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Direct *B*-Alkyl Suzuki–Miyaura Cross-Coupling of Trialkylboranes with Aryl Bromides in the Presence of Unmasked Acidic or Basic Functions and Base-Labile Protections under Mild Non-Aqueous Conditions

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Abstract: An efficient and chemoselective palladium-catalyzed direct *B*-alkyl Suzuki–Miyaura cross-coupling of trialkylboranes with diversely functionalized aryl bromides is described. A wide variety of unmasked acidic or basic functions are tolerated. The mild non-aqueous conditions are compatible with aldehydes, ketones, nitriles, chloro substitution as well as base-labile phenolic Piv and TBS protecting groups. The anhydrous conditions were found to be advantageous for aryl bromide substrates. A potent CEPT inhibitor was efficiently synthesised using this protocol.

Keywords: alkylation; boranes; cross-coupling; palladium; Suzuki–Miyaura reaction

Introduction

Alkylarenes are ubiquitous in all fields of organic chemistry. In medicinal chemistry, the seemingly simple alkyl side-chains are not merely bystanders and the biological activities of drug-like molecules are often profoundly influenced by them (Figure 1).[1] Traditionally, the preparation of alkylarenes employs the Friedel–Crafts alkylation[2] or an acylation[3]-reduction[4] sequence. In recent decades, the Suzuki–Miyaura,[5] Negishi[6] and Stille–Migita–Kosugi[7] cross-couplings of alkyl-metal species with aryl halides or sulfonates have emerged as excellent alternatives, due to their site-specificity, selectivity and the mildness of palladium catalysis. Among them, the Suzuki coupling is particularly popular, thanks to its environmental friendliness as well as the ease of preparation and work-up of organoboron compounds.

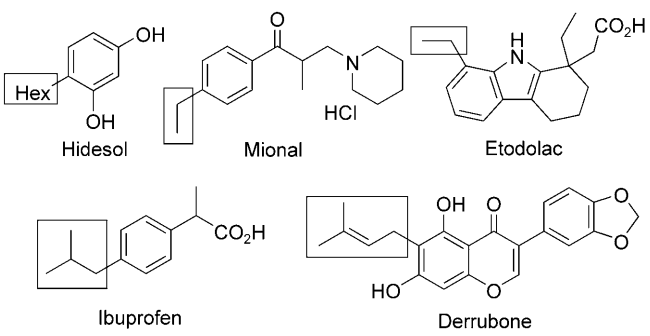


Figure 1. Drugs and bioactive natural products with alkyl side-chains.

The alkyl-metal reagents in Suzuki couplings were normally *B*-alkyl-9-BBNs, which must be prepared and used *in situ*, necessitating protection for many sensitive functions and precluding some others. In particular, from a practical point of view, the preparation of 9-BBN derivatives bearing lower alkyls is inconvenient as it involves hydroboration of volatile alkenes or other tedious operations.[8] Alkyltrifluoroborates[9] and alkylboronic acids[10] have been introduced as stable coupling partners to widen the scope of the Suzuki reaction. On the other hand, coupling using

readily available tri-*n*-alkylboranes[11] has only been documented sporadically, in which the electrophiles were limited to the most reactive aryl iodides or activated heterocyclic triflates,[5b,12a–c] or the use of highly toxic Tl_2CO_3 as the base was mandatory.[12d,e] Thus, the utility of trialkylboranes for the practical introduction of lower alkyls has not been fully explored and this approach could have its own merit.

Synthesis without invoking protective groups has been an attractive yet difficult goal in organic chemistry.[13] A systematic study on the direct *B*-alkyl Suzuki coupling in the presence of acidic functions proper (e.g., carboxylic acids and phenols) is lacking.[14] Besides, basic functions such as amines might interfere with transition metal catalysis.[15] In view of the fact that these functions are the cornerstones of combinatorial chemistry, sparing the two-step detour of protection and deprotection would be highly beneficial to both academia and industry. Indeed, considering the protolysis of trialkylboranes by carboxylic acids[16] or phenols,[17] and the strong coordination of amines with boranes or boronic acids,[18] this type of direct coupling is non-trivial. For example, reaction of 4-bromobenzoic acid with methylboronic acid was unsatisfactory.[19] 4-Bromophenol failed to couple with potassium alkyltrifluoroborates.[9b] Unprotected indole NH was often detrimental to Suzuki coupling.[20] As a partial solution to these issues, Blum and co-workers achieved cross-methylation using aluminum and indium reagents.[21] Bumagin reported that excess Grignard reagents coupled with some halobenzoic acids, but apparently aldehydes and ketones cannot survive this condition.[22] Recently, Knochel's group accomplished Negishi coupling for substrates with relatively acidic OH and NH groups.[15]

