JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

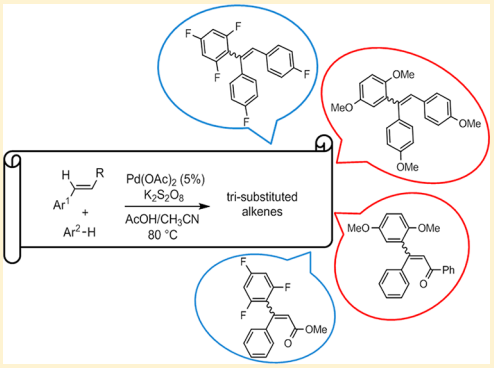
Synthesis of Trisubstituted Alkenes via Direct Oxidative Arene−Alkene Coupling

Roderick C. Jones, Michał Gałęzowski, and Donal F. O'Shea*

School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

Supporting Information

ABSTRACT: The use of an inorganic oxidant with an acetic acid/acetonitrile solvent combination has been identified as optimal for direct arene/1,2-disubstituted alkene oxidative couplings, providing an efficient route to trisubstituted alkenes. The acetonitrile cosolvent dramatically accelerates the rate of reaction, and an insoluble inorganic oxidant limits unwanted oxidation of substrates. The scope of this procedure is illustrated with arenes and alkenes containing electron-donating and -withdrawing substituents resulting in a general synthetic strategy to trisubstituted alkenes. In situ ESI-MS analysis of the reaction components has identified the key Pd intermediates in the Fujiwara−Moritani catalytic cycle.



INTRODUCTION

Transition-metal-promoted cross-coupling reactions of arenes and alkenes offer an excellent means of synthesizing tri- and tetrasubstituted alkenes. The importance of these transformations can be recognized through their widespread application in synthetic, medicinal, and materials chemistry.[1] Classical methods such as the Suzuki−Miyaura (boronic acid/halide), Negishi (zinc/halide), Stille (tin/halide), Hiyama (silane/halide), and Mizoroki−Heck (aryl halide/alkene) reactions involve using one or two preactivated coupling components.[2]

Recently, the selective activation of sp^2 aryl C−H bonds utilizing transition metals has attracted substantial research focus as it provides opportunities for general approaches to removing the necessity for preactivation of the cross-coupling partners.[3] When specifically applied to alkene derivatization, the Fujiwara−Moritani (F-M) oxidative coupling via C−H arene activation and alkene coupling offers the potential to have neither cross-coupling partner activated.[4] This direct approach to increasing the substituent number on a carbon−carbon double bond has been predominately explored for the conversion of monosubstituted alkenes such as acrylates into disubstituted products.[5] Of late, our own research focus has been the development of novel strategies for the synthesis of tri- and tetrasubstituted alkenes.[6] In this report we describe our efforts toward a general set of reaction conditions for the direct arylation of 1,2-disubstituted alkenes using a Pd-catalyzed oxidative coupling approach. The use of C−H bond activation for the synthesis of trisubstituted alkenes is rare in comparison to 1,2-disubstituted derivatives, with no general approach yet developed.

RESULTS AND DISCUSSION

The synthesis of trisubstituted alkenes via oxidative F-M arene/alkene couplings offers a distinct set of challenges in identifying a set of reaction conditions capable of capturing a broad spectrum of substrate reactivity. Presuming the rate-limiting step of the reaction is the Pd insertion into the arene C−H bond, substrate reactivity would be expected to follow a similar trend as electrophilic aromatic substitution with electron-rich arenes more amenable to coupling than electron-deficient arenes.[7] Coupling with 1,2-disubstituted alkenes presents an additional reactivity barrier as they are less reactive than monosubstituted derivatives such as acrylates. Furthermore, consideration must be given to the oxidant, which plays a central role in the Pd catalytic cycle. Desirable, yet sometimes difficult to reconcile, is the use of a relatively strong oxidant as this must be done in the presence of alkene and arene substrates that are susceptible to oxidation themselves. Previously reported efforts have investigated metallic oxidants such as AgOAc and $Cu(OAc)_2$, with organic peroxides, peroxyesters, and benzoquinones also utilized.[4e] The requirement for an oxidant limits the scope of ligands that can be employed to enhance the Pd electrophilic reactivity due to their instability under the reaction conditions. To date, the most successful ligands employed have been heterocyclic pyridines and amino acids.[5a,e,h,i] Previous reports of trisubstituted alkene generation via F-M couplings have been restricted to benzene or electron-rich arene substrates with oxygen/cocatalyst or organic peroxides as the terminal oxidant.[4d,5a,l−n]

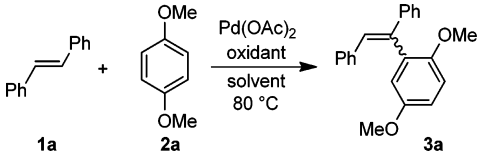
Received: June 19, 2013
Published: July 10, 2013

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

Our oxidative coupling optimization strategy was to use $Pd(OAc)_2$ as palladium source and acetic acid as the primary solvent, with potassium persulfate ($K_2S_2O_8$) as an inexpensive and relatively insoluble inorganic oxidant.[8] The rationale for selecting a sparingly soluble oxidant was that it would act with a slow release mechanism during the course of the reaction. In this way it was anticipated that the inorganic oxidant would help facilitate the coupling of electron-deficient arenes, yet due to its insolubility minimize unwanted oxidation of coupling reactants and thereby also allow its use with electron-rich arenes. It would be expected that in acetic acid alone there would be insufficient reactivity to achieve F-M couplings with electron-deficient arenes. As such, our approach was to identify a cosolvent that would generally enhance reactivity and thereby provide a broader substrate scope for the synthesis of trisubstituted alkenes.

The coupling of (*E*)-stilbene **1a** and 1,4-dimethoxybenzene **2a** was selected to identify reaction conditions and to screen cosolvents for the formation of the triaryl-substituted alkene **3a** (Table 1). The preliminary reaction utilizing 5 mol % of $Pd(OAc)_2$ and a 7.5-fold excess of arene in acetic acid was slow, with consumption of the **1a** taking 24 h (entry 1). Following chromatography a 72% yield of the triaryl alkene **3a** was obtained with an *Z*/*E* selectivity of 2:1. It was noticeable that during the course of the reaction a palladium mirror formed. Next, the addition of a series of cosolvents (*i*PrOH, DMF, dioxane, CH_3CN) was examined (entries 2−5). Clear trends were observed when 1:1 ratios of acetic acid to cosolvent were used such that dioxane significantly slowed the consumption of **1a**, whereas DMF, CH_3CN, and *i*PrOH all increased it. Yet analysis of reaction products showed that DMF was the poorest as only trace amount of desired product **3a** was produced with a complex mixture of oxidation byproducts observed (entry 2). 2-Propanol gave a 70% yield of **3a** but only marginally decreased reaction time when compared to acetic acid alone (entry 3). 1,4-Dioxane (entry 4) gave 74% product yield and minimal byproduct formation, but the rate of conversion was considerably slower, taking 48 h to achieve complete conversion of the starting material.

Table 1. Optimization of Reaction Conditions



1a 2a 3a

entry	solvent	oxidant	time (h)	*Z*/*E*[c]	% yield[d]
1[a]	AcOH	$K_2S_2O_8$	24	2:1	72
2[a]	AcOH/DMF (1:1)	$K_2S_2O_8$	3		<5
3[a]	AcOH/*i*PrOH (1:1)	$K_2S_2O_8$	16	4:1	70
4[a]	AcOH/dioxane (1:1)	$K_2S_2O_8$	48	3:1	74
5[a]	AcOH/MeCN (1:1)	$K_2S_2O_8$	7	7:1	75
6[a]	**AcOH/MeCN (4:1)**	$K_2S_2O_8$	**8**	**7:1**	**79**
7[b]	AcOH/MeCN (4:1)	$K_2S_2O_8$	24	7:1	75
8	AcOH/MeCN (4:1)	$(Bu_4N)_2S_2O_8$	12		<5
9	AcOH/MeCN (4:1)	$(NH_4)_2S_2O_8$	12		<5
10	AcOH/MeCN (4:1)	O_2 (1 atm)	48	6:1	74

[a]2 mmol (*E*)-stilbene, 15 mmol 1,4-dimethoxybenzene, 0.1 mmol $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$, [b]7.5 mmol 1,4-dimethoxybenzene. [c]Determined by GC of crude product. [d]Yield after chromatography.

