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Award Accounts

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Aryne, *ortho*-Quinone Methide, and *ortho*-Quinodimethane: Synthesis of Multisubstituted Arenes Using the Aromatic Reactive Intermediates

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A useful synthetic method for building up multisubstituted arenes of structural complexity and diversity by use of aromatic reactive intermediates is described. Regardless of the transient character arising from a highly strained carbon–carbon triple bond, arynes have been found to undergo facile insertion into an element–element σ-bond and three-component coupling reactions. In addition, *ortho*-quinone methides and *ortho*-quinodimethanes have also been demonstrated to be convertible into multisubstituted arenes by utilizing their *exo*-dienyl moieties.

1. Introduction

Reactions by use of carbon reactive intermediates, including carbenes, carbocations, carbon radicals, carbanions, etc., have played a pivotal role in synthetic organic chemistry, because they offer potent and unique methods for constructing carbon frameworks, which would not be achievable with stable compounds, leading to production of diverse invaluable molecules.[1] On the other hand, a main bottleneck in the development of new reactions employing the reactive intermediates comes from difficulties in controlling their salient reactivities, which often cause undesirable side reactions. In this context, we envisaged that there should be a number of unexploited reactions of potential synthetic significance, which would be feasible under controlled reaction conditions with the aid of designed reactants and/or catalysts. Among the carbon reactive intermediates listed in Figure 1, our attention has been focused on those bearing carbon–carbon multiple bonds, that is, arynes (didehydroarenes),[2] *ortho*-quinone methides (6-methylene-2,4-cyclohexadienones),[3] and *ortho*-quinodimethanes (5,6-dimethylene-1,3-cyclohexadienes),[4] because they are good molecular scaffoldings for building up aromatic skeletons ubiquitously found in various functional organic molecules.

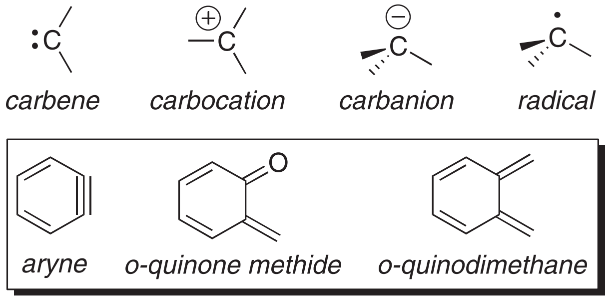
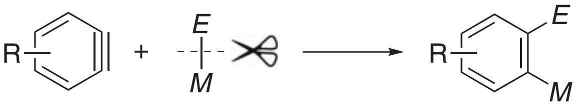


Figure 1. Representative carbon reactive intermediates.

2. Reaction Using Arynes

2.1 Catalytic Insertion Reaction into an Element–Element σ-Bond. The transition-metal-catalyzed insertion reactions of unsaturated carbon–carbon bonds into a metal-containing σ-bond have attracted considerable attention as a powerful method for the straightforward synthesis of highly functionalized organometallic compounds, in which carbon–metal and carbon–element bonds are generated simultaneously in a regio- and stereoselective manner.[5] The resulting organometallic compounds are convertible into complex molecular skeletons through subsequent carbon–carbon bond formation and/or introduction of functional groups by utilizing their carbon–metal bonds. Although many insertion reactions using various combinations of metallic compounds (metal: B, Si, Sn, …) and unsaturated carbon–carbon bonds (alkyne, 1,3-diene, 1,2-diene, and simple alkene) have been accomplished thus far, no report was available on such reactions with transient arynes until our success in carbostannylation, despite their great potential for the synthesis of functionalized arylmetal compounds (Scheme 1).[6]

2.1.1 C–Sn σ-Bond: The insertion reaction into a carbon–tin σ-bond[7] smoothly took place when in situ-generated benzyne (didehydrobenzene, from 2-(trimethylsilyl)phenyl triflate (**1a**)[8] and a fluoride ion) was allowed to react with



Scheme 1. Insertion reactions of arynes into a metal-containing σ-bond.

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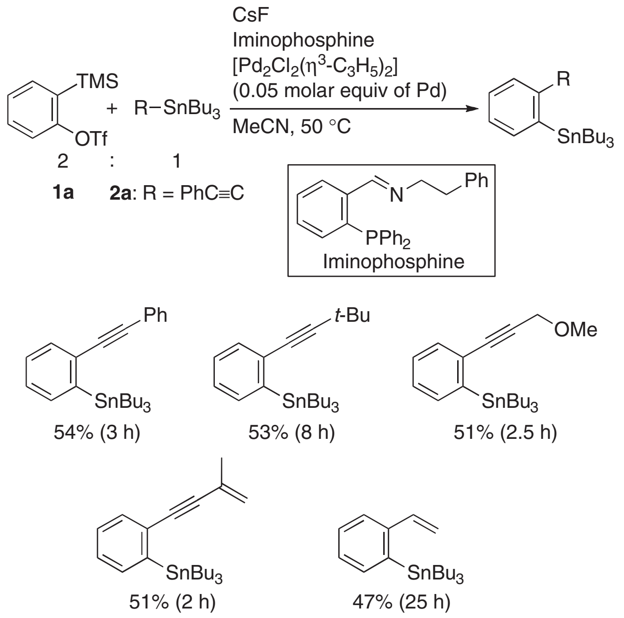
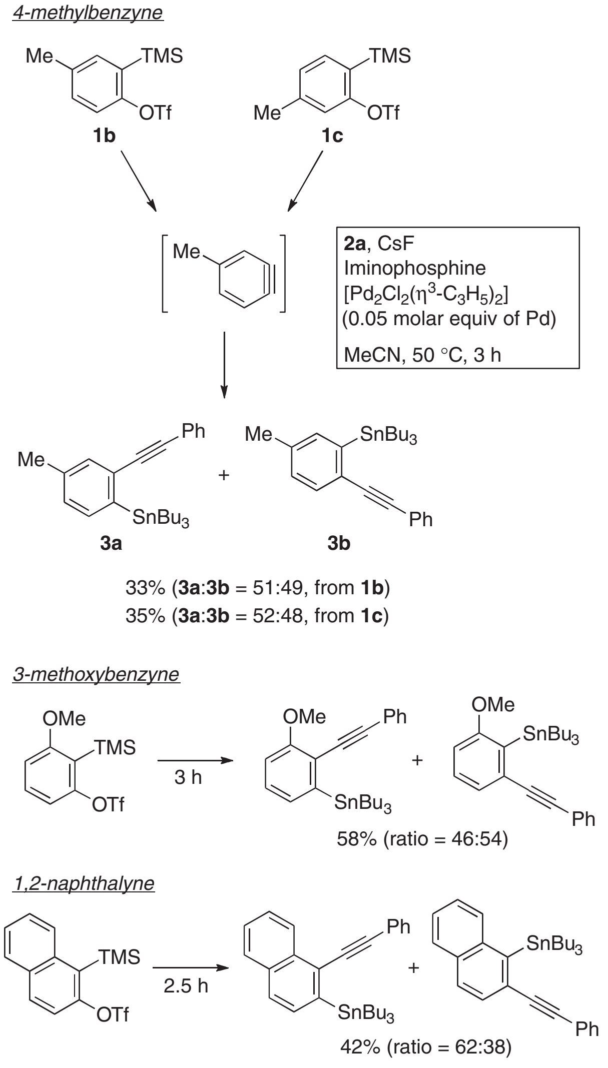
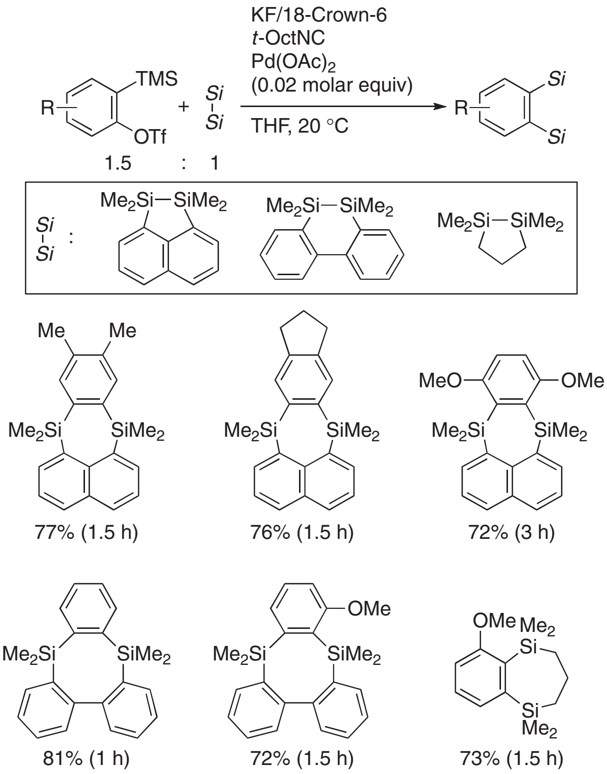


Scheme 2. Pd–iminophosphine-catalyzed carbostannylation of benzyne.



Scheme 3. Carbostannylation of unsymmetrical arynes.

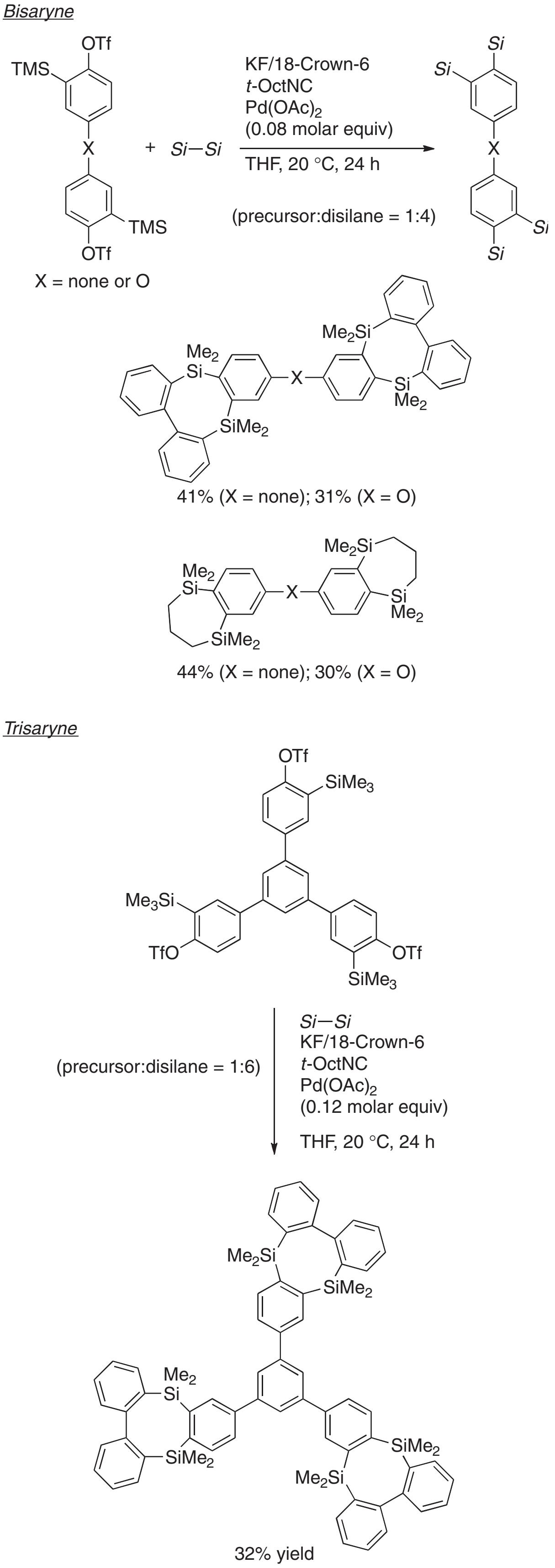


Scheme 4. Pd–isocyanide-catalyzed disilylation of arynes.

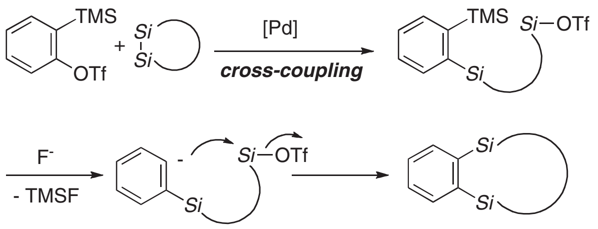
tributyl(phenylethynyl)tin (**2a**) in acetonitrile by use of $[Pd_2Cl_2(\eta^3\text{-}C_3H_5)_2]$ (0.05 molar equiv of Pd) and an iminophosphine ligand, providing tributyl[2-(phenylethynyl)-phenyl]tin in 54% yield (Scheme 2).[9] The reaction was also applicable to tributyl(3,3-dimethyl-1-butynyl)tin, tributyl(3-methoxy-1-propynyl)tin, and conjugated ethynylstannane to give the respective carbostannylation products, and furthermore, benzyne was found to be inserted into the $C(sp^2)$–Sn σ-bond of tributyl(vinyl)tin.

The reaction of **2a** with 4-Me-substituted benzyne precursor **1b** provided regioisomeric products **3a** and **3b** in a ratio of 51:49 (Scheme 3). A similar ratio of **3a** and **3b** was formed in the reaction of 5-Me-substituted benzyne precursor **1c**, which indicates that common intermediate 4-methylbenzyne must be involved in both reactions. In addition, 3-methoxybenzyne and 1,2-naphthalyne (1,2-didehydronaphthalene) underwent the carbostannylation with **2a** to afford the insertion products consisting of two regioisomers in 58% and 42% yield.

2.1.2 Si–Si σ-Bond: The use of 1,1,3,3-tetramethylbutyl isocyanide (*t*-OctNC)[10] as a supporting ligand of a palladium catalyst in lieu of the iminophosphine allowed the insertion reaction into a silicon–silicon σ-bond to occur under mild conditions.[11] As described in Scheme 4, the silicon–silicon bond of 1,1,2,2-tetramethyl-1,2-(1,8-naphthylene)disilane readily added to the triple bond of variously substituted arynes to afford the seven-membered disilacarbocycle, 7,7,12,12-tetramethyl-7,12-dihydro-7,12-disilapleiadene. In addition, the disilylation was found to be also applicable to a benzo-condensed six-membered cyclic disilane (1,1,2,2-tetramethyl-1,2-(2,2′-biphenylene)disilane) and a simple five-membered cyclic disilane (1,1,2,2-tetramethyl-1,2-disilacyclopentane), giving



Scheme 5. Reactions using bisarynes or a trisaryne.



