

Published in final edited form as:

Tetrahedron Lett. 2010 December 22; 51(51): 6748–6752. doi:10.1016/j.tetlet.2010.10.087.

Studies of microwave-enhanced Suzuki-Miyaura vinylation of electron-rich sterically hindered substrates utilizing potassium vinyltrifluoroborate

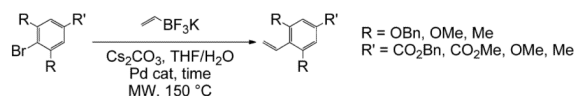
Matthew D. Brooker^a, Stefan M. Cooper Jr.^b, Dena R. Hodges^b, Rhiannon R. Carter^b, and Justin K. Wyatt^{b,*}

^aDepartment of Chemistry, Trident Technical College, 7000 Rivers Ave. Charleston, SC 29455, USA

^bDepartment of Chemistry and Biochemistry, College of Charleston, 66 George St., Charleston SC 29424, USA

Abstract

The Suzuki-Miyaura cross-coupling of sterically hindered and electron-rich *ortho,ortho'*-substituted aryl halides with potassium vinyltrifluoroborate utilizing microwave irradiation has been conducted while adjusting solvent ratio, irradiation time, and catalyst loading to find optimal conditions. Coupling of benzyl 3,5-bis(benzyloxy)-4-bromobenzoate leads to a mixture of the desired styrene derivative, and the reduced product. 4-Bromo-1,3,5-trimethoxybenzene, methyl 4-bromo-3,5-dimethoxybenzoate, and mesitylene bromide were also coupled to test the breadth and scope of this methodology. Of these substrates tested only 4-bromo-1,3,5-trimethoxybenzene was not vinylated successfully, which is believed to be due to the electron rich nature of this system.



Keywords

Suzuki-Miyaura; Potassium vinyltrifluoroborate; Styrenes; Palladium catalysis; Hindered aryl bromides

Substituted styrenes (typically assembled using a transition metal-mediated cross-coupling) are useful intermediates in both the formation of new polymeric material and in the formation of specialty chemicals.¹ Mild vinylation of aryl bromides and/or iodides using trivinylcyclotrioxane,¹ vinylmagnesium bromide,² vinyltrimethylsilane,³ and vinylpolysiloxanes⁴ has been observed. N-Heterocyclic carbenes bearing palladium (II) catalysts have demonstrated high catalytic activity capable of coupling unactivated aryl chlorides.⁵ Aryl bromides and activated aryl chlorides also undergo mild palladium-catalyzed couplings at room temperature with alkenes utilizing dicyclohexylmethylamine as

© 2010 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: 843-953-6587; fax 843-953-1404; wyattj@cofc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

a base.⁶ Potassium vinyltrifluoroborate is a stable alternative that circumvents the limitations of vinylboronic acids, and derivatives of vinylboronic esters.⁷⁻¹⁰ Molander first reported the Suzuki-Miyaura cross-coupling vinylation of aryl halides with potassium vinyltrifluoroborate in 2002;⁸ other examples have been reported in the literature since.¹⁰⁻¹⁶ However, most of the literature is dominated by Suzuki-Miyaura type couplings involving boronic acids or their derivatives.^{5,6,12-21} This paper investigates the Suzuki-Miyaura cross-coupling reaction between various sterically hindered and electron-rich arenes including benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**, Scheme 1) with potassium vinyltrifluoroborate (**2**) with the assistance of microwave irradiation.

Scheme 1 illustrates the first reaction of interest, and the two possible products of the cross-coupling reaction; the desired vinylated product, benzyl 3,5-bis(benzyloxy)-4-vinylbenzoate (**3**), and reduced product, benzyl 3,5-bis(benzyloxy)benzoate (**4**). As with conventional conditions¹⁴ the reduced product was observed under microwave conditions, but only in trace amounts (less than 1% of the total product distribution). Product ratios were determined, if necessary, using ¹H NMR integration of the crude reaction mixture using the methylene hydrogens from the benzyl ethers of the starting material **1**, as well as for the vinyl product **3**; chemical shifts of 5.18 ppm (s, 4H) and 5.14 ppm (s, 4H), respectively. The amount of reduced product **4**, if any, was determined by integration of the triplet at 6.80 ppm (t, *J* = 2.4 Hz, 1H).

