Cationic-Palladium Catalyzed Regio & Stereoselective Dicarbofunctionalization of Unsymmetrical Internal Alkynes

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Supporting Information Placeholder

ABSTRACT: Reported is the discovery of an approach to regio- and stereoselective *syn*-1,2-dicarbofuctionalization of unsymmetrical alkynes. A cationic Pd-catalyzed three-component coupling of two distinct carbon-bearing functionalities aryl diazonium salts and aryl boronic acids/olefins with unsymmetrical alkynes enables accessing to all-carbon substituted unsymmetrical olefins. The transformation features broad scope with labile functional group tolerance building a novel chemical space of structural diversity (82 molecules) and is scalable. The cationic Pd species plays crucial; notably, density functional theory (DFT) studies establish this observation. Synthetic versatility of the modifiable carboxylate bearing highly-substituted olefins is also presented.

Peripheral decorated tetrasubstituted- and π-extended olefins are widespread in numerous natural products, leading drugs of biological importance, and agrochemicals. They also exert potential applications in electron-transport materials and light-emitting-diodes.[1,2] Along this line, the metal-catalyzed alkene dicarbofunctionalization by interrupting two cross-coupling strategies [for example: Suzuki and Heck/Wacker oxidation] is undisputedly well investigated.[3] While such dicarbofunctionalization of alkyne, which enables synthetically diverse tetra-substituted olefins, often suffers from inhabitable regioselectivity issues. Mostly, the state-of-the-art regioselective carbometalation of alkynes are confined to electronically diverse, inherently polarized, and/or in-build chelation species containing substrates (Fig 1a).[4-8] Meanwhile, an amino-pyridine directing group (DG) guided regioselective hydroarylation of alkyne with aryl boronic acid makes trisubstituted olefins (Fig 1b).[9] As DG and electron-biasness played essential for alkyne difunctionalization, its synthetic elaboration has therefore been severely affected. Hence, *devising a ligand free regioselective syn-1,2-dicarbofunctionalization of unactivated alkynes is worth pursuing.*

We herein discovered cationic Pd-catalyzed 1,2-dicarbofunctionalization of unactivated alkyne, i.e. yne-acetate (Fig 1c). The reaction relies a site-selective coordination of ligated cationic Pd(II) species, generated in-situ by the oxidative insertion of an aryl diazonium salt with Pd(0), to an electronically unbiased yne acetate (**I**) to result a *syn*-α-arylated-Pd intermediate **II** (Fig 1c). While the lone pair repulsion between carboxylate moiety and the ligated-Pd-complex possibly excludes *syn*-β-arylated-Pd intermediate **III** (Fig 1c). Further functionalization of vinyl-Pd(II)-cationic species **Int-II** with aryl boronic acids/olefins would deliver highly-substituted olefins (Fig 1c). This conceptual imprint has thus led to structurally diverse all-carbon-functionalized olefins (82 molecules) in a single-step from easily accessible yne-acetates. In the absence of external ligand and DG, the transformation is highly regio- and stereoselective; DFT study validates these observations.

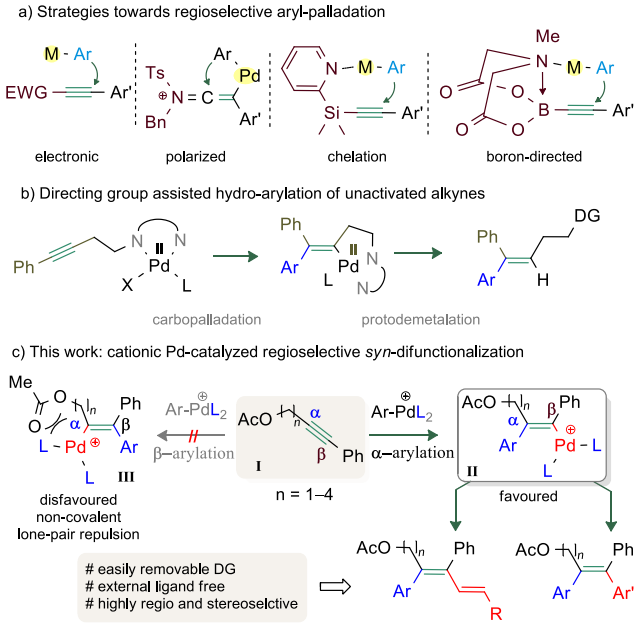
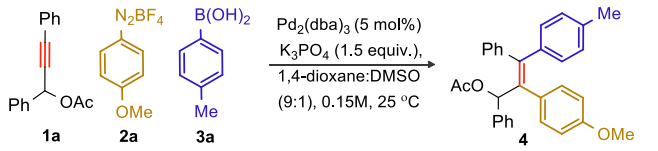


