$Ph_2P(O)$ as a New Protecting Group for Terminal Acetylenes

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Chapter 1 General Introduction

1.1 Acetylene compounds

The carbon-carbon triple bond is a common and vital structural motif in organic chemistry.[1] Acetylene chemistry has also driven the development of new methodology such as electrophilic addition reactions that allow the derivatization of this high-energy functional group into hetero- and carbocycles of significant interest to both synthetic and medicinal chemists.[2] Alkynes are versatile synthetic building blocks for the formation of natural product analogues and hybrid structures. For example, the hydrophobic, rigid and linear attributes of acetylenes affords their derivatives with interesting structural properties and biological activity such as antibacterial, antifungal, pesticidal and antitumor activity.[3] Aromatic acetylenes are capable of giving rise to unique structures as well as electronic properties due to their skeletal persistency and rich π electrons.

π-Conjugated structural system with arylene-ethynylene array are important organic materials such as organic field-effect transistors (OFET), organic light-emitting diodes (OLED) and dye-sensitized solar cell (DSSC).[4] A series of 9,10-anthrylene-substituted phenyleneethynylenes having Ph_2N and CN group are synthesized and applied as organic dye for dye-sensitized solar cell (Figure 1.1).[5]

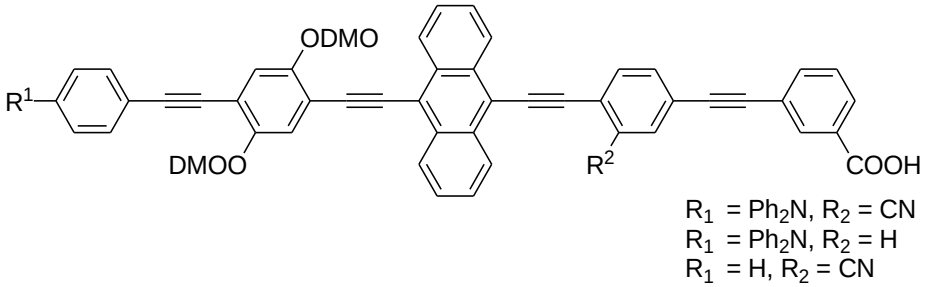


Figure 1.1 π-Conjugated Structural System for Dye-sensitized Solar Cell [5]

The particular structural properties of acetylenes make them likely candidates for liquid crystalline materials, organic semiconducting materials in field-effect transistors, and hole-conducting layers in photovoltaic devices.[6] As the rigid molecular core, the π-stacking interactions play an important role in discotic liquid crystals. Therefore many shape-persistent macrocycles have been designed and fabricated for this purpose (Figure 1.2).[7]

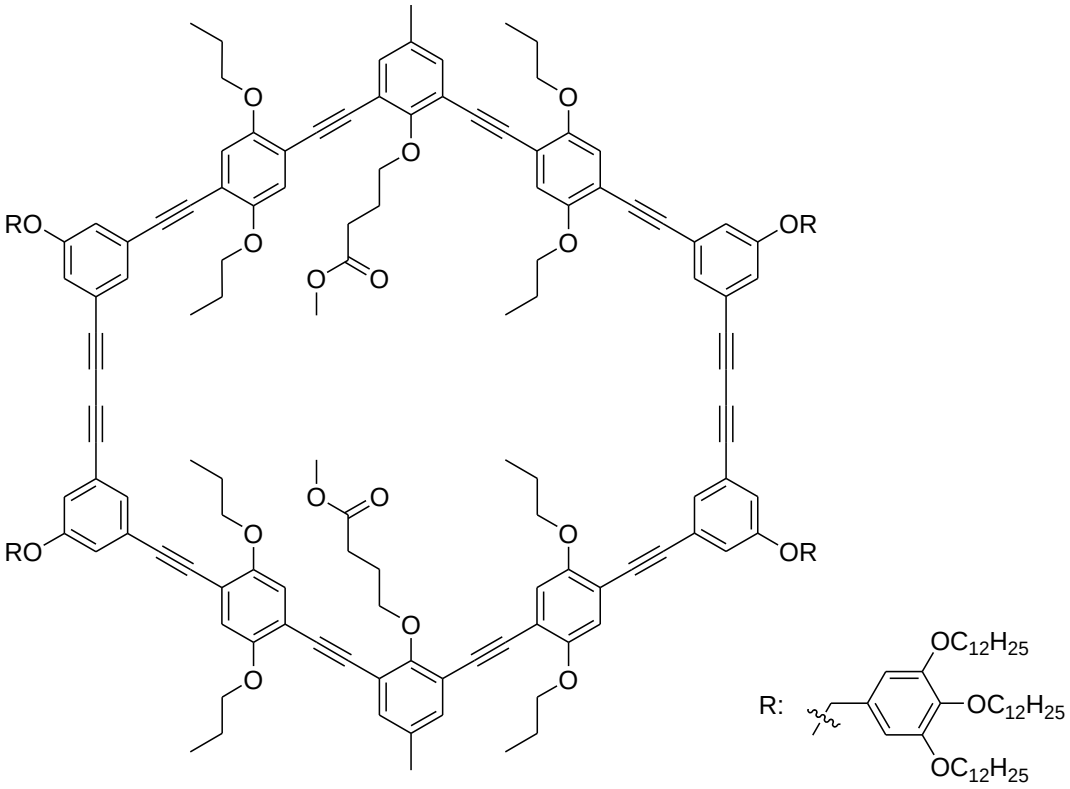


Figure 1.2 Shape-persistent Macrocycles for Liquid Crystal[7a]

Construction of 2D molecular networks on solid surfaces based on self-assembly is a subject of intense interest owing to the perspective of various applications in the filed of nanoscience and nanotechnology.[8] A series of alkyl- and alkoxy-substituted rhombic-shaped bisDBA derivatives were synthesized for the purpose of the formation of porous networks at 1,2,4-trichlorobenzene (TCB)/graphite interface (Figure 1.3).[9]

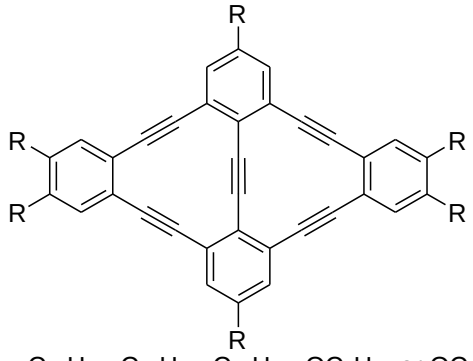


Figure 1.3 Rhombic-shaped BisDBA Derivatives for Porous Networks[9]