Herein we report our results for the direct Suzuki cross-alkylation of aryl bromides bearing unmasked acidic or basic functions as well as common polar functional groups.

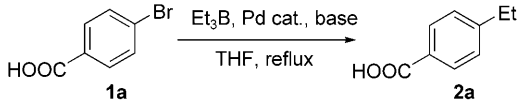
Results and Discussion

4-Bromobenzoic acid (**1a**) was used as the test substrate to explore the reaction conditions (Table 1). It was found that the palladium source played a significant role. Commercial Pd(0) catalysts such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ with added mono- and bidentate phosphane ligands was inactive (entries 1–4). Pd(0) prepared *in situ* showed promising results, albeit at a high catalyst loading (10 mol%). Shifting the catalyst to $Pd(PPh_3)_2Cl_2$ improved the conversion marginally. Gratifyingly, with 2 mol% $Pd(dppf)Cl_2$, the reaction was complete within 2–3 h in excellent yield (99%). With 3.0 equiv. of Et_3B the reaction went to completion within 3 h, while a prolonged reaction time was required using reduced amounts of trialkylborane (entries 7–9). Next, a number of bases were screened, among them K_2CO_3, $NaHCO_3$, NaOAc, and Et_3N were all ineffective. Cs_2CO_3 (2 equiv.) was by far the most effective, while K_3PO_4 (in DMF-THF) or silver salts such as Ag_2CO_3 gave inferior results in terms of conversion and yield. Notably, the protocol in Suzuki's seminal paper[5b] (3 M aqueous KOH) resulted in generally lower yields, revealing the intricate difference between bromoarenes and their iodo analogues. In this connection, anhydrous conditions seemed to be superior for aryl bromides, not only for the reduced risk of hydrolysis of base-sensitive groups, but with some underlying mechanistic causes that are not clear yet.[10a]

This observation was contrary to the general notion that water was beneficial or even indispensable for Suzuki coupling in various catalytic systems.[23] A similar rare exception was also noted by Molander's group in the coupling of aryl triflates with potassium alkynyltrifluoroborates.[24] In their protocol, however, this exception was not universal, most aryl halides still required 5 vol% water as the co-solvent, as did the reactions of potassium alkyltrifluoroborates[9a,b] which are more relevant to this work.

To shed some light on the role of the base as well as the trace amount of water which could arise from

Table 1. Optimization of reaction conditions.[a]



1a 2a (1)

Entry	Catalyst (mol%)	Base (equiv.)	Conv. [%]	**2a** [%][b]
1	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2)	trace	nd
2	$Pd_2(dba)_3$-4 PPh_3 (5)	Cs_2CO_3 (2)	trace	nd
3	$Pd_2(dba)_3$-2 dppf (5)	Cs_2CO_3 (2)	trace	nd
4	$Pd_2(dba)_3$-2 dppp (5)	Cs_2CO_3 (2)	trace	nd
5	$Pd(OAc)_2$-4 PPh_3 (10)	Cs_2CO_3 (2)	40	37
6	$Pd(PPh_3)_2Cl_2$ (3)	Cs_2CO_3 (2)	58	54
7	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	100	99
8[c]	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	56	52
9[d]	$Pd(dppf)Cl_2$ (2)	Cs_2CO_3 (2)	70	66
10	$Pd(dppf)Cl_2$ (2)	K_2CO_3 (3)	<5	nd
11[e]	$Pd(dppf)Cl_2$ (2)	K_3PO_4 (3)	90	75
12	$Pd(dppf)Cl_2$ (2)	Ag_2CO_3 (2)	42	37
13	$Pd(dppf)Cl_2$ (2)	$NaHCO_3$	trace	nd
14	$Pd(dppf)Cl_2$ (2)	NaOAc	trace	nd
15	$Pd(dppf)Cl_2$ (2)	Et_3N (3)	<5	nd
16	$Pd(dppf)Cl_2$ (2)	3 M KOH (3)	100	82

