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Palladium-Catalyzed Intermolecular *trans*-Selective Carbofunctionalization of Internal Alkynes to Highly Functionalized Alkenes

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KEYWORDS: palladium, alkenes, C−H activation, silylation, borylation

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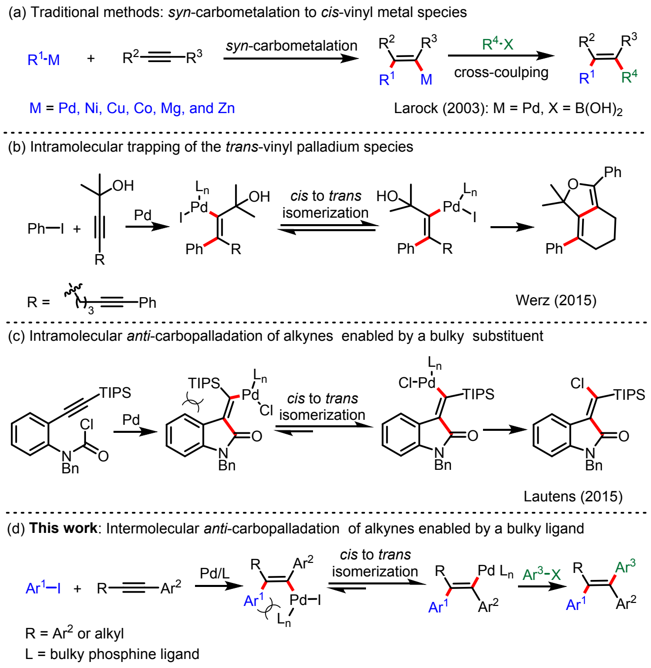
ABSTRACT: A palladium/DPEphos-catalyzed intermolecular *trans*-selective carbofunctionalization of internal alkynes has been established herein. This method proceeds through a formal *anti*-carbopalladation, forming *trans*-alkenyl palladium species, which was trapped by aryl boronic acids to provide all-carbon tetrasubstituted alkenes in 32−92% yields. The *trans*-selective arylsilylation/remote C–H silylation and hydroarylation/remote C–H borylation of internal alkynes were also achieved by using hexamethyldisilane and *bis*(pinacolato)diboron as trapping reagents, respectively. The reaction features good regio- and stereoselectivity and high functional group tolerance. A preliminary mechanistic study and DFT calculations show that a *cis* to *trans* isomerization of *cis*-alkenyl palladium species was involved in this transformation.

Introduction

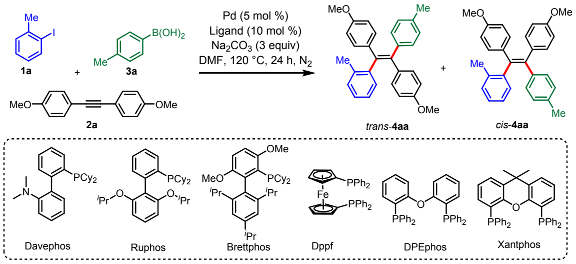
Tetrasubstituted alkenes are a highly important motif in many natural products,[1] pharmaceuticals,[2] and functional materials.[3] Their efficient regio- and stereoselective synthesis has provided major challenges to synthetic organic chemists due to the congested nature of the double bond.[4] The carbometalations of internal alkynes are the most straightforward and widely used methods to form tetrasubstituted alkenes.[5] These methods are understood to proceed through *syn*-carbometalation, forming alkenyl metal complexes, followed by a range of further reactions to provide *cis*-tetrasubstituted alkenes. (Scheme 1a). Noteworthy among them is the Larock's palladium-catalyzed three-component reaction of aryl iodides, internal alkynes, and aryl boronic acids, which could deliver all-carbon tetrasubstituted alkenes with high efficiency.[6,7] Although the initial *syn*-carbopalladation across the π bond may be stereospecific, in some cases *cis* to *trans* isomerization of alkenyl palladium species was observed, which could deliver *trans*-products as minor isomers.[7f–j,8] Recently, the intramolecular capture of the *trans*-alkenyl palladium species, which were formed via *cis* to *trans* isomerization, has been well documented for the synthesis of *trans*-tetrasubstituted alkene-containing cyclic compounds by Werz's group (Scheme 1b).[9] In 2015, Lautens described a sterically hindered substrate and ligand controlled intramolecular formal *anti*-carbopalladation reaction for the synthesis of chlorocarbamoylation products with high stereoselectivity (Scheme 1c).[10] Undoubtedly, expanding this chemistry to intermolecular *trans*-selective carbofunctionalization of internal alkynes is considerably appealing yet conceptually challenging. To the best of our knowledge, there are no reports on the three-component reactions of aryl iodides, alkynes, and electrophiles, generating *trans*-tetrasubstituted alkenes through intermolecular formal *anti*-carbopalladation/cross-coupling sequence (Scheme 1c). Inspired by Lautens' work, we envisaged that steric hindrance between the substrate and the ligand could enable the intermolecular formal *anti*-carbopallation of internal alkynes, and the subsequent trapping of the *trans*-alkenyl palladium species would lead to a variety of *trans*-tetrasubstituted alkenes (Scheme 1d). Herein, we disclose a palladium/DPEphos (*bis*[(2-diphenylphosphino)phenyl]ether) catalyst system that enables the intermolecular *trans*-selective diarylation, arylsilylation/remote C–H silylation, and hydroarylation/remote C–H borylation of internal alkynes to deliver highly functionalized *trans*-acyclic alkenes with remarkable regio- and stereoselectivity.