Rigid molecular architectures which consist of a trivalent core and three π extended arms are currently attracting attention because of potential application as devices, such as light-emitting diodes (LEDs) and nonlinear optics (NLO).[10] The star-shaped architectures that comprise a 1,3,5-triethynylbenzene core and methoxy group substituted oligo(p-phenyleneethynylene) arms have been prepared for this purpose (Figure 1.4). [11]

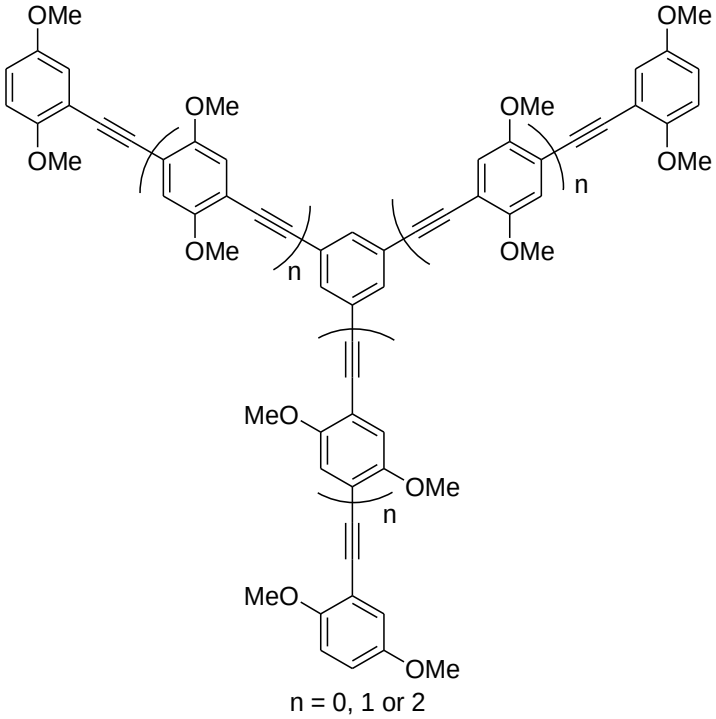
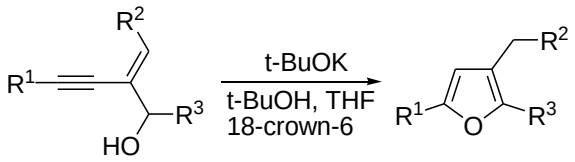


Figure 1.4 Star-shaped Architectures for Light-emitting Material[11]

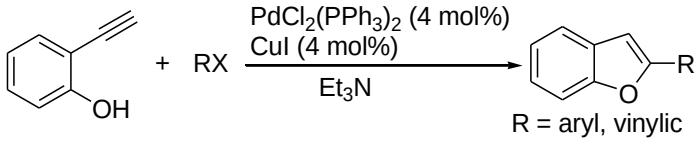
1.2 Chemical Reactions of Acetylenes

A series of oxygen-containing heterocycles have been prepared by the cyclization of acetylenic alcohols.[12] For example, furan is obtained by the cyclization of akenynols using t-BuOK as a catalyst (Scheme 1.1).[13]



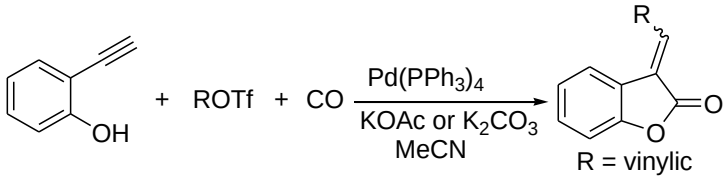
Scheme 1.1 Cyclization of Akenynols for Preparation of Furan[13]

The cyclization of acetylenic phenols is a convenient way to prepare benzofurans. In the presence of $PdCl_2(PPh_3)_2$, cyclization of 2-ethynyl- phenols and ary halides affords benzofurans (Scheme 1.2).[14]



Scheme 1.2 Cyclization of Ethynylphenol for Preparation of Benzofurans[14]

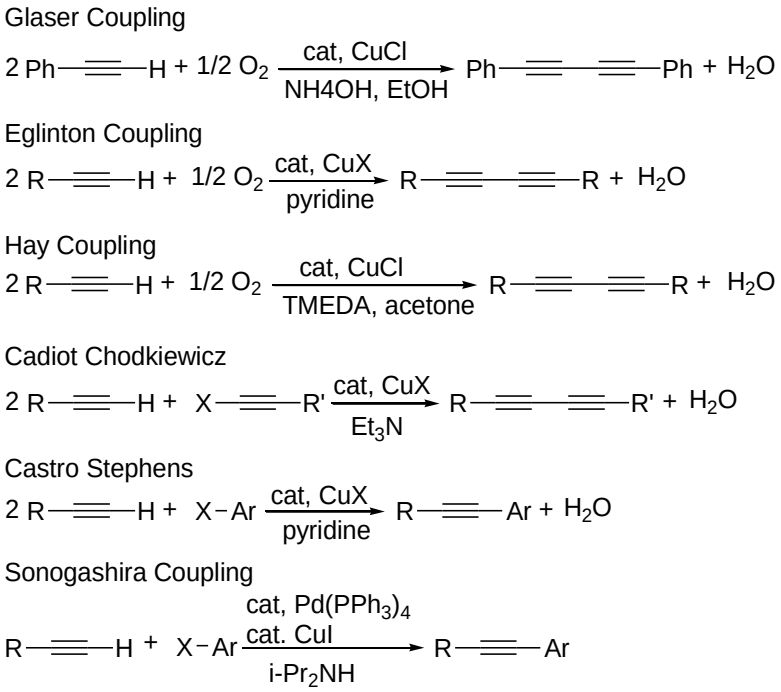
2-Ethynylphenols is cyclized to carbonyl-containing product by treatment with CO and a palladium catalyst. In the presence of CO and vinylic triflates, the cyclization of 2-ethynylphenols afforded 3-alkylidene-2- coumaranones (Scheme 1.3).[15]