[a] All reactions run on 1.0 mmol scale, with 3.0 equiv. of Et_3B in 5.0 mL THF under reflux for 2–3 h, unless otherwise noted.
[b] Isolated yields, based on reacted starting material.
[c] With 1.2 equiv. of Et_3B.
[d] With 2.0 equiv. of Et_3B.
[e] In DMF-THF (1:1), no reaction in THF.

Table 2. Effect of water on *B*-alkyl Suzuki coupling of **1a**.[a]

Entry	Water (v/v%)	Base (equiv.)	Conv. [%]	**2a** [%][b]
1[c]	0	Cs_2CO_3 (2)	85	81 (95)
2	5.0	Cs_2CO_3 (2)	100	92
3	0.5	K_2CO_3 (3)	10	9 (94)
4	1.0	K_2CO_3 (3)	23	21 (94)
5	1.5	K_2CO_3 (3)	35	32 (92)
6	5	K_2CO_3 (3)	62	54 (87)
7	10	K_2CO_3 (3)	>95	79 (83)

[a] All reactions run on 1.0 mmol scale, 0.02 mmol $Pd(dppf)Cl_2$, 3.0 mmol Et_3B, in 5.0 mL THF under reflux for 3 h (1.0 v/v% water amounts to *ca.* 2.8 equiv.).

[b] Isolated yields, for easy comparison of trends, yields based on reacted **1a** are given in parenthesis.

[c] 4-BrC_6H_4COONa as substrate, conversion and yield both >95% after 6 h.

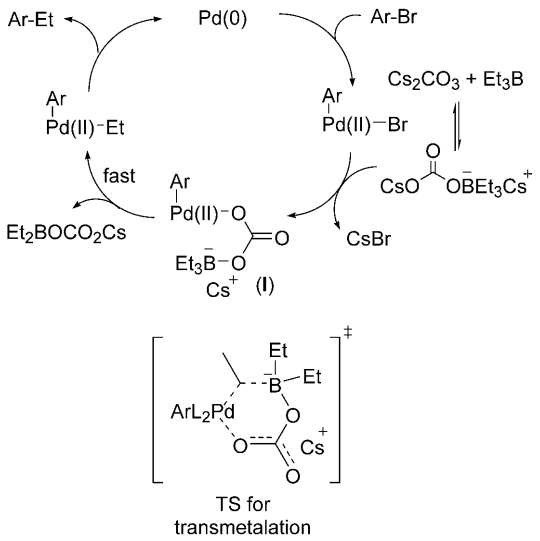


Figure 2. Schematic catalytic cycle (ligands omitted) and plausible transition state for transmetalation.

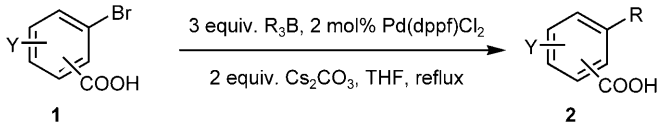
the reaction of **1a** with Cs_2CO_3, the effect of added water on the reaction rate was investigated (Table 2). First, sodium 4-bromobenzoate instead of the free acid was coupled under strict anhydrous conditions to preclude water or hydroxide from participating in the reaction. Interestingly, this led to a reaction rate and yield comparable to that obtained under optimized conditions (entry 1). Furthermore, it was found that added water (5% v/v) slightly eroded the yield when Cs_2CO_3 was used as the base.