Scheme 1. Carbometalation of Internal Alkynes for the Synthesis of Tetrasubstituted Alkenes


(a) Traditional methods: *syn*-carbometalation to *cis*-vinyl metal species
(b) Intramolecular trapping of the *trans*-vinyl palladium species
(c) Intramolecular *anti*-carbopalladation of alkynes enabled by a bulky substituent
(d) **This work**: Intermolecular *anti*-carbopalladation of alkynes enabled by a bulky ligand

Results and Discussion

Table 1. Selected Optimization Studies[a]

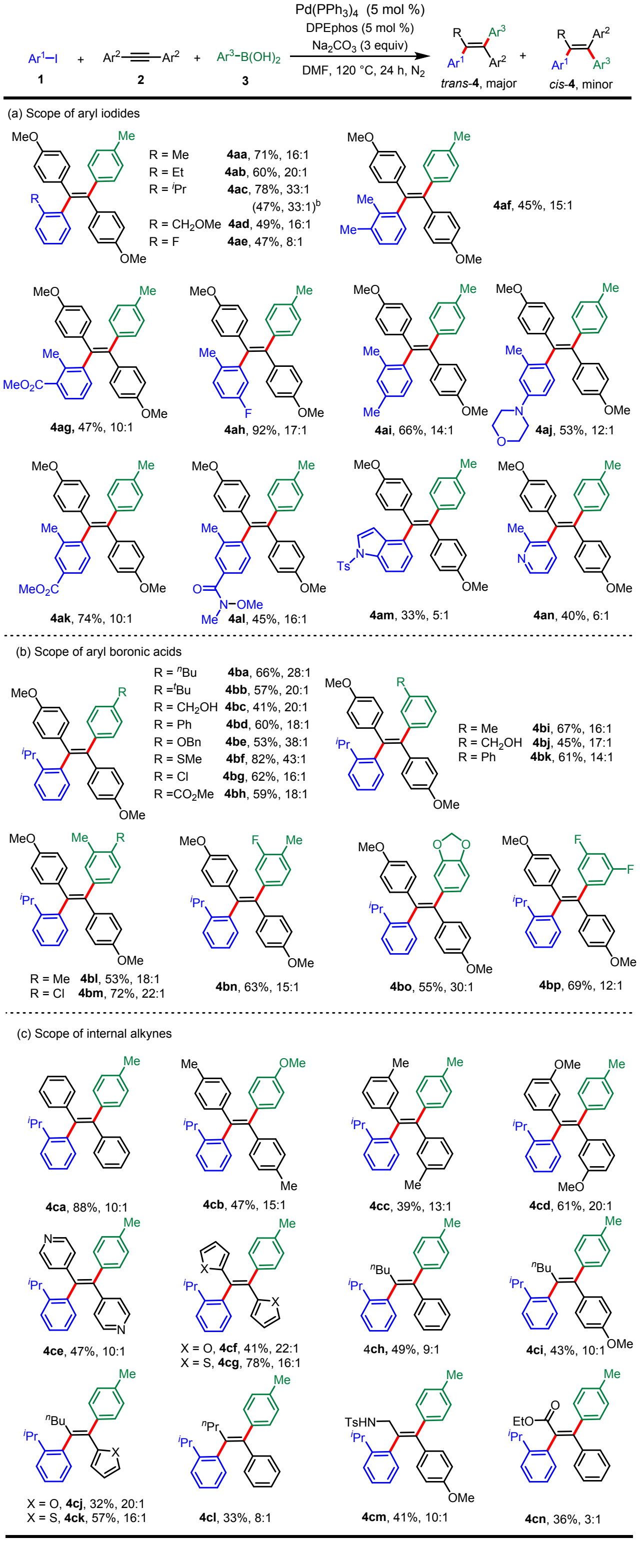


entry	ligand	catalyst	yield (%)[b]	*trans* :*cis*[c]
1	P(1-naphthyl)$_3$	Pd(OAc)$_2$	45	1:1
2	PCy$_3$	Pd(OAc)$_2$	72	4:1
3	Davephos	Pd(OAc)$_2$	70	5:1
4	Ruphos	Pd(OAc)$_2$	72	8:1
5	Brettphos	Pd(OAc)$_2$	69	5:1
6	Dppf[d]	Pd(OAc)$_2$	72	11:1
7	DPEphos[d]	Pd(OAc)$_2$	68	14:1
8	Xantphos[d]	Pd(OAc)$_2$	66	12:1
9	DPEphos[d,e]	Pd(OAc)$_2$	74	10:1
10	DPEphos[d,f]	Pd(OAc)$_2$	72	9:1
11	**DPEphos[d]**	**Pd(PPh$_3$)$_4$**	**71**	**16:1**
12	DPEphos[d]	PdCl$_2$	66	13:1
13	DPEphos[d]	Pd(acac)$_2$	60	13:1
14	-	Pd(PPh$_3$)$_4$	60	6:1

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), **3a** (0.2 mmol), Pd (5 mol%), ligand (10 mol%), and base (0.3 mmol) in DMF (1 mL) at 120 °C under nitrogen atmosphere for 24 h. [b] Isolated combined yields. [c] Isomeric ratios were determined by analysis of ^1H NMR spectra of isolated inseparable products. [d] Ligand (5 mol %) was used. [e] K_2CO_3 was used instead of Na_2CO_3. [f] CS_2CO_3 was used instead of Na_2CO_3. DMF = *N*,*N*-dimethylformamide.

