ORGANIC LETTERS

2006
Vol. 8, No. 1
63−66

Vinylation of Aryl Bromides Using an Inexpensive Vinylpolysiloxane

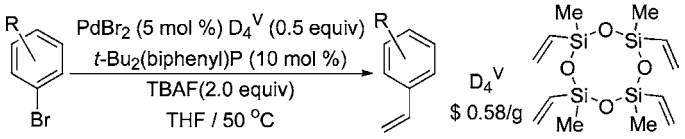
Scott E. Denmark* and Christopher R. Butler

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801

denmark@scs.uiuc.edu

Received October 17, 2005

ABSTRACT



A mild and general method for the palladium-catalyzed vinylation of aryl bromides has been developed. The use of tetrabutylammonium fluoride (TBAF) as the activator and an inexpensive and nontoxic vinyl donor, 1,3,5,7-tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (D_4^V, 1), allows for a general and high-yielding preparation of substituted styrenes.

Substituted styrenes are important building blocks in fine chemical[1] and polymer synthesis.[2] In addition, the emergence of important transformations over the last two decades such as olefin metathesis,[3] asymmetric hydrogenation,[4] and heterocycle construction,[5] along with dramatic advances in polymer chemistry, has driven the demand for mild and efficient access to substituted styrenes. The classical preparations of styrenes[6] involve either strongly basic dehydration or Hoffman elimination conditions and are therefore incompatible with many functional groups. In contrast, the advent of transition-metal-catalyzed, cross-coupling reactions which take place under milder conditions has allowed the preparation of styrenes bearing sensitive functionality. These methods include the vinylation of aryl halides using magnesium-,[7] boron-,[8] silicon-,[9] and tin-based[10] vinyl donors that can couple to a variety of aryl halides. However, these vinyl donors also suffer from a number of drawbacks, including high reactivity, cost,[11] or toxicity.[12]

Recent reports from these laboratories have demonstrated the successful palladium-catalyzed vinylation of aryl and vinyl iodides using inexpensive, readily available, nontoxic polyvinylsiloxanes with tetrabutylammonium fluoride (TBAF) as an activator (Scheme 1).[13] Although a variety of polyvinysiloxanes served successfully as donors, it was shown

(1) (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485−2506. (b) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200−9201. (c) RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68*, 8431−8446.

(2) (a) *Modern Styrenic Polymers: Polystyrenes and Styrenic Copolymers*; Scheirs, J., Priddy, D. B., Eds.; John Wiley & Sons: Chichester, UK, 2003. (b) Hirao, A.; Loykulnant, S.; Ishizone, T. *Prog. Polym. Sci.* **2002**, *27*, 1399−1471. (c) Schellenberg, J.; Tomotsu, N. *Prog. Polym. Sci.* **2002**, *27*, 1925−1982.

(3) (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; John Wiley & Sons: Ltd.: Weinheim, 2003.

(4) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356−5362.

(5) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(6) Emerson, W. S. *Chem. Rev.* **1949**, *49*, 347−383.

(7) Bumagin, N. A.; Luzikova, E. V. *J. Organomet. Chem.* **1997**, *532*, 271−273.

(8) (a) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968−4971. (b) Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075−1082. (c) Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875−1883. (d) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293−300. (e) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Synlett* **2005**, 529−531. (f) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107−109.

(9) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918−920. (b) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673−1676.

(10) (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348. (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119−122. (c) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422−424.

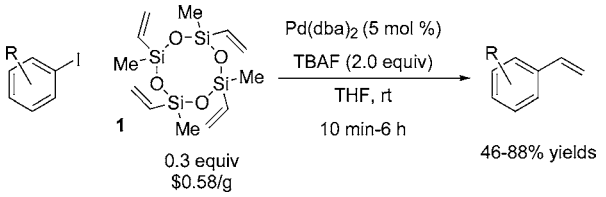
(11) (a) 2,4,6-Trivinylcyclotriboroxane (Aldrich, catalog no. 637998): $3851/mol. (b) Tributyl(vinyl)tin (Aldrich, catalog no. 271438): $3032/mol.