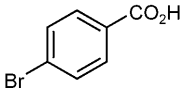
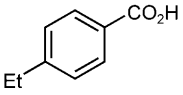
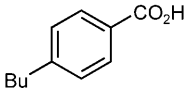
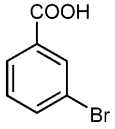
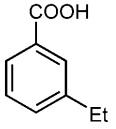
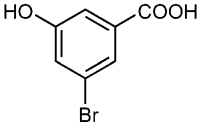
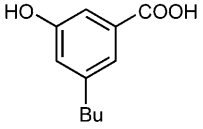
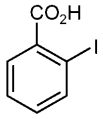
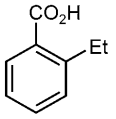
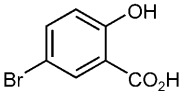
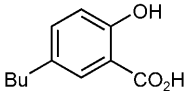
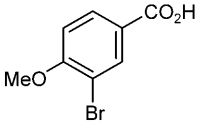
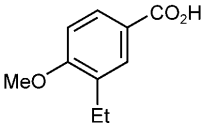
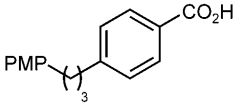
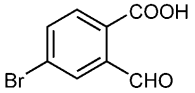
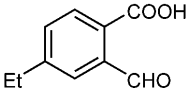
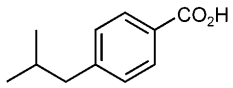
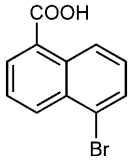
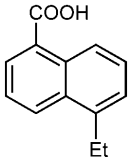
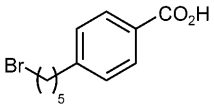
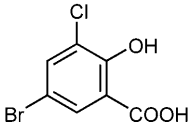
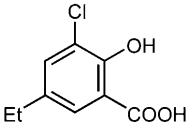
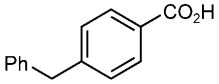
On the other hand, with the addition of 0.5% water (2.8 equiv.), a low conversion (10%) was observed in 3 h using K_2CO_3 as the base. A double or triple dose of water produced roughly proportional increases in conversion. Further increases of water content to 5% and 10% raised the conversion at the expense of yield. With the rising water content, the decreasing yield approached the level obtained by using aqueous KOH, suggesting that the actual base might be HO^- resulting from partial hydrolysis of CO_3^{2-}. Thus, these experiments showed that, albeit being ideal for iodoarenes, water or hydroxide anion tend to cause noticeable (up to 17%) side reactions for bromoarene substrates. Moreover, adventitious moisture cannot account for the high efficiency of Cs_2CO_3 in the present anhydrous protocol, which must emanate from the base itself.

Although direct measurement of the reaction mixture was difficult, ^{11}B NMR of a 1:1 mixture of Et_3B ($\delta = +80.3$ ppm)[25] and Cs_2CO_3 in THF-d_8 showed the emergence of a new peak at +2.4 ppm. This diagnostic signal of boron quaternization was absent when K_2CO_3 was used as the base. Such a drastic difference between the two bases could be attributed primarily to the higher degree of dissociation of Cs salts.[26] We further observed a marked dependence of the reaction rate on the halide of the substrate. The coupling of 4-bromobenzoic acid is much faster than that of its 4-iodo analogue. Addition of an external I^- source (0.6 equiv. TBAI) also significantly retarded the reaction of **1a**. Hence the rate-limiting step occurs prior to transmetalation, in line with the elegant study by Soderquist.[27] It is likely that the base first coordinated with the highly Lewis acidic borane as suggested by ^{11}B NMR, then the resulting Cs salt displaced the halide from L_2ArPdX to form complex **I** (Figure 2).[28] As the collapse of **I** is fast, we propose that it proceeded *via* a six-membered transition state (Figure 2). Such an "unorthodox" TS for transmetalation is unavailable when using monodentate bases (hydroxides and alkoxides), whereas it is reminiscent of borane protolysis by carboxylic acids.[16] Taken together, these observations demonstrate that, under anhydrous conditions, Cs_2CO_3 is a superior and mechanistically unique base.