Initially, we focused on optimizing the vinylation of benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**) (a compound that has been of interest for this lab towards the synthesis of derivatives of the antibiotic cytosporone E14) using 9 mol % of the palladium catalyst, [PdCl₂(dppf)CH₂Cl₂], 5 equivalents of potassium vinyltrifluoroborate (**2**), 3 equivalents of cesium carbonate, and 0.051 M solution of THF/H₂O (10:1), with respect to **1**, at 150 °C (entries 1-8, Table 1). For all the reactions that gave the desired product, **3**, an average yield of 51% was observed. Entries 5-7 demonstrate that time frames longer than 20 min did not increase the yield above 57%. It is also apparent from Entries 1-4 that at least 20 min is needed to ensure completion of the reaction. This is a significant improvement from the 3-4 days required for the conventional process and a decrease in the formation of the reduced product **4**.¹⁴ Interestingly, the average yield was observed to be lower if the times were divided (avg. 47%) despite that many entries had the same overall irradiation times. (i.e. Entries 1 vs. 5, 20 min; Entries 2 and 3 vs. 6, 30 min.)

Entries 9 and 10, shown in Table 2, were designed to emulate the conventional reaction, which required two additions of 9 mol % PdCl₂(dppf)CH₂Cl₂ catalyst.¹⁴ In both cases the reactions went to completion, but the yields were similar to entries 1-3 in Table 1, where irradiation times were split to allow for the second addition of catalyst (avg. 47%). This suggested that only one addition of catalyst (and only 9 mol%) was sufficient for the reaction. (These reactions were monitored by TLC in between catalyst loading and revealed that nearly all of the starting material, **1**, was consumed at the point of second addition.)

Further optimization of the conditions in this cross-coupling reaction probed the use of a variety of Pd (II) catalysts including: [PdCl₂(dppf)CH₂Cl₂], Pd(OAc)₂ and PdCl₂ and phosphine ligands, where warranted, [X-Phos, RuPhos, and PPh₃] (entries 11-17, Table 3). A few reactions (entries 15-17, Table 3) included the addition of tetrabutylammonium iodide, which has been shown to increase the nucleophilicity of the potassium organotrifluoroborates,^{14,22} but it had no positive effect with our substrate. The only reaction that yielded only the desired product was Entry 12, which employed PdCl₂ and X-Phos.²³ However, these reagents were added as 2 mol % and 6 mol % respectively in two additions over 60 min (for a total of 4 mol % of PdCl₂, and 12 mol % of X-Phos), yielding only 29% yield of **3**. Utilizing PPh₃ or RuPhos (Entries 13 and 14) also gave a poor product

distribution, and these conditions mirror Molander's conditions for sterically hindered *ortho,ortho*'-substituted electron-rich aryl halides.¹² These results, along with previous results, necessitated the employment of the original catalyst PdCl₂(dppf)CH₂Cl₂ versus PdCl₂, X-Phos for success (Tables 1, 2 and 3).^{12,22,24}

The effect of solvent molarity for the reaction was also reinvestigated (Table 4, Entries 18-20), while keeping the solvent ratio of THF:H₂O (10:1).¹⁴ The optimum concentration was still determined to be the 0.051 M in comparison to entries 5 and 10 (Tables 1 and 2), under microwave conditions, but it was found that the coupling could tolerate concentrations up to a 0.091 M solution with a slight drop in yield (entry 19, Table 4).

During optimization of the conventional reaction¹² it was found that the reaction needed 5 equivalents of potassium vinyltrifluoroborate (**2**); therefore, this variable was studied again with the microwave reaction (Entries 21-22, Table 5). **2** was varied from 1.1 to 10 equivalents where it was found that 5 equivalents still gave the best overall yield (57%; Entry 5 & 6, Table 1). The use of 10 equivalents was an interesting result because when the reaction is under conventional control the use of an extreme excess of **2** increases the yield to 87%.¹⁴ Notably, under microwave conditions the yield decreased to 44% (Entry 22, Table 5).

