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Pd(0)-Catalyzed 1,1-Diarylation of Ethylene and Allylic Carbonates

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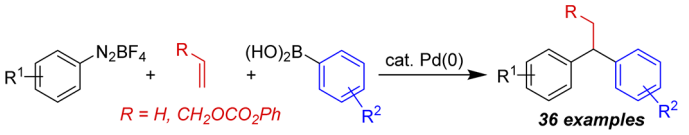
ABSTRACT



An efficient protocol for the one-step synthesis of biologically relevant 1,1-diarylalkanes has been described. This reaction introduces two different aryl groups across the terminal end of simple feedstock alkenes such as ethylene and allylic carbonates. The propensity to generate π-benzylpalladium intermediates dictates the exclusive 1,1-regioselectivity observed in the product.

The 1,1-diarylalkane structural motif is present in numerous biologically active compounds, which have notable efficacy profiles against a diverse range of therapeutic targets.[1] In this regard, we have recently disclosed a 1,1-diarylalkane (Scheme 1a, **C-6**) that is active against patient-derived metastatic and chemoresistant breast cancer cells.[2] Additionally, **C-6** is highly selective in that minimal cell death is observed in patient-derived nontumorigenic cells. Preliminary mechanistic investigations indicate that the promising selectivity of **C-6** is not due to interruption of commonly targeted therapeutic signaling pathways. The exciting possibility of identifying new breast cancer target(s) using **C-6** has stimulated a focused effort on the synthesis of 1,1-diarylalkane analogues.

Our original synthesis of **C-6** employed an oxidative Pd(II)-catalyzed hydroarylation of styrenes (Scheme 1a).[3,4] This method allows access to various diarylethanes as it is limited to terminal styrenes and also requires rather complex reaction conditions. Many attractive alternative methods[5] have been reported to access diarylalkanes, including enantioselective hydrogenation of 1,1-diarylalkenes,[6] rhodium-catalyzed Tsuji–Wilkinson decarbonylation,[7] and enantiospecific metal-catalyzed cross-coupling reactions.[8]

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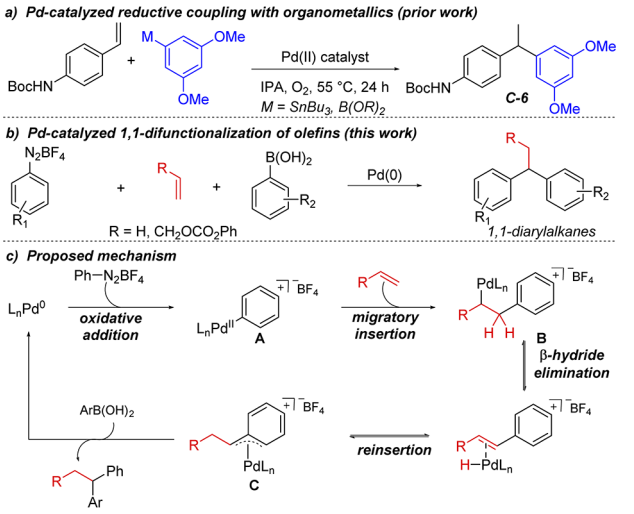
Nevertheless, these approaches often require multiple steps to access the substrates or some of the methods have limited functional group tolerance.

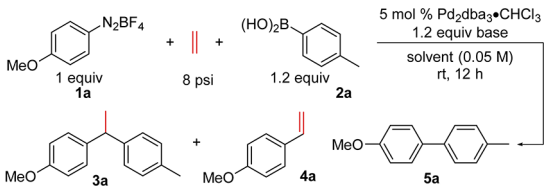
Scheme 1. Proposed 1,1-Difunctionalization of Ethylene/Terminal Olefins with Aryldiazonium Salts and Boronic Acids



A streamlined approach to diverse 1,1-diarylalkanes would allow installation of both aryl groups using an alkene difunctionalization reaction. Such an approach would enable the use of simple feedstock starting materials toward a convergent and rapid increase in molecular complexity.[9] Our group has been engaged in utilizing reactions of this type to perform 1,2-difunctionalization reactions of conjugated alkenes and 1,1-difunctionalization reactions of terminal alkenes effectively.[10,11] In these examples, we have previously been able to perform alkene diarylation reactions only with the introduction of the same arene (from an organostannane), which clearly diminishes the potential synthetic utility of the reaction.[11] Therefore, to access diverse 1,1-diarylalkanes through alkene diarylation, a method enabling the introduction of two distinct aryl groups would have to be developed (Scheme 1b). Herein we present the development of a Pd-catalyzed 1,1-diarylation of both ethylene and allylically substituted alkenes with aryldiazonium and arylboronic acid derivatives to access diverse 1,1-diarylalkanes efficiently.