Next, the scope and limitation of the reaction was examined with a series of bromo-substituted aromatic acids (Table 3). For these compounds with diverse substitution patterns, including salicylic acid derivatives (entries 7 and 10), good to excellent yields were obtained, except for the case of 2-bromobenzoic acid, a reportedly "difficult" substrate under all conditions. Its exclusive reductive de-bromination was probably due to coordination of the *ortho*-carboxyl to the metal center to form a palladacycle which is much more prone to β-H elimination.[19] Fortunately, this was remedied by the successful coupling of the analogous 2-iodobenzoic acid (59% yield), while using standard procedures in the literature resulted in complete de-iodination. To the best of our knowledge, this is the first example of a direct *B*-alkyl Suzuki–Miyaura coupling of 2-halobenzoic acid. However, when 3-iodoindole-2-carboxylic acid was subject to the same conditions, only a trace amount of the desired cou-

Table 3. Direct *B*-alkyl Suzuki coupling of bromo aromatic acids.[a]



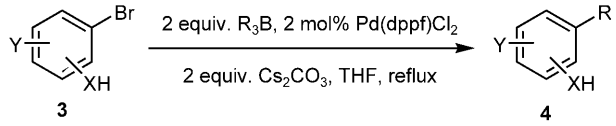
Entry	Ar-Br **1**	Borane	Product **2** (%)[b]	Entry	Ar-Br **1**	Borane	Product **2** (%)[b]
1	**1a** 	Et_3B	**2a** (99) 	8	**1a**	*n*-Bu_3B	**2h** (80) 
2	**1b** 	Et_3B	**2b** (88) 	9	**1i** 	*n*-Bu_3B	**2i** (94) 
3[c]	**1c** 	Et_3B	**2c** (59) 	10	**1j** 	*n*-Bu_3B	**2j** (91) 
4	**1d** 	Et_3B	**2d** (73) 	11[d]	**1a**	PMP-(CH2)3-9-BBN	**2k** (90) 
5	**1e** 	Et_3B	**2e** (90) 	12[e]	**1a**	*i*-Bu_3B	**2l** (57) 
6	**1f** 	Et_3B	**2f** (92) 	13	**1a**	B[(CH2)5Br]3	**2m** (85) 
7	**1g** 	Et_3B	**2g** (81) 	14	**1a**	B(Ph)3	**2n** (0) 

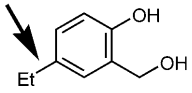
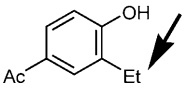
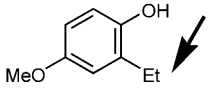
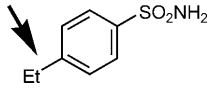
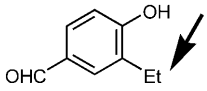
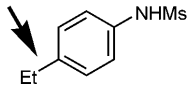
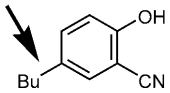
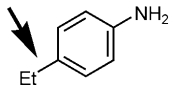
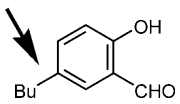
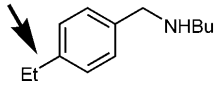
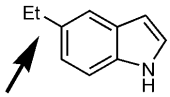
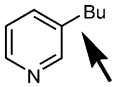
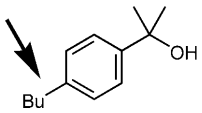
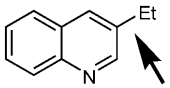
[a] *Reaction conditions:* 1.0 mmol substrate, 0.02 mmol $Pd(dppf)Cl_2$, 3.0 mmol borane, 2.0 mmol Cs_2CO_3, 5.0 mL THF, reflux 3–6 h.
[b] Isolated yields.
[c] CsOAc as the base.
[d] PMP = 4-$MeOC_6H_4$.
[e] 10 mol% Catalyst, reflux 48 h.

