Pd(II) or Pt(II)-Catalyzed Hydroarylation of Alkynes by Arenes

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Abstract: Efficient inter- and intramolecular hydroarylations of C–C triple bonds by simple electron-rich arenes have been realized in the presence of Pd(II) or Pt(II) catalysts and an acid such as trifluoroacetic acid and acetic acid. The reaction of heteroarenes such as pyrroles and indoles occurs under very mild conditions (e.g. at room temperature in neutral solvents such as CH₂Cl₂). The reaction provides a very good strategy for functionalization of arenes as well as heteroarenes, affording arylalkenes. The intramolecular reaction offers a concise and straightforward route to biologically interesting heterocycles such as coumarins, quinolinones and thiocoumarins. The possible mechanism involving electrophilic metalation of aromatic C–H bonds by a cationic metallic species such as [Pd(O₂CCF₃)]⁺ and the formation of a vinyl cationic species is discussed.

1. Introduction

Catalytic addition reaction is regarded as one of most atom economical reactions in synthesis.¹ Catalytic activation of aromatic C–H bonds leading to useful addition or coupling reactions with new C–C bond formation is of considerable interest for the chemical and pharmaceutical industries, and remains a challenge to chemists,² because it would provide simple and economical methods for producing aryl-substituted compounds directly from simple arenes and no pre-functionalization like halogenation is involved.

The study of the reactivity of aryl C–H bonds in the presence of transition metal compounds began around the 1960s despite the quite early discovery of Friedel–Crafts alkylation and acylation reactions with Lewis acid catalysts. In 1967, we reported Pd(II)-mediated coupling reaction of arenes with olefins in refluxing AcOH.³ The reaction involves the electrophilic substitution of aromatic C–H bonds by a Pd(II) species (Scheme 1),^{3c} and this may be one of the earliest examples of aromatic C–H bond activation by transition metal compounds. Although there are many examples of stoichiometric reaction of aromatic C–H bonds with transition metal compounds,¹ few catalytic systems are available for synthetic purposes. The direct use of aromatic compounds in synthesis is generally restricted to the activation of groups other than the C–H bonds (e. g., C–Br, C–Cl bonds).⁴ However, the manufacture of aryl halides is not an environmentally friendly process, and thus the future of bulk synthesis of aryl derivatives may lie in the direct activation of C–H bonds. Activation of aromatic C–H bonds by *ortho*-chelating assisted oxidative addition to low-valent transition metal compounds, leading to addition to C–C multiple bonds, has been recognized as another promising route.^{2b}

In our attempt to extend the coupling reaction of arenes with alkenes to alkynes, it was found that the reaction of arenes with ethyl propiolate gave addition products instead of coupling products in TFA (trifluoroacetic acid) (Scheme 2).⁵ This addition reaction has been extended to various alkynes and various arenes and also to intramolecular reactions for

preparation of heterocycles such as coumarins, quinolinones, and thiocoumarins.

Scheme 1. The reaction aryl–Pd complexes

Scheme 2. Pd-Catalyzed reaction of 1,4-dimethoxybenzene with ethyl propiolate in TFA

2. Intermolecular Hydroarylation of Alkynes by Arenes

2.1 The Reaction of Benzenoid Arenes

In the course of our studies of oxidative coupling of arenes with olefins, the possibility to extend the coupling reaction to terminal alkynes was investigated by the reaction of *p*-dimethoxybenzene with ethyl propiolate in the presence of an oxidant and a catalytic amount of Pd(OAc)₂ in TFA. Instead of the expected coupling product, ethyl 3-(2,5-dimethoxyphenyl) propiolate, the reaction gave ethyl (2Z)-3-(2,5-dimethoxyphenyl)-2-propenoate (**1**) (*J*_{H–H} = 12.3

Hz) as the main product, together with small amounts of the corresponding *E*-isomer (**2**) ($J_{\text{H-H}}=16.2$ Hz) and an arene/alkyne 2/1 adduct, ethyl 3,3-bis(2,5-dimethoxyphenyl) propionate (**3**).^{5b} Apparently, the compounds **1** and **2** (1/1 adducts) resulted from mono-addition of the arene to the alkyne, and **3** resulted from subsequent addition of another molecular arene to compound **2** (or **1**). This has been confirmed by the addition reaction of arenes to alkenes. The addition reaction proceeds smoothly regardless of whether oxidants such as *t*-BuOOH and benzoquinone were employed or not. However, the reaction did not occur without either TFA or Pd(OAc)₂.