Although the reaction worked moderately well with 9 mol % of the catalyst PdCl₂(dppf)CH₂Cl₂ (Table 1, Entries 5 and 6), decreasing the catalyst loading was still desired. To directly explore this variable the catalyst loading was sequentially adjusted from 9 mol % to 3 mol %, (Entries 23-25, Table 6). It was found that employing 3 mol % or 7 mol % of the catalyst resulted in incomplete reactions or lowered yields (Entries 23 and 25, Table 6). Using 7 mol % of the referred catalyst was experimentally similar to using 9 mol % of the catalyst, giving a 50% yield when compared to Table 1 (Entries 5 and 6). Using 5 mol % of the catalyst PdCl₂(dppf)CH₂Cl₂ produced the desired product **3** with a 77% yield (Table 6, Entry 24). This factor not only increased the yield, but further confirmed that only one addition of catalyst was needed and the presence of the reduced product **4** was also not seen via ¹H NMR.

Solvent systems have been a particular point of interest in cross-coupling reactions; particularly when microwave irradiation is employed due to the need for a solvent with an appreciable dielectric constant.¹⁹ A variety of solvents and solvent mixtures have been employed with superb results in cross-coupling reactions.^{5,6,12,14,21,22,24,25} We chose to investigate the effects of changing the solvent ratios of THF and H₂O and irradiation time with respect to the optimized conditions: 5 mole % of PdCl₂(dppf)CH₂Cl₂, 0.051 M solvent concentration, 5 equiv of **2** (CH₂=CHBF₃K), and irradiation at 150 °C; THF:H₂O ratios were varied from 11:1 to 9:1 irradiation times of 30 and 20 min were employed, respectively (Tables 7 and 8).

Decreasing the water concentration of the solvent system reduced, which is demonstrated by Entry 26 of Table 7, affording a modest yield of **3** (61% yield), with no reduced product observed. Decreasing the amount of H₂O in the (THF:H₂O) mixture was discontinued after these results due to the reduced yield compared to the yield previously observed for a (10:1) ratio (Entry 24, Table 6). These screenings also revealed that the 10:1 (THF:H₂O) conditions at 20 min and 30 min yielded identical (Entry 24 in Table 6, and Entry 27 in Table 8), acceptable results of 77% yield of **3**. (Interestingly, similar reactivity occurred in Table 1, Entries 5 and 7; where 20 and 30 min irradiation times yielded 57% of **3**.) Ultimately, the 9:1 (THF:H₂O) mixture was the most successful, affording **3** with similar yields again at 20 and 30 min irradiation times with 93% and 89%, (Entry 29 in Table 8, and Entry 27 in Table

7 respectively).¹² Increasing the reaction time for the 9:1 mixture did not result in any improved results (not shown).

With the optimized reaction conditions (being 5 mol% PdCl₂(dppf)CH₂Cl₂, 5 equiv of potassium vinyltrifluoroborate, 3 equiv cesium carbonate, 0.051 M THF/H₂O (9:1), and heating at 150 °C for 20 min) for **3** in hand we studied the applicability and scope of our method with other activated, *ortho,ortho'*-hindered aryl halides; 1-bromo-2,4,6-trimethoxybenzene **5** (Scheme 2), methyl 3,5-dimethoxy-4-bromobenzoate **8** (Scheme 3), and 2-bromomesitylene **11** (Scheme 4).

Vinylation attempts of 2-bromo-1,3,5-trimethoxybenzene **5** with our optimized (Scheme 2) conditions yielded only starting material. Regardless of the time employed, (Entries 30-32, Table 9). The strongly activated ring is believed to account for this outcome, as has been noted in the literature.^{12,14,20,21} It should be noted here for the reader that although our methodology was unproductive, Fu and Nolan's pre-mentioned vinylation methods appear to be a more amenable to substrates involving extremely electron rich and sterically hindered aryl halides.^{5,6}

The vinylation of methyl 4-bromo-3,5-dimethoxybenzoate **8** (see Scheme 3) was found to be strongly time dependent as the time was increased from 20 minutes to 30 min. Entries 33 and 34 demonstrate this observation (44% to 82%; respectively, Table 10). Experiments running longer than 30 min did not show any increase in yield. Both substrates **5** and **8** are similar in that they both have the *ortho,ortho'*-hindering alkoxy groups but differ in the functional group that is *para* to the bromo substituent. The success of substrate **8** is believed to be attributed to the presence of the electron-withdrawing methyl ester present in the molecule as seen with substrate **3**.

