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Regioselective polyfluoroarylation of alkenyl C–H bonds *via* aryl to vinyl 1,4-palladium migration†

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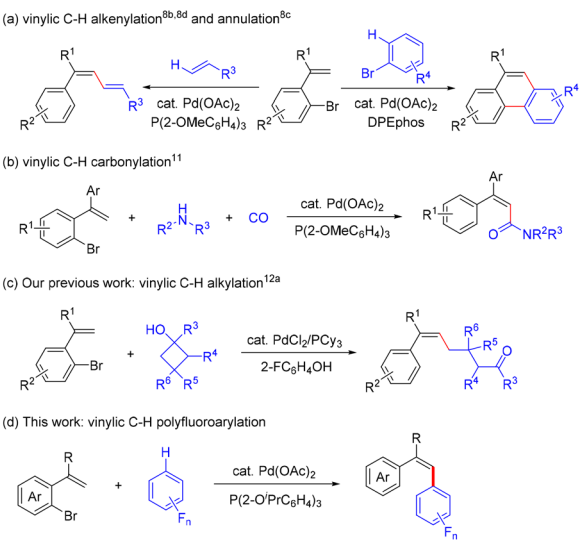
Efficient palladium-catalyzed regioselective vinylic C–H polyfluoroarylation of *gem*-disubstituted ethylenes with polyfluoroarenes was realized to access a variety of polyfluorinated triarylethenes. An aryl to vinyl 1,4-palladium migration is proposed to achieve high regio- and stereoselectivities for the target products. This strategy features broad substrate scopes and good functional group tolerance. Mechanistic studies have suggested that a protonation–deprotonation process reversibly occurs between a five-membered palladacycle and the vinyl–palladium intermediates, and aromatic C–H cleavage of polyfluoroarenes contributes to the rate-limiting step in the overall catalytic cycle.

Introduction

Transition-metal-catalyzed C–H activation has recently been extensively applied for carbon–carbon and carbon–heteroatom bond formations in modern organic synthesis.[1] 1,*n*-Migration of a transition metal has been developing as an indirect and promising C–H activation strategy to functionalize the C–H bonds of complex substrates under controllable conditions.[2] In this context, 1,4-palladium migration has provided an alternative route to selective distal C–H bond functionalization which is usually difficult to realize by the conventional methods.[3] To date, various 1,4-palladium migration processes such as vinyl to aryl,[4] aryl to aryl,[5] aryl to alkyl,[6] and alkyl to acyl[7] have been documented. Since Lin and Feng's seminal work on palladium-catalyzed migratory olefinic C–H borylation of 2-bromostyrenes with diboron reagents,[8a] considerable efforts have been devoted to functionalizing aromatic alkenes *via* aryl to vinyl 1,4-palladium migration.[8b–11] Vinylic C–H alkenylation of *gem*-disubstituted ethylenes was developed for the regio- and stereoselective synthesis of 1,3-dienes *via* a 1,4-palladium migration/Heck sequence,[8b,d] and a sequential cross-coupling/annulation of *o*-vinyl bromobenzenes was realized to access polycyclic aromatic compounds[8c] (Scheme 1a). Arylidene γ-lactams and indanone derivatives were constructed *via* a palladium migration/C(sp^3)–H activation pathway,[9] and 2,2-diaryl 2*H*-chromenes were prepared through palladium-catalyzed annulation of *o*-vinyl bromobenzenes with *N*-tosylhydrazones of *o*-hydroxybenzaldehydes.[10] A highly regioselective three-component reaction of styrenes, CO and amines occurred to give multisubstituted α,β-unsaturated amides (Scheme 1b).[11] We recently accomplished regioselective C–H alkylation of bromobenzenes with cyclobutanols *via* a 1,4-palladium migration/ring-opening C–C cleavage



Scheme 1 C–C bond formation *via* aryl to vinyl 1,4-palladium migrations.

