

# $\pi$ -Conjugated carbocycles and heterocycles via annulation through C-H and X-Y activation across CC triple bonds

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This account is dedicated to Professor J. S. Yadav, in honor of his distinguished career in synthetic organic chemistry, and of his 65<sup>th</sup> birthday

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## Abstract

In this account our own research results on the methods of annulation and hetero-annulation across alkynes are summarized, especially emphasizing the annulation and hetero-annulation through C-H and X-Y activation. A wide range of quinolines, isoquinolines, indoles, benzofurans, indenes, and benzothiophenes can be synthesized via mono-annulation of ortho-alkynylaryl derivatives using transition metal catalysts and/or iodine reagents. Benzocarbazoles, benzonaphthothiophenes, and indenochromenes can be synthesized via cascade annulation of 1,2-dialkynyl substituted benzene derivatives. Palladium-catalyzed crossover annulation of compounds bearing two vicinal CC triple bonds attached to an unsaturated ring gives dibenzopentalenes through C-H activation, and intramolecular cross annulation of bis-biarylalkynes affords 9,9-bifluorenylidenes via dual C-H activation.

**Keywords:** Optoelectronic materials, quinolines, isoquinolines, indoles, benzofurans, indenes, benzothiophenes, C-H activation, palladium catalysis, gold catalysis

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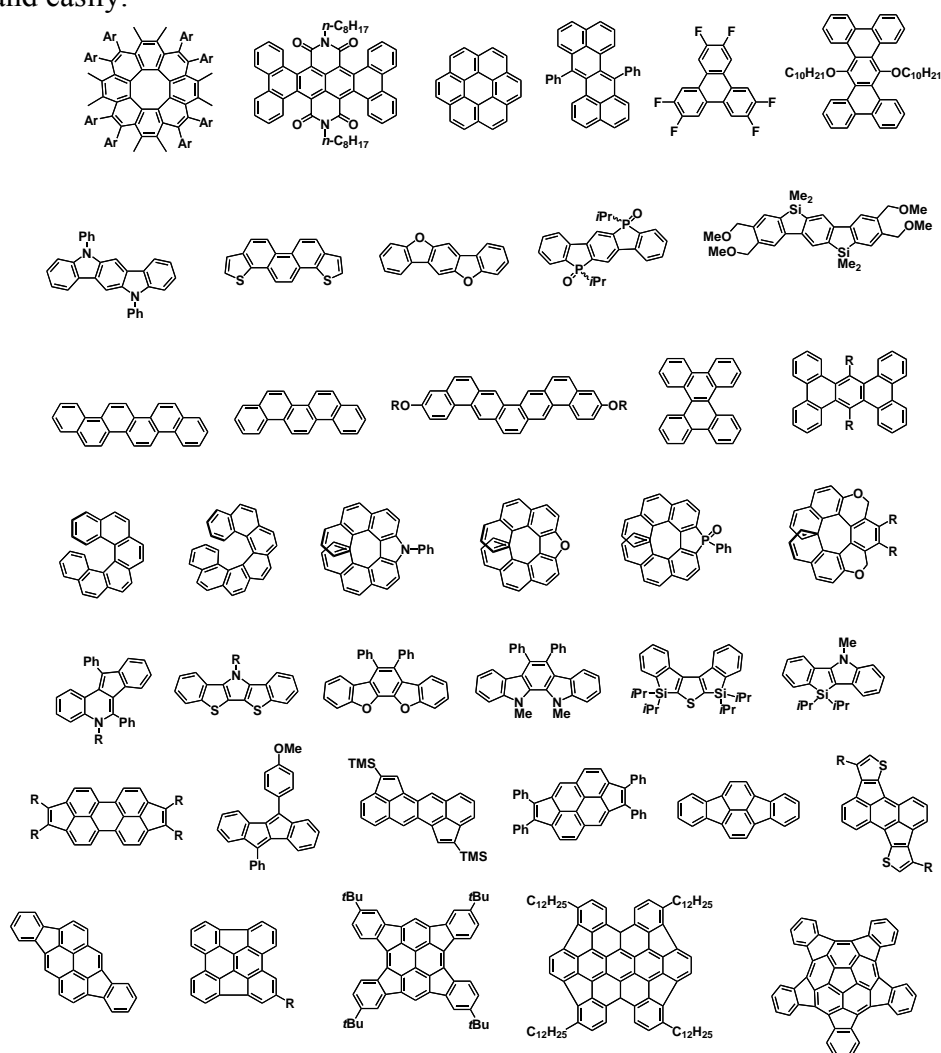
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## Introduction

$\pi$ -Conjugated carbocycles and heterocycles have attracted the keen interest of organic chemists and materials scientists in recent years, since these molecules are becoming increasingly important as optoelectronic organic materials in DSSCs (dye-sensitized solar cells), OLETs (organic light emitting transistors), OLEDs (organic light emitting diodes), OFETs (organic field effect transistors), and so on. Accordingly, a number of structurally interesting  $\pi$ -conjugated molecules have been synthesized in the past few years (Figure 1),<sup>1</sup> and new methods including transition metal-catalyzed reactions have been developed for synthesizing those compounds efficiently and easily.<sup>1</sup>



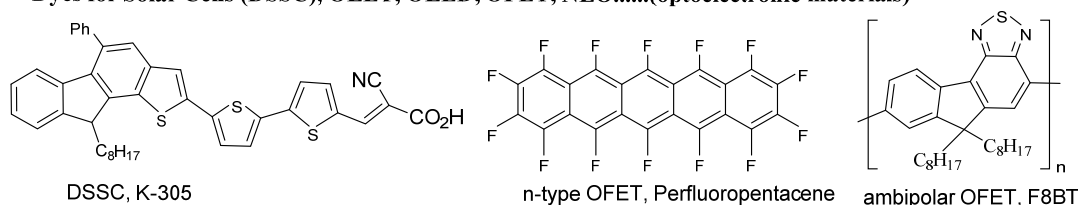
**Figure 1.** Representative  $\pi$ -conjugated carbocycles and heterocycles synthesized by transition metal-catalyzed reactions.

In general, polysubstituted benzenes can be synthesized through the transition metal-catalyzed [2+2+2] cyclotrimerization of alkynes,<sup>2-10</sup> the Diels-Alder reaction of conjugated 1,3-dienes with alkynes,<sup>11-17</sup> the dihydro-Diels-Alder reaction<sup>18-26</sup> and the [4+2] benzannulation of conjugated enynes and diynes.<sup>27-48</sup> However, these standard benzannulation reactions have not been used so often for the synthesis of  $\pi$ -conjugated carbo- and hetero-cycles, perhaps because those structures (as shown in Scheme 1) are too complicated, preventing the application of simple benzannulation procedures.

Why have  $\pi$ -conjugated carbo/heterocycles become important in recent years? As mentioned above, those compounds are increasingly important as materials for optoelectronics. There are two major synthetic methods for those substrates; one is Suzuki-type cross- and homo-coupling of aromatic and hetero-aromatics, and the other is annulation with alkynes. In this account, we summarize our own efforts on annulations across alkynes; mono-annulation, cascade annulation, and crossover annulation. What kinds of  $\pi$ -conjugated materials are needed and useful for optoelectronic materials? Questions and Answers regarding why, how, and what are summarized in Figure 2.

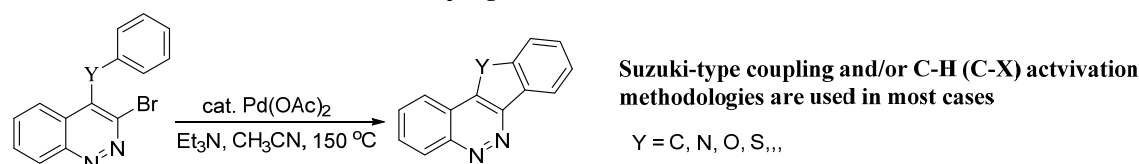
### 1. Why $\pi$ -conjugated carbo- and hetero-cycles?

Dyes for Solar Cells (DSSC), OLET, OLED, OFET, NLO.....(optoelectronic materials)

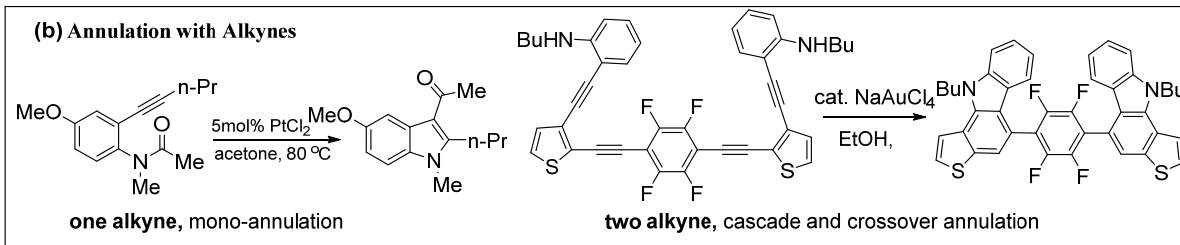


### 2. How to synthesize desirable $\pi$ -conjugated materials?

(a) Intra- and Inter-molecular Cross-coupling



(b) Annulation with Alkynes



### 3. What kinds of materials are needed and useful ?

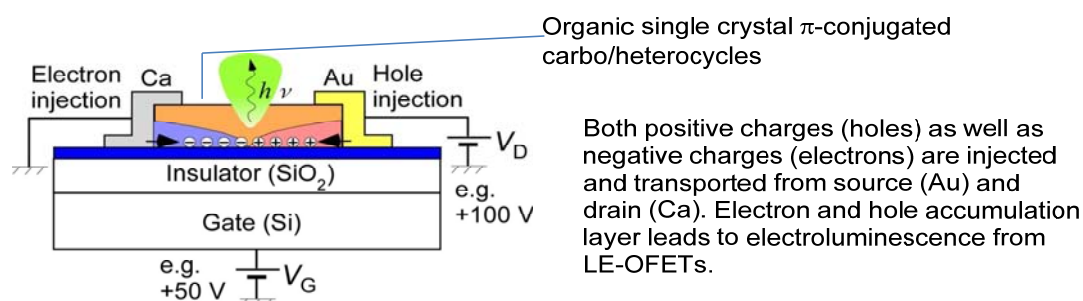
For example, OFET; performance data of devices constructed with  $\pi$ -conjugated system, synthesized by a new method  $\longrightarrow$  feedback to molecular design  $\longrightarrow$  better performance

**Figure 2.** Why, how, and what regarding  $\pi$ -conjugated carbo/heterocycles.

Regarding what kinds of materials are needed, firstly device construction using a conjugated system is made, and secondly performance data of the device are obtained. Evaluation of those data is carried out, and the feedback from the results is utilized in molecular design for next experiments (Figure 2). Before proceeding to the synthesis of  $\pi$ -conjugated carbo-/hetero-aromatics, a brief summary on the research process of OFET is given in Figure 3, to help clarify what kinds of molecule are needed.

Single crystalline  $\pi$ -conjugated carbo-/hetero-cycles are placed between source (Au) and drain (Ca), as shown in the device structure. Both positive charges (holes) and negative charges (electrons) are injected from Au and Ca, respectively, and hole-accumulation layer leads to electroluminescence from the LE-OFETs. High carrier mobility of both holes and electrons, high luminescence efficiency, and robustness of the organic materials are required. To accomplish such requirements, for example, well-controlling HOMO-LUMO gap, as well as heteroatom contacts and  $\pi$ - $\pi$  interactions to control of  $\pi$ -aggregation, should be considered for the molecular design of  $\pi$ -conjugated aromatics and hetero-aromatics.

### Device structure of ambipolar LE-OFETs (light emitting OFETs)



**Performance** High carrier mobilities (holes and electrons). High luminescence efficiency. Robustness of organic compounds.