(12) National Institute of Occupational Health and Safety; Pub. No. 77-115; U.S. Government Printing Office: Washington, 1976.

(13) (a) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999−1003. (b) Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *621*, 372−375.

10.1021/ol052517r CCC: $33.50
Published on Web 12/13/2005

Scheme 1. Vinylation of Aryl Iodides



that one of the most inexpensive agents, 1,3,5,7-tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (D_4^V, **1**),[14] was optimal. Each of the four vinyl groups in D_4^V is active for transfer under the described conditions.

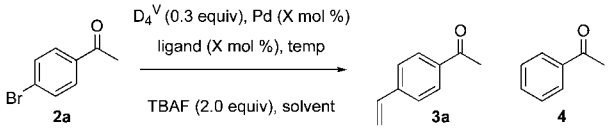
The application of this technology to include aryl bromides would significantly broaden its utility. Aryl bromides present numerous advantages over aryl iodides, including increased stability, lower cost, and wider availability. The increased stability, however, implies a decreased inherent reactivity, and therefore requires more vigorous cross-coupling conditions to engage this class of acceptors. Such modifications usually involve ligands that aid in the oxidative addition of palladium to the carbon−bromine bond. Herein, we report the successful extension of the vinylation reaction using this inexpensive reagent D_4^V to include the less reactive but more widely available aryl bromides.

As point of entry, we chose 4-bromoacetophenone (**2a**), a very active substrate, to establish the viability of the method. We examined the role of solvents, palladium sources, and ligands to elucidate the general reaction conditions with the goal of high yields (>80% isolated) for a wide survey of substrates. We hoped to achieve good reactivity (complete reaction in less than 3−4 h) with this active substrate and then apply these conditions to more difficult substrates.

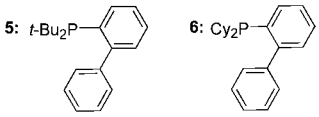
The optimal conditions developed from the vinylation of aryl iodides ($Pd(dba)_2$, (5 mol %), TBAF (2.0 equiv), D_4^V (0.3 equiv), THF, Scheme 1) afforded a suitable starting point for our investigation. Employing these conditions provided none of the desired styrene and returned only starting material (Table 1, entry 1). Orienting experiments using allylpalladium chloride dimer (APC) led to competitive reduction of the aryl bromide (entry 2). This unwanted process presumably arises from the ability of ethereal solvents to act as hydride donors.[15] Alternate solvents suppressed the reduction process but also did not provide any of the desired product (entries 3 and 4). The use of phosphine or arsine ligands also prevented reduction, but again without productive coupling (entries 5 and 6). However, the use of 2-(di-*tert*-butylphosphino)biphenyl (BPTBP, **5**) as the ligand did provide the desired product albeit rather slowly (entry 7). Changing the palladium(II) source to $PdBr_2$ (10 mol %) afforded complete conversion to the corresponding styrene in 18 h at rt (entry 8). Surprisingly, the use of 2-(dicyclohexylphosphino)biphenyl, **6**, provided none of the product (entry 9). Increasing the temperature to 50 °C in the presence of **5** provided complete reaction in 3 h with only a 5 mol % loading of $PdBr_2$ (entry 10). On the basis of these experiments, we chose to use the air stable biphenyl-derived ligand **5** as it afforded the product within the desired time frame at 50 °C.

Gratifyingly, these optimized conditions translated well to the preparative scale (2 mmol), providing an 85% yield of 4-vinylacetophenone (Table 2, entry 1). However, a brief substrate survey performed under these conditions revealed a surprising lack of generality. Although 2-bromonaphthalene (**2b**) afforded an 82% yield of the corresponding styrene (entry 2), extension to electron-rich bromides, such as 4-bromoanisole (**2c**) or 2-bromotoluene (**2d**), afforded reduced yields of the corresponding styrenes (entry 3 and 4). Ultimately, it was found that the lower yields resulted from

