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Geometry-Constrained Iminopyridyl Palladium-Catalyzed Hydroarylation of Alkynes to Prepare Tri-substituted Alkenes Using Alcohol as Reductant

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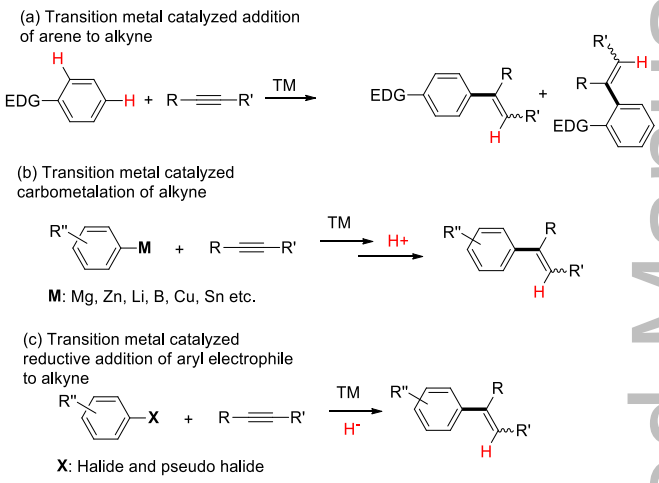
Abstract. We developed an efficient and straightforward method to prepare tri-substituted alkenes through palladium-catalyzed hydroarylation of alkynes with aryl bromides. Diarylacetylenes and alkyl(aryl)acetylenes could be well hydroarylated with various aryl bromides in moderate to excellent yields. Mechanistic studies suggested that alcohol was the reductant to provide hydride through β-H elimination. Gram scale reaction further demonstrated the practicality and efficiency of the newly developed strategy.

Keywords: Hydroarylation; Alkyne; Palladium; Tri-substituted alkene

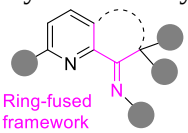
Multi-substituted alkenes are prevalent structures in natural products, drug molecules and organic materials. They are also important synthetic intermediates for preparing fine chemicals. Among different approaches to construct these compounds, transition metal-catalyzed alkyne hydroarylation has gained particular attention as for an attractive route for its potential directly constructing tri-substituted alkene structures, as well as its fundamentally challenging transformation.[1-4] Generally, three strategies have been applied in the hydroarylation of alkynes (**Scheme 1**): (a) Addition of arene to alkyne,[5-12] which usually requires electron-rich arenes and leads to mixtures of *ortho*- and *para*-alkenylarene isomers; (b) Carbometalation of alkyne with arylmetallic reagent,[13] such as aryl-magnesium,[14-18] -zinc,[19-22] -lithium,[23,24] and -boron[25-32] reagents, and final protodemetalation giving rise to the hydroarylation product;[33] (c) Reductive addition of aryl electrophile to alkyne.[34-36] Overall, an aryl anion / proton provides the hydroarylation partner in the first two routes, while the third one employs an aryl cation / hydride, instead. Great efforts have been devoted to the first two routes, while surprisingly, the last one received much less attentions although it looks like much more straightforward.



Scheme 1. Three potential strategies for alkyne hydroarylation.

Among transition metal catalysts for the hydroarylation of alkynes via reductive strategy, palladium played an overwhelmed role in this area. Developed by Cacchi and coworkers, a formate-palladium system has been successfully applied in the hydroarylation of alkynes with aryl electrophiles.[37-42] In this catalytic system, the reactions underwent the syn-addition of the *in situ* formed arylpalladium intermediate to the C-C triple bonds, followed by the attack with $HCOO^-$. Subsequent decarboxylation and reductive elimination of vinylpalladium hydride species give rise to the target hydroarylation product.[35,42] However, only aryl iodides could serve as the electrophiles in the above mentioned methods, which might arise to the relative sluggish oxidative condition step to alkyne-ligated Pd(0) species. When aryl bromide was