pling product was observed, the major reaction pathway being probably the dimerization *via* a palladacycle.[29] On the other hand, chloro substitution was not affected under the present conditions (entry 7). Variation of the borane coupling partner was also carried out. Use of tri-*n*-butylborane gave the anticipated products in comparable yields (entries 8–10). In addition, *B*-alkyl-9-BBN also proved to be a suitable coupling partner under the anhydrous conditions, demonstrating that our protocol can provide access to products with a more elaborate alkyl appendage (entry 11). Furthermore, an ω-functionalized borane was prepared and coupled with **1a** smoothly, without affecting the primary alkyl bromide function (entry 13). β-Branched primary alkyls can also be introduced using this protocol (entry 12), although a higher catalyst loading and prolonged reaction time are required (48 h). Remarkably, this has not been achieved with borane-type nucleophiles under non-aqueous conditions.[5a,30] However, attempts to extend our protocol to the α-branched tris-(2-propyl)borane were unsuccessful, due to increased steric hindrance around boron that prevented coordination with the steric-demanding carbonate moiety required for subsequent transmetalation. Tribenzyl- and triallylboranes were also tested without success, in these cases, apart from steric factors, the unsaturated moiety might retard transmetalation.

Results for substrates bearing other acidic OH or NH functions and basic amine functions are summar-

Table 4. Direct *B*-alkyl Suzuki coupling of bromoarenes.[a]



Entry	Product **4**	Yield [%][b]	Entry	Product **4**	Yield [%][b]
1		**4a** (73)	8		**4h** (70)
2		**4b** (72)	9		**4i** (88)
3		**4c** (55)	10		**4j** (84)
4		**4d** (95)	11		**4k** (82)
5		**4e** (93)	12		**4l** (92)
6		**4f** (85)	13		**4m** (88)
7		**4g** (92)	14		**4n** (90)

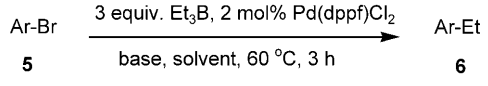
[a] *Reaction conditions:* 1.0 mmol substrate, 0.02 mmol $Pd(dppf)Cl_2$, 1.5–2.0 mmol R_3B, 2.0 mmol Cs_2CO_3, 5.0 mL THF, reflux 3–6 h. Arrows indicate alkyls introduced by the coupling reaction.

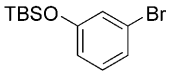
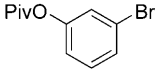
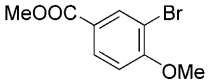
[b] Isolated yields.

ized in Table 4. We focused on unactivated bromoarenes, as the coupling of these substrates is more challenging than those activated by electron-withdrawing groups in the *para*-position, although compounds of the latter class are also suitable substrates. In these cases, the amount of boranes can be reduced to 1.5–2.0 equiv. without sacrificing conversion. Free phenolic and benzylic hydroxy groups did not interfere with the reaction. Moreover, aldehydes and enolizable methyl ketones were both intact (entries 3, 5 and 8). Various ring substitutions with diverse electronic effects did not exhibit a very pronounced influence, except that the electron-donating free hydroxy *ortho*-to bromo tends to cause diminished yields and the formation of minor amounts of reductive de-bromination by-products (entries 2, 3 and 8). An excellent yield was obtained for nitrile **4d**, which also possesses a phenolic proton. Acidic NH groups in indole, sulfonamide and sulfanilide posed no difficulty for the reaction either (entries 6, 9 and 10). As expected, the use of tri-(*n*-butyl)borane gave butylation products in excellent yields (entries 4, 5, 7 and 13). Unfortunately, the nitro group cannot survive and resulted in a complex mixture, similar to results obtained by *B*-alkyl-9-BBN.[31] The smooth coupling of 4-bromoaniline, a problematic substrate, was illustrative of the scope of this protocol (entry 11). Furthermore, our protocol also worked well with substrates bearing highly electron-donating amine functions and nitrogen heterocycle (entries 12–14).

Since a base was indispensible for most Suzuki reactions except those of diazonium salts, base-induced hydrolysis, decomposition and racemization were serious side reactions frequently encountered. This has compromised the utility of Suzuki coupling in many aspects and forced chemists to seek alternatives to standard conditions. Although some modifications in reaction parameters proved successful in a number of cases,[32] a general mild protocol is still highly desirable. Thus, the compatibility of selected common base-labile protective groups with our anhydrous protocol was investigated (Table 5). TBS and Piv are popular protective groups for phenols.[33] It turned out that substrates bearing these protections were coupled in

Table 5. Comparative studies on protective group compatibility.