Scheme 1.3 Cyclization of Ethynylphenol for Preparation of Coumaranones[15]

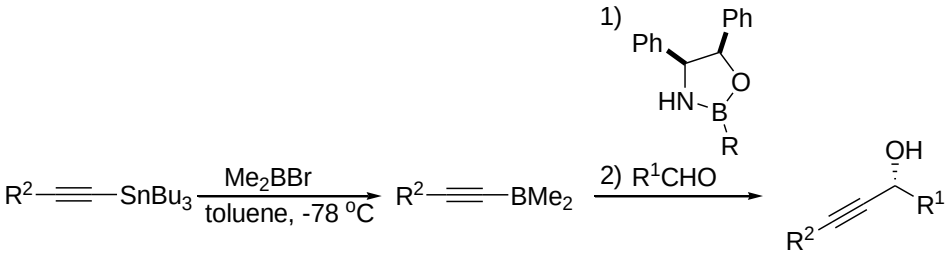
A number of other acetylenic derivatives such as acetylenic ethers, acetylenic acids, acetylenic aldehydes and acetylenic amines have been cyclized to yield a wide array of heterocycles and carbocycles by electrophilic processes.[16]

The terminal acetylenes are readily deprotonated because of the high proportion of s character associated with the carbon atom. This property of terminal acetylenes enables the generation of acetylides capable of participating in C-C bond formation. The classic Glaser reaction, which was firstly reported in 1869, involves the oxidative coupling of terminal acetylenes and became the cornerstone for the development of Eglinton, Hay, Cadiot-Chodkiewicz, Castro-Steohens and Sonogashira coupling reactions (Scheme 1.4).[17]



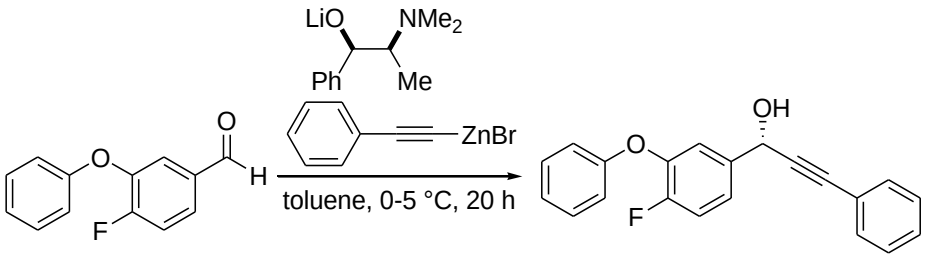
Scheme 1.4 Classic Coupling Reactions of Terminal Acetylenes[17]

In 1994, Corey and Cimprich reported the effective use of borohydride reductions of ketones afford a guiding paradigm for the study of acetylide additions (Scheme 1.5).[18] These asymmetric additions of acetylide are mediated by the chiral oxazaborolidene, and afford the products in 98% *ees*.



Scheme 1.5 Asymmetric Additions of Acetylide[18]

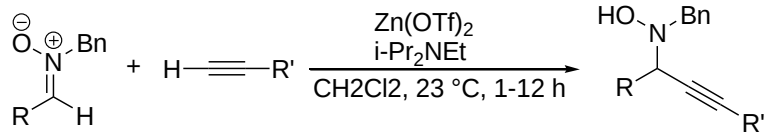
The zinc acetylide reagent generated by transmetalation of lithiated acetylide was used in the addition reaction as well. Treatment of zinc acetylide with lithium alkoxide salt and aldehyde gave propargyl alcohol in 88% *ee* and 80% yield (Scheme 1.6).[19]



Scheme 1.6 AdditionReaction of Zinc Acetylide Reagent[19]

Recently, it has attracted increasing attention that the development of methodology in which terminal acetylenes are activated in situ under mild deprotonation conditions and are subsequently subject to C = N addition

reactions.[20] In the presence of 10 mol% $Zn(OTf)_2$ and 25 mol% Hünig's base, terminal acetylenes undergo deprotonation and subsequently participate in nucleophilic additions to nitrones and afford propargyl N-hydroxyamines in up to 99% yield (Scheme 1.7).[21]

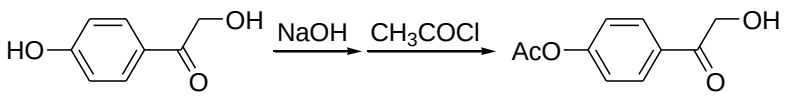


Scheme1.7 Addition of Terminal Acetylenes to C = N[21]

1.3 Protective Groups in Organic Synthesis

The protection/deprotection of functional group is one of the fundamental technologies in organic synthesis. Other reactive sites must be temporarily blocked if we want to carry out a chemical reaction selectively at one reaction site in a multifunctional compound. Therefore, many protective groups have been, and are being, developed. An ideal protecting group needs to satisfy the following issues: (i) facile introduction to the target functional group, (ii) stability during the desired transformation such as C-C bond formation and (iii) facile deprotection under mild reaction conditions.[22]

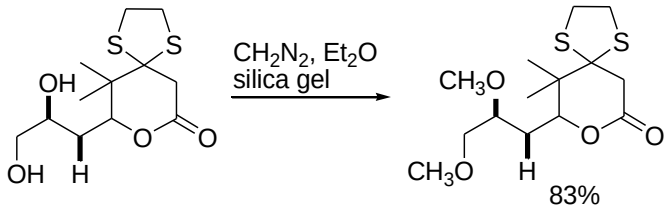
In early transformations, the chemists select a standard derivative known to be stable to the subsequent reactions. For example, by treatment with silver ion, the aliphatic-OH group displaced the bromide ion in a bromoglucoside. And then the acetate group was removed by basic hydrolysis (Scheme 18).[23]



Scheme 1.8 Selective Protection of Phenolic-OH Group.[23]

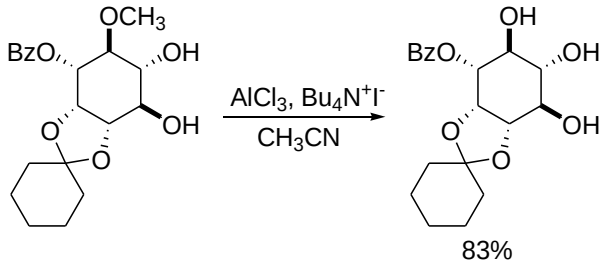
A number of more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds were developed for preparation of more complicated molecules.[24]