Initiation of the proposed alkene functionalization sequence relies on oxidative addition of an aryl electrophile wherein two key features were considered (Scheme 1c): (1) ease of oxidative addition and (2) introduction of a poorly coordinating counterion from the oxidant, which ultimately leads to the formation of a cationic Pd(II)-intermediate **A**. Such an intermediate should facilitate migratory insertion to yield **B** instead of transmetalation leading to Suzuki products. These requirements led us to select aryldiazonium tetrafluoroborates as the electrophile (Scheme 1c).[12] To continue the catalytic cycle, site-selective benzylic β-hydride elimination is followed by alkene reinsertion to migrate the Pd(II) to the benzylic position, resulting in a stabilized π-benzylpalladium species **C**. The stability of this intermediate likely will result in cross-coupling of the boronic acid, ultimately delivering the 1,1-diarylation product selectively.

Table 1. Optimization for the 1,1-Diarylation of Ethylene



entry	base	solvent	yield of **3a**[a] (%)	ratio **3a**:**4a**:**5a**
1[b]	$NaHCO_3$	DMA	0	**4a** only
2[b]	$NaHCO_3$	THF	trace	**4a** only
3	$NaHCO_3$	THF	4	7:87:6
4	$NaHCO_3$	^{t}AmOH	33	33:66:1
5	K_3PO_4	^{t}AmOH	41	47:47:6
6[c]	K_3PO_4	^{t}AmOH	50	67:27:6
7[d]	K_3PO_4	^{t}AmOH	65	70:23:7
8[d,e,f]	K_3PO_4	^{t}BuOH	75	83:10:7
9[d,e,f]	$NaHCO_3$	^{t}BuOH	70	86:11:3
10[d,e,f]	$NaHCO_3$	^{t}AmOH	60	74:24:2

[a] Determined by GC using an internal standard. [b] Reaction performed at 15 psi. [c] Reaction performed at 55 °C. [d] Reaction performed at 80 °C. [e] 2 mol % $Pd_2dba_3 \cdot CHCl_3$ used. [f] Reaction performed for 4 h.

To initiate our investigation, we evaluated ethylene as the alkene substrate using aryldiazonium salts and boronic acids as the distinct arene sources (Table 1). The use of conditions similar to those previously reported for the vinylarylation of ethylene resulted only in the observation of the Heck product (**4a**, entry 1).[9] Changing to a less coordinating solvent (THF) and lowering the pressure of ethylene resulted in a low but measurable yield of the desired three-component coupling product (entries 2 and 3). Further improvement was found by changing the solvent to a tertiary alcohol and heating the reaction, potentially to promote transmetalation as some Suzuki coupling product is also formed (entries 4–7). It should be noted that K_3PO_4 and $NaHCO_3$ perform similarly. The best observed results are found when the catalyst loading is reduced to 2 mol % and the reaction time is 4 h (entries 8–10). It should be noted that addition of exogenous ligands did not produce **3a**.

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(12) For recent examples of the use of aryldiazonium salts in Pd-catalyzed Heck reactions, see: (a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (b) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692. For recent reviews, see: (c) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, *2011*, 1403. (d) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

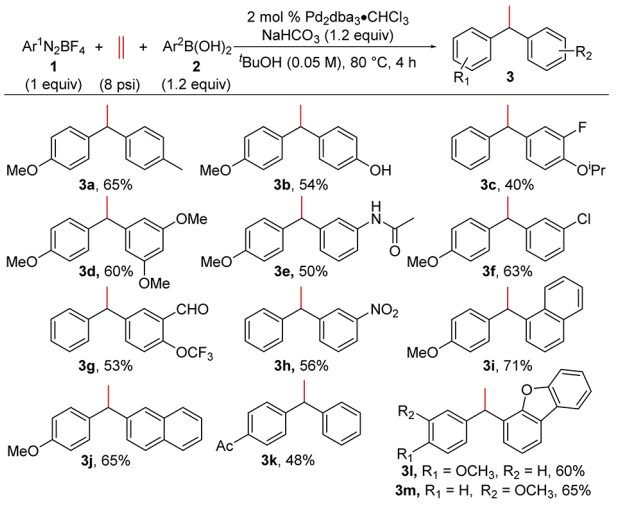

Figure 1. Scope of the 1,1-diarylation of ethylene.