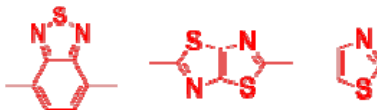
### Molecular design



Electron acceptors  
strong EWG  
change aromaticity  
stabilize core/charge

as  $\pi$ -spacer, for example

Electron donors  
strong EDG  
change aromaticity  
stabilize core/charge



# Well-controlling HOMO-LUMO gap, heteroatom contacts, sufficient  $\pi$ - $\pi$  interactions (control of  $\pi$ -aggregation)

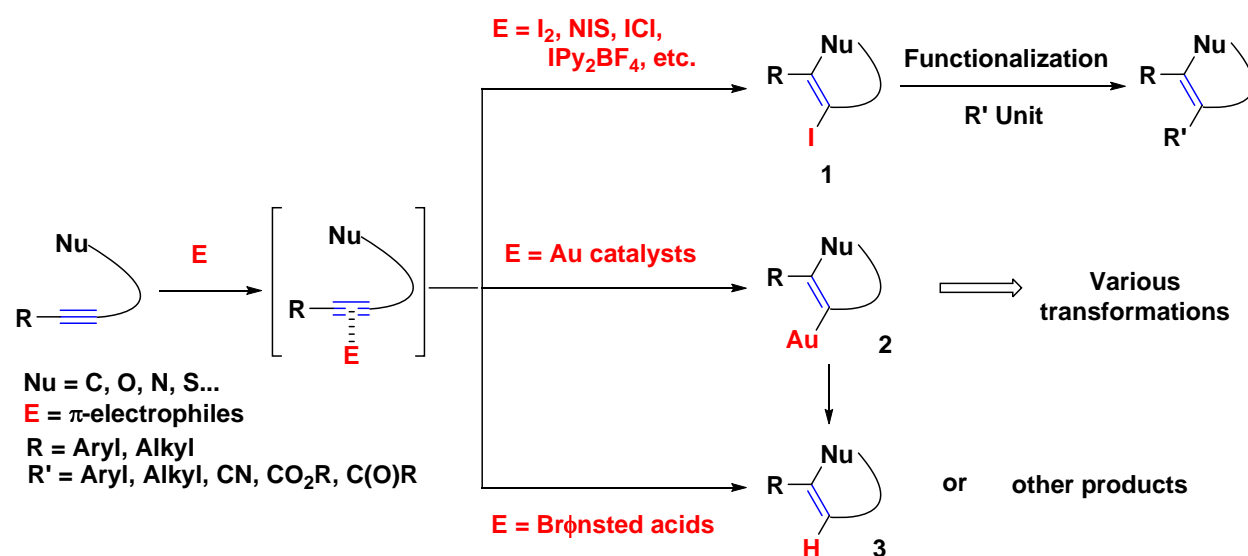
# Readily available and robust compounds

# Fine tuning of electrical properties by chemical functionalization

**Figure 3.** OFET device configuration, performance, and molecular design.

## 2. Annulation with a single alkyne, activated by $\pi$ -electrophiles

Hetero- and carbocycle synthesis via activation of alkynes with  $\pi$ -electrophilic reagents and catalysts is summarized in Scheme 1.<sup>49-53</sup> Coordination of alkyne to  $\pi$ -electrophilic reagents such as I<sub>2</sub> and NIS, followed by nucleophilic attack of Nu to the electron deficient coordinated alkyne, gives the cyclic product **1** having an iodoalkenyl group. Similarly, treatment with gold catalysts affords an alkenyl gold intermediate **2**, which undergoes various transformations via reactions of the C-Au bond. For example, protonolysis of the C-Au bond with water gives a cycloalkene or heterocycloalkene product **3**, which is also obtained by the treatment of alkyne with Brønsted acids. This general scheme is applicable to the synthesis of aliphatic,<sup>54-62</sup> as well as aromatic, carbo- and heterocycles, and not only a CC triple bond but also other unsaturated units such as allenes<sup>54-62</sup> and alkenes can be transformed. Here we focus on the synthesis of aromatic/heteroaromatic compounds via a triple bond.

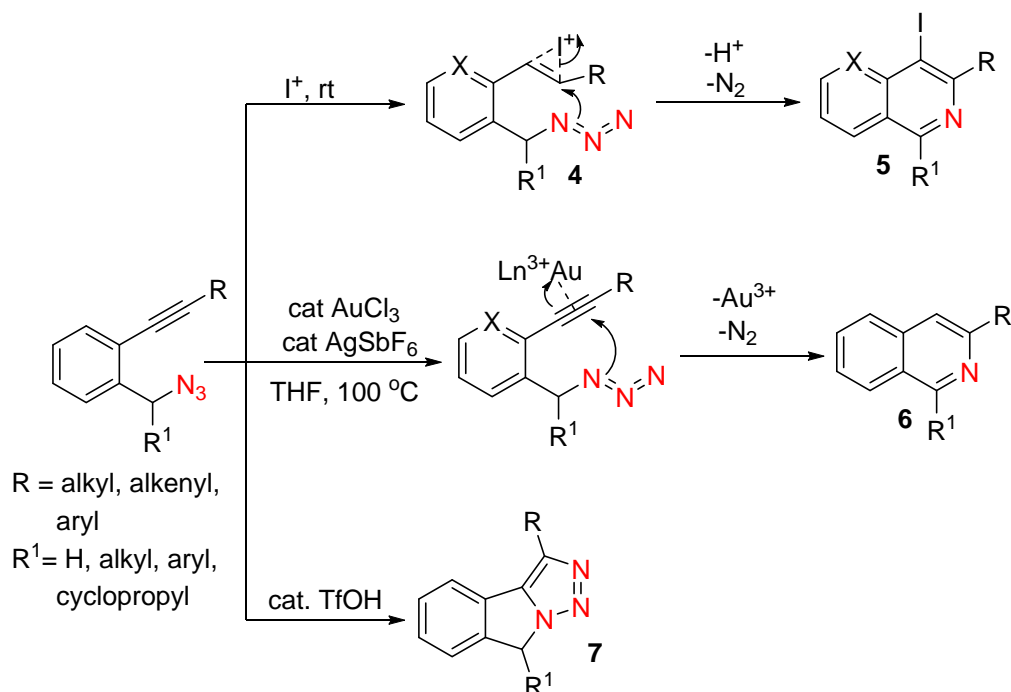


**Scheme 1.**  $\pi$ -Electrophile-mediated and catalyzed cyclization of alkynes.

A typical example of this type of reaction for the synthesis of isoquinolines is shown in Scheme 2. Iodine addition to alkyne of *ortho*-alkynylbenzyl azides gave an iodonium ion intermediate **4**, which underwent addition of the carbon-bound N-atom of the azide group, leading to 4-iodo-3-R-1-R<sup>1</sup>-substituted isoquinolines **5** via elimination of N<sub>2</sub> and H<sup>+</sup>.<sup>63,64</sup> On the other hand, Au<sup>+</sup> catalyzed reaction of the *ortho*-alkynylbenzyl azides produced 3-R-1-R<sup>1</sup>-substituted isoquinolines **6**.<sup>65</sup> Interestingly, treatment with TfOH gave the heterocycles **7** derived from the ordinary [3+2] cycloaddition between azide and alkyne.<sup>49,63,64</sup>

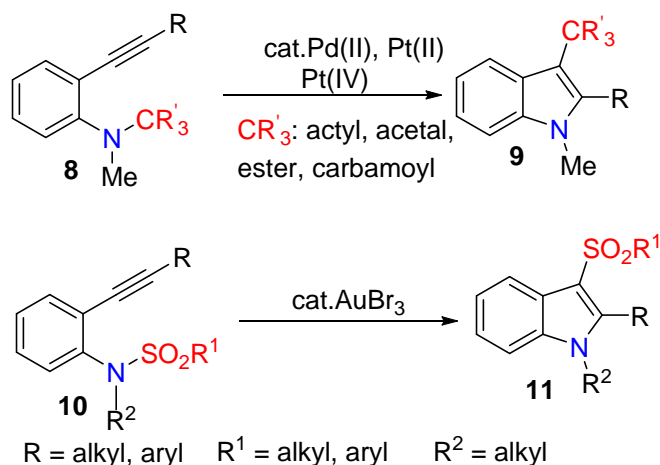
Similarly, iodine-mediated electrophilic cyclization of *ortho*-alkynylbenzaloximes afforded 4-iodo-3-R-1-R<sup>1</sup>-substituted isoquinoline *N*-oxides.<sup>66</sup> Not only isoquinolines,<sup>67,68</sup> but also quinolines could be synthesized through a similar reaction of 1-azido-2-(2-propynyl)-

benzenes.<sup>69,70</sup> The intramolecular cyclization of 1-azido-2-(2-propynyl)benzenes proceeded smoothly in the presence of electrophilic reagents (I<sub>2</sub>, Br<sub>2</sub>, ICl, NBS, NIS) or in the presence of catalytic amounts of AuCl<sub>3</sub>/AgNTf to afford the corresponding quinolines. Here also, treatment with TfOH (or HCl) gave the [3+2] cycloaddition product between azide and alkyne. More recently, a novel and efficient method for the synthesis of allylated quinolines or isoquinolines *via* palladium-catalyzed cyclization-allylation of 1-azido-2-(2-propynyl)benzenes or 2-alkynyl-benzyl azides, respectively, with allyl methyl carbonate has been reported.<sup>71,72</sup>



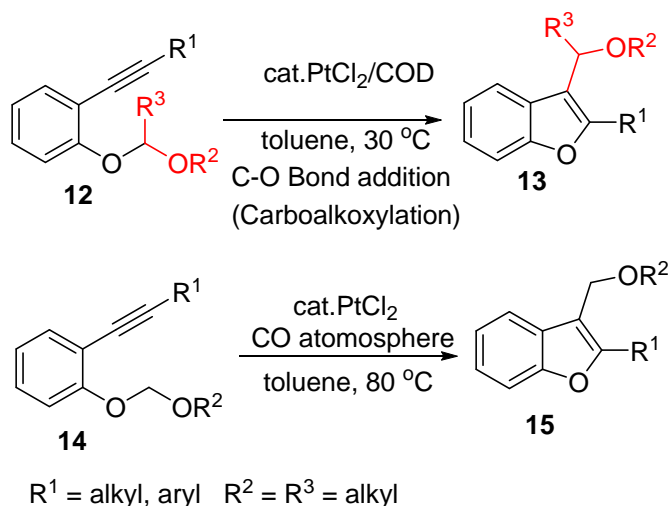
**Scheme 2.** Isoquinoline synthesis via iodine-mediated and gold-catalyzed reactions of benzyl azides.

Platinum(II)-catalyzed intramolecular aminoacylation of alkyne of *ortho*-alkynylamides **8** (CR'<sub>3</sub> = acyl) produced indoles having 3-CR'<sub>3</sub> substituent **9** (Scheme 3).<sup>73,74</sup> In the case of **8** (CR'<sub>3</sub> = CH<sub>2</sub>OMe), that means, in the case of N,O-acetal instead of amide group, the Pt(II)-catalyzed reaction also produced indoles **9** having 3-CH<sub>2</sub>OMe group.<sup>75</sup> Similarly, 1,3-shift of carbamoyl and ester groups (CR'<sub>3</sub> = C(O)NR''<sub>2</sub> and C(O)OR'') took place in Pt(II)-catalyzed reactions of *ortho*-alkynylphenylureas and carbamates **8**, respectively.<sup>76</sup> Palladium(II)-catalyzed reaction of *ortho*-alkynylarylaldimines **8**, in which -N=CHR<sup>1</sup> was substituted instead of -N(Me)-CR'<sub>3</sub>, gave 3-alkenyl-2-R<sup>1</sup>-substituted indoles **9**, in which the alkenyl group originated from R of alkyne.<sup>77-79</sup> Gold(III) or In(III)-catalyzed reaction of *ortho*-alkynyl-*N*-sulfonylanilines **10** produced 3-sulfonylindoles **11**;<sup>80-81</sup> under certain conditions accompanied by the formation of 6-sulfonylindoles.