A hydroxyl group must be protected during oxidation, acylation, halogenation with phosphorus or hydrogen halides, or dehydration reactions. Ethers are among the most useful protective groups in organic synthesis. For protection of hydroxyl group, methyl ethers are formed from CH_2N_2, Me_2SO_4, MeI, $(MeO)_2POH$, or CF_3SO_3Me (Scheme 1.9).[25]



Scheme 1.9 Methylether as a Protective Group for Hydroxyl Group[25a]

Ether groups are removed under a wide variety of conditions such as Me_3SiI, BBr_3, AlX_3 (X = Br, Cl), $SiCl_4$/NaI, t-BuCOCl/NaI, $Ac_2O/FeCl_3$, Me_2BBr, etc (Scheme 1.10).[26]

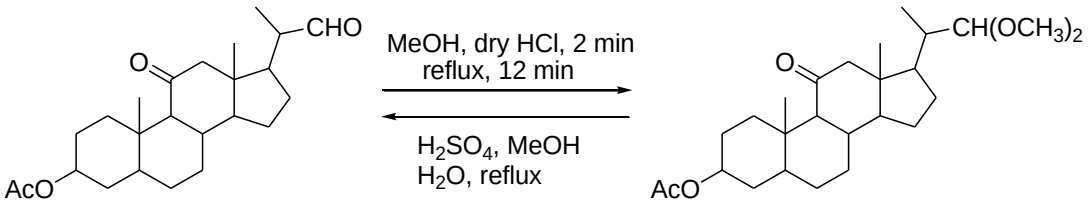


Scheme 1.10 Cleavage of Methylether[26c]

A wide variety of other functional groups such as methoxymethyl, acetate ester, carbonate and methanesulfonate are developed as protective groups for hydroxyl group as well.[27] And some the protective groups develop for alcohol are

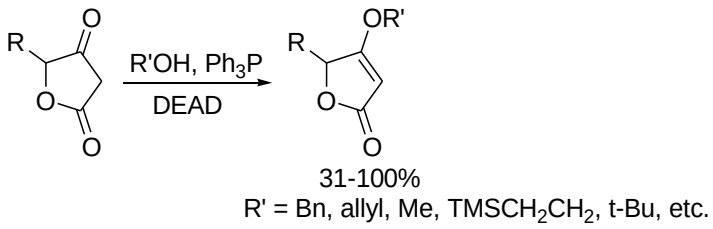
applicable to phenol protection as well.[28] Especially, the usefulness of diols in synthetic design and in natural source has led to the development of various protective groups such as cyclic acetals or ketals, chiral ketones, cyclic ortho esters, silyl derivatives and cyclic cabonates or boromates.[29]

A series of protective groups are investigated to protect a carbonyl group against attack by strong or moderately strong nucleophiles, including organometallic reagents, reductant and oxidant.[22a] Acyclic and cyclic acetals or ketals are the most widely used protective groups for carbonyl groups.[30] In the presence of acid with an alcohol, dimethyl acetal is introduced to aldehyde, the formed acetal is readily cleaved by acidic hydrolysis (Scheme 1.11).[31]



Scheme 1.11 Dimethylacetal as a Protective Group for Carbonyl Group [31]

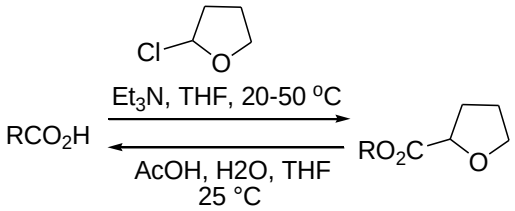
In order to protect α- and β-diketones selectively, a number of protective group such as enol ethers, thioenol ethers, enol acetates and enamines are developed (Scheme 1.12).[32]



Scheme 1.12 Protection of Dicarbonyl Compounds[32b]

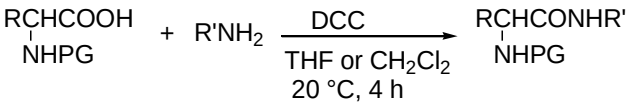
The acidic proton of carboxylic acids interferes with base-catalyzed reactions

and the carbonyl group of carboxylic acids undergoes nucleophilic addition reactions. For these reasons, a number of protective groups for carboxylic acids are developed.[33] Carboxylic acids are commonly protected as esters, including heptyl esters, choline ester, tetrahydrofuranyl ester, benzyloxymethyl ester, acetol ester, etc (Scheme 1.13).[34]



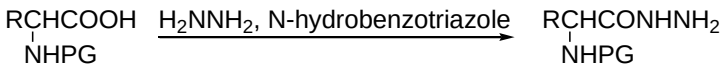
Scheme 1.13 Protection of Carboxylic Acids as Etrahydrofuranyl Ester[34c]

In some cases, carboxyl acids have been protected as amides and hydrazides as well.[35] In the presence of DCC, carboxyl acids react with amines to form amides (Scheme 1.14).



Scheme 1.14 Protection of Carboxylic Acids as Amides[35a]

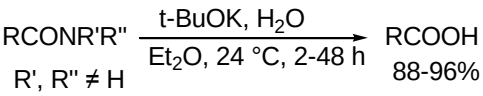
Hydrazides are obtained by treatment of carboxyl acids with hydrazine and triazole (Scheme 1.15).



Scheme 1.15 Protection of Carboxylic Acids as Hydrazides[35b]

Amides can be cleaved by a number of mild methods such as hydrolysis, photolytic cleavage and intramolecular assistance.[36] Potassium t-butoxide is

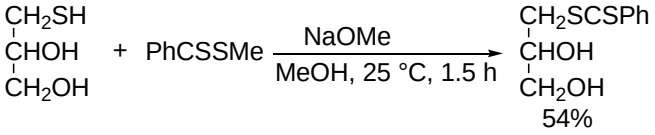
usually used to selective cleaved tertiary amides in the presence of primary or secondary amides because only tertiary amides are cleaved by Potassium t-butoxide (Scheme 1.16).[37]



Scheme 1.16 Cleavage of Amides[37]