Figure 1. Background and current work

To investigate 1,2-diarylation of structurally simple yne-acetates [i.e. propargyl acetates (PAs)], a three-component reaction of 1,3-diphenylprop-2-yn-1-yl acetate (**1a**), *p*–methoxyphenyl diazonium tetrafluoroborate (**2a**), and *p*–tolyl boronic acid (**3a**) in presence of $Pd_2(dba)_3$ catalyst and base was performed (Table 1; see Table S3, SI). An extensive screening led to the optimized reaction conditions: [**1a** (1.0 equiv), **2a** (3.0 equiv), **3a** (1.5 equiv), $Pd_2(dba)_3$ (5.0 mol %), and K_3PO_4 (1.5 equiv), in 1,4-dioxane : DMSO (9:1) at 25 °C overnight]; the unsymmetrical *syn*-diarylation product **4** was isolated in 73 % yield (Table 1, entry 1). $NaHCO_3$ and KH_2PO_4 proved to be far less efficient bases (entries 2 & 3). Comparable results were observed when other Pd(0) catalysts [$Pd(dba)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$, and $Pd(PPh_3)_4$] were used (entries 4–6). The solvents THF, 1,4–dioxane, DMSO, or toluene did not

benefit the reaction (entries 7–10). The current breakthrough thus inspired us investigating the reaction scope (Scheme 1–3).

Table-1. Optimization Table[a]



	conditions	4 (%)		conditions	4 (%)
1	None	73%	6	$Pd(PPh_3)_4$	47%
2	$NaHCO_3$	56%	7	THF	26%
3	KH_2PO_4	62%	8	1,4-dioxane	49%
4	$Pd(dba)_2$	58%[b]	9	DMSO	55%
5	$Pd_2dba_3.CHCl_3$	63%	10	toluene	23%

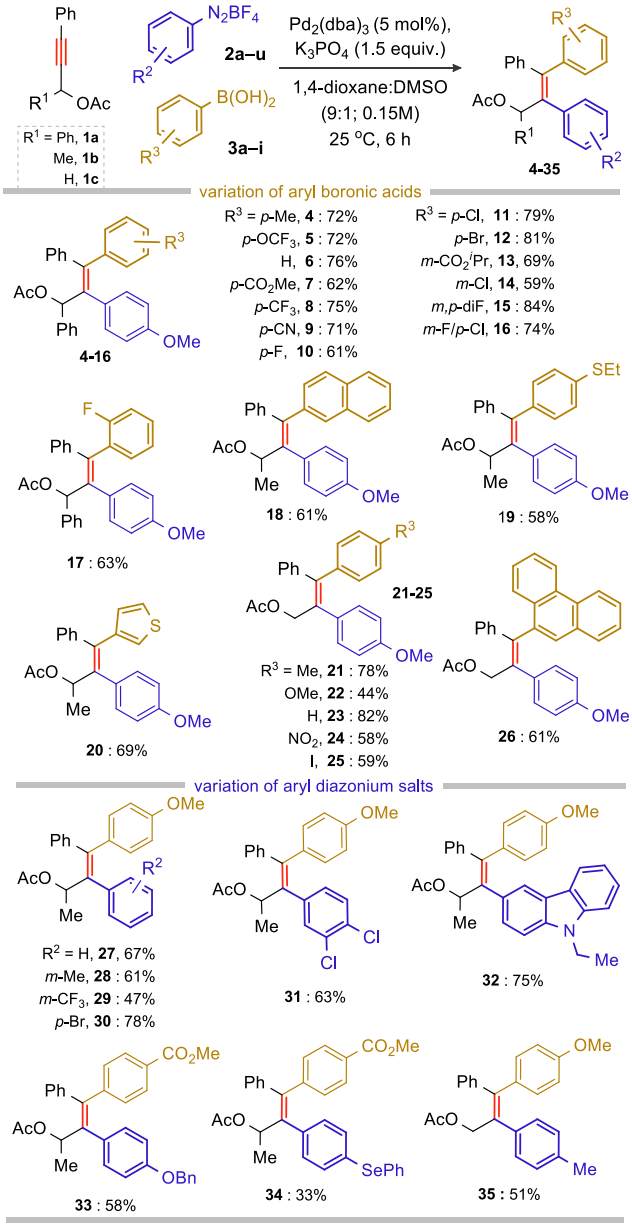
[a]Isolated yield. **1a** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.3 mmol), cat. (0.01 mmol) and base (0.45 mmol). [b]10 mol %.

The reactivity of aryl boronic acid partners was at first probed (Scheme 1). The reaction of electron-rich *p*-substituted aryl boronic acids [*p*-Me (**3a**), *p*-OCF_3 (**3b**)] with **1a** and **2a** provided **4** and **5** in good yields. Likewise, the tetrasubstituted olefins **6**–**9** (62–76 %) were constructed from phenyl boronic acid (**3c**) and electron-poor [*p*-CO_2Me (**3d**), *p*-CF_3 (**3e**), *p*-CN (**3f**)] aryl boronic acids when exposed independently to **1a** and **2a**. Being the halo groups are amenable to cross-couplings under Pd(0)-catalysts, to our delight, the respective halo [*p*-F (**3g**), *p*-Cl (**3h**), *p*-Br (**3i**)] bearing aryl boronic acids were compatible to make **10**–**12** in good yields. The transformation was susceptible to *meta*- and *ortho*-substituted aryl boronic acids; accordingly, densely functionalized tetrasubstituted olefins **13**–**17** (59-84%) were made. The desired 2-naphthyl, 4-ethylthiophenyl, 3-thienyl-bearing allyl-acetates **18**–**20** (58–69%) were constructed. The unsubstituted propargyl acetate **1c** was also amenable; various aryl boronic acids [*p*-Me (**3a**) and *p*-OMe (**3r**), phenyl (**3c**), *p*-NO_2 (**3s**), and *p*-I (**3t**)] were coupled to provide **21**–**25**. The bulky 9-phenanthere boronic acid was not an exception providing π-extended product **26** in 61% yield. Next, the three-component couplings of aryl diazonium tetrafluoroborates **2** with **1b** and **3r**/**3d** were surveyed (Scheme 1). An independent reaction of **1b**, **3r** with respective arene diazonium salts [phenyl (**2b**), electron-rich *m*-Me (**2c**), electron-poor *m*-CF_3 (**2d**), modifiable *p*-Br (**2e**), and *m*,*p*-diCl (**2f**)] provided **27**–**31** in good yields. A carbazole bearing diarylation product **32** was isolated in 75% yield. The OBn protecting group and the oxidizable SePh group were unaffected under the Pd-catalysis giving access to **33** and **34**. Likewise, **35** (51%) was made from the reaction of **1c** with **2j** and **3r**.

We next scrutinized the reactivity of unsymmetrical alkynes diversity (Scheme 2). The reaction of PAs [having aryl motifs: (*p*-Me and *p*-OMe), labile halo group (*p*-F and *p*-Br), and modifiable (*p*-CF_3, *p*-COMe, *p*-CO_2Me, *m*-CN, *m*-NO_2, *m*,*m'*-diNO_2, and *m*,*p*-methylenedioxy) at the alkyne terminus] with **2a** and **3c** independently furnished the desired products **36**–**47** (62–93%). Likewise, π-extended 2-naphthyl (**48**), and heteroaryl 2-thienyl (**49**) enabled tetrasubstituted olefins were constructed. Irrespective of *n*-propyl and various aryl-moieties in the propargyl position of PAs, the diarylation was equally effective making **50**–**57**. In general, sterically bulky substituents severely affect the cross-couplings. Despite these challenges, *syn*-diarylation of cyclohexyl, and cyclobutyl tethered PAs with **2a** and **3c** provided all-carbon-substituted olefins **58**–**59**. X-ray analysis confirms the structure **58**. A macrocycle dodecane tethered diarylation product **60** was also fabricated. The product complexity justifies moderate yield (< 50%); in such cases, the reaction was incomplete with recovery of unreacted PAs.

To understand coordination proximity of the carboxylate group, diarylation of yne-acetates with different chain length among alkyne and acetate group was probed.

Scheme 1: Scope of Propargyl Acetates, Aryl Boronic Acids, and Aryl Diazonium Salts[a]



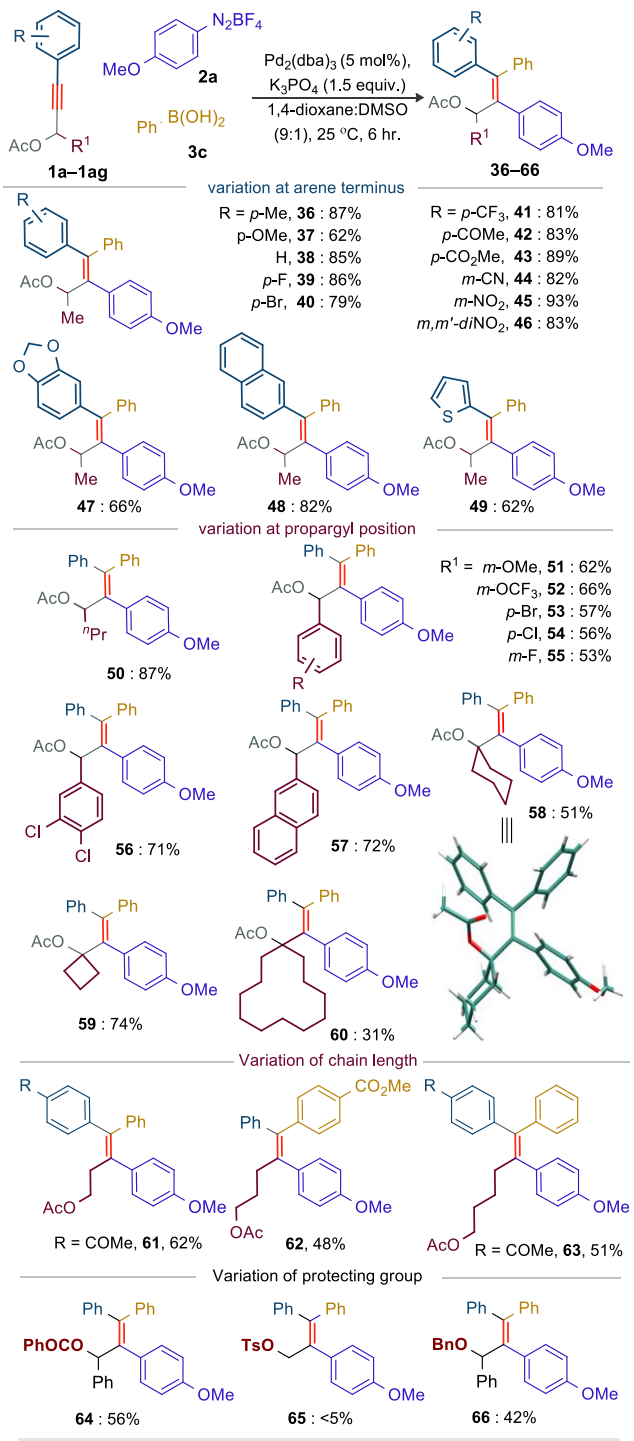
[a]**1** (0.3 mmol), **2** (0.9 mmol), **3** (0.45 mmol).

Irrespective of the acetate position in yne-acetates, *syn*-diarylation of alkyne-motifs was highly regioselective making **61**–**63** in moderate yields (Scheme 2). Next, the reaction of O-benzoate and O-benzyl protected propargyl alcohols with **2a** and **3c**, respectively, afforded **64** (56%), and **66** (42%) (Scheme 2). While reaction of O-tosyl protected alkyne led to complex mixture providing **65** (<5%); the low turnout is possibly due to the facile cleavage of labile C–OTs bond.

The π-conjugated skeletons are widely found in the molecules of pharmaceutical importance and light-emitting-diode materials. We thus realized to trap the vinyl-cationic palladium species, obtained in the aryl-palladation of alkyne moiety, with olefins for constructing peripheral decorated π-conjugated diene skeleton (Scheme 3). As envisaged, the reaction of **1b**, **2a**, and ethyl acrylate (**67a**) under the optimized conditions of entry 1, Table 1 suc-

cessfully led to **68** in 67% yield. To enhance the reaction productivity, bases and solvents were further screened (Table S4, SI). The Na_2HPO_4 base and DMSO:DMF (1:1) solvent combination

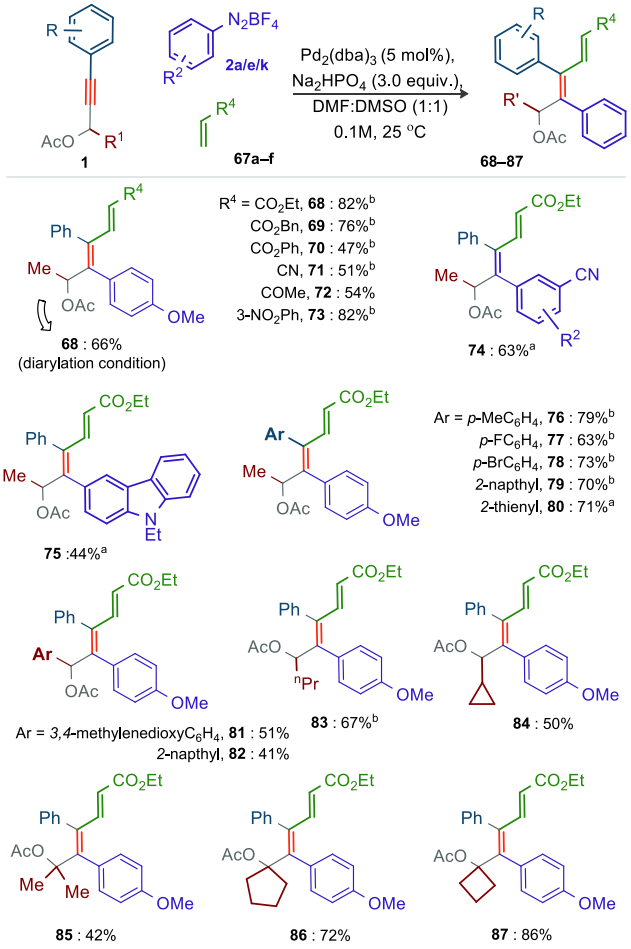
Scheme 2: Scope of Diarylation of Alkynes[a]



[a]**1** (0.3 mmol), **2a** (0.9 mmol), **3a** (0.45 mmol). Ts = *p*–toluenesulfonyl

was found optimum; **68** was isolated in 82% yield. Next, the reaction of wide ranges acrylates and acrylonitrile with **1b** and **2a** under the modified catalytic systems furnished the conjugated dienes **68**–**71** (Scheme 3). Methyl vinyl ketone is susceptible to polymerization; despite the challenges, **72** was isolated in 54% yield. This difunctionalization was even worked with styrene affording **73** in 82% yield. The products **74** (63%) and **75** (44%) were made from the couplings of **1b** and **67a** with **2e** and **2k**, respectively. The PAs [having aryl motifs: electron-rich (*p*-Me), labile (*p*-F and *p*-Br), π-extended 2-naphthyl or 2-thienyl at the

Scheme 3: Scope of Aryl-Olefination of Alkynes[a]



[a]**1** (0.3 mmol), **2a** (0.9 mmol), **66** (0.45 mmol). [a]7–10% (inseparable isomeric mixture)

alkyne terminus)] were independently coupled with **2a** and **67a** to deliver **76**–**80**. Likewise, **81**–**84** were made albeit in moderate yield from the reaction of PAs [with variation of substituents, *m*,*p*-methylenedioxy-phenyl, 2-naphthyl, *n*-Pr, and cyclopropyl in the propargyl position] with **2a** and **67a**. Even the sterically encumbered di-Me, cyclopentyl, and cyclobutyl tethered PAs were successfully provided unusual π-conjugated dienes **85**–**87** (42–86%). Thus, the cationic Pd-catalytic systems did not virtually affect the reaction outcome; and the strained cyclopropyl ring, labile halo groups, and easily modifiable functional groups are well tolerated (Scheme 1–3).

To gain insight into the reaction mechanism and the stereo/regioselective 1,2-diarylation of PAs, DFT calculations were performed (Figure 2, see the SI). The transformation begins with the barrier less oxidative insertion of $Pd(DMSO)_2$ (**I**) to the phenyl diazonium tetrafluoroborate **2b** to provide the cationic Pd-complex ^{1}**A**. Next, coordination of ^{1}**A** with propargyl acetate **1c** is possible with the concomitant replacement of N_2. However, this process could happen in three different ways, via, i) the co-ordination of C≡C bond in **1c** to form complex ^{1}**B** by releasing 6.7 kcal/mol free energy (Fig. 2; blue) ii) the co-ordination of both C≡C bond and ester group in **1c** to provide ^{1}**E** with the release of 4.5 kcal/mol free energy (Fig. 2; red), and iii) the co-ordination of ester group in **1c** to generate ^{1}**G**; the process is endothermic re-

quiring 1.8 kcal/mol (Fig. 2; grey). Thus, the ester group participation for the replacement of N_2 in **^{1}A** is ruled out. Next, a supra-facial α-aryl migration from Pd to the C≡C bond of

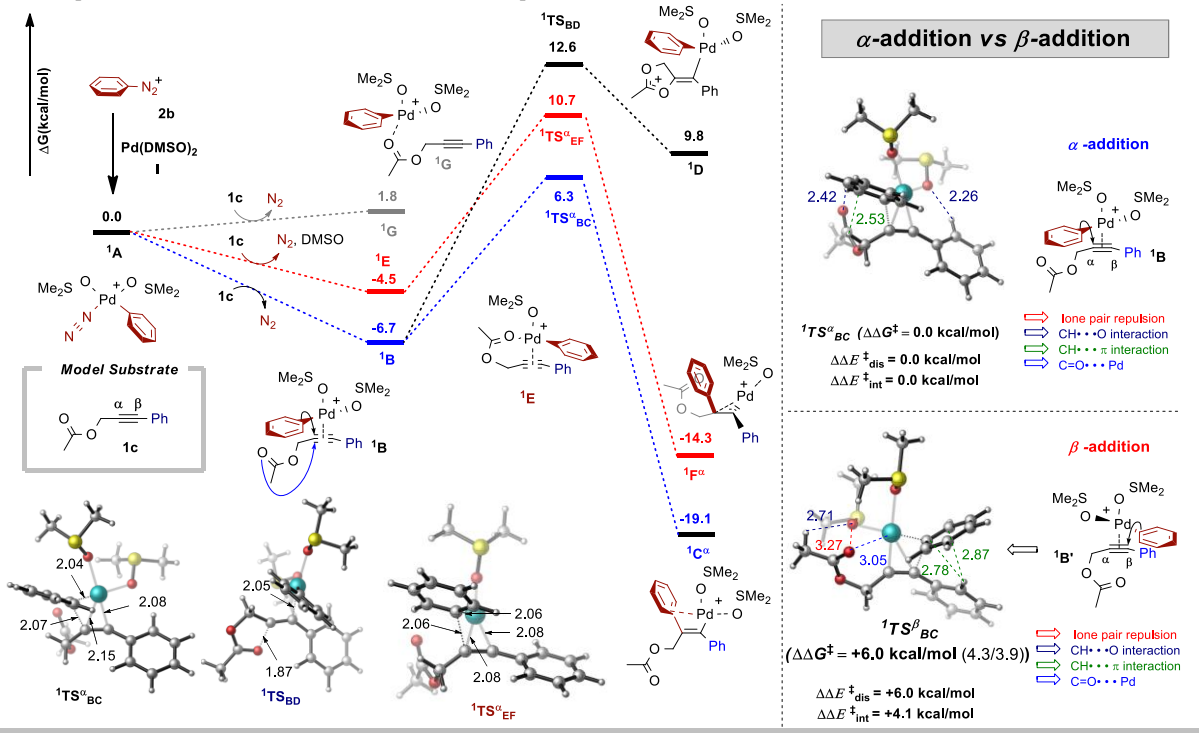


Fig-2. DFT calculation

^{1}B (*syn*-insertion)proceeds through a transition state **^{1}TS$^α_{BC}$**, found at 6.3 kcal/mol on the free energy surface, and results the Pd-alkenyl ester complex **^{1}C^α** (vide-infra). The complex **^{1}C^α** lies at –19.1 kcal/mol with *trans*-relationship of two phenyl groups. While intramolecular neighboring group participation (NGP) of the ester group at $C^α$ of **^{1}B** can provide Pd-alkenyl heterocyclic complex **^{1}D** through **^{1}TS$_{BD}$** (12.6 kcal/mol); this process needs an additional 6.3 kcal/mol energy barrier to overcome **^{1}TS$^α_{BC}$** and thus ruled out. Alternatively, α-aryl migration of ester chelate **^{1}E** forms intermediate **^{1}F^α** (–14.3 kcal/mol) through **^{1}TS$^α_{EF}$** (10.7 kcal/mol). The energy barrier is 2.2 kcal/mol higher than **^{1}TS$^α_{BC}$**; this pathway is thus not preferred. A detailed comparison of all the options justify the feasibility of bottom pathway **^{1}B→^{1}C^α** (marked in blue). Like normal Suzuki reaction, transmetalation of **^{1}C** with aryl boronic acid followed by reductive elimination gives the final diarylation product.

On the other hand, the $C^α$-arylation process is always favored over the $C^β$-arylation (see: right side in Figure 2). To rationalize this selectivity, a distortion analysis of the aryl migration transition states **^{1}TS$^α_{BC}$** and **^{1}TS$^β_{BC}$** (that includes substrate fragment and aryl-palladium fragment) are performed. The large rotation angle for β-aryl migration (see the SI: 36.12° for **^{1}TS$^β_{BC}$** and 7.34° for **^{1}TS$^α_{BC}$**) contributes to excess distortion energy [+6.0 kcal/mol; that includes both arylpalladium (+3.68 kcal/mol) and substrate (+2.32 kcal/mol) distortion]. In addition, a large level of non-covalent lone pair repulsion of the carboxylate moiety with ligated DMSO for **^{1}TS$^β_{BC}$** (+4.1 kcal/mol) relative to **^{1}TS$^α_{BC}$** was detected.

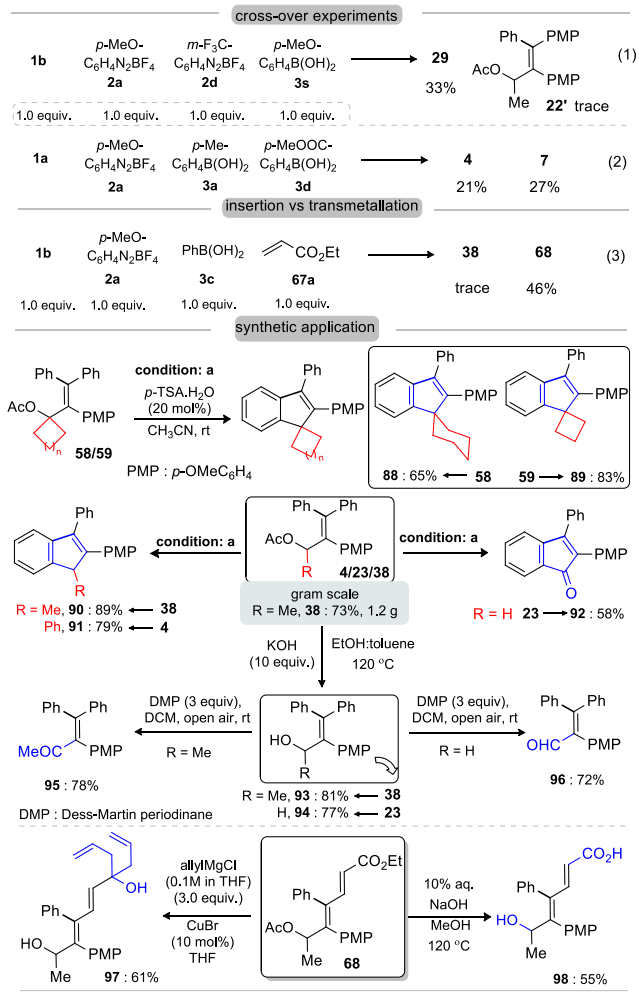
To further understand the reactivity behavior, a crossover experiment of electronically-diverse diazonium salts **2a** and **2d**, with **1b** and **3s** was performed (Scheme 4, eq 1). Formation of **29** (33 %) and trace **22'** clearly justifies that the oxidative addition of **2d** with Pd(0) is facile over **2a**. Likewise, probing the reaction **1a** and **2a** with electronically-different **3a** and **3d** gave **4** (21 %) and **7** (27 %) [Scheme 4, eq 2]. Thus, activated boronic acid **3d** undergoes transmetalation faster over **3a**; a feature is very common in cross-couplings. On the other hand, isolation of **68** (46%) in a competitive reaction of **1b**, **2a**, **3c**, and **67a** suggests that the aryl-olefination is preferred over di-arylation [Scheme 4, eq 3].

The reaction is scalable to the gram-scale preparation **38** (1.2 g, 73 %) from the coupling of **1a** (1.0 g, 2.67 mmol), **2a** (1.77g, 8.01 mmol), and **3c** (0.5g, 4.00 mmol) in $Pd_2(dba)_3$ (3.0 mol %) [Scheme 4]. We next probed synthetic versatility of the newly constructed tetrasubstituted allyl-acetates (Scheme 4). The *p*-TSA driven intramolecular Friedel-Crafts arene cyclization with the acetate center of **58**/**59** led to unusual cyclohexyl/cyclobutyl spiro-fused indene derivatives **88** (65 %) and **89** (83%), respectively, and peripheral-substituted indenes **38→90** (89 %) and **4→91** (79%). Likewise, electrophilic cyclization of **23** provided indanone **92** in 58% yield. Fully substituted propargyl alcohols [**38→93** (81%); **23→94** (77%)] were accessed from the KOH facilitated hydrolysis of acetate-motif. Dess-Martin periodinane (DMP)-mediated oxidation of **93** and **94** delivered peripheral decorated methyl-vinyl ketone **95** (78%) and acrolein **96** (72%), respectively; further functionalization of carbonyl groups is therefore possible. Allylation and hydrolysis of π-extended ester **68** yielded allylic-3°-alcohol **97** and α,β-unsaturated carboxylic acid **98** (Scheme 4).

In summary, a regio- and stereoselective insertion of structurally distinct carbon functionalities to the unactivated alkynes has led to discovery of dicarbofunctionalization of unsymmetrical alkynes. The cationic Pd^{II}-catalyst plays essential modulating regioselective insertion of aryl-diazonium salts, and boronic acids/olefins to the unsymmetrical alkynes. The transformation proceeds at room temperature and tolerates oxidizable halo-species (I/Br), easily transformable functionalities (CO_2Me, CN), and strained rings exhibiting a broad chemical space [82 examples], and even successful on a gram scale. DFT studies rationalize the α-arylation preference over β-arylation of PAs and discard direct participation of DG. The highly-substituted olefins are subsequently used for the construction of functionalized indene, methyl-vinyl ketone, and acrolein skeletons. The current finding paves the way in dis-

covering unknown difunctionalization strategies of unactivated alkynes.

Scheme 4: Competitive Experiments, Gram Scale Preparation, and Synthetic Application



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All authors have given approval to the final version of the manuscript.

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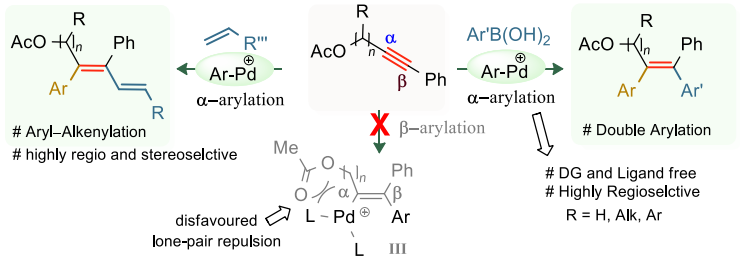
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# Double Arylation
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