**Scheme 3.** Indole synthesis via N-C and N-S bond addition across an alkyne.

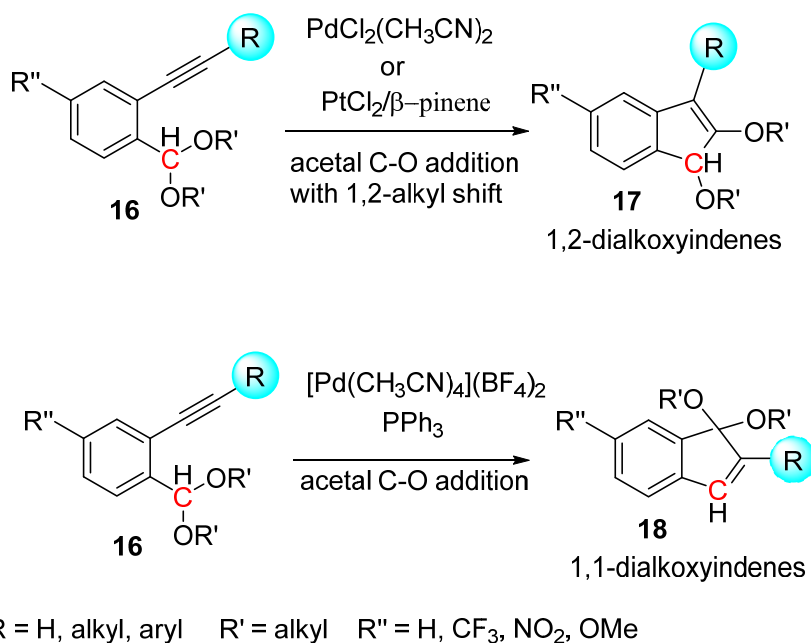
Platinum(II)-olefin-catalyzed reaction of *ortho*-alkynylphenyl acetals **12** gave 3-(1-alkoxyethyl)-2-alkylbenzofurans **13** in high yields (Scheme 4).<sup>82</sup> Pt(II), such as PtCl<sub>2</sub>, was stable as a dimer, and olefins such as COD and 1-hexene are needed to change the dimer to more reactive monomer by coordination. This Pt-olefin catalyst is also useful for the cyclization of 6-(1-alkoxyethyl)hex-2-ynoates **14**, which led to multisubstituted 3-alkoxymethylbenzofurans **15**.<sup>83</sup> The PtCl<sub>2</sub>-CO catalyst system was similarly useful for the synthesis of benzofurans from *ortho*-alkynylphenyl acetals.<sup>84</sup> Here also, CO perhaps changes the dimeric platinum chloride to a more reactive monomeric form.



**Scheme 4.** Benzofuran synthesis via O-C bond addition.

Neutral Pd(II) catalyst, such as PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, was effective for converting *ortho*-alkynylaryl acetals **16** to 1,2-dialkoxyindenes **17** via 1,2-alkyl (R) shift and migration of OR' of

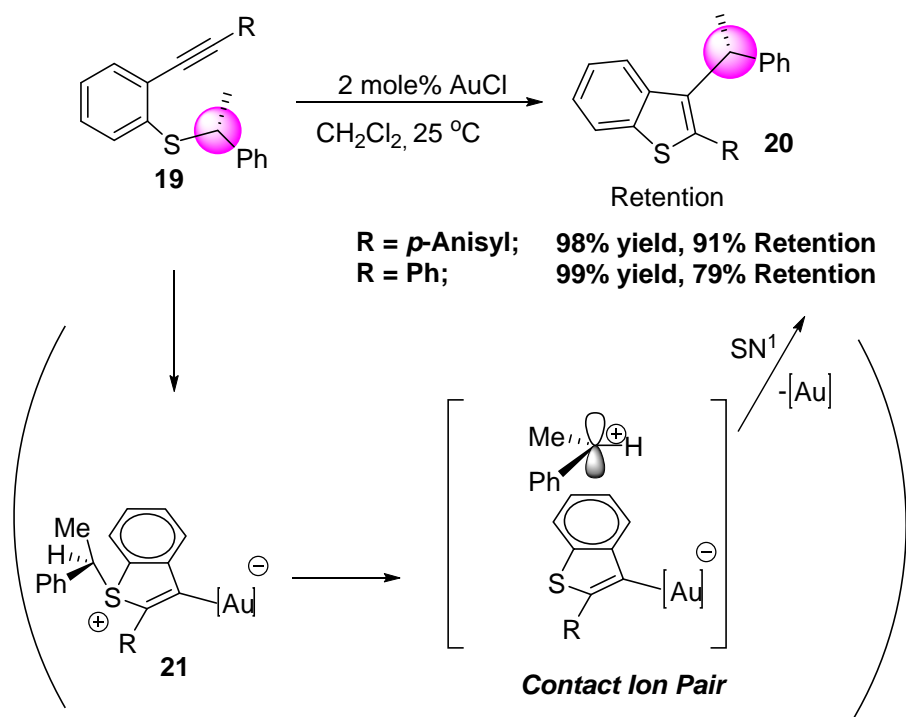
acetal to alkynyl carbon (Scheme 5).<sup>85</sup> Not only the neutral Pd(II) but also PtCl<sub>2</sub>-olefin, such as β-pinene or 1,5-COD, was active for this type of transformation.<sup>82</sup> A similar catalytic system, PtCl<sub>2</sub>-benzoquinone, was also active for the cyclization of related acetals, whereas the optimal catalyst for the reaction of thioacetals was PdI<sub>2</sub>; *ortho*-alkynylaryl thioacetals, which did not undergo a 1,2-alkyl shift, gave 1,3-di(alkylsulfonyl)indenes.<sup>86</sup> Contrary to the neutral palladium(II), *ortho*-alkynylaryl acetals **16** was converted to 1,1-dialkoxyindenes **18** with cationic palladium(II) catalyst system such as Pd(CH<sub>3</sub>CN)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub>-PPh<sub>3</sub> (Scheme 5).<sup>87</sup> Mechanistic study using DFT calculations suggested that π-coordination of cationic Pd<sup>+</sup> to the benzene ring would be a key step; a stepwise delivery of two methoxy groups would take place via the palladium cationic center coordinated to the aromatic ring. This mechanistic consideration helps to understand why many useful transformations of *ortho*-alkynylaryl amines, acetals, imines, etc., mentioned above, take place rather readily with Pd and transition metal catalysts, but those of the corresponding aliphatic analogues do not occur easily.



**Scheme 5.** Indene synthesis via C-O bond addition.

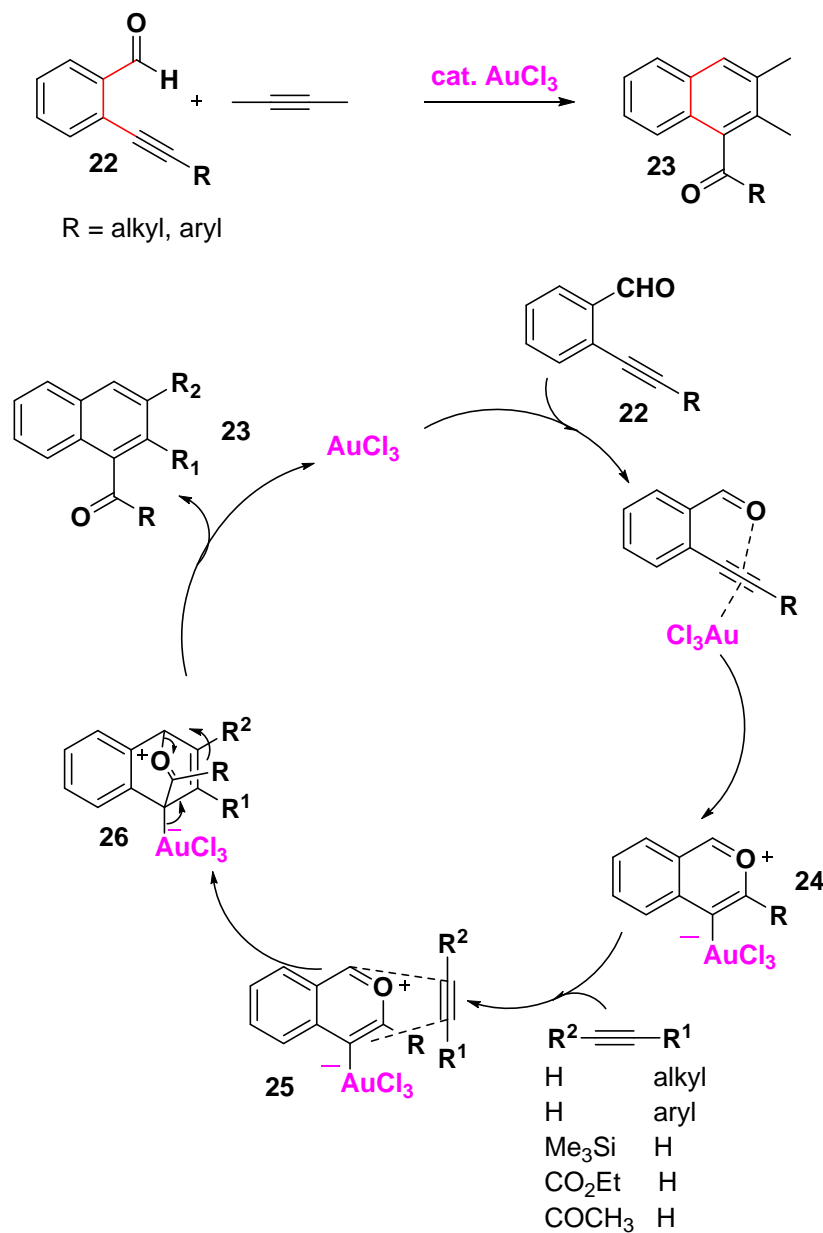
The gold-catalyzed cyclization of 1-methylbenzyl(*ortho*-alkynylphenyl)sulfides **19** proceeded with retention of configuration of 1-methylbenzyl group to give **20** (Scheme 6).<sup>88</sup> Here, nucleophilic attack of sulfur atom to the CC triple bond activated by AuCl coordination, affords cyclized sulfonium intermediate **21**. The 1,3-migration of 1-methylbenzyl group would involve a contact ion pair intermediate, followed by C-C bond formation at 3-position of benzothiophenes. Gold-catalyzed cyclization of α-alkoxyalkyl(*ortho*-alkynylphenyl)sulfides gave 2,3-disubstituted benzothiophenes in excellent yields.<sup>89</sup> Similarly, gold-catalyzed cyclization of (*ortho*-alkynylphenylthio)silanes gave 3-silyl-substituted benzothiophenes.<sup>90</sup>