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cascade (Scheme 1c),[12a] and also achieved vinylic C–H alkenylation and allenylation of such *gem*-diarylsubstituted ethylenes with *N*-tosylhydrazones through a 1,4-palladium migration/carbene insertion cascade.[12b]

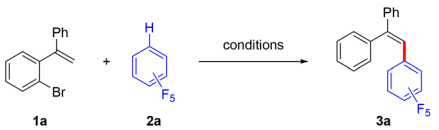
Polyfluoroarenes represent an important motif in pharmaceuticals, agrochemicals and functional materials owing to the unique properties of the fluorine atom.[13] Direct functionalization of polyfluoroarenes includes arylation,[14] alkenylation,[15] alkynylation,[16] alkylation,[17] allylation[18] and amination.[19] As for C–H alkenylation of polyfluoroarenes, the regio- and stereoselective construction of polyfluorinated triarylethenes has not yet been developed. In line with the relevant work,[8–11] and given our continuing efforts on vinylic C–H functionalization,[12,20] it was reasonably envisaged that 1,4-palladium migration of *gem*-diaryl alkenes might be potent for the catalytic alkenylation of polyfluorobenzenes to achieve synthetically useful and highly regio- and stereoselective construction of polyfluorinated triarylethenes. Herein, we disclose a new C–H olefination protocol of fluoroarenes *via* 1,4-palladium migration under mild conditions (Scheme 1d).

Results and discussion

Initially, the reaction of 1-bromo-2-(1-phenylvinyl)benzene (**1a**) with pentafluorobenzene (**2a**) in a 1 : 3 molar ratio was conducted at 100 °C to screen the reaction conditions (Table 1). With 5 mol% $Pd(OAc)_2$ as the catalyst, CsOAc as the base, and toluene as the reaction medium, a series of phosphine ligands were tested in the model reaction. It was found that 2-alkoxy-substituted PAr_3-type ligands could remarkably accelerate the desired aryl to vinyl 1,4-palladium migration process (Table 1, entries 1–8; see the ESI† for details), in which 2-OMe (**L4**) and 2-O^{i}Pr (**L7**)-substituted PAr_3 ligands enabled the formation of **3a** in 51% and 79% yields, respectively. The nature and loading of the bases had a significant impact on this transformation, and CsOAc (3 equiv.) was screened to be the most effective base (Table 1, entries 9–12). The 1 : 2.5 molar ratio reaction of **1a** and **2a** resulted in **3a** with 96% yield, and further lowering of the loading of pentafluorobenzene (**2a**) led to decreased yields (Table 1, entries 13–15). Neither decreasing the ligand loading from 10 mol% to 6 mol% nor performing the reaction at 90 °C affected the reaction efficiency (Table 1, entries 16–18). Other palladium sources such as $PdCl_2$, $Pd(PPh_3)_4$ and $Pd(O_2CCF_3)_2$ were also tested, but they all effected the reaction much less efficiently than $Pd(OAc)_2$ (see the ESI† for details). Eventually, the reaction was carried out on a 0.3 mmol scale of **1a** to afford the target product **3a** in 96% isolated yield (Table 1, entry 19). Notably, direct cross-coupling at the *ipso* position of 1-bromo-2-(1-phenylvinyl)benzene (**1a**) with **2a** was not observed, presumably owing to the intrinsic steric hindrance around the alkenyl functionality.

