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Palladium(II)-catalyzed vinylic geminal double C–H activation and alkyne annulation reaction: synthesis of pentafulvenes†

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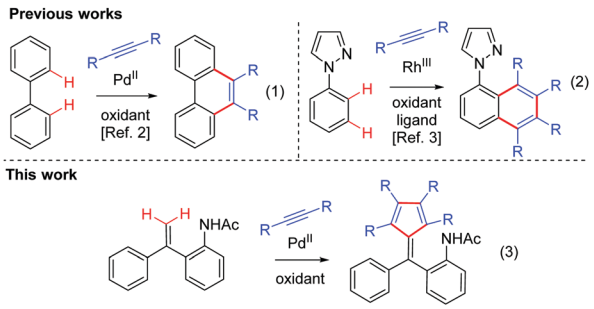
The first transition-metal-catalyzed vinylic geminal double C(sp^2)–H activation and di-substituted alkyne annulation reaction is reported. This palladium(II)-catalyzed, amide directed reaction of vinylic compounds with di-substituted alkynes offers an efficient synthetic path to pentafulvenes, which are very important compounds because of their bioactivity and interesting optical properties. A $FeCl_3$-mediated transformation of pentafulvenes to fluorescent cyclopenta[*b*]quinolines is also developed.

The transition-metal-catalyzed activation of C(sp^2)–H bonds and alkyne insertion reactions have been extensively used for the construction of various heterocycles for the last two decades.[1] Among these reactions, the metal-catalyzed double C(sp^2)–H bond activation and double alkyne insertion reactions have been developed lately as potential approaches for the synthesis of polyaromatic and heteroaromatic compounds. For example, Jiao *et al.* developed a Pd(II)-catalyzed double activation of two aromatic C(sp^2)–H bonds of biphenyl compounds followed by an insertion of alkyne to synthesize polycyclic aromatic hydrocarbons (Scheme 1, eqn (1)).[2] Miura *et al.* developed an Rh(III)-catalyzed directing group assisted method for polyarylated naphthyl and anthrylazole derivatives which proceeded *via* the activation of two aromatic C(sp^2)–H bonds and the insertion of two molecules of alkynes (Scheme 1, eqn (2)).[3] In spite of the importance of metal-catalyzed double C(sp^2)–H activation and alkyne insertion reactions for the synthesis of annulated carbocycles and heterocycles, until now, these reactions are confined to the double activation of aromatic C(sp^2)–H bonds. Single vinylic C(sp^2)–H bond activation and alkyne annulation reactions are known in the literature for the synthesis of heterocycles.[4] However, the double C(sp^2)–H activation of both the vinylic geminal C(sp^2)–H bonds and alkyne annulation, which could be an easy route to construct important pentafulvene derivatives, still remains unexplored. To extend our work further for the development of new metal-catalyzed reactions,[5] herein, we disclose the first transition-metal-catalyzed activation of both the vinylic geminal C(sp^2)–H bonds and alkyne annulation reactions (Scheme 1, eqn (3)). This Pd(II)-catalyzed amide directed reaction of the acetyl derivative of 2-(1-phenylvinyl)-aniline and di-substituted alkyne afforded an efficient synthetic route for pentafulvenes.[6a–e] Pentafulvenes are now considered as wonder molecules because of their unique aromaticity, dipole moment, reactivity and applications.[6f–i] They are the key structural element of a wide range of bioactive compounds[6h,i] and organometallic compounds.[7] Recently, many pentafulvenes have emerged as promising candidates for electroluminescent and display device systems (Fig. 1).[8] It is noteworthy to mention that very recently, Zeng and Li described a Pd(II)-catalyzed alkyne annulation reaction of the tosyl derivative of 2-(1-phenylvinyl)aniline and di-substituted alkyne for the synthesis of cyclopenta[*b*]quinolines.[9] Again, the cyclopenta[*b*]quinoline scaffold is the key structure of several bioactive natural products and pharmaceutically important compounds which exhibit anticancer, antimalarial and Alzheimer's disease inhibitory activity.[10] Because of the importance of this scaffold, we developed a very efficient method to transform the pentafulvenes to cyclopenta[*b*]quinolines, which is also reported herein.