**Scheme 6.** Benzothiophene synthesis with retention of configuration of 1-methylbenzyl group.

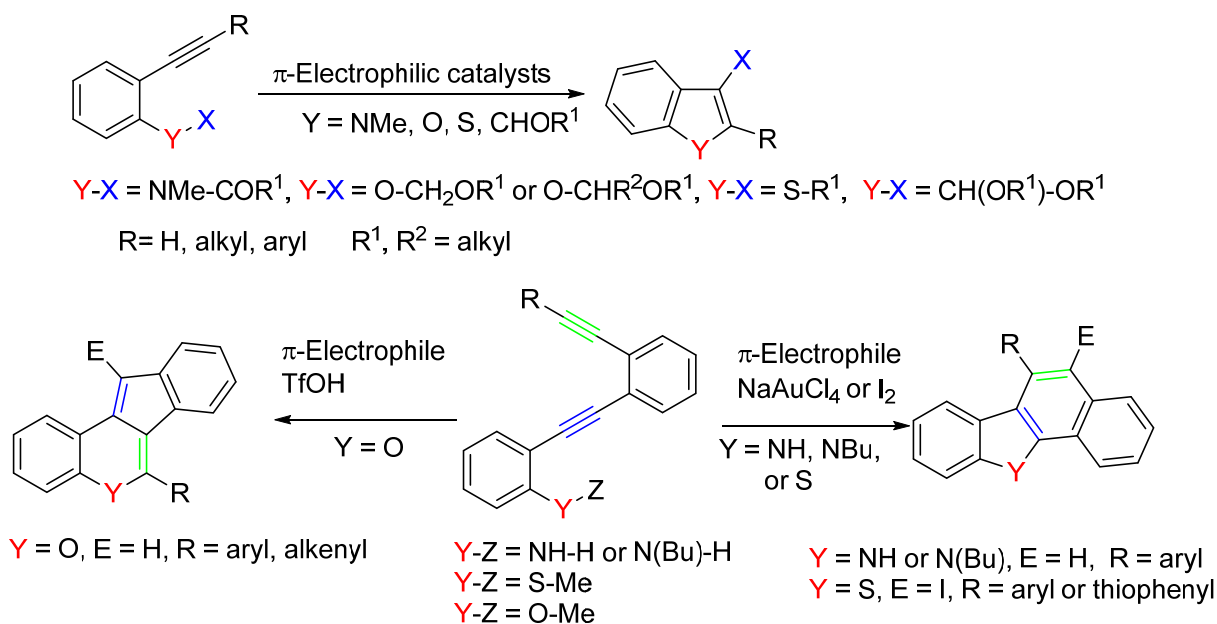
Gold-catalyzed and/or copper-catalyzed benzannulation reactions between *ortho*-alkynylbenzaldehydes **22** and alkynes gave naphthyl carbonyl compounds **23** in high to good yields (Scheme 7).<sup>91-97</sup> Coordination of  $\pi$ -electrophilic gold to the CC triple bond, followed by addition of carbonyl oxygen to electron deficient triple bond, produces benzopyrylium intermediate **24**, which undergoes [4+2] cycloaddition with alkynes as shown in **25**. Bond rearrangement in **26** affords **23** and regenerates gold catalyst. Not only naphthalene derivatives but also polynuclear aromatic hydrocarbons, in which the number of fused aromatic rings increases, can be synthesized through this type of benzannulation method. An interesting and wise extension of this type of [4+2] cycloaddition was the benzannulation of each alkyne of a substituted poly(phenylene ethynylene) using  $\text{Cu}(\text{OTf})_2/\text{CF}_3\text{CO}_2\text{H}$ , which gave polyphenylene.<sup>98</sup>



**Scheme 7.** Naphthalene and polynuclear aromatics via gold-catalyzed benzannulation.

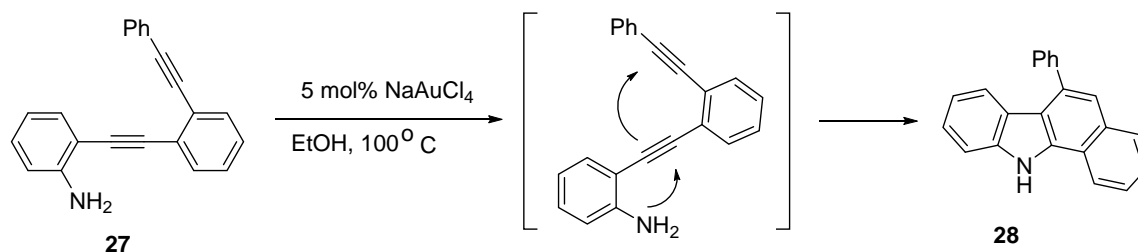
### 3. Cascade annulation with two alkynes, activated by $\pi$ -electrophiles

In the above section, annulation with a mono-alkyne of *ortho*-alkynylaryl system ( $Y=NR'$ , O, S, CH, or O=CH in the case of Scheme 7), which leads to indoles, benzofurans, benzothiophenes, indenes, or naphthalenes is mentioned. In this section, cascade annulation of two alkynes of 1,2-dialkynyl substituted aromatics ( $Y=NR$ , S, O, or O=CH in the case of Scheme 7) is shown (Scheme 8).



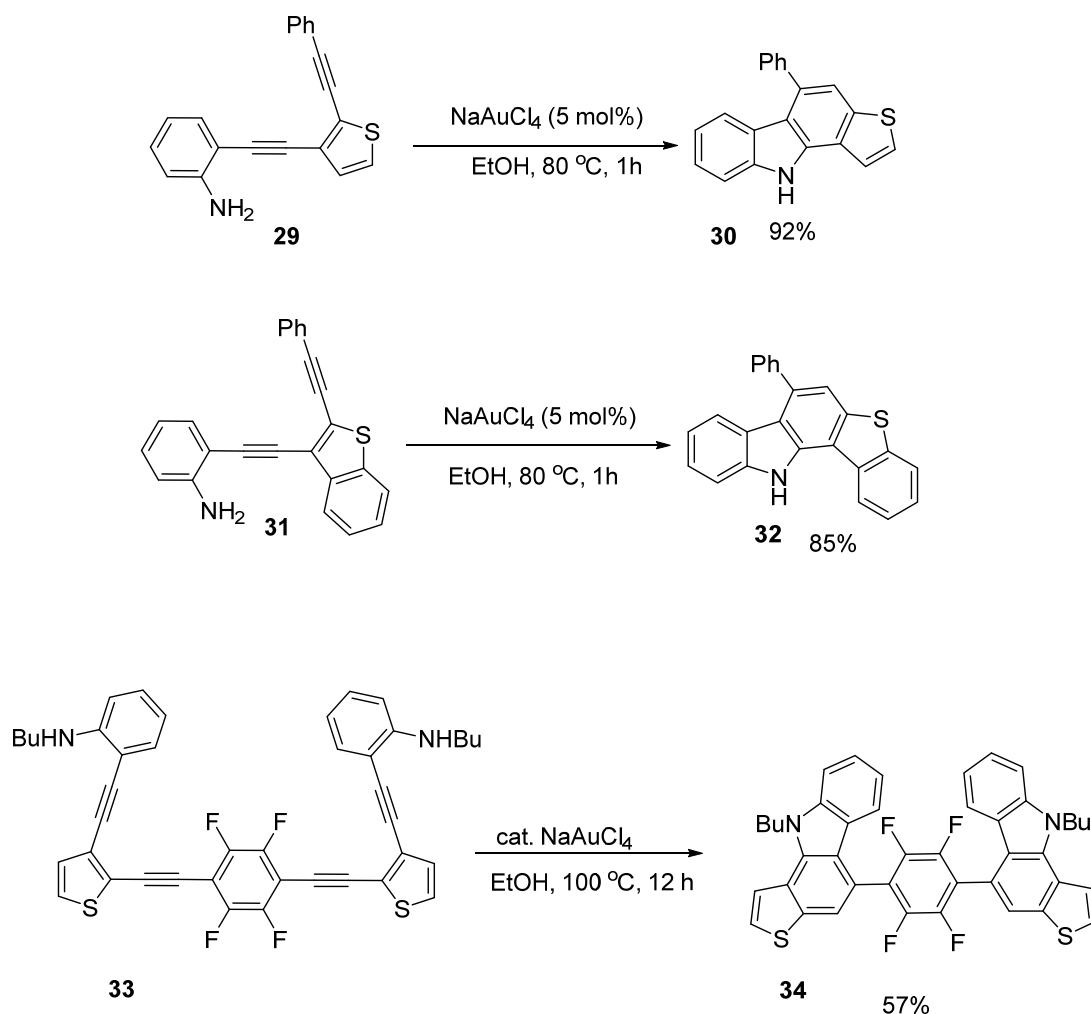
**Scheme 8.** Cascade annulation of two CC triple bonds vs mono-annulation of mono-alkyne.

Gold-catalyzed cascade annulation of *ortho*-aniline-substituted aryldiyne **27** is shown in Scheme 9.<sup>99</sup> Among Pd, Pt, and gold catalysts, NaAuCl<sub>4</sub> gave the best result, giving benzo[*a*]carbazole **28** in high yield. The use of other solvents such as toluene and CH<sub>3</sub>CN led to lower yields of the product.



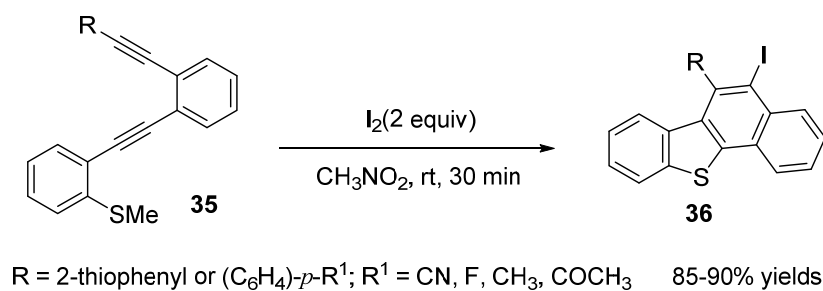
**Scheme 9.** Benzo[*a*]carbazole synthesis via cascade annulation.

Other examples for this type of cascade reactions are shown in Scheme 10. Thiophene is incorporated into  $\pi$ -conjugated heterocycles; for example, **28** vs. **30**. Other thienocarbazole ring **32** and more complicated  $\pi$ -conjugated system **34** can be synthesized in good to high yields. A thienocarbazole ring containing dye was applied to DSSC, and its photo-to-current efficiency (PCE) was 6.62%.<sup>100-101</sup>



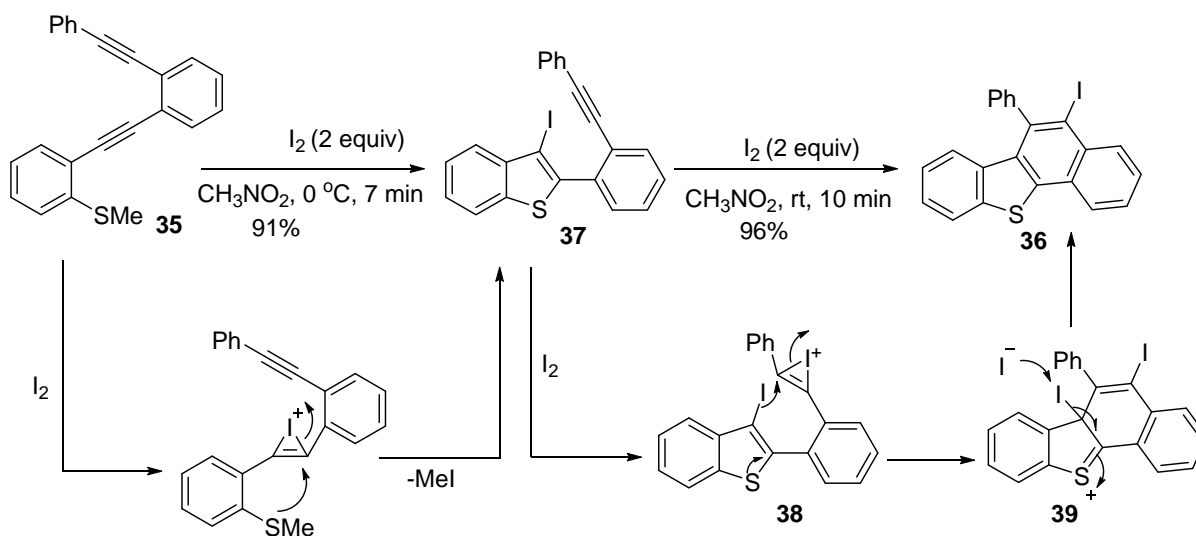
**Scheme 10.** Cascade annulation to carbazole  $\pi$ -conjugated system.

