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Efforts Directed toward the Synthesis of Colchicine: Application of Palladium-Catalyzed Siloxane Cross-Coupling Methodology

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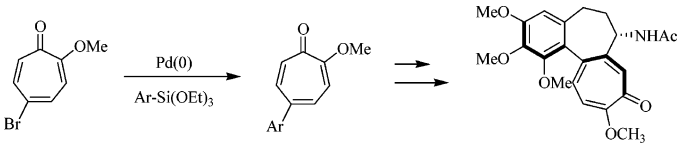


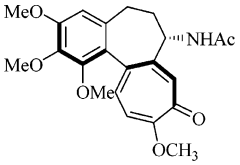
colchicine

Colchicine is an important and synthetically challenging natural product. The key synthetic step in this approach to the synthesis of colchicine involved a palladium-catalyzed cross-coupling reaction between 5-bromotropolone (**4**) and an aryl siloxane to form the aryl-tropolone bond. The coupling of a variety of highly functionalized aryl siloxane derivatives was investigated and optimized coupling conditions were developed. It was discovered that a palladium catalyst with a high degree of phosphine ligand coordination (5 equiv of phosphine/mol Pd) was necessary to efficiently couple aryl siloxanes with 5-bromotropolone (**4**). In addition, the coupling approach has provided a direct comparison between siloxane and boronic acid coupling technologies that demonstrated that aryl siloxanes and boronic acids produce similar yields of highly functionalized biaryl products.

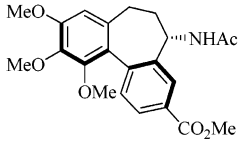
Introduction

Colchicine (**1**) was first isolated from the meadow saffron *Colchicum autumnale* over 100 years ago and is used in the treatment of gout.[1] More recently, the activity of colchicine as a spindle poison has been reported. Its mechanism of action involves binding to tubulin monomers and prevention of the formation of microtubules, which are essential to cellular mitosis.[2−6] Tubulin binding leads to mitotic arrest and subsequent cell death. Attempts to develop colchicine as an antitumor compound have been ineffective due to its potent broad spectrum cytotoxicity. The mitigation of the cytotoxicity of colchinoids has been extensively investigated in an effort to find new antitumor agents with improved therapeutic properties.[3−10]

Colchicine has attracted the attention of many synthetic chemists over the years.[11] Its deceptively simple structure poses several significant challenges, most notably the synthesis of the tropolone ring system.[12,13] In addition to the troplone ring, the formation of the 6-7-7 fused ring system of colchicine, and the 6-7-6 system in the colchinoid analogue allocolchicine (**2**), present another unique synthetic challenge.



(-)-(aR, 7S)-colchicine (**1**)



(-)-(aR, 7S)-allocolchicine (**2**)

The majority of the total syntheses of colchicine have been linear in approach and suffer from one or more steps

(1) LeHello, C. In *The Alkaloids*; Cordell, G. A., Ed.; Chemical Society: London, 2000; Vol. 53.
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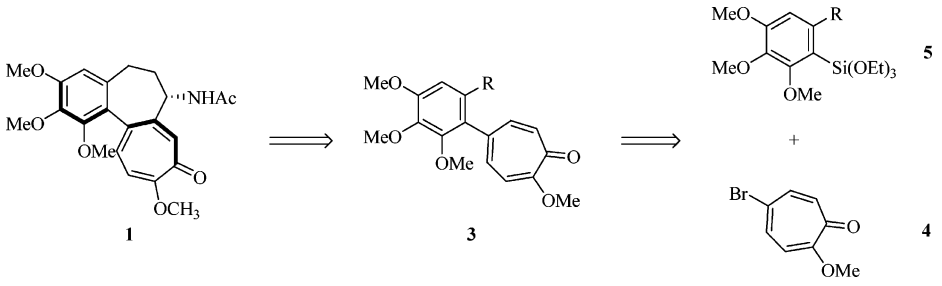
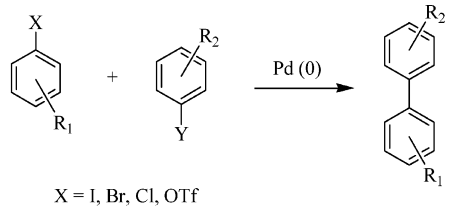
SCHEME 1



that proceed in poor yields. Recently, several synthetic approaches have been developed that allow for a more efficient construction of the carbocyclic framework.[11] Our approach to the synthesis of colchicine and its derivatives employed a palladium-catalyzed siloxane cross-coupling reaction to form the carbon−carbon bond between the aryl ring and the troplone ring (Scheme 1). This coupling would allow facile access to functionalized derivatives of Fitzgerald's compound (**3**, R=H), which has been shown to possess the same biological activity as colchicine.[2] Formation of the aryl-tropolone bond by a cross-coupling reaction has been investigated previously in model systems using Stille couplings[14] and Fitzgerald's compound (**3**) has been prepared using Suzuki coupling.[15,16] We chose to investigate the siloxane coupling reaction developed in our laboratory for the synthesis of the colchicine/colchicinoid carbocyclic framework. This study would yield a direct comparison of the siloxane reaction to other cross-coupling strategies.