The right balance for reaction rate and yield was struck using MeCN as a cosolvent, though some oxidation byproducts could be detected (entry 5). As such, the ratio of acetic acid/MeCN was adjusted to 4:1, which gave a 79% yield (*Z*/*E* 7:1 ratio) in an 8 h reaction time (entry 6). It was observed in successive experiments that a reduction of the excess of arene **2a** could be achieved to 3.75 equiv with no detrimental effect on yield, though reaction time lengthened to 24 h (entry 7). Illustrative experiments were also conducted to highlight the benefits of the chosen oxidant $K_2S_2O_8$. For example, when the organic soluble variants tetrabutylammonium persulfate $(Bu_4N)_2S_2O_8$ and ammonium persulfate $(NH_4)_2S_2O_8$ were utilized as the oxidant, the alkene substrate **1a** was consumed but very little desired coupling product was detected (entries 8, 9). This can be attributed to the competing oxidation of starting material by the strong solubilized oxidants. In addition, the use of 1 atm of O_2 proved less effective than $K_2S_2O_8$ with the reaction conversion considerably slower though a 74% yield was obtained after 48 h (entry 10).

A more detailed assessment of the influence of acetonitrile and dioxane cosolvents on the reaction was carried out by a relative comparison of product formation for the first 8 h of reaction (Figure 1). Acetic acid alone gave a steady conversion to product with a ∼40% product formation after 8 h. When 1,4-dioxane was used as cosolvent the rate of conversion was suppressed, reaching only ∼15% after 8 h. Encouragingly, the use of MeCN as a cosolvent had a dramatic effect with more than 85% conversion of the starting material in under 3 h with reaction deemed complete at 8 h. This could be attributed to the fact that MeCN can act as an effective ligand to Pd in the presence of acetic acid. The rate enhancing effect of using MeCN alone as solvent for the *ortho*-palladation of benzylamines has been previously described.[9] Overall, these results reaffirmed that AcOH/MeCN (4:1) using $K_2S_2O_8$ as an oxidant provided the best results from the conditions screened. Interestingly, an examination of the product *Z*/*E* ratio during the course of the reaction in AcOH/MeCN showed a change from 4:1 at earlier time points (1−2 h) to 7:1 upon reaction completion. This is consistent with the palladium playing an additional role in isomerizing the product **3a** to the most stable stereoisomer distribution during the course of the reaction. It is also of note that the cosolvent had a significant effect on the

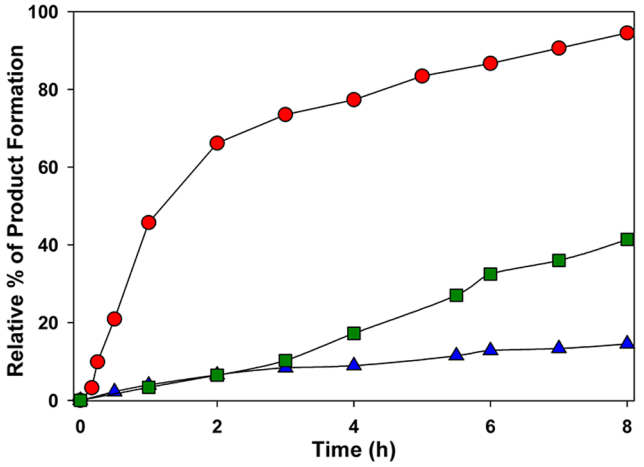
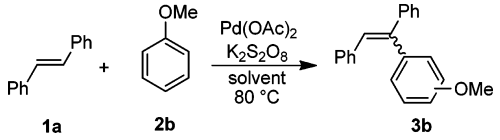


Figure 1. Relative percentage of formation of **3a** from **1a** and **2a** with $K_2S_2O_8$ at 80 °C over time in AcOH (green); AcOH/1,4-dioxane (4:1) (blue); AcOH/MeCN (4:1) (red).

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

reaction stereoselectivity as the Z/E ratio in acetic acid alone was 2:1, whereas with dioxane as cosolvent it was 3:1 upon reaction completion.

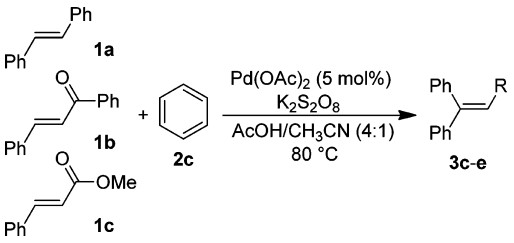
Table 2. Analysis of Anisole Stilbene Cross-Coupling[a]



entry	solvent	time (h)	*ortho*:*meta*:*para*[b]	% yield[c]
1	AcOH/MeCN (4:1)	7	1:0:2	84
2	AcOH	24	2:1:7	76

[a]Reaction conditions: **1a** (2 mmol), **2b** (15 mmol), $K_2S_2O_8$ (4 mmol), $Pd(OAc)_2$ (5 mol %). [b]Determined by GC. [c]Yield after chromatography.

Table 3. Alkene Coupling with Benzene[a]



entry	alkene	time (h)	product	R	% yield[c]
1	**1a**	48	**3c**	Ph	48
2	**1a**	24	**3c**	Ph[b]	74
3	**1b**	40	**3d**	COPh	59
4	**1c**	24	**3e**	CO_2Me	67

[a]Reaction conditions: **1a** (2 mmol), **2c** (15 mmol), $K_2S_2O_8$ (4 mmol). [b]**2c** (40 mmol). [c]Yield after chromatography.

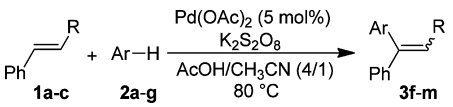
The cross-coupling of **1a** with anisole **2b** was next examined under the CH_3CN cosolvent conditions. Anisole has the potential to undergo palladium insertion at either the *ortho*, *meta*, or *para* positions with previous reports showing that the *para* position is the most favored followed by *ortho*, with *meta* being the regioisomer least produced.[4c,d] Coupling of **1a** and **2b** in $AcOH/CH_3CN$ as solvent system was complete in 7 h with the mixture of isomeric products **3b** isolated in an excellent 84% yield. Analysis by GC–MS and NMR with comparison to individually synthesized authentic samples showed it to be 1:2 *ortho*:*para* mixiture with no *meta*-isomer observed (Table 2). As in the previous example above, the reaction in acetic acid alone was considerably slower taking 24 h to reach completion and with lower selectivity as all three regioisomers were obtained in a *ortho*:*meta*:*para* ratio of 2:1:7.

Next, using benzene as a moderately reactive arene, the three alkenes (*E*)-stilbene **1a**, (*E*)-chalcone **1b**, and (*E*)-methyl cinnamate **1c** were examined for their ability to participate in a F-M coupling. The reaction was successful in each case, with the trisubtituted olefins **3c–e** isolated in good to moderate yields of 48%, 59%, and 67%, respectively (Table 3, entries 1, 3, 4). As would be expected, cinnamate **1c** was the most reactive of the alkenes and stilbene **1a** the least. Increasing the equivalence of benzene to 20-fold for the coupling with stilbene gave the product triphenylethylene **3c** in an improved yield of 74% (entry 2).

In order to demonstrate the scope of the optimized reaction conditions, the coupling of a series of activated and deactivated arenes with these three alkenes was examined (Table 4). Direct coupling of 1,4-dimethoxybenzene **1a** with alkenes **1b** and **1c** gave good yields of 66% and 80%, respectively, with reaction times shorter than that observed for benzene (entries 1, 2). The reactions of stilbene **1a** with *p*-xylene and thiophene each gave a good yield of isolated products (entry 3, 4). Encouragingly, the electron-deficient 1,4-difluorobenzene **2f** also effectively coupled with each of the alkene substrates under the reaction conditions, giving the trisubstituted olefin products **3j–l** in 43–56% yield (entries 5–7).[10] Additionally, coupling of the 1,3,5-trifluorobenzene **2g** with cinnamate **1c** gave a good 73% yield of the coupling product **3m**. Taken together these results give a clear indication that the developed solvent/oxidant system can be used for a variety of electron-rich and -deficient arenes. In each case, the products **3f–m** were isolated as a mixture of *E*/*Z* isomers that could be characterized by comparison to literature data or by NOE NMR experiments following stereoisomer separation. In the case of **3m**, both isomers were confirmed by single crystal X-ray structure following separation by silica gel chromatography (Supporting Information).

As stilbene **1a** was the least reactive of the three alkene substrates examined, the two further substituted stillbenes (*E*)-1,2-bis(4-methoxyphenyl)ethene **1d** and (*E*)-1,2-bis(4-fluorophenyl)ethene **1e** were synthesized and tested for their ability to undergo coupling reactions with both electron-rich and -poor arenes (Table 5). It was of interest to explore if the

Table 4. Coupling of 1a–c with Electron-Rich and -Poor Arenes[a]

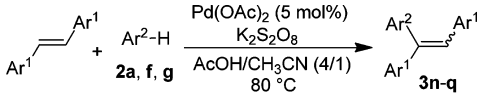


entry	1	2	time (h)	3	R	Ar	% yield[c]
1	**b**	**a**	7	**f**	COPh	$1,4\text{-}(OMe)_2C_6H_3$	66
2	**c**	**a**	7	**g**	CO_2CH_3	$1,4\text{-}(OMe)_2C_6H_3$	80
3	**a**	**d**	7	**h**	Ph	$1,4\text{-}(Me)_2C_6H_3$	75
4	**a**	**e**	24	**i**	Ph	C_4H_3S	69
5	**a**	**f**	48	**j**	Ph	$1,4\text{-}(F)_2C_6H_3$[b]	43
6	**b**	**f**	48	**k**	COPh	$1,4\text{-}(F)_2C_6H_3$[b]	56
7	**c**	**f**	40	**l**	CO_2CH_3	$1,4\text{-}(F)_2C_6H_3$[b]	53
8	**c**	**g**	48	**m**	CO_2CH_3	$1,3,5\text{-}(F)_3C_6H_2$[b]	73

[a]Conditions: 2 mmol of alkene, 15 mmol of arene, 5 mol % $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$, AcOH/MeCN (4:1). [b]40 mmol of arene. [c]Yield after chromatography.