Table 1. Effect of Pd catalysts on the reaction of 1,4-dimethoxybenzene with ethyl propiolate in TFA^a

Entry	Catalyst (mol%)	Time (h)	Yield (%) ^b		
			1	2	3
1	Pd(OAc) ₂ , (0.1)	180	68	4	7
2	Pd(OAc) ₂ , (1)	45	72 (56)	6	5
3	Pd(OAc) ₂ , (5)	27	26	15	2
4	Pd(OAc) ₂ , (5)	70	< 3	5	(31)
5	Pd(OAc) ₂ , (1) ^c	48	58	3	3
6	Pd(OAc) ₂ , (1) + P[C ₆ H ₃ (OMe) ₂] ₃ , (1)	45	70	5	6
7	Pd(OAc) ₂ , (1) + PPh ₄ , (4)	45	41	trace	
8	Pd(PPh ₃) ₄ , (2)	48	5	trace	
9	Pd (5%) / Carbon (5)	48	8	trace	
10	Pd(acac) ₂ , (1)	48	68	3	2
11	PdCl ₂ , (1)	48	36	3	< 1
12	Pd(O ₂ CCF ₃) ₂ (PPh ₃) ₂ , (1)	48	69	5	6
13	Pd(O ₂ CCF ₃) ₂ (PPh ₃) ₂ , (1) ^d	48	< 3	trace	
14	PdCl ₂ , (1) + AgO ₃ SCF ₃ , (2) ^e	48	10	trace	
15	no catalyst	60	no reaction		

^a Reaction conditions: *p*-dimethoxybenzene (30 mmol), ethyl propiolate (5 mmol), TFA (4 mL), r. t. ^b GC yield (yields in parenthesis refer to isolated yields) based on the alkyne. ^c 10 mmol of the arene employed. ^d AcOH (4 mL) + TFA (0.5 mL) used as the solvent and CF₃CO₂Na (0.025 mmol) added. ^e CH₂Cl₂ (4 mL) + CF₃SO₃H (0.5 mL) used as a solvent.

Prior to surveying the scope of this addition reaction, the reaction conditions were optimized and the results are listed in Table 1. Pd(II) catalysts such as Pd(OAc)₂, Pd(O₂CCF₃)₂ (PPh₃)₂, and Pd(acac)₂ showed higher catalytic activity than Pd(0) catalysts such as Pd/Carbon and Pd(PPh₃)₄ (see entries 2, 10, 12, 8, 9 in Table 1). The reaction was enhanced greatly by increasing the amount of Pd(OAc)₂ (from 0.1% to 1%, entries 1 and 2 in Table 1). When it was increased to 5%, the 2/1 adduct **3** was obtained as the main product (entry 4 in Table 1). This means whether the reaction gives 1/1 or 2/1 adducts as the main product can be controlled by the concentration of Pd(OAc)₂. Higher concentration of Pd(II) facilitates the overall reaction. The tris(2,6-dimethoxyphenyl) phosphine was added (1 equiv. to Pd, entry 6 in Table 1) to the system in order to improve the addition reaction,^{4,5b} but was found to have very little effect. However, adding more phosphine (4 equiv. to Pd, entry 7 in Table 1) decreased the catalytic activity of the system presumably because of blocking of the coordination sites of Pd(II). The best results were obtained with Pd(OAc)₂/TFA and Pd(O₂CCF₃)₂(PPh₃)₂/TFA systems (entries 2 and 12 in Table 1). Attempts to reduce the amount of TFA used in the reaction or to use

another Pd(II) cationic system such as PdCl₂/CF₃SO₃Ag only resulted in low yields (entries 13 and 14 in Table 1).