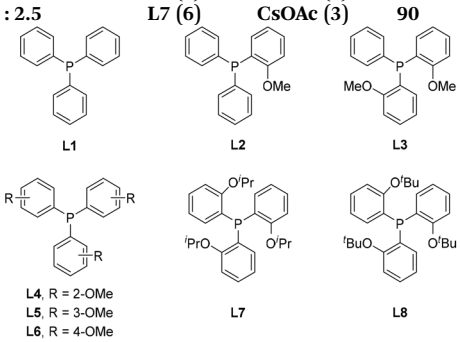
Under the optimal conditions, the scope of 1-bromo-2-vinylbenzenes (**1**) was explored (Table 2). In a fashion similar to the synthesis of **3a** (Table 1, entry 19), 1-bromo-2-(1-(substituted) phenylvinyl)benzenes (**1b–1j**) reacted with pentafluorobenzene (**2a**) to give the target polyfluorinated triarylethene products **3b–3j** in 76–98% yields with tolerance of electron-donating and electron-withdrawing substituents such as methyl, methoxy, fluoro, chloro, trifluoromethyl, and trifluoromethoxy at the *para*-, *meta*-, and *ortho*-positions of the phenyl ring. It was observed that 4-Me (**3b**, 94%) and 4-MeO (**3c**, 86%) were more favorable for the desired transformation than 4-CF_3 (**3f**, 76%) and 4-CF_3O (**3g**, 84%), respectively, and in other cases the product yields were higher than 90%. It is noteworthy that 2-methyl-substituted alkene **1j** reacted smoothly with **2a** to afford the target product **3j** in 91% yield, showing no obvious steric effect. Similar reactions also proceeded well for 1-bromo-2-vinylbenzenes bearing an electron-rich aryl group such as 2-naphthyl (**3k**, 90%) or 2-thienyl (**3l**, 68%). When the 2-(1-(substituted))phenyl group was replaced by an electron-withdrawing ester group (CO_2Me), compound **3m** was also efficiently obtained in 85% yield. However, replacement of such an

Table 1 Optimization of the reaction conditions[a]