Scheme 1 Alkyne annulation by double C(sp^2)–H activation.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of the ^{1}H NMR, ^{13}C NMR and HRMS spectra of the synthesized compounds. CCDC 1952908 (**3ca**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc09564k

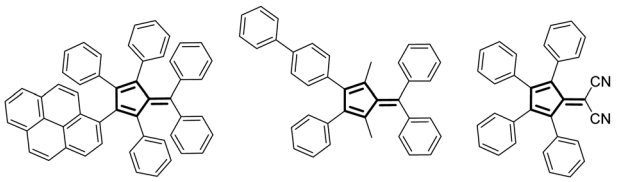
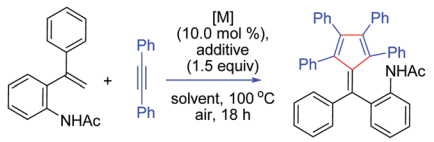


Fig. 1 Examples of potential pentafulvenes for use in electroluminescent and display devices.[8a,b]

Table 1 Optimization of the reaction conditions for **3aa**[a]



1a 2a 3aa

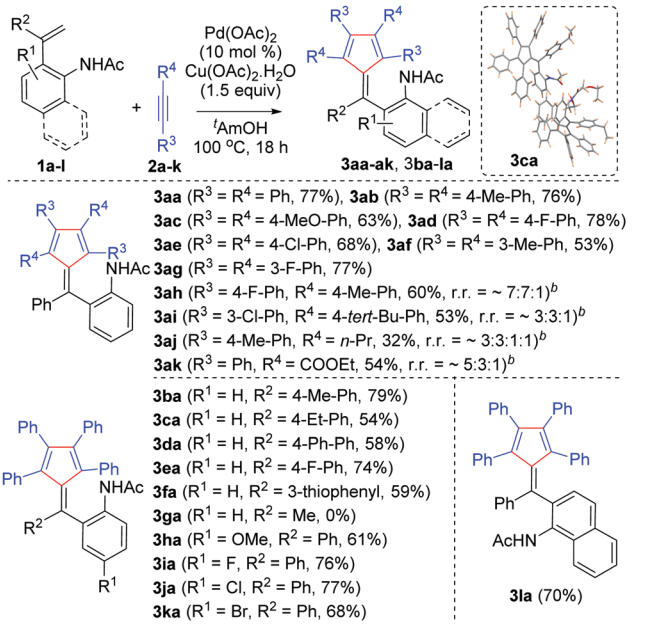
Entry	Catalyst	Additive	Solvent	3aa[b] (%)
1	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	0
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	0
3	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	48
4	$PdCl_2$	$Cu(OAc)_2{\cdot}H_2O$	MeCN	21
5	$Pd(OAc)_2$	CsOAc	MeCN	36
6	$Pd(OAc)_2$	NaOAc	MeCN	16
7	$Pd(OAc)_2$	AgOAc	MeCN	39
8	$Pd(OAc)_2$	Ag_2O	MeCN	15
9	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	77
10	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-Dioxane	63
11	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	DMF	41
12	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	DMSO	0
13[c]	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	58
14[d]	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	61

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (10.0 mol%), additive (0.75 mmol) and solvent (4.0 mL) at 100 °C under air for 18 h; unless otherwise mentioned. [b] Isolated yields. [c] Under argon. [d] Additive (0.5 mmol).

Initially, the reaction was tried with phenylvinylacetamide **1a** and diphenylacetylene (**2a**) for the synthesis of pentafulvene **3aa** (Table 1). The screening of various transition metal complexes using acetonitrile as the solvent showed the $Pd(OAc)_2$ catalyst to be the ideal catalyst which provided 48% yield of **3aa** in the presence of $Cu(OAc)_2$ as an additive (entry 3). The commonly used additives in Pd-catalyzed reactions, for instance CsOAc, NaOAc, AgOAc and Ag_2O, could not raise the yield of **3aa** (entries 5–8).[1e] Other additives such as oxone, $PhI(OAc)_2$ and $K_2S_2O_8$ provided 42%, 18% and 52% yields of **3aa**, respectively. Then, to our delight, screening of some solvents revealed that the choice of solvent was very important to improve the yield of **3aa**. These solvent studies afforded ^{t}AmOH as the optimal solvent for this reaction which yielded 77% of **3aa** (entry 9). Under inert conditions or the use of 1.0 equivalent of additive, this reaction afforded an inferior yield of **3aa** (entries 13 and 14). When DMSO was used as the solvent, the acetyl derivative of 3-phenyl-1*H*-indole was the only compound formed by an intramolecular coupling reaction. Thus, the best conditions to synthesize **3aa** were obtained by using $Pd(OAc)_2$ (10 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv.) in ^{t}AmOH at 100 °C for 18 h.