At the beginning of study, 2-iodotoluene (**1a**), 1,2-*bis*(4-methoxyphenyl)ethyne (**2a**), and 4-tolylboronic acid (**3a**) were chosen as model substrates to explore the reaction conditions (Table 1, see the Supporting Information, Table S1 for details). The reaction was conducted using Pd(OAc)$_2$, P(1-naphthyl)$_3$, Na_2CO_3 as catalyst, ligand, and base, respectively, in a solution of DMF at 120 °C for 24 hours to afford 45% yield of the desired product (**4aa**) with poor stereoselectivity (*trans*:*cis* 1:1, Table 1, entry 1). Encouraged by this result, we then investigated a series of monodentate bulky phosphine ligands (entries 2−5). Gratifyingly, higher yields of **4aa** were obtained, albeit in moderate isomeric ratios (4:1 to 8:1). Excitedly, the stereoselectivity was significantly improved when bidentate ligands were employed, and DPEphos was found to give the best performance (*trans*:*cis* 14:1, entries 6−8). Other bases slightly improved the conversion and were accompanied by noticeable erosion in stereoselectivity (entries 9 and 10). In our subsequent screenings of catalysts (entries 11−13), we discovered that Pd(PPh$_3$)$_4$ was an effective catalyst to promote the desired reaction, affording **4aa** in 71% yield with 16:1 isomeric ratio (entry 11). The stereoselectivity was dramatically decreased in the absence of DPEphos, which highlighted the importance of steric effect from the ligand in this current transformation (entry 14). Finally, the optimized reaction conditions were identified as follows: **1a** (0.3 mmol), **2a** (0.1 mmol), **3a** (0.2 mmol), Na_2CO_3·(0.3 mmol), Pd(PPh$_3$)$_4$