Table 1. Survey of Catalysts and Ligands

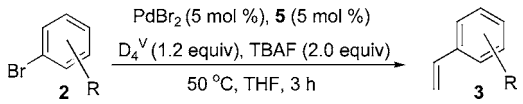


entry:	X mol %	"Pd"	ligand	solvent	temp, °C	**3**, yield, %[a] 3 h:	18 h:
1	5	$Pd(dba)_2$	--	THF	rt	0	0
2	5	APC	--	THF	rt	0 (88)[b]	ND[c]
3	5	APC	--	dioxane	rt	ND[c]	0 (23)[b]
4	5	APC	--	DMF	rt	ND[c]	0 (10)[b]
5	5	APC	dppb	THF	rt	ND[c]	0 (17)[b]
6	5	APC	$AsPh_3$	THF	rt	0	0
7	5	APC	**5**	THF	rt	ND[c]	54
8	10	$PdBr_2$	**5**	THF	rt	41	100
9	10	$PdBr_2$	**6**	THF	rt	0	0
10	5	$PdBr_2$	**5**	THF	50	100	--



[a] Yield based on GC analysis relative to an internal standard. [b] Yield of **4** in parentheses. [c] Not determined.

Table 2. Initial Survey of Aryl Bromides



entry	R	series	yield,[a] %
1	4-COMe	**a**	85
2	2-naphthyl	**b**	82
3	4-OMe	**c**	32
4	2-Me	**d**	(75)[b]

[a] Yields of chromatographically homogeneous material. [b] Conversion by ^1H NMR analysis relative to starting material.

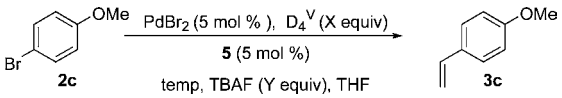
(14) 1,3,5,7-Tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (Lancaster, catalog no. 16645): $176/mol.

(15) (a) Kabir-ud-Din; Plesch, P. H. *J. Chem. Soc., Perkin Trans. 2* **1978**, 937−938. (b) Melikyan, G. G.; Deravakian, A. *J. Organomet. Chem.* **1997**, *544*, 143−145.

consumption of the products in a subsequent Heck reaction with a second molecule of aryl bromide to afford the corresponding stilbene.

To suppress the formation of the stilbene byproduct, the influence of temperature, D_4^V and TBAF stoichiometry, were examined (Table 3). Increasing the temperature, either in THF (entry 2), dimethoxyethane (entry 3), or dioxane (entry 4), left the styrene-to-stilbene ratio essentially unchanged. However, increasing the loading of D_4^V and TBAF and raising the temperature concomitantly did show a marked decrease in stilbene formation (entry 5). Further increase to 0.9 equiv of D_4^V (3.6 vinyl groups) and 6.0 equiv of TBAF eliminated the stilbene formation (entry 6). In an effort to minimize cost, we lowered the TBAF loading to be equimolar with the number of vinyl equiv used (entry 7). Although the yield remained about the same, a small amount of stilbene reemerged. Raising the amount of TBAF to 4.0 equiv was sufficient to suppress stilbene formation and still deliver the product in high yield (entry 8).

Table 3. Stilbene Minimization



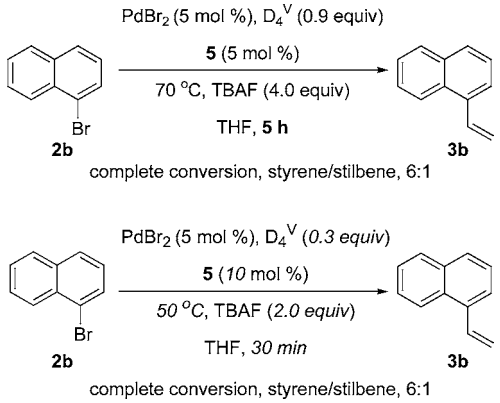
entry	T, °C	solvent	vinyl, equiv	TBAF, equiv	yield,[a] %	styrene/stilbene[b]
1	50	THF	1.2	2.0	32[c]	
2	70	THF	1.2	2.0	67	5:1
3	85	DME	1.2	2.0	64	5:1
4	100	dioxane	1.2	2.0	70	6:1
5	70	THF	2.4	4.0	74	27:1
6	70	THF	3.5	6.0	93	>99:1
7	70	THF	3.6	3.6	94	38:1
8	70	THF	3.6	4.0	94	>99:1

[a] Yield based on ^{1}H NMR analysis relative to an internal standard. [b] Ratio determined by ^{1}H NMR spectroscopy, comparing relative integration. [c] Yield of chromatographically homogeneous material.