Mesitylene bromide (**11**) was chosen for its three moderately activating methyl groups and the *ortho,ortho'* hindrance of the bromo substituent (Scheme 4). The vinylation of mesitylene bromide **11** (Scheme 4) was treated similarly to the 1,3,5-trimethoxybenzene **5** due to their electron rich nature. Hence reaction times were begun at 30 min and ranged to 60 min (Entries 35-37, Table 11). Entry 36 showed a 67% yield of a (1:5.1:0:0) mixture of **11**, **12**, **13**, and **14** after irradiation for 45 min with no stilbene side product observed. Extending irradiation times increased the vinylated product yield (80%), but also introduced the Heck product **14** (see Entry 37). This was an improvement over the conventional conditions, which converted substrate **11** almost exclusively to the stilbene product **14**.¹⁴ It should also be noted that Denmark and Butler have recently reported superior results (99% yield) with substrate **11** via polyvinylsiloxanes.^{4b} Buchwald has also modestly coupled **11** (using conventional conditions) with a 83% yield of **12** with no side products.²⁴

In conclusion, microwave assistance (compared to the conventional conditions)¹⁴ for this cross-coupling reaction has reduced the amount of catalyst loading by over three-fold from 18 mol % to 5 mol %, it has demonstrated a dramatic decrease in reaction time from 3-4 days to 20 minutes (nearly 300 times faster), and it has increased the yield from 73% to 93% for benzyl ester **1**. This investigation also revealed that the reaction methodology is more tolerant to solvent ratios with all substrates employed than previously believed and that proper catalyst loading and correct irradiation time can help eliminate the production of the reduced product. It has also been shown that the vinylation with potassium vinyltrifluoroborate is best accomplished with *ortho,ortho'*-substituted aryl halides with at least one electron-withdrawing group present thus reducing the electron-rich nature of the aromatic halide (which is common to the Suzuki-Miyaura reaction in general).

Experimental

Typical Suzuki-Miyaura coupling conditions

A dry 10 mL Pyrex tube (from CEM) fitted with an airtight rubber septa was charged with a stir bar, potassium vinyltrifluoroborate (**2**) (133 mg, 0.995 mmol), cesium carbonate (194 mg, 0.597 mmol), PdCl₂(dppf)CH₂Cl₂ (7.2 mg, 0.0099 mmol), and benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**) (100 mg, 0.199 mmol) was flushed with argon. Degassed THF (3.87 mL) and degassed deionized H₂O (0.430 mL) were then added. The rubber septum was replaced with a septum cap from CEM to give a sealed system. The resulting rust-red colored solution was placed in a CEM Discover microwave unit and allowed to react for 30 minutes at 150 °C. The resulting brown solution was diluted with 7 mL of H₂O and extracted with Et₂O (10 mL × 3). The combined organic layers were then washed with 1 M HCl (10 mL) and brine (10 mL). The clear, yellow solution was dried over MgSO₄ and filtered. The solvent was removed under reduced pressure using a rotary evaporator. The red-brown residue was purified using flash chromatography (3% EtOAc/5% CHCl₃/Hexanes) to yield benzyl 3,5-bis(benzyloxy)-4-vinylbenzoate **3** as a colorless solid in 93% yield (76 mg). mp = 102-103 °C. ¹H NMR (CDCl₃; 300 MHz): δ 7.44-7.28 (m, 17H), 7.08 (dd, *J* = 18.1 and 12.2 Hz, 1H), 6.25 (dd, *J* = 18.0 and 2.5 Hz, 1H), 5.52 (dd, *J* = 12.2 and 2.6 Hz, 1H), 5.34 (s, 2H), 5.12 (s, 4H). ¹³C NMR (CDCl₃; 300 MHz): 166.2, 157.6, 136.8, 136.2, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 127.7, 127.0, 121.6, 120.4, 106.9, 71.0, 67.0. IR (solid): *ν* = 3063, 3026, 1708, 1623, 1567, 1120, 1114 cm⁻¹.

Typical CEM Discover microwave settings

Power: 150 W, Ramp time: 02:00 min, Hold time 30:00 min, Temperature: 150 °C, with stirring. The pressure feedback from the CEM Discover instrument ranged from 150 psi to 175 psi.