Scheme 2. Scope of Aryl Iodides, Aryl Boronic Acids, and Internal Alkynes[a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), **3** (0.2 mmol), Pd(PPh$_3$)$_4$ (5 mol %), DPEphos (5 mol %), and Na_2CO_3 (0.3 mmol) in DMF (1 mL) at 120 °C under nitrogen atmosphere for 24 h. [b] 1-Bromo-2-isopropylbenzene was used as substrate.

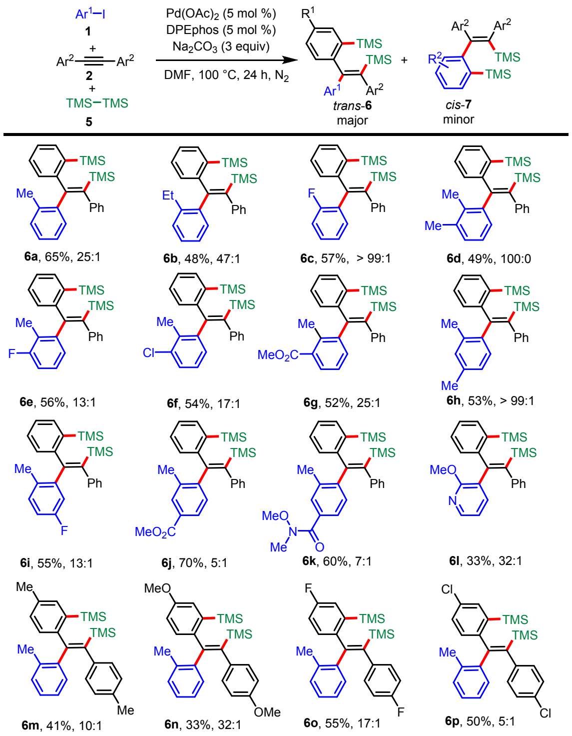
(5 mol %), and DPEphos (5 mol %) in a solution of DMF (1 mL) at 120 °C for 24 hours (entry 11).

Adopting the optimized three-component sequential transformation protocol, the generality of this method was first evaluated via a variety of aryl iodides (Scheme 2a). It was observed that the steric hindrance on the 2-position of phenyl iodides improved the stereoselectivity (**4aa−ae**). The less sterically hindered 2-fluoro phenyl iodide could give the corresponding desired product (**4ae**) in 8:1 isomeric ratio. Other phenyl iodides bearing ester, fluoro, morpholine, and Weinreb amide groups also could give the corresponding products in moderate to good yields with excellent stereoselectivity (**4af−al**). Notably, heteroaryl iodides could give the desired products (**4m** and **4n**) in 33% and 40% yields, respectively. However, no desired product was observed when (2-iodophenyl)trimethylsilane (**1o**) was used. Aryl bromide was also identified as the suitable substrate for this reaction, delivering product (**4ac**) in 47% yield with similar stereoselectivity. We then turned our attention to examining the scope of aryl boronic acid substrates (Scheme 2b). Both the electron-donating and electron-withdrawing groups on aryl boronic acid were well tolerated to afford **4ba−bp** in moderate to good yields with higher than 12:1 isomeric ratios. Importantly, benzyl alcohol (**4bc**, **4bj**) was well tolerated in this reaction system. A variety of 1,2-di(hetero)aryl ethynes were also tested, and given **4ca−cg** with high stereoselectivity (Scheme 2c). Unsymmetrical internal alkynes have been successfully employed in this process and the desired products (**4ch−cm**) were isolated with decent regio- and stereoselectivity, albeit in lower yields. It was noteworthy that ethyl 3-phenylpropiolate was also employed to provide the corresponding product (**4cn**) in 36% yield with 3:1 isomeric ratio. Finally, this reaction was not applied to (3,3-dimethylbut-1-yn-1-yl)benzene (**2p**), (phenylethynyl)(p-tolyl)sulfane (**2q**), and dec-5-yne (**2r**). These results showed that our work is a good complement to Werz's intramolecular *anti*-carbopalladation,[9] in which internal alkynes with *tert*-butyl, silyl, and methylthio (rather than aryl) groups directly attached to the triple bond are suitable substrates. It should be noted that the connectivity of the obtained product (**4aa**) was unambiguously established by single-crystal X-ray crystallography, and the *trans*-configuration of **4ck** was determined by NOE measurement (Supporting Information, Figure S1).