Cascade annulation of thioanisole-substituted aryldiynes **35** using iodine gave iodo-substituted benzo[*b*]naphtho[2,1-*d*]thiophenes **36** in high chemical yields (Scheme 11).<sup>102</sup> Here,  $\text{CH}_3\text{NO}_2$  was the best solvent, but  $\text{CH}_3\text{CN}$  and  $\text{CH}_2\text{Cl}_2$  also gave good results. A wide range of substituted thiophenes can be synthesized in high yields. This type of benzonaphthothiophene  $\pi$ -conjugated system was also applied to organic dyes for DSSC.<sup>102</sup>



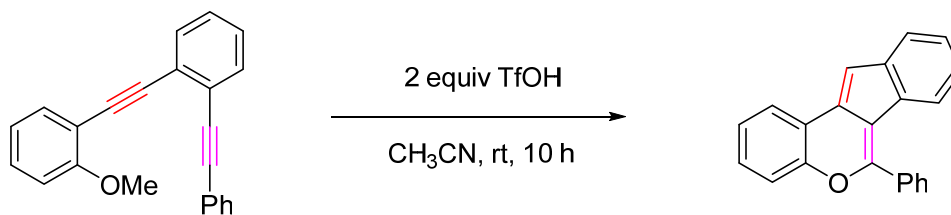
**Scheme 11.** Cascade annulation to benzonaphthothiophene  $\pi$ -conjugated system.

A proposed mechanism of this cascade iodo-cyclization is shown in Scheme 12. The first iodo-cyclization takes place at the alkyne *ortho* to SMe of **35**, leading to 3-iodo-substituted benzothiophene **37** via elimination of MeI. The second iodo-cyclization at the alkyne *ortho* to benzothiophene substituent gives the  $\pi$ -conjugated benzonaphthothiophene derivative **36** through **38** and **39**.<sup>102</sup>



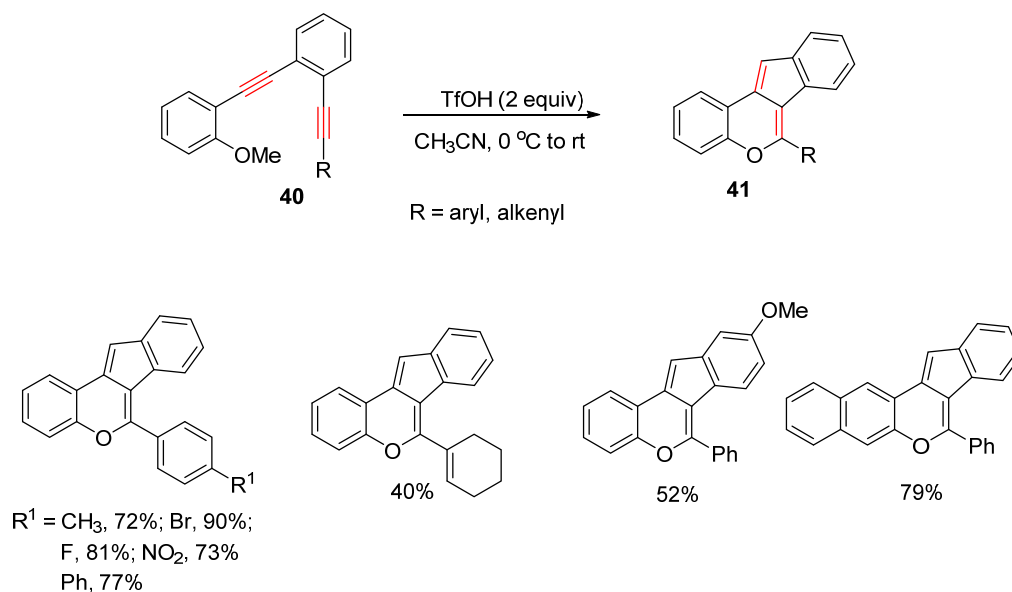
**Scheme 12.** A proposed mechanism for cascade iodo-cyclization.

As mentioned above, cascade annulation of *ortho*-alkynyl aniline and thioanisoles (Y=NR and/or S in Scheme 11) proceeded smoothly by the use of gold catalysts and/or iodine. However, in the case of anisoles **40** (Y=O in Scheme 8), iodine-mediated and  $\pi$ -electrophilic transition metal-catalyzed cyclization did not give the desired  $\pi$ -conjugated product (Scheme 13).<sup>103</sup> Instead, use of 2 equivalents of TfOH in CH<sub>3</sub>CN afforded the indenochromene  $\pi$ -conjugated system **41** in a very high yield.



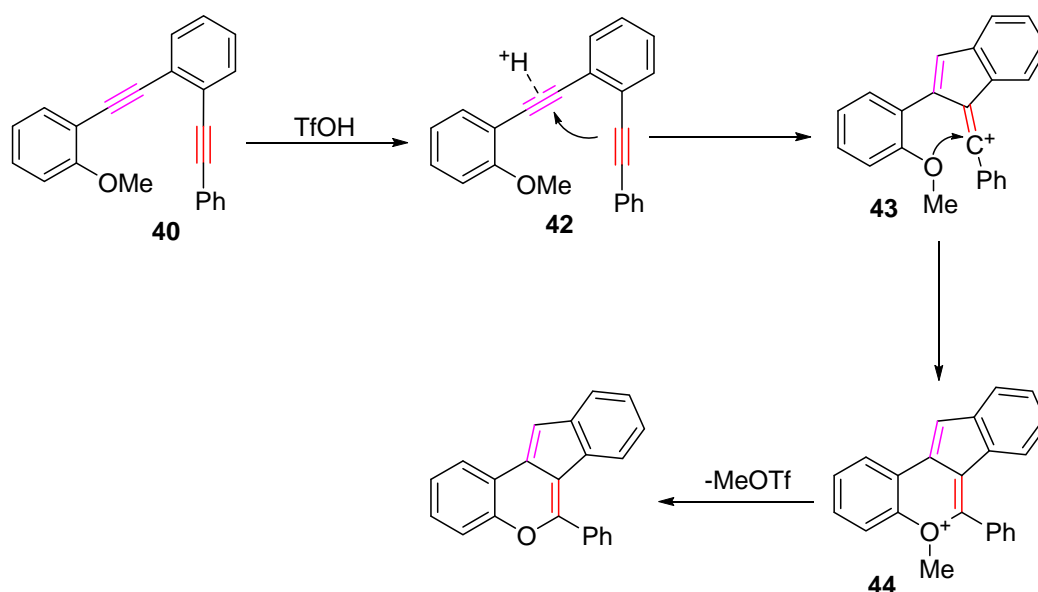
**Scheme 13.** TfOH-mediated cascade annulation to indenochromene.

The scope of this TfOH-mediated cascade annulation is shown in Scheme 14. Many interesting  $\pi$ -conjugated heterocycles containing chromene framework can be synthesized in good to high chemical yields. Some chromene-dyes, synthesized by this method, were applied to DSSCs, and POE ( $\eta$ , power conversion efficiency) was in a range of 5.07-6.71%.<sup>103</sup>



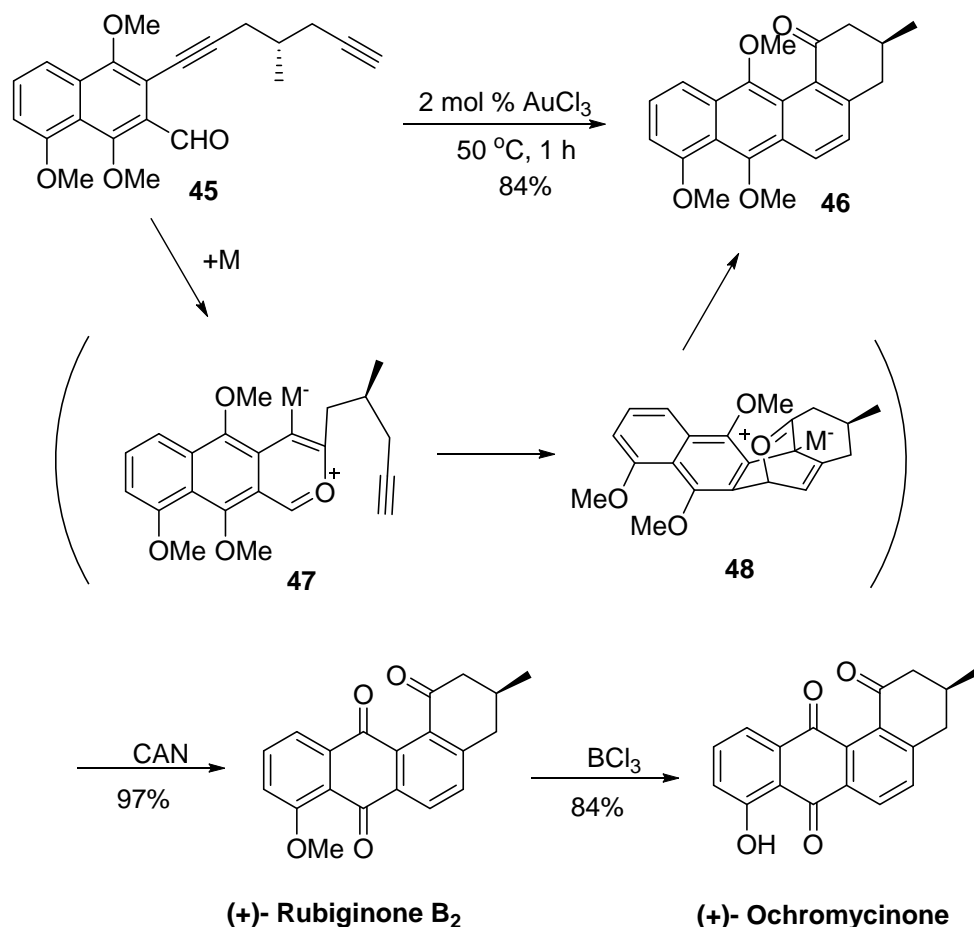
**Scheme 14.** Cascade annulation to chromene  $\pi$ -conjugated systems.

A proposed mechanism for this TfOH-mediated cyclization is shown in Scheme 15. TfOH activates the electron rich triple bond *ortho* to anisole. Then, 5-*endo-dig* alkyne-alkyne cyclization (as shown in **42**) leads to intermediate **43**, which is followed by intramolecular nucleophilic attack of OMe group to give intermediate **44**. Elimination of MeOTf affords the chromene  $\pi$ -conjugated product.



**Scheme 15.** A proposed mechanism for TfOH mediated cascade annulation of *ortho*-anisole **40**.

In Scheme 7, the gold- and copper-catalyzed intermolecular benzannulation between *ortho*-alkynyl aldehydes and alkynes is shown. Intramolecular version of this type of benzannulation affords polynuclear aromatic derivatives<sup>104</sup> (Scheme 16). For example, the reaction of enantiomerically pure **45** with catalytic amounts of AuCl<sub>3</sub> gave **46** in a high chemical yield with high ee, which was converted to (+) Rubiginone B<sub>2</sub> and (+) Ochromycinone.<sup>105</sup> First naphthopyrylium ion **47** is formed, and secondly intramolecular [4+2] cycloaddition gives intermediate **48**, and finally bond rearrangement affords **46**. Further, gold-catalyzed intramolecular carbocyclization of alkynyl ketones gives fused tri- and tetracyclic enones,<sup>106-107</sup> though they are not  $\pi$ -conjugated aromatics but aliphatic carbocycles.