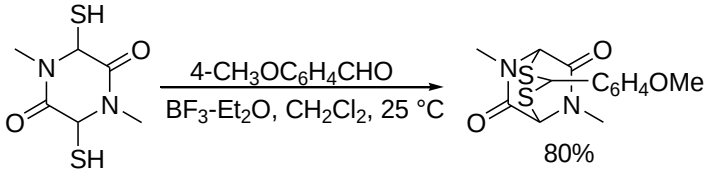
There are few reported methods for protection of sulfonic acids. Usually, sulfonic acids are protected as neopentyl ester, N-BOC-4-amino-2,2- dimethylbutyl sulfonate, isobutyl sulfonate and isopropyl sufonate.[38]

Protection of thiol group plays a vital role in peptide, protein syntheses.[39] A free –SH group is commonly protected as a thioether, a thioester, or an unsymmetrically substituted disulfide.[40] Treatment of thiothreitol with methyl dithiobenzoate and sodium metoxide selectively protects a thiol group as an S-thiobenzoyl derivatives in the presence of a hydroxyl group (Scheme 1.17).[41] Thioesters can be cleaved by NaOH, aqueous NH_3, NaSMe or CF_3CO_2H.[40]

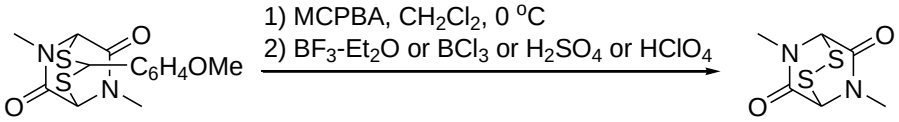


Scheme 1.17 Protection of Thiol Group[41]

Dithio acetals and ketals are prepared to protect dithiols. Treatment of dithiol with 4-methoxybenzaldehyde protects dithio group to S,S'-p-methoxy-benzylidene derivative (Scheme 1.18). S,S'-p-Methoxy-benzylidene derivative is cleaved in the presence of MCPBA (Scheme 1.19).[42]

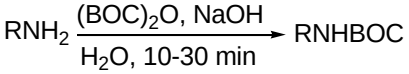


Scheme 1.18 Protection of Dithiol Group[42]

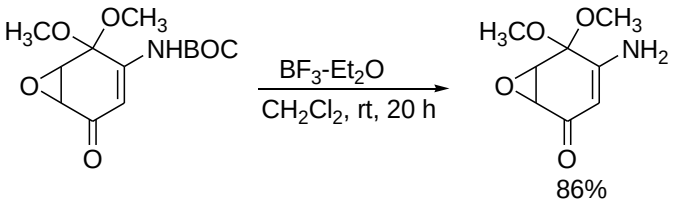


Scheme 1.19 Cleavage of S,S'-p-Methoxy-benzylidene Derivative[42]

The protection of amino group is very important in organic synthesis. Carbamates are commonly used for protection of amino group in peptide syntheses to minimize racemization.[39] Amino groups have been protected by many carbamates such as methyl carbamate, ethyl carbamate, isopropylallyl carbamate, etc.[43] The most useful compounds are t-butyl carbamates (BOC) $(CH_3)_3COC(O)NR_2$, which do not proceed hydrolysis under basis conditions and is inert to other nucleophilic reagents.[44] The more common methods for introduction if the BOC group is treatment with $(BOC)_2O$ and NaOH (Scheme 1.20).[45] t-Butylcarbamates are cleaved by a lot of reagents such as HCl, AcCl/MeOH, CF_3COOH/PhSH, TsOH, BF_3-Et_2O, etc (Scheme 1.21).[46]

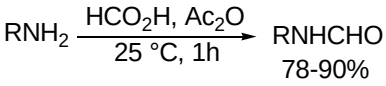


Scheme 1.20 Protection of Amino Group as t-Butylcarbamates[45]

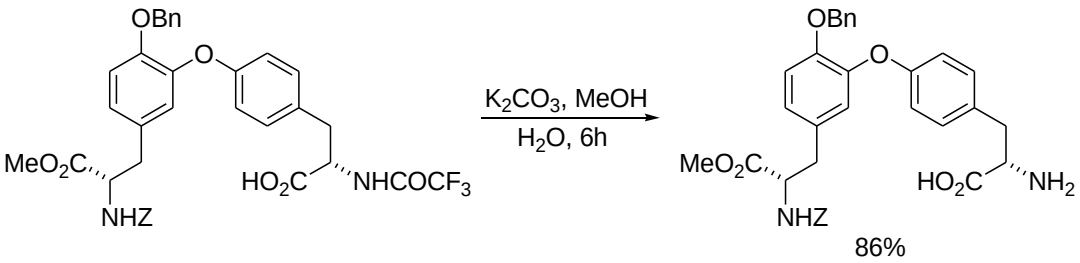


Scheme 1.21 Cleavage of t-Butylcarbamates[46e]

While amides are widely used in syntheses of alkaloids and for the protection of the nitrogen bases adenine.[47] Generally, they are prepared from the acid chloride or the anhydride and are hydrolyzed by heating in strongly acidic or basic solutions (Scheme 1.22, 1.23).[48]



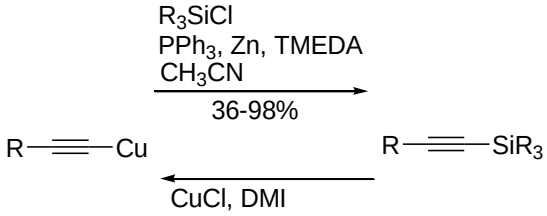
Scheme 1.22 Protection of Amino Group as Amides[48]



Scheme 1.23 Cleavage of Amides[48]

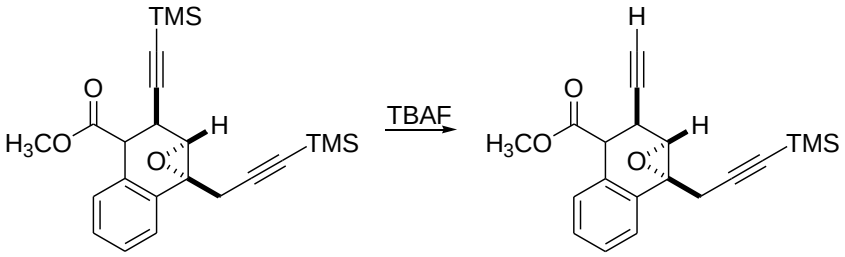
Protection of an acetylenic hydrogen is necessary for its acidity. Trialkylsilyl groups are widely used as protection groups for terminal acetylenes for the bulk of silane.[49] Trialkylsilylacetylenes are often used as a convenient method for introducing an acetylenic unit because they tend to be easily handled liquids or solids, as opposed to gaseous acetylene.[22] Trialkylsilanes are usually formed by addition of a lithium or Grignard reagent to the silyl chloride,[50] and thus discussions related to formation of the silyl acetylene bond will be kept to a minimum. In the presence of PPh_3, Zn and TMEDA, alkynylcopper reagents react with trialkylsilyl chloride to afford the trialkylsilyl protected acetylenes (Scheme 1.24). It is interesting to note that the reaction can be reversed to give the alkynylcopper(I) reagent in the presence of CuCl and