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044–8053

Table 5. Coupling of 1d−e with Electron-Rich and -Poor Arenes[a]



1d: Ar^1 = 4-$MeOC_6H_4$
1e: Ar^1 = 4-FC_6H_4

entry	1	2	time (h)	prod	Ar^1	Ar^2	% yield[c]
1	**d**	**a**	3	**3n**	4-$MeOC_6H_4$	1,4-$(MeO)_2C_6H_3$	69
2	**d**	**f**	24		4-$MeOC_6H_4$	1,4-$(F)_2C_6H_3$[b]	0
3	**e**	**a**	48	**3o**	4-FC_6H_4	1,4-$(MeO)_2C_6H_3$	76
4	**e**	**f**	48	**3p**	4-FC_6H_4	1,4-$(F)_2C_6H_3$[b]	42
5	**e**	**g**	48	**3q**	4-FC_6H_4	1,3,5-$(F)_3C_6H_2$[b]	59

[a]Conditions: 2 mmol of alkene, 15 mmol of arene, 5 mol % $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$, AcOH/MeCN (4:1). [b]40 mmol of arene. [c]Yield after chromatography.

inclusion of electron-donating groups on the aryl rings of **1d** would increase formation of oxidation byproducts when reacted with an electron-deficient arene of relatively low reactivity (a reactivity mis-match), whereas the inclusion of an electron-withdrawing fluorines in **1e** may impede reactivity with an electron-rich arene.

Oxidative coupling of **1d** with dimethoxybenzene **2a** (both containing electron-donating substituents) gave a good 69% yield following purification of olefin **3n** after only 3 h reaction time (Table 5, entry 1). In contrast, coupling of **1d** with 1,4-difluorobenzene **2f** (alkene electron-donating and arene electron-withdrawing substituents) for 24 h gave no coupling product with only alkene degradation observed (entry 2). Interestingly, the reaction of difluorinated stilbene **1e** with the electron-rich and -poor arenes **2a**, **2f**, respectively, both gave the corresponding trisubstituted alkenes **3o** and **3p** in yields of 76% and 42%. In both cases a longer reaction time of 48 h was required. The results of this substituent study indicate that, in the case of stilbene containing the electron-donating methoxy groups, a substituent match with the arene is necessary in order to facilitate a coupling reaction. In contrast, the electron-deficient difluoro-substituted stilbene **1e** could effectively react with both electronically opposite arene classes under our reaction conditions. Futher illustration of this point was achieved with the synthesis of 4,4′-(1-(2,4,6-trifluorophenyl)-ethene-1,2-diyl)bis(fluorobenzene) **3q** from the direct coupling of **1e** with 1,3,5-trifluorobenzene **2g** (entry 5). Overall, three of the possible four substrate electron-donating/-withdrawing substituents combinations could be successfully coupled under our reaction conditions.

The mechanistic cycle for the F-M reaction has been investigated for the coupling of arenes with acrylates[11] and shown to first involve a C−H activation of the arene component generating an $ArPd^{(II)}OAc$ intermediate. Alkene insertion into the Pd-aryl bond followed by β-H elimination yields the product and HPdOAc, which generates $Pd^{(0)}$, and the catalytic cycle completes by its oxidation to $Pd^{(II)}$. To investigate the catalytic cycle under our conditions, stilbene **1a** and dimethoxybenzene **2a** were used as substrates and the reaction monitored by MS analysis.[12] ESI(+)-MS analysis was carried out on three key reagent and reaction compositions (i) $Pd(OAc)_2$ in acetic acid/CH_3CN (ii) $Pd(OAc)_2$ in acetic acid/CH_3CN with **2a** and (iii) $Pd(OAc)_2$ in acetic acid/CH_3CN with **1a**, **2a** and $K_2S_2O_8$. In each case the MS analysis showed intermediates consistent with the F-M catalytic cycle (Figures 2−4).

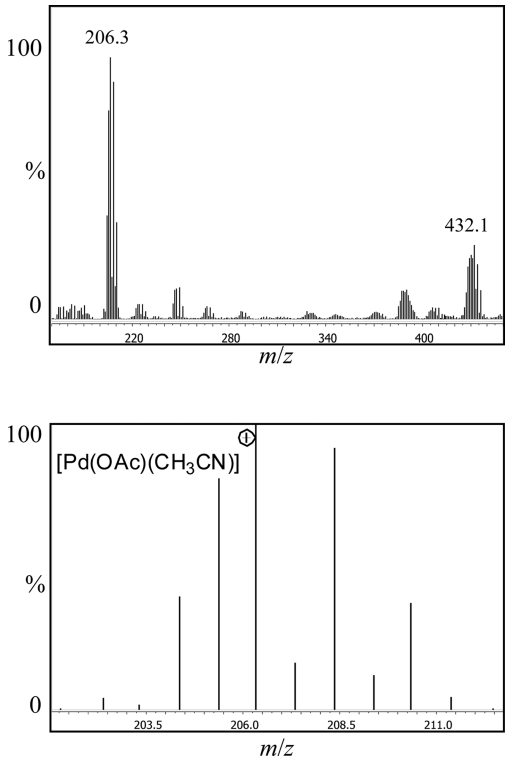


Figure 2. ESI(+)-MS of $Pd(OAc)_2$ in AcOH/MeCN (4:1). (Top) MS in range from 200 to 450 m/z. (Bottom) Expansion of most abundant cluster at m/z 206.3.

Analysis of composition (i) showed two main isotopic clusters centered at m/z of 206.3 and 432.1 (Figure 2, top). The mass and isotope distribution of the most abundant cluster centered at m/z 206.3 was consistent with an acetonitrile-bound monomeric palladium species $[Pd(OAc)(CH_3CN)]^+$, with the 431.1 mass being that of a palladium dimer, $[Pd_2(OAc)_3CH_3CN]^+$. In both cases it would be anticipated that these mono positively charged species detected would arise from a loss of a molecule of acetate. The predominance of the monomeric palladium $Pd(OAc)_2(CH_3CN)_2$ in the acetic acid/CH_3CN solvent mixture is consistent with the observed increase in reactivity over acetic acid alone. This contrasts sharply with the ESI-MS of $Pd(OAc)_2$ in acetic acid alone, which gave no discernible palladium species in this mass range, in agreement with previous reports that it exists as a trimer in acetic acid.[13]

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

With the key monomeric palladium species for C−H insertion step confirmed, the MS analysis of mixture (ii) generated following the addition of 1,4-dimethoxybenzene **2a** to solution (i) was carried out. This showed the most abundant m/z at 324.9, which can be assigned to $[Pd(C_8H_9O_2)(CH_3CN)_2]^+$, and is indicative of the intermediate from Pd C−H insertion into **2a** $Pd(C_8H_9O_2)(OAc)(CH_3CN)_2$ having lost an acetate (Figure 3, top and lower expansion).

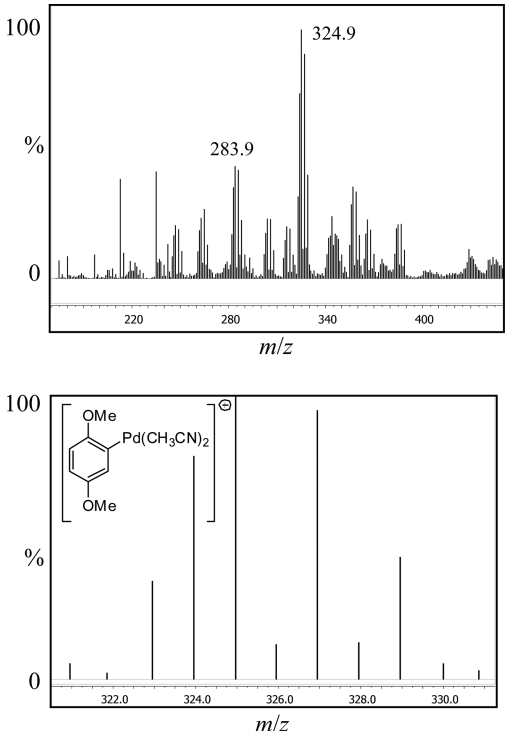


Figure 3. ESI(+)-MS of $Pd(OAc)_2$ and **2a** in AcOH/MeCN (4:1) after heating at 80 °C for 15 min. (Top) MS in range from 200 to 450 m/z. (Bottom) Expansion of most abundant cluster at m/z 324.9.