Alkenylsilanes are versatile intermediates in organic synthesis.[11] We previously disclosed a three-component *bis*-silylation reaction of aryl iodides, norbornadiene, and hexamethyldisilane for the assembly of (*Z*)-β-substituted alkenylsilanes.[12a,12b] Based on this work, we envisioned that a palladacycle, generated upon intramolecular C–H activation of alkenyl palladium intermediate,[13] might be trapped by hexamethyldisilane to produce the disilylated product.[12] In line with the above hypothesis, we commenced the investigation by using hexamethyldisilane **5** as the *bis*-silylation reagent to evaluate the substrate scope (Scheme 3). To our delight, a variety of aryl iodides could be smoothly transferred into the desired products (**6a−i**) in 48−70% yields with excellent stereoselectivity (>13:1), while 5:1 and 7:1 isomeric ratios were obtained in the cases of **6j** and **6k**, respectively. Various functional groups were well tolerated, such as halide, ester, and Weinreb amide. In addition, a pyridine ring (**6l**) was compatible to the reaction conditions, demonstrating the compatibility of this typically coordinating functional group. Furthermore, internal alkynes containing an electron-donating aryl substituent (R^1 = Me, MeO; **6m**, **6n**) or an electron-withdrawing aryl substituent (R^1 = F, Cl; **6o**, **6p**) could also be incorporated into the product with satisfactory stereoselectivity. The configuration of product (**6a**) was confirmed by single-crystal X-ray crystallography.

Considering the broad utility of arylboron reagents in synthesis, we questioned whether borylation reaction is compatible with this *anti*-carbopalladation strategy (Scheme 4). We commenced the investigation by using **1a** and **2b** as substrates and *bis*(pinacolato)diboron (**8**) as the borylation reagent to verify the hypothesis. Surprisingly, *trans*-hydroarylation/remote C–H borylation product *trans*-**9a** was isolated as major isomer.[14] We then use a variety of aryl iodides and internal alkynes to evaluate the substrate scope. The reactions proceeded smoothly to provide the corresponding *ortho*-alkenyl phenylboronic acid pinacol esters (**9a−l**) in acceptable yields (47-65%). In all cases, remarkable stereoselectivity (*trans*:*cis* > 10:1) were achieved. Despite our optimization efforts, only moderate regioselectivities (*trans*-**9**:*trans*-**10**; 3:1 to 5:1) were obtained. In contrast with the recently reported C−H borylation via aryl to alkenyl 1,4-palladium migration,[15c] our work represents a rare example on C–H borylaton involving alkenyl to aryl 1,4-palladium migration.[15,16] The *trans*-configuration of **9e** was determined by NOE measurement (Supporting Information, Figure S2).

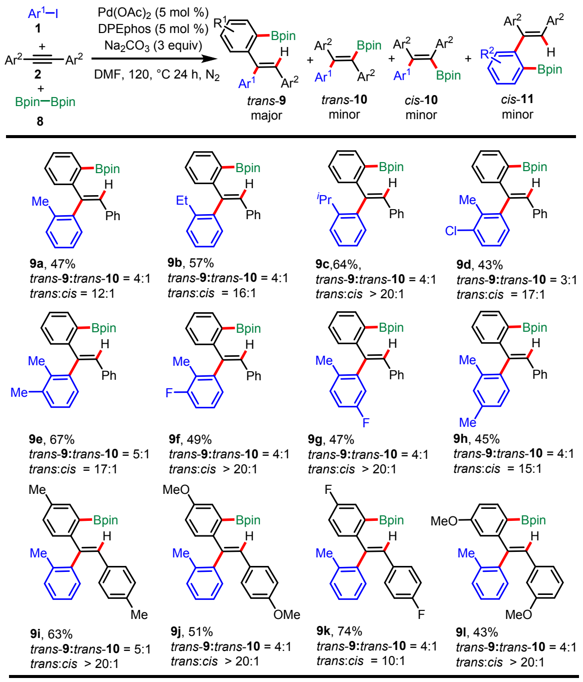
Scheme 3. Scope of Aryl Iodides and Internal Alkynes[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), hexamethyldisilane (0.15 mmol), $Pd(OAc)_2$ (5 mol %), DPEphos (5 mol %), and Na_2CO_3 (0.3 mmol) in DMF (1 mL) at 100 °C under nitrogen atmosphere for 24 h. Isomeric ratios were determined by analysis of ^1H NMR spectra of the crude products.