employed, the reduction adduct of alkyne has been observed as the major products.[43] Recently, arenediazonium salts have been successfully applied in Pd-catalyzed hydroarylation of alkynes with silane as the reductant.[44] Zhu and coworkers reported a Pd/PCy_3-catalyzed hydroarylation of ynol ethers with aryl iodides using alcohol as the reductant.[45] Cazin and coworkers developed a cooperative Pd/Cu-catalyzed system to construct tri-substituted alkenes from alkynes and aryl bromides in the presence of B_2pin_2.[46] To provide a more practical and accessible protocol to construct multi-substituted alkene motif, it thus remains of significant importance in developing novel and efficient palladium catalytic system for the hydroarylation of alkynes.

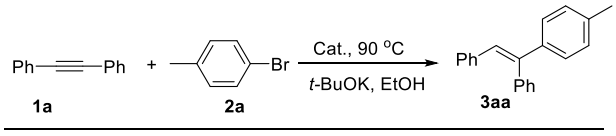


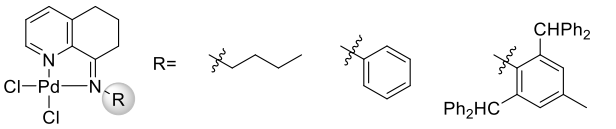
Scheme 2. Geometry-constrained iminopyridyl compounds.

In palladium catalysis, it is no doubt that phosphorus compounds are the most common ligands, while, nitrogen ligands are ranked as the second group and never lost their attention.[47-50] Bidentate nitrogen ligands, such as bi-pyridine, phenanthroline, bi-imine, bis-oxazoline, pyridine–oxazoline and pyridine-benzoxazole *etc*, have been widely employed in many Pd-catalyzed transformations for their relatively thermos stability and exhibited interesting selectivity and activity, including the excellent work lately examplified by Sigman,[51-56] Liu,[57-59] Hong[60] *et al*. Recently, we have developed a series of geometry-constrained iminopyridyl compounds (Scheme 2).[61-63] Their corresponding palladium complexes showed satisfied catalytic efficiency for both Suzuki coupling and Heck coupling involving aryl bromides and aryl chlorides.[64-66] Compared to these commonly used bidentate nitrogen ligands, our developed ligand involved a regulable ring-fused framework being able to establish a strained environment for better stability toward the palladium center. Furthermore, the Csp3 substituent on the imine site could provide a steric effect, which was not easily realized with the related bidentate nitrogen ligands. These properties further inspired us that the geometry-constrained iminopyridyl-Pd complex might be suitable to tolerate the less active aryl electrophiles towards the hydroarylation of alkyne. In this hence, we herein reported our research in Pd-catalyzed hydroarylation of alkynes with aryl bromides to tri-substituted alkenes using alcohol as the reductant. This newly developed protocol provides a simple strategy for constructing tri-substituted alkenes with *i*-PrOH as the reductant. The bidentate geometry-constrained iminopyridyl ligand played an important role in stabilizing the palladium center for promoting this transformation.

Initially, using the reaction between 1,2-diphenylacetylene (**1a**) and 4-bromo-toluene (**2a**) with *t*-BuOK as base in ethanol as the model reaction, the catalytic effects of different iminopyridyl palladium complexes were investigated (Table 1). To our delight, the desired hydroarylation of 1,2-diphenylacetylene was observed in this catalytic system. By changing the imino sites of the bidentate ligands, we found that **Pd-2** with the bulky steric-hindered groups displayed best efficiency comparing to the one with *n*-butyl or phenyl group, which showed consistent with our previous reports that increasing the steric environment favored for stabilizing the palladium center.[66] The preliminary promising results inspired us to further optimize the reactions using **Pd-2** as the catalyst.