Palladium-catalyzed coupling reactions play an ever increasing role in organic synthesis.[17] The ability to efficiently form carbon−carbon bonds in molecules with complex chemical architecture remains a challenging task. Work in our laboratory has focused on the formation of aryl−aryl bonds using hypercoordinate siloxane derivatives,[18−28] a variant of the Hiyama cross-coupling reaction.[29−35] This reaction has advantages over traditional cross-coupling protocols[36] such as the Suzuki-Miyaura[37−41] (organoboron) or Stille[42−46] (organostannae) coupling reactions (Scheme 2) because the siloxane methodology eliminates the purification difficulties associated with organoboron reagents,[47] and the toxic byproducts associated with the use of organotin compounds.[46] The goal of this study was to demonstrate that siloxane-based couplings could be employed effectively in complex natural product synthesis. In addition, the use of colchicine (**1**) and colchicinoids (i.e., **2**) as targets would also allow for the direct comparison of the siloxane and boronic acid based strategies.

SCHEME 2



Results and Discussion

The aryl bromide coupling partner for the key siloxane coupling reaction is 5-bromotropolone (**4**). Banwell and co-workers have developed an efficient synthesis of this

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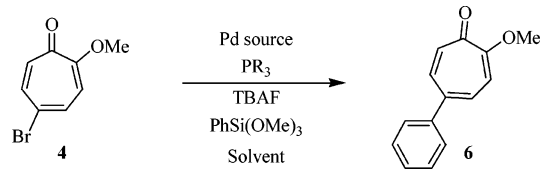
TABLE 1. Optimization of 5-Bromotropolone Coupling with Phenyl Trimethoxysilane[a]



entry	Pd source (mol%)	PR_3 (mol%)	solvent[b]	yield (%)[c]
1	$Pd(OAc)_2$ (10)	$P(o\text{-}tol)_3$ (20)	DMF	0
2	$Pd(OAc)_2$ (10)	PPh_3 (20)	DMF	15
3	$Pd(OAc)_2$ (10)	PPh_3 (40)	THF	51
4	$Pd(OAc)_2$ (10)	PPh_3 (50)	THF	86
5	**$Pd(OAc)_2$ (5)**	**PPh_3 (25)**	**THF**	**84**
6	$Pd(PPh_3)_4$ (1)	PPh_3 (5)	THF	52
7	$Pd(PPh_3)_4$ (10)		DMF	0
8	$Pd(PPh_3)_4$ (10)		THF	24
9	$Pd(PPh_3)_4$ (10)	PPh_3 (10)	THF	84
10	$Pd(PPh_3)_4$ (10)	PPh_3 (20)	THF	88
11	$Pd(PPh_3)_4$ (5)	PPh_3 (10)	THF	23
12	$Pd(PPh_3)_4$ (10)		dioxane	0
13	$Pd(dba)_2$ (10)		DMF	0
14	$Pd(dba)_2$ (10)		THF	0
15	$Pd(dba)_2$ (10)	PPh_3 (50)	THF	46
16	$Pd(dba)_2$ (10)	PPh_3 (100)	THF	54
17	$Pd(dba)_2$ (10)	$P(cy)_2$(o-biphenyl) (10)	DMF	0
18	$Pd(dba)_2$ (10)	$P(t\text{-}Bu)_2$(o-biphenyl) (10)	DMF	0
19	$[Pd(allyl)Cl]_2$ (10)	PPh_3 (20)	THF	0
20	$[Pd(allyl)Cl]_2$ (10)	PPh_3 (20)	DMF	0
21	$[Pd(allyl)Cl]_2$ (10)	$P(cy)_2$(o-biphenyl) (10)	DMF	0

[a] Reactions were stirred for 10 h unless otherwise noted. [b] Reactions conducted in THF or dioxane were performed at the reflux temperature of the solvent. Reactions in DMF were heated to 90 °C. [c] Isolated yields. In reactions that produced no product, starting material was recovered. In reactions that yielded coupled product, the remainder of the starting material decomposed.

compound and we adopted a modified Banwell sequence for this study.[48] With this compound in hand, an investigation was undertaken to elucidate conditions that would allow for the successful cross-coupling with phenyltrimethoxysilane to form 5-phenyltropolone (**6**) and the results are summarized in Table 1. A variety of catalyst and phosphine combinations were tested. The use of palladium acetate and triphenyl phosphine in a 1:5 ratio was found to be the optimum catalyst for the cross-coupling reaction (entries 4 and 5). An extensive series of reduced $Pd(OAc)_2$:phosphine ratios in either THF or DMF were screened (entries 1−3, data from additional reactions not shown) and consistently lead to poor yields of coupled product. The reaction could be conducted with no appreciable loss in yield with as little as 5 mol % catalyst (entry 5). Similar results could be obtained using tetrakis(triphenylphosphine) palladium(0) with the addition of 10−20 mol % of excess phosphine (entries 9 and 10). However, it was interesting to note that, without the additional phosphine, $Pd(PPh_3)_4$ was a poor catalyst for the reaction (entry 8).