The scope and generality of this reaction were explored first using various commercially available arenes and acetylenes (Tables 2 and 3). The addition of the arenes to ethyl propiolate gave *cis*-adducts, ethyl (2*Z*)-3-aryl-2-propenoates ($J_{\text{H-H}} = 11.7 \pm 0.6$ Hz), predominantly in most cases (entries 1–15 in Table 2). The corresponding *trans*-isomers as the minor product were isolated (entry 15 in Table 2) or identified in the mixture of adducts by ¹H NMR ($J_{\text{H-H}} = 15.9$ –16.5 Hz) in some cases (entries 4 and 14 in Table 2). Arene/alkyne 1/2 adducts, (2*E*,4*Z*)-4-(ethoxycarbonyl)-5-aryl-2,4-pentadienoates, as the minor products were observed in the reaction (e.g., entries 1, 6–9 in Table 2), and also arene/alkyne 2/1 adducts, ethyl 3-bisarylpropionates, were found to be the main products in some cases (entries 14 and 16 in Table 2).

The reaction exhibited very good chemoselectivity with unprotected OH and Br substituents in arenes, all proving to be compatible (entries 10–13 in Table 2). A coumarin was obtained from the reaction of *p*-*t*-butylphenol with ethyl propiolate (entries 10 and 11 in Table 2), apparently resulting from the first addition of the phenol to the alkyne followed by cyclization via ester exchange (Scheme 3). When the *ortho*-positions of a phenol were occupied by two methyl groups, the reactions gave a 1/1 adduct (entry 12 in Table 2). The reaction of mesityl bromide with ethyl propiolate afforded 1/1 adduct, ethyl (2*Z*)-3-(2,4,6-trimethyl-3-bromophenyl)-2-propenoate (entry 13 in Table 2). No corresponding debrominated adduct or debrominated arene was isolated or observed by ¹H NMR from the reaction mixture, suggesting that the catalytic cycle may not involve the Pd(0) species.

Scheme 3. The formation of coumarins from the reaction of phenol with alkynoates or alkynoic acids

A diene, ethyl (2*Z*)-3-{2,4,6-trimethyl-3-[(*Z*)-2-ethoxycarbonyl-ethenyl]phenyl}propenoate, was obtained from the reaction of ethyl (2*Z*)-3-mesitylpropenoate with 1.5 equiv. of ethyl propiolate (entry 5 in Table 2) or directly from the reaction of mesitylene with ethyl propiolate (entry 8 in Table 2). This provides a new and simple way to aryldienes from simple arenes and alkynes, and similar compounds would be prepared from diiodoarenes by the Heck reaction.⁶

The internal alkynes that bear functional groups such as CHO, COMe and CO₂H proved to be compatible to the reaction (see Table 3). The reaction affords thermodynamically unfavorable *cis*-arylalkenes predominantly in most cases (entries 3–17, 19–26 in Table 3), giving good yields of adducts especially in the PtCl₂/2AgOAc system.

Inspired by the higher selectivity of the PtCl₂/2AgOAc sys-

Table 2. Pd and Pt-catalyzed addition of arenes to ethyl propiolate^a

Entry	Ar-H	Time (h)	Product and yield ^b
1		2	85%
2 ^c		24	95% ^d 6% 0% ^d
3		48	(45%)
4		24	(45%) (Z/E = 2)
5 ^f		24	62% 49% trace 8% (63%) (5%) (11%) (13%) (44%) (10%)
6 ^e		24	45% 12%
7 ^f		24	45% 12%
8 ^g		29	45% 12%
9		20	45% 12%
10		40	51%
11 ^e		40	(71%)
12		48	57%
13		48	(46%)
14		12	10% (Z/E = 4) 38%
15 ^e		45	(78%) (Z/E = 8) (7%)
16		2	30%

^a General conditions: arene (10 mmol), ethyl propiolate (5 mmol), Pd(OAc)₂ (0.05 mmol), TFA (4 mL) and CH₂Cl₂ (1 mL) at r.t. ^b Isolated yield (GC yield in parenthesis) based on the acetylene. ^c PtCl₂ (0.25 mmol) + AgOAc (0.5 mmol) used as catalyst. ^d Yield determined by ¹H NMR spectrum. ^e Arene (30 mmol) added. ^f Arene (3.4 mmol) and alkyne (5 mmol) used, and the yield based on the arene. ^g Arene (3.4 mmol) and alkyne (10 mmol) used, and the yield based on the arene.

