

Regioselective [4+2] Benzannulation : Synthesis of Polysubstituted Benzenes

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INTRODUCTION

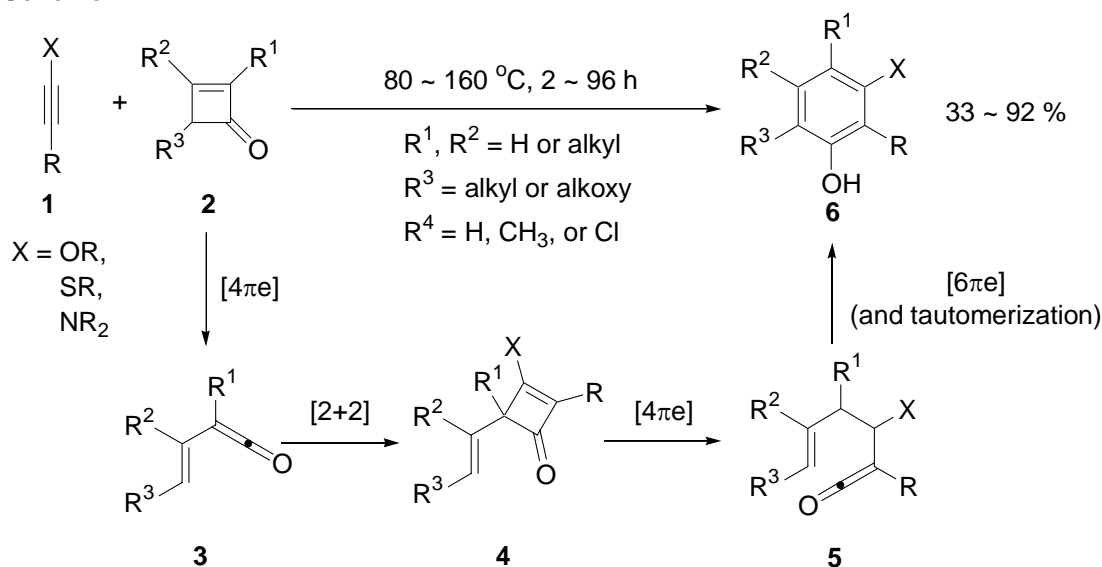
Traditionally, polysubstituted benzenes have been synthesized by substitution reactions on readily available aromatic precursors.¹ However, with aromatic substitutions, it can be difficult to obtain a desired isomer because of low regioselectivity. And, in some cases, over substitution becomes a problem. Moreover for aromatic precursors that bear multiple substituents it can be difficult to add additional substituent with high regioselectivities by classical aromatic substitution reactions. The alternative approach of directed *ortho* metalation can be useful but requires precursors which are stable to the metallating agents.² Thus, in order to obtain polysubstituted benzenes, novel synthetic strategies have been designed.

A synthetically useful approach which provides polysubstituted aromatic compounds quite efficiently is the cyclization of unsaturated acyclic compounds. This methodology is related to the work of Berthelot *et al.* who, in 1866, reported that benzene could be formed as a minor product from acetylene via thermal cyclotrimerization.³ In more recent works, this process has been transformed into a synthetically useful methodology. The first efficient examples were reported in 1948 by Reppe *et al.* for the transition metal catalyzed cyclotrimerization of alkynes.⁴ This trimerization reaction was applied to the synthesis of a variety of polysubstituted benzenes with poor regiocontrol for intermolecular cases. However it was observed that good regiocontrol could be achieved in related intramolecular cyclizations. The problem of formation of isomers by trimerization could be resolved by a Diels-Alder like [4+2] benzannulation. In this approach the regioselectivity would be simplified because there are only two components. And the four carbon component has four centers established. This abstract will summarize [4+2] benzannulation strategy for the efficient synthesis of polysubstituted benzenes.