Table 1. Initial test of geometry-constrained iminopyridyl palladium reactivity in alkyne hydroarylation. [a]

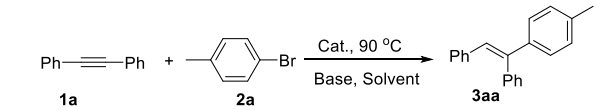




Cat.	Pd-0	Pd-1	Pd-2
Yield.%[b]	27	28	50

[a] Reaction conditions: **cat**. (2 mol%), **1a** (1.0 mmol), **2a** (1.3 mmol), *t*-BuOK (1.5 mmol), EtOH (6 mL), 90 °C, 12 h. [b] GC yields with naphthalene as the internal standard.

Table 2. Optimizing the reaction conditions for Pd-catalyzed hydroarylation of 1,2-diphenylacetylene. [a]



Entry	Base	Cat.	Solvent	Yield.%[b]
1	*t*-BuOK	**Pd-2**	EtOH	55
2			n-BuOH	46
3			*i*-PrOH	77
4			cyclohexanol	63
5	NaOH	**Pd-2**	*i*-PrOH	67
6	Na_2CO_3			1
7	Cs_2CO_3			45
8	K_2CO_3			43
9	*t*-BuONa			66
10	K_3PO_4			52
11	KOH			86
12[d]	KOH	**Pd-2**	*i*-PrOH	86(80[c])
13[d]		$Pd(OAc)_2$		61
14[d]		$PdCl_2(CH_3CN)_2$		51
15[d]		$PdCl_2(PPh_3)_2$		11

[a] Reaction conditions: **cat**. (2 mol%), **1a** (0.3 mmol), **2a** (0.39 mmol), base (0.45 mmol), solvent (2 mL), 90 °C, 12 h. [b] GC yields with naphthalene as the internal standard. [c] Isolated yield. [d] **1a** (1 mmol), **2a** (1.3 mmol), KOH (1.5 mmol), **cat**. (2 mol%), solvent (6 mL), 90 °C, 12 h.

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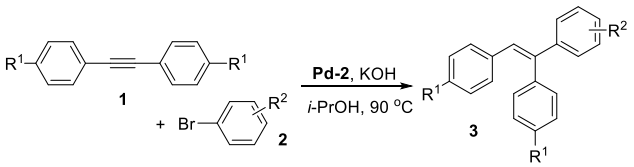
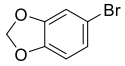
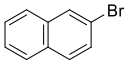
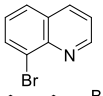
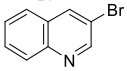
Alcohol has been widely employed as a mild reductant in many transformations.[45, 67-70] We first tested different alcohols, including EtOH, *n*-BuOH, *i*-PrOH and cyclohexanol (CyOH) (Table 2). Obviously, the secondary alcohols gave better results than the primary ones, and the reaction yield was significantly improved from 55% to 77% when *i*-PrOH was used instead of EtOH (Table 2, entries 1 and 3). Base also played important role in this transformation and was then subsequently evaluated. Strong bases, *t*-BuOK, *t*-BuONa, NaOH and KOH, could efficiently promote the conversion, while KOH provided an obviously advantage and was thus chosen in the final protocol (Table 2, entry 11). To further confirm the superiority that the geometry-constrained iminopyridyl ligand generated towards the palladium center, ligand-free $Pd(OAc)_2$ and $PdCl_2(CH_3CN)_2$ catalyzed hydroarylation of **1a** under the identical reaction conditions were performed and moderate yields and poor selectivity were obtained (Table 2, entries 14 and 15). Using $PdCl_2(PPh_3)_2$ instead, only 11% of the desired product was observed (Table 2, entry 16).

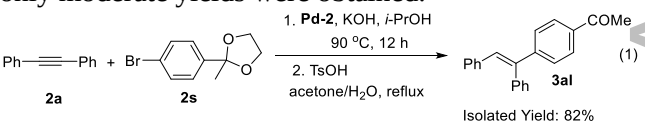
Table 3. Pd-catalyzed hydroarylation of diarylacetylene with different aryl bromides.