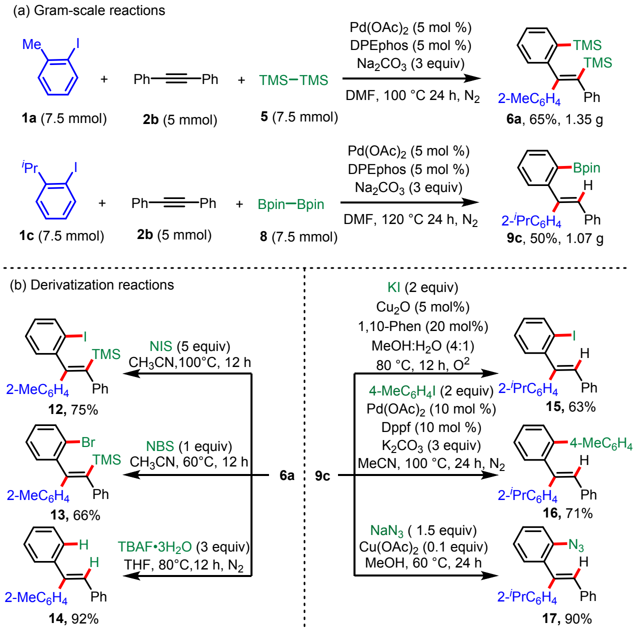
The utility of this chemistry was demonstrated by the gram-scale synthesis of **6a** and **9c**. The reactions of **1a**, **2b**, and **5** or **1c**, **2b**, and **8** completed within 24 h, producing the desired products (**6a**) and (**9c**) in 65% and 50% yields, respectively (Scheme 5a). It is worth mentioning that aryl silanes and aryl boronic acid pinacol esters are versatile synthetic intermediates and could be converted into various compounds. For example, the selective halogenation of aryl TMS group could be achieved to give compounds (**12**) and (**13**), in which the TMS group at the alkene was not cleaved. The desilylation reaction of **6a** would lead to tri-aryl substituted alkene (**14**) (Scheme 5b, left). The aryl boronic acid pinacol ester (**9c**) can be further elaborated through well-established iodination, cross-coupling, and azidation reactions to generate synthetically useful tri-aryl substituted alkenes (**15**−**17**), which are difficult to make by other methods (Scheme 5b, right).

Scheme 4. Scope of Aryl Iodides and Internal Alkynes[a]

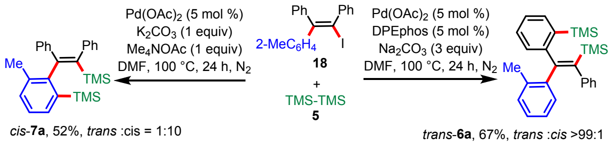


[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), *bis*(pinacolato)diboron (0.15 mmol), $Pd(OAc)_2$ (5 mol %), DPEphos (5 mol %), and Na_2CO_3 (0.3 mmol) in DMF (1 mL) at 100 °C under nitrogen atmosphere for 24 h. Isomeric ratios were determined by analysis of ^1H NMR spectra of the crude products.