Table 3. Transition metal-catalyzed addition of arenes to internal alkynes

$\text{Ar-H} + \text{R}^1\text{—}\equiv\text{R}^2 \xrightarrow[\text{TFA / CH}_2\text{Cl}_2, \text{ r.t.}]{\text{Pd(II) or Pt(II)}} \text{Ar}-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-$				
Entry	Ar-H	Alkyne	Catalyst / Time (h)	Product and Yield ^{a,b}
1		Ph—≡—Ph	Pd / 42 h	(36%)
2		Ph—≡—Ph	Pt / 42 h	(56%)
3		Ph—≡—CO ₂ Et	Pd / 48 h	11% 42%
4		Ph—≡—CO ₂ H	Pd / 48 h	 R = Me (62%) ^c
5		Me—≡—CO ₂ H	Pd / 48 h	
6		Me—≡—CO ₂ H	Pd / 48 h	
7		Ph—≡—CHO	Pd / 24 h	(8%)
8		Ph—≡—CHO	Pt / 48 h	60%
9		Ph—≡—Ph	Pd / 24 h	(58%)
10		Ph—≡—Ph	Pt / 24 h	63% (70%)
11		Ph—≡—Me	Pt / 24 h	50% (61%)
12		Ph—≡—COMe	Pd / 24 h	15%
13		Ph—≡—COMe	Pt / 72 h	(72%)
14		Me—≡—CO ₂ Et	Pd / 46 h	78%
15		Ph—≡—CO ₂ H	Pd / 48 h	(40%)
16		Ph—≡—CO ₂ H	Pt / 48 h	71%
17		EtO ₂ C—≡—CO ₂ Et	Pd / 48 h	60%
18		n-C ₃ H ₇ —≡—C ₃ H ₇ -n	Pd / 40 h	60% (Z/E = 1)
19		Ph—≡—CO ₂ Et	Pd / 5 h	71% 5%
20		Ph—≡—CO ₂ Et	Pd / 12 h	(98%)
21		Ph—≡—CO ₂ Et	Pt / 24 h	95% (98%)
22		Ph—≡—CO ₂ Et	PtCl ₂ / 24 h	(78%)
23 - 26		Ph—≡—CO ₂ Et	Rh > Ir > Ni, Ru / 140 h	(46 ~ 22%)

^a General conditions: arene (10 mmol), alkyne (5 mmol), TFA (4 mL), CH₂Cl₂ (1 mL), r.t. Pd, Pt, Rh, Ir, Ni, and Ru refer to Pd(OAc)₂, PtCl₂/2AgOAc, Rh₂(OAc)₄, IrCl₃/3AgOAc, Ni(OAc)₂, and RuCl₃/3AgOAc, respectively. ^b Isolated yield (GC yield in parenthesis) based on the alkyne. ^c Trifluoroacetic anhydride (5 mmol) was added.

tem(entries 1 and 2 of Table 2), several other transition metals such as Rh(III), Ir(III), Ru(III) and Ni(II) were tested in the reaction of pentamethylbenzene with ethyl phenylpropiolate in order to screen the catalytic systems by comparison with the Pd(II) and Pt(II) systems(entries 19–26 in Table 3). Ethyl (2Z)-3-(pentamethylphenyl)cinnamate and the corresponding hydrolyzed (2Z)-3-(Pentamethylphenyl)cinnamic acid were isolated upon usual work-up (entry 19 in Table 3). The results summarized in Table 3 indicate that Pd(OAc)₂ and PtCl₂/AgOAc as catalysts are superior to other transition metal systems(entries 19–26 in Table 3). Pd(OAc)₂ has been found to be the most active catalyst. The reaction with PtCl₂/AgOAc was slower(lower conversion of alkynes) than that with Pd(OAc)₂(entries 20 and 21 in Table 3), but gave higher yields at the same conversion level(entries 7–16 in Table 3). The catalytic activity of the transition metals decreases in the order: Pd(II) > Pt(II) > Rh(III) > Ir(III) > Ni(II), Ru(III), in accordance with the activity difference in electrophilic metalation of aromatic C–H bonds by these metal ions.^{2a}

The regio- and stereochemistry of all adducts(in Tables 2 and 3) was unambiguously established on the basis of chemical shifts and coupling constants in the ¹H NMR spectra, and differential NOE experiments. The structures of 1-(pentamethylphenyl)-1-phenyl-2-phenylethylene and 1-(pentamethylphenyl)-1-phenylpropene were further confirmed to be(Z)-configuration by the X-ray crystal structure.