1	2		3 Yield(%)[b]	*E/Z* [c]
R^1= H **1a**	R^2= *p*-Me—	**2a**	**3aa** 80	99:1
	H	**2b**	**3ab** 72	-
	o-Me—	**2c**	**3ac** 91	99:1
	m-Me—	**2d**	**3ad** 79	99:1
	2,6-$(Me)_2$—	**2e**	**3ae** 79	96:4
	p-MeO—	**2f**	**3af** 89	99:1
	o-MeO—	**2g**	**3ag** 81	99:1
	p-NH_2—	**2h**	**3ah** 93	80:20
	p-Cl—	**2i**	**3ai** 74	98:2
	p-F—	**2j**	**3aj** 76	> 99:1
	p-CF_3—	**2k**	**3ak** 59	98:2
	p-CH_3CO—	**2l**	**3al** 24	99:1
		**2m**	**3am** 65	97:3
		**2n**	**3an** 80	96:4
		**2o**	**3ao** 30	>99:1
		**2p**	**3ap** 33	>99:1
		**2q**	**3aq** 48	>99:1
		**2r**	**3ar** 37	96:4
R^1 = OMe	R^2= *p*-MeO—	**2f**	**3bf** 82	-
1b	*p*-CF_3—	**2k**	**3bk** 58	5:95
R^1 = CF_3	R^2= *p*-MeO—	**2f**	**3cf** 86	<1:99
1c	*p*-CF_3—	**2k**	**3ck** 65[d]	-

[a] Reaction conditions: **Pd-2** (2 mol%), **1a** (1.0 mmol), **2** (1.3 mmol), KOH (1.5 mmol), *i*-PrOH (6 mL), 90 °C, 12 h. [b] Isolated yields. [c] *E/Z* ratios were determined by GC analysis or ^{1}H NMR spectra. [d] The isolated yield was obtained from 0.3 mmol scale reaction.

With the optimal conditions in hand, aryl bromides with different substituents were applied to react with symmetrical diarylacetylenes in this hydroarylation reaction (Table 3). The hydroarylation products of diphenylacetylene with various aryl bromides were isolated in moderate to excellent yields, especially the steric ones with *ortho* substituents (Table 2, **3ac**, **3ae** and **3ag**), which were rather problematic in the reported with the corresponding aryl iodides.[44] The reaction could well tolerate a variety of electron-donating and electron-withdrawing substituents, including amino (**3ah**) and halides (**3ai** and **3aj**). When *p*-bromoacetophenone (**2l**) was used as the substrate, only 24% of the desired product **3al** was isolated. It was postulated that the carbonyl group was reduced to the hydroxyl group under strong basic environment and thus elimination to generate a vinyl group. However, when the carbonyl group was converted to the protected form (**2s**) (eqn 1), the reaction proceeded smoothly, and subsequently performing de-protection during work-up allowed us to obtain the corresponding hydroarylation product **3al** in 82% isolated yield. It is noteworthy that heteroaryl bromides can be able to form the desired products, although the isolated yields were lower than others. We noted that the competitive reductive de-bromination side reactions were dominant for these electron-deficient aryl and heteroaryl bromides, which was frequently observed under the ROH/base conditions.[71,72] Besides, high stereoselectivities for the tested substrates were attained and most *E/Z* ratios are up to or higher than 99:1 except the one with –NH_2 group (**2h**). Methoxy and trifluoromethyl substituted diarylacetylenes (**1b** and **1c**) were also examined under the standard conditions. Similar to diphenylacetylene, the hydroarylation products were achieved in 82% and 86% isolated yields, respectively (**3bf** and **3cf**) when using electron-rich aryl bromides (**2f**). When electron-deficient aryl bromide was employed, for example, *para*-trifluoromethylphenyl bromide (**2k**), no matter hydroarylation with **1b** or **1c**, only moderate yields were obtained.