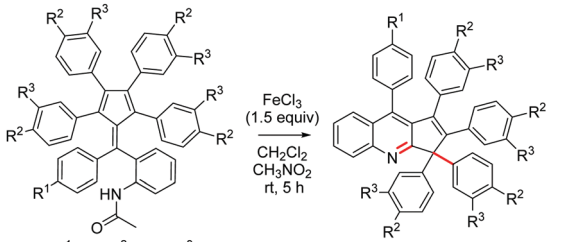
The optimized reaction conditions (Table 1, entry 9) were then examined first with some of the di-substituted alkynes **2a–l**

Table 2 Scope of alkynes and vinylacetamides[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), catalyst (10.0 mol%), additive (0.75 mmol) and solvent (4.0 mL) at 100 °C under air for 18 h. [b] One probable isomer is shown, ratio of regioisomers (r.r.) was determined by ^{1}H NMR.

and phenylvinylacetamide **1a**, which is shown in Table 2. Thus, the symmetrically substituted di-aryl alkynes possessing electron-donating and electron-withdrawing substituents *viz.*, methyl, methoxy, fluoro and chloro substituents at the *para*-position of the phenyl ring (**2b–e**) smoothly provided the corresponding annulated products **3ab–ae** in good yields. Similarly, di-aryl alkynes substituted at the *meta*-position with methyl (**2f**) and fluoro (**2g**) were also tested which provided the pentafulvenes **3af–ag**. The unsymmetrical di-aryl substituted alkynes **2h–i** afforded a mixture of regioisomers **3ah** (7 : 7 : 1) and **3ai** (3 : 3 : 1) with **1a** in good yields. The representative arylalkyl alkyne **2j** and arylester alkyne **2k** also provided a mixture of regioisomers **3aj** (3 : 3 : 1 : 1) and **3ak** (5 : 3 : 1) with **1a**, respectively. The di-alkyl group substituted alkynes, terminal alkynes, and diester group containing alkynes could not afford the desired annulated products. Then, this reaction was tested with some phenylvinylacetamides **1b–l** with alkyne **2a** (Scheme 2). The 1-substituted *N*-(2-vinylphenyl)acetamides, substituted with *para*-tolyl, 4-ethylphenyl, 1,1′-biphenyl, 4-fluorophenyl and 3-thiophenyl substituents **1b–f** were all found to be good substrates to afford the pentafulvenes **3ba–3fa**. Unfortunately, the reaction of arylalkyl substituted vinylphenylamide **1g** with **2a** could not provide the desired compound **3ga**. Then, some of the *N*-(2-(1-phenylvinyl)phenyl)acetamides holding substituents such as methoxy (**1h**), fluoro (**1i**), chloro (**1j**) and bromo (**1k**) at the fourth position of the phenyl ring of the *N*-phenylacetamide moiety **1h–k** were reacted with **2a** to provide **3ha–3ka**. Finally, the reaction of vinylnaphthylamide **1l** was tested with **2a**, which afforded a good yield of the desired compound **3la**. It is observed that the yield of this reaction is relatively unaffected by the electron-rich and electron-poor

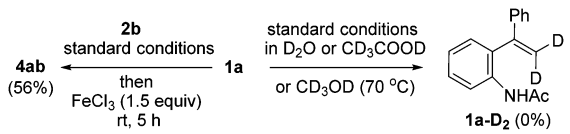


3ab (R^1 = H, R^2 = Me, R^3 = H)
3ac (R^1 = H, R^2 = OMe, R^3 = H)
3ad (R^1 = H, R^2 = F, R^3 = H)
3af (R^1 = H, R^2 = H, R^3 = Me)
3ba (R^1 = Me, R^2 = H, R^3 = H)
3ca (R^1 = Ph, R^2 = H, R^3 = H)