A close examination of all the results listed in Tables 2 and 3 reveals that the nature of the substituents in alkyne has a considerable effect on the regiochemistry of the reaction products and also on the reactivity of alkynes. The alkynes conjugated to an electron-withdrawing group such as CHO, CO₂H, COMe or CO₂Et act as good acceptors of aryl nucleophiles, providing β-aryl substituted alkenes exclusively and being *cis*-alkenes predominantly in most cases. The regiochemistry of this reaction is dominated by electronic effects of the substituents in alkyne rather than steric effects, similarly to the effect of the substituents in arenes. The reaction with internal alkynes is slower than that with terminal alkynes. For instance, the reactivity of acetylenes RC≡CCO₂Et decreases with the substituent R in the order:(R=) H > Ph > Me.

A possible side reaction is the addition of trifluoroacetic acid to the C–C triple bonds of alkynes followed by hydrolysis to give ketones.⁷ This has been also observed in a few cases under our reaction conditions, especially in the absence of the arene or in the presence of inactive arenes, while in the absence of the Pd catalyst no such side reaction occurs.

2.2 The Reaction of Heteroarenes

The reaction of heteroarenes with alkynoates occurs under very mild conditions.^{5d} Initially, the effects of catalysts and solvents on the reaction of pyrrole with ethyl phenylpropiolate were investigated and the results are shown in Table 4. With Ni(OAc)₂ or Cu(OAc)₂ as the catalyst or without the transition metal catalysts(entries 1–3 in Table 4), no reaction product was detected by the GC method. Ethyl (Z)-3-(2-pyrrolyl)phenylpropenoate was obtained in 76% yield as the only isolated product in the presence of 5 mol% Pd(OAc)₂ in AcOH in 2 h(entry 5 in Table 4). The configuration of the adduct was unambiguously established by ¹H nuclear Overhauser effect(NOE) experiments. The catalyst of PtCl₂ was

much less active than Pd(OAc)₂, giving a low yield(entry 4 in Table 4). The rate of reaction was apparently reduced if less Pd(OAc)₂(1 mol%) was used(entry 6 in Table 4). Furthermore, it was found that this reaction could proceed without any solvent or in various solvents such as dichloromethane as well as water(entries 8–12 in Table 4). However, acetic acid is the best one among all solvents tested in the reaction.

Table 4. Effects of catalysts and solvents on the addition of pyrrole to ethyl phenylpropiolate

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) ^a
1	None	AcOH	48	None
2	Cu(OAc) ₂ (5)	AcOH	48	None
3	Ni(OAc) ₂ (5)	AcOH	48	None
4	PtCl ₂ (5)	AcOH	24	8
5	Pd(OAc) ₂ (5)	AcOH	2	86 (76)
6	Pd(OAc) ₂ (1)	AcOH	8	91
7	Pd(OAc) ₂ (5)	AcOH	2	60 ^b
8	Pd(OAc) ₂ (5)	None	24	91
9	Pd(OAc) ₂ (5)	CH ₂ Cl ₂	48	40
10	Pd(OAc) ₂ (5)	Ether	96	42
11	Pd(OAc) ₂ (5)	AcEt	96	24
12	Pd(OAc) ₂ (5)	H ₂ O ^c	40	78

^a Isolated yield of adduct from the reaction of pyrrole (3 mmol) with alkynoate (1 mmol) in the presence of Pd(OAc)₂ (5 mol %) in a solvent (1 mL) at r.t. ^b Pyrrole (1 mmol), ethyl phenylpropiolate (3 mmol). ^c H₂O (0.5 mL).

Heteroaromatic compounds such as pyrroles, furans and indoles readily undergo addition reaction with alkynoates at room temperature in the presence of a catalytic amount of Pd(OAc)₂ in acetic acid or CH₂Cl₂, affording *cis*-heteroarylalkenes in most cases(Table 5). This reaction provides a synthetic protocol to heteroarylalkenes, especially *cis*-alkenes, from simple heteroarenes. Various heteroarenes and alkynoates were tested in the present reaction at room temperature and the results are shown in Table 5. The reaction either gave mono-addition products, 3-arylpropenoates and in *Z*-configuration in most cases, or diaddition products, 3-diarylpropanoates, depending on the substituents(R) of alkynoates and the solvent.