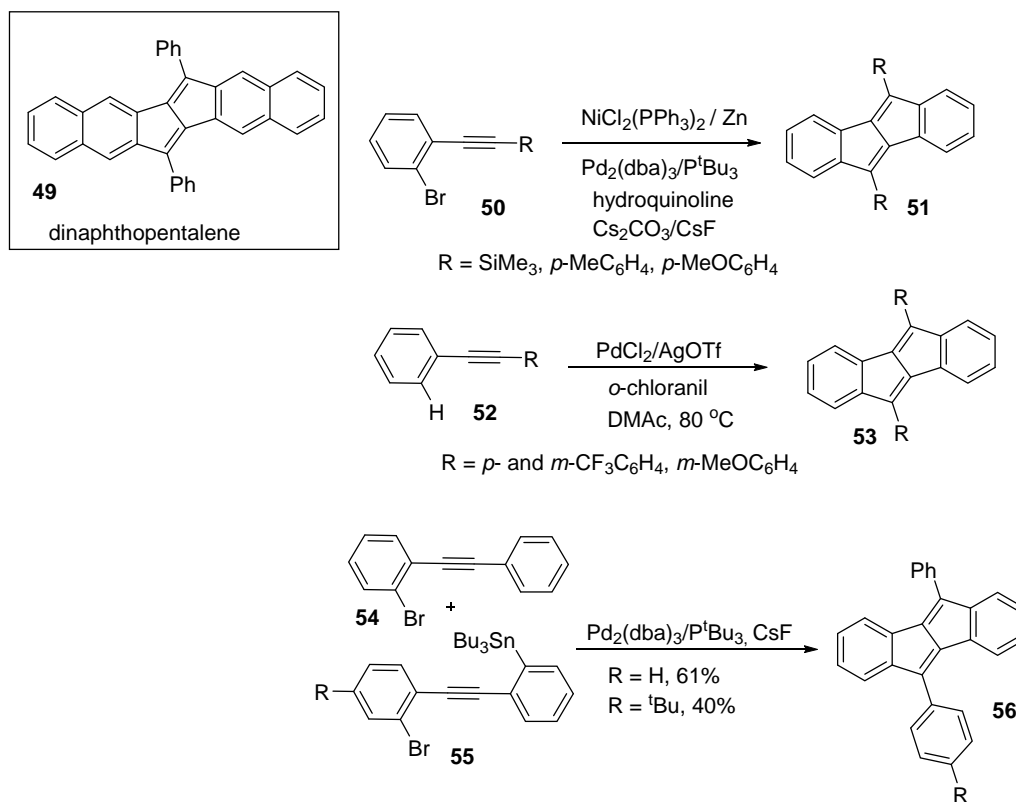


**Scheme 16.** Cascade benzannulation of *ortho*-alkynylaryl aldehyde **45**.

#### 4. Crossover annulation across alkynes through C-X and C-H activation

The dibenzopentalene framework, having two five-membered rings and two external benzene rings, attracts the keen interest of organo-materials chemists because of its increased stability and more extended  $\pi$ -conjugation than simple pentalene itself. For example, OFET performance data

of dinaphthopentalene **49**, shown in Scheme 20, were obtained in recent years.<sup>108</sup> Until now, a number of synthetic methods for dibenzo[*a,e*]pentalene derivatives have been reported. A few representative examples for catalytic homo- and crossover-annulations of alkynes are shown in Scheme 17. Homo-annulation of **50** via C-Br/C-Br cascade gave low yields of dibenzopentalenes **51**.<sup>109</sup> Homo-annulation of **52** via C-H/C-H cascade afforded good yields of the products **53**, but in a certain case the reaction did not proceed very well.<sup>110</sup> Most of the previous methods provide dibenzopentalenes symmetrically substituted at 5- and 10-positions, and only a limited number of approaches have been reported for the synthesis of unsymmetrically 5,10-disubstituted dibenzopentalenes, which are available through crossover annulation of two different alkynes. Crossover annulation between **54** and **55** via C-Br/C-Sn cascade of two different alkynes gave good yields of dibenzopentalenes **56** having two different substituents at C-5 and C-10 positions.<sup>111</sup> However, it is highly desirable to synthesize such differently substituted dibenzopentalenes via crossover annulation, which proceeds efficiently through C-H bond activation, instead of C-Sn bond activation.

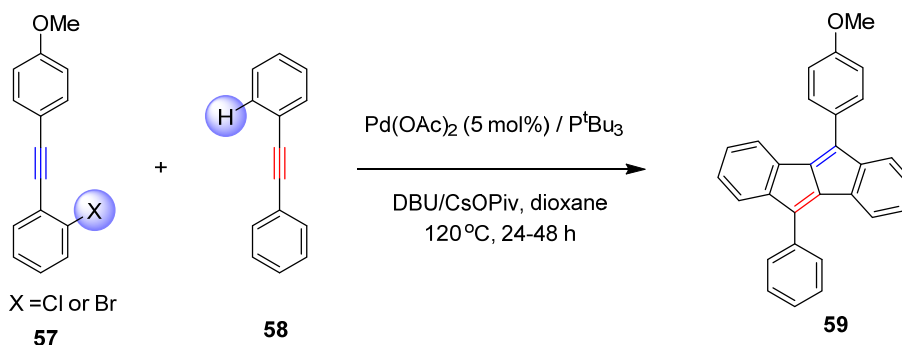


**Scheme 17.** Transition-metal catalyzed homo- and crossover-annulation to dibenzopentalenes.

We have found that cascade crossover annulation of two different alkynes, *ortho*-alkynylarylhalides **57** and diarylacetylenes **58**, proceeded very well using Pd(OAc)<sub>2</sub> catalyst together with appropriate ligand and base.<sup>112</sup> Optimization of reaction conditions are shown in

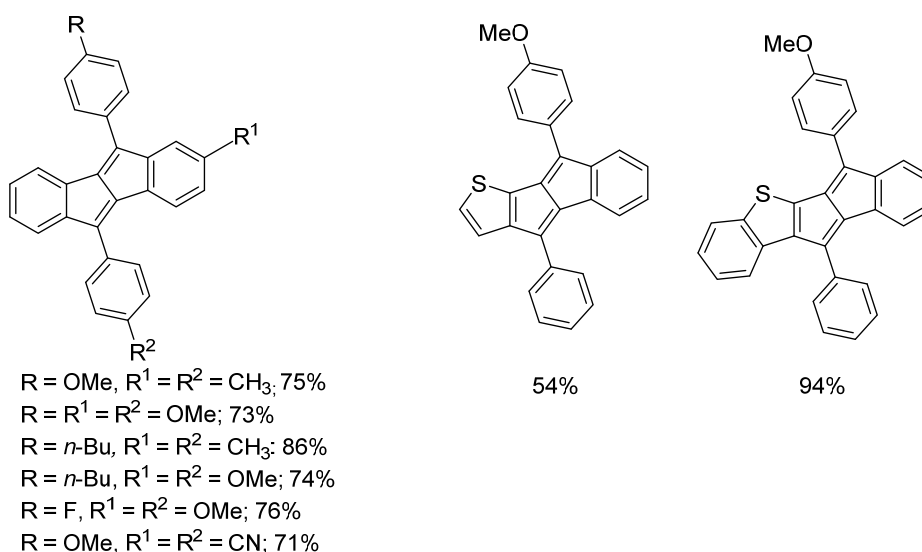


Scheme 18. The use of  $P(t\text{-Bu})_3$  ligand (15 mol%) and 3 equivalents of DBU/CsOPiv in the presence of 5 mol% of  $\text{Pd}(\text{OAc})_2$  afforded the crossover annulation product **59** in a high chemical yield. This is an intermolecular C-X/C-H crossover annulation.



**Scheme 18.** Crossover annulation of two different alkynes via C-X/C-H activation.

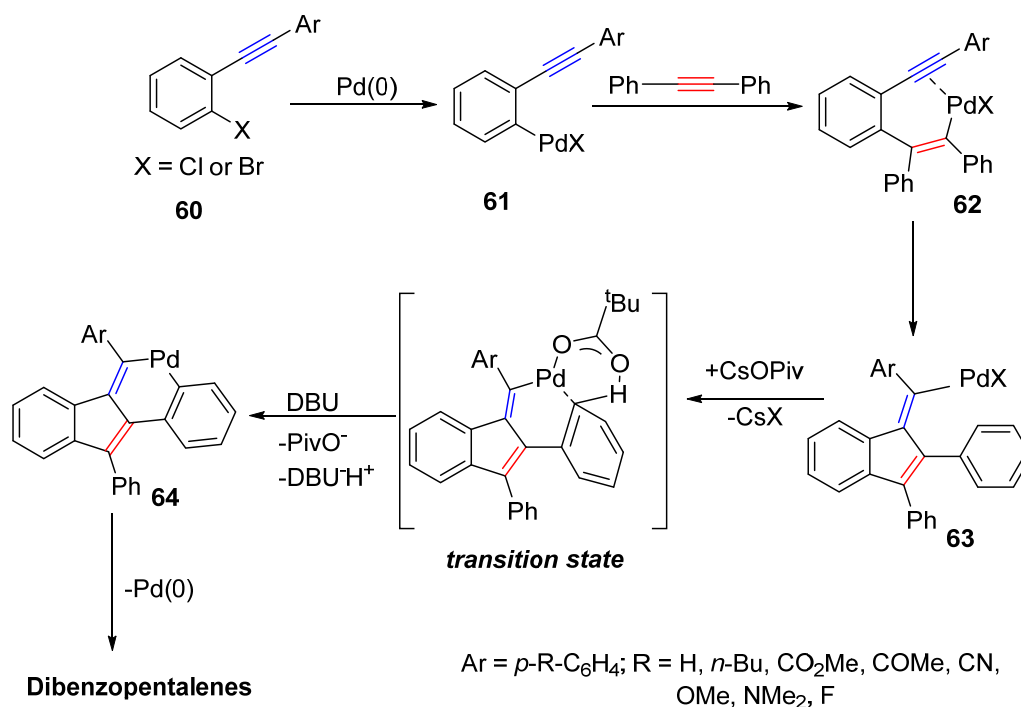
The representative dibenzopentalenes synthesized via this crossover annulation are shown in Scheme 19. A wide range of dibenzopentalene derivatives, having different (as well as same) substituents at C-5 and C-10 positions, and thiophene containing pentalenes can be synthesized in good to excellent yields.<sup>112</sup>



**Scheme 19.** Crossover annulation via C-X/C-H activation leading to a wide range of pentalenes.

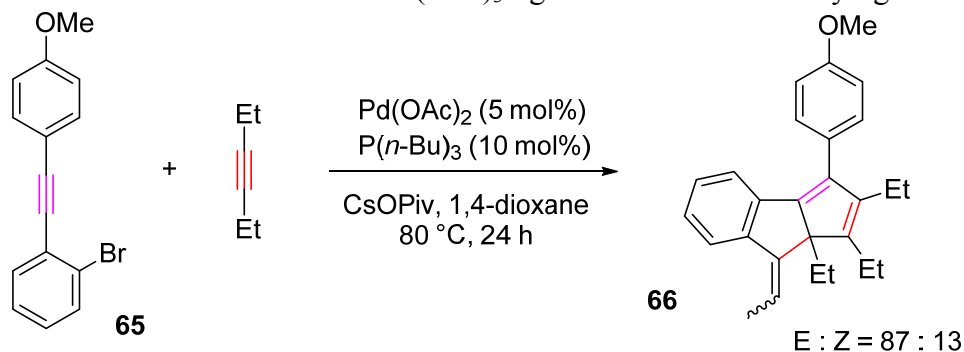
A proposed mechanism of the crossover annulation via C-X/C-H activation is shown in Scheme 20. Insertion of  $\text{Pd}(0)$  into C-X bond of *ortho*-alkynylaryl halide **60** gives intermediate **61**, which reacts with diphenylacetylene leading to intermediate **62**. Intramolecular carbopalladation of triple bond of **62** produces intermediate **63**. Ligand exchange between X and OPiv affords a transition state structure, in which C-H bond of benzene ring is activated through

interaction with oxygen atom of pivalate ligand. The formation of C-Pd bond and elimination of PivOH take place concomitantly, leading to intermediate **64**. A strong but non-nucleophilic base, DBU, converts PivOH to PivO<sup>-</sup> which is used again as a ligand of Pd. Reductive elimination of Pd(0) from **64** gives the desired crossover annulation dibenzopentalene.