Clearly, the optimum catalyst for the reaction requires a high degree of triphenylphosphine ligation to palladium. This observation is particularly evident when the palladium source is changed to bis(dibenzylideneacetone)-palladium(0) ($Pd(dba)_2$). No cross-coupling occurred (entries 13 and 14) unless a large excess (5 equiv) of triphenylphosphine was added (entry 15). The addition of further equivalents of phosphine did not improve the yield (entry 16). Additionally, the yield was poor compared to those of the palladium acetate and $Pd(PPh_3)_4$ systems.

These results indicate that even though the active catalyst in each case is a palladium(0) triphenylphosphine complex, the original ligands on the palladium source (OAc, PPh_3, dba) play important roles in determining the activity of the catalyst. Particularly in the case of $Pd(dba)_2$, the original ligand (dba) may be effectively competing with triphenylphosphine for ligation to the metal, thus decreasing the activity of the catalyst. The detrimental effect of dba on palladium(0) catalyst efficiency was observed by Amatore and Jutand.[49] In addition, other studies have shown that dba slows the oxidative addition of Pd(0) and aryl halides.[50]

With the optimum conditions in hand for the palladium-catalyzed coupling of 5-bromotropolone with phenyltrimethoxysilane, attention turned to the preparation of siloxanes that would be suitable tropolone coupling partners for the colchicine synthesis. The preparation of functionalized siloxanes is presented in Table 2. All of the selected siloxanes contain highly electron-rich aryl rings, which can prove to be difficult substrates for palladium-catalyzed coupling reactions. Using (triethoxysilyl)-2,3,4-trimethoxybenzene (**7**, entry 1) as the coupling partner with 5-bromotropolone (**4**) would allow for

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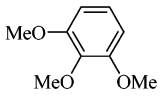
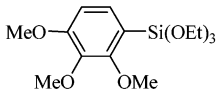
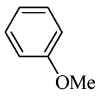
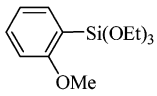
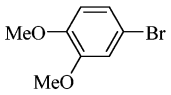
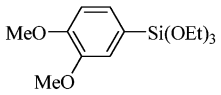
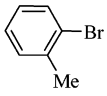
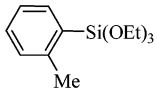
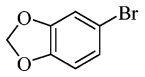
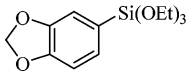
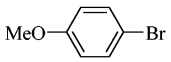
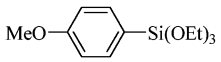
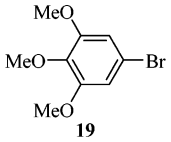
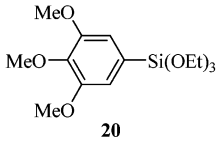
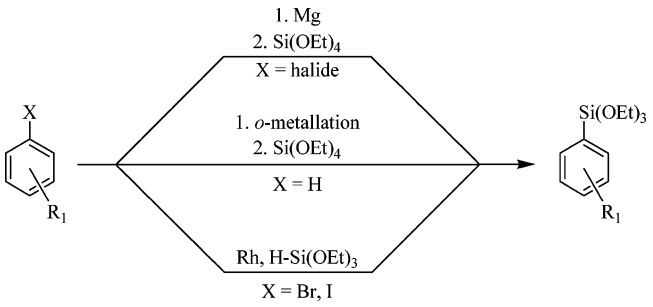
TABLE 2. Synthesis of Siloxanes as Substrates for the Palladium-Catalyzed Coupling with Bromotropolone[a]

entry	starting material	siloxane	method[a]	yield (%)[b]
1	 **7**	 **8**	ortho-metallation[c]	77
2	 **9**	 **10**	ortho-metallation[c]	62
3	 **11**	 **12**	Grignard	61
4	 **13**	 **14**	Grignard	81
5	 **15**	 **16**	Grignard	59
6	 **17**	 **18**	Grignard	82
7	 **19**	 **20**	hydrosilylation	66

[a] See Experimental Section for full details. [b] Isolated yields of purified product. [c] While these two compounds could have been prepared using Grignard chemistry, ortho-metalation offers an inexpensive alternative to the use of costly aryl bromides. A discussion of this topic is contained in ref 27.

the formation of Fitzgerald's compound (**3**). Entries 2−7 would help to define the scope and limitations of the siloxane coupling technology by demonstrating the ability to couple highly substituted electron-rich aryl rings. All of the siloxanes were readily prepared cleanly and in high yields using either ortho-metalation (entries 1 and 2),[27] Grignard (entries 3−6),[24] or hydrosilylation (entry 7)[21,51,52] reactions. These three methods are complementary and together allow for the synthesis of virtually any aryl siloxane (Scheme 3).