With small R groups such as Me or *n*-C₅H₁₁ in alkynoates, the reaction in AcOH mainly afforded diaddition products(entries 3, 4 and 18 in Table 5), while the reaction gave mono-addition products with a relatively bulky R group like Ph under the same conditions(entries 1, and 10–16 in Table 5). It has been confirmed that the diaddition products were produced by further addition of heteroarenes to the arylalkenes in AcOH. However, even with small R substituents such as Me and H in alkynoates, the reaction can be controlled to stop at the mono-addition step to give arylalkene when CH₂Cl₂ was used as the solvent(entries 2, 6 and 9 in Table 5), although the reactions in CH₂Cl₂ were slow.

For pyrrole, 1-methylpyrrole, 2-methylfuran, and 2,3-dimethylfuran, the substitution of aromatic C–H bonds occurs exclusively at the 2 or 5-position of arenes(e.g. entries

Table 5. Pd-catalyzed hydroarylation of alkynoates by hetero-aromatic compounds

$$\text{Ar-H} + \text{R}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et} \xrightarrow[\text{HOAc or CH}_2\text{Cl}_2, \text{ r.t.}]{\text{Pd(OAc)}_2} \text{Ar}-\text{C}(\text{R})=\text{CH}-\text{CO}_2\text{Et}$$

$$\xrightarrow[\text{HOAc, r.t.}]{\text{Ar-H}} \text{Ar}-\text{C}(\text{R})_2-\text{CH}_2-\text{CO}_2\text{Et}$$

Entry	Ar-H	R	Time (h)	Adduct and Yield (%) ^a
1		Ph	2	 78
2		Me	48	 64 ^b (Z/E = 2)
3		Me	24	 57
4		nC ₅ H ₁₁	24	 40 5
5		H	5	 18 ^b
6		H	20	 52 ^c
7		Ph	24	 83
8		Ph	20	 30
9		H	20	 30 (E/Z = 1.3:1)
10		Ph	6d	 40
11		Ph	48	 72
12		Ph	20	 66
13		Ph	48	 25 ^d
14		Ph	24	 82
15		Ph	48	 69
16		Ph	24	 80
17		Ph	24	 78
18		Me	72	 45

^a Isolated yield from heteroarenes (2 mmol) with alkynoates (1 mmol) in HOAc (1 mL) at r.t. ^b CH₂Cl₂ (1 mL) as the solvent. ^c Ethyl propiolate (3 mmol) and pyrrole (1 mmol) were used, and CH₂Cl₂ (1 mL) was used as solvent. ^d TFA/AcOH (1:2) as the solvent

1, 7, 11 and 12 in Table 5), being characteristic of electrophilic substitution. For indole and 1-methylindole, the reaction occurred at the 3-position predominantly while very small amounts (<3%) of 2-substituted adducts could be detected by ¹H and ¹³C NMR spectra. However, when the 2, 5-positions of pyrrole and the 3-position of indole were occupied by the substituent(s), the reaction could proceed smoothly at the 3-position of pyrrole and the 2-position of indole or (entries 8, 9 and 14 in Table 5) although they are not the most favorable positions for the electrophilic substitution.

3. Intramolecular Reactions for the Synthesis of Coumarins, Quinolinones and a Thiocoumarin

3.1 Synthesis of Coumarins

Initially, we investigated the cyclization of 4'-*tert*-butylphenyl phenylpropiolate to screen the catalytic systems, and the results are given in Table 6.^{5c} Treatment of 4'-*tert*-butylphenyl phenylpropiolate in the presence of 1 mol % Pd(OAc)₂ and trifluoroacetic acid as solvent gave cleanly 4-phenyl-6-*tert*-butylcoumarin as the sole product within 30 min in 90% yield (entry 2 in Table 6). Analysis of the reaction mixture using ¹H NMR, ¹³C NMR spectra and GC revealed no side reaction. Several transition metals such as Pd(II), Pt(II), Rh(II) and Ni(II) compounds were selected as catalysts for this reaction. The results are summarized in Table 6. Pd catalysts were found to be the most active in the reaction (entries 2 and 5 in Table 6). The reaction with Pt(II), Ni(II) or Rh(II) catalysts is slow and does not complete within 24 h (entries 6–8 in Table 6). The catalytic activity of these transition metals decreases in the order Pd(II) > Pt(II) > Ni(II) > Rh(II) (entries 2, 3, and 6–8 in Table 6), in accordance with the activity difference in electrophilic metalation of aromatic C–H bonds by these metal ions.^{2a} The reaction is greatly enhanced by increasing the quantity of Pd(OAc)₂ (entries 2 and 3 in Table 6). Almost no reaction was observed in the absence of either a transition metal catalyst or TFA (entries 1, 9 and 10 in Table 6).