For the next phase in the optimization, we examined the more conventional use of 2.0 equiv of phosphine ligand with respect to palladium and were delighted to discover that a second equivalent of phosphine allowed for a decrease in reaction temperature and reaction time (Scheme 2). Most likely, the first equivalent of phosphine is consumed in the reduction of the palladium(II) source and the second is the "active" ligand. An additional benefit from using 2 equiv of ligand **5** is that the loading of both D_4^V and TBAF could be reduced to their original levels (1.2 and 2.0 equiv, respectively) without compromising the styrene/stilbene ratio.

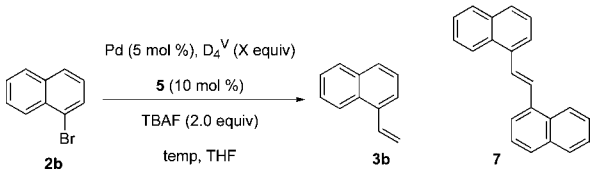
In view of the importance of phosphine stoichiometry, we decided to re-optimize the reaction conditions to eliminate the stilbene. We chose initially to minimize the amount of fluoride used in the reaction, limiting ourselves to only 2.0 equiv of fluoride, varying only the amount of D_4^V (Table 4). Using the original stoichiometry of D_4^V (0.3 equiv, 1.2 equiv of vinyl groups) at room temperature provided a 10:1

Scheme 2. Phosphine Dependence



ratio of styrene to stilbene, although the reaction was considerably slower (6 h, entry 1). Increasing the temperature to 50 °C provided a shorter reaction time, but a decrease in selectivity (entry 2). The use of a "pre-reduced" Pd(0) source led to a significantly slower reaction (entry 3).[16] As before, only an increase in the amount of D_4^V, first to 0.4 and further to 0.5 equiv (1.6 and 2.0 vinyl groups, respectively, entries 4 and 5), satisfactorily eliminated the stilbene side product. The final conclusions of these optimizations are that (1) the formation of stilbene could be nearly completely suppressed by increasing the level of D_4^V and (2) the use of 2.0 equiv of **5** leads to faster reactions at lower temperature and also allows for the D_4^V and TBAF stoichiometry to be kept to synthetically practical levels.

Table 4. Optimization of D_4^V Loading



entry	D_4^V (vinyl equiv)	Pd source	T, °C	time[a], h	**3b/7**[b]
1	0.3 (1.2)	$PdBr_2$	25	6	10:1
2	0.3 (1.2)	$PdBr_2$	50	0.5	6:1
3[c]	0.3 (1.2)	$Pd(dba)_2$	50	6[d]	20:1
4	0.4 (1.6)	$PdBr_2$	50	1[e]	24:1
5	0.5 (2.0)	$PdBr_2$	50	2.5	30:1

[a] Time to 100% conversion, determined by ^{1}H NMR analysis. [b] Ratio determined by ^{1}H NMR spectroscopy, comparing relative integration. [c] 5 mol % of phosphine **5** was used. [d] Reaction did not go to 100% conversion; 9% of **2b** remains. [e] 3% of **2b** remains.

To establish the generality of the vinylation protocol, a variety of aromatic bromides were tested under the optimized

(16) The origin of the decreased reaction rate is ambiguous. This may arise from the dba ligand as an inhibitor or there may be a beneficial effect of having both phosphine and phosphine oxide in the mixture for enhanced reaction rate.