SCHEME 3

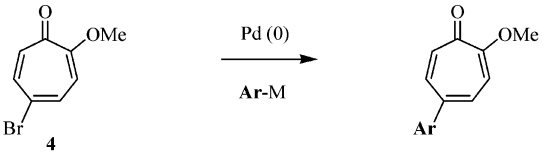


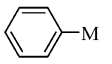
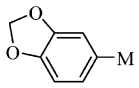
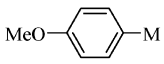
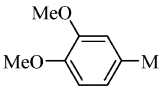
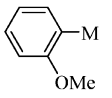
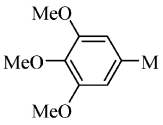
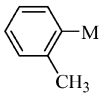
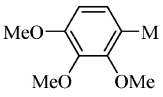
The next facet of the study was to investigate the cross-coupling reaction between these siloxane substrates and 5-bromotropolone (**4**). In addition to coupling reactions using aryl siloxanes, we were presented with an opportunity to directly compare the coupling efficiency of aryl stannanes and boronic acids with aryl siloxanes. Banwell has reported the coupling of a variety of aryl stannanes with bromotropolone,[14] and Nair[16] has reported the synthesis of Fitzgerald's compound (**3**) using boronic acid coupling. With use of the aryl stannane coupling results of Banwell, and the aryl boronic acid and siloxane couplings from our laboratory, a side-by-side comparison of the coupling methodologies could be made.

The results of this comparison study are presented in Table 3. In the case of aryl siloxanes, the coupling reaction is tolerant of both meta- and para-substitution patterns, as well as electron-rich substrates where excellent yields are obtained (entries 1, 2, and 4−7). The

(51) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843−1845.
(52) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569−8571.

TABLE 3. Coupling of Aryl Siloxanes with 5-Bromotropolone[a]



entry	Ar-M	yield (%)[b] M = $SnBu_3$[c]	$B(OH)_2$	$Si(OEt)_3$	entry	Ar-M	yield (%)[b] M = $SnBu_3$[c]	$B(OH)_2$	$Si(OEt)_3$
1	 **6**	98	89	84	5	 **24**	60	92	87
2	 **21**	53	87	81	6	 **25**	57	89	88
3	 **22**	31	80	0	7	 **26**	59	87	89
4	 **23**	-	96	81	8	 **27**	0	94[d]	92[e](0)[f]

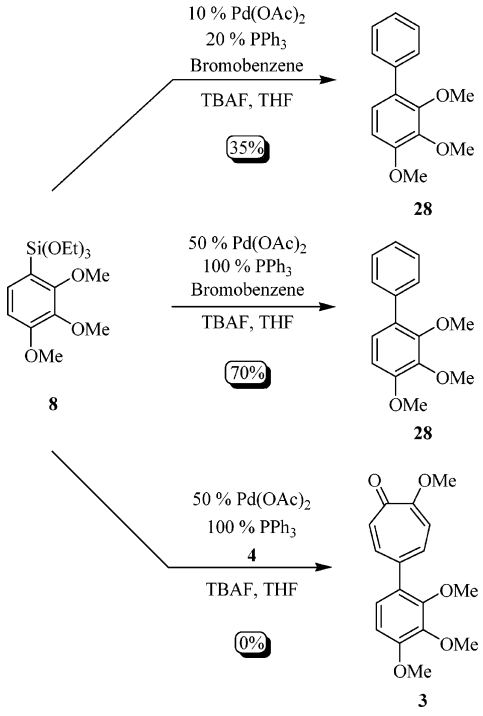
[a] All coupling reactions performed with 5 mol % catalyst unless otherwise noted. See Experimental Section (boronic acid, siloxane) or ref 14 (organostannane) for details. [b] Isolated yield of purified product. [c] Data from ref 14. [d] Reference 16. [e] Bromotropolone premixed with a stoichiometric amount of palladium before addition of the siloxane. See Experimental Section for details. [f] Reaction performed with 5 mol % catalyst.

coupling of *o*-methoxy-substituted siloxanes **22** and **27** (entries 3 and 8) proved to be problematic and no coupling product was observed under standard coupling conditions (vide infra). On the other hand, the coupling of *o*-methyl siloxane (entry 4) proceeded smoothly under standard conditions.

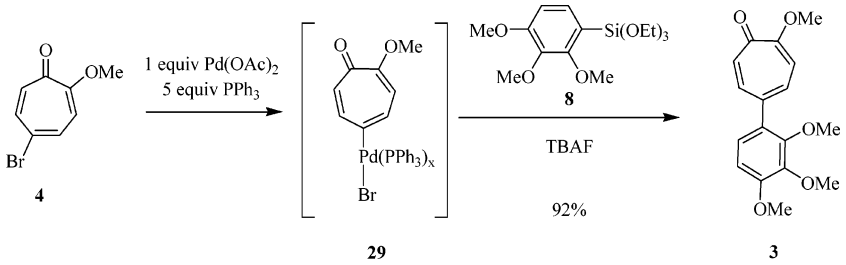
The *o*-methoxy siloxane results were not unexpected as it had been previously observed that siloxanes containing an *o*-methoxy substituent were rapidly protodesilylated under the cross-coupling conditions, yielding poor yields of coupled product.[27] This propensity for protodesilylation could be overcome, to a degree, by increasing the catalyst loading to 50 mol % (Scheme 4).[27] In the case of the tropolone ring system, increasing the catalyst loading to 50 mol % failed to provide any coupled product and the siloxane was quantitatively protodesilylated. In contrast to the tropolone coupling, when siloxane **8** was coupled with bromobenzene to generate biaryl **28**, good yields of coupled product could be isolated (see Scheme 4).