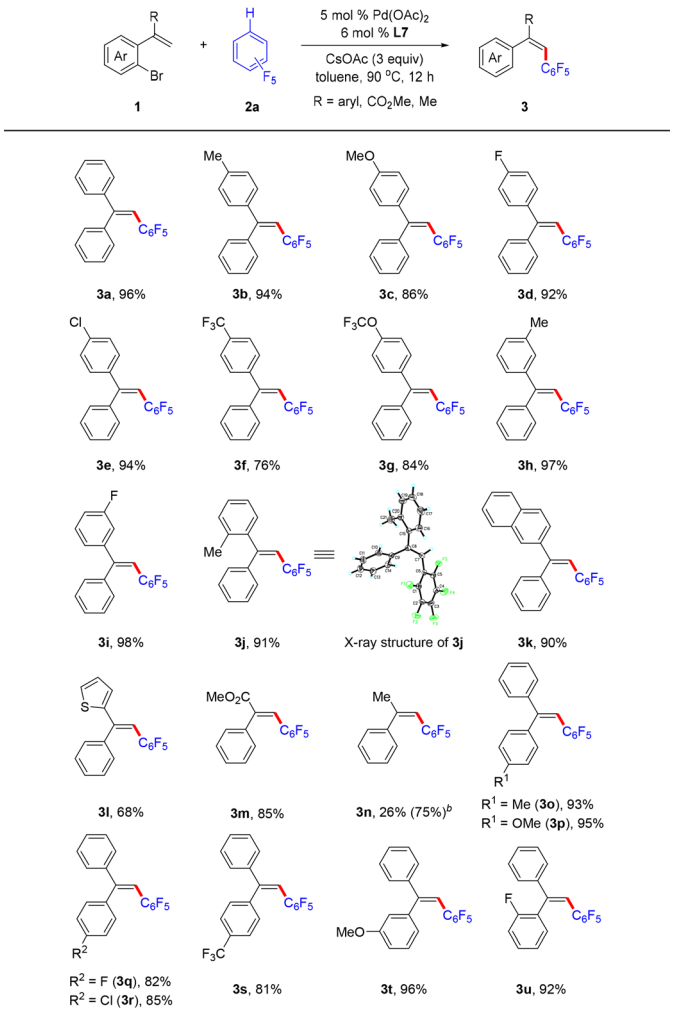
1a 2a 3a

Entry	**1a : 2a** (molar ratio)	Ligand (mol%)	Base (equiv.)	Temp (°C)	Yield of **3a**[b] (%)
1	1 : 3	**L1** (10)	CsOAc (2)	100	Trace
2	1 : 3	**L2** (10)	CsOAc (2)	100	Trace
3	1 : 3	**L3** (10)	CsOAc (2)	100	27
4	1 : 3	**L4** (10)	CsOAc (2)	100	51
5	1 : 3	**L5** (10)	CsOAc (2)	100	Trace
6	1 : 3	**L6** (10)	CsOAc (2)	100	0
7	1 : 3	**L7** (10)	CsOAc (2)	100	79
8	1 : 3	**L8** (10)	CsOAc (2)	100	30
9	1 : 3	**L7** (10)	KOAc (2)	100	Trace
10	1 : 3	**L7** (10)	Cs_2CO_3 (2)	100	15
11	1 : 3	**L7** (10)	CsOPiv (2)	100	30
12	1 : 3	**L7** (10)	CsOAc (3)	100	96
13	1 : 2.5	**L7** (10)	CsOAc (3)	100	96
14	1 : 2	**L7** (10)	CsOAc (3)	100	84
15	1 : 1	**L7** (10)	CsOAc (3)	100	42
16	1 : 2.5	**L7** (6)	CsOAc (3)	100	96
17	**1 : 2.5**	**L7 (6)**	**CsOAc (3)**	**90**	**96**
18	1 : 2.5	**L7** (6)	CsOAc (3)	80	82
19[c]	**1 : 2.5**	**L7 (6)**	**CsOAc (3)**	**90**	**97 (96)**[d]



[a] Conditions: **1a** (0.2 mmol), **2a**, $Pd(OAc)_2$ (5 mol%), ligand, base, toluene (2 mL), argon, 12 h. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxylbenzene as an internal standard. [c] **1a** (0.3 mmol), **2a** (0.75 mmol), toluene (3 mL). [d] Isolated yield given in parentheses.

Table 2 Scope of 1-bromo-2-vinylbenzenes[a]

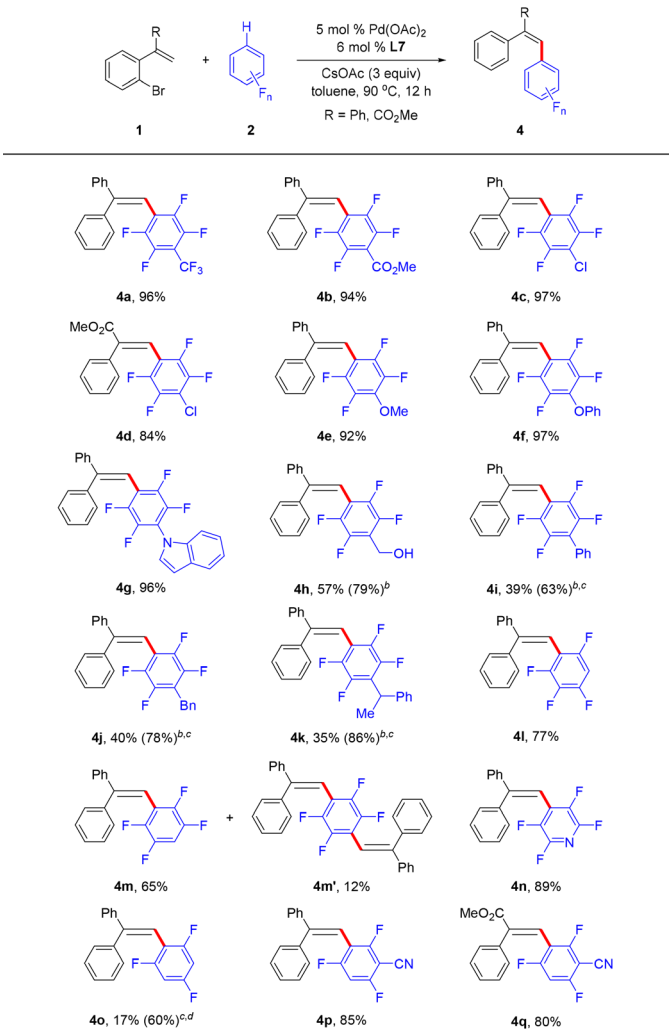


[a] Conditions: **1** (0.3 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (5 mol%), **L7** (6 mol%), CsOAc (3 equiv.), toluene (3 mL), 90 °C, argon, 12 h. [b] Pd $(OAc)_2$ (10 mol%), **L7** (12 mol%), 48 h.