[4+2] BENZANNULATIONS BETWEEN VINYLKETENES AND ALKYNES

One of the earliest examples, reported by Danheiser *et al.* in 1984, utilizes a ring opening of the cyclobutenone **1** to generate a vinylketene.^{5a} In the overall reactions cyclobutenone derivatives react with heteroatom substituted alkynes **2** to produce polysubstituted phenols **6** with high regioselectivity. This annulation proceeds via a cascade of four pericyclic reactions (Scheme 1). The regioselectivity of this reaction arises from the regiospecific [2+2] cycloaddition between a ketene **3**, generated upon heating the cyclobutenone derivatives, and the acetylene derivative. This method is very useful for construction of polysubstituted phenols, but the limited availability of cyclobutenone precursors diminishes the synthetic utility of this process.

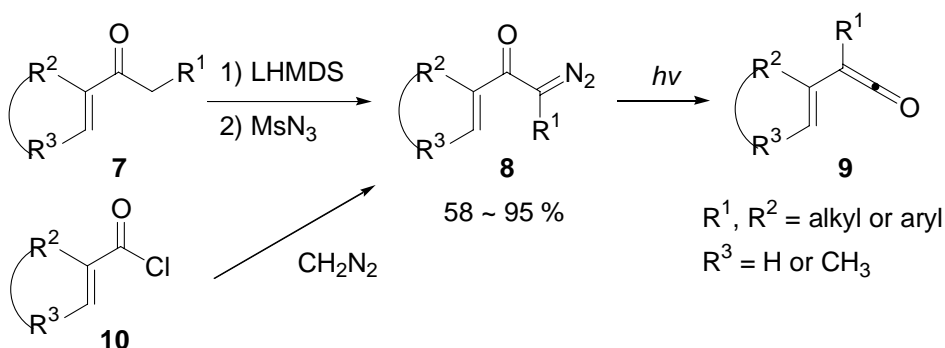
Scheme 1.



As an alternative to the use of cyclobutenone precursors, Danheiser *et al.* developed a photochemical version of this reaction (Scheme 2).^{5b} In this approach the vinylketene **9** is generated from an

unsaturated α -diazo ketone **8** via a photochemical Wolff rearrangement. This vinyl ketene can then undergo the [2+2] cycloaddition with alkynes as shown in Scheme 1.

Scheme 2.



Since a wide variety of functionalized vinyl α -diaz ketones can be obtained in one step from simple ketones **7** and the acid chloride **10**, the scope of this method is significantly expanded by this development. By applying this benzannulation approach, Danheiser *et al.* have synthesized a variety of natural products (Figure 1).^{5c-e}

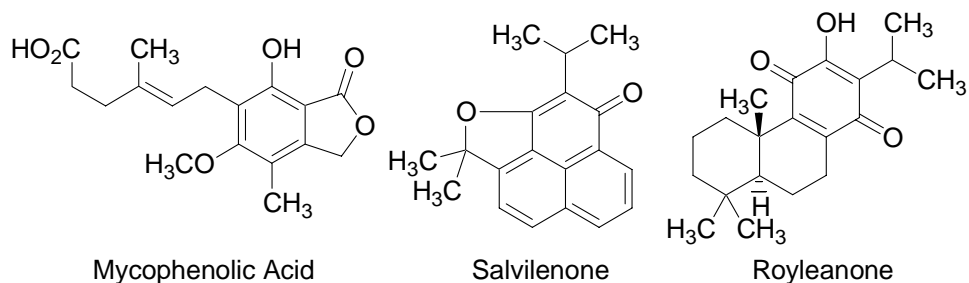
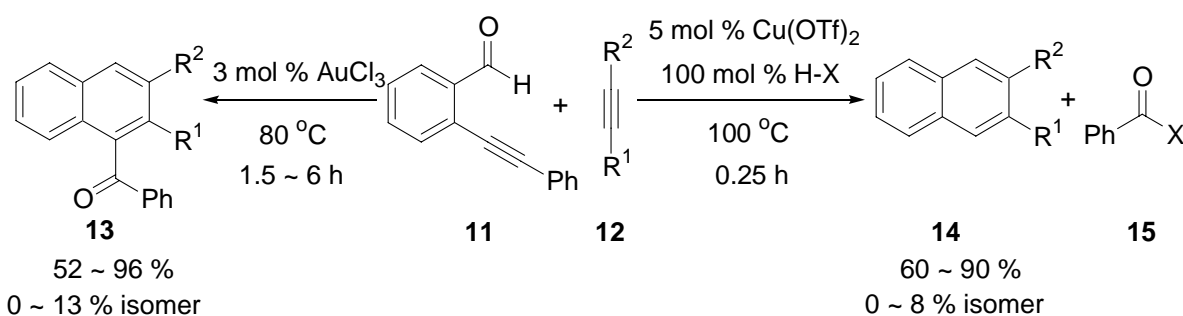


Figure 1.