In general, when the three methodologies are compared, the aryl siloxanes provide similar yields to the corresponding boronic acids, while both the siloxanes and boronic acids provide superior yields to organostannane reagents. All three methodologies efficiently coupled a simple phenyl group (entry 1); however, the coupling of electron-rich substrates proved more problematic for the Stille couplings (entries 2, 3, and 5−8). Notable is the fact that only the boronic acid was able to efficiently provide coupled product for the 2,3,4-trimethoxy moiety (**27**), while the Stille reaction failed to provide any

SCHEME 4



SCHEME 5



product,[14] and the siloxane coupling required a stoichiometric amount of palladium to yield the desired biaryl.

The failure of the bromotropolone ring system to couple with *o*-methoxy containing siloxanes is attributed to a slower oxidative addition step for the tropolone coupling, thus permitting protodesilylation to consume the siloxane before coupling can occur. In support of this hypothesis, treatment of 5-bromotropolone *with a stoichiometric* amount of the palladium catalyst, followed by the addition of siloxane **8** and TBAF, gave a 92% yield of the coupled product (Scheme 5). There are several notable features of the coupling reaction under these conditions: the oxidative addition product **29** was formed, and upon addition of the siloxane and TBAF, transmetalation occurred faster than protodesilylation to give Fitzgerald's compound (**3**). The isolation and characterization of a palladium(0)−aryl halide oxidative addition product has been accomplished previously.[53−55] In their study, however, Hartwig and co-workers used haloarenes as substrates and were able to isolate and fully characterize the product. No studies exist that report the synthesis and characterization of a bromotropolone oxidative insertion product such as **29**. Thus, we were disappointed when all attempts at isolation and characterization of **29** were unsuccessful.[56]

It is plausible that the premixing of the palladium, phosphine, and 5-bromotropolone is actually allowing time for the formation of Pd(0), and not necessarily the formation of the oxidative addition product. In their study of the rates and mechanism of formation of zerovalent palladium from $Pd(OAc)_2$ and PPh_3, Amatore and Jutand have indicated that the reduction of Pd(II) to Pd(0) requires approximately 10−15 min at 60 °C in THF.[57,58] Consequently, if protodesilylation is complete after 10 min, then it would be expected that no coupled product would be observed.

In view of that, premixing palladium acetate and triphenylphosphine, followed by the simultaneous addition of 5-bromotropolone, aryl siloxane **8**, and TBAF, should yield coupled product. When this experiment was conducted, however, the yield of coupled product was low (43%). This result indicated that the slow formation of Pd(0) is indeed allowing significant protodesilylation to occur; however, since the yield of coupled product is still low after allowing the formation of Pd(0), a slow oxidative addition is also hindering the reaction.

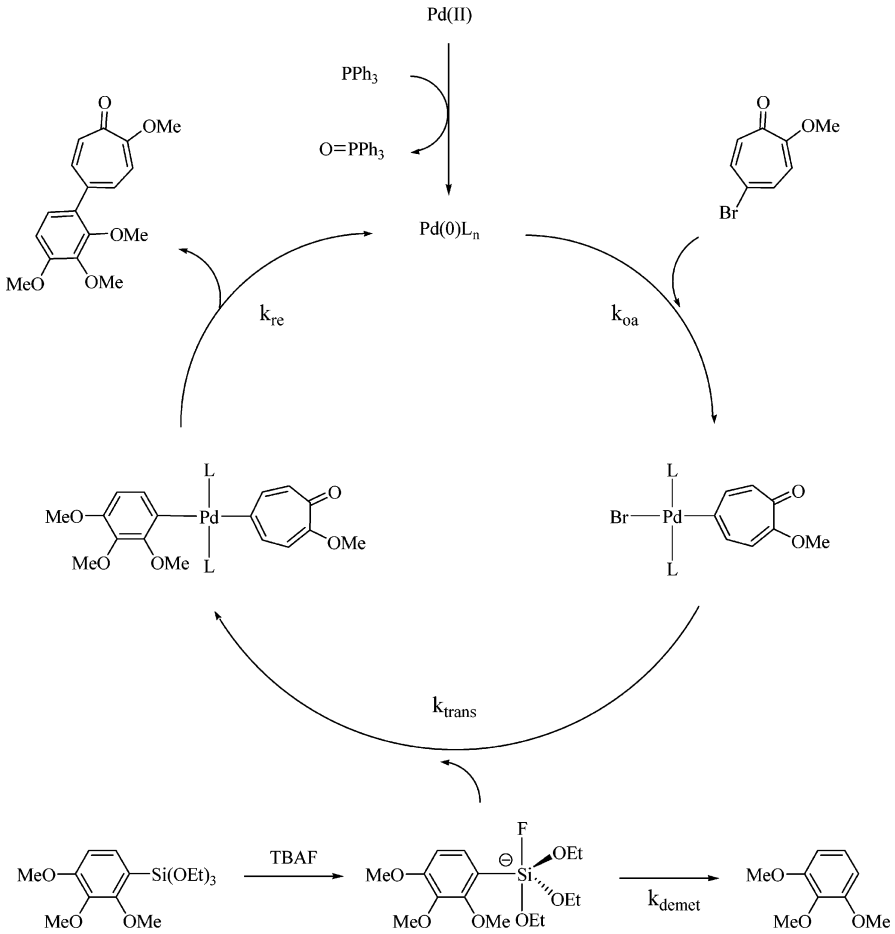
Based on our initial observations, we can propose relative rates of reaction for several key steps in the catalytic cycle for the coupling of siloxane **7** with bromotropolone (**4**) (Scheme 6). The oxidative addition reaction for the catalytic cycle (k_{oa}) is the slowest step. The high yield of coupled product obtained (92%) after allowing the Pd catalyst and bromotropolone (**4**) to be premixed (Scheme 5) shows that the rate of transmetalation (k_{trans}) is much faster than the rate of protodesilylation (k_{demet}). Without the premixing of the Pd(0) catalyst and bromotropolone (**4**), no coupled product is observed, with the only product being protodesilylated siloxane. Because $k_{trans} > k_{demet}$, the lack of coupled product is most likely due to a slow oxidative addition step, which allows time for all of the siloxane to be protodesilylated before any oxidative insertion product is generated. Therefore, the relative rates for the reaction are $k_{trans} > k_{demet} \gg k_{oa}$.