Interpretation of the next most abundant cluster centered at m/z 283.9 supported this assignment as it could be attributed to $[Pd(C_8H_9O_2)(CH_3CN)]^+$ in accord with the loss of acetate and acetonitrile from $Pd(C_8H_9O_2)(OAc)(CH_3CN)_2$ (Figure 3, top).

Following combination of all of the reaction components in AcOH/MeCN and heating at 80 °C for 15 min, the most abundant new cluster observed was at m/z of 422.8 in addition to that of the arene C−H inserted Pd species (283.9) previously observed in solution (ii). Provisionally, the m/z 422.8 could be attributed to $[C_{22}H_{20}O_2Pd]^+$, which would be in agreement with the palladium/product complex as shown in Figure 4 ,bottom panel. Overall this study confirms the a F-M catalytic cycle is in operation under our reaction conditions for 1,2-disubstituted alkene substrates.

CONCLUSION

In conclusion, we have developed an efficient protocol for direct arene−1,2-disubstituted alkene couplings to generate trisubstituted alkenes. Couplings were successful with a variety of electron-rich and -deficient arenes with stilbenes, chalcones, and cinnamates. Use of the reaction solvent mixture AcOH/MeCN (4:1) and the inorganic oxidant $K_2S_2O_8$ are key to achieving positive reaction outcomes, with MeCN playing an important role in accelerating the reaction. ESI-MS of in situ reaction intermediates has identfied several of the key organopalladium species expected for an F-M catalytic cycle. The application of these coupling conditions to other C−H bond activation processes is ongoing.

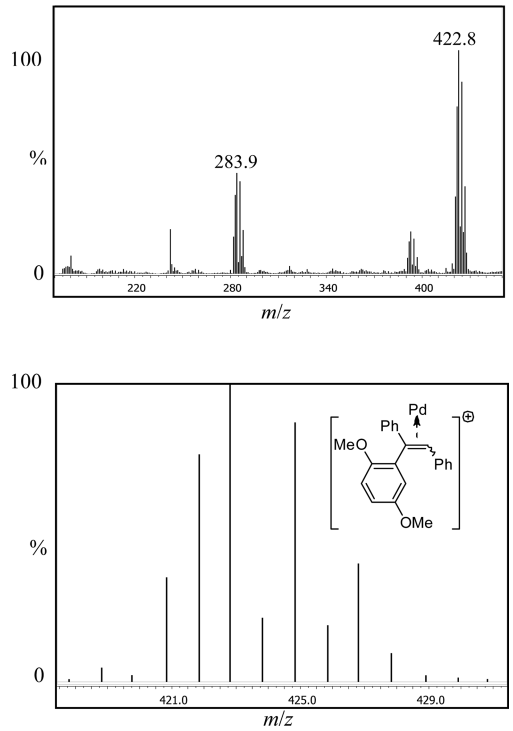


Figure 4. ESI(+)-MS of $Pd(OAc)_2$, **1a**, **2a**, and $K_2S_2O_8$ in AcOH/MeCN (4:1) after heating at 80 °C for 15 min. (Top) MS in range from 200 to 450 m/z. (Bottom) Expansion of most abundant cluster at m/z 422.8.

EXPERIMENTAL SECTION

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. Chromatography was performed on silica gel 60 PF254 or aluminum oxide 90. ^1H and ^{13}C NMR spectrum were recorded on a 400 or 500 MHz instrument. THF was dried over sodium benzophenone before use. Substituted alkenes **1d** and **1e** were prepared according to literature methods.[14] Anhydrous *i*PrOH, MeCN, and all other reagents were used as supplied. Preparative HPLC separations were conducted on an OD (250 mm × 20 mm i.d.) column. ES and EI HRMS measurements were taken on TOF mass analyzers.

Synthesis of Authentic Product Standards. Synthesis of (*E*)-(1-(2,5-Dimethoxyphenyl)ethene-1,2-diyl)dibenzene (*E*)-3a.[15] (*E*)-1-Bromo-1,2-diphenylethene[16] (150 mg, 0.58 mmol), $Pd(OAc)_2$ (12.99 mg, 0.058 mmol), PPh_3 (30.4 mg, 0.12 mmol), 2,5-dimethoxyphenylboronic acid (158 mg, 0.87 mmol, 1.5 equiv), KOH (65.1 mg, 1.2 mmol), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with Et_2O/heptane (2:98) affording the product as a colorless oil (180 mg, 87%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24−7.19 (m, 5H), 7.15−7.12 (m, 3H), 7.09−7.07 (m, 2H), 6.86−6.85 (m, 1H), 6.82−6.81 (m, 3H), 3.77 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 151.7, 140.8, 140.2, 137.4, 134.9, 130.3, 129.5, 129.5, 128.0, 127.9,

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

126.8, 126.6, 116.9, 113.6, 113.2, 56.6, 55.7. HRMS (EI) m/z $[M]^+$: found 316.1471 $[C_{22}H_{20}O_2]^+$, calcd 316.1463.

Synthesis of (*Z*)-(1-(2,5-Dimethoxyphenyl)ethene-1,2-diyl)-dibenzene (*Z*)-3a.[15] 1-Bromo-2,5-dimethoxybenzene (100 mg, 0.46 mmol), $Pd(OAc)_2$ (10.34 mg, 0.046 mmol), PPh_3 (24.1 mg, 0.092 mmol), (*E*)-(1,2-diphenylvinyl)boronic acid[6b] (155 mg, 0.69 mmol, 1.5 equiv), KOH (51.6 mg, 0.92 mmol, 2 equiv), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with toluene/heptane (50:50) affording the product as a colorless oil (75.7 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.36 (m, 2H), 7.32−7.30 (m, 2H), 7.26−7.25 (m, 1H), 7.15−7.11 (m, 3H), 7.07−7.05 (m, 3H), 6.88 (s, 2H), 6.68 (s, 1H), 3.69 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 151.7, 142.5,138.6, 137.5, 130.3, 129.0, 128.9, 128.2, 127.9, 127.2, 126.2, 126.8, 126.6, 116.9, 114.0, 113.2, 56.4, 55.7. HRMS (EI) m/z $[M]^+$: found 316.1475 $[C_{22}H_{20}O_2]^+$, calcd 316.1463.

Synthesis of (*E*)-(1-(2-mMethoxyphenyl)ethene-1,2-diyl)-dibenzene ((*E*)-*o*-3b). (*E*)-1-Bromo-1,2-diphenylethene[16] (150 mg, 0.58 mmol), $Pd(OAc)_2$ (12.99 mg, 0.058 mmol), PPh_3 (30.4 mg, 0.12 mmol), 2-methoxyphenylboronic acid (158 mg, 0.87 mmol, 1.5 equiv), KOH (65.1 mg, 1.2 mmol, 2 equiv), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over $MgSO_4$, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with Et_2O/heptane (2:98) affording the product as a colorless oil (140 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.25 (m, 2H), 7.22−7.17 (m, 5H), 7.13−7.09 (m, 3H), 7.08−7.06 (m, 2H), 6.95 (dt, 1.0, 7.5 Hz, 1H), 6.87 (dd, 1.0, 7.4 Hz, 1H), 6.79 (s, 1H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 141.1, 140.4, 137.5, 133.7, 131.1, 130.2, 129.6, 129.5, 128.8, 128.0, 127.9, 126.7, 126.6, 120.6, 111.8, 55.7. HRMS (ES) m/z $[M + H]^+$: found 287.1434 $[C_{21}H_{19}O]^+$, calcd 287.1436.

Synthesis of (*E*)-(1-(4-Methoxyphenyl)ethene-1,2-diyl)-dibenzene ((*E*)-*p*-3b). (*E*)-1-Bromo-1,2-diphenylethene[16] (150 mg, 0.58 mmol), $Pd(OAc)_2$ (12.99 mg, 0.058 mmol), PPh_3 (30.4 mg, 0.12 mmol), 4-methoxyphenylboronic acid (158 mg, 0.87 mmol, 1.5 equiv), KOH (65.1 mg, 1.2 mmol, 2 equiv), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with Et_2O/heptane (2:98) affording the product as a colorless oil (131 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.28 (m, 3H), 7.27−7.23 (m, 2H), 7.21−7.19 (m, 2H), 7.12−7.07 (m, 3H), 7.01−6.99 (m, 2H), 6.89 (s, 1H), 6.84 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 142.1, 140.6, 137.6, 136.1, 130.4, 129.4, 128.8, 128.6, 127.9, 127.3, 126.5, 126.4, 113.6, 55.3. HRMS (ES) m/z $[M + H]^+$: found 287.1426 $[C_{21}H_{19}O]^+$, calcd 287.1436.