ester group with a methyl group obviously diminished the alkene reactivity to form **3n** in 26% yield under the standard conditions. By increasing the catalyst loading to 10 mol% and extending the reaction time to 48 h, a good yield (75%) was obtained for **3n**. Notably, neither 2-bromostyrene nor 1-bromo-2-(2,2-dimethyl-1-methylenepropyl)benzene (the substrate obtained by replacement of the methyl group with a *tert*-butyl group in **1n**) reacted with **2a** to afford the desirable products. These results suggested that the reactivity of *gem*-diarylated alkene substrates is especially susceptible to both the electronic and steric effects around the alkenyl functionality. In the case of substituted 1-bromo-2-(1-phenylvinyl)benzenes (**1o–1u**), the target products **3o–3u** were efficiently furnished in 81–96% yields. Although substituents such as methyl, methoxy, fluoro, chloro and trifluoromethyl were well tolerated at the *para*-position of the bromo-functionalized phenyl ring, electron-donating methyl and methoxy groups in **3o** (93%) and **3p** (95%) worked better than electron-withdrawing fluoro (82%), chloro (85%) and trifluoromethyl (81%) groups in **3q–3s**. Both 5-methoxy and 6-fluoro-functionalized *gem*-diaryl ethylenes **1t** and **1u** efficiently underwent the reaction with **2a** to give the corresponding products **3t** and **3u** in excellent yields (92–96%), exhibiting no obvious substituent effect. Notably, all the products were completely regio- and stereoselectively formed as the single (*E*) or (*Z*)-isomers in which the vinyl functionalities of compounds **3b–3f** exhibited different NMR spectral features from those of compounds **3o–3s**, respectively, and the molecular structures of products **3** were further confirmed by the X-ray single crystal structural determination of compound **3j** (see the ESI† for details).

Next, the scope of polyfluoroarenes (**2**) was investigated in the same manner (Table 3). Various substituted tetrafluorobenzenes proved to be compatible in forming the corresponding polyfluorinated triarylethenes (**4a–4k**) in 63–97% yields. Those

Table 3 Scope of polyfluoroarenes[a]

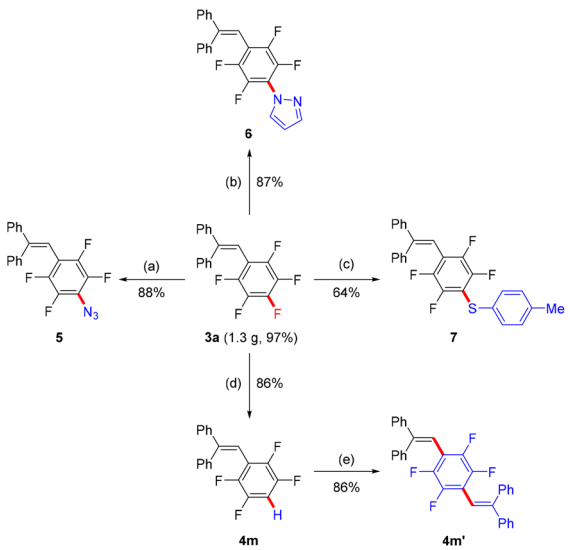


[a] Conditions: **1** (0.3 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (5 mol%), **L7** (6 mol%), CsOAc (3 equiv.), 3 mL of toluene, 90 °C, argon, 12 h. [b] 24 h. [c] $Pd(OAc)_2$ (10 mol%), **L7** (12 mol%). [d] 48 h.