Scheme 6. Tentative pathway for disilylation via cross-coupling reaction.

1,4-dihydrotribenzo-1,4-disilocine and tetrahydrobenzo-1,4-disilepine, respectively.

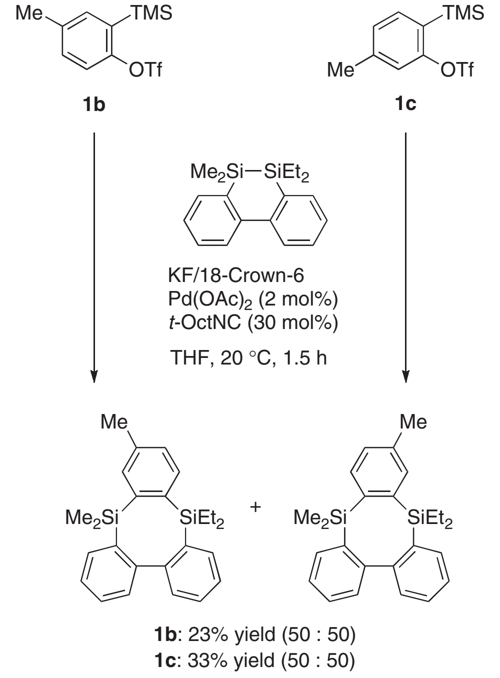
The disilylation could be applied to arynes bearing plural carbon–carbon triple bonds (Scheme 5). Thus, the reaction of a bisaryne having a biphenyl or diphenyl ether backbone yielded tetrasilylated products in 30–44% yields,[11b] and furthermore, six carbon–silicon bonds were formed all in one step in the reaction of a trisaryne, where moderate yields of silicon-containing PAHs (polycyclic aromatic hydrocarbons) were produced.[11c]

Because aryl halides are known to undergo cross-coupling reaction with disilanes in the presence of a palladium catalyst,[12] the disilylation might proceed through a pathway which does not involve an aryne intermediate: cross-coupling of an aryne precursor at a C–OTf moiety with a disilane followed by fluoride ion-induced intramolecular silicon–silicon exchange as shown in Scheme 6. Therefore, we examined the disilylation of **1b** or **1c** (a 4-methylbenzyne precursor) with an unsymmetrical disilane, supposing that one of the silyl moieties ($SiMe_2$ or $SiEt_2$) is introduced into the C–OTf moiety of **1b** or **1c** preferentially according to the above-mentioned cross-coupling pathway.[13] Contrary to the supposition, both of the reactions afforded two regioisomeric products in equal ratio, indicating the intermediacy of an aryne in the disilylation (Scheme 7).

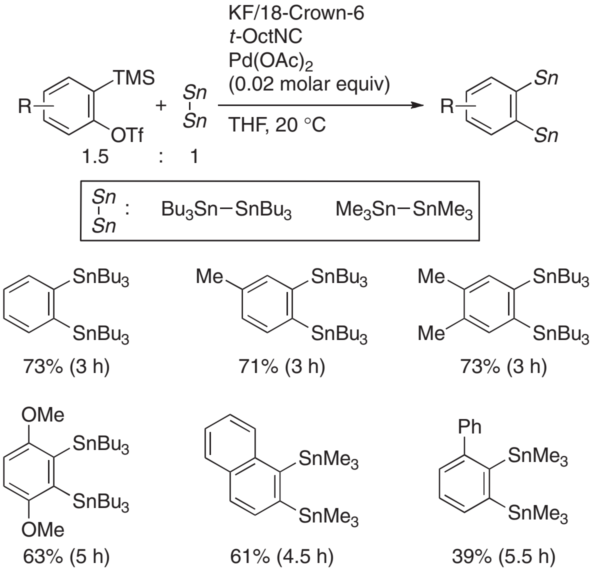
2.1.3 Sn–Sn σ-Bond: The palladium–isocyanide complex also showed effective catalysis for the insertion reaction into a tin–tin σ-bond.[14] For example, treatment of benzyne with hexabutyldistannane in the presence of $Pd(OAc)_2$ (0.02 molar equiv) and *t*-OctNC gave the distannylation product, 1,2-bis(tributylstannyl)benzene, in 73% yield (Scheme 8). In addition to hexabutyldistannane, hexamethyldistannane could also participate in the reaction, where even less-reactive 1,2-naphthalyne and 3-phenylbenzyne were found to be inserted into the tin–tin bond.

Similarly to the case with the disilylation, we examined the reaction of 4-(trimethylsilyl)phenyl triflate, a regioisomer of benzyne precursor **1a**, with hexabutyldistannane in order to clarify whether the distannylation proceeds through a cross-coupling pathway (Scheme 6) or not. As shown in Scheme 9, this reaction did not lead to the formation of 1,4-bis(tributylstannyl)benzene, which should be generated according to the cross-coupling pathway, being suggestive of the intermediacy of an aryne also in the distannylation.

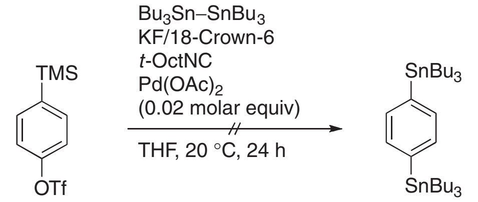
The mode of distannylation could be changed by a ligand. Thus, when the reaction of benzyne with hexamethyldistannane was conducted by use of a bicyclic phosphite, ETPO (4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane),[15] as a ligand, insertion of two molar equivalents of benzyne into the tin–tin



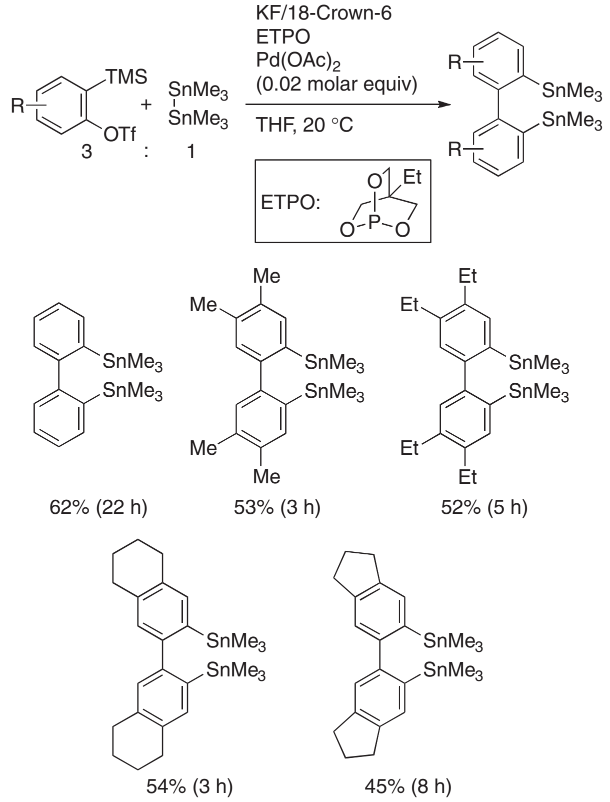
Scheme 7. Disilylation of an unsymmetrical disilane with **1b** or **1c**.



Scheme 8. Pd–isocyanide-catalyzed distannylation of arynes.



Scheme 9. Reaction of 4-(trimethylsilyl)phenyl triflate with $Bu_3Sn–SnBu_3$.



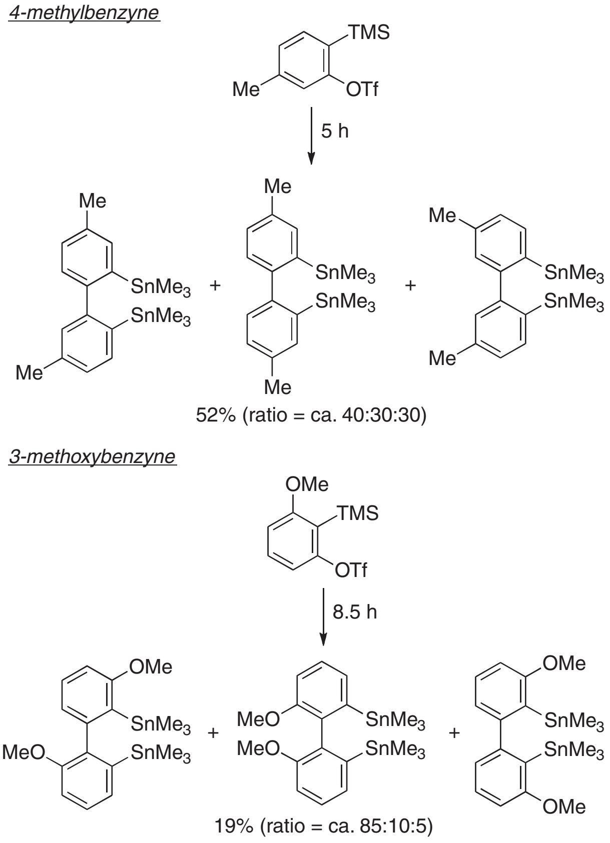
Scheme 10. Pd–phosphite-catalyzed dimerization–distannylation of arynes.

σ-bond took place predominantly to afford 2,2′-bis(trimethylstannyl)biphenyl in 62% yield (Scheme 10).[16] The dimerization–distannylation of symmetric arynes occurred facilely, offering a convenient method to assemble biaryl skeletons with the introduction of two stannyl moieties into their 2- and 2′-positions.

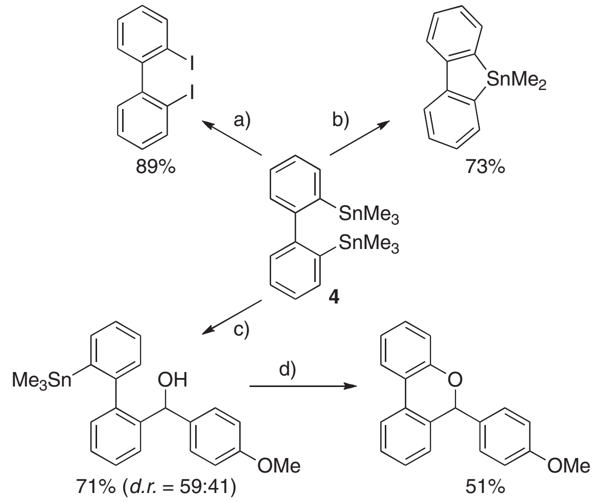
An unsymmetrical aryne, 4-methylbenzyne, could also participate in the dimerization–distannylation to afford a 52% yield of a mixture of three regioisomers in the ratio of ca. 40:30:30, respectively, which indicates that a substituent at the 4-position of an aryne exerts little effect on the regioselectivity of the reaction (Scheme 11). In sharp contrast, the reaction of 3-methoxybenzyne proceeded regioselectively, resulting in the predominant formation of 2,2′-bis(trimethylstannyl)-3,6′-dimethoxybiphenyl.

Variously substituted biaryls could be synthesized by utilizing the carbon–tin bonds of the dimerization–distannylation product (Scheme 12). Thus, iododestannylation of **4** gave 2,2′-diiodobiphenyl in 89% yield. Furthermore, an aryl anion, generated from **4** with methyllithium, underwent intramolecular cyclization at 0 °C to produce a 73% yield of 9,9-dimethyl-9-stannafluorene. On the other hand, the aryl anion could be trapped by 4-methoxybenzaldehyde at −78 °C to afford stannyl-substituted benzhydrol as a mixture of diastereomers (ratio = 59:41) in 71% yield, which was further convertible into a dibenzopyran derivative via intramolecular arylation of the hydroxy moiety in the presence of copper(II) chloride.

2.1.4 B–B σ-Bond: The insertion reaction into a boron–boron σ-bond was found to be facile when benzyne was treated with bis(pinacolato)diboron [(pin)B–B(pin)] in the presence of $Pt(dba)_2$ (0.05 molar equiv) and 1-adamantyl isocyanide (1-AdNC), giving 1,2-diborylbenzene **5** in 77% yield



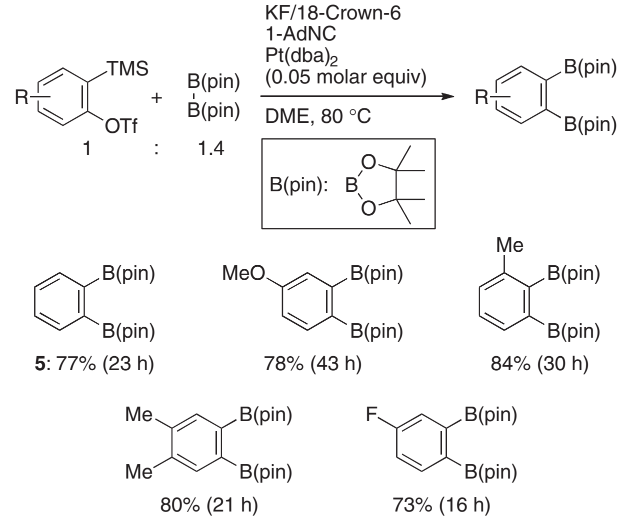
Scheme 11. Dimerization–distannylation of unsymmetrical arynes.



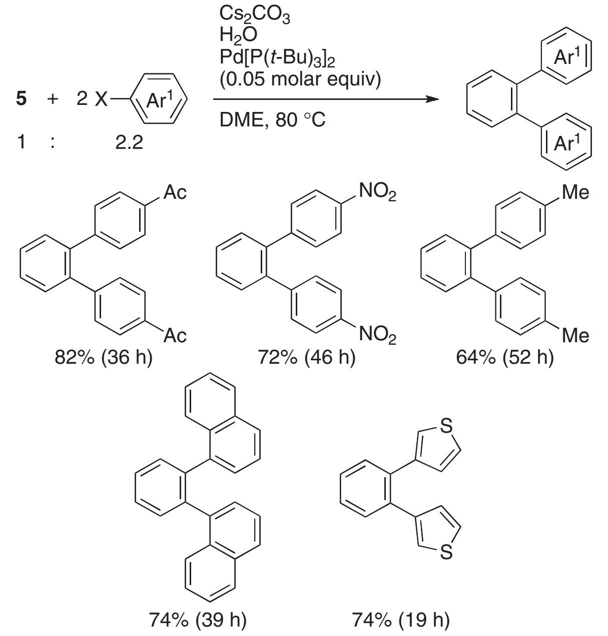
Reagents and conditions: a) I_2 (2.1 equiv), CH_2Cl_2, 20 °C, 1.5 h; b) MeLi (1.5 equiv), THF, 0 °C, 1.5 h; c) MeLi (1.5 equiv), THF, -78 °C, 1 h, then 4-$MeOC_6H_4CHO$ (3 equiv), -78 °C to 20 °C, 18 h; d) $CuCl_2$ (1 equiv), DMSO, 50 °C, 8 h.