Synthesis of (*Z*)-(1-(2-Methoxyphenyl)ethene-1,2-diyl)-dibenzene ((*Z*)-*o*-3b). 1-Iodo-2-methoxybenzene (100 mg, 0.46 mmol), $Pd(OAc)_2$ (10.34 mg, 0.046 mmol), PPh_3 (24.1 mg, 0.092 mmol), (*E*)-(1,2-diphenylvinyl)boronic acid[6b] (155 mg, 0.69 mmol, 1.5 equiv), KOH (51.6 mg, 0.92 mmol, 2 equiv), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with Et_2O/heptane (2:98) affording the product as a colorless oil (108 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.24 (m, 6H), 7.13−7.06 (m, 5H), 7.03−7.00 (m, 2H), 6.96−6.92 (m, 2H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 142.8, 138.9, 137.6, 131.6, 129.0, 128.9, 128.8, 128.1, 127.9, 127.8, 127.2, 126.7, 126.5, 121.1, 111.7, 55.6. HRMS (ES) m/z $[M + H]^+$: found 287.1430 $[C_{21}H_{19}O]^+$, calcd 287.1436.

Synthesis of (*Z*)-(1-(4-Methoxyphenyl)ethene-1,2-diyl)-dibenzene ((*Z*)-*p*-3b). 1-Iodo-4-methoxybenzene (100 mg, 0.46 mmol), $Pd(OAc)_2$ (10.34 mg, 0.046 mmol), PPh_3 (24.1 mg, 0.092 mmol), (*E*)-(1,2-diphenylvinyl)boronic acid[6b] (155 mg, 0.69 mmol, 1.5 equiv), KOH (51.6 mg, 0.92 mmol, 2 equiv), *i*PrOH (3 mL), and THF (3 mL) were combined in a flask under N_2. The pale yellow solution was then stirred at rt for 24 h after which 1 M NaOH was added (10 mL), and the solution was extracted with Et_2O (3 × 10 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel with Et_2O/heptane (2:98) affording the product as a colorless oil (104 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 5H), 7.14−7.05 (m, 7H), 6.90 (s, 1H), 6.85 (d, 6.6 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 143.8, 142.3, 137.7, 132.5, 131.6, 129.5, 128.2, 127.9, 127.8, 127.7, 127.5, 126.6, 114.0, 55.2. HRMS (ES) m/z $[M + H]^+$: found 287.1431 $[C_{21}H_{19}O]^+$, calcd 287.1436.

General Experimental Procedure for Pd-Mediated Arene/1,2-Disubstituted Alkene Coupling. $Pd(OAc)_2$ (22.0 mg, 5 mol %), $K_2S_2O_8$ (0.81 g, 3 mmol), 1,2-disubstituted alkene (2 mmol), arene (15 mmol, 7.5 equiv unless otherwise specified), acetic acid (8 mL), and MeCN (2 mL) were placed in a 20-mL scintillation vial containing a magnetic stir bar. The flask was sealed with a Teflon-lined crimped cap, and the reaction solution was stirred vigorously at 80 °C until alkene had been consumed as indicated by TLC and GC. The reaction solution was then filtered, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel.

Synthesis of (*E*/*Z*)-(1-(2,5-Dimethoxyphenyl)ethene-1,2-diyl)dibenzene (3a). Prepared by the general procedure using (*E*)-stilbene **1a** (359 mg, 2 mmol), 1,4-dimethoxybenzene (2.07 g, 15 mmol), $Pd(OAc)_2$ (21.4 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 8 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (95:5) gave the product as a colorless oil (499 mg, 79%). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data obtained for authentically synthesized samples described above.

Synthesis of (*E*/*Z*)-(Methoxyphenyl)ethene-1,2-diyl)-dibenzene (Mixture of (*E*/*Z*)-*o*-3b and (*E*/*Z*)-*p*-3b). Prepared by the general procedure using (*E*)-stilbene **1a** (360 mg, 2 mmol, 1.0 equiv), anisole (1.63 mL, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.5 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 7 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (95:5) gave the (*E*/*Z*) product as a pale yellow oil (515 mg, 84%). ^{1}H and ^{13}C NMR spectral data of the isolated material matched the spectral data obtained for authentically synthesized samples described above.

Synthesis of Triphenylethylene (3c).[17] Prepared by the general procedure using (*E*)-stilbene **1a** (361 mg, 2 mmol, 1.0 equiv), benzene (3.57 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (22.6 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), NaOAc (324 mg, 4 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 48 h. Purification by silica gel column chromatography using cyclohexane (100%) gave the product as a colorless oil (646 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.28 (m, 8H), 7.22−7.19 (m, 2H), 7.14−7.10 (m, 3H), 7.04−7.02 (m, 2H), 6.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 142.6, 140.3, 137.4, 130.4, 129.5, 128.6, 128.2, 128.1, 127.9, 127.6, 127.5, 127.4, 126.7. HRMS (ES) m/z $[M + H]^+$: found 257.1328 $[C_{20}H_{17}]^+$, calcd 257.1330.

Synthesis of 3,3-Diphenylacrylophenone (3d).[18] Prepared by the general procedure using (*E*)-chalcone **1b** (418 mg, 2 mmol, 1.0 equiv), benzene (1.34 mL, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (21.8 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), NaOAc (327 mg, 4 mmol), acetic acid (8

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 40 h. Purification by silica gel column chromatography using cyclohexane/Et_2O (90:10) gave the product as a pale yellow solid, mp 90−91 °C (403 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, 1.5, 7.0 Hz, 2H), 7.48−7.46 (m, 1H), 7.40−7.35 (m, 7H), 7.27−7.25 (m, 3H), 7.18−7.16 (m, 2H), 7.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 154.7, 141.4, 139.0, 138.2, 132.6, 129.7, 129.3, 128.7, 128.6, 128.4, 128.3, 128.0, 124.0, 110.0. HRMS (EI) m/z $[M]^+$: found 284.1205 $[C_{21}H_{16}O]^+$, calcd 284.1201.

Synthesis of Methyl 3,3-Diphenyl-2-propenoate (3e).[19] Prepared by the general procedure using methyl (*E*)-cinnamate **1c** (323 mg, 2 mmol, 1.0 equiv), benzene (1.34 mL, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (21.8 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), NaOAc (329 mg, 4 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 24 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (20:1) gave the product as a pale yellow oil (318 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.28 (m, 8H), 7.22−7.20 (m, 2H), 6.37 (s, 1H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 157.0, 140.8, 138.8, 129.4, 129.0, 128.4, 128.3, 128.2, 127.9, 116.8, 51.2 HRMS (ES) m/z $[M + H]^+$: found 239.1069 $[C_{16}H_{14}O_2]^+$, calcd 239.1072.

Synthesis of (*E*/*Z*) 3-(2,5-Dimethoxyphenyl)-1,3-diphenylpropenone (3f). Prepared by the general procedure using (*E*)-chalcone **1b** (417 mg, 2 mmol, 1.0 equiv), 1,4-dimethoxybenzene (2.072 g, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.4 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 7 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (95:5) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 85:15 (489 mg, 66%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.5:0.5) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3f**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93−7.92 (m, 2H), 7.45−7.43 (m, 1H), 7.35−7.33 (m, 2H), 7.16 (*ps*, 5H), 6.97 (s, 1H), 6.88 (*ps*, 2H), 6.78 (s, 1H), 3.74 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 153.4, 151.7, 150.5, 139.6, 137.9, 132.6, 132.2, 129.1, 128.9, 128.2, 127.9, 127.7, 127.4, 116.9, 114.5, 113.3, 56.5, 55.7.HRMS (ES) m/z $[M + H]^+$: found 345.1494 $[C_{23}H_{21}O_3]^+$, Calc. Mass: 345.1491.

(*Z*)-**3f**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.89 (m, 2H), 7.48−7.46 (m, 1H), 7.42−34 (m, 7H), 7.22 (s, 1H), 6.80−6.74 (m, 2), 6.61 (d, 3.01 Hz, 1H), 3.68 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1, 153.3, 150.8, 150.1, 140.8, 138.4, 132.4, 129.0, 128.5, 128.4, 128.2, 127.8, 124.7, 116.6, 114.2, 112.2, 110.0, 55.9, 55.7. HRMS (ES) m/z $[M + H]^+$: found 345.1500 $[C_{23}H_{21}O_3]^+$, calcd 345.1491.

Synthesis of (*E*/*Z*) (2,5-Dimethoxyphenyl)-3-phenylacrylic Acid Methyl Ester (3g). Prepared by the general procedure using methyl (*E*)-cinnamate **1c** (320 mg, 2 mmol, 1.0 equiv), 1,4-dimethoxybenzene (2.08 g, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (20.2 mg), $K_2S_2O_8$ (0.80 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 7 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (90:10) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 60:40 (530 mg, 80%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99:5:0.5) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3g**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.28 (m, 5H), 6.89−6.88 (m, 2H), 6.64−6.61 (m, 1H), 6.45 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 153.4, 152.9, 150.9, 139.9, 129.3, 129.1, 128.4 127.5, 117.8, 115.9, 113.8, 112.4, 56.5, 55.7, 51.2. HRMS (ES) m/z $[M + H]^+$: found 299.1211 $[C_{18}H_{19}O_4]^+$, calcd 299.1205.