1,3-dimethyl-2-imidazolidinone.[51]



Scheme 1.24 Introduction of Trialkylsilyl Groups to Terminal Acetylenes[51]

Silylacetylenes are cleaved by many reagents such as KF, $Na(MeO)_3BH$, $AgNO_3$, TBAF, K_2CO_3, KOH, etc (Scheme 1.25).[52]



Scheme 1.25 Cleavage of Trialkylsilyl Protected Acetylenes[51d]

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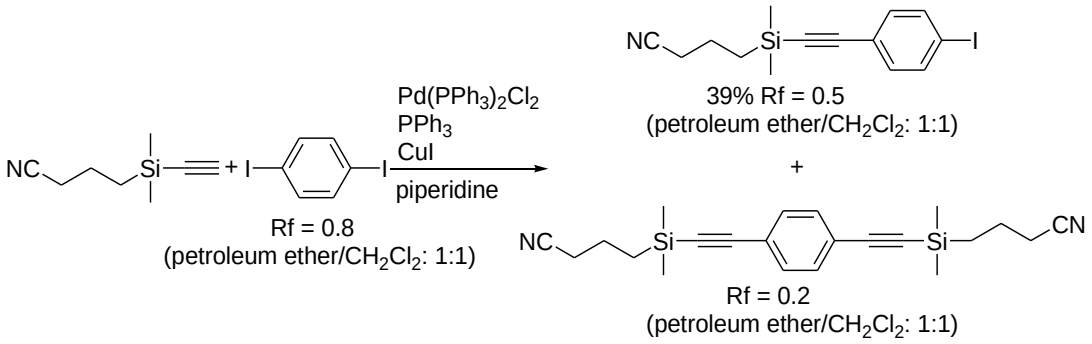
Chapter 2 $Ph_2P(O)$ as a New Protecting Group for Terminal Acetylenes

2.1 Abstract

A new protecting group for terminal acetylenes was developed. The $Ph_2P(O)$ group was introduced readily to terminal acetylenes by CuI-catalyzed phosphination and subsequent oxidation with H_2O_2 or by lithium acetylide involved one-pot process. $Ph_2P(O)$-protected ethynes remained intact in Sonogashira coupling, and their high polarity enabled facile isolation of the desired product from byproducts and the remaining starting compounds. By treatment with t-BuOK, $Ph_2P(O)$-protected ethynes were transformed to the corresponding terminal ethynes. By treatment with TBAF, TMS group was deprotected selectively in the presence of $Ph_2P(O)$ group. While by treatment with MeMgBr, $Ph_2P(O)$ was deprotected selectively in the presence of TMS group.

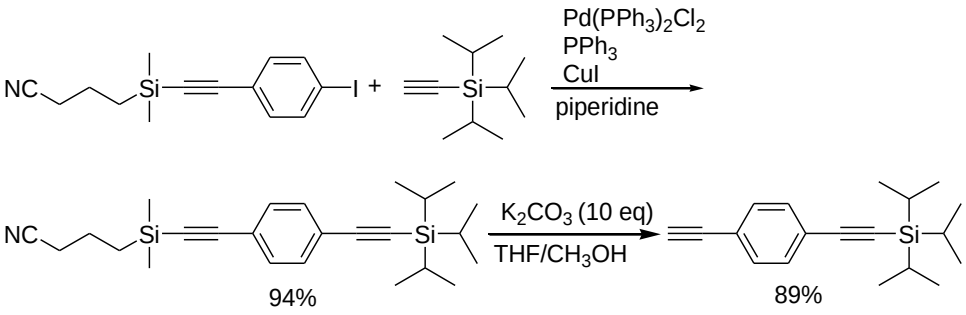
2.2 Introduction

Although we take advantage of Sonogashira coupling,[1] we frequently experience troublesome separation of the desired compound from the remaining starting materials and byproducts because of their similar polarities. In order to achieve facile isolation, some high polar protecting groups for terminal acetylenes were developed. The high polarity of (3-cyanopropyl)dimethylsilyl (CPDMS) enabled facile separation of starting compound, mono- and bis-CPDMS-adducts for their significantly deferent Rf values (Scheme 2.1).[2]



Scheme 2.1 CPDMS as a protecting group for terminal acetylenes[2]

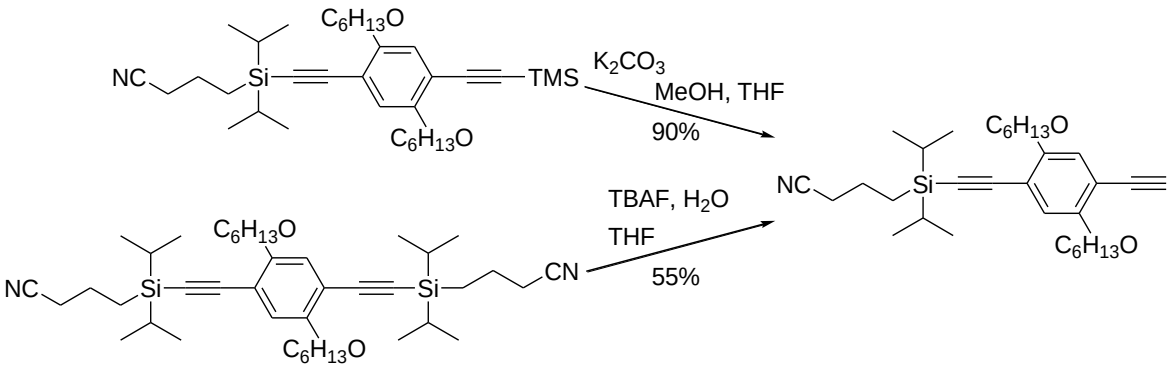
Coupling of the mono-CPDMS-adduct with TIPS-acetylene, purification of the CPDMS- and TIPS-protected-diyne and subsequent treatment with potassium carbonate gives the mono-TIPS-protected-diyne in nearly quantitative yield (Scheme 2.2).[2] But the (3-cyanopropyl) dimethylsilyl (CPDMS) group is not very stable and combines the mild cleaving conditions of the trimethylsilyl group with the high polarity of hydroxyl-containing protecting groups.