Entry	Ar-Br	Method[a]	**6**, Yield [%][b]
1		this work	**6a**, 91
2	**5a**	A	(100)
3		B	(100)
4		this work	**6b**, 83
5	**5b**	A	(40)
6		B	(28)
7		this work	**6c**, 90
8	**5c**	C	(45)

[a] Method A: K_3PO_4/DMF. Method B: K_2CO_3/DMF. Method C: 3 M aqueous NaOH/THF. For simplification, methods A–C were run without borane and catalyst.

[b] Isolated yields. Data in parenthesis refer to percentage of decomposition of the starting materials in 3 h.

high yields in the present protocol without trouble (entries 1 and 4). In contrast, aryl TBS ether was incompatible with K_3PO_4 or K_2CO_3, which are highly basic in DMF or other polar aprotic solvents. In both cases, complete desilylation was observed within 3 h. Similarly, Piv protection for phenol was also vulnerable towards these bases, resulting in considerable decomposition (entries 5 and 6). The methyl ester was also preserved in the present protocol (entry 7), while using aqueous NaOH or KOH as the base caused extensive saponification (entry 8), and presumably this condition would also remove phenolic Piv and TBS protections. Thus, the advantage of the combination of Cs_2CO_3, a relatively weak base, with non-aqueous conditions is significant and valuable.

With this mild and efficient protocol in hand, we set out to synthesize a potent cholesterol ester transfer protein (CETP) inhibitor **9** ($IC_{50}=15$ nM).[34] Being an analogue of penicillide,[35] it features a dibenzo-dioxocinone skeleton highly substituted at both rings A and C. This compound has been prepared using the Negishi or Stille cross-coupling to introduce the required C-10 ethyl substitution,[34] which is responsible for the optimum *in vivo* stability of **9** according to SAR studies. However, in both cases the yields for this key step were rather unsatisfactory. Moreover, lower alkylstannanes such as Et_4Sn are highly toxic and need to be avoided in the pharmaceutical industry. As shown in Scheme 1, the Suzuki coupling of the fully substituted, electron-rich bromoarene **7** smoothly delivered the desired ethylation product **8** in 60–65% yield. The efficiency of the cross-coupling is remarkable: for comparison, in our hands, the Negishi coupling using Et_2Zn gave **8** in only 40% yield (lit. yield 42%).[34a] It is also noteworthy that thanks to the non-aqueous conditions, the base-labile eight-membered lactone ring remained intact. Acylation of the C-11 phenol following the literature method furnished the target compound **9** in excellent yield. Its structure was further confirmed by X-ray crystallography (Figure 3).[36]

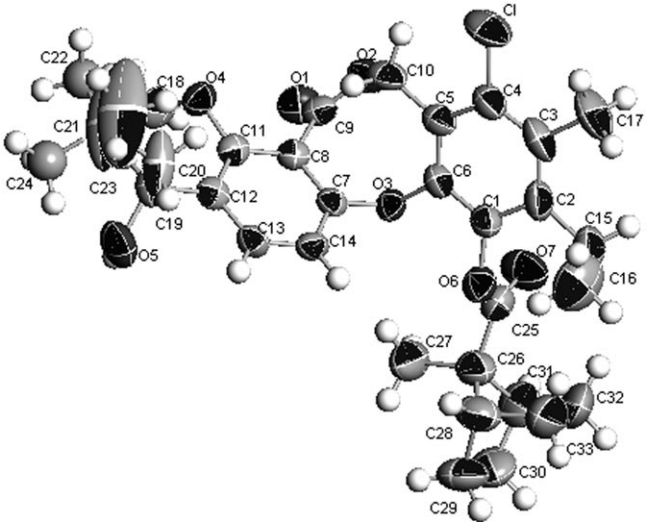
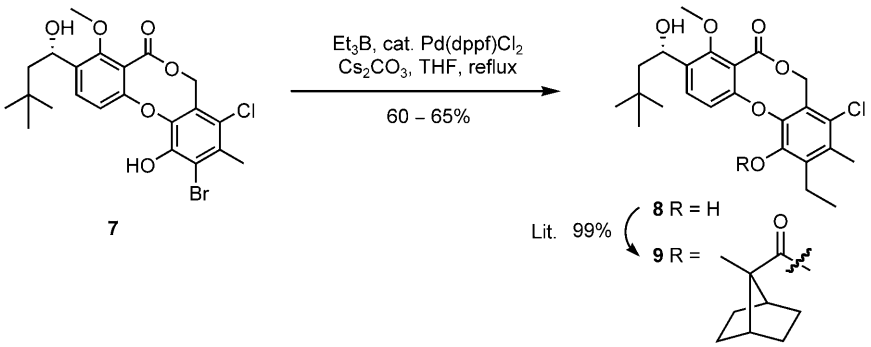