(*Z*)-**3g**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.28 (m, 3H), 7.25−7.21 (m, 2H), 6.85−6.81 (m, 2H), 6.71−6.68 (d, 5 Hz, 1H), 6.28 (s, 1H), 3.73 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 154.1, 153.3, 151.5, 139.5, 132.1, 128.6, 127.9, 127.5, 119.9, 116.8, 114.6, 113.4, 56.4, 55.7, 51.2. HRMS (ES) m/z $[M + H]^+$: found 299.1208 $[C_{18}H_{19}O_4]^+$, calcd 299.1205.

Synthesis of (*E*/*Z*)-1-(2,5-Dimethylphenyl)-1,2-diphenylethene (3h).[20] Prepared by the general procedure using (*E*)-stilbene **1a** (350 mg, 2 mmol, 1.0 equiv), *p*-xylene (1.85 mL, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.9 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 7 h. Purification by silica gel column chromatography using cyclohexane (100%) gave the product was as a mixture of known (*E*/*Z*) isomers in a ratio of 20:80 (414 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.23 (m), 7.19 (m), 7.16−7.07 (m), 7.05−7.03 (m), 6.97−6.94 (m), 2.32 (s, CH_3, minor), 2.28 (s, CH_3, major), 2.07 (s, CH_3, minor), 1.99 (s, CH_3, major). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 143.1, 142.5, 141.4, 140.3, 139.5, 137.5, 137.5, 137.4, 135.8, 135.0, 133.3, 133.1, 130.8, 130.5 130.4, 130.3, 129.9, 129.8, 129.4, 128.9, 128.4, 128.3, 128.2, 128.1, 127.9, 127.3, 127.1, 126.8, 126.7, 126.6, 21.0, 20.9, 20.0, 19.1. HRMS (EI) m/z $[M]^+$: found 284.1569 $[C_{22}H_{20}]^+$, calcd 284.1565.

Synthesis of (*E*/*Z*)-2-(1,2-Diphenylethenyl)thiophene (3i).[21] Prepared by the general procedure using (*E*)-stilbene **1a** (359 mg, 2 mmol, 1.0 equiv), thiophene (1.20 mL, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.4 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 24 h. Purification by silica gel column chromatography using cyclohexane (100%) gave the product was as a mixture of known (*E*/*Z*) isomers in a ratio of 35:65 (361 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42−7.29 (m), 7.21−7.15 (m), 7.11, 7.07 (m), 7.05 (s), 7.00 (dd, 3.5 Hz, 5.1 Hz), 6.96 (m), 6.93 (dd, 3.5 Hz, 5.1 Hz), 6.88 (dd, 1.1 Hz, 3.5 Hz), 6.73 (dd, 1.1 Hz, 3.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 143.2, 141.6, 140.6, 139.4, 137.2, 136.6, 136.2, 135.2, 130.4, 129.9,129.4, 129.3, 128.8, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.4, 127.1, 127.1, 126.8, 126.4, 126.3, 126.0, 124.7. HRMS (ES) m/z $[M + H]^+$: found 262.0811 $[C_{18}H_{14}S]^+$, calcd 262.0816.

Synthesis of (*E*/*Z*)-(1-(2,5-Difluorophenyl)ethene-1,2-diyl)-dibenzene (3j). Prepared by the general procedure using (*E*)-stilbene **1a** (351 mg, 2 mmol, 1.0 equiv), 1,4-difluorobenzene (4.11 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (22.5 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 48 h. Purification by silica gel column chromatography using cyclohexane (100%) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 60:40 (245 mg, 43%). The two isomers were separated by preparative HPLC using heptane:2-propanol (99.8:0.2) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3j**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.28 (m, 3H), 7.19−7.18 (m, 2H), 7.15−7.14 (m, 3H), 7.05−7.04 (m, 2H), 7.01 (dt, 4.6 Hz, 9.0 Hz, 1H), 6.95−6.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5 (dd, 1.9 Hz, 209.1 Hz), 156.1 (dd, 2.0 Hz, 213.3 Hz), 139.5, 136.6, 136.1, 132.9−132.7 (m), 132.5, 132.4, 129.7, 129.5, 128.6, 128.0, 127.6, 127.2, 117.4 (dd, 3.6 Hz, 24.2 Hz), 116.9 (dd, 8.8 Hz, 25.9 Hz,), 115.1 (dd, 8.7 Hz, 24.0 Hz,). ^{19}F NMR (376 MHz, $CDCl_3$): δ −119.4 (m, 1F), −120.1 (m, 1F). HRMS (EI) m/z $[M]^+$: found 292.1062 $[C_{20}H_{14}F_2]^+$, calcd 292.1064.

(*Z*)-**3j**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.29 (m, 5H), 7.20−7.15 (m, 3H), 7.13 (s, 1H), 7.07−7.01 (m, 4H), 6.89 (ddd, 2.9 Hz, 5.3 Hz, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (d, 242.1 Hz), 156.3 (d, 241.0 Hz), 141.5, 136.6, 134.9, 130.9, 129.2 (m), 128.9, 128.4, 128.2, 127.8, 127.4, 126.7, 118.5 (dd, 4.2 Hz, 23.7 Hz), 117.1 (dd, 8.9 Hz, 25.1 Hz,), 116.0 (dd, 8.4 Hz, 24.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.7 (m, 1F), −119.5 (m, 1F). HRMS (EI) m/z $[M]^+$: found 292.1058 $[C_{20}H_{14}F_2]^+$, calcd 292.1064.

Synthesis of (*E*/*Z*)-3-(2,5-Difluorophenyl)-1,3-diphenylpropenone (3k). Prepared by the general procedure using (*E*)-chalcone **1b** (414 mg, 2 mmol, 1.0 equiv), 1,4-difluorobenzene (4.11 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (23.0 mg, 5 mol %), $K_2S_2O_8$ (0.82 g, 3 mmol), NaOAc (340 mg, 4 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 48 h. Purification by silica gel column chromatography using cyclohexane/Et_2O (90:10) gave the product as a mixture of (*E*/*Z*) isomers

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

in a ratio of 80:20 (*E*:*Z*) (357 mg, 56%). (*E*)-Isomer purification was achieved using preparative HPLC with heptane/2-propanol (99.5:0.5) as a mobile phase. The (*Z*)-isomer was not isolated in sufficient quantities. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3k**: yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, 1.1 Hz, 8.2 Hz, 2H), 7.49−7.46 (m, 1H), 7.36 (t, 7.7 Hz, 2H), 7.24−7.20 (m, 3H), 7.18−7.15 (m, 2H), 7.10 (td, 4.5 Hz, 9.3 Hz, 1H), 7.06−7.03 (m, 1H), 7.02 (s, 1H), 6.89 (ddd, 3.0 Hz, 5.8 Hz, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 158.3 (dd, 2.5 Hz, 241.7 Hz), 156.3 (dd, 2.6 Hz, 245.1 Hz), 145.9, 138.1, 137.4, 132.9, 130.6−130.4 (m), 129.0, 128.9, 128.8, 128.6, 128.4, 128.2, 117.9 (dd, 3.0 Hz, 24.4 Hz), 117.3 (dd, 8.6 Hz, 25.7 Hz), 116.7 (dd, 8.6 Hz, 23.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.5 (m, 1F), −119.6 (m, 1F). HRMS (ES) *m*/*z* [M + H]$^+$: found 321.1086 [$C_{21}H_{15}OF_2$]$^+$, calcd 321.1091.

Synthesis of (*E*/*Z*)-(2,5-Difluorophenyl)-3-phenylacrylic Acid Methyl Ester (3l). Prepared by the general procedure using methyl (*E*)-cinnamate **1c** (316 mg, 2 mmol, 1.0 equiv), 1,4-difluorobenzene (4.11 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (23.0 mg, 5 mol %), $K_2S_2O_8$ (0.808 g, 3 mmol), NaOAc (327 mg, 4 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 40 h. Purification by silica gel column chromatography using cyclohexane/Et_2O (95:5) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 80:20 (280 mg, 53%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.5:0.5) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3l**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.36 (m, 3H), 7.24−7.21 (m, 2H), 7.06−6.97 (m, 2H), 6.80 (ddd, 3.1 Hz, 5.9 Hz, 8.9 Hz, 1H), 6.35 (s, 1H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 158.4 (dd, 2.1 Hz, 208.5 Hz), 155.9 (dd, 2.0 Hz, 215.1 Hz), 149.5, 138.0, 130.2 (dd, 2.6 Hz, 22.0 Hz), 128.7, 128.6, 128.0, 127.8, 121.7, 117.7 (dd, 2.9 Hz, 24.8 Hz), 117.3 (dd, 8.6 Hz, 25.7 Hz), 116.9 (dd, 8.8 Hz, 24.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.5 (m, 1F), −119.2 (m, 1F). HRMS (ES) *m*/*z* [M + Na]$^+$: found 297.0695 [$C_{16}H_{12}O_2F_2Na$]$^+$, calcd 297.0703.

