivity of aryl triflates is comparable to that of bromoarenes and markedly higher than usual, and, in some cases, good to excellent triflate-selectivity (>6:1) could be achieved. Mechanistically, a neglected six-membered transition-state model is proposed to give alternative insight into the key process of transmetalation. It differs from the textbook mechanism not only in the composition and geometry of the TS, but in that it suggests a new mode of action for bidentate bases in Suzuki coupling reactions. Awareness of the essential and versatile roles of carboxylate anions as η^1 ligands capable of activating reaction components through the nucleophilic carbonyl oxygen atom could have a significant bearing on the design of novel metal-catalyzed reactions such as cross-coupling and C–H functionalization.

Experimental Section

General Information: All reactions were performed in oven-dried glassware under an atmosphere of argon. All ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature in CDCl$_3$ unless otherwise noted. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad), coupling constant, and integration. Optical rotations were measured at ambient temperature, and concentrations are reported in g per 100 mL. GC-MS spectra were recorded on an Agilent 6890N apparatus coupled with an Agilent 5975 mass spectrometer, by using an HP-5MS column (30 m × 250 µm × 0.25 µm). Melting points were uncorrected. THF was distilled from sodium benzophenone ketyl, and all other solvents and chemical reagents were used as received.

General Procedure: Triethylborane (1.0 M in THF, 2.0 mL, 2.0 mmol) was added to a suspension of aryl triflate (1.0 mmol), Pd(dppf)Cl$_2$ (15 mg, 0.02 mmol), and CsOAc (384 mg, 2.0 mmol) in THF (3.0 mL) under an argon atmosphere, and the mixture was heated at reflux for 0.5–6 h until all the starting material was consumed. After cooling, the reaction mixture was diluted with diethyl ether, washed with aq. NaHCO$_3$ and brine, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by silica gel flash column chromatography.

2-[(3-Butylphenoxy)methyl]oxirane (2r): Triflate **1r** (129 mg, 0.43 mmol) coupled with nBu$_3$B to afford **2r** (70 mg, 79% yield) as a colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.18 (t, J = 7.8 Hz, 1 H, Ar-H), 6.82–6.70 (m, 3 H, Ar-H), 4.19 (dd, J = 10.5, 3.0 Hz, 1 H, 3-H$_a$), 3.96 (dd, J = 10.8, 5.7 Hz, 1 H, 3-H$_b$), 3.36 (m, 1 H, 2-H), 2.90 (dd, J = 5.1, 3.9 Hz, 1 H, 1-H$_a$), 2.75 (dd, J = 5.1, 2.4 Hz, 1 H, 1-H$_b$), 2.58 (t, J = 7.8 Hz, 2 H, ArCH_2), 1.65–1.53 (m, 2 H, ArCH$_2$CH_2), 1.42–1.27 (m, 2 H, CH_2CH$_3$), 0.92 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ = 158.4, 144.7, 129.2, 121.4, 114.9, 111.4, 68.6, 50.2, 44.8, 35.6, 33.5, 22.3, 14.0 ppm. HR-ESI-MS: calcd. for C$_{13}$H$_{18}$O$_2$Na [M + Na]$^+$ 229.1204; found 229.1199.

Supporting Information (see footnote on the first page of this article): Characterization data and NMR spectra for new compounds are presented.

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