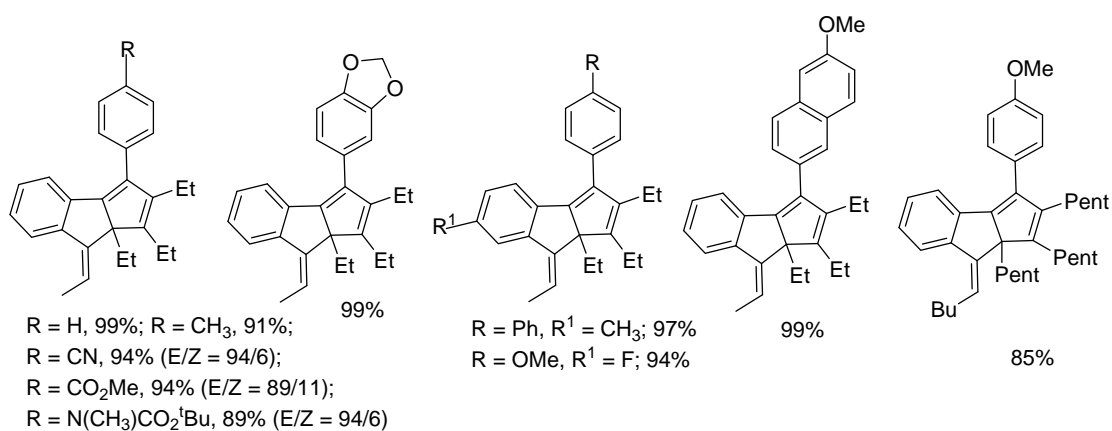
**Scheme 20.** A plausible mechanism for crossover annulation via C-X/C-H activation.

Differently substituted dibenzopentalenes can be synthesized very smoothly as shown above, but in that case the partners of *ortho*-alkynylhalides are diarylacetylenes. If dialkylacetylenes are used as a partner, a different type of annulation takes place<sup>113</sup> (Scheme 21). The reaction between diethylacetylene and *ortho*-alkynylaryl bromide **65** afforded **66** as a mixture of *E*- and *Z* isomers, and optimization of the reaction conditions is shown in the Scheme.<sup>113</sup> Here, the use of P(*n*-Bu)<sub>3</sub> ligand gave a better result than the use of P(*t*-Bu)<sub>3</sub> ligand and the other bulky ligands.

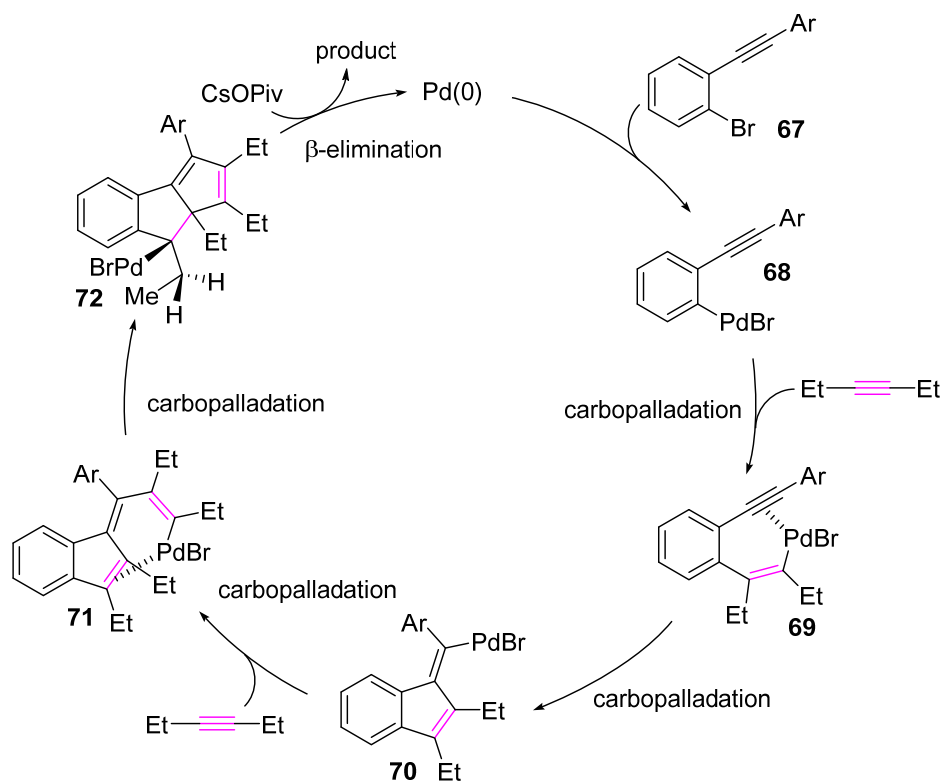


**Scheme 21.** Cascade cyclization between *ortho*-alkynylaryl bromide and diethylacetylene.

The scope of this cascade cyclization is shown in Scheme 22. A wide range of new  $\pi$ -conjugated aromatics can be synthesized through this crossover cyclization.



**Scheme 22.** Crossover annulation between *ortho*-alkynylaryl bromides and dialkylacetylenes.

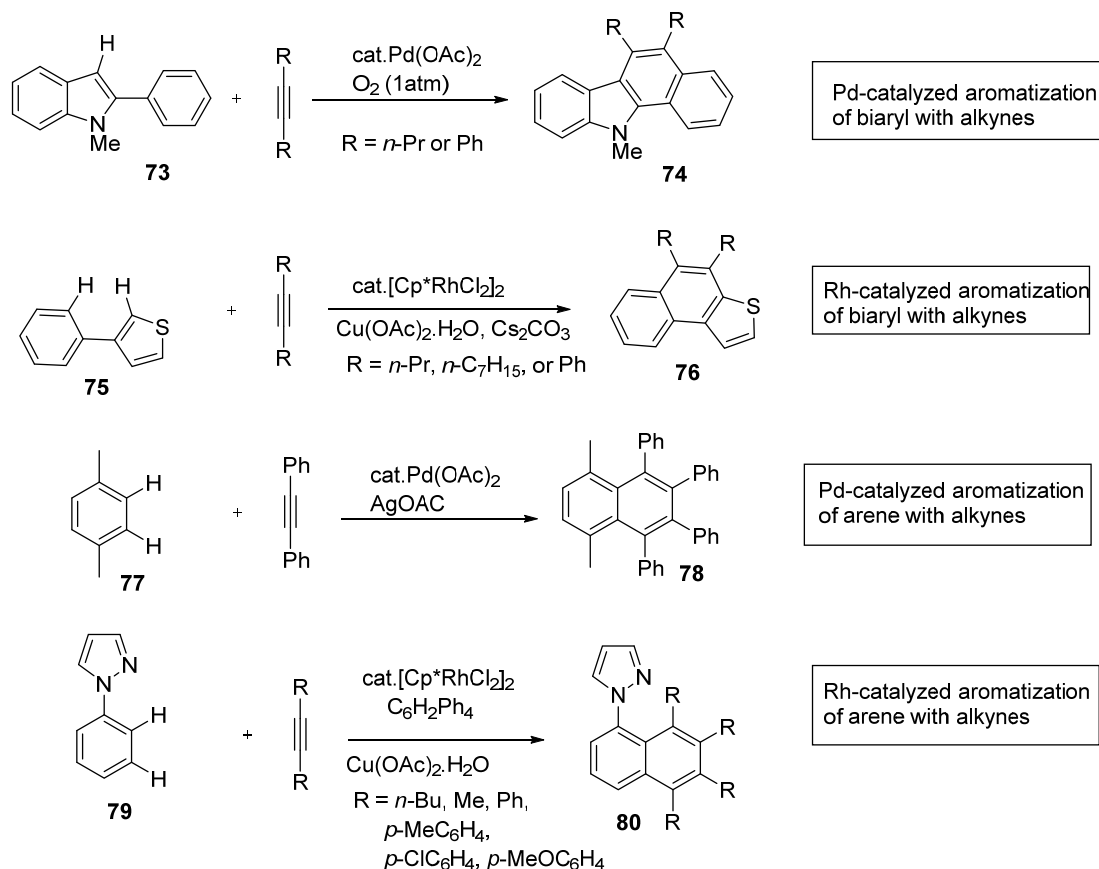


**Scheme 23.** A plausible mechanism for crossover annulation between *ortho*-alkynylaryl bromides and diethylacetylene.

A proposed mechanism for this crossover annulation is shown in Scheme 23. The formation of intermediate **68** from **67**, followed by intermolecular carbopalladation leading to intermediate

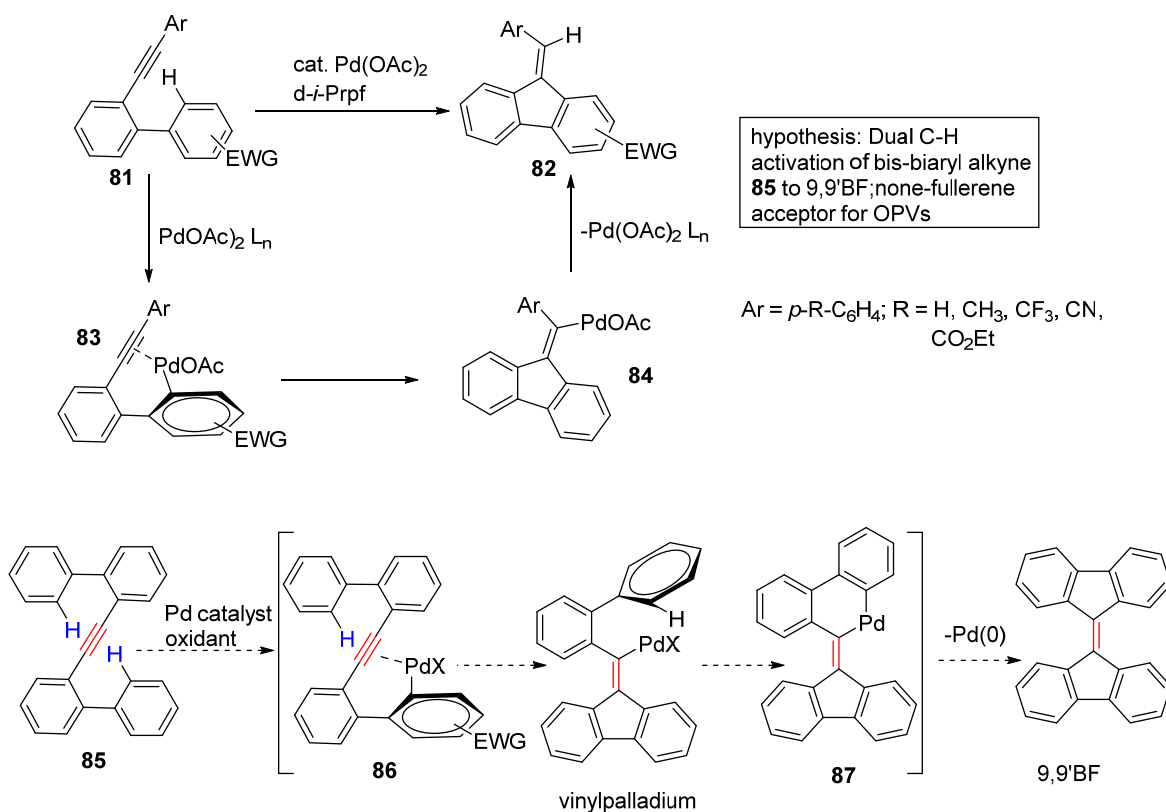
**69** and subsequent intramolecular carbopalladation to intermediate **70**, are very similar as those shown in Scheme 20. Since there is no C-H bond of benzene at cyclopentene ring of **70**, the third carbopalladation takes place between **70** and diethylacetylene, leading intermediate **71**. Further, the fourth carbopalladation produces intermediate **72**, which undergoes  $\beta$ -elimination of H-Pd by the assistance of CsOPiv to give the  $\pi$ -conjugated product.

Besides C-X/C-H activation mentioned above, if crossover annulation between arenes and alkynes via C-H/C-H activation becomes feasible, such a reaction is very desirable and ideal for constructing  $\pi$ -conjugated aromatics. Some representative previous reactions are shown in Scheme 24. Pd- and Rh-catalysts are effective for aromatization between biaryls (**73** and **75**) and alkynes,<sup>114,115</sup> giving the aromatization compounds **74** and **76**, respectively. Also, the catalysts are useful for the annulation between **77** and diphenylacetylene, and between **79** and alkynes, to give the annulation products **78** and **80**, respectively.<sup>116,117</sup> Recently, our group reported Rh(III)-catalyzed regioselective annulation between naphthylen-1-ylcarbamates and alkynes ( $\text{RC}\equiv\text{CR}$ );<sup>118</sup> the use of neutral Rh catalyst,  $[\text{Cp}^*\text{RhCl}_2]_2$ , gave 2,3-di-R-substituted-1H-benzo[de]quinolines through *peri*-C-H activation, while the use of cationic Rh catalyst,  $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ , afforded 2,3-di-R-substituted-1H-benzo[g]indoles via *ortho*-C-H activation. Those annulations proceed via intermolecular reactions.