According to the previous hydroarylation of aryl iodides and related palladium-catalyzed additions of "arylpalladium halides" to alkynes, a lack of regioselectivity was observed when applying the approach to unsymmetrical diarylacetylene. Under our optimized conditions, we also carefully studied the hydroarylation of unsymmetrical diarylacetylenes (Scheme 3). The role of electronic effects from

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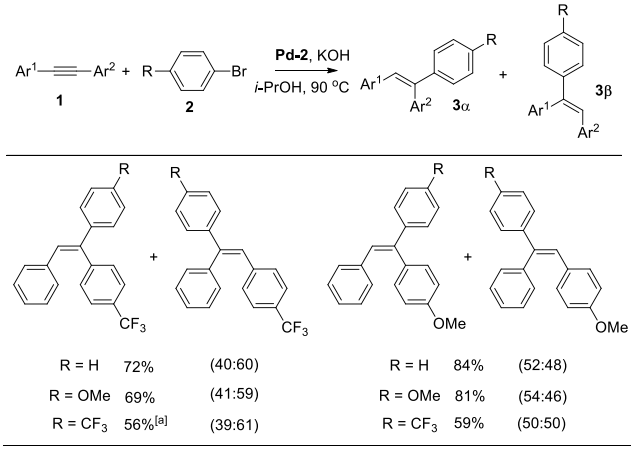
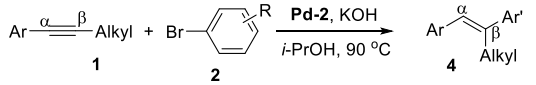
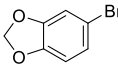
alkynes and aryl bromides on the regioselectivity of this hydroarylation process was explored. To our disappointment, the results obtained were almost same as those in the previous reports, and suggested that the electronic effects either from the alkyne or from the aryl bromides, could not obviously influence the ratio of the regioisomeric products.[35]



Scheme 3. Pd-catalyzed hydroarylations of unsymmetrical diarylacetylene with different aryl bromides (The regioisomers were not assigned)

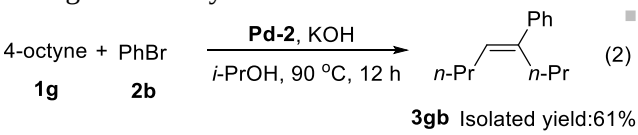
Table 4. Pd-catalyzed hydroarylation of aryl(alkyl) acetylenes with different aryl bromides. [a]



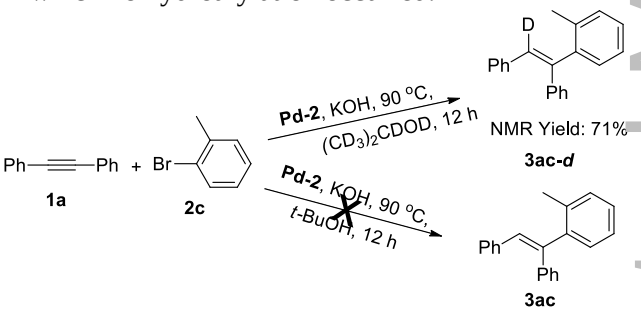
1	2			4β+4α Yield(%)[b]	4β/4α[c]
Ph—≡— **1d**	R=	*p*-Me—	**2a**	**4da** 91	95:5
		H	**2b**	**4db** 75	80:20
		o-Me—	**2c**	**4dc** 82	80:20
		m-Me—	**2d**	**4dd** 97	88:12
		2,6-$(Me)_2$—	**2e**	**4de** 84	77:23
		p-NH_2—	**2h**	**4dh** 74	92:8
		p-Cl—	**2i**	**4di** 89	94:6
		p-CF_3—	**2k**	**4dk** 59	96:4
			**2m**	**4dm** 73	94:6
nC_8H_{17}—≡— **1e**	R =	H	**2a**	**4ea** 81	88:12
		p-MeO—	**2f**	**4ef** 85	88:12
		p-CF_3—	**2k**	**4ek** 68	88:12
MeO— —≡—*t*-Bu **1f**	R =	H	**2a**	**4fa** 78[d]	50:50
		p-MeO—	**2f**	**4ff** 86	37:63
		p-CF_3—	**2k**	**4fk** 67[d]	44:56

[a] Reaction conditions: **Pd-2** (2 mol%), **1** (1.0 mmol), **2** (1.3 mmol), KOH (1.5 mmol), *i*-PrOH (6 mL), 90 °C, 12 h. [b] Isolated yields. Only trace amount of anti-addition product was observed from GC-MS analysis. [c] *α/β* products ratios were determined by GC and ^{1}H NMR analysis, [d] NMR yield was obtained with 1,2-dibromoethane as the internal standard.