Scheme 5. Gram-Scale Reactions and Derivatization Reactions



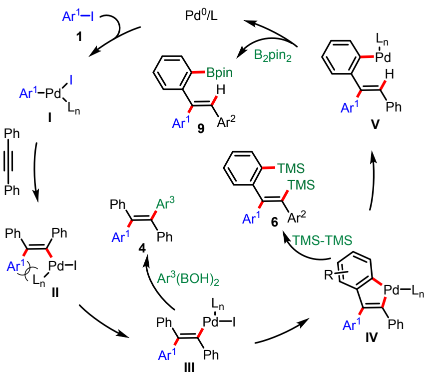
To understand the reaction mechanism, we conducted an experiment of *cis*-alkenyl iodide (**18**) with hexamethyldisilane under the standard reaction conditions. The desired product *trans*-**6a** was obtained in 67% yield as almost a single isomer (Eq. 1). Whereas the reaction was performed in the absence of ligand, the *cis*-**7a** was isolated as major product with high steroselectivity (*trans*:*cis* 1:10), which indicated that DPEphos plays an important role in the *cis* to *trans* isomerization of alkenyl palladium species.



(1)

On the basis of this result and literature reports, we proposed that the reaction would proceed as shown in Scheme 6. This reaction is initiated by Ar−I oxidative addition to Pd^0, followed by *syn*-carbopalladation of internal alkyne to generate a *cis*-alkenyl palladium species (**II**). The steric hindrance-promoted *cis* to *trans* isomerization of (**II**) could take place to form the thermodynamically more stable *trans*-alkenyl palladium species (**III**). The subsequent Suzuki-Miyaura cross-coupling reaction of (**III**) with aryl boronic acids could give tetrasubstituted alkenes (**4**). In another scenario, (**III**) could further undergo C−H activation to generate a palladacycle (**IV**), which can react with hexamethyldisilane leading to the alkenyl silanes (**6**). Furthermore, alkenyl palladium species (**III**) undergoes 1,4-palladium migration to give aryl palladium intermediate (**V**), which could further captured by *bis*(pinacolato)diboron (**8**) to furnish the desired products (**9**) and regenerate the Pd^0 catalyst.

Scheme 6. Plausible Catalytic Cycle



Mechanistic Computational Study.

In the possible catalytic cycle of *trans*-selective bis-functionalization of internal alkynes, the key step would be considered as the *cis* to *trans* isomerization of alkenyl palladium intermediate. To further understand this process, a density functional theory (DFT) calculation was employed to study this process by using M06 density functional. As depicted in Figure 1, when a tetra-coordinated *cis*-alkenyl palladium (II) species **19** is formed, the *cis* to *trans* isomerization of alkenyl group would occur via a three-membered ring type transition state **20-ts**. In the geometry of this transition state, the length of C1-C2 bond is increased to 1.41 Å, which represents a single bond character. The bond length of Pd-C1 is 1.92 Å, which is shorter than a typical Pd-C single bond. The distance between palladium and C2 is only 2.22 Å, which reveals a strong interaction between those two atoms. Therefore, the rotation alkenyl group in transition state **20-ts** can be considered as a η2-ligand by using 4e sharing with palladium. DFT calculation found that in transition state **20-ts**, phosphine ligand should be partially dissociated to keep 16e configuration of palladium. Therefore, the calculated activation free energy for the rotation of alkenyl group in intermediate **19** is as high as 27.7 kcal/mol due to the dissociation of phosphine. Following this idea, we proposed that the dissociation of iodide would be benefit for the *cis* to *trans* isomerization of alkenyl group. DFT calculation found that the dissociation of iodide is 5.6 kcal/mol endergonic, which provides a tri-coordinated cationic palladium intermediate **22**. The corresponding *cis* to *trans* isomerization of alkenyl group can take place via transition state **23-ts** to afford intermediate **24**. The calculated overall activation free energy for this step is only 23.2 kcal/mol, which could be achieved under a reaction temperature of 120 °C.