**Scheme 24.** Arene/alkyne cross annulation via C-H/C-H activation to  $\pi$ -conjugated aromatics.

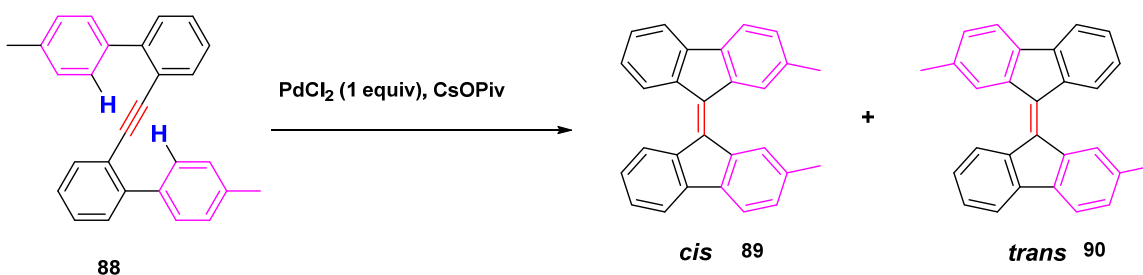
Intramolecular annulation between alkynes and arenes of **81**, in which EWG group was substituted, via C-H activation was catalyzed by Pd(OAc)<sub>2</sub>/d-*i*-Prpf (1,1'-bis(diisopropylphosphino)ferrocene) system, giving fluorene derivatives **82** in very high *cis*-selectivity (Scheme 25).<sup>119</sup> The C-H activation takes place at EWG substituted benzene (as shown in **83**), and following carbopalladation gives **84**. It occurred to us that 9,9'-bisfluorenylidene (9,9'BF) would be produced via dual C-H activation if bis-biaryl alkyne **85** was used instead of biaryl-aryl alkyne **81** (Scheme 25); such 9,9'BF is interesting acceptor for OPVs (organic photovoltaics). The first C-H activation would give **86**, which would afford **87** via the second C-H activation.



**Scheme 25.** Fluorene vs. bisfluorene synthesis via C-H vs dual C-H activation.

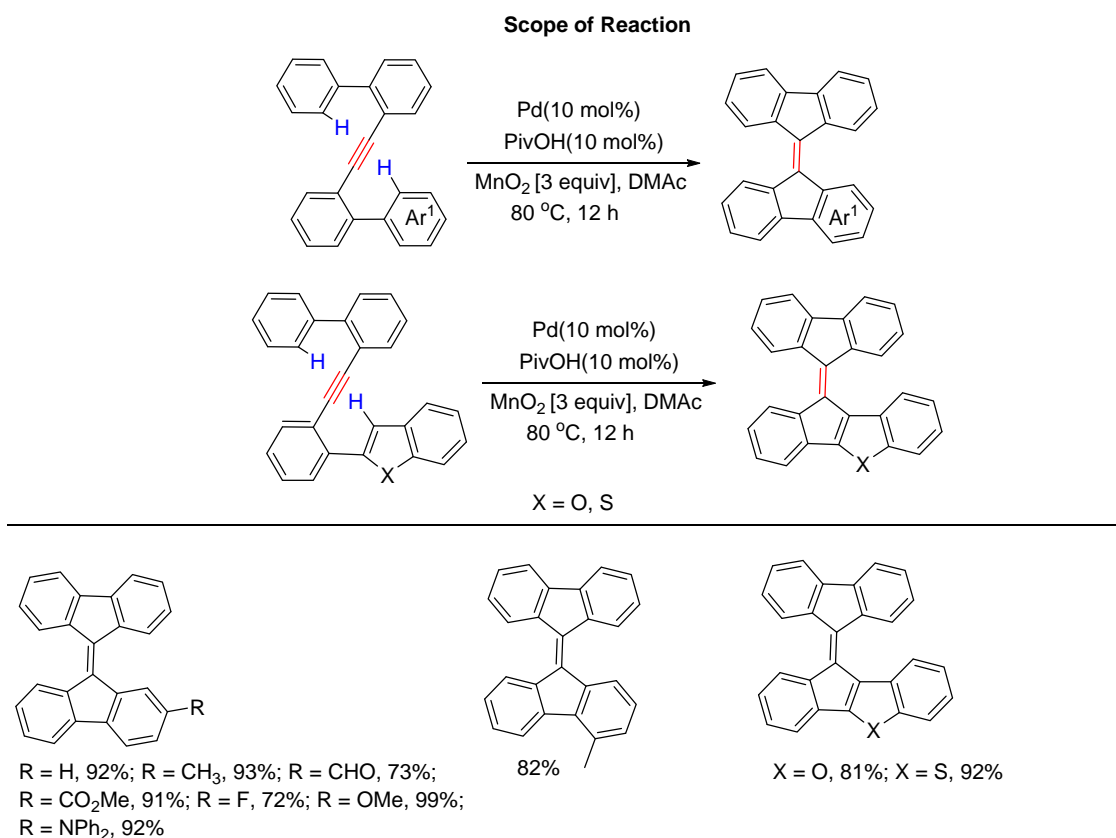
Screening of the reaction conditions for the dual C-H bond activation of **88** was carried out and the optimized conditions are shown in Scheme 26. The conditions shown in Schemes 18, 24, and 25 were not effective at all. The use of one equivalent of PdCl<sub>2</sub> together with CsOPiv gave 9,9'BF, **89** and **90**, in 89 % yield, but the yield decreased dramatically to 5 % by the use of 10 mol% of PdCl<sub>2</sub>. This result clearly indicated that the use of appropriate oxidant would be needed for the catalytic reaction. We found that the use of 3 equivalents of MnO<sub>2</sub> oxidant together with 10 mol% of PivOH in the presence of 10 mol% PdCl<sub>2</sub> catalyst is the best condition, leading to 98 % yield of 9,9BF, as a mixture of *cis*-**89** and *trans*-**90** (Scheme 26).<sup>120</sup> In general, a mixture of *cis*- and *trans*-isomers was obtained, and the reaction at low temperatures (for example, room

temperature) gave the *cis*-isomer predominantly, whereas at higher temperatures the ratio of the *trans*-isomer increased. Detailed experiments using NMR indicated that isomerization from *cis*- to *trans*-isomer took place at higher temperatures or even at room temperature by keeping for prolonged time of period.



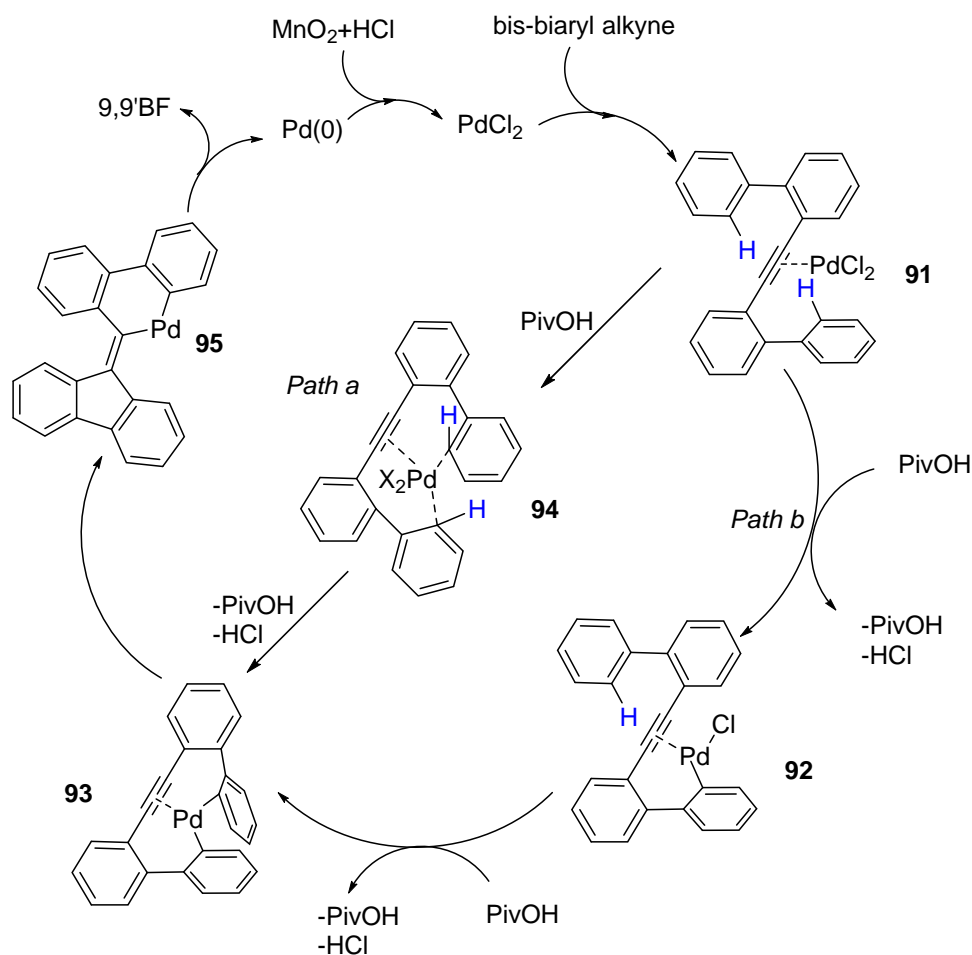
**Scheme 26.** Optimization of the reaction conditions for dual C-H activation.

Scope of the dual C-H activation for the synthesis of 9,9-BFs is summarized in Scheme 27. A wide range of 9,9-BFs including heterocycles can be synthesized in high chemical yields through this method.



**Scheme 27.** Dual C-H activation of bis-biaryls to 9,9-BFs.

A plausible mechanism for this dual C-H activation is shown in Scheme 28.<sup>120</sup> There are two possible pathways from intermediate **91**, in which a triple bond coordinates to Pd(II). Ligand exchange of chlorine atom (or two chlorine atoms at the same time) to PivO gives the transition state intermediate **94** shown in path a. Then C-H replacement with Pd affords intermediate **93**. Alternatively, a stepwise process is conceivable as shown in path b, which also gives intermediate **93** through **92**. Then, carbopalladation of triple bond with C-Pd bond produces intermediate **95**. Reductive elimination of Pd(0) from the palladium(II) intermediate **95** gives 9,9-BF and regenerates Pd(0) catalytic species.



**Scheme 28.** A plausible mechanism for dual C-H activation of bis-biarylalkyne.

## Conclusions

$\pi$ -Conjugated carbo- and hetero-cycles are synthesized through annulation across alkyne of *ortho*-alkynylaryl substrates, using iodine-mediated and/or transition metal-catalyzed, as well as Brønsted acid-catalyzed, reactions. Cascade annulation across two alkynes of 1,2-dialkynyl

substituted substrates gives carbo- and heterocycles having more complicated and congested  $\pi$ -system. Intermolecular crossover annulation of two different bis-arylalkynes via palladium-catalyzed C-H bond activation affords dibenzo[*a,e*]pentalenes having two different substituents at C-5 and C-10 positions. Intramolecular crossover annulation of bis-biarylalkynes via palladium-catalyzed dual C-H bond activation gives 9,9'-bis-fluorene derivatives.

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major projects funded by NPST, King Saud University. He has 4 PCT patents and more than 80 research articles. He is acting as expert reviewer for some reputed international journals. His area of research includes synthesis of novel organic small molecules through a domino multi-component and cycloaddition reactions and their biological studies.