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Palladium-Catalyzed Cross-Coupling of Aryl Triethylammonium Bis(catechol) Silicates with Aryl Bromides Using Microwave Irradiation

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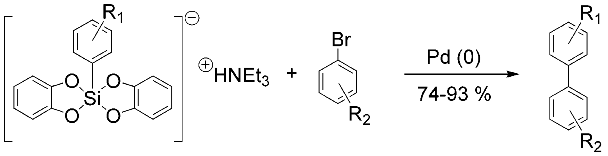
ABSTRACT



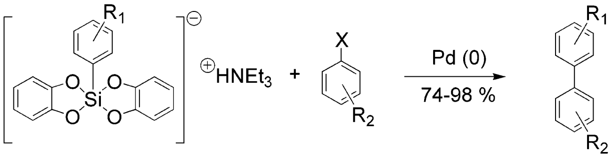
The scope of the palladium-catalyzed cross-coupling reaction of aryl bis(catechol) silicates has been extended to include the coupling of aryl bromides by employing microwave irradiation. This new set of coupling conditions is tolerant of electron-rich and -deficient aryl bromides. In addition, a variety of substituted aryl bis(catechol) silicates have been successfully cross-coupled.

The palladium-catalyzed cross-coupling reactions of organosilanes (Hiyama coupling)[1] with aryl halides and triflates to form unsymmetrical biaryl compounds has garnered support in recent years as a result of the ease of preparation and manipulation of the organosilane reagents over organoboron (Suzuki−Miyaura)[2] or organostannane (Stille)[3] reagents. Work in this laboratory has concentrated on the preparation and subsequent cross-coupling of siloxanes, silatranes, and aryl bis(catechol) silicates.[4]

The use of microwave irradiation has emerged as a valuable method for inducing chemical reactions, and this method has been successfully applied to Heck,[5] Stille,[5,6] Suzuki−Miyaura,[5,7] and Sonogashira couplings.[8] Microwave-assisted reactions are known for their fast reaction times and are proposed to involve localized high reaction temperatures.[9] These conditions allow for fast, uniform energy transfer to the reagents, potentially minimizing undesired side products and reactions.

In a recent report, we disclosed that aryl bis(catechol) silicates (**1**) underwent coupling with aryl iodides and triflates to provide unsymmetrical biaryl derivatives (Scheme 1).[4e]

Scheme 1. Cross-Coupling of Aryl Iodides and Triflates



1

X=I or OTf

However, under these reaction conditions, it was not possible to couple aryl bromides in greater than 40% yield. We have recently explored the application of microwave irradiation to the coupling of aryl bromides and bis(catechol) silicates. These silicates are readily prepared from the corresponding

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[1] Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61−85.

[2] Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59.

[3] Fugami, K.; Kosugi, M. *Top. Curr. Chem.* **2002**, *219*, 87−130.

[4] (a) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688. (b) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140. (c) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655−1658. (d) McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779−4782. (d) Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106−8109. (e) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137−1143.

[5] Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584.

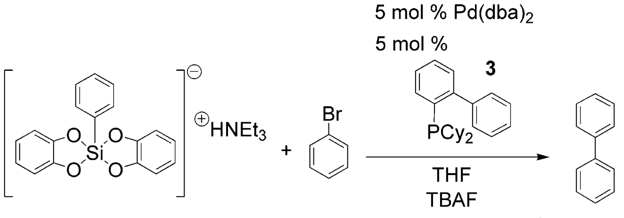
[6] Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583−5587.

10.1021/ol048044q CCC: $27.50

aryl siloxane, 2 equiv of catechol, and triethylamine. This report details the successful application of microwave irradiation to the coupling of aryl bis(catechol) silicates with aryl bromides.

The coupling of silicate **2** with bromobenzene under *idealized thermal conditions* had resulted in the formation of biphenyl in a yield of only 38%.[4e] However, under the influence of microwave irradiation, rapid and efficient cross-coupling of aryl bromides was realized (Scheme 2).

Scheme 2



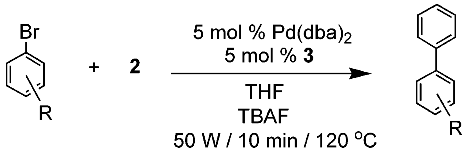
2

Reaction conditions for this coupling are analogous to the thermal reaction and entailed 5 mol % Pd(dba)$_2$ as the Pd(0) source, 5 mol % dicyclohexyl phosphinobiphenyl (**3**), and 1.5 equiv of tetrabutylammonium fluoride (TBAF) in THF (Scheme 2). Exposure of the reaction mixture to microwave irradiation (50 W/10 min/120 °C) led to efficient cross-coupling of bromobenzene with triethylammonium phenyl bis(catechol) silicate (**2**). In the absence of irradiation, the yield of coupling product under identical conditions was <40%.[4e]

Having demonstrated the effectiveness of microwave irradiation for the coupling reaction, the functional group tolerance of substituted aryl bromides was investigated, and the results are summarized in Table 1. The data indicates that the reaction is tolerant of both electron-donating (entries 1−5) and electron-withdrawing (entries 8 and 9) functional groups.