An alternative approach to the coupling reaction would be to employ a siloxane derived from 5-bromotropolone and 2,3,4-trimethoxybromobenzene as the coupling partners. However, attempts to form the tropolone siloxane via metalation[24] or rhodium-[51,52] or palladium-catalyzed[21] silylation were unsuccessful. Additionally, attempts to form the corresponding boronate ester using established protocols were unsuccessful.[59−64]

In conclusion, these studies of the synthesis of aryl tropolone derivatives have allowed for a side-by-side comparison between tin, boron, and silicon cross-coupling reagents. The organoboron and organosilicon reagents were found to couple in comparable yields, with the exception of *o*-methoxy containing siloxanes. Both methods produced higher yields of coupled product than the organotin reagents. With use of a stoichiometric amount of palladium to overcome a slow oxidative addition step,

(53) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944−13945.
(54) Stambuli, J. P.; Buhl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346−9347.
(55) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374.
(56) Attempts to employ $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst were unsuccessful. It was observed that if the reaction mixture was allowed to stir for longer than 15 min before the addition of the siloxane, significant decomposition resulted. Additionally, if the reaction mixture was quenched before the addition of the siloxane, then only tropolone was recovered, indicating replacement of the bromide by a hydrogen.
(57) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013.
(58) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818−1826.
(59) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450.
(60) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459.
(61) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168.
(62) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392−402.
(63) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813−9816.
(64) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.

SCHEME 6



the siloxane coupling to form Fitzgerald's compound (**3**) could be realized. The inability to conduct this coupling reaction catalytically is disappointing; however, efforts are currently underway to overcome this obstacle.

Experimental Section

4-(Triethoxysilyl)-1,2,3-trimethoxybenzene (8). Siloxane was prepared according to the ortho-lithiation procedure of DeShong[27] and purified by column chromatography (TLC, R_f = 0.41, 4:1 hexanes/EtOAc) to yield a colorless oil (77%). IR (CCl_4) 3071 (w), 2978 (s), 2940 (s), 2895 (s), 2836 (m), 1587 (s), 1493 (s), 1455 (s), 1400 (s), 1293 (s), 1234 (s), 1089 (vs), 958 (s); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.0, 9H), 3.87 (q, J = 7.0, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 6.65 (d, J = 8.4, 1H), 7.27 (d, J = 8.4, 1H); ^{13}C NMR ($CDCl_3$) δ 18.3, 55.9, 58.6, 60.6, 60.8, 107.4, 116.7, 131.7, 141.5, 156.2, 158.7; LRMS (FAB$^+$) *m/z* 331 (M^+ +H, 95), 330 (92), 285 (100), 241 (40), 163 (40); HRMS (EI$^+$) *m/z* calcd for $C_{18}H_{26}O_6Si$ 330.1499, found 330.1513.

2-(Triethoxysilyl)anisole (10). The title compound was synthesized according to a published procedure.[27] The spectral data match those reported previously.[27]

4-(Triethoxysilyl)-1,2-dimethoxybenzene (12). Siloxane was prepared according to the metalation procedure of DeShong.[24] Kugelrohr distillation (130 °C, 0.1 mmHg) yielded a colorless oil (61%). IR (CCl_4) 3054 (w), 2971 (s), 2936 (s), 2898 (s), 2833 (m), 1590 (s), 1507 (s), 1466 (m), 1390 (m), 1259 (s), 1114 (vs), 962 (s); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.0, 9H), 3.86 (q, J = 7.0, 6H), 3.90 (s, 3H), 3.91 (s, 3H), 6.90 (d, J = 8.4, 1H), 7.15 (m, 1H), 7.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.3, 55.7, 55.8, 58.7, 110.9, 116.8, 122.2, 128.4, 148.6, 150.9; LRMS (FAB$^+$) *m/z* 300 (M^+, 100), 299 (15), 255 (48), 163 (38); HRMS (EI$^+$) *m/z* calcd for $C_{14}H_{24}O_5Si$ 300.1393, found 300.1385.