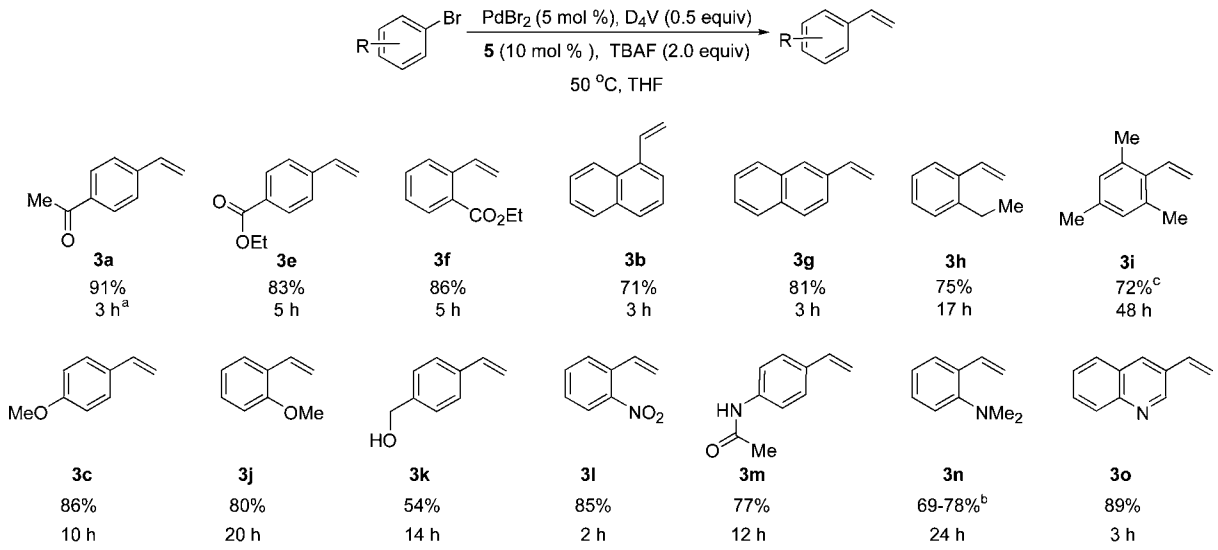


Figure 1. Vinylation of various aryl bromides. Key: (a) yields of chromatographically homogeneous, isolated products; (b) contains 10% dimethylaniline; (c) contains 5% bromomesitylene.

conditions. The survey was designed to probe the compatibility of common functional groups under the coupling conditions and also test the effects of steric hindrance and electronic character of the aryl group on the rate and yield of the vinylation. The results of this survey (Figure 1) show good functional compatibility with the ketone, ester, ether, hydroxyl and nitro groups. Although 4-bromoaniline provided a less than desirable yield (32%), other bromides which bear nitrogen-containing functional groups such as the acetamide and quinoline did participate in the coupling well. The dimethylamino group was also compatible, but it was not possible to remove a small amount of the reduction byproduct.

In general, electron-deficient aryl bromides react faster than electron-rich substrates, but yields are not affected. Steric effects are evident and decrease the reaction rate, but again yields remain high.

This substrate survey was perfomed using reaction conditions designed to minimize cost (TBAF) and which were optimized to suppress the formation of stilbene with 1-bromonaphthalene. Other substrates may require modulation of the D_4^V/TBAF levels for optimization. For example, electron-rich bromides, whose products are more prone to the secondary Heck reaction, may require an increased level of TBAF and D_4^V to adequately suppress the stilbene formation. For substrates less prone to the Heck process, the increased level of D_4^V may not be needed, and reducing the amount of D_4^V and TBAF will provide adequate yield and selectivity.

In conclusion, we have developed a general method for the vinylation of aryl bromides using an inexpensive, readily available, nontoxic vinylpolysiloxane. The conditions are mild and allow for the facile introduction of a vinyl group in the presence of a variety of common functional groups. Current work is focused on the development of fluoride-free vinylation conditions as well as the extension to aryl chlorides and aryl triflates.

Acknowledgment. We are grateful for the National Institutes of Health for generous financial support (R01 GM63167-01A1). C.R.B. acknowledges Procter & Gamble and Abbott Laboratories for graduate fellowships.

Supporting Information Available: Key optimization experiments, detailed procedures, and characterization of all products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052517R