[4+2] BENZANNULATIONS BETWEEN *O*-ALKYNYL BENZALDEHYDE AND ALKYNES

Another type of [4+2] benzannulation was developed by Yamamoto *et al.* This approach utilizes an ortho alkyne aromatic aldehyde as the 4-carbon component (Scheme 3).⁶ In the presence of a catalytic amount of AuCl_3 , the naphthyl ketone derivatives **13** are obtained with high regioselectivity starting from the aldehyde **11** and the alkyne **12**. When $\text{Cu}(\text{OTf})_2$ is used as a catalyst in the presence of a stoichiometric amount of a Brønsted acid H-X , debenzoylated naphthalene **14** can be obtained with high regioselectivity.

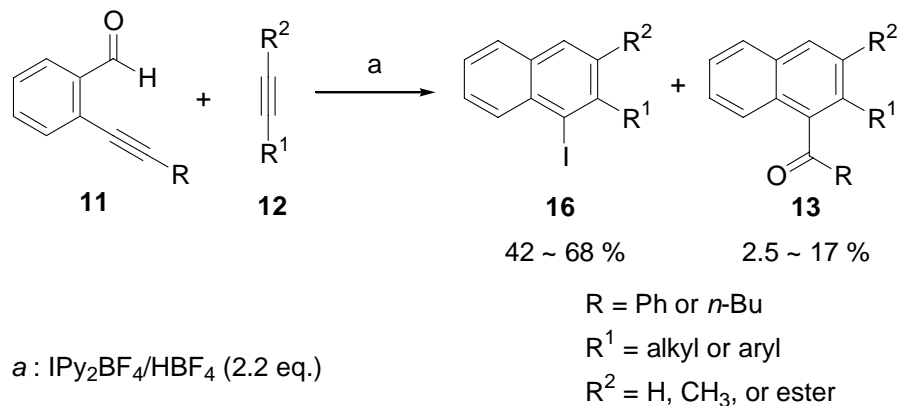
Scheme 3.



Recently, a similar reaction was reported by Barluenga *et al.* utilizing *in situ* "I" rather than metal Lewis acids to activate the aldehydes **11** (Scheme 4).⁷ When the alkynes **12** were used as two carbon components, the idonaphthalene derivatives **16** were formed as major products with complete

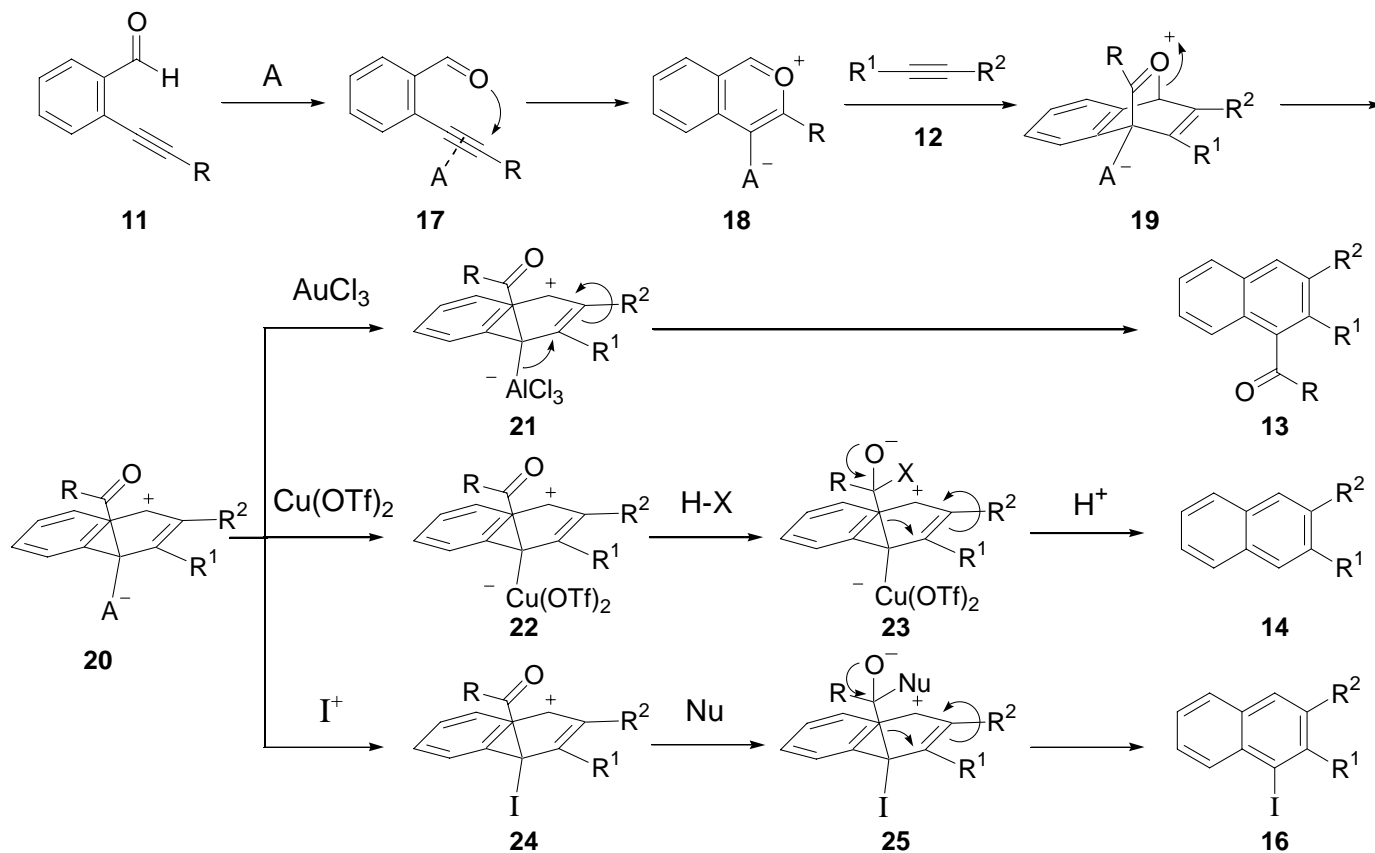
regioselectivity. The naphthyl ketone derivatives **13**, which were major product when AlCl_3 was used, were only minor products.

Scheme 4.



The observed products and regioselectivity can be rationalized by the proposed reaction mechanism (Scheme 5). The coordination of the triple bond of **11** to the promoter can be considered to activate it to nucleophilic attack by the carbonyl oxygen to give the complex **18**. Subsequent formal [4+2] cycloaddition

Scheme 5.



between the pyrylium ylide **18** and alkyne **12** generates the complex **19**. After C-O bond is broken, the stable carbocation **20** is generated. Without H-X, the elimination of AlCl₃ illustrated in **21** would proceed to produce **13**. However in the presence of H-X, the attack of X⁻ would produce **23**, which undergoes the β-elimination and subsequent protolysis of the Cu-O bond to generate **14**. Also, in the case of I⁺ promotion, a nucleophile (possibly pyridine) can attack **24** to afford **25**. After the β-elimination, **16** is generated.

The cycloaddition between **18** and **12** is believed to be stepwise or concerted asynchronous processes. The observed regioselectivity can be explained by considering the stability of the positive charge at the vinyl position in Figure 2. The alkyl groups favor the R¹ position more than protons because alkyl groups can stabilize the α-carbocation through hyperconjugation. Silyl groups prefer the R² position because they can stabilize the β-carbocation. Electron withdrawing groups prefer the R² position because they would destabilize the α-carbocation.

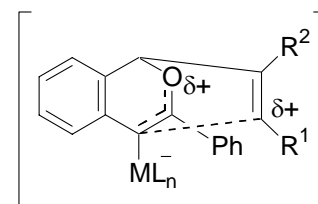


Figure 2.

As a result, some different substitution patterns of naphthalenes can be obtained by changing the mode of activations. The regioselectivities are generally very high and the reactions take only several hours. However, these reactions are limited to the synthesis of naphthalene derivatives.

[4+2] BENZANNULATION BETWEEN ENYNES AND ALKYNES

Enynes can be used as four carbon components for [4+2] benzannulations. Although enynes have been used in intramolecular benzannulations since 1994,⁸ more recently their utility has been significantly enhanced by the development of intermolecular [4+2] benzannulations.

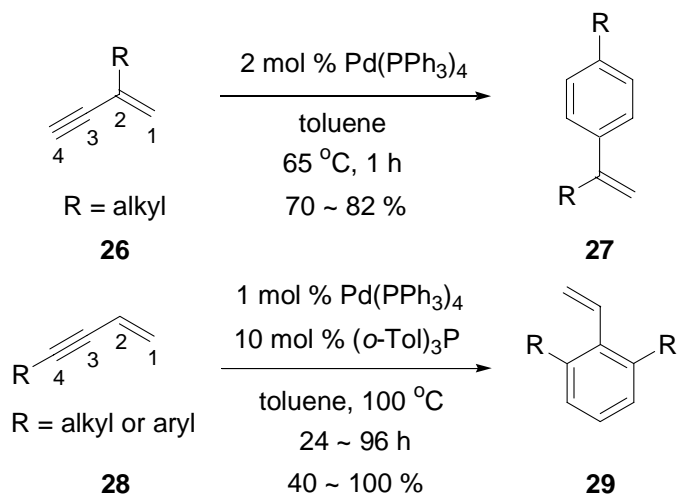
Yamamoto *et al.* first demonstrated the formation of aromatic compounds by dimerization of enynes (Scheme 6).^{9,10} In the presence of Pd(0) catalyst, the 2-substituted enyne **26** and the 4-substituted enyne **28** dimerize to give corresponding benzene derivatives **27** and **29** with complete regioselectivity. Other possible isomeric products were not detected. Since **28** is less reactive than **26**, the additional ligand and higher temperature are required to promote the slow dimerization of **28**. The cross dimerization between

two different enynes was also attempted. But the significant amounts of products derived from homo-dimerization were always observed.

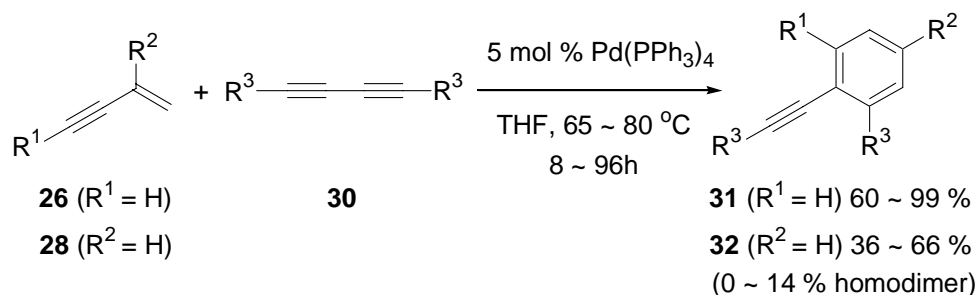
Although 2- and 4-substituted enynes can dimerize successfully, dimerization of 1-substituted, disubstituted, or trisubstituted enynes still remains a challenging task. The unreactive nature of highly substituted enynes seems to be the source of this limitation.

In order to develop cross-benzannulation reactions between enynes and other two carbon components, the homo-dimerization of enynes must be avoided. For this result the poor reactivity of highly substituted enynes is beneficial. When diyne **30** is used as a two carbon component for the benzannulation reaction with a 2-substituted enyne **26**, the homo-dimerization is not significant (Scheme 7).¹¹ This is due to the significant rate difference between the cross-benzannulation and the homo-dimerization. Moreover, the reaction is chemo- as well as regioselective. The 1,2,4-trisubstituted benzene **31** is obtained as a single isomer. However, when a bulky diyne ($R^3 = \text{TMS}$) is employed, the cross-benzannulation becomes slower. Thus, less reactive enynes must be added slowly in order to avoid homo-dimerization. When 4-substituted enyne **28** was used in the cross-benzannulation, the situation becomes even more problematic (Scheme 7).¹² In this case, although the cross-benzannulation product **32** was obtained with high regioselectivity, the homodimer **29** was also detected. This observation indicates that the homo-dimerization becomes competitive with the cross-benzannulation and the reactivities of **28** and **30** as two carbon components are not very different.

Scheme 6.

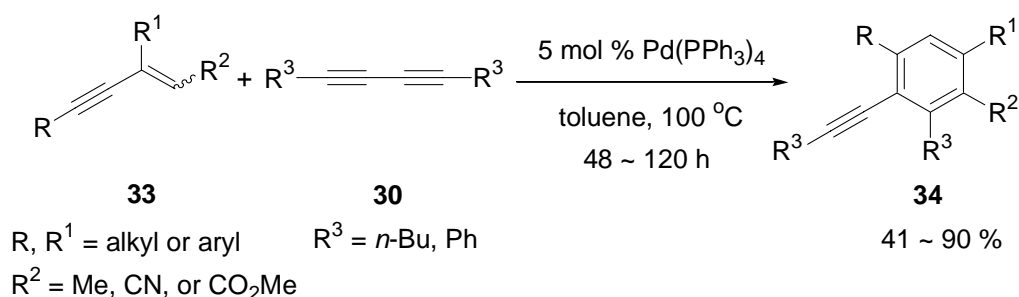


Scheme 7.



In the case of di- and tri-substituted enynes **33**, there is not a chemoselectivity issue since di- and tri-substituted enynes do not dimerize readily (Scheme 8).¹² However, the reaction conditions for these substrates required high temperature due to the low reactivity of di- and tri-substituted enynes. Interestingly, there is a significant reactivity difference between geometric isomers of **33**. It was found that the *E*-isomer is less reactive than the *Z*-isomer. Nonetheless tetra- and penta-substituted benzenes **34** can still be accessed with complete regio- and chemoselectivity.

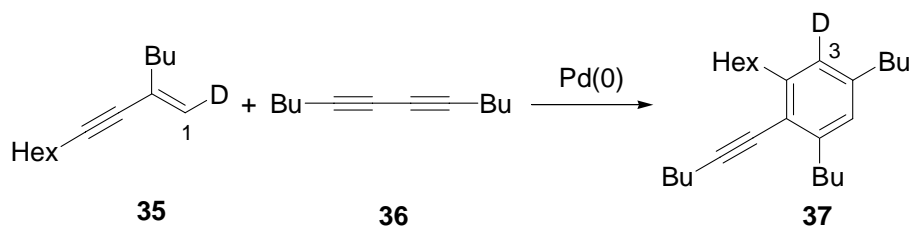
Scheme 8.



In order to clarify the reaction mechanism, Yamamoto *et al.* have undertaken a mechanistic study employing deuterium labeling (Scheme 9).¹² In a series of experiments, each proton of the enyne was deuterated separately. The isotope distribution in the products from the labeled enynes was then analyzed. The result indicated that the deuterium atom at the *E*-position of C1 in the enyne **35** migrate to the C3 position in benzene **37**. The exact mechanism of the deuterium migration is still unclear. However, the involvement of this hydrogen migration seems to be responsible for the reactivity difference between *E*- and *Z*-isomers of the enyne. The elucidation of detailed mechanism of the entire process and the origin of regioselectivity are still under

investigation.

Scheme 9.



CONCLUSION

It is clear that the [4+2] benzannulation approach to highly substituted benzenes has advantages over the traditional substitution approaches or the alkyne cyclotrimerization approaches. The problem of

oversubstitution is avoided and the regioselectivity is well-controlled, even in the case of intermolecular reactions. As a result, tri-, tetra-, and penta-substituted benzenes can be easily synthesized with high regioselectivity by [4+2] benzannulation approach. The examples shown above usually employ only catalytic amounts of metal. In future work, more reactive catalytic systems, higher yields, and the substrates with a variety of functional groups need to be investigated. Nonetheless [4+2] benzannulation is not only synthetically useful but also advantageous from the viewpoint of atom economy.

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