Scheme 2.2 Synthesis of Mono-TIPS-protected diyne[2]

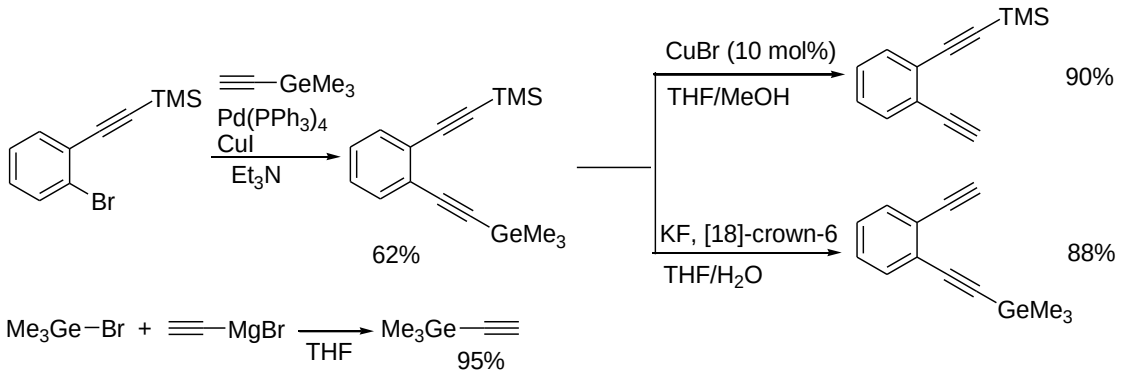
High polar protecting group (3-cyanopropyl) diisopropylsilyl (CPDIPS) is more stable than CPDMS group. By treatment with potassium carbonate, The TMS- and CPDIPS-protected-diyne can be selectively TMS-deprotected to give mono-CPDIPS-protected-diyne in 90% yield. CPDIPS-protected- diyne are ideally suited for partial deprotection. The addition of small amounts of water results in slower fluoride-induced desilylation. In this way, the

mono-CPDIPS-protected-diyne is obtained in 55% yield (Scheme 2.3). But it is difficult to obtain mono TMS- protected-diynes by using CPDMS or CPDIPSA as a protecting group for terminal acetylenes.[3]



Scheme 2.3 Synthesis of Mono-CPDIPS-protected diyne[3]

In order to obtain pure mono TMS- protected-diynes. In 1996, A. Ernst prepared several TMS- and $GeMe_3$-protected diynes and achieved mono regioselective deprotection by protodesilylation and protodegermylation. Treatment of ortho-substituted TMS- and $GeMe_3$-protected diyne with CuBr gave the mono-TMS-protected diyne in 90% yield. Subjection of ortho-substituted TMS- and $GeMe_3$-protected diyne to KF/[18]-crown-6- catalyzed deprotection produced the mono-$GeMe_3$-protected diyne in 88% yield. The starting compound ethynyltrimethylgermane was prepared from ethynylmagnesium bromide and bromotrimethylgermane. And bromotrimethylgermane is kind of expensive (10,100 per 1 gram) (Scheme 2.4).[4]



Scheme 2.4 $GeMe_3$ as a Protecting Group for Terminal Acetylenes [4]

Herein, we have developed a new cheap and polar protecting group, diphenylphosphoryl group, $Ph_2P(O)$, for terminal acetylenes. Highly polar features of $Ph_2P(O)$-protected ethynes allow their facile separation from byproducts which are inseparable or difficult-to-separate when trimethysilyl (TMS) group is used instead of $Ph_2P(O)$. Selective desilylation and dephosphination was realized by changing the deprotecting reagents and afforded the mono-$Ph_2P(O)$- and mono-TMS-protected diynes in excellent yields.

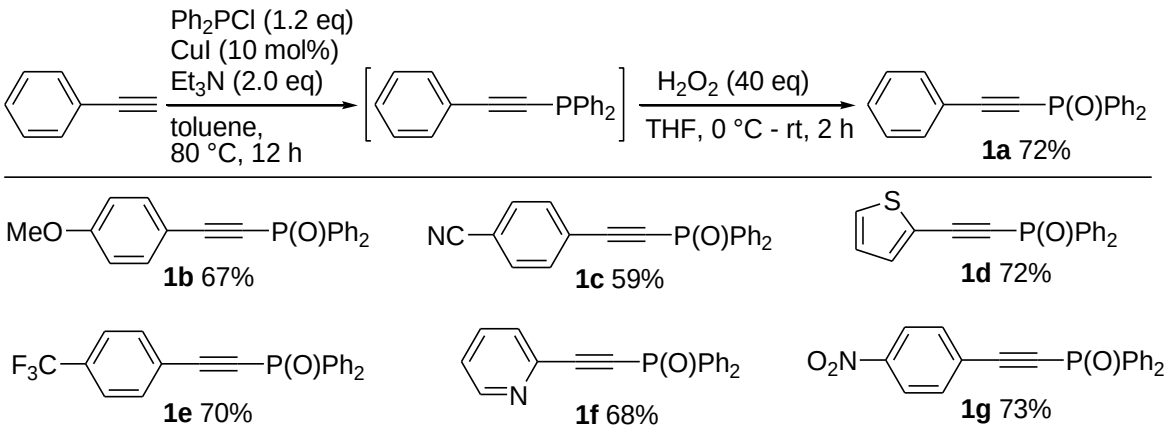
2.3 Results and Discussion

Introduction of $Ph_2P(O)$ to terminal acetylenes

The $Ph_2P(O)$ group was introduced to terminal ethynes by phosphination with Ph_2PCl followed by oxidation with H_2O_2. All phosphorylethynes could be purified by column chromatography on silica gel.