Scheme 12. Transformation of a dimerization–distannylation product.

(Scheme 13).[17] The diborylation of substituted arynes likewise occurred, providing a convenient and general method for the synthesis of diverse 1,2-diborylarenes, which are hardly accessible by conventional ways.

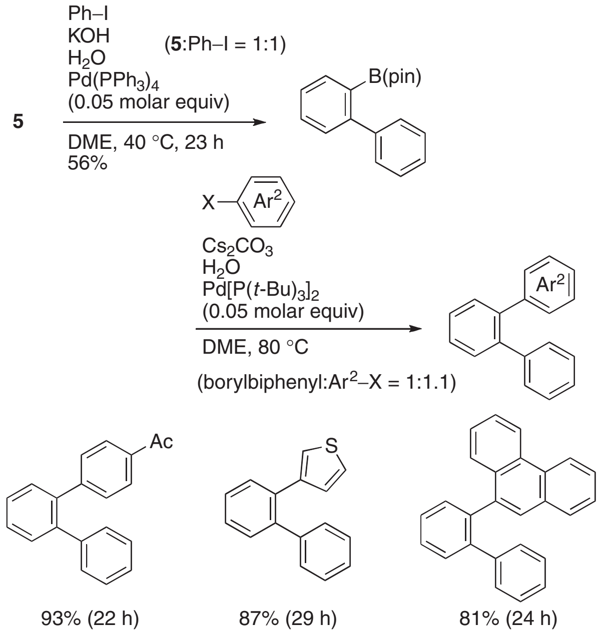


Scheme 13. Pt–isocyanide-catalyzed diborylation of arynes.

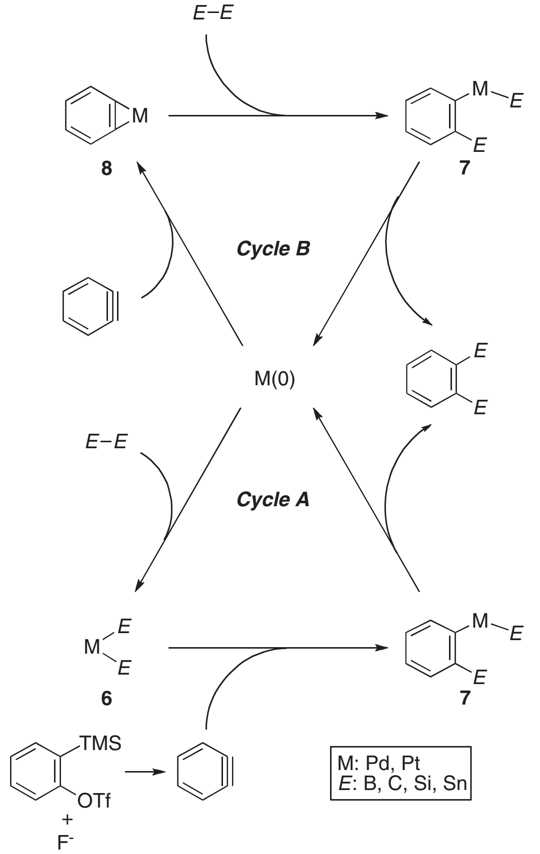


Scheme 14. Synthesis of symmetric *ortho*-terphenyls via Suzuki–Miyaura coupling.

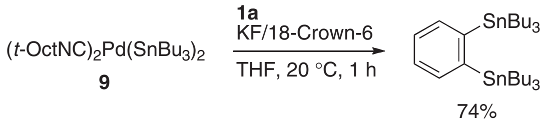
We next examined Suzuki–Miyaura coupling of the resulting diborylarenes[18] with aryl halides in order to demonstrate their synthetic utility, and found that variously substituted *ortho*-terphenyls could be prepared in a straightforward manner. As depicted in Scheme 14, treatment of **5** with various aryl halides (2.2 molar equiv) by use of $Pd[P(t\text{-}Bu)_3]_2$ (0.05 molar equiv) catalyst and Cs_2CO_3 furnished high yields of doubly coupled products, regardless of the electronic properties of the aryl halides. Moreover, the coupling reaction using diborylarene **5** was extended to synthesis of unsymmetrical *ortho*-terphenyls (Scheme 15). At first, **5** was transformed into monoborylbiphenyl by the reaction with iodobenzene (1.0 molar equiv) in the presence of $Pd(PPh_3)_4$ catalyst (0.05 molar equiv) and KOH. Subsequent coupling reaction with a second aryl halide gave the desired products.



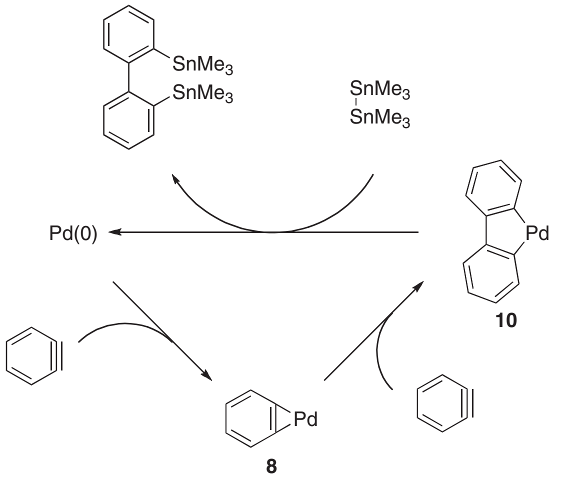
Scheme 15. Synthesis of unsymmetrical *ortho*-terphenyls via stepwise Suzuki–Miyaura coupling.



Scheme 16. Plausible catalytic cycles for the insertion reactions.



Scheme 17. Stoichiometric reaction of complex **9** with benzyne.



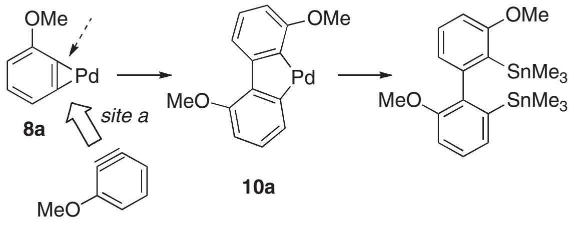
Scheme 18. A plausible catalytic cycle for dimerization–distannylation.

2.1.5 Catalytic Cycle: On the basis of the accepted mechanism of the transition-metal-catalyzed insertion reactions of other unsaturated carbon–carbon bonds, a plausible catalytic cycle (Cycle A) is depicted in Scheme 16.[5] First, complex **6** is formed through oxidative addition of a metal-containing σ-bond to a palladium(0) or platinum(0) complex. Subsequent insertion of an in situ-generated aryne produces arylpalladium (or platinum) complex **7**, which then undergoes reductive elimination to provide an insertion product with regeneration of the catalyst. Alternatively, another catalytic cycle (Cycle B), in which the catalyst first interacts with an aryne, is possibly operative. The resulting metallacycle **8**[19] furnishes the product via reaction with the metallic compound.[20] Although we have little evidence that determines the reaction pathway decisively, Cycle A of the distannylation is exceptional, which has been verified to be actually in operation by stoichiometric reaction using oxidative adduct **9** (Scheme 17).

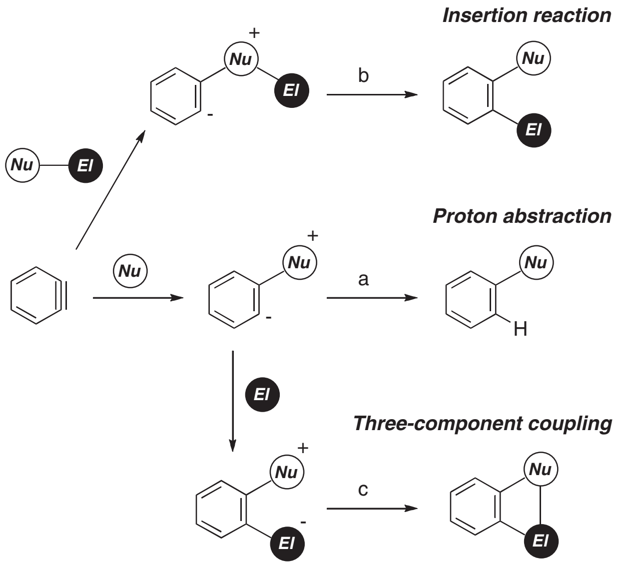
Since neither trimerization–distannylation products nor higher oligomers were generated in the course of the dimerization–distannylation, the reaction should be initiated by formation of palladacycle **8** from a palladium–ETPO complex and an aryne (Scheme 18). Subsequent interaction of **8** with a second aryne gives a [Pd(2,2′-biphenyl)] species **10**, which reacts further with hexamethyldistannane to afford a distannylbiaryl.[20]

The regioselectivity observed in the reaction of 3-methoxybenzyne can be rationally explained by preferential formation of palladacycle **10a**, resulting from insertion of second 3-methoxybenzyne into the sterically less hindered site (site a) of **8a** with an orientation which avoids unfavorable steric repulsion between the methoxy group of the incoming aryne and the palladium atom (Scheme 19).

2.2 Insertion Reaction into a Nu–El σ-Bond. Owing to their low-lying LUMO, arynes exhibit salient electrophilicity, being completely opposite to the nucleophilic character of alkynes, and even neutral nucleophiles readily add to arynes.[2b]



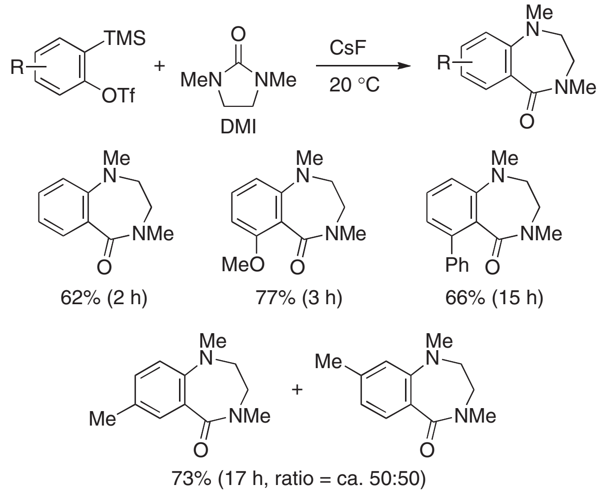
Scheme 19. Regioselectivity in the reaction of 3-methoxybenzyne.



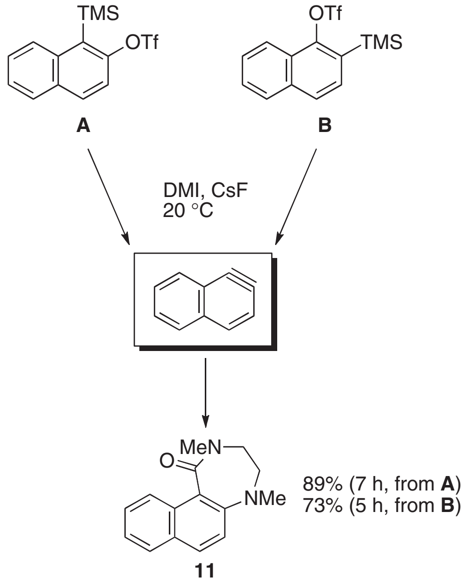
Scheme 20. Electrophilic coupling of arynes.

Hence, considerable attention has been paid to the electrophilic couplings of arynes, which have been exploited in the construction of complex aromatic compounds. The couplings proceed through an initially formed zwitterion and can be divided into three categories (Scheme 20): (a) formation of a monosubstituted arene via proton abstraction, (b) insertion into a σ-bond between a nucleophilic site and an electrophilic site (Nu–El σ-bond) via intramolecular nucleophilic substitution,[6,21] and (c) three-component coupling by trapping the zwitterion with an electrophile.[22] Among these, our attention has been riveted on reactions of type (b) and (c), since both of the carbon ends of the triple bond can be functionalized all at once.

2.2.1 N–C σ-Bond: A nitrogen–carbonyl σ-bond of ureas readily added to arynes to provide in one step a wide variety of 1-amino-2-(aminocarbonyl)arenes including 1,4-benzodiazepine and 1,5-benzodiazocine derivatives.[23] Treatment of **1a** and CsF in 1,3-dimethyl-2-imidazolidinone (DMI) at 20 °C gave 1,4-dimethyl-2,3,4,5-tetrahydro-(1*H*)-1,4-benzodiazepin-5-one in 62% yield (Scheme 21). Perfect regioselectivity was observed in the reaction of 3-substituted arynes, and thus 3-methoxybenzyne or 3-phenylbenzyne gave the respective product as a single isomer, which possesses the amide moiety (an electrophilic site) at the more sterically hindered position. In contrast, 4-methylbenzyne provided almost equal amounts of a mixture of regioisomeric products, suggesting that a substituent at the 4-position of an aryne exerts little influence on the regioselectivity.



Scheme 21. Aminocarbamoylation of arynes with DMI.

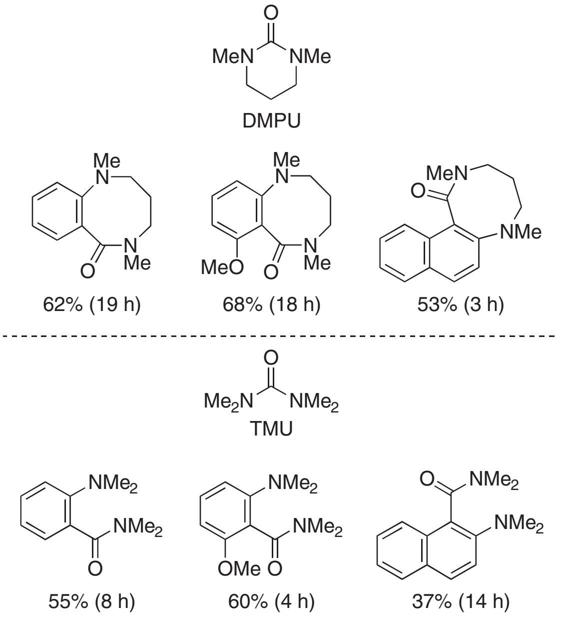


Scheme 22. Aminocarbamoylation of 1,2-naphthalyne.