Various aryl alkynoates undergo smoothly the intramolecular hydroarylation reactions in the catalytic system Pd(OAc)₂/TFA. The representative examples in Table 7 illustrate the generality of this reaction.^{5c} In all cases, the cyclization is highly regioselective, affording kinetically favored 6-membered rings.⁸ Analysis of the crude reaction mixture using ¹H NMR, ¹³C NMR spectra and GC separation indicated no other regioisomers were observed. The reaction exhibits high chemoselectivity with Br, CHO, or heterocyclic groups in the aromatic moiety (entries 7, 14 and 15 in Table 7) and with either terminal or internal C–C triple bonds (entries 4 and 3 in Table 7), which all proved to be compatible. Most of the reactions (monitored by ¹H NMR spectrum) are very fast and complete within less than 30 min, especially for those substrates bearing electron-rich aromatic rings (entries 1–8 and 15 in Table 7), showing the characteristics of electrophilic substitutions. Moreover, the reactivity of 2'-, 3'-, and 4'-methylphenyl phenylpropiolates decreases in the order: 3' > 2' > 4' (entries 9, 10 and 11 in Table 7), revealing the same characteristics in electrophilic substitutions. The slow cyclization reaction of 4'-methylphenyl phenylpropiolates can be improved by adding more catalyst (5%) to the reaction mixture (entries 11 and 12 in Table 7).

Table 6. Transition-metal catalyzed cyclization of 4'-*tert*-butylphenyl phenylpropiolate to 4-phenyl-6-*tert*-butylcoumarin

Entry	Catalyst (mol %)	Time (h)	Yield ^a
1	None	24	0
2	Pd(OAc) ₂ , (1 %)	0.5	90
3	Pd(OAc) ₂ , (0.06 %)	60	32
4	Pd(O ₂ CCF ₃) ₂ (PPh ₃) ₂ , (1 %)	0.5	92
5	Pd(PPh ₃) ₄ , (1 %)	1	90
6	PtCl ₂ (2 %) + AgOAc (4 %)	24	46
7	Ni(OAc) ₂ (2 %)	24	41
8	Rh ₂ (OAc) ₄ (2 %)	24	30
9	Pd(OAc) ₂ (1 %) + NaO ₂ CCF ₃ (5%)	24	Trace ^b
10	Pd(O ₂ CCF ₃) ₂ (PPh ₃) ₂ (1 %)	24	Trace ^b

^a GC yield with diethyl phthalate as internal standard.

^b Acetic acid (2 mL) employed as solvent instead of TFA.

3.2 Synthesis of Quinolinones and a Thiocoumarin

The extension of this intramolecular addition to the synthesis of N, S-containing heterocycles, 2(1*H*)-quinolinones and a thiocoumarin, has been made possible with the same catalytic system (entries 1–9 and 10 in Table 8).^{5c} The alkynilides prepared from the corresponding alkynoic acid and anilines are readily cyclized in the presence of 2–3 mol% Pd(OAc)₂ in a mixed solvent containing TFA at room temperature, giving 2(1*H*)-quinolinones in good yields.

On the other hand, the intermolecular reaction of alkynoic acids and anilines did not afford 2(1*H*)-quinolinones, presumably because the amino groups in anilines are converted in TFA to ammonium ions which act as electron-withdrawing groups and consequently deactivate the aromatic rings (Scheme 4). Therefore, the intramolecular process offers a unique and efficient method for the synthesis of 2(1*H*)-quinolinones.