In addition, it was possible to couple di-ortho-substituted aryl bromides, demonstrating that even highly hindered biaryls could be realized under these conditions (entry 6). The only functional group that was found to fail in the coupling study was the amino group, which gave starting materials in high yield (entry 10). We attribute the failure of this coupling reaction to poisoning of the catalyst by the amino function. The analogous triflate coupling under thermal conditions had also failed in the presence of free amino groups.[4e]

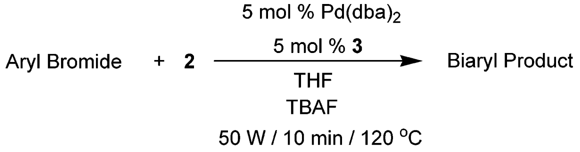
Table 1. Probing the Functional Group Tolerance of the Microwave Assisted Coupling Reaction

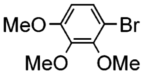
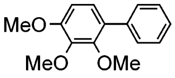
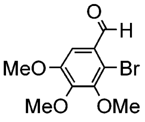
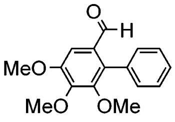
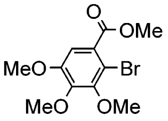
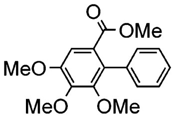
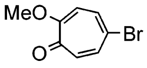
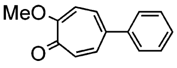


entry	R	yield (%)
1	H	89
2	4-OCH$_3$	81
3	2-OCH$_3$	84
4	4-*t*-Bu	88
5	2-CH$_3$	86
6	2,6-dimethyl	80
7	1-naphthyl	84
8	4-COCH$_3$	89
9	4-NO$_2$	93
10	4-NH$_4$	0

Once the feasibility of the coupling of simple aryl bromides had been demonstrated, attention turned to the cross-coupling of more complex substrates bearing multiple functional groups. In the less idealized world of natural product synthesis, one can determine the full scope of the new coupling protocol only by investigating these more complex substrates. The results of these investigations are shown in Table 2. As was observed in the simpler substrates,

Table 2. Coupling of Complex Aryl Bromides



entry	aryl bromide	biaryl product	yield (%)
1			84
2			74
3			79
4			76

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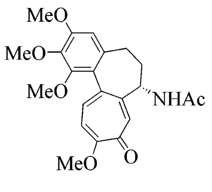
(7) (a) Wang, Y.; Sauer, D. R. *Org. Lett.* **2004**, *6*, 2793−2796. (b) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219−8222. (c) Zhang, W.; Chen, C. H. T.; Lu, Y. M.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473−1476. (d) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180. (e) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888−892. (f) Blettner, C. G.; Koenig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−3890. (g) Schulz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, *6*, 3265−3268.

(8) Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165−4169.

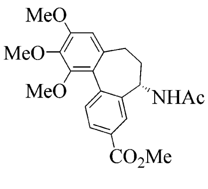
(9) For several recent reviews, see: (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (d) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727.

electron-rich aryl bromides (entries 1−3) couple in good to excellent yields. Particularly noteworthy are the couplings shown in entries 2 and 3 that involved substrates with di-ortho substitution. Even though the silicate is bulky, coupling at highly hindered centers occurred.

Another noteworthy achievement of the microwave method was the coupling of 5-bromo tropolone with silicate **2** (entry 4). Previous studies in our group had found that siloxane and silicate derivatives underwent coupling with this tropolone to provide low yields of biaryl product. The excellent yield of coupling with silicate **2**, on the other hand, bodes well for an approach to the natural products colchicine (**4**) and allocolchicine (**5**) based on this method.[10]



4

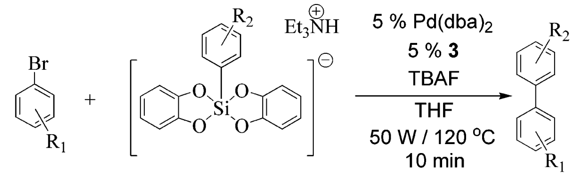


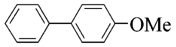
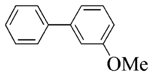
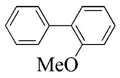
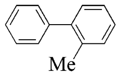
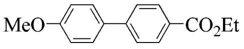
5

To explore the scope and limitations of the coupling reaction fully, the coupling of a select number of substituted aryl bis(catechol) silicates with aryl bromides was also studied (Table 3).

Substituents in the para and meta positions were well tolerated and gave adducts in yields comparable to their unsubstituted counterpart (entries 1, 2, and 5). In addition, electronic effects associated with the substituent did not manifest themselves in either the yields of adduct obtained or the conditions required to achieve the coupling. However, coupling efficiency was significantly altered when ortho substituents were present on the bis(catechol) silicate (entries 3 and 4). This effect on the yield by ortho substituents was also observed in the thermal coupling of aryl triflates with silicates.[4e]

Table 3. Coupling of Substituted Bis(catechol) Silicate Complexes



entry	R_1	R_2	coupled product	yield (%)
1	H	4-OMe		88
2	H	3-OMe		84
3	H	2-OMe		49
4	H	2-Me		47
5	4-OMe	4-CO_2Et		82

In conclusion, we have extended the palladium-catalyzed cross-coupling method of aryl bis(catechol) silicates (**1**) to aryl bromides to form unsymmetrical biaryls. Aryl bis(catechol) silicates are particularly attractive reagents for coupling reactions because of their ease of formation, crystallinity, and stability. These results, combined with our previous studies, provide a valuable resource for the cross-coupling of aryl bromides, iodides, and triflates with aryl bis(catechol) silicates. Full disclosure of our studies with these substrates, as well as their application to natural product synthesis, will be reported in due course.

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Supporting Information Available: General experimental procedures, compound characterization information, and ^{1}H NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048044Q

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(10) For a recent review on the synthetic approaches to colchicine, see: Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230−3256.