4ab (R^1 = H, R^2 = Me, R^3 = H, 90%)[b]
4ac (R^1 = H, R^2 = OMe, R^3 = H, 79%)
4ad (R^1 = H, R^2 = F, R^3 = H, 89%)
4af (R^1 = H, R^2 = H, R^3 = Me, 88%)
4ba (R^1 = Me, R^2 = H, R^3 = H, 86%)
4ca (R^1 = Ph, R^2 = H, R^3 = H, 90%)

Scheme 2 Synthesis of cyclopenta[*b*]quinolines.[a a] Reaction conditions: **3** (0.03 mmol), $FeCl_3$ (1.5 equiv.), CH_2Cl_2 (2.0 mL), CH_3NO_2 (0.5 mL), room temperature under N_2 for 5 h.

substituents present on the aromatic ring of **1**. The structure of these compounds was established with the help of NMR spectra and single X-ray crystallography studies of **3ca**.[11] To check the synthetic utility of this methodology, we performed a gram-scale experiment of **1j** and **2a** under the standard conditions, which provided **3ja** in 66% yield. Because of the importance of the cyclopenta[*b*]quinolines, next we attempted to transform the pentafulvene **3ab** to cyclopenta[*b*]quinoline **4ab** (Scheme 2). We hypothesized that a Scholl type intramolecular cyclization proceeded *via* deacetylation and aromatization would be a very good method for the conversion of these pentafulvenes to cyclopenta[*b*]quinolines. Initially, we tried to perform the intramolecular cyclization using commonly used oxidants such as $ZnCl_2$, $AlCl_3$, $FeCl_3$ and DDQ. Fortunately, in the presence of $FeCl_3$ (1.5 equiv.) and DDQ (1.5 equiv.), the pentafulvene **3ab** provided 90% yield and 69% yield of **4ab**, respectively, at room temperature in CH_2Cl_2 and CH_3NO_2 (Scheme 2). To check the substrate scope of this reaction, we tested this $FeCl_3$-mediated cyclization reaction with some more pentafulvenes **3ac–ad**, **3af**, and **3ba–ca**. The pentafulvenes possessing an electron-rich and electron-poor aryl functionality on the five membered ring of fulvene (**3ac–ad**, **3af**) reacted smoothly to furnish very good yields of the corresponding products **4ac–ad** and **4af**, irrespective of the substituents present on the ring. The other two pentafulvenes containing *para*-tolyl and 1,1′-biphenyl substituents at the sixth position of the fulvene scaffold **3ba–ca** were also examined to afford **4ba–ca** in very good yields. Our attempt to convert **1a** and **2b** to **4ab** in one-pot provided less yield of **4ab** (56%, Scheme 3). However, this two-step procedure (both one-pot and two-pot reactions) provided a better yield of cyclopenta[*b*]quinoline **4ab** (68% two-pot, 56% one-pot) as compared to the reported 23% yield of **4ab**.[9] The hydrogenation reaction of **3ab** at 60 psi pressure, using Pd/C as the catalyst and MeOH as the solvent could not



1a-D$_2$ (0%)

Scheme 3 One pot synthesis of **4ab** and the deuterium experiment.

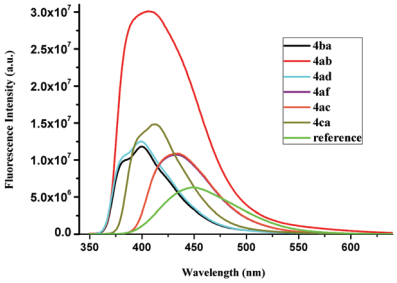
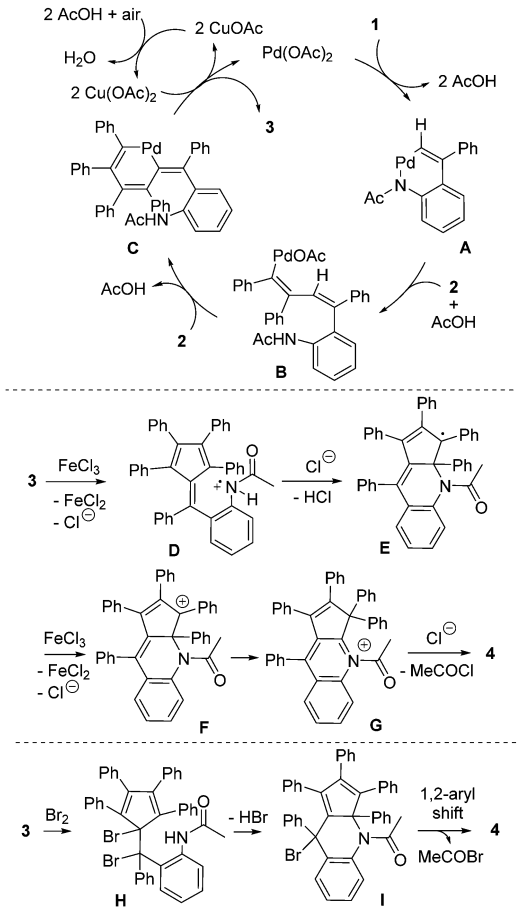