(*Z*)-**3l**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.31 (m, 5H), 7.10−7.04 (m, 2H), 6.84 (ddd, 2.9 Hz, 5.4 Hz, 8.4 Hz, 1H), 6.52 (s, 1H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 158.6 (dd, 2.3 Hz, 228.3 Hz), 155.5 (dd, 2.5 Hz, 241.9 Hz), 149.0, 138.8, 129.9, 128.6, 127.7 (dd, 8.2 Hz, 19.3 Hz), 127.6, 119.2, 117.1 (dd, 3.7 Hz, 24.6 Hz), 116.4 (m), 116.2 (m), 51.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −119.3 (m, 1F), −120.9 (m, 1F). HRMS (ES) *m*/*z* [M + Na]$^+$: found 297.0701 [$C_{16}H_{12}O_2F_2Na$]$^+$, calcd 297.0703.

Synthesis of (*E*/*Z*)-(2,4,6-Trifluorophenyl)-3-phenylacrylic Acid Methyl Ester (3m). Prepared by the general procedure using methyl (*E*)-cinnamate **1c** (322 mg, 2 mmol, 1.0 equiv), 1,3,5-trifluorobenzene (4.14 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (22.2 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), NaOAc (317 mg, 4 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 48 h. Purification by silica gel column chromatography using cyclohexane/Et_2O (95:5) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 75:25 (424 mg, 73%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.8:0.2) as a mobile phase. Individual isomer assignments were determined by 1D NOESY and 2D NMR techniques and single crystal X-ray spectrometry.

(*E*)-**3m**: colorless waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 3H), 7.27 (m, 2H), 6.69 (m, 2H), 6.13 (s, 1H), 3.64 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 162.5 (dt, 15.4 Hz, 251.4 Hz), 160.2 (ddd, 9.4 Hz, 15.0 Hz, 251.6 Hz), 143.5, 137.7, 128.6, 128.1, 127.9, 123.8, 115.5 (m), 100.6 (m), 51.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.85 (m, 1F), −108.62 (m, 2F). HRMS (ES) *m*/*z* [M + Na]$^+$: found 315.0595 [$C_{16}H_{12}O_2F_2Na$]$^+$, calcd 315.0609.

(*Z*)-**3m**: colorless waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 5H), 6.74 (m, 2H), 6.62 (s, 1H), 3.68 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 162.7 (dt, 14.9 Hz, 250.3 Hz), 159.9 (ddd, 10.2 Hz, 14.9 Hz, 249.5 Hz), 143.6, 138.1, 130.0, 128.8, 126.9, 120.8, 111.9 (m), 100.2 (m), 51.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −107.71 (m, 1F), −109.08 (m, 2F). HRMS (ES) *m*/*z* [M + Na]$^+$: found 315.0609 [$C_{16}H_{11}O_2F_3Na$]$^+$, calcd 315.0617.

Single crystals of (*E*)-**3m** and (*Z*)-**3m** were grown by slow evaporation of dicholomethane. CIF files of the obtained structures can be found in Supporting Information.

Synthesis of (*E*/*Z*)-4,4′-(1-(2,5-Dimethoxyphenyl)ethene-1,2-diyl)bis(methoxybenzene) (3n). Prepared by the general procedure using (*E*)-4,4′-dimethoxystilbene **1d** (487 mg, 2 mmol, 1.0 equiv), 1,4-dimethoxybenzene (2.07 g, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.2 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 3 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (90:10) gave the product was as a mixture of (*E*/*Z*) isomers in a ratio of 80:20 (526 mg, 69%). Isomer separation was not achieved.

(*E*/*Z*)-**3n**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m), 7.11 (d, 8.6 Hz), 7.03 (d, 8.6 Hz), 6.97−6.91 (m), 6.89−6.86 (m), 6.84−6.76 (m), 6.70−6.65 (m), 3.80 (s, CH_3), 3.78 (s, CH_3), 3.76 (s, CH_3), 3.74 (s, CH_3), 3.70 (s, CH_3), 3.54 (s, CH_3), 3.53 (s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 158.4, 158.2,154.1, 153.6, 151.8, 151.7, 144.1, 138.0, 135.9, 135.4, 133.4, 130.8, 130.7, 130.4, 130.2, 130.1, 129.3, 127.5, 126.6, 116.9, 116.8, 113.8, 113.7, 113.5, 113.4, 113.3, 112.9, 56.8, 56.5, 55.7, 55.3, 55.1, 55.0. HRMS (ES) *m*/*z* [M + H]$^+$: found 377.1764 [$C_{24}H_{25}O_4$]$^+$, calcd 377.1753.

Synthesis of (*E*/*Z*)-4,4′-(1-(2,5-Dimethoxyphenyl)ethene-1,2-diyl)bis(fluorobenzene) (3o). Prepared by the general procedure using (*E*)-4,4′-difluorostilbene **1e** (432 mg, 2 mmol, 1.0 equiv), 1,4-dimethoxybenzene (2.073 g, 15 mmol, 7.5 equiv), $Pd(OAc)_2$ (22.4 mg), $K_2S_2O_8$ (0.80 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). Complete conversion of the starting alkene was achieved after 3 h. Purification by silica gel column chromatography using cyclohexane/EtOAc (95:5) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 85:15 (535 mg, 76%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.5:0.5) as a mobile phase. Isomer assignments were determined by 1D NOESY NMR.

(*E*)-**3o**: pale green oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.28 (m, 2H), 6.98 (m, 5H), 6.88 (*pd*, 1.7 Hz, 2H), 6.82 (*pt*, 8.8 Hz, 2H), 6.63 (*pt*, 1.7 Hz, 1H), 3.69 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, 246.0 Hz), 160.7 (d, 248.0 Hz), 154.0, 151.5, 138.5 (d, 3.2 Hz), 137.4 (d, 1.9 Hz), 133.5 (d, 3.4 Hz), 130.4 (d, 7.9 Hz), 129.6, 128.1 (d, 8.0 Hz), 127.4 (d, 1.6 Hz), 116.9, 115.0 (d, 21.0 Hz), 114.8 (d, 21.0 Hz), 114.0, 113.1 56.2, 55.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.78 (m, 1F), −115.33 (m, 1F). HRMS (EI) *m*/*z* [M]$^+$: found 352.1284 [$C_{22}H_{18}F_2O_2$]$^+$, calcd 352.1275.

(*Z*)-**3o**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (dd, 5.6 Hz, 8.6 Hz, 2H), 7.02 (dd, 5.6 Hz, 8.6 Hz, 2H), 6.92 (t, 8.8 Hz, 2H), 6.86−6.81 (m, 5H), 6.74 (s, 1H), 3.78 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (d, 247.0 Hz), 161.5 (246.0 Hz), 153.6, 151.5, 139.2, 136.5 (d, 3.4 Hz), 134.3, 133.2 (d, 3.4 Hz), 131.1 (d, 11.5 Hz), 131.0 (d, 12.0 Hz), 129.2, 116.9, 115.0 (d, 21.3 Hz), 114.9 (d, 22.3 Hz), 113.3, 56.4, 55.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.8 (m, 1F), −115.2 (m, 1F). HRMS (EI) *m*/*z* [M]$^+$: found 352.1276 [$C_{22}H_{18}F_2O_2$]$^+$, calcd 352.1275.

Synthesis of (*E*/*Z*)-4,4′-(1-(2,5-Difluorophenyl)ethene-1,2-diyl)bis(fluorobenzene) (3p). Prepared by the general procedure using (*E*)-4,4′-difluorostilbene **1e** (430 mg, 2 mmol, 1.0 equiv), 2,4-difluorobenzene (4.11 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (21.8 mg), $K_2S_2O_8$ (0.82 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). The reaction was stopped after 48 h; however, complete conversion of the starting alkene was not achieved. Purification by silica gel column chromatography using heptane/Et_2O (99.8:0.2) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 65:35 (276 mg, 42%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.8:0.2) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3p**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16−7.12 (m, 2H), 7.04−6.97 (m, 5H), 6.97−6.92 (m, 1H), 6.91−6.83 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (dd, 39.1 Hz, 246.0 Hz), 158.4 (dd, 2.2 Hz, 240.0 Hz), 156.2 (dd, 2.4 Hz, 243.0 Hz), 135.1 (d, 3.5 Hz), 134.9, 132.4 (d, 3.5 Hz), 131.5, 131.4 (d, 8.1 Hz), 131.2 (d, 7.9 Hz), 117.3 (dd, 3.5 Hz, 24.2 Hz), 117.0 (dd, 8.04, 25.0 Hz), 115.8,

dx.doi.org/10.1021/jo401326f | J. Org. Chem. 2013, 78, 8044−8053

115.6, 115.4 (dd, 8.2 Hz, 23.0 Hz), 115.2, 115.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.7 (m, 1F), −113.8 (m, 1F), −119.2 (m, 1F), −120.0 (m, 1F), −120.1 (m, 1F). HRMS (EI) m/z $[M]^+$: found 328.0870 $[C_{20}H_{12}F_4]^+$, calcd 328.0875.