4. Reaction Mechanism

Isotope experiments reveal that D-atoms were incorporated to the vinyl position of adducts either in inter- (Eq. 1 in

Table 7. Synthesis of coumarins via Pd-catalyzed intramolecular hydroarylation reactions from various aryl alkynoates

Entry	Substrate	Time (h)	Product and Yield (%) ^a
1		0.5	70
2		0.5	90
3		0.5	71
4		0.5	60
5		0.5	87
6		0.5	91
7		0.5	85
8		0.5	65
9		5	79
10		0.5	78 4' (4 : 4' = 2 : 1) ^b
11		10	50
12		2	(68) ^c
13		1	75
14 ^c		1	71
15		0.5	75 5' (5 : 5' = 1 : 3) ^b

^a Isolated yields following the general procedure (1% Pd(OAc)₂ and 1 mmol substrate in TFA/CH₂Cl₂ (1.5 mL/0.5 mL at r.t.)) ^b The ratio was determined by ¹H NMR spectra. ^c 5% Pd(OAc)₂, the yield was determined by ¹H NMR.

Table 8. Synthesis of quinoliones and a thiocoumarin via Pd-catalyzed intramolecular hydroarylation

Entry	Substrate	Product and Yield (%) ^a
1		70
2		88
3		85
4		80
5		76
6		75
7		82
8		75 (6 : 6' = 2 : 1) ^b
9		91
10		55 ^c

^a Isolated yields following the general procedure (2-3% Pd(OAc)₂ and 1 mmol substrate in TFA / CH₂Cl₂ (1.5 mL / 0.5 mL at r.t. for 2-5 h). ^b The ratio was determined by ¹H NMR spectra. ^c 5% Pd(OAc)₂, 55 h.

Scheme 5) or intramolecular reactions when the reaction was run in *d*-TFA.^{5b,c} The reactions of heteroarenes with alkynoates in AcOD gave similar results.^{5d} Also, addition of heteroaromatic C-D bonds to the C-C triple bonds (Eq. 2 in Scheme 5) and the large isotope effect (*k*_H/*k*_D = 3) between pyrrole and *d*₅-pyrrole in the reaction with ethyl phenylpropionate have been observed.^{5d}

Thus, a possible mechanism involving σ-aryl-Pd complexes (7) similar to those involved in the coupling of arenes with olefins has been suggested [route (a) in Scheme 6].^{3c}

Similar aryl-Pt(II) complexes have been synthesized from cationic Pt(II) complexes.^{9a,b} The facile formation of such Pd-aryl complexes from Pd(II) and arenes in TFA has been indicated by the coupling reaction of arenes with arenes,^{9c,d} and also demonstrated by formation of aromatic acid from simple arenes with carbon monoxide (Scheme 1),¹⁰ and both

Scheme 4. Synthesis of quinoliones

Scheme 5. The selected isotope reactions

at room temperature. Although the *trans*-insertion of aryl-Pd complexes to C-C triple bonds is not well understood, similar *trans*-insertion has been reported in several reactions of alkynes,^{11,12} including photo-induced *trans*-hydrophenylation of alkynes by benzene with a Rh catalyst.¹¹ The formation of vinyl-Pd complexes (9) has been suggested by the formation of adducts of two alkynes and one arene (Scheme 7).

The use of TFA as solvent facilitates the generation of a highly cationic [Pd(II) O₂CCF₃]⁺ species to form σ-aryl-Pd complexes through electrophilic substitution of aromatic C-H bonds. On the other hand, the involvement of a vinyl cationic species (such as 8, route b in Scheme 5) in the reaction cannot be ruled out.^{5b, c, 7b, 13} In this context, we have found that the reaction of 3-butyne-2-one with mesitylene can occur without Pd(OAc)₂ (Scheme 8), clearly indicating the involvement of a vinyl cationic species generated from alkynes and H⁺ in this reaction. The yield difference in the presence and absence of Pd(OAc)₂ may be explained by the competition between [Pd(II) O₂CCF₃]⁺ and the vinyl cationic species in electrophilic substitution of aromatic C-H bonds.

Scheme 6. The possible mechanism for inter- and intramolecular hydroarylations

Scheme 7. Formation of the adduct of two alkynes and one arene

Scheme 8. The reaction of mesitylene with 3-butyne-2-one

5. Conclusion

We have found a very useful addition reaction for direct functionalization of arenes and heteroarenes. The intramolecular reactions have been used to synthesize biologically important heterocycles. Further extension of the reaction to synthesis of functionalized materials is under way.

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