2-(Triethoxysilyl)toluene (14). The title compound was synthesized according to a published procedure.[24] The spectral data match those reported previously.[24]

1-(Triethoxysilyl)-3,4-methylenedioxybenzene (16). The title compound was synthesized according to a published procedure.[24] The spectral data match those reported previously.[25]

4-(Triethoxysilyl)anisole (18). The title compound was synthesized according to a published procedure.[24] The spectral data match those reported previously.[24]

5-(Triethoxysilyl)-1,2,3-trimethoxybenzene (20). Siloxane was prepared according to the hydrosilylation procedure of Masuda[51] using 1-bromo-2,3,4-trimethoxybenzene, which was prepared according to a literature procedure.[14] Title compound was isolated as a colorless oil (66%) using column chromatography (TLC, R_f = 0.21, 9:1 hexane/EtOAc). IR (CCl_4) 3078 (w), 2974 (s), 2926 (s), 2881 (m), 2836 (w), 1576 (s), 1500 (m), 1459 (m), 1400 (s), 1307 (s), 1110 (vs), 969 (m); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.0, 9H), 3.86 (q, J = 7.0, 6H), 3.87 (s, 3H), 3.89 (s, 6H), 6.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 18.3, 56.1, 58.8, 60.8, 111.3, 125.8, 140.1, 153.1; LRMS (FAB$^+$) *m/z* 330 (M^+, 100), 329 (15), 285 (23), 162 (37); HRMS (EI$^+$) *m/z* calcd for $C_{15}H_{26}O_6Si$ 330.1499, found 330.1493.

Representative Procedure for the Palladium-Catalyzed Cross-Coupling of 5-Bromotropolone (4) with Aryl Siloxanes. (a) 2-Methoxy-5-phenylcyclohepta-2,4,6-trien-1-one (6). To a 25 mL round-bottom flask were added 5-bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (104 mg, 0.480 mmol), 10.8 mg of $Pd(OAc)_2$ (0.0480 mmol), 63.0 mg of PPh_3 (0.240 mmol), and phenyl trimethoxysilane (180 μL, 0.970 mmol). The flask was placed under argon and 5 mL of THF was added, followed by 0.970 mL of a 1.0 M solution of TBAF in THF

(0.970 mmol). The reaction was refluxed for 12 h. Following this time, the reaction mixture was poured into 20 mL of water and extracted three times with CH_2Cl_2 (50 mL). The organic extracts were combined and dried (Na_2SO_4) and evaporated to produce a dark brown oil. Column chromatography (TLC, $R_f = 0.38$, EtOAc) yielded 86.0 mg of a light tan solid (84%) mp 139.2−140.4 °C (lit. 140−141 °C).[65] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[65]

(b) 2-Methoxy-5-(4′-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (21). Title compound was prepared in a similar manner as described above using siloxane (**18**) and was purified via column chromatography (TLC, $R_f = 0.30$, EtOAc) to provide 94.0 mg of a light tan solid (81%) mp 148.5−148.9 °C (lit. 151.5−152.0 °C).[14] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[14]

(c) 2-Methoxy-5-(2′-methylphenyl)cyclohepta-2,4,6-trien-1-one (23). Title compound was prepared in a similar manner as described above using siloxane (**14**) and was purified via column chromatography (TLC, $R_f = 0.30$, EtOAc) to provide 88.3 mg of a light tan solid (81%) mp 110.0−110.5 °C. IR (CCl_4) 3080 (w), 3057 (w), 3020 (w), 2957 (w), 2933 (w), 2863 (w), 2840 (w), 1632 (m), 1596 (s), 1483 (m), 1248 (s), 1204 (m), 1117(s); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.99 (s, 3H), 6.80 (d, $J = 10.4$, 1H), 7.03 (d, $J = 10.4$, 1H), 7.18 (m, 1H), 7.26−7.29 (m, 2H), 7.46−7.55 (m, 2H), 7.65−7.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 56.3, 112.4, 128.4, 129.1, 130.6, 130.8, 131.9, 132.6, 133.6, 139.3, 142.0, 142.3, 164.5, 180.1; LRMS (FAB^+) *m/z* 227 (M^+, 100), 226 (10), 164 (10); HRMS (EI^+) *m/z* calcd for $C_{15}H_{15}O_2$ 227.1072, found 227.1081.

(d) 2-Methoxy-5-(3′,4′-methylenedioxyphenyl)cyclohepta-2,4,6-trien-1-one (24). Title compound was prepared in a similar manner as described above using siloxane (**16**) and was purified via column chromatography (TLC, $R_f = 0.30$, 4:1 EtOAc/ hexanes) to provide 107 mg of a light tan solid (87%) mp 150−151 °C. IR (CCl_4) 3081 (w), 3061 (w), 3009 (w), 2964 (w), 2926 (w), 2850 (w), 1635 (m), 1587 (m), 1507 (m), 1486 (m), 1245 (s), 1121 (m); ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H), 6.02 (s, 2H), 6.81−6.94 (m, 1H), 6.95−6.96 (m, 1H), 7.19−7.22 (m, 1H), 7.29−7.32 (m, 1H), 7.47−7.50 (m, 2H), 7.68−7.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 56.3, 101.5, 107.7, 108.7, 112.8, 121.2, 128.4, 128.6, 130.6, 137.0, 137.9, 141.4, 148.3, 164.1, 179.8; LRMS (FAB^+) *m/z* 257 (M^+, 20), 245 (100), 243 (30), 239 (20); HRMS (EI^+) *m/z* calcd for $C_{15}H_{13}O_4$ 257.0814, found 257.0822.