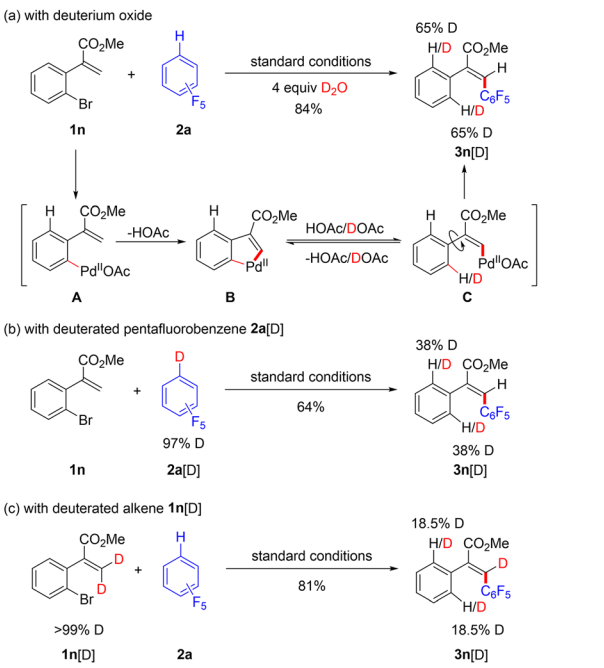
tetrafluorobenzenes bearing a strong electron-withdrawing or electron-donating substituent such as CF_3, CO_2Me, Cl, OMe, OPh, or *N*-indolyl could all be efficiently converted to the corresponding target products **4a–4g** in 84–97% yields. The weak electron-donating groups CH_2OH, Ph, Bn, and 1-phenylethyl deteriorated the substrate reactivity, leading to **4h–4k** in low to moderate yields (35–57%), but these transformations could be obviously improved to give the products in 63–86% yields by extending the reaction time to 24 h and/or increasing the catalyst loading to 10 mol%. Non-substituted 1,2,3,5- and 1,2,4,5-tetrafluorobenzenes also effectively reacted with **1a** to afford **4l** (77%) and **4m** (65%)/**4m′** (12%), respectively. Interestingly, in the case of 1,2,4,5-tetrafluorobenzene, the target product **4m** underwent a similar 1,4-Pd migration process to form 1,4-di(vinyl)-substituted tetrafluorobenzene **4m′**. The formation of **4m′** from **4m** was identified by a separate synthetic process (Scheme 2). 2,3,5,6-Tetrafluoropyridine (**2n**) also efficiently interacted with **1a** to afford **4n** (89%). Trifluorobenzenes such as 1,3,5-tetrafluorobenzene (**2o**) only exhibited a poor reactivity under the stated conditions, and the formation of **4o** (60%) should be assisted by increasing the catalyst loading and prolonging the reaction time. However, a strong electron-withdrawing substituent such as cyano remarkably enhanced its reactivity to furnish the target trifluoroarylation products **4p** and **4q** in decent yields (80–85%). It should be noted that neither 1,4-difluorobenzene nor fluorobenzene reacted with **1a** under the standard conditions owing to their less acidic aromatic C–H bonds.[21]

To demonstrate the applicability of the synthetic protocol, the gram-scale preparation of compound **3a** was performed under the standard conditions, achieving 97% yield (Scheme 2). In all the cases, the transformations occurred at the *para* position of the pentafluorophenyl functionality in **3a** under mild conditions, demonstrating a selectively nucleophilic substitution pathway.[22] By employing different bases, solvents, and temperatures, product **3a** bearing a reactive C_6F_5 functionality could readily undergo chemoselective coupling with NaN_3, pyrazole, 4-methylbenzenethiol,[23] and $NaBH_4$,[24] yielding perfluoroarylated compounds **5** (88%), **6** (87%), **7** (64%) and **4m** (86%), respectively. Perfluoroaryl azide **5** can be promising for synthetically useful purpose in organic synthesis as the $C_6F_4N_3$ moiety can be used for conjugation reactions with phosphines, aldehydes and enamines, and also for C–H functionalization of inert polyolefins.[17a,23] Compound **4m** as a monoalkenylated polyfluoroarene substrate could further react with alkene **1a** to give divinylated perfluorobenzene **4m′** in 86% yield (see the ESI† for details).