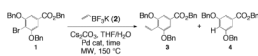
Acknowledgments

The authors thank the NIH Grant Number P20 RR-016461 from the National Center for Research Resources NIH SC-INBRE grant, ACS PRF (Type G 39541-GB1), and the College of Charleston Department of Chemistry and Biochemistry for support.

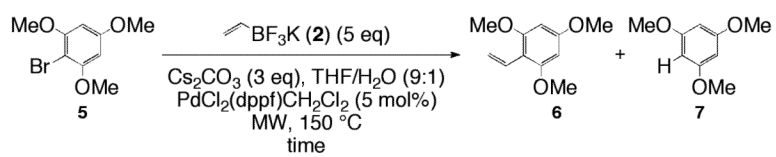
References

- (1). Kerins F, O'Shea DF. *J. Org. Chem* 2002;67:4968–4971. [PubMed: 12098315]
- (2). Bumagin NA, Luzikova EV. *J. Organomet. Chem* 1997;532:271–273.
- (3). Jeffery T. *Tetrahedron Lett* 1999;40:1673–1676.
- (4). a) Denmark SE, Wang Z. *J. Organomet. Chem* 2001;624:372–375. b) Denmark SE, Butler CR. *Org. Lett* 2006;8:63–66. [PubMed: 16381568]
- (5). a) Navarro O, Kaur H, Mahjoor P, Nolan SP. *J. Org. Chem* 2004;69:3173–3180. [PubMed: 15104459] b) Marion N, Navarro O, Edwin SD, Scott NM, Nolan SP. *J. Am. Chem. Soc* 2006;128:4101–4111. [PubMed: 16551119]
- (6). Littke AF, Fu GC. *J. Am. Chem. Soc* 2001;123:6989–7000. [PubMed: 11459477]
- (7). Vedejs E, Chapman RW, Fields SC, Lin S, Schrimf MR. *J. Org. Chem* 1995;60:3020–3027.
- (8). a) Darses S, Michaud G, Benet J-P. *Tetrahedron Lett* 1998;39:5045–5048. b) Molander GA, Rivero MR. *Org. Lett* 2002;4:107–109. [PubMed: 11772102]
- (9). a) Matteson DS. *J. Am. Chem. Soc* 1960;82:4228–33. b) Onak, T. *Organoborane Chemistry*. Academic Press; New York: 1975.
- (10). Molander GA, Figueroa R. *Aldrichimi. Acta* 2005;38:49–56.
- (11). Molander GA, Bernardi CR. *J. Org. Chem* 2002;67:8424–8429. [PubMed: 12444620]
- (12). Molander GA, Brown AR. *J. Org. Chem* 2006;71:9681–9686. [PubMed: 17168585]