Under these conditions, the substrate scope of the ethylene 1,1-difunctionalization reaction was investigated. A wide range of arylboronic acids were found to be compatible with this transformation, affording the product in moderate to good yields. For example, electron-donating substituents such as methyl, hydroxy, and isopropoxy at the *para* position yielded the desired products (Figure 1, **3a**−**c**). *Meta*-substituted arylboronic acids including halogens, a secondary amide, and an aldehyde are viable partners (**3c**−**g**). Additionally, compatibility with challenging functional groups such as nitro-substituted arenes allows the installation of a valuable synthetic handle for further functionalization (**3h**). Sterically encumbered 1- and 2-naphthylboronic acids served as effective coupling partners (**3i**,**j**). Electron-deficient arydiazonium salts such as 4-acetyl phenyldiazonium tetrafluoroborate gave moderate yields of the corresponding 1,1-diarylation product (**3k**). Although oxygen-containing heteroaromatic boronic acids such as dibenzofuran (**3l**,**m**) gave good yield of the 1,1-diarylation product, nitrogen-containing heteroaromatic cross-coupling partner 3-quinoline boronic acid was not a capable reactant, possibly due to the coordination of nitrogen to the palladium center.

To evaluate the alkene scope beyond ethylene, 5-hexen-2-one was submitted to the optimal reaction conditions (Table 2, entry 1). Disappointingly, a mixture of alkene isomers and their Heck products was observed, suggesting that the stability of the π-benzylpalladium intermediate is not sufficient to override Pd-hydride migration along the alkyl chain.[13] To circumvent this deleterious process while also incorporating a useful functional group, several alkenes were evaluated with substitution at the allylic position (entries 2−7). This strategy to slow isomerization was successful in that the three-component coupling product **7** is observed albeit in poor yields. Significant improvement

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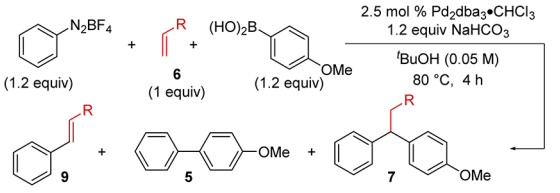
Table 2. Evaluation of Olefin Partner and Optimization for 1,1-Diarylation of Allylic Substituted Terminal Alkenes



entry		substrate	yield of **7** (%)[a]	ratio of **7**:**5**:**9**
1[b]	**6a**	Ac	5	25:15:60
2	**6b**	AcO	15	38:12:50
3	**6c**	PhthN	32	73:7:20
4	**6d**	TsHN	12	49:19:32
5	**6e**	NC	17	77:10:13
6	**6f**	PhO_2CO	50	90:5:5
7[c]	**6f**	PhO_2CO	48	90:5:5
8[c,d,e]	**6f**	PhO_2CO	75(72)[f]	91:4:5

[a] Determined by ^{1}H NMR and GC using an internal standard. [b] Mixture of Heck product isomers was observed. [c] Reaction performed at room temperature. [d] THF was used as a solvent. [e] Reaction performed with 2.5 mol % Pd_2dba_3 and [0.1 M] alkene for 2 h. [f] Isolated yield in parentheses.

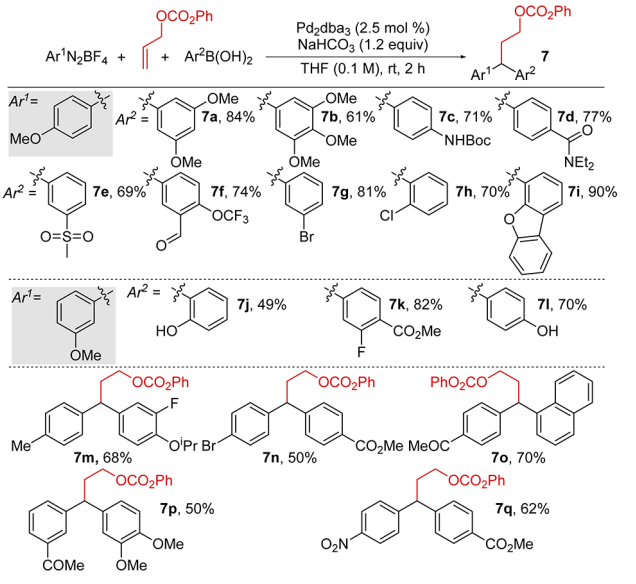


Figure 2. Scope of 1,1-diarylation of allyl phenyl carbonate.

was found by using an allylic carbonate, and after further optimization of the reaction conditions (see Supporting Information for details), excellent selectivity and good yields were observed for the formation of the 1,1-diarylation product **7** (entry 8). This is a somewhat surprising substrate for this reaction as allylic carbonates are classical oxidants of Pd(0) in Tsuji−Trost reactions.[14] However,

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in this system, the allylcarbonate may be preserved due to the faster oxidative addition of aryldiazonium salts as they are more effective oxidants of Pd(0).