Control experiments were conducted to probe into the 1,4-Pd migration event *via* isotope-labeling (Scheme 3). When alkene **1n** was reacted with pentafluorobenzene (**2a**) in the presence of 4 equiv. of D_2O under the standard conditions, only 0.7 H (<1 H) was observed at the *ortho*-positions, showing that both the *ortho*-positions of the phenyl ring were partially deuterated with 65% deuterium incorporation at each site, suggesting that the aryl to vinyl 1,4-palladium migration step, or the proposed protonation–deprotonation process between five-membered palladacycle **B** and vinyl–palladium intermediate **C**, might be reversible (Scheme 3a). Deuterated pentafluorobenzene **2a**[D] reacted with alkene **1n** to form **3n**[D] with 38%



Scheme 2 Gram-scale preparation and derivatization. Conditions: (a) **3a** (0.3 mmol), NaN_3 (0.6 mmol), DMF (2 mL), 60 °C, 48 h. (b) **3a** (0.33 mmol), pyrazole (0.3 mmol), NaO^tBu (0.33 mmol), DMA (3 mL), 0 °C–rt, 12 h. (c) **3a** (0.3 mmol), 4-(methylthio)phenol (0.33 mmol), K_2CO_3 (0.6 mmol), DMF (6 mL), 25 °C, 12 h. (d) **3a** (0.3 mmol), $NaBH_4$ (0.6 mmol), DMSO/THF (v/v = 1 : 1, 6 mL), 65 °C, 24 h. (e) **1a** (0.3 mmol), **4m** (0.75 mmol), $Pd(OAc)_2$ (5 mol%), **L7** (6 mol%), CsOAc (3 equiv.), toluene (3 mL), 90 °C, argon, 24 h.



Scheme 3 H/D exchange experiments.

deuterium incorporation onto each of the *ortho*-positions (Scheme 3b), while deuterated alkene **1n**[D] delivered the product with 18.5% deuterium incorporation (Scheme 3c), which implicates that the hydrogen atoms at the *ortho*-positions of the phenyl ring in **3n**[D] partially came from both pentafluorobenzene (**2a**) and alkene **1n** (see the ESI† for details). The loss of deuterium is presumably attributed to the reaction medium, which is supported by the high deuterium incorporation ratio in the presence of D_2O.[8a,12a]

The kinetic isotope effect (KIE) was also measured (Fig. 1). A primary KIE value of 2.17 from the parallel comparison reactions of pentafluorobenzene (**2a**) and its deuterated form **2a**[D] with alkene **1n** reveals that C–H cleavage of polyfluoroarenes probably contributes to the rate-limiting step in the overall catalytic cycle (Fig. 1a), while the 1,4-Pd migration event might not contribute to the rate-limiting step due to a KIE value of 1.21 from the parallel comparison reactions of **1n** and **1n**[D] with **2a**, respectively[25] (Fig. 1b) (see the ESI† for details).

Intermediate verification experiments were then performed. Arylpalladium(II) complex **A** and vinylpalladium(II) complex **C′** (analog of the proposed intermediate complex **C** in the mechanism scheme) were prepared by our previously reported methods,[12b] respectively, and were applied as the catalysts for the reaction of **1a** and **2a** under the standard conditions (Scheme 4). Under the stated conditions, the target product **3a** was formed in 89–91% NMR yields, suggesting that both