The previous Pd-catalyzed hydroarylation of unsymmetrical di-substituted alkynes also demonstrated that the regioselectivity was greatly controlled by the steric hindrance. Regarding to this, we then applied 1-phenyl-1-butyne in this chemistry (Table 4). For the tested aryl bromides, the hydroarylation products **4** could be produced in moderate to excellent yields. The strategy is indeed more efficient for electron-rich aryl bromides. For the regioselectivity, as we expected, the addition of aryl group from Ar-Pd-X species to the carbon-carbon triple bonds was favorable for the less steric sides, finally delivering the β-arylated products in 82-96% regioselectivity. Increasing the steric hindrance of aryl bromides slightly decreased the regioselectivities (**4dc** and **4de**). Extending the alkyl chain to 1-phenyl-1-decyne (**1e**), to our delight, the reactions still proceeded well with identical regiochemical outcomes. When the alkyl group is *t*-Bu (**1f**), good yields were obtained while with obvious decreases in the regioselectivity.

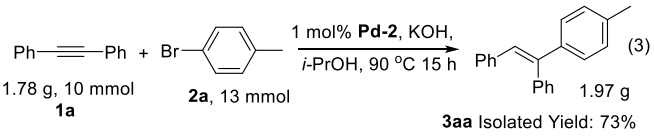


In addition, the developed palladium system was also tested with a dialkylacetylene. When using 4-octyne to react with **2b**, the hydroarylated product was isolated in 61% yield (eqn 2). Noteworthy, a small amount (<5%) of double alkyne insertion side product was also observed.[73] Moreover, phenylacetylene was also examined to react with **2b**, in which no hydroarylation occurred.



Scheme 4. Deuterium-Labelling Experiments

To gain some insights into the mechanism for this Pd-catalyzed hydroarylation of alkynes, the reactions between **1a** and **2c** were carried out under the standard conditions in $(CD_3)_2CDOD$ (Scheme 4). The deuterated hydroarylation product **3ac**-*d* was obtained in 71% NMR yield. In contrast, when the reaction was performed in *t*-BuOH instead, no desired hydroarylation product was observed. These results indicated that *i*-PrOH played a reductant role as a hydride donor through β-H elimination process after the *syn*-addition of arylpalladium intermediate to the C-C triple bonds.



Finally, to further demonstrate the practicality and efficiency of the developed system, we performed a scale-up reaction (eqn 3). 1 mol% amount of **Pd-2** was used and the reaction time was elongated to 15 h. 1.97 g of hydroarylated product **3aa** (73%) was successfully isolated from 10 mmol of **1a**.

In summary, we developed an efficient Pd-catalyzed hydroarylation of alkynes with aryl bromides using *i*-PrOH as the reductant. The geometry-constrained iminopyridyl ligand played an important role in stabilizing the Pd center. Different internal alkynes, involving symmetrical or unsymmetrical diarylacetylenes and alkyl(aryl)acetylenes, could be well tolerated to react with various aryl bromides in moderate to excellent yields. The regioselectivity for unsymmetrical alkynes was demonstrated to be controlled by steric hindrance. Further investigations for improving this chemistry via modifying ligands are ongoing in our group.

Experimental Section

To a Young tube, was added 1,2-diphenylacetylene (178 mg, 1 mmol), 4-bromo-toluene (222 mg, 1.3 mmol), **Pd-2** (14.9 mg, 2 mol%), KOH (84 mg, 1.5 mmol) and isopropanol (6 mL). The mixture was stirred at 90 ºC for 12 hours. Then, solvent was removed in vacuo. 216 mg of **3aa** (80%) was isolated by column chromatography on silica gel (petroleum ether as the eluent).

Acknowledgements

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