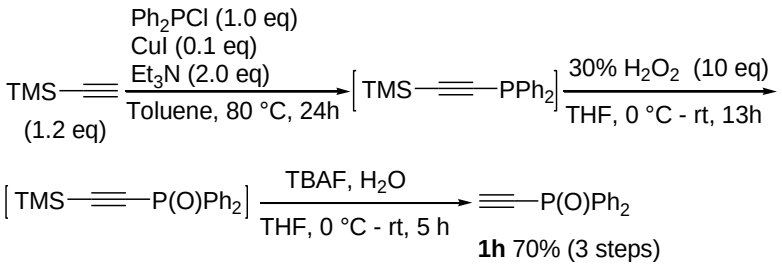
As representative synthetic route for phosphorylethyne **1a**, treatment of phenyl acetylene with chlorodiphenylphosphine, copper(I) iodide and triethylamine afforded diphenyl(phenylethynyl)phosphine, after workup with NH_4Claq and CH_2Cl_2, we obtained the crude diphenyl(phenylethynyl) phosphine product. Addition of H_2O_2 to the THF solution of the crude

diphenyl(phenylethynyl)phosphine gave the desired product **1a** in 72% yield. Phosphorylethynes (**1a-1g**) were prepared in moderate to good yields by the same procedure (Scheme 2.5).



Scheme 2.5 Introduction of $Ph_2P(O)$ to Terminal Acetylenes by two steps

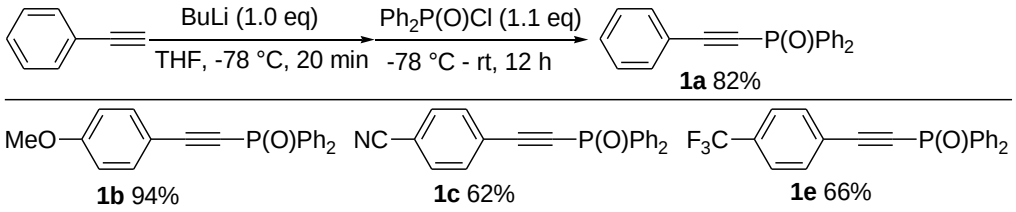
$Ph_2P(O)$-protected acetylene **1h** was prepared from TMS-acetylene through phosphination, oxidation and selective deprotection of TMS group using TBAF as a cleaving reagent (Scheme 2.6).



Scheme 2.6 Synthesis of $Ph_2P(O)$-protected terminal acetylene

Phosphorylethynes could be prepared by one-pot procedure involving lithium acetylide as well. Addition of diphenylphosphinic chloride to THF solution of lithium phenylacetylide afforded phenylphosphorylethyne **1a** in 82% yield. According to this one-pot procedure, we prepared phosphorylethyne **1b, 1c** and **1e**

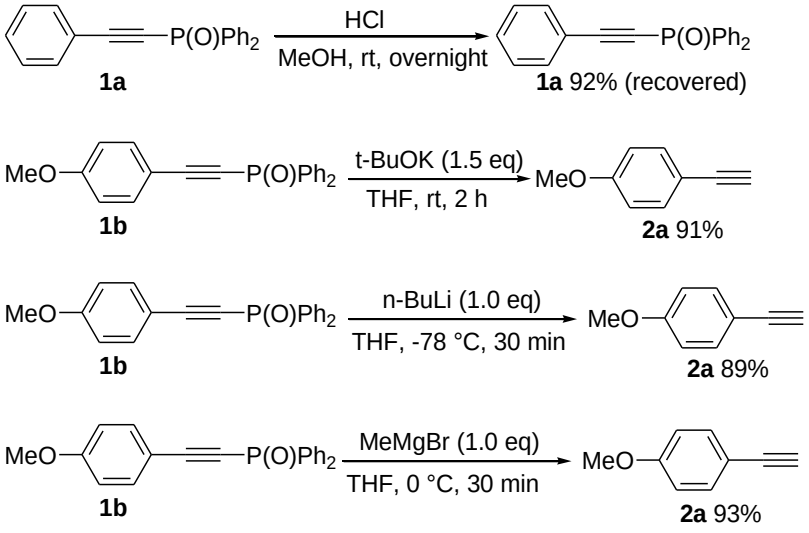
in moderate to excellent yields (Scheme 2.7).



Scheme 2.7 Introduction of $Ph_2P(O)$ by One-pot Procedure

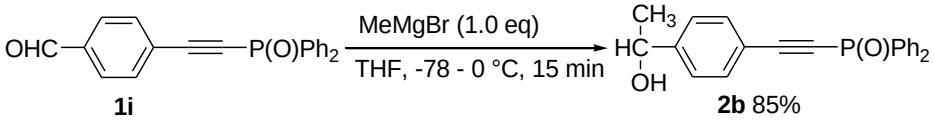
Stability of $Ph_2P(O)$ under acidic or basic conditions

In order to investigate stability of the $Ph_2P(O)$ protecting group, phosphorylethynes were subjected to acidic or basic conditions. As shown in Scheme 2.8, treatment of phosphorylethyne **1a** with MeOH/HCl aqueous solution recovered 92% of **1a**. $Ph_2P(O)$ protecting group was stable under acidic conditions. In sharp contrast to this, treatment of **1b** with t-BuOK, n-BuLi or MeMgBr followed by aqueous workup gave the terminal ethyne in excellent yields (Scheme 2.8).



Scheme 2.8 Stability of $Ph_2P(O)$ in acidic and basic conditions

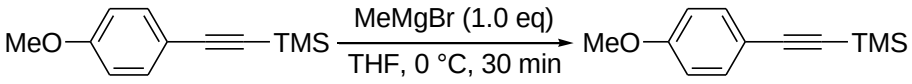
More Interestingly, in the presence of aldehyde group, $Ph_2P(O)$ group remained unchanged under THF solution of MeMgBr. Nucleophilic addition of MeMgBr to formyl group occurred by treatment of 4-((diphenylphosphoryl)ethynyl)benzaldehyde **1i** with 1.0 equivalent of MeMgBr at -78 to 0 °C, and the corresponding alcohol **2b** was produced in 85% yield (Scheme 2.9).



1i **2b** 85%

Scheme 2.9 Stability of phosphorylethynylbenzaldehyde in MeMgBr

TMS-protected ethyne remained intact under MeMgBr at 0 °C. As shown in Scheme 2.10, treatment of ((4-methoxyphenyl)ethynyl)trimethylsilane with MeMgBr recovered 98% of starting compound.