Fig. 2 Fluorescence (2.0×10^{-5} M, excitation at 320 nm) spectra of **4ab–ad**, **4af** and **4ba–ca** in toluene using quinine sulfate as the reference.

provide any hydrogenated compound in 24 hours at room temperature. Whereas, the bromination reaction of **3ab** performed by the addition of one equivalent of Br_2 to a stirred solution of **3ab** in $CHCl_3$ afforded 77% yield of **4ab** at room temperature in 8 hours. Next, on account of the recent emergence of pentafulvenes as potential candidates in organic light-emitting diodes, we were interested to study the preliminary optical properties of all the synthesized compounds.[12] The absorption bands of all the synthesized compounds appeared in the region 318 to 327 nm depending upon the substituent present in the molecule. Among all the compounds studied, only the cyclopenta[*b*]quinolines **4ab–ad**, **4af** and **4ba–ca** exhibited fluorescence in the range from 405 to 431 nm with quantum efficiency (Φ of 59% (**4ab**), 12% (**4ac**), 10% (**4ad**), 14% (**4af**), 11% (**4ba**) and 16% (**4ca**)) (Fig. 2).

To understand the mechanism of the pentafulvene formation, some control experiments were performed. Under the standard reaction conditions and in the absence of the directing amide group, the vinylic compound ethene-1,1-diyldibenzene could not afford the alkyne annulated product with the alkyne **2a**. The reactivity of this reaction is also dependent on the amine protecting group. The benzamide derivative *N*-(2-(1-phenylvinyl)phenyl)benzamide could not afford its corresponding pentafulvene with **2a** under the standard reaction conditions. Again, the vinylacetamide **1a** could not provide the deuterium-hydrogen exchanged vinylacetamide **1a-D$_2$** in deuterated solvents such as D_2O, CD_3COOD and CD_3OD (70 °C) under the standard reaction conditions (Scheme 3), indicating the irreversible formation of a cyclopalladium intermediate. Based on our experiments and literature reports,[1e,6e] a probable mechanism for the formation of the pentafulvene **3** and cyclopenta[*b*]quinoline **4** is shown in Scheme 4. Initially, Pd(II)-catalyzed amide group directed vinylic C(sp^2)–H activation of **1** affords the 6-membered palladacycle **A**.[6e] Then, coordination of **2** with the metal followed by carbopalladation generates a Pd-complex **B**. Then, carbopalladation of another molecule of **2** and subsequent vinylic C(sp^2)–H activation affords a 6-membered palladacycle **C**. Finally, a reductive elimination of the metal with the help of air and $Cu(OAc)_2$ resulted in the formation of pentafulvene **3** and regenerates the active Pd-catalyst. The $FeCl_3$ mediated conversion of amide **3** to cyclopenta[*b*]quinoline **4** might have occurred *via* a radical cation mechanism similar to the Scholl reaction.[13] Thus, the $FeCl_3$-mediated single electron transfer (SET) process might have generated a radical intermediate **E**. This intermediate on another SET process resulted in the carbocation **F** which



Scheme 4 Possible mechanism.

on subsequent 1,2-aryl shift and acyl deprotection provided **4**. In the presence of bromine, **3** forms a dibromo compound **H** which on intramolecular cyclization, subsequent aromatization by 1,2-aryl shift and acyl deprotection afforded **4**.

In conclusion, a new vinylic geminal double C(sp^2)–H activation and alkyne annulation reaction was developed. This amide group directed annulation reaction provided an efficient synthetic route for the important pentafulvene derivatives. In addition to this, a ferric chloride mediated method was developed for the conversion of pentafulvenes to fluorescent cyclopenta[*b*]quinolines with a very high yield.

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Conflicts of interest

There are no conflicts to declare.

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