(e) 2-Methoxy-5-(3′,4′-dimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (25). Title compound was prepared in a similar manner as described above using siloxane (**12**) and was purified via column chromatography (TLC, $R_f = 0.30$, EtOAc) to provide 115 mg of a light tan solid (88%) mp 168.1−168.3 °C (lit. 168−168.5 °C).[14] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[14]

(f) 2-Methoxy-5-(3′,4′,5′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (26). Title compound was prepared in a similar manner as described above using siloxane (**20**) and was purified via column chromatography (TLC, $R_f = 0.40$, EtOAc) to provide 129 mg of a light tan solid (89%) mp 137−138 °C (lit. 138−139 °C).[14] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[14]

(g) 2-Methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (27). To a 25 mL round-bottom flask were added 50.0 mg (0.233 mmol) of 5-bromotropolone, 225 mg (0.253 mmol) of $Pd(OAc)_2$, and 336 mg (1.28 mmol) of PPh_3. The contents of the flask were placed under argon and THF (5 mL) was added. The reaction was refluxed for 15 min, and 154 mg (0.466 mmol) of 4-(triethoxysilyl)-1,2,3-trimethoxybenzene (**7**) in 2.0 mL of THF was added via syringe, followed by 0.466 mL of TBAF (1.0 M in THF, 0.466 mmol). The reaction was maintained at reflux for an additional 30 min, poured into water (50 mL), and extracted three times with 50 mL of CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography (TLC, $R_f = 0.21$, EtOAc) yielded 70.4 mg of a light tan powder (92%) mp 116−117 °C (lit. 112−117 °C).[14] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[14]

(h) 2,3,4-Trimethoxybiphenyl (28). 4-(Triethoxysilyl)-1,2,3-trimethoxybenzene (**8**) (496 mg, 1.50 mmol), bromobenzene (157 mg, 1.00 mmol), $Pd(OAc)_2$ (112 mg, 0.500 mmol), and PPh_3 (262 mg, 1.00 mmol) were combined in a 25 mL round-bottom flask and placed under argon. THF (10 mL) was added, followed by 1.50 mL (1.50 mmol) of TBAF (1.0 M in THF). The reaction was heated to reflux for 1 h. The reaction mixture was cooled to room temperature and diluted with ether (20 mL). The organic layer was washed with water (20 × 2), dried ($MgSO_4$), and evaporated to yield a brown oil. Column chromatography (TLC, $R_f = 0.31$, 9:1 hexanes/EtOAc) yielded a yellow oil which was recrystallized (hexane) to give 171 mg of a white solid (70%) mp 47.2−47.9 °C (lit. 46−47 °C).[66] The ^{1}H and ^{13}C NMR and IR match that reported by Banwell.[66]

Representative Procedure for the Palladium-Catalyzed Cross-Coupling of 5-Bromotropolone (4) with Aryl Boronic Acids: 2-Methoxy-5-(2′-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (22). 2-Bromoanisole (748 mg, 4.00 mmol) was added to a suspension of Mg (107 mg, 4.40 mmol) in 10 mL of THF. The reaction mixture was heated to reflux until all of the aryl bromide had been consumed (3 h). After cooling to −78 °C, the aryl Grignard reagent was transferred via cannula to a −78 °C solution of trimethyl borate (538 μL, 4.80 mmol) in 15 mL of THF. The reaction mixture was allowed to warm to room-temperature overnight, at which time the yellow solution was poured into 50 mL of 1 M HCl. The aqueous layer was extracted three times with 40 mL of ether. The combined ether extracts were washed with three 50 mL portions of 1 M NaOH. The combined basic extracts were acidified with 2 M HCl. The boronic acid was then extracted into CH_2Cl_2 and dried ($MgSO_4$) and the solvent evaporated to provide the boronic acid as a white solid which was used without further purification in the coupling reaction.

The palladium-catalyzed cross-coupling reaction is a modified procedure of Nair.[16] To a 50 mL round-bottom flask were added 5-bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (**4**) (215 mg, 1.00 mmol) and 57.8 mg of $Pd(PPh_3)_4$ (0.05 mmol). The flask was placed under an Ar atmosphere and 10 mL of toluene was added. The boronic acid (228 mg, 1.50 mmol), dissolved in 1.5 mL of EtOH, was added by syringe, followed by 1.50 mL of a 2.0 M Na_2CO_3 solution. The reaction mixture was refluxed for 5 h to consume all of the aryl bromide. The reaction was cooled to room temperature, 5 drops of 20% H_2O_2 was added, and the mixture was stirred for a another hour. Following this time, the reaction mixture was poured into 20 mL of water and extracted three times with CH_2Cl_2 (50 mL). The organic extracts were combined, dried (Mg_2SO_4), and evaporated to produce a dark brown oil. Purification via column chromatography (TLC, $R_f = 0.27$, EtOAc) provided 194 mg (80%) of the title compound as a pale yellow oil. The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[14]

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Supporting Information Available: General experimental details, as well as ^{1}H NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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