- (13). a) Joucla L, Cusati G, Pinel C, Djakovitch L. *Tetrahedron Lett* 2008;49:4738–4741. b) Caneque T, Cuadro AM, Alvarez-Builla J, Vaquero JJ. *Tetrahedron Lett* 2009;50:1419–1422.
- (14). Carter RR, Wyatt JK. *Tetrahedron Lett* 2006;47:6091–6094. b) Using conventional conditions this reaction needed 3–4 days at 150 °C to proceed to completion and required 18 mol % (added in two equimolar catalytic portions) of the palladium catalyst [PdCl₂(dppf)CH₂Cl₂] along with 5 equiv of potassium vinyltrifluoroborate to attain a 73% isolated yield.
- (15). a) Kappe CO. *Angew. Chem., Int. Ed* 2004;43:6250–6284. b) Kappe CO, Dallinger D. *Nat. Rev. Drug Discov* 2006;5:51–63. [PubMed: 16374514] c) Nilsson P, Olofsson K, Larhed M. *Top. Curr. Chem* 2006;266:126–134.
- (16). a) Harker RL, Crouch DR. *Synthesis* 2007;25–27. b) Arvela RK, Leadbeater NE, Mack TL, Kormos CM. *Tetrahedron Lett* 2005;47:217–220.
- (17). a) Kabalka GW, Zhou L-L, Naravane A. *Lett. Org. Chem* 2007;4:325–328. b) Kabalka GW, Al-Masum M. *Tetrahedron Lett* 2005;46:6329–6331.
- (18). Kabalka GW, Al-Masum M, Mereddy AR, Dadush E. *Tetrahedron Lett* 2006;47:1133–1136.
- (19). Kabalka GW, Dadush E, Al-Masum M. *Tetrahedron Lett* 2006;47:7459–7461.
- (20). Singh BK, Cavalluzzo C, De Maeyer M, Debyser Z, Parmar VS, Van der Eycken E. *Eur. J. Org. Chem* 2009:4589–4592.
- (21). a) Billingsly KL, Andersom KW, Buchwald SL. *Angew. Chem. Int. Ed* 2006;45:3484–3488. b) Barden TE, Buchwald SA. *Org. Lett* 2004;6:2649–2652. [PubMed: 15281735]
- (22). Batey RA, Quach TD. *Tetrahedron Lett* 2001;42:9099–9103.
- (23). Molander GA, Biolatto B. *Org. Lett* 2002;4:1867–1870. [PubMed: 12027634]
- (24). Billingsley KL, Anderson KW, Buchwald SL. *Angew. Chem., Int. Ed* 2006;45:3484–3488.
- (25). a) Molander GA, Jean-Gerrard. *J. Org. Chem* 2009;74:1297–1303. [PubMed: 19133770] b) Molander GA, Canturk BL. *J. Org. Chem* 2009;74:973–980. [PubMed: 19105735] c) Dreher SD, Lim S-E, Sandrock DL, Molander GA. *J. Org. Chem* 2009;74:3626–3631. [PubMed: 19271726]



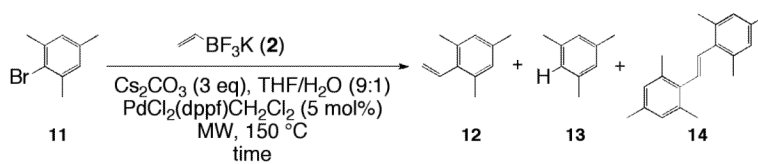
Scheme 1.
Microwave-enhanced vinylation of benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**).



Scheme 2.
Attempted vinylation of 2-bromo-1,3,5-trimethoxybenzene (**5**) employing optimized conditions.



Scheme 3.
Vinylation of methyl 4-bromo-3,5-dimethoxybenzoate (**8**).



Scheme 4.
Vinylation of mesitylene bromide (**11**).

Table 1Effect of irradiation time on benzyl 3,5-bis(benzloxy)-4-bromobenzoate (**1**)

Entry ^a	Time	1:3:4 ^b	Yield of 3 ^c
1	10 min × 2	0:1:trace	45
2	10 min × 3	0:1:trace	49
3	15 min × 2	0:1:trace	48
4	15 min	11:50:1	n/a
5	20 min	0:1:trace	57
6	30 min	0:1:trace	57
7	45 min	0:1:trace	56
8	60 min	0:1:trace	56

^a 9 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (10:1) at 0.051 M, 5 equiv of **2**, 3 equiv Cs₂CO₃, 150 °C.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 2

Effect of doubling the catalyst loading from 9 mol % to 18 mol % with benzyl 3,5-bis(benzloxy)-4-bromobenzoate (**1**)

Entry ^a	Time	1:3:4 ^b	Yield of 3 ^c
9	15 min × 2	0:1:trace	45
10	30 min, 15 min	0:1:trace	49

^a 18 mol % PdCl₂(dppf)CH₂Cl₂ (added in two equal 9 mol% portions), THF:H₂O (10:1) at 0.051 M, 5 eq. of **2**, 3 eq. C₂CO₃, 150 °C.

^b Isolated yield.

^c Determined by ¹H NMR integration of the crude mixture.