Figure 3. ORTEP drawing of **9** at 50% thermal ellipsoid probability. Large thermal displacements were observed for the *tert*-butyl group and the bicyclic moiety.



Scheme 1. Synthesis of the CETP inhibitor (**9**) *via B*-alkyl Suzuki coupling.

Conclusions

In summary, an efficient and chemoselective direct Suzuki–Miyaura cross-coupling of trialkylboranes with bromoarenes in the presence of unmasked acidic or basic functions has been achieved using the weak base Cs_2CO_3 under mild non-aqueous conditions. Aldehydes, ketones, nitriles, chloro substitution as well as base-labile phenolic TBS and Piv protections were all tolerated. Thus, it is useful for the incorporation of primary alkyls, particularly lower *n*-alkyls, to complex aromatics as demonstrated in the key step of ethylation in our synthesis of a dibenzodioxocinone derivative **5**. The reasonable catalyst loading, the non-aqueous environment and the short reaction time required (2–6 h) are additional advantages. Mechanistically, we have shown that the non-aqueous condition was beneficial for the cross-coupling of bromoarenes, and the role of the base was proposed.

Experimental Section

General Procedure

To a mixture of bromoarene (1.0 mmol), Cs_2CO_3 (977 mg, 3.0 mmol) and Pd(dppf)Cl_2 (15 mg, 2 mol%) in a Schlenk tube under an argon atmosphere was added freshly distilled THF (2.0 mL). To the stirred suspension was added trialkylborane (3.0 mL, 1 M solution in THF, 3.0 mmol) in one portion, and the mixture was refluxed for 2–6 h. The reaction was cooled to 0 °C and quenched by 10% aqueous NaOH and 30% aqueous H_2O_2. After stirring for 30 min at 25 °C, the mixture was acidified by dilute aqueous HCl, and extracted with ether (3×10 mL). The combined organic layer was washed successively with aqueous $FeSO_4$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

Alternative acidic work-up: To the cooled reaction mixture was added 50% aqueous HOAc (2 mL) and the whole was refluxed for 30 min. The cooled solution was extracted with ether (3×10 mL). The combined organic layer was washed successively with water and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

4-(3-(4-Methoxyphenyl)propyl)benzoic acid (2k): mp 148–150 °C; ^{1}H NMR ($CDCl_3$): δ=8.03 (d, 2H, J=8.4 Hz), 7.27 (d, 2H, J=8.1 Hz), 7.09 (d, 2H, J=8.7 Hz), 6.83 (d, 2H, J=9.0 Hz), 3.79 (s, 3H), 2.70 (t, 2H, J=7.8 Hz), 2.60 (t, 2H, J=7.5 Hz), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=172.1, 157.8, 149.0, 133.9, 130.3, 129.3, 128.6, 126.9, 113.8, 55.2, 35.4, 34.4, 32.8.

4-(2-Methylpropyl)benzoic acid (2l): mp 141–143 °C; ^{1}H NMR ($CDCl_3$): δ=8.02 (d, 2H, J=7.8 Hz), 7.25 (d, 2H, J=7.8 Hz), 2.55 (d, 2H, J=6.9 Hz), 1.91 (m, 1H), 0.92 (d, 2×3H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$): δ=171.7, 148.3, 130.1, 129.2, 126.7, 45.4, 30.1, 22.3.

Supporting Information

Characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds are provided in the Supporting Information.

Acknowledgements

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