(*Z*)-**3p**: colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48−7.43 (m, 2H), 7.30−7.26 (m, 1H), 7.07−6.99 (m, 6H), 6.98 (s, 1H), 6.91−6.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (dd, 21.4 Hz, 247.6 Hz), 161.8 (td, 15.8 Hz, 247.0 Hz), 158.7 (dd, 2.4 Hz, 254.5 Hz), 156.3 (dd, 2.71 Hz, 255.7 Hz), 132.6 (d, 3.6 Hz) 130.5 (d, 7.8 Hz), 129.5 (m), 128.3 (d, 8.0 Hz), 127.8 (d, 8.0 Hz), 127.2 (m), 118.3 (dd, 3.9 Hz, 23.7 Hz), 117.3 (dd, 8.7 Hz, 25.1 Hz), 116.3 (8.3 Hz, 24.0 Hz), 115.7, 115.5, 115.4 (dd, 14.1 Hz, 21.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.21 (m, 1F), −118.31 (m, 1F), −119.54 (m, 1F). HRMS (EI) m/z $[M]^+$: found 328.0882 $[C_{20}H_{12}F_4]^+$, calcd 328.0875.

Synthesis of (*E*/*Z*)-4,4′-(1-(2,4,6-Trifluorophenyl)ethene-1,2-diyl)bis(fluorobenzene) (3q). Prepared by the general procedure using (*E*)-4,4′-difluorostilbene **1e** (432 mg, 2 mmol, 1.0 equiv), 1,3,5-trifluorobenzene (4.14 mL, 40 mmol, 20 equiv), $Pd(OAc)_2$ (22.6 mg), $K_2S_2O_8$ (0.81 g, 3 mmol), acetic acid (8 mL), and MeCN (2 mL). The reaction was stopped after 48 h, without complete consumption of the starting alkene. Purification by silica gel column chromatography using cyclohexane:EtOAc (90:10) gave the product as a mixture of (*E*/*Z*) isomers in a ratio of 65:35 (408 mg, 59%). The two isomers were separated by preparative HPLC using heptane/2-propanol (99.8:0.2) as a mobile phase. Isomer assignments were determined by 1D NOESY and 2D NMR techniques.

(*E*)-**3q**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (m, 2H), 7.06 (m, 2H), 6.95 (*pt*, 8.70 Hz, 2H), 6.88 (*pt*, 8.71 Hz, 2H), 6.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1(d, 246.1 Hz), 161.9 (d, 246.8 Hz), 161.8 (dt, 15.2 Hz, 248.1 Hz), 160.6 (ddd, 9.6 Hz, 14.8 Hz, 249.4 Hz), 134.9 (d, 3.6 Hz), 133.2, 132.0 (d, 3.5 Hz), 131.1 (d, 8.1 Hz), 130.8 (d, 8.0 Hz), 128.1, 115.6 (d, 21.5 Hz), 115.2 (d, 21.48 Hz), 100.4 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −108.63 (m, 1F), −109.43 (m, 2F), −113.56 (m, 1F), −113.89 (m, 1F). HRMS (EI) m/z $[M]^+$: found 346.0792 $[C_{20}H_{11}F_5]^+$, calcd 346.0781.

(*Z*)-**3q**: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.27 (m, 2H), 7.14 (s, 1H), 7.06−7.00 (m, 4H), 6.90 (*pt*, 8.7 Hz, 2H), 6.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (dt, 15.3 Hz, 250.8 Hz), 162.6 (d, 247.9 Hz) 162.0 (d, 248.4 Hz), 160.6 (ddd, 10.5 Hz, 14.7 Hz, 250.4 Hz), 136.8 (d, 3.1 Hz), 132.8 (d, 3.4 Hz), 131.7, 129.9 (d, 8.1 Hz), 127.8 (d, 8.0 Hz), 127.6, 115.42 (m), 110.8 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ −107.4 (m, 1F), −107.9 (m, 2F), −113.3 (m, 1F), −114.1 (m, 1F). HRMS (EI) m/z $[M]^+$: found 346.0789 $[C_{20}H_{11}F_5]^+$, calcd 346.0781.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

All ^{1}H, and ^{13}C NMR spectra and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: donal.f.oshea@ucd.ie or donalfoshea@rcsi.ie.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the European Research Association ERA-Chemistry and the Irish Research Council (IRC) (EMPOWER postdoctoral fellowship PD/2011/2132) for financial support. Thanks to Dr. Y. Ortin for NMR support and Dr. H. Müller-Bunz for X-ray crystallography.

■ REFERENCES

(1) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838−2840.

(2) (a) Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 1811−1814. (b) King, A.; Okukado, N.; Negishi, E. *Chem. Commun.* **1977**, 683−684. (c) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422−424. (d) Nakao, Y.; Imanaka, H.; Chen, J.; Yada, A.; Hiyama, T. *J. Organomet. Chem.* **2007**, *692*, 585−603. (e) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320−2322.

(3) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677−685. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (e) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(4) (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *12*, 1119−1122. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166−7169. (c) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681−1683. (d) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097−2100. (e) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170−1214.

(5) (a) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760−1763. (b) Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 226−229. (c) Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011**, *13*, 6137−6139. (d) Liu, X.; Hii, K. K. *J. Org. Chem.* **2011**, *76*, 8022−8026. (e) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137−14151. (f) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315−319. (g) Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 5421−5424. (h) Schiffner, J. A.; Wöste, T. H.; Oestreich, M. *Eur. J. Org. Chem.* **2010**, 174−182. (i) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072−5074. (j) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125−3129. (k) Lee, G. T.; Jiang, X.; Prasad, K.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921−1924. (l) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476−1477. (m) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512−3515. (n) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221−1226.

(6) (a) Tricotet, T.; Fleming, P.; Cotter, J.; Hogan, A-M. L.; Strohmann, C.; Gessner, V. H.; O'Shea, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 3142−3143. (b) Cotter, J.; Hogan, A-M. L.; O'Shea, D. F. *Org. Lett.* **2007**, *9*, 1493−1496. (c) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2006**, *71*, 9552−9555.

(7) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754−13755. (b) Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218−20229.

(8) For examples of the use of persulfate as an oxidant in other palladium calaylzed reactions, see: (a) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109−8111. (b) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745−1747. (c) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476−479. (d) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504−9509. (e) Gary, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013**, *3*, 700−703.

(9) Kurzeev, S. A.; Kazankov, G. M.; Alexander D. Ryabov, A. D. *Inorg. Chim. Acta* **2002**, *340*, 192−196.

(10) For examples of F-M coupling with polyfluorinated arenes and their medicinal applications, see: (a) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506−4507. (b) Zhang, W.; Sviripa, V.; Chen, X.; Shi, J.; Yu, T.; Hamza, A.; Ward, N. D.; Kril, L. M.; Vander Kooi, C. W.; Zhan, C.-G.; Evers, B. M.; Watt, D. S.; Liu, C. *ACS Chem. Biol.* **2013**, *8*, 796−803.

(11) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820.

(12) For MS study of acrylate coupling, see: Vasseur, A.; Harakat, D.; Muzart, J.; Le Bras, J. *J. Org. Chem.* **2012**, *77*, 5751−5758.

(13) (a) Bajwa, S. E.; Storr, T. E.; Hatcher, L. E.; Williams, T. J.; Baumann, C. G.; Whitwood, A. C.; Allan, D. R.; Teat, S. J.; Raithby, P.

R.; Fairlamb, I. J. S. *Chem. Sci.* **2012**, *3*, 1656−1661. (b) Skapski, A. C.; Smart, M. L. *Chem. Commun.* **1970**, 658−659.
(14) (a) Hau, G.; Li, Y.; Slawin, A. M. Z.; Woolins, J. D. *Dalton Trans.* **2007**, *15*, 1477−1484. (b) Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 1733−1737.
(15) Koelsch, C. F.; Prill, E. J. *J. Am. Chem. Soc.* **1945**, *67*, 1296−1299.
(16) Al-Hassan, M. I. *Synth. Commun.* **1989**, *19*, 463−472.
(17) Mahesh, M.; Murphy, J. A.; Wessel, H. P. *J. Org. Chem.* **2005**, *70*, 4118−4123.
(18) Uyanik, M.; Fukatsu, R.; Ishihara, K. *Org. Lett.* **2009**, *11*, 3470−3473.
(19) Zeng, H.; Hua, R. *J. Org. Chem.* **2008**, *73*, 558−562.
(20) Choi, D. S.; Kim, J. H.; Shin, U. S.; Deshmukh, R. R.; Song, C. E. *Chem. Commun.* **2007**, 3482−3484.
(21) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, *9*, 507−510.