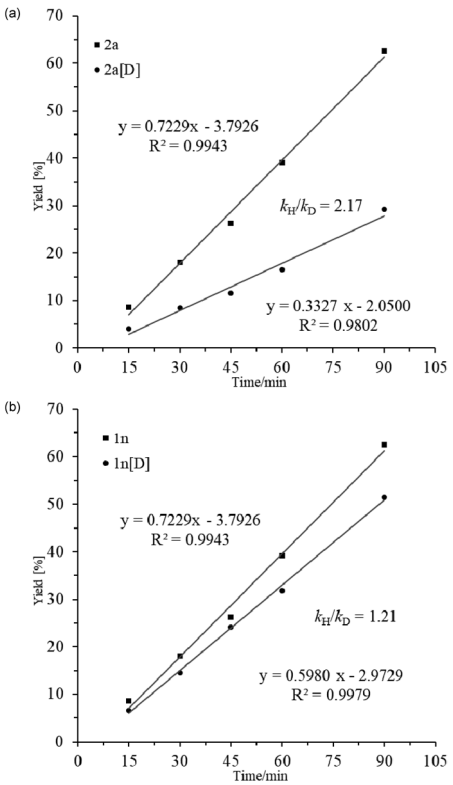
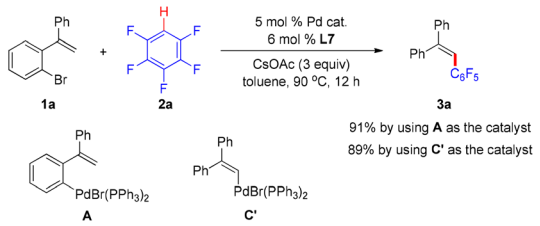
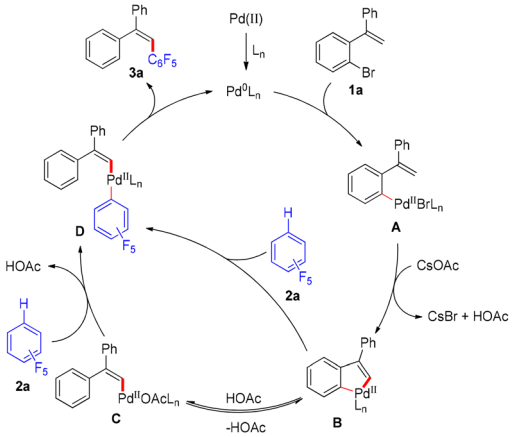


Fig. 1 (a) KIE measured from the parallel reactions of polyfluoroarenes (**2a** and **2a**[D]) with alkene **1n**. (b) KIE measured from the parallel reactions of alkenes (**1n** and **1n**[D]) with **2a**.



Scheme 4 Intermediate verification experiments.



Scheme 5 Proposed mechanism.

in situ generated aryl–Pd(II) and vinyl–Pd(II) species are the possible reactive intermediates and/or catalytically active species for the desired reaction (see the ESI† for details).

A plausible reaction mechanism is proposed in Scheme 5. Initially, *ortho*-bromo-substituted vinylbenzene **1a** undergoes oxidative addition to the Pd(0) species to generate aryl–Pd(II) intermediate **A**, followed by cyclopalladation in the presence of the CsOAc base to form palladacycle **B** through a possible concerted metalation–deprotonation process.[8,12] Protonation of species **B** results in vinyl–Pd(II) complex intermediate **C** *via* a net 1,4-palladium migration from aryl to vinyl. Subsequently, the reaction of species **C** with the *in situ* generated anion[21,26] from pentafluorobenzene **2a** results in aryl–Pd(II)–vinyl complex **D**. The direct interaction of palladacycle **B** with **2a** may also lead to Pd(II) complex species **D**. Eventually, reductive elimination occurs to afford the target product **3a** and regenerate the catalytically active Pd(0) species to complete the catalytic cycle.

Conclusions

In conclusion, a 1,4-palladium migration cascade of bromo-functionalized *gem*-diarylsubstituted ethylenes and polyfluoroarenes has been successfully established, providing a direct and modular approach to access a diverse array of synthetically useful polyfluorinated triarylethenes. The present protocol features high regio- and stereoselectivities, broad substrate

scopes, good functional group tolerance and mild reaction conditions.

Author contributions

J. L. started and performed the experiments and prepared the ESI.† J. M. and L. D. W. partially analyzed and interpreted the results. K. K. W. synthesized some of the 1-bromo-2-vinylbenzenes. Y.-G. Z. supervised some of the experiments. Z. K. Y. conceived and directed the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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