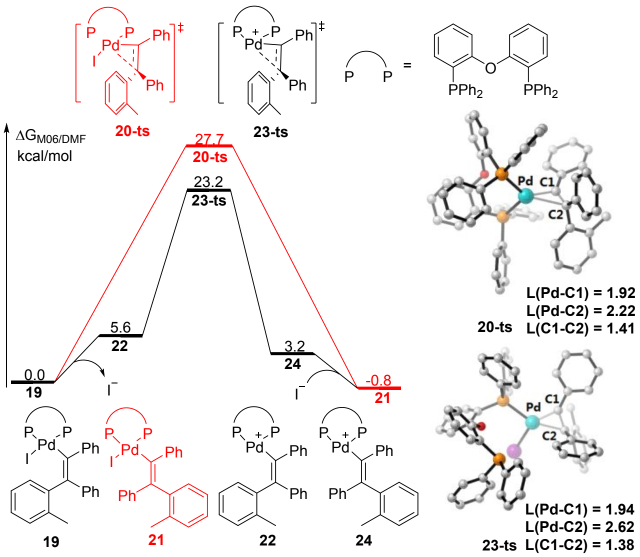


Figure 1. Calculated relative Gibbs energies for the *cis* to *trans* isomerization of [R-Pd(L)I]. Energy values are given in kcal/mol and represent the relative free energies calculated by using the M06 method in solvent. Bond lengths are given in Å.

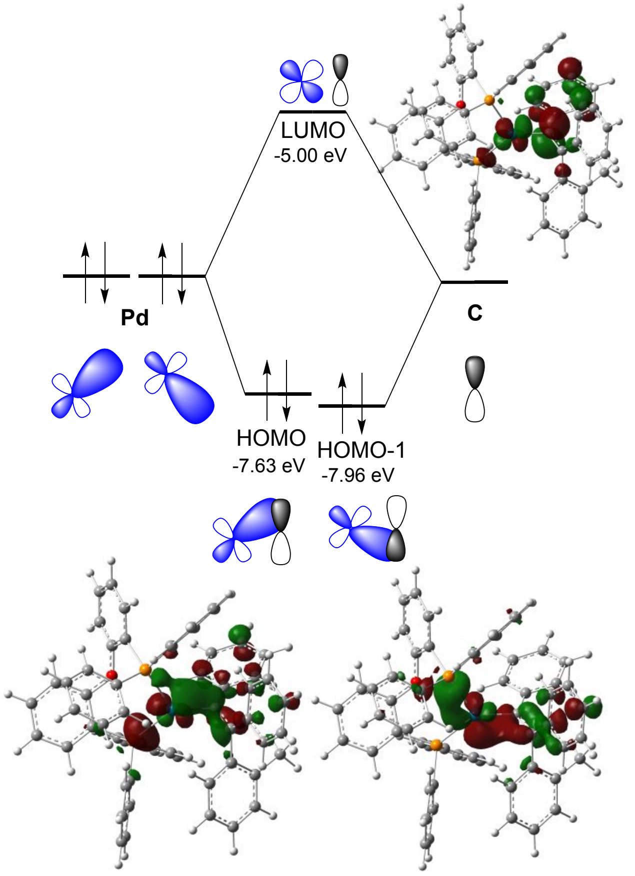


Figure 2. FMOs of transition state **23-ts**.

Moreover, the frontier molecular orbitals (FMOs) of transition state **23-ts** are given in Figure 2. The energy level of highest occupied molecular orbital (HOMO) and HOMO-1 of **23-ts** are -7.63 and -7.96 eV, respectively, which are about 2.63 eV lower than that of lowest unoccupied molecular orbital (LUMO) of **23-ts**. The profiles of HOMO, HOMO-1 and LUMO clearly reveals that those three molecular orbitals are contributed by two occupied polarized d orbitals from Pd and an unoccupied p orbital form C1. Those three molecular orbitals represent the significant back donation of electrons from Pd to C1. Therefore, twisted C1-C2 bond in transition state **23-ts** can be stabilized by this back donation interaction of Pd to achieve the isomerization.

Conclusion

In summary, we have devised a highly efficient palladium-catalyzed intermolecular *trans*-selective carbofunctionalization reaction that provides access to tri- and tetrasubstituted alkenes with remarkable regio- and stereoselectivity. Diarylation, arylsilylation/remote C−H silylation, and hydroarylation/remote C−H borylation of internal alkynes have been achieved by using aryl boronic acids, hexamethyldisilane, and *bis*(pinacolato)diboron as trapping reagents, respectively. Detailed mechanistic studies and DFT calculations have provided support for a *cis* to *trans* isomerization of alkenyl palladium species promoted by steric bulk of both the substrate and the ligand.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray data for **4aa (**CCDC 1890761**)** and **6a (**CCDC 1893368)

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Table of Contents