Table 3

Effect of catalyst and additives on the yield of benzyl 4-bromo-3,5-bis(benzloxy)benzoate (**3**)

Entry ^a	Catalyst ^b	Mole %	Time	1:3:4 ^c	Yield of 3 ^d
11	PdCl ₂ , X-Phos	2,6	30 min	2:1:trace	n/a
12	PdCl ₂ , X-Phos	(2,6) × 2	30 min × 2	0:1:trace	29
13	PdCl ₂ , PPh ₃	2,6	30 min	2.3:1:trace	n/a
14	PdCl ₂ , RuPhos	2,6	30 min	1.6:1:0	n/a
15 ^b	Pd(OAc) ₂ , dppb	5,5	30 min	0:3:1	n/a
16 ^b	PdCl ₂ (dppf)CH ₂ Cl ₂	9	60 min	1:3:1	n/a
17 ^b	PdCl ₂ (dppf)CH ₂ Cl ₂	9	90 min	0:5:1	n/a

^a THF:H₂O (10:1) at 0.051 M, 5 equiv of **2**, 3 equiv Cs₂CO₃, 150 °C.^b Employed Bu₄NI.^c Determined by ¹H NMR integration of the crude mixture.^d Isolated yield.

Table 4

Toleration of vinylation reaction to changes in solvent molarity with benzyl 3,5-bis-(benzloxy)-4-bromobenzoate (**1**)

Entry ^a	Time	Molarity	1:3:4 ^b	Yield of 3 ^c
18	30 min	0.027 M	7:15:1	n/a
19	30 min	0.091 M	0:1:trace	44
20	30 min	0.18	0:9:1	n/a

^a 9 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (10:1) at 0.051 M, 5 equiv of **2**, 3 equiv Cs₂CO₃, 150 °C for 30 min

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 5

The effect of varying equivalents of potassium vinyltrifluoroborate with benzyl 3,5-bis-(benzloxy)-4-bromobenzoate (**1**)

Entry ^a	Moles of 2	1:3:4 ^b	Yield of 3 ^c
21	1.1	0:11:1	n/a
22	10	0:1:trace	44

^a 9 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (10:1) at 0.051 M, 3 equiv Cs₂CO₃, 150 °C for 30 min.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 6Effect of molar percent of PdCl₂(dppf)CH₂Cl₂ catalyst loading

Entry ^a	Mole % catalyst	1:3:4 ^b	Yield of 3 ^c
23	3	1:7:trace	n/a
24	5	0:1:0	77
25	7	0:1:trace	50

^a PdCl₂(dppf)CH₂Cl₂, THF:H₂O (10:1) at 0.051 M, 3 equiv Cs₂CO₃, 150 °C for 30 min.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 7

Effect of different solvent ratios at 30 minutes of irradiation time

Entry ^a	Solvent Ratio THF:H ₂ O	1:3:4 ^b	Yield of 3 ^c
26	11:1	0:1:trace	61
27	9:1	0:1:0	89

^a 5 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O at 0.051 M, 3 eq. Cs₂CO₃, 150 °C for 30 min.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 8

Effects of different solvent ratios at 20 minutes of irradiation time

Entry ^a	Solvent Ratio THF:H ₂ O	1:3:4 ^b	Yield of 3 ^c
28	10:1	0:1:trace	77
29	9:1	0:1:0	93

^a 5 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O at 0.051 M, 3 equiv Cs₂CO₃, 150 °C for 20 min.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 9Vinylations attempts with 2-bromo-1,3,5-trimethoxybenzene (**5**)

Entry ^a	Time	5:6:7 ^b	Yield of 6 ^c
30	20 min	1:0:0	n/a
31	30 min	1:0:0	n/a
32	60 min	1:0:0	n/a

^a 5 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (9:1) at 0.051 M, 3 equiv Cs₂CO₃, 150 °C.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 10Vinylation results with methyl 4-bromo-3,5-dimethoxybenzoate (**8**)

Entry ^a	Time	8:9:10 ^b	Yield of 9 ^c
33	20 min	1.5:1:0	44
34	30 min	0:1:0	82

^a 5 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (9:1) at 0.051 M, 3 equiv Cs₂CO₃, 150 °C.

^b Determined by ¹H NMR integration of the crude mixture.

^c Isolated yield.

Table 11Vinylolation of mesitylene bromide (**11**)

Entry ^a	Time	11:12:13:14 ^b	Yield of 12 ^b
35	30 min	1:4:0:0	37
36	45 min	1:5.1:0:0	67
37	60 min	1:9:0:1	80

^a 5 mol % PdCl₂(dppf)CH₂Cl₂, THF:H₂O (9:1) at 0.051 M, 3 equiv Cs₂CO₃, 150 °C.

^b Yields and ratios determined by n-dodecane internal standard and ¹H NMR integration.