After optimization, the scope of the 1,1-diarylation of allylic carbonates was evaluated with an initial focus on electron-rich aryldiazonium salts, as the in situ generated π-benzylpalladium intermediate should have enhanced stability (Figure 2).[11] Generally good to excellent yields were observed with a variety of boronic acids (**7a**–**i**). A broad range of functional groups were tolerated in this reaction, highlighted by a carbamate (**7c**), an amide (**7d**), a sulfone (**7e**), an aldehyde (**7f**), halides (**7g**,**h**), and an oxygen-containing heterocycle (**7i**). Electronically varied aryldiazonium salts were also examined. Although electron deficient aryldiazonium salts likely form less stable π-benzylpalladium intermediates, good yields are still observed under these reaction conditions (**7n**–**q**). Several additional functional groups were found to be compatible with the reaction including phenols (**7j**,**l**), ketones (**7o**,**p**), an ester (**7k**,**n**,**q**), and a nitro group (**7q**). *Ortho*-substitution does not adversely influence the reaction outcome (**7j**,**o**). The successful use of these latter coupling partners is notable as a broad range of 1,1-diarylalkanes can be accessed with this method.

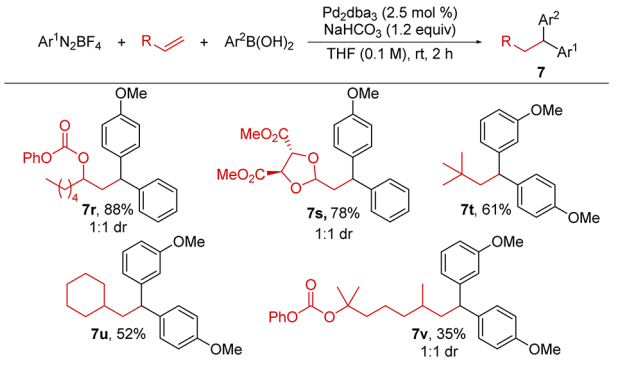
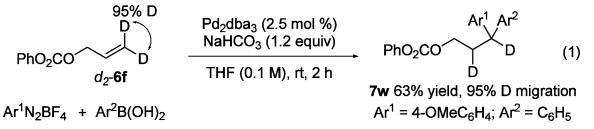


Figure 3. Scope of 1,1-diarylation of various alkenes.

Several alkenes were also explored for the 1,1-diarylation process with aryldiazonium salts and boronic acid (Figure 3). The use of a racemic carbonate protected allylic alcohol led to excellent yield (**7r**) with a 1:1 mixture of diastereomers. This suggests the carbonate is unlikely engaged with Pd during the key bond-forming events. Similarly, a dimethyl (+)-tartrate protected acrolein derivative provided the corresponding product in good yield as a nearly equimolar mixture of diastereomers (**7s**). Therefore, to determine the role of the allylic functional group further, the allylic carbonate was replaced with substituents that do not contain a heteroatom. These substrates were designed to test if a steric effect could also influence migration of Pd. In support of this hypothesis, both **7t** and **7u** were observed as products in good yield when submitting allylically hindered terminal alkenes. Additionally, a modest yield of **7v** was obtained with a less sterically encumbered substituent.

To probe that the allylic carbonate prevents β-hydride elimination at the allylic position, an isotopically labeled substrate (d_2-**6f**) with 95% deuterium incorporation at the terminal position was prepared and submitted to the optimized reaction conditions. The deuterium atoms were conserved in the product, with 95% D-migration to the β-carbon suggesting β-hydride elimination and reinsertion to form a π-benzyl intermediate. In addition, when an equimolar mixture of d_2-**6f** and 4-methoxylphenyl allyl carbonate were used in combination, no crossover was observed, which suggests that the alkene does not dissociate prior to the formation of the 1,1-diarylation product.



In summary, a one-step protocol for the 1,1-diarylation of ethylene and alkenes with allylic substitution was developed. This functional group-tolerant transformation provides a direct method by which to access biologically important diarylmethine motifs in good to excellent yields from very simple coupling partners. Of mechanistic importance, installation of a heteroatom or a group with significant sterics at the allylic site prevents β-hydride elimination and promotes the formation of a π-benzyl intermediate. Future work is focused on evaluating the biological activity of these compounds and related analogs as well as identifying approaches to enable an enantioselective variant, as common chiral ligands thus far impede the desired three-component coupling process.

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Supporting Information Available. Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.