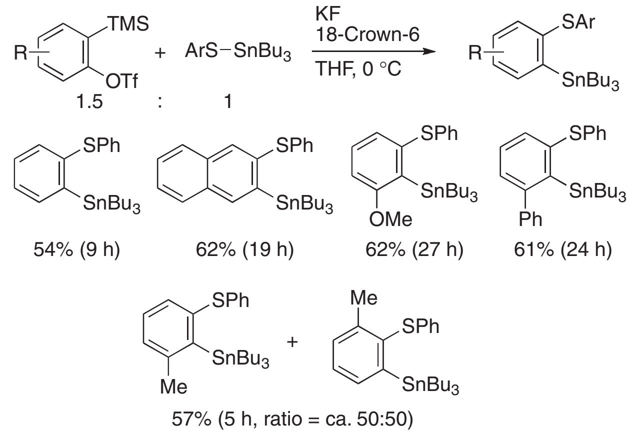
The reaction of 1-(trimethylsilyl)-2-naphthyl triflate, a 1,2-naphthalyne precursor, proceeded regioselectively to afford **11** solely in 89% yield (Scheme 22). Exclusive formation of **11** was observed also in the reaction of 2-(trimethylsilyl)-1-naphthyl triflate, indicating that both reactions proceed through the 1,2-naphthalyne intermediate.

A six-membered cyclic urea, *N*,*N*′-dimethyl-*N*,*N*′-trimethyleneurea (DMPU) also reacted readily with arynes to give 1,5-benzodiazocin-6-ones straightforwardly, and furthermore, an acyclic urea such as *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) participated in the reaction (Scheme 23).

2.2.2 S–Sn σ-Bond: Stannyl sulfides underwent the insertion reaction of arynes at their sulfur–tin σ-bond.[24] Diverse 2-(arylthio)arylstannanes were produced directly by the thiostannylation of substituted arynes as well as simple benzyne (Scheme 24). As was the case of the insertion reaction into ureas, methoxy or phenyl groups in 3-substituted arynes controlled the regioselectivities perfectly to offer the respective product as a single isomer, where the arylthio moiety



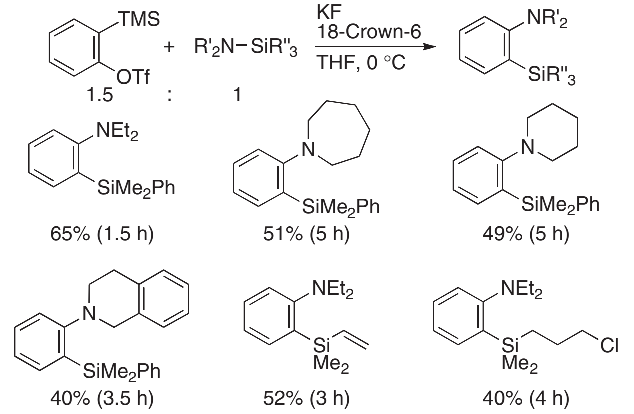
Scheme 23. Aminocarbamoylation of arynes with DMPU or TMU.



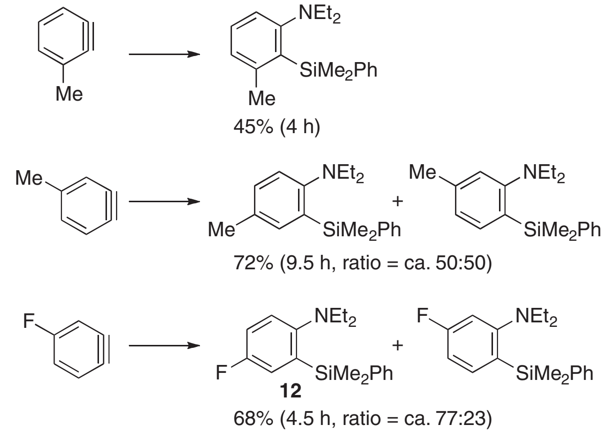
Scheme 24. Thiostannylation of arynes.

(a nucleophilic site) was introduced into the *m*-position of the methoxy or phenyl substituent. In marked contrast, the reaction of 3-methylbenzyne gave a mixture of regioisomers in ca. 1:1 ratio.

2.2.3 N–Si σ-Bond: A variety of 2-silylaniline derivatives could be synthesized in one step via the insertion reaction into a nitrogen–silicon σ-bond of aminosilanes (Scheme 25).[25] For example, treatment of benzyne with (diethylamino)dimethylphenylsilane afforded the aminosilylation product, 2-(dimethylphenylsilyl)-*N*,*N*-diethylaniline, in 65% yield. Cyclic amine-derived aminosilanes could participate in the reaction as well, which resulted in the introduction of 1-azepinyl, piperidino, or 2-isoquinolyl moieties into the aromatic skeleton. It should be noted that vinyl or 3-chloropropyl groups on the silicon atom did not interfere with the course of the aminosilylation, leading to the formation of the products with these reactive functional groups remaining intact.



Scheme 25. Aminosilylation of benzyne.



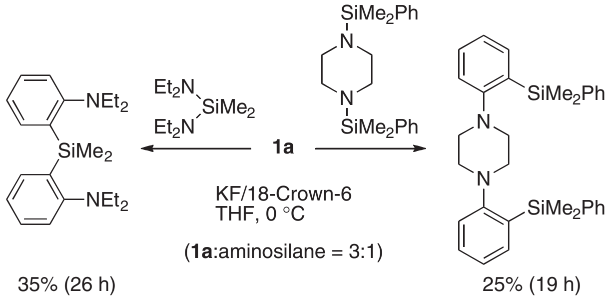
Scheme 26. Aminosilylation of unsymmetrical arynes.

In sharp contrast to the result of the thiostannylation, the regioselectivity of the aminosilylation with 3-methylbenzyne was perfect, in which the diethylamino group (a nucleophilic site) was introduced into the *m*-position of the methyl substituent (Scheme 26). Although 4-methylbenzyne gave almost equal amounts of regioisomeric products, preferential formation of **12** was observed in the reaction of 4-fluorobenzyne.

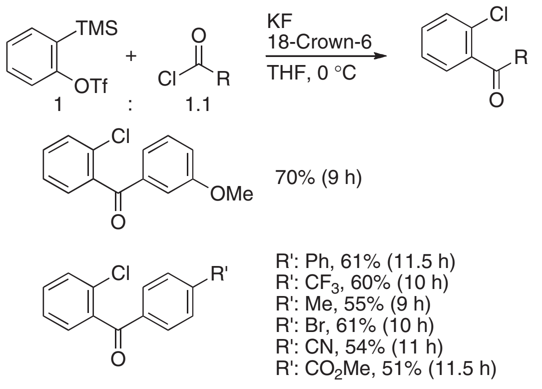
Utility of the aminosilylation has been demonstrated by application to aminosilanes bearing two reaction sites. Thus, benzyne was inserted into each of the nitrogen–silicon σ-bonds to afford bis(2-aminophenyl)silane or *N*,*N*′-bis(2-silylphenyl)piperazine in 35% or 25% yield, respectively (Scheme 27).

2.2.4 Cl(Br)–C σ-Bond: The prominent electrophilicity of arynes enables even a halogen moiety to serve as a nucleophilic site in the insertion reaction. Thus, the insertion into a chlorine–carbonyl σ-bond took place smoothly by the reaction of benzyne with 3-methoxybenzoyl chloride in THF at 0 °C, giving 2-chloro-3′-methoxybenzophenone in 70% yield (Scheme 28).[26] Various aroyl chlorides possessing electron-neutral, -withdrawing, or -donating groups could be applied to the reaction, and furthermore, treatment of bromo-, cyano-, or methoxycarbonyl-substituted benzoyl chloride with benzyne yielded the products without injuring these functional groups, which demonstrates the high functional group-compatibility of the insertion reaction.

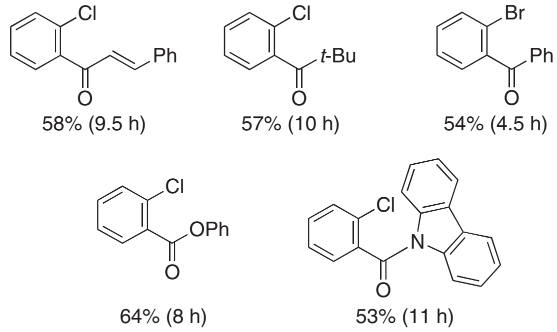
(*E*)-Cinnamoyl chloride and aliphatic acid chlorides could participate in the reaction, and a bromine–carbonyl σ-bond of acid bromides also readily underwent the insertion of benzyne,



Scheme 27. Aminosilylation with aminosilanes bearing two reaction sites.



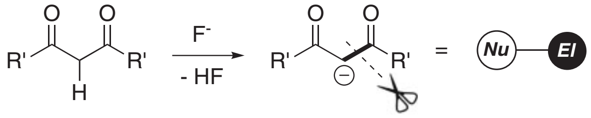
Scheme 28. Insertion of benzyne into substituted benzoyl chlorides.



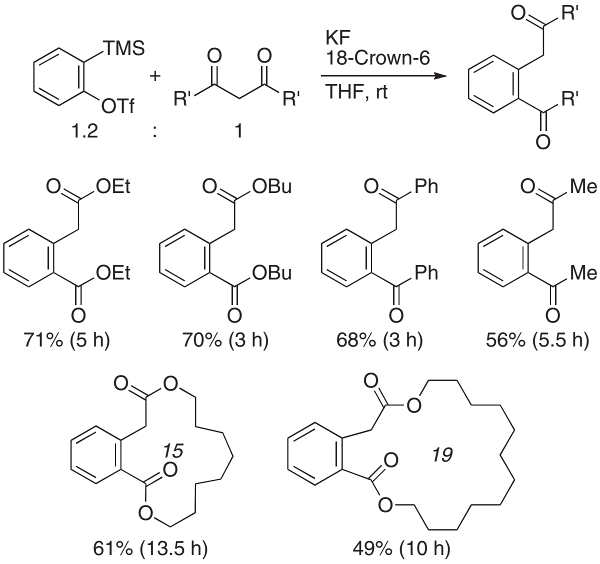
Scheme 29. Insertion of benzyne into various acid halides.

enabling acyl and bromo moieties to be introduced into the adjacent positions of the aromatic ring (Scheme 29). In addition, a chloroformate or a carbamoyl chloride was found to react with benzyne at their chlorine–carbonyl σ-bonds exclusively to provide the insertion products, where the respective oxygen–carbonyl or nitrogen–carbonyl σ-bonds remained unchanged. The insertion reaction would be of high synthetic utility as a novel acylation reaction of aromatic rings, in which an acyl moiety is incorporated into an *ortho*-position of a halogen moiety, since Friedel–Crafts acylation reactions of halogenated arenes afford mainly or solely *para*-substituted products.[27]

2.2.5 C–C σ-Bond: All of the foregoing insertion reactions into a Nu–El σ-bond are triggered by a nucleophilic attack of a heteroatom (nitrogen, sulfur, or halogen) to an aryne (Scheme 20b). Subsequent intramolecular nucleophilic substitution at an electrophilic site (carbonyl carbon, tin, or silicon) affords the insertion products. Based upon the reaction mechanism, we envisaged that β-dicarbonyl compounds should be appropriate reagents for the insertion reaction of arynes into their active methylene (potentially nucleophilic)–carbonyl (electrophilic) σ-bonds, because deprotonation of the active methylene moiety by a fluoride ion of moderate basicity would generate a carbanionic species in situ, which can play a similar role to the heteroatom (Scheme 30). The insertion reaction into a carbon–carbon σ-bond provides new organic transformations for constructing complex carbon frameworks through two carbon–carbon bond-forming processes, and thus, is of high synthetic significance.



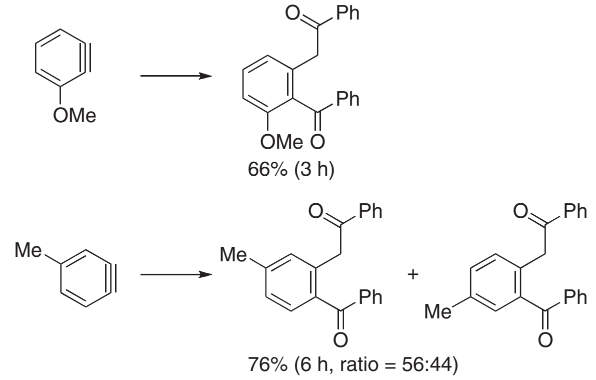
Scheme 30. A scenario for insertion reaction into a C–C σ-bond.



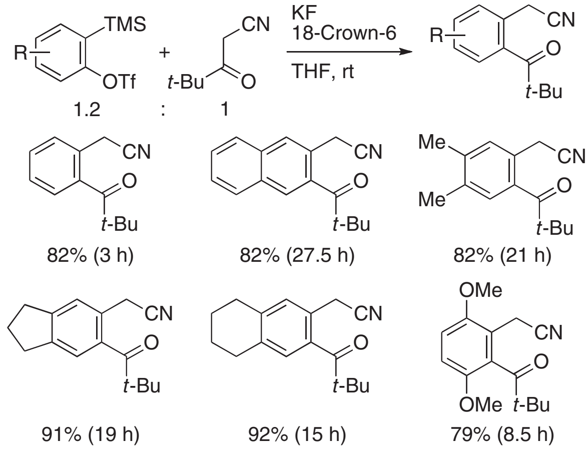
Scheme 31. Insertion of benzyne into β-dicarbonyl compounds.

First we carried out the reaction of benzyne with diethyl malonate and observed that the insertion into the methylene–carbonyl σ-bond indeed proceeded under extremely mild conditions, resulting in direct introduction of different carbon functional groups into the 1,2-positions of the aromatic skeleton (Scheme 31).[28–30] Dibutyl malonate, dibenzoylmethane, or acetylacetone could also participate in the reaction, and furthermore, benzo-annulated macrocyclic compounds were readily available depending upon the insertion reaction, and thus treatment of a cyclic malonate with benzyne afforded a 15-membered or 19-membered ring straightforwardly in 61% or 49% yield, respectively.

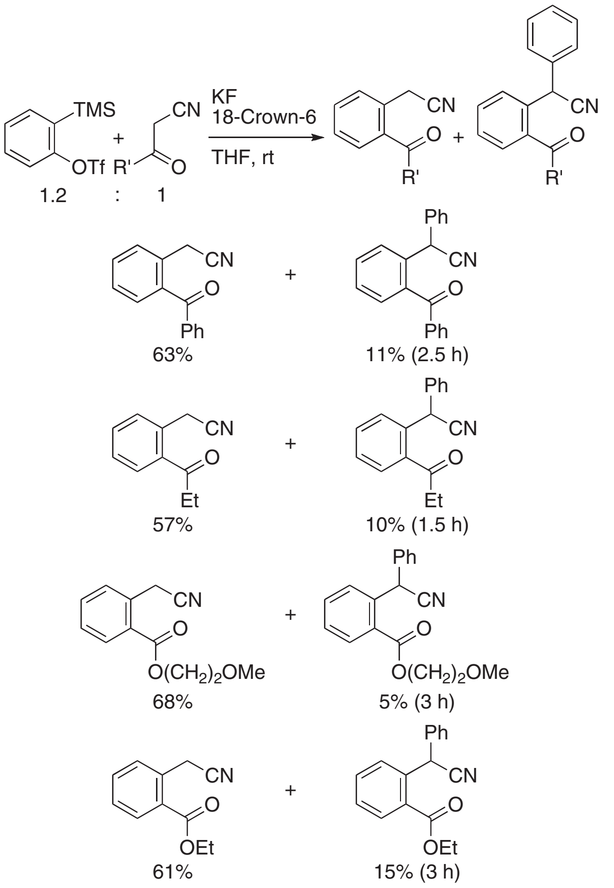
The reaction of 3-methoxybenzyne proceeded with perfect regioselectivity to afford the product bearing the benzoylmethyl moiety (a nucleophilic site) at the sterically less hindered position of the aryne, whereas 4-methylbenzyne furnished almost equal amounts of regioisomeric products (Scheme 32).



Scheme 32. Insertion of unsymmetrical arynes into dibenzoylmethane.



Scheme 33. Insertion of arynes into pivaloylacetonitrile.



Scheme 34. Insertion of benzyne into various α-cyanocarbonyl compounds.

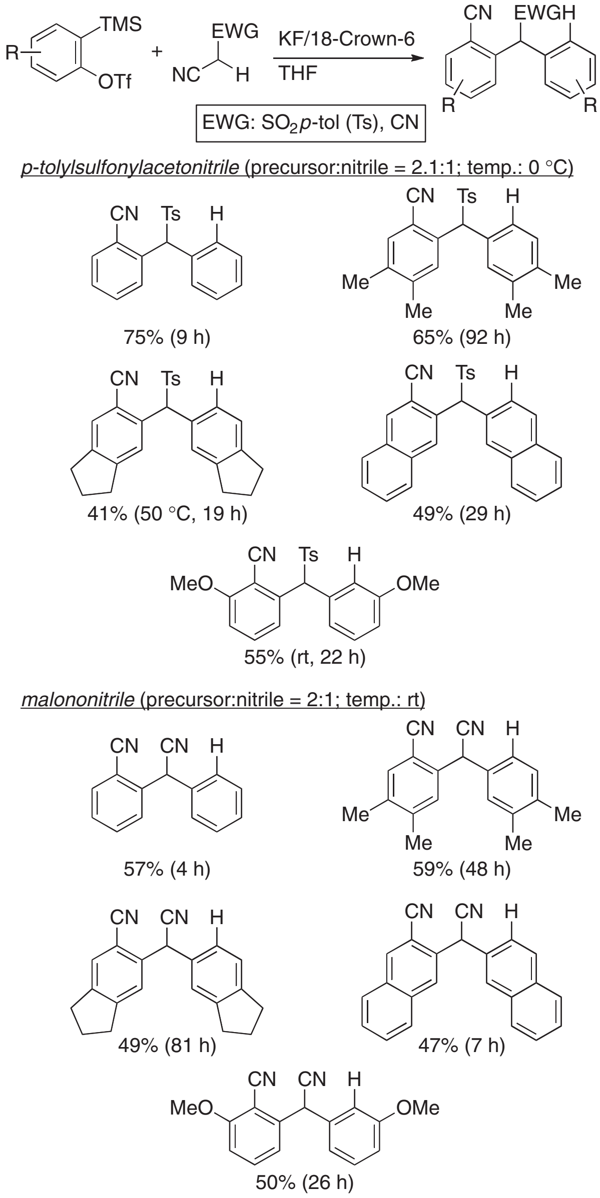
Having established the insertion reaction into a carbon–carbon σ-bond of β-dicarbonyl compounds, we next investigated the reaction using other active methylene compounds, and have found that α-cyanocarbonyl compounds add across arynes at their methylene–carbonyl moieties exclusively, leading to simultaneous introduction of carbonyl and cyanomethyl moieties into the neighboring positions of the aromatic skeletons.[31] For example, the reaction of benzyne with pivaloylacetonitrile afforded an 82% yield of *t*-butyl 2-(cyanomethyl)phenyl ketone solely, and a product arising from insertion into the methylene–cyano bond was not formed at all (Scheme 33).

A methylene–carbonyl bond of benzoylacetonitrile or propanoylacetonitrile added to benzyne to give the insertion product, being accompanied by the formation of a diarylmethane derivative (a 2:1 coupling product), which holds the phenyl moiety at the benzylic position (Scheme 34). A mixture of the 1:1 product and the 2:1 product was also produced in the reaction of esters of cyanoacetic acid.

The 2:1 coupling reaction of arynes with active methylene compounds prevailed over the usual insertion reaction by employing *p*-tolylsulfonylacetonitrile: two molar amounts of benzyne were inserted into the methylene carbon–cyano carbon and methylene carbon–hydrogen bonds to afford (2-cyanophenyl)phenyl(*p*-tolylsulfonyl)methane in 75% yield, in which three carbon–carbon and one carbon–hydrogen bonds were formed all in one pot (Scheme 35).[32,33] Arynes possessing alkyl substituents at their 4,5-positions or 2,3-naphthalyne also reacted efficiently, giving the respective diarylmethanes in moderate yield. It should be noted that the reaction of 3-methoxybenzyne occurred with perfect regioselectivity, where the methine carbon was connected to the *meta*-positions of each methoxy moiety. In addition, the successive aryne insertion into malononitrile took place with the same scope and regioselectivity as those of *p*-tolylsulfonylacetonitrile.

Since the key for the successful insertion reaction is smooth formation of a carbanionic species [$(EWG)_2RC^-$] (EWG: electron-withdrawing group) via rapid deprotonation induced by two EWGs, the use of another molecular scaffold having a C–H moiety of suitable acidity has resulted in a new C–C bond cleavage reaction, broadening synthetic applicability of this protocol. Thus, treatment of benzyne with 9-fluorenyl isopropyl ketone led to facile insertion into the methine–carbonyl bond to give the acylfluorenylation product, where formation of the key carbanionic species is facilitated by its aromatic stabilization (Scheme 36).[34] A variety of fluorenyl ketones or esters of fluorenecarboxylic acid underwent the insertion of arynes and moreover, perfect regioselectivities were observed in the reaction of 1,2-naphthalyne or 3-methoxybenzyne, where the fluorenyl moiety (a nucleophilic site) was attached to the less congested site exclusively.

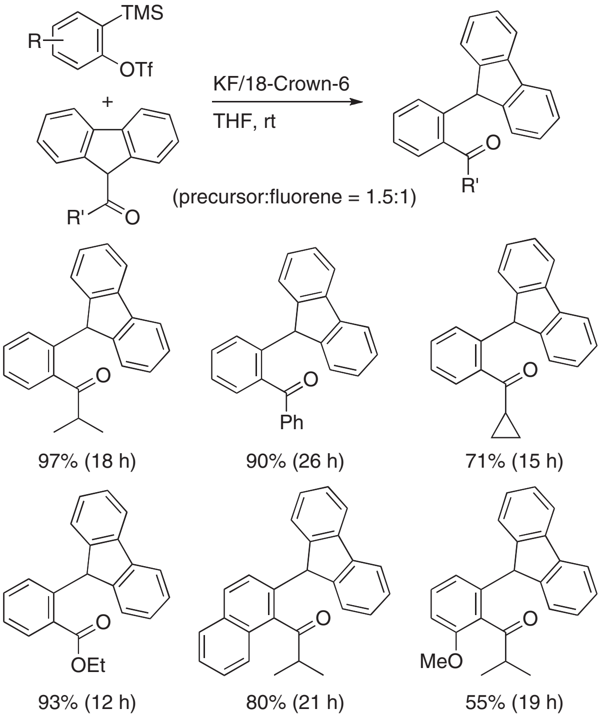
A fluorenyl moiety plays a vital role in the insertion reaction to proceed, and thus no trace of the desired product was formed



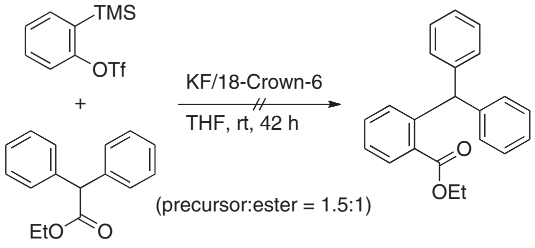
Scheme 35. A 2:1 coupling reaction of arynes with *p*-tolylsulfonylacetonitrile or malononitrile.

in the reaction using ethyl diphenylacetate of diminished acidity despite its structural resemblance to ethyl fluorene-9-carboxylate (Scheme 37).

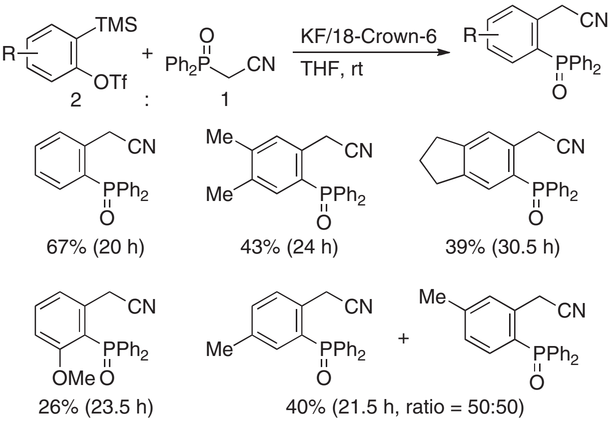
2.2.6 C–P σ-Bond: Besides carbonyl and cyano moieties, a phosphine oxide moiety can serve as an electrophilic site in the insertion reaction, which provides an efficient method for introducing carbon and phosphorus functional groups into an aromatic skeleton. Thus when cyanomethyldiphenylphosphine oxide was allowed to react with arynes, insertion into the methylene–phosphorus σ-bond took place smoothly to afford carbophosphinylation products solely (Scheme 38).[35] As were the cases with other active methylene compounds, addition of cyanomethyl moiety (a nucleophilic site) to 3-methoxybenzyne occurred at the *meta*-position of the methoxy group, while the reaction of 4-methylbenzyne provided a mixture of regioisomers.



Scheme 36. Acylfluorenylation of arynes.

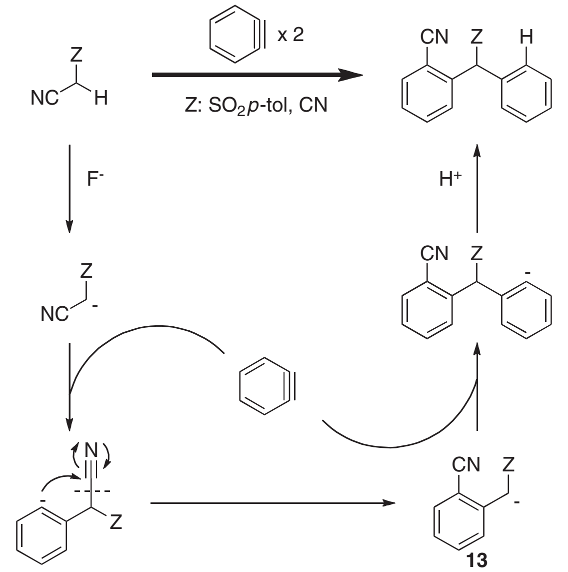


Scheme 37. Reaction using ethyl diphenylacetate.



Scheme 38. Carbophosphinylation of arynes.

2.2.7 Reaction Pathway: A reaction pathway for the insertion reactions has already been outlined in path (b) of Scheme 20, in which a heteroatom or an in situ-generated carbanion acts as the nucleophilic site. Based on this reaction pathway, formation of the 2:1 coupling reaction products from arynes and certain nitriles can be rationalized by supposing



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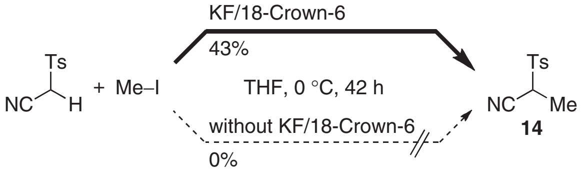
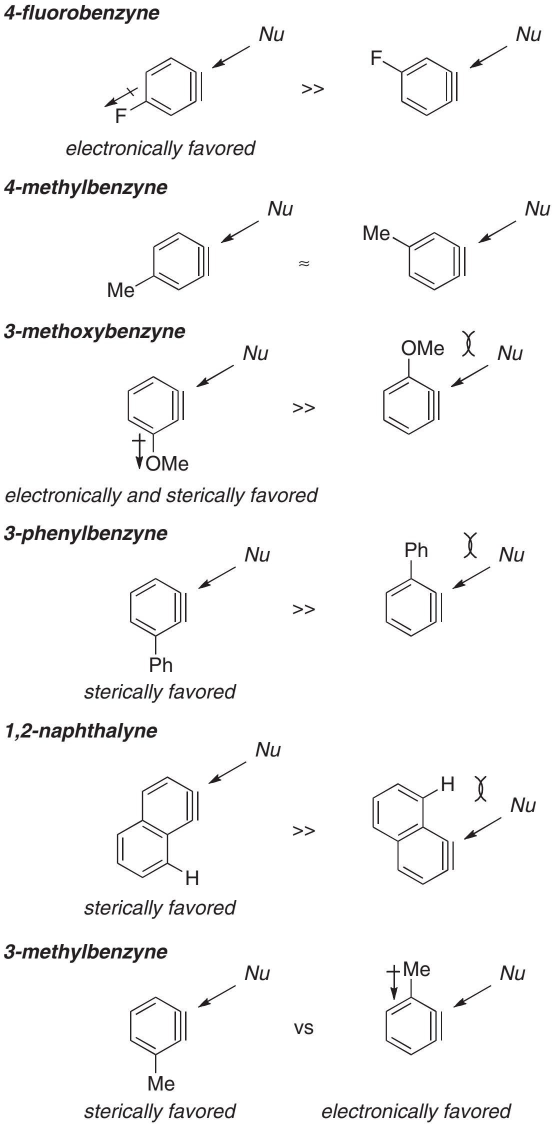
Scheme 39. A pathway for the 2:1 coupling reaction.



Scheme 40. A fluoride ion as a base.

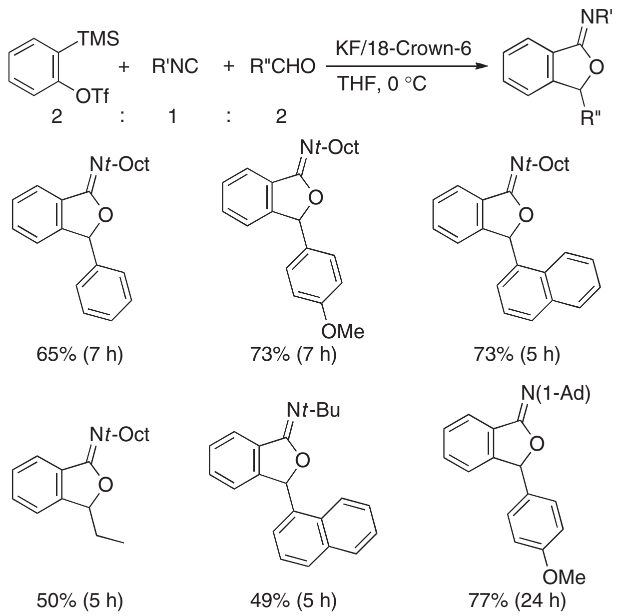
nucleophilic attack of intermediary benzyl anion **13** to a second aryne (Scheme 39). Furthermore, treatment of *p*-tolylsulfonylacetonitrile with methyl iodide in the presence of KF/18-crown-6 resulted in the formation of methylated product **14**, whereas no trace of **14** was produced without an added fluoride ion, confirming that a fluoride ion acts not only as an aryne generator but also as a base for the formation of a carbanionic species from an active methylene compound (Scheme 40).

The observed regioselectivities in the reaction of the unsymmetrical arynes is ascribable to electronic and/or steric effects of a substituent on the arynes (Scheme 41). Owing to an electron-withdrawing inductive effect (−I effect) of a fluorine atom (4-fluorobenzyne), the developing negative charge at the closer position to the fluorine atom is stabilized markedly in the transition state for the nucleophilic attack, which results in the preferential addition of a nucleophilic moiety to the *para*-position of the fluorine atom. In contrast, a methyl group at 4-position should not induce an electronic difference, and thus, 4-methylbenzyne accepts the nucleophilic attack on both ends of the triple bond equally. The exclusive introduction of the nucleophilic moiety into the less congested site of 3-methoxybenzyne, 3-phenylbenzyne, or 1,2-naphthalyne can be rationally explained by disfavored steric repulsion between the substituent (MeO, Ph, or *peri*-hydrogen) in the aryne and the incoming nucleophile. In addition to this steric effect, the methoxy group of 3-methoxybenzyne exerts an electron-withdrawing inductive effect, which also directs the nucleophilic attack toward the *meta*-position of the methoxy moiety. In the case of 3-methylbenzyne, the steric effect would compete with the electron-donating effect (+I effect) of the methyl group, which prefers generation of the aryl anion at the *meta*-position, leading to no consistency in the regioselectivities depending upon the reagents (thiostannylation vs. aminosilylation).



Scheme 41. Regioselectivities in the reactions of unsymmetrical arynes.

2.3 Three-Component Coupling. 2.3.1 Aryne–Isocyanide–Carbonyl Compound: The reaction of benzyne with 1,1,3,3-tetramethylbutyl isocyanide (*t*-OctNC) and benzaldehyde in THF at 0 °C was found to give the three-component coupling product, (3-phenyl-3*H*-isobenzofuranylidene)(1,1,3,3-tetramethylbutyl)amine, in 65% yield (Scheme 42).[36] Aromatic and aliphatic aldehydes also underwent the reaction efficiently, affording the respective three-component coupling products, and an alkyl isocyanide bearing a *tert*-butyl or 1-adamantyl group could participate in the reaction. When 1-(trimethylsilyl)-2-naphthyl triflate, a 1,2-naphthalyne precursor, was allowed to react with *t*-OctNC and 4-methoxybenzaldehyde, **15** was formed as the sole product (Scheme 43). Exclusive formation of **15** was also observed in the reaction of 2-(trimethylsilyl)-1-naphthyl triflate, which confirms the intermediacy of an aryne in the three-component coupling. The



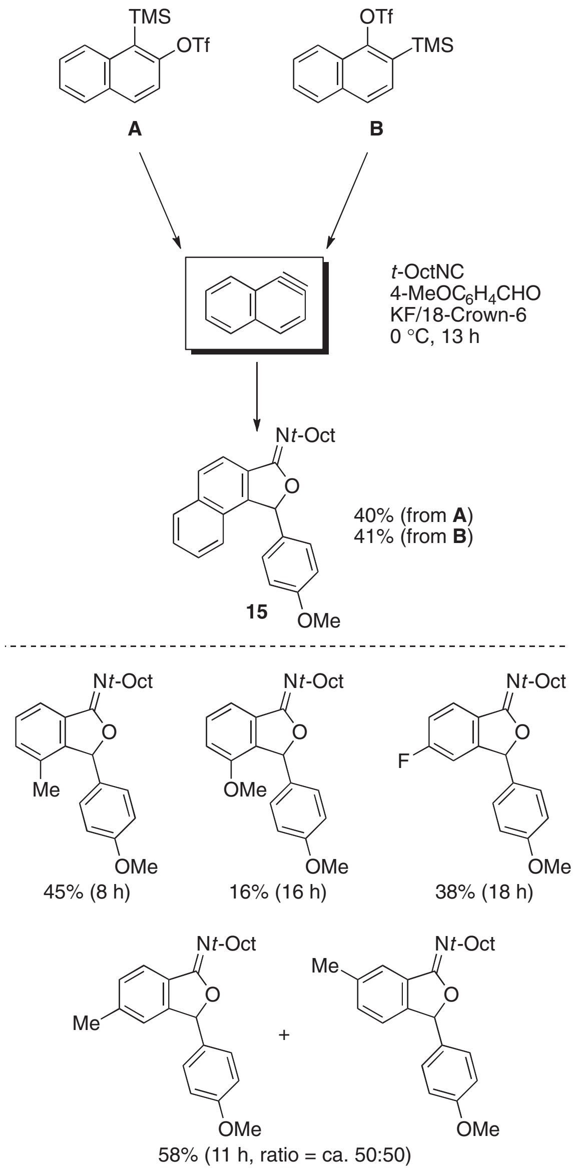
Scheme 42. Three-component coupling of benzyne, isocyanides, and aldehydes.

reaction of 3-methylbenzyne or 3-methoxybenzyne took place with perfect regioselectivity, where the imino moiety was attached to the sterically less hindered position of the aryne. A fluoro substituent at the 4-position of an aryne controlled the regioselectivity to afford a single product having the imino moiety at the *para*-position of the fluoro substituent, whereas the reaction of 4-methylbenzyne furnished almost equal amounts of regioisomeric products.

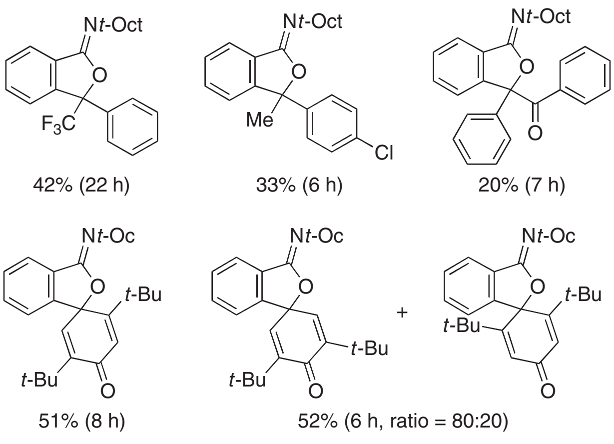
Similarly to the case of aldehydes, several ketones (acetophenone and 1,2-diketone) could be used as a third component (electrophile), although the yields were somewhat lower than those with aldehydes (Scheme 44).[36b] On the other hand, the reaction using benzoquinones of increased electron-deficiency furnished a spiro type of iminodihydroisobenzofurans in 51% or 52% yield, and the predominant isomer in the reaction of 2,6-di-*t*-butylbenzoquinone arose from cyclization at the less congested carbonyl group.

2.3.2 Aryne–Isocyanide–Sulfonylimine: By changing electrophiles from carbonyl compounds to sulfonylimines, the three-component coupling could be utilized for direct synthesis of five-membered nitrogen heterocycles.[36b,37] When the reaction of benzylidenetosylamine with benzyne and *t*-OctNC was conducted in THF at room temperature, (3-phenyl-2-tosylisoindolinylidene)(1,1,3,3-tetramethylbutyl)amine was formed in 64% yield (Scheme 45). Although the reaction of 3-methoxybenzyne with a sulfonylimine took place with the same regioselectivity as that with an aldehyde, opposite regioselectivity was observed in the reaction of 3-methylbenzyne, despite using the same isocyanide (cf. Scheme 43), which is ascribable to reversibility in the nucleophilic addition of *t*-OctNC to 3-methylbenzyne.

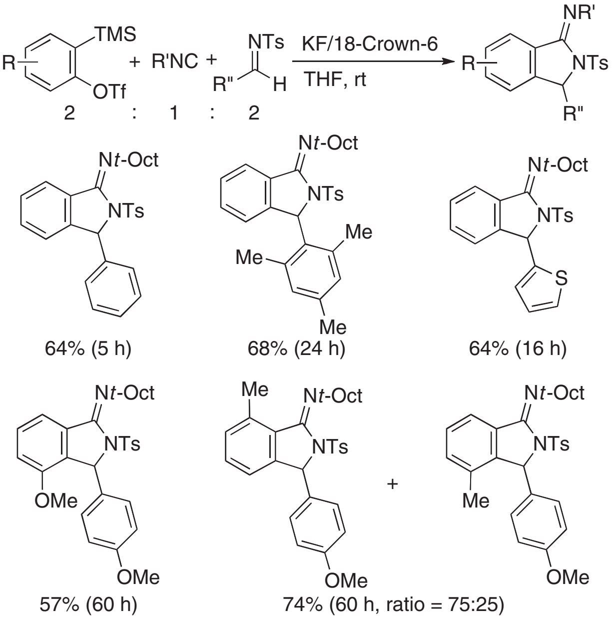
2.3.3 Aryne–Imine–CO_2: As depicted in path (c) of Scheme 20, pivotal intermediates in the three-component couplings are zwitterions arising from nucleophilic attack of neutral nucleophiles to arynes, and these reactive zwitterions



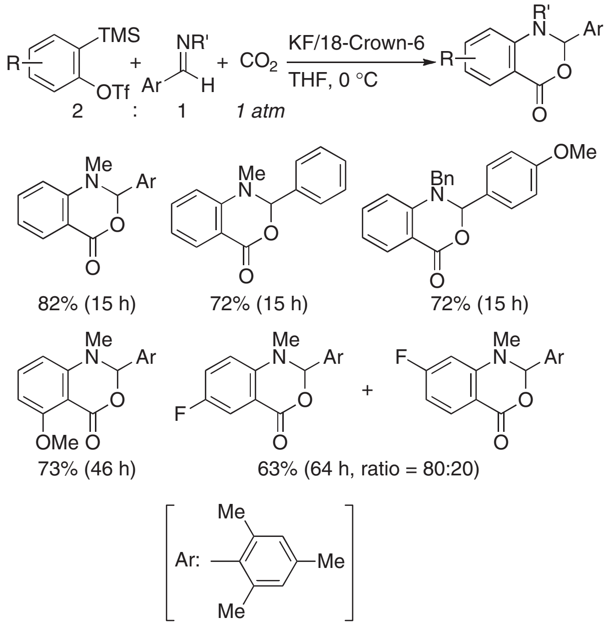
Scheme 43. Three-component coupling of unsymmetrical arynes.



Scheme 44. Three-component coupling using ketones.

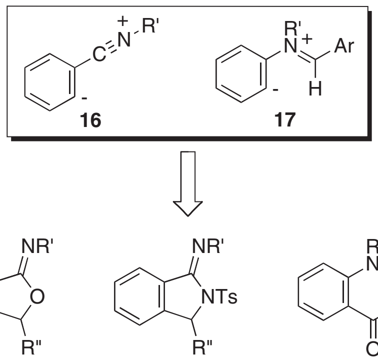


Scheme 45. Three-component coupling of arynes, isocyanides, and sulfonylimines.



Scheme 46. Three-component coupling of arynes, amines, and CO_2.

have been found to serve as effective molecular scaffolds for the capture of CO_2.[38] At first, we carried out the reaction of benzyne with methyl(2,4,6-trimethylbenzylidene)amine under a CO_2 atmosphere (1 atm), and found that the three-component coupling product, benzoxazinone was produced in 82% yield (Scheme 46). Variously substituted imines and arynes underwent the reaction with CO_2, assembling the benzoxazinone skeletons of structural diversity with high efficiency, whereas *N*-*t*-Bu or *N*-Ph imine did not give the desired product at all, which indicates that steric congestion or decreased nucleophilicity of the nitrogen moiety strictly retards the reaction. The observed regioselectivies in the reaction of 3-methoxybenzyne or 4-fluorobenzyne, where an imine (nucleophile) was added to the electronically favored site preferentially (*meta*-position of MeO or *para*-position of F, Scheme 41), were almost same as those of the reaction using an isocyanide.



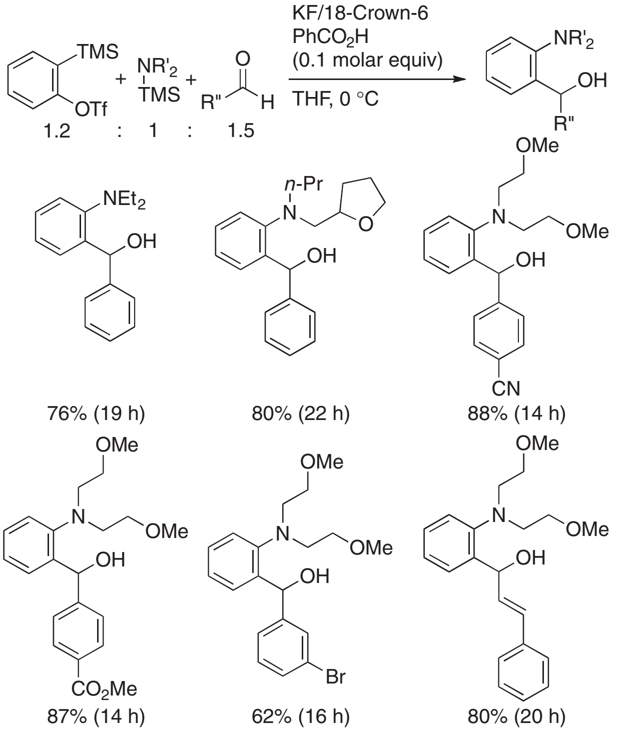
Scheme 47. Key intermediates in the formation of benzo-annulated cyclic structures.

2.3.4 Aryne–Aminosilane–Carbonyl Compound: Because formation of the benzo-annulated cyclic framework in the three-component coupling products results from unsaturated structure of a cationic site in intermediate **16** or **17** (Scheme 47), the use of saturated nucleophiles in lieu of unsaturated ones (isocyanide and imine) has led to three-component couplings of a different type, in which the intramolecular cyclization is impeded entirely.

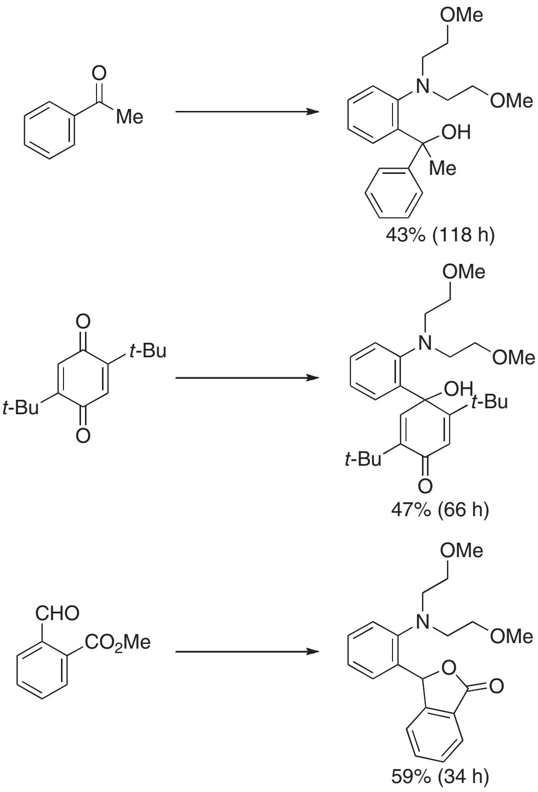
The reaction of benzyne, (diethylamino)trimethylsilane (saturated nucleophile), and benzaldehyde in the presence of benzoic acid (0.1 molar equiv) afforded the three-component coupling product, 2-(diethylamino)benzhydrol, in 76% yield (Scheme 48).[39a] No trace of the product was obtained in the absence of benzoic acid, which confirms its vital role in the present reaction. It is worth noting the excellent chemoselectivity of the reaction: treatment of cyano-, methoxycarbonyl-, or bromo-substituted benzaldehyde with benzyne and an aminosilane provided 2-aminobenzhydrols exclusively, leaving these functional groups intact. Furthermore, (*E*)-cinnamaldehyde gave an 80% yield of the 1,2-addition product, whose stereochemistry was retained unchanged.

Acetophenone or benzoquinone could also be used as the third component, although the reaction became sluggish (Scheme 49).[39b] In addition, treatment of methyl 2-formylbenzoate with benzyne and an aminosilane afforded phthalide, which would be formed through the coupling at the formyl moiety followed by intramolecular cyclization between the resulting alkoxide and the ester moieties.

2.3.5 Aryne–Aminosilane–Sulfonylimine: Simultaneous introduction of amino and aminomethyl moieties into aromatic skeletons could also be achieved by employing sulfonylimines as electrophiles.[39b] Under similar reaction conditions to those described above, (arylmethylene)tosylamines were coupled with benzyne and dialkylaminosilanes to give the respective 2-aminobenzhydrylamine derivatives (Scheme 50), although the yields were rather lower than those of 2-aminobenzhydrols on the whole. Variously substituted 2-aminobenzhydrylamine derivatives were readily synthesized by the reaction of substituted arynes, and almost the same regioselectivities as those above were observed in the reaction using unsymmetrical

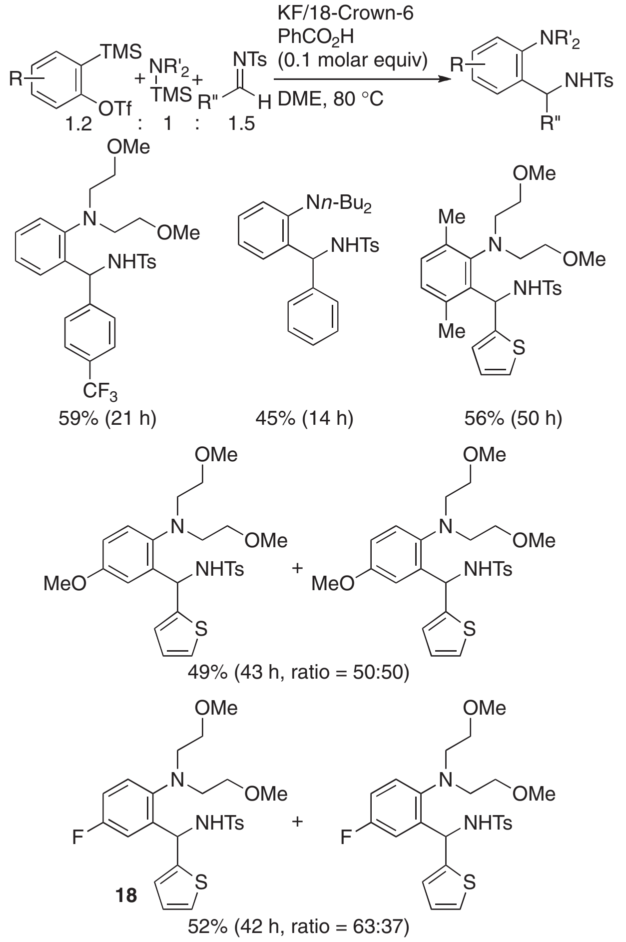


Scheme 48. Three-component coupling of benzyne, aminosilanes, and aldehydes.

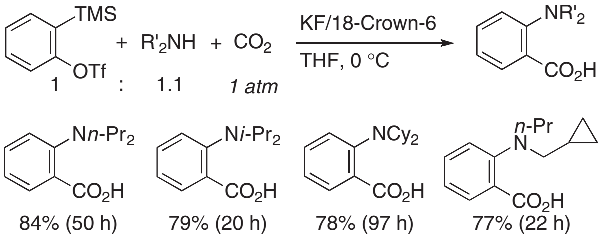


Scheme 49. Three-component coupling using ketones or methyl 2-formylbenzoate.

arynes: 4-methoxybenzyne produced equal amounts of regioisomers, and **18** was obtained as the major product in the reaction of 4-fluorobenzyne.

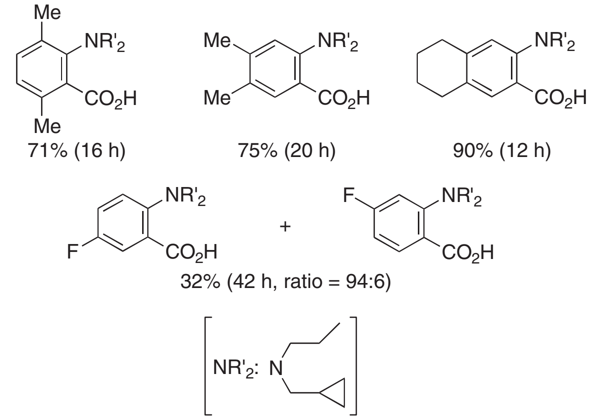


Scheme 50. Three-component coupling of arynes, aminosilanes, and sulfonylimines.

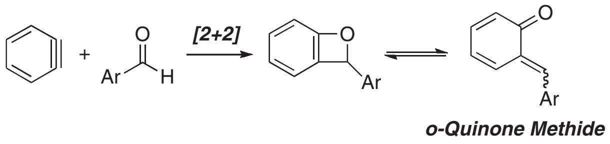


Scheme 51. Three-component coupling of benzyne, amines, and CO_2.

2.3.6 Aryne–Amine–CO_2: A combination of aryne and CO_2 in the three-component coupling reaction can be utilized for synthesizing anthranilic acid derivatives. Thus, when benzyne was treated with dipropylamine in THF at 0 °C under a CO_2 atmosphere (1 atm), *N*,*N*-dipropylanthranilic acid was formed in 84% yield (Scheme 51).[40] The high selectivity for the formation of the anthranilic acid is worth noting, because amines are apt to be arylated in the reaction with arynes to produce aniline derivatives.[41] Diisopropyl- and dicyclohexylamine were smoothly coupled with benzyne and CO_2, regardless of the steric hindrance around the nitrogen atom, and moreover, (cyclopropylmethyl)propylamine could participate in the reaction to give a good yield of the product, leaving the strained cyclopropyl group intact. Multisubstituted anthranilic



Scheme 52. Synthesis of multisubstituted anthranilic acids.



Scheme 53. Formation of *o*-quinone methides via a formal [2 + 2] cycloaddition of arynes with aldehydes.

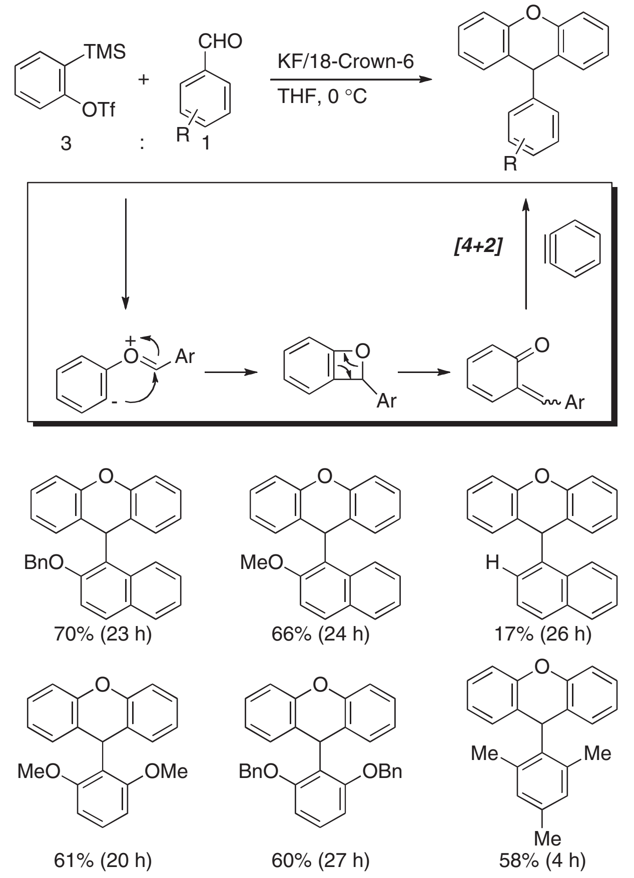
acids could readily be constructed by the reactions of substituted arynes including 3,6-dimethylbenzyne, 4,5-dimethylbenzyne, and cyclohexane-fused aryne as depicted in Scheme 52, and 4-fluorobenzyne accepted nucleophilic attack of an amine at the *para*-position of the fluoro group preferentially.

2.3.7 Reaction Pathway: Key zwitterionic species in the three-component couplings arising from nucleophilic attack of neutral nucleophiles to arynes are described in Scheme 47. Subsequent capture of the resulting aryl anion moieties by electrophiles generates the three-component coupling products (path (c), Scheme 20). The regioselectivities observed in the reactions of unsymmetrical arynes can rationally be explained as previously mentioned (Scheme 41).

3. [4 + 2] Cycloaddition of *ortho*-Quinone Methides

The salient electrophilicity of arynes also allows a formal [2 + 2] cycloaddition with carbonyl moieties of aldehydes to occur as shown in Scheme 53, generating *ortho*-quinone methides of high synthetic utility[3] via valence isomerization of benzoxetes.[42,43]

Owing to the high reactivity of the resulting *ortho*-quinone methides, they facilely undergo a [4 + 2] cycloaddition with second arynes to give xanthene derivatives.[44] For example, treatment of benzyne with 2-benzyloxy-1-naphthaldehyde in THF has been found to produce a 70% yield of 9-(2-bezyloxy-1-naphthyl)xanthene through a formal insertion of two molar equivalents of benzyne into both of the carbon–oxygen bonds of the carbonyl moiety (Scheme 54). 2-Methoxy-1-naphthaldehyde also reacted with benzyne to afford the xanthene with high efficiency, whereas the reaction of 1-naphthaldehyde resulted in a low yield, indicating that the use of an electron-rich aldehyde is indispensable for the reaction to proceed smoothly. In addition, the coupling reaction was applicable to a variety of benzaldehydes. Thus, when 2,6-dimethoxy-, 2,6-dibenzyloxy-, or 2,4,6-trimethylbenzaldehyde was allowed to react with benzyne, the corresponding xanthenes were formed in 61%, 60%, or 58% yield. In marked contrast, the reaction of 4-trifluoromethylbenzaldehyde did not form the xanthene at all.

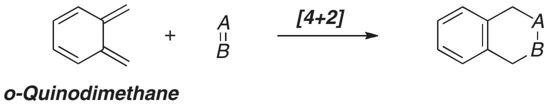


Scheme 54. Synthesis of xanthenes via a [4 + 2] cycloaddition of *o*-quinone methides with arynes.

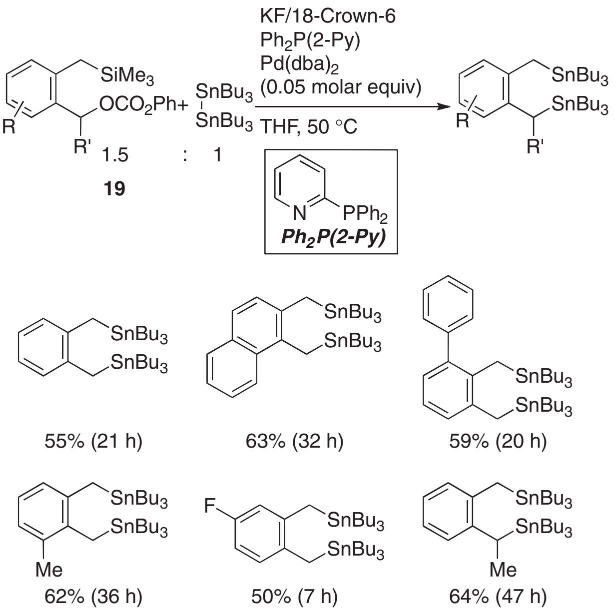
Facile formation of the xanthene derivatives in the reaction of electron-rich aldehydes can be rationally explained by enhanced nucleophilicity of the carbonyl oxygen atom toward an aryne, which enables efficient generation of an *o*-quinone methide.

4. Catalytic Insertion Reaction of *ortho*-Quinodimethanes into an Element–Element σ-Bond

ortho-Quinodimethanes are recognized as potent reactive intermediates in organic synthesis, which have been utilized as an efficient four-carbon unit in constructing 6-membered carbocyclic frameworks via [4 + 2] cycloaddition (Scheme 55).[4] Although the wide applicability of the cycloaddition enables diverse functional molecules to be synthesized in a straightforward manner, little has been known about a different type of transformation using *ortho*-quinodimethanes, despite the significant synthetic potential arising from their highly reactive character.[45,46] As described above, a transient carbon–carbon triple bond of arynes can be inserted into an element–element σ-bond with the aid of a transition-metal catalyst, and therefore, we envisaged that a transient 1,3-diene moiety of *ortho*-quinodimethanes would also be applicable to the catalytic insertion reaction.



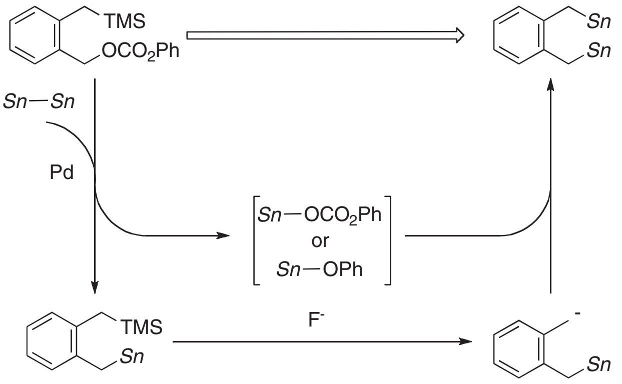
Scheme 55. A [4 + 2] cycloaddition using *o*-quinodimethanes.



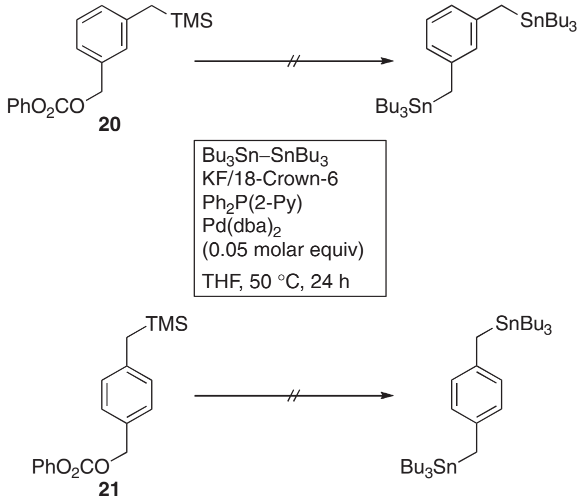
Scheme 56. Pd–pyridylphosphine-catalyzed distannylation of *o*-quinodimethanes.

4.1 Sn–Sn σ-Bond. The insertion reaction into a tin–tin σ-bond has been found to take place smoothly, when simple *ortho*-quinodimethane, generated in situ from 2-[(trimethylsilyl)methyl]benzylphenyl carbonate (**19**) and a fluoride ion,[47,48] was treated with hexabutyldistannane in the presence of bis(dibenzylideneacetone)palladium (0.05 molar equiv) and diphenyl-2-pyridylphosphine [$Ph_2P(2\text{-}Py)$], giving the distannylation product, α,α′-bis(tributylstannyl)-*ortho*-xylene in 55% yield (Scheme 56).[49] The reaction of *ortho*-quinodimethane bearing a naphthalene backbone or a phenyl moiety afforded good yields of the distannylation products, and other substituted *ortho*-quinodimethanes also underwent the addition of the distannane. Furthermore, a methyl group of α-methyl-*ortho*-quinodimethane (5-ethylidene-6-methylene-1,3-cyclohexadiene) did not inhibit the course of the distannylation.

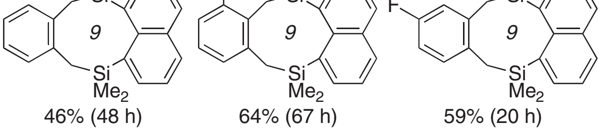
Since a precursor of *ortho*-quinodimethane has electrophilic ($C\text{–}OCO_2Ph$) and nucleophilic ($C\text{–}SiMe_3$) sites at each benzylic position, the distannylation might proceed through a pathway which does not involve an *ortho*-quinodimethane intermediate (Scheme 57): cross-coupling of the precursor at a $C\text{–}OCO_2Ph$ moiety with hexabutyldistannane followed by fluoride ion-induced tin–silicon exchange between the resulting 2-[(tributylstannyl)methyl]benzylsilane and Bu_3SnOCO_2Ph (and/or Bu_3SnOPh). Therefore, we examined the reaction of **20** or **21**, a regioisomer of **19**, and observed that no trace of the respective product was formed, which eliminates the cross-coupling pathway in the distannylation (Scheme 58).



Scheme 57. Tentative pathway for distannylation via cross-coupling reaction.

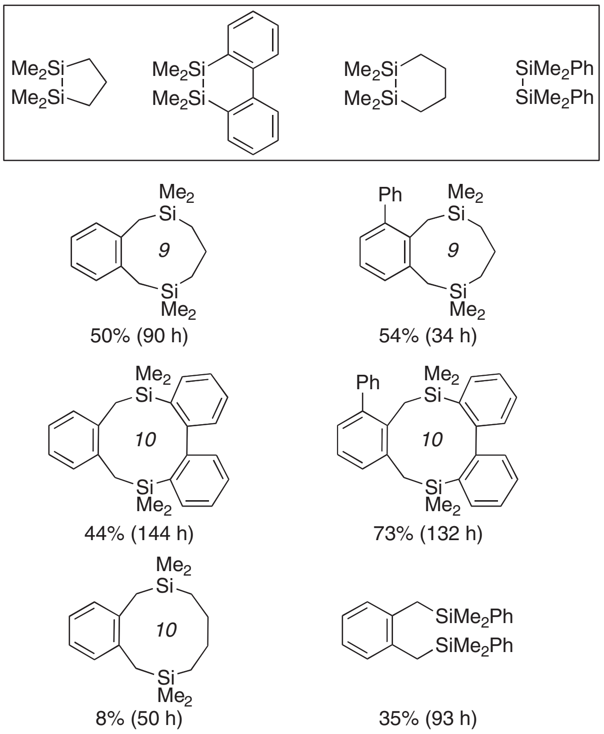


Scheme 58. Reaction of $Bu_3Sn\text{–}SnBu_3$ with **20** or **21**.

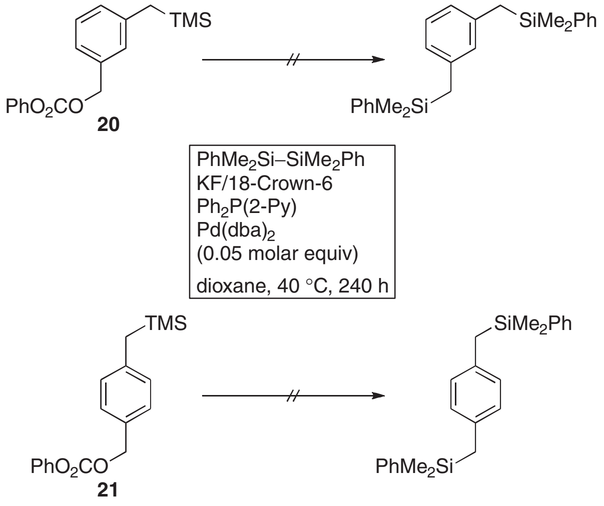


Scheme 59. Pd–pyridylphosphine-catalyzed disilylation of *o*-quinodimethanes with naphthalene-fused disilacyclopentane.

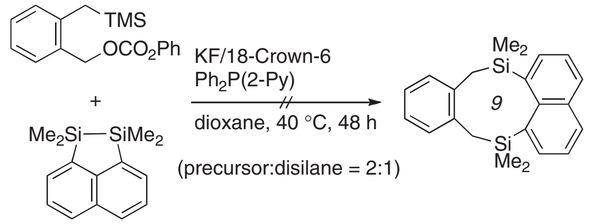
4.2 Si–Si σ-Bond. The palladium–$Ph_2P(2\text{-}Py)$ catalyst promotes the insertion reaction into a silicon–silicon σ-bond.[50] Thus, naphthalene-fused disilacyclopentane readily underwent the insertion of variously substitued *ortho*-quinodimethanes at their *exo*-diene moieties, furnishing 9-membered disilacarbocycles, benzodisilonines straightforwardly (Scheme 59). The disilylation was also applicable to simple disilacyclopentane, giving moderate yields of a benzodisilonine, and furthermore, a



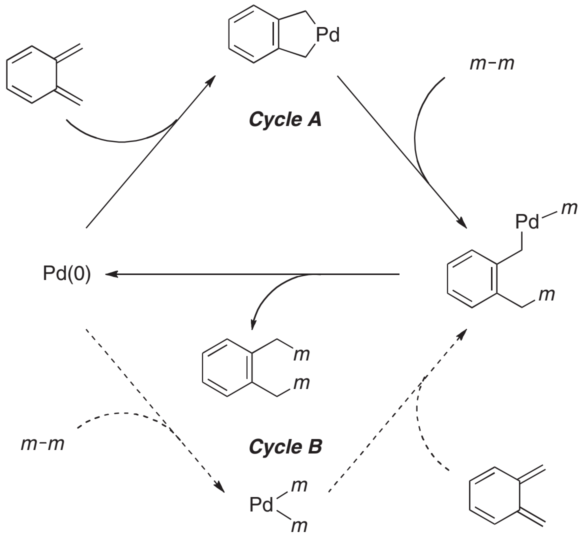
Scheme 60. Disilylation of *o*-quinodimethanes with various disilanes.



Scheme 61. Reaction of $PhMe_2Si–SiMe_2Ph$ with **20** or **21**.



Scheme 62. Reaction of *o*-quinodimethane with a disilane in the absence of the Pd.



Scheme 63. Plausible catalytic cycles for the dimetallations.

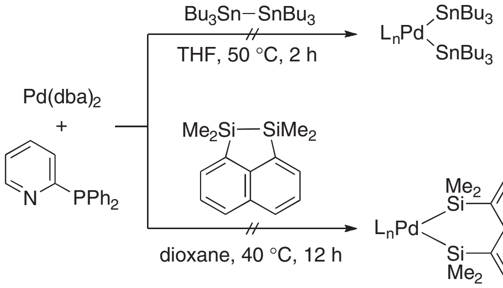
10-membered disilacarbocycle, benzodisilecine could be synthesized by treatment of biphenyl-fused disilacyclohexane with *ortho*-quinodimethanes, while the reaction of simple disilacyclohexane furnished the disilylation product only in 8% yield. Although the yield was slightly lower than those observed with cyclic disilanes, an acyclic disilane participated in the reaction to provide a disilyl-*ortho*-xylene (Scheme 60).

As shown in Scheme 61, the reaction of **20** or **21** with an acyclic disilane did not afford the respective products at all, verifying that the cross-coupling pathway (Scheme 57) is not operative in the disilylation. In addition, Scheme 62 describes the indispensability of the palladium catalysis for the disilylation. Thus, the disilylation product was not formed at all when the reaction of naphthalene-fused disilacyclopentane was carried out in the absence of the palladium catalyst. This result rules out a pathway where a fluoride ion acts as a catalyst, as previously reported in the disilylation of 1,3-dienes.[51]

4.3 Catalytic Cycle. A catalytic cycle for the dimetallations (Cycle A), which is triggered by formation of palladacycle[52,53] from an *ortho*-quinodimethane and a Pd(0) complex, is depicted in Scheme 63. The resulting palladacycle then reacts with a dimetal reagent (Sn–Sn or Si–Si) to produce benzylpalladium complex, which undergoes reductive elimination of a product with regeneration of the Pd(0) complex. Although another catalytic cycle (Cycle B), which involves oxidative addition of the dimetal reagent to the Pd(0) complex, might be operative, we are now in a position that Cycle A would be more plausible than Cycle B, since stoichiometric reactions of the dimetal reagents with the Pd(0)–Ph_2P(2-Py) complex did not give oxidative adducts (Scheme 64).

5. Conclusion

A variety of new synthetic transformations for constructing multisubstituted arenes have been developed by the use of aromatic reactive intermediates such as arynes, *ortho*-quinone methides, and *ortho*-quinodimethanes. Under the controlled reaction conditions with designed reactants and catalysts, an aryne triple bond is facilely inserted into a metal (boron, silicon, or tin)-containing σ-bond, despite their transient character, affording diverse aryl metal compounds that are otherwise difficult to prepare. Furthermore, the salient electro-



Scheme 64. Stoichiometric reaction of dimetals with a Pd–$Ph_2P(2\text{-}Py)$ complex.

philicity of arynes also enables insertion reactions into an element–element σ-bond of different type to take place without an added catalyst. With this reaction system, even a strain-free carbon–carbon σ-bond can be cleaved with high efficiency. By regulating the electrophilicity with selected neutral nucleophiles, arynes can be used for three-component coupling reactions, and serve as constituents for generation of *ortho*-quinone methides, which further undergo a [4 + 2] cycloaddition with second arynes. We have also demonstrated that *ortho*-quinodimethanes can be inserted into a tin–tin or silicon–silicon σ-bond at their *exo*-diene moieties with the aid of a transition-metal catalyst, uncovering the new synthetic characteristics of the transient conjugated dienes.

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