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Regioselective *syn*-1,2-Hydroarylation of Internal Alkynes

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The regioselective hydro-functionalization reaction is a powerful method to convert readily available alkynes into structurally diverse olefins. Such an efficient *syn*-1,2-hydroarylation of yne-acetates is described herein using aryl diazonium salts and silanes as aryl and hydride sources, respectively. The transformation shows excellent functional group tolerance and applications to late-stage functionalization, providing a straightforward entry to trisubstituted allyl acetates. DFT analysis sheds light on the mechanism, particularly on the role of DMSO solvent in assisting the Si–H bond cleavage.

Introduction

Peripherally decorated olefins are commonly found in various natural products/drugs and organic materials.[1] They are also useful precursors for synthesizing substituted 3-membered carbo/heterocycles.[2] In particular, tri-substituted olefins as well as allyl alcohol derivatives stand out as various drug building blocks (Figure 1A).[3] Though tri-substituted olefins appear structurally simple at first glance, their regioselective synthesis has always been challenging.[4] Among various approaches, hydroarylation via the carbometallation of the alkynes pathway appears to be the most efficient and the most modular.[5] Except unsymmetrical alkynes which face regioselectivity issues in the carbometallation step, various research groups have used symmetrical alkynes for the synthesis of tri-substituted olefins via C–H functionalization or through the addition of polar/radical species.[6,7] For unsymmetrical alkynes, use of a directing group (DG) has displayed promising regioselectivity in the δ-carbometallation step (Engle group, Figure 1B).[8] Additionally, Lautens work on β-arylation of propargyl alcohols also exhibits high regioselectivity.[9,10] Interestingly secondary propargyl amines (α-disubstituted) undergo β-arylation with excellent regioselectivity (the ligated metal goes to the γ-carbon to avoid steric hindrance).[11] In this context, Cacchi's work on internal alkynes is particularly noteworthy; however, the primary concern is its moderate regioselectivity.[12c] Despite these advancements in the field, there is still room for uncovering a sustainable regioselective hydroarylation of unsymmetrical alkynes (propargyl acetate).[12] The present synthetic method aims to address the undisputed problems linked to the non-removable nature of the pyridyl-DG,[13] the use of external ligands,[14] the use of an expensive Rh-catalyst,[15] and the requirement to employ harsh reaction conditions.

In light of our recent work on cationic Pd-catalysed dicarbofunctionalization of unsymmetrical alkynes (yne-acetates),[16] regioselective hydroarylation of unsymmetrical alkynes could be achieved in the presence of a hydride source (Figure 1C). We surmise the site-selective coordination of cationic aryl-Pd(II), enabling regioselective carbo-palladation, followed by trapping with a hydride source. DFT computations shed light on this hypothesis.

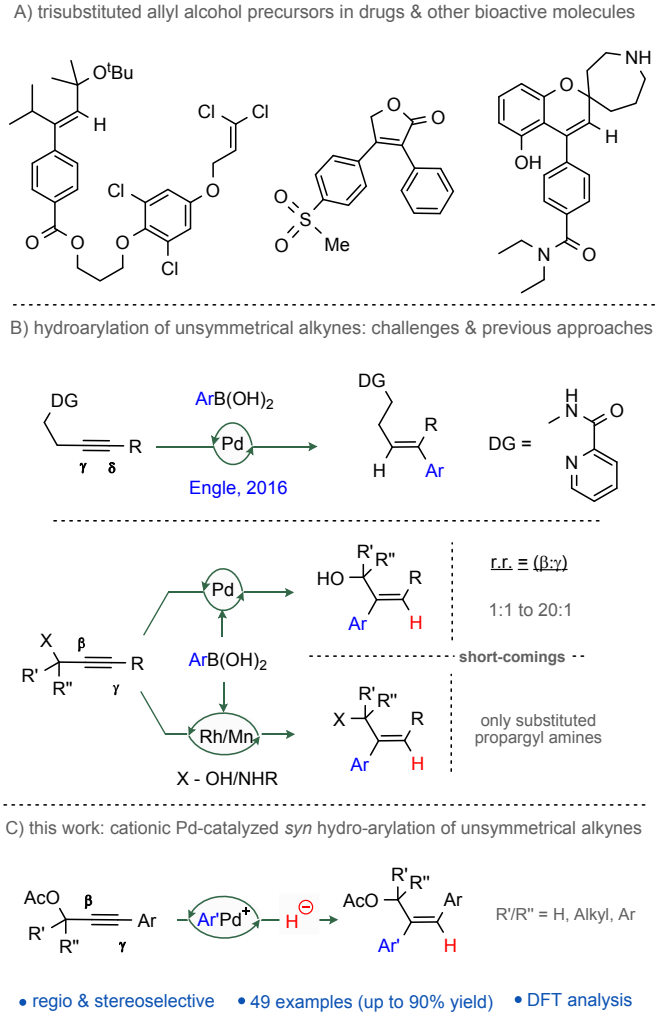

Figure 1 Prior works and our hypothesis

Results and discussion

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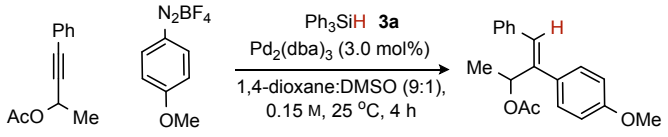
Initial tests were focused on the use of triphenyl silane **3a** as a hydride source in the three-component reaction of 4-phenylbut-3-yn-2-yl acetate (**1a**) with *p*-methoxyphenyl diazonium tetrafluoroborate (**2a**) (Table 1). An extensive screening of reaction parameters such as catalysts, solvents and temperatures led us to the optimized conditions: [**1a** (1.0 equiv), **2a** (3.0 equiv), **3a** (1.2 equiv), and $Pd_2(dba)_3$ (3.0 mol%) in 1,4-dioxane/DMSO (9:1), 0.15 M at 25 °C, for 30 min to 4 h]; the desired hydroarylation product **4** was isolated in 94% yield (entry 1). Other Pd(0) catalysts [$Pd(dba)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$] led to reduced yields of **4** (entries 2 and 3). The solvents 1,4-dioxane, DMSO, DMF, and 1,2-DME were found less effective than the 1,4-dioxane/DMSO mixture, furnishing **4** in 61–77% yield (entries 4–7). On the other hand, the use of toluene only led to traces of **4** (entry 8). Lowering the reaction temperature to 0 °C or raising it to 40 °C diminished the product yield (entries 9 and 10). While triethyl silane **3b** also proved to be an effective hydride source, phenyl silane ($PhSiH_3$) **3c** failed (entries 11 and 12). Lastly, aryl iodide (**2a'**) and aryl trifluoromethane sulfonate (**2a''**) in place of **2a** only provided **4** in trace amounts (entries 13 and 14). Then, a series of aryl diazonium salts (**2a**–**2x**) were tested in the reaction of **1a** and **3a** under the optimized conditions (Scheme 1).

Table 1 Reaction optimization



1a **2a** **4**

	deviations from the S.C.[a]	yield of **4** (%)[b]
1	none	94
2	6.0 mol% $Pd(dba)_2$	73
3	$Pd_2(dba)_3{\cdot}CHCl_3$	82
4	1,4-dioxane	77
5	DMSO	61
6	DMF	65
7	1,2-DME	62
8	toluene	trace
9	0 °C	71
10	40 °C	75
11	Et_3SiH (**3b**) as hydride source	82
12	$PhSiH_3$ (**3c**) as hydride source	trace
13	4-iodoanisole (**2a'**) as aryl source	trace
14	4-$MeOC_6H_4OTf$ (**2a''**) as aryl source	trace

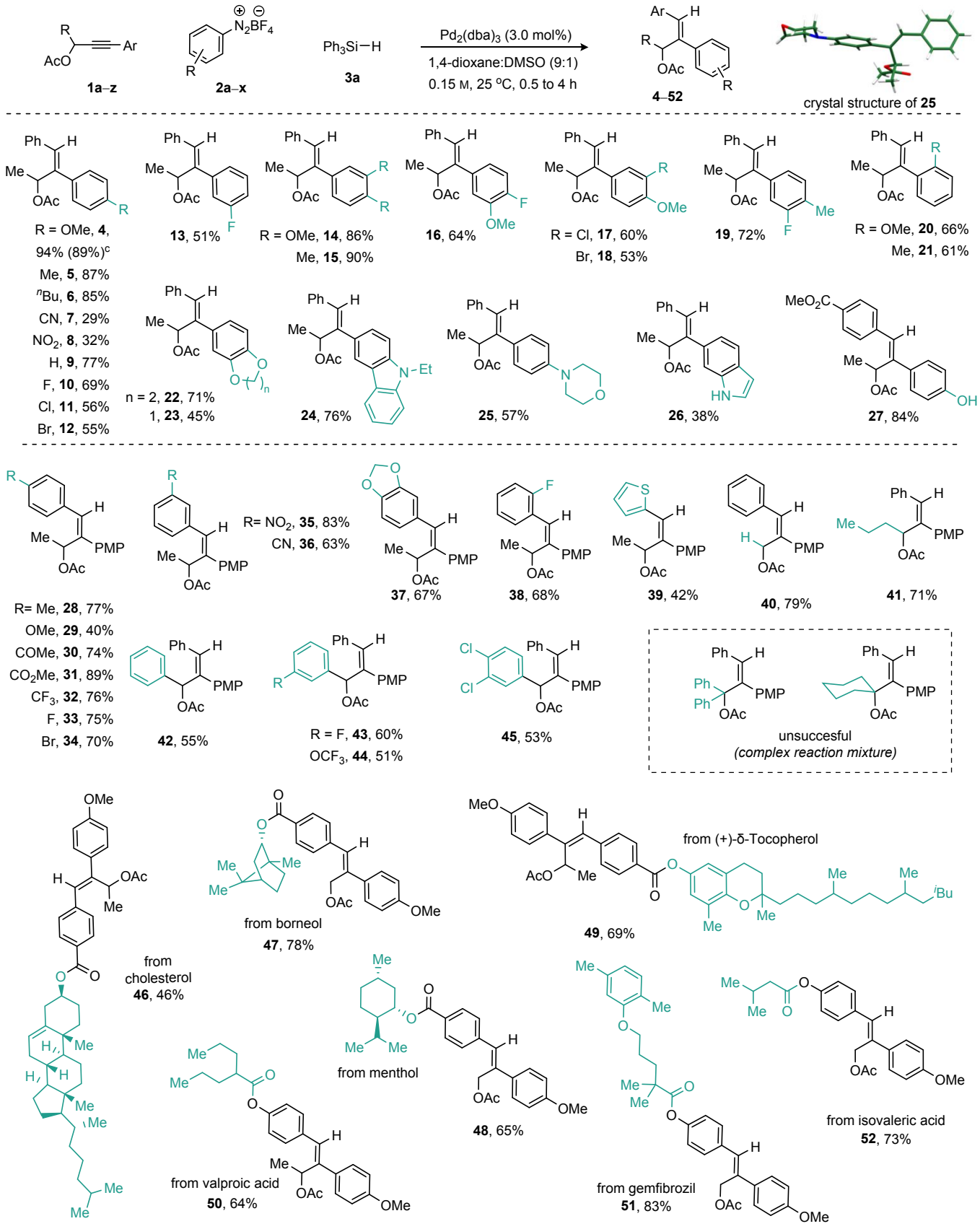
[a]Standard Conditions (S.C.): **1a** (0.2 mmol), **2a** (0.6 mmol), silane **3a** (0.24 mmol), Pd-catalyst (3.0 mol%) in solvent (0.15 M), at 25 °C for 4 h; [b]Isolated yield.

The results demonstrate that the electron-rich *p*-(OMe, Me, and ^{n}Bu)-substituted arene diazonium salts **2a**–**2c** delivered better results when compared to the respective electron-poor *p*-(CN and NO_2)-arene diazonium salts **2d**–**2e**; the desired allyl acetates **4**–**8** were isolated in 29–94% yield. The large variation of the yield could be a consequence of the facile oxidative addition of electron-poor diazonium salts to the Pd(0)-catalyst leading to faster decomposition. Likewise, compound **9** was made from the reaction of electron-neutral phenyl diazonium salt **2f** with **1a** and **3a** (77% yield). Notably, the labile halo (-F, -Cl, and -Br) groups were tolerated under the oxidative conditions, with compounds **10**–**12** being synthesized in good yields. Similarly, compounds **13**–**21** were constructed from the reaction of *meta/para/ortho*-mono/di-substituted arene diazonium salts **2j**–**2r** independently with **1a** and **3a**. Moreover, heterocycles such as 2,3-dihydrobenzo[*b*][1,4]-dioxine, benzo[*d*][1,3]dioxole, 4-carbazole, 4-morpholine phenyl, and 6-indole-containing diazonium salts **2s**–**2w** also actively participated in the coupling reaction, delivering **22**–**26** in 38–76% yield. The single crystal X-ray crystallographic analysis of **25** unambiguously confirmed the product regioselectivity. Notably, 4-hydroxyl phenyl diazonium salt **2x**, despite having an acidic -OH group, reacted smoothly with **1e** to give the desired hydroarylation product **27** in 84% yield.

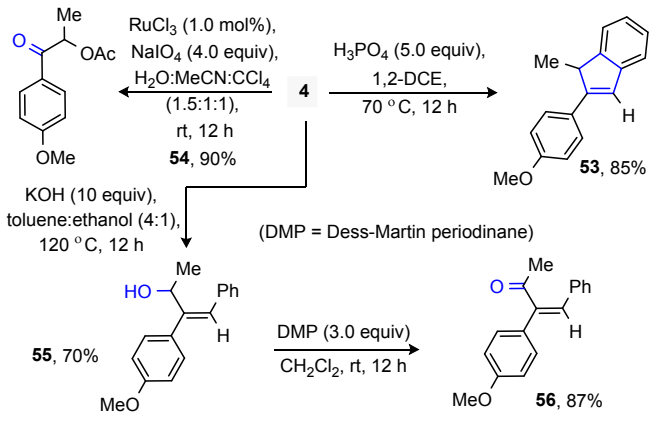
Next, we probed the effect of various aryl groups at the alkyne terminus. A wide range of *para*-electron-rich (Me and OMe), electron-poor (COMe, CO_2Me, and CF_3), and halogen (F and Br) phenyl-containing alkynes (**1b**–**1h**) were allowed to react with **2a** under the standard conditions to afford the desired hydroarylation products **28–34** in moderate to excellent yields as single regioisomer (40–89%). In addition, compounds with *m*-(NO_2 and CN) groups, as well as crowded *m*,*p*-methylenedioxy-substituted propargyl acetates (**1i**–**1k**), yielded products **35**–**37** in good yields. Moreover, single regioisomers were observed in sterically demanding *o*-F and heterocyclic 2-thienyl-containing products **38** and **39**. Intrigued by these excellent results, we next explored the substitution at the propargyl position (**1n**–**1s**). While the unsubstituted propargyl acetate delivered **40** in 79% yield; *n*-propyl, phenyl, *m*-F phenyl, *m*-OCF_3 phenyl, and *m*,*p*-diCl phenyl substituted propargyl acetates led to lower yields of the respective hydroarylation products **41**–**45**, yet with absolute regioselectivity. Next, late-stage hydroarylation of unsymmetrical alkynes **1t**–**1z** containing biologically relevant motifs (BRMs) were performed with **2a** and **3a** under the standard conditions. The trisubstituted allyl acetate-bearing steroid [cholesterol (**46**)], terpenoid [borneol (**47**) and menthol (**48**)], or fatty alcohol [tocopherol (**49**)] were constructed in 46–78% yields. Interestingly, the reaction of the marketed drugs valproic acid (anti-epileptic drug) and gemfibrozil (abnormal blood lipid level preventer) coupled with propargyl acetates (**1x** and **1y**) delivered the respective allyl acetates **50** (64%) and **51** (83%). Similarly, the isovaleric acid containing allyl acetate **52** was isolated in 73% yield.

The practicability of the methodology was tested by scale-up synthesis of **4** in 1.32 g scale (89% yield, Scheme 1, within parentheses[c]) under the standard conditions.

After the successful gram scale synthesis, the synthetic versatility of the newly constructed trisubstituted allyl-acetates was probed. Brønsted acid-mediated Friedel-Crafts cyclization of tri-substituted allyl acetate **4** afforded the highly substituted indene **53** (85%; Scheme 2). The Ru-catalyzed oxidative cleavage of the substituted olefin **4** provided acetyl ketone **54** (90%).



Scheme 1 Reaction Scope. [a]Reaction conditions: **1a**–**1z** (0.2 mmol), **2a**–**2x** (0.6 mmol), and silane **3a** (0.24 mmol) in 1,4-dioxane:DMSO (9:1; 0.15 M), at 25 °C for 0.5 to 4 h; [b]Isolated yield; [c]Yield in parentheses represents the scale-up reaction of 5.0 mmol of **1a** with **2a** and **3a** in S.C.

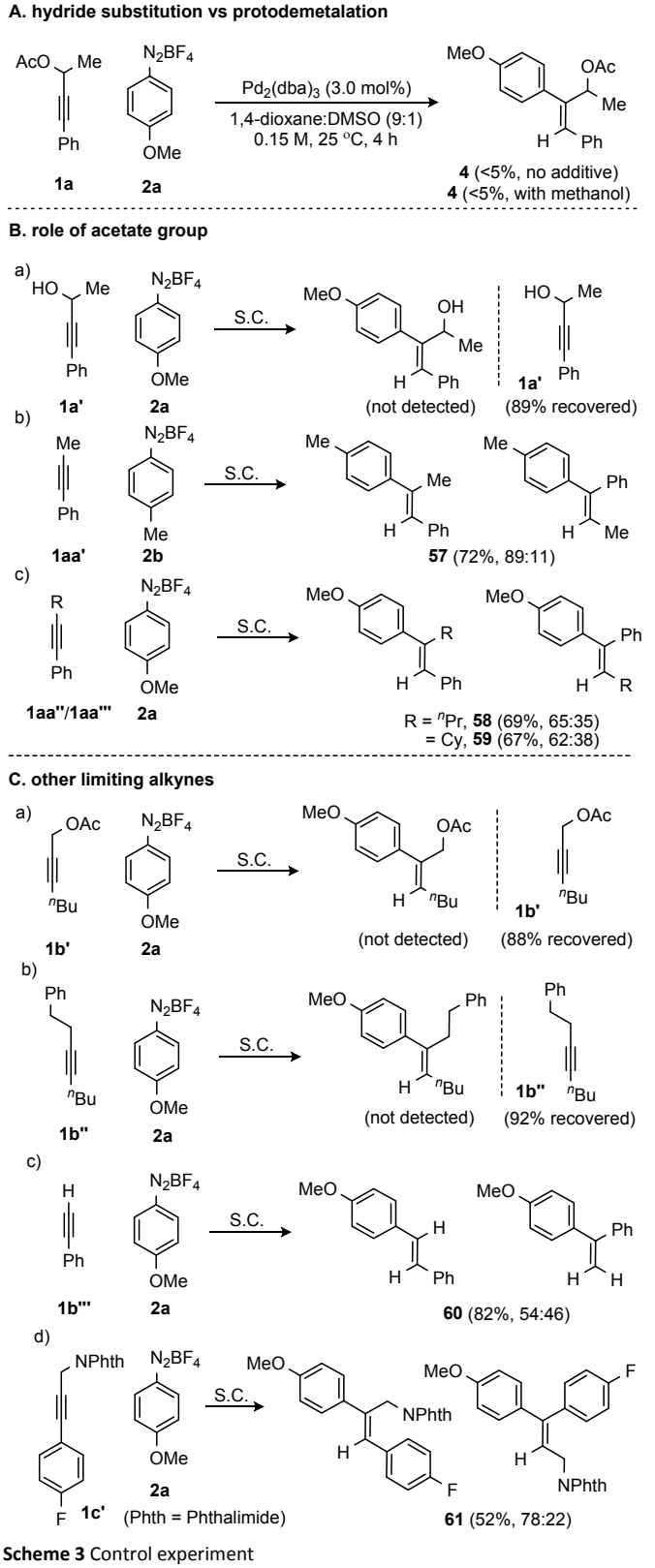


Scheme 2 Synthetic application

Moreover, KOH-mediated acetate deprotection followed by Dess-Martin periodinane (DMP)-assisted oxidation of **4** furnished vinyl ketone **56** (61% over the two steps).

To shed light on the reaction mechanism, a few control experiments were performed. First, the title reaction in the absence of silane failed to produce **4** in detectable amount (Scheme 3A). To discard the possibility of protodemetalation in the reaction pathway, methanol was added as an additive in place of the silane; however, no desired product **4** was observed. To establish the pivotal role of the acetate group, propargyl alcohol **1a'** was subjected to the optimized conditions (Scheme 3B, equation a). The rection was unsuccessful in the presence of a free alcohol group and **1a'** was recovered in 89% yield. Although the reaction was successful in the case of unsymmetrical aryl-alkyl bearing internal alkynes **1aa'** (72% of **57**), **1aa''** (69% of **58**), and **1aa'''** (67% of **59**), the regioselectivity was uncontrolled (Scheme 3B, equations b–c). In contrast, the reaction of aliphatic propargyl acetate (**1b'**) and dialkyl alkyne (**1b''**) did not provide the desired hydroarylation product (Scheme 3C–a and 3C–b). This may be attributed to the absence of an aromatic ring, which likely hinders the initial insertion step. While a terminal alkyne (**1b'''**) and phthalimide-protected propargyl amine (**1c'**) successfully produced **60** (82%) and **61** (52%), respectively, although with uncontrolled regioselectivity (Scheme 3C–c and 3C-d). However, it is worth noting that the possible ligand substitution by the hydride group of silane occurs in the absence of any O/F-salts susceptible to accepting the resulting silylium ion.

Hence, to understand reaction mechanism, DFT calculations were performed (Figure 2).[18] In our previous work,[16,17] we have shown that oxidative addition of $Pd(DMSO)_2$ into the C–N bond of phenyl diazonium cation **A**, coordination of the alkyne π-system to **A** followed by the *syn*-insertion of the alkyne into the Pd–Ph bond leading to **D** was achieved through the overall release of 19.1 kcal/. Focusing now on the reactivity of Ph_3SiH, we first envisaged the substitution of DMSO by the silane. It provided the complex **E** (–11.1 kcal/mol) in which the Si–H bond serves as ligand (1.62 Å in **E** vs 1.50 Å in Ph_3SiH). The formation of **E** is endergonic by 8.0 kcal/mol. The breaking of the Si–H bond was modelled through $\mathbf{TS_{EF}}$, located at 9.0 kcal/mol (rate-determining step). The DMSO ligand captures the resulting silylium ion Ph_3Si^+ by its oxygen atom. The resulting hydride complex **F** (–2.9 kcal/mol) is coordinated to DMSO both by the S and the O atoms. Several efforts failed to obtain the reductive



Scheme 3 Control experiment

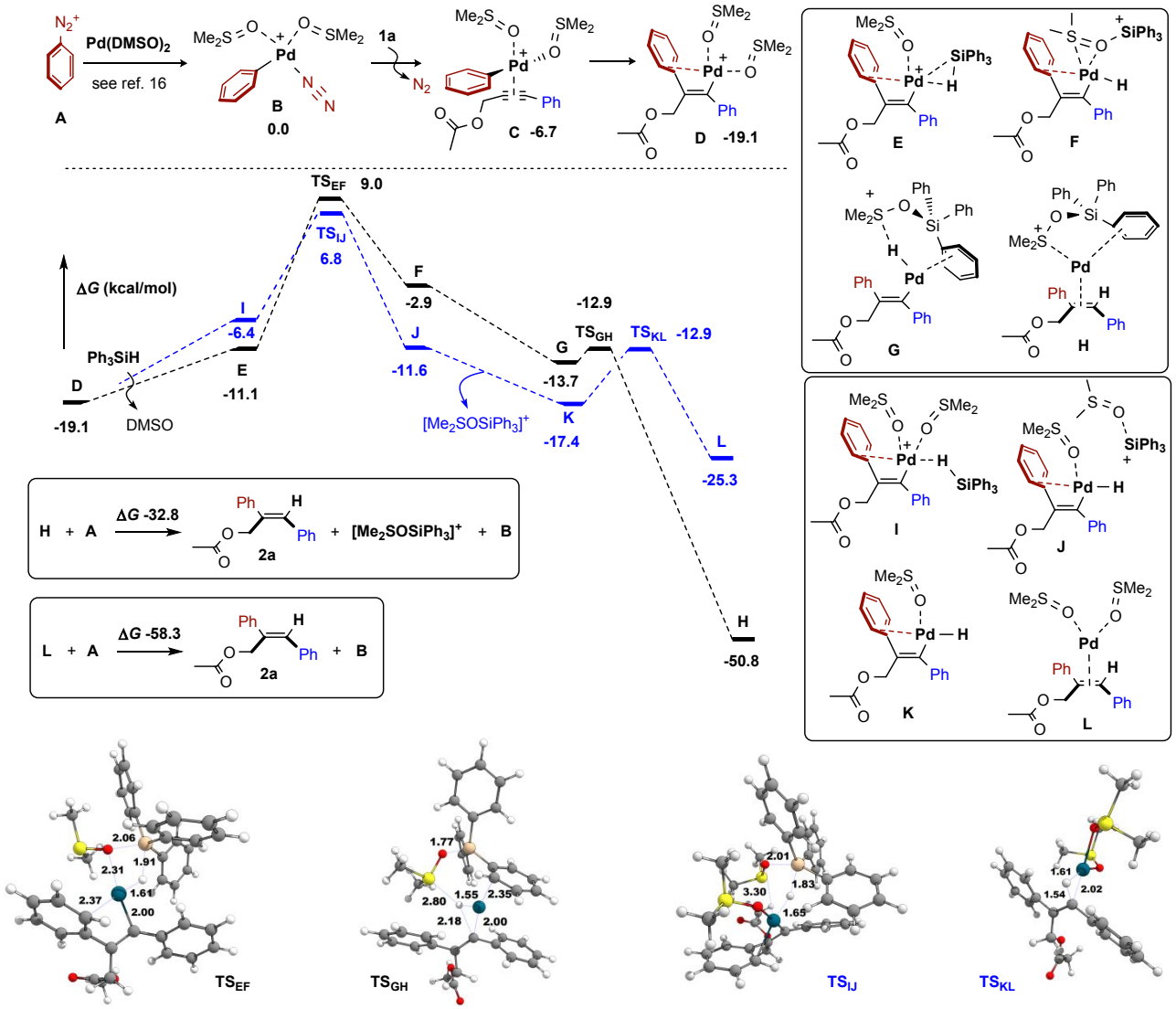


Figure 2 Computed free energy profiles (M06L/def2-TZVPP; selected distance in Å)

elimination of the latter. The $[Me_2SOSiPh_3]^+$ moiety can be used differently to coordinate the metal centre and engage in stabilizing interactions. In complex **G** (–13.7 kcal/mol), Pd is bound to one Ph group, allowing the S atom to establish a strong hydrogen bond with the hydride ligand (ρ_{max} = 0.028 eÅ^3). With the assistance of this noncovalent interaction, the reductive elimination becomes straightforward, the corresponding transition state $\mathbf{TS_{GH}}$ lying only 0.8 kcal/mol above **G** (–12.9 kcal/mol). This last step is strongly exergonic, leading to **H** at –50.8 kcal/mol. In this complex, the $[Me_2SOSiPh_3]^+$ moiety acts as a chelating ligand by the S atom and one Ph group. Finally, the recycling of the catalytically active species **B** from **H** is exergonic by 32.8 kcal/mol. Unfortunately we are unable to provide any experimental support for the existence of $[Me_2SOSiPh_3]$+ complex.

We then studied the formation of a pentavalent addition complex between **D** and DMSO. Formation of the corresponding species **I** (–6.4 kcal/mol) is endergonic by 12.7 kcal/mol. However, the oxidative addition transition state $\mathbf{TS_{IJ}}$ (6.8 kcal/mol) lies 2.2 kcal/mol lower in energy than the tetravalent transition state $\mathbf{TS_{EF}}$ (9.0 kcal/mol; see Figure 2). Again here, the DMSO ligand assists the formation of the Pd–H bond by catching the Ph_3Si^+ ion. In the resulting Pd hydride **J**, the tetravalent neutral part is clearly separated from the $[Me_2SOSiPh_3]^+$ moiety. Its removal to give **K** (-17.4 kcal/mol) is exergonic by 5.8 kcal/mol. Reductive elimination takes place through $\mathbf{TS_{KL}}$ (–12.9 kcal/mol), with a low barrier of 4.5 kcal/mol. It yields the neutral species **L** (–25.3 kcal/mol), from which dissociation and regeneration of **B** is a highly favourable process (–58.3 kcal/mol). Thus, there is a kinetic preference for the pathway involving two DMSO molecules (blue pathway), however, both energy profiles with one or two DMSO are viable and exchanges between species by association/dissociation (e.g. **E**/**I**) are perfectly conceivable.

Conclusions

In summary, a palladium-catalysed three-component *syn*-1,2-hydroarylation of internal-alkynes is described. The reaction uses readily accessible coupling partners yne-acetates, aryl diazonium salts, and silanes. The method offers a straightforward entry to unusual trisubstituted allyl acetates. The scope is broad, showing excellent functional-group tolerance. The transformation is fully regioselective as well as stereoselective. Moreover, the biologically relevant motifs (BRM) bearing yne-acetates are also used for the late-stage s*yn*-1,2-hydroarylation process. The reaction is even successful on a gram scale. The trisubstituted allyl acetates are further used for the construction of functionalized indene and vinyl ketone derivatives. The DFT studies rationalize the role of the acetate group in the regioselective aryl-palladation of unsymmetrical yne-acetates and reveal the role of DMSO solvent in assisting the Si–H bond cleavage. The current finding paves the way for the discovery of other difunctionalization strategies of unsymmetrical alkynes.

Conflicts of interest

There are no conflicts to declare.

Data availability

Details on experimental procedures, mechanistic experiments, characterization data of all the trisubstituted allyl acetates and X-ray data of **25**. The details are available in the ESI of the manuscript.

Author contributions

S. D. and A. K. S. conceived and designed the project. M. S., A. M. and, A. S. performed and analysed the experimental data. S. D. wrote the manuscript with input from all authors under the supervision of A. K. S. The DFT calculations were performed by V.G.

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18 See the Supporting Information (SI) for details.

Data Availability Statement

Details on experimental procedures, mechanistic experiments, characterization data of all the trisubstituted allyl acetates compounds; X-ray data of **25**: CCDC 2170362. For ESI and crystallographic data in CIF or other electronic format are available in DOI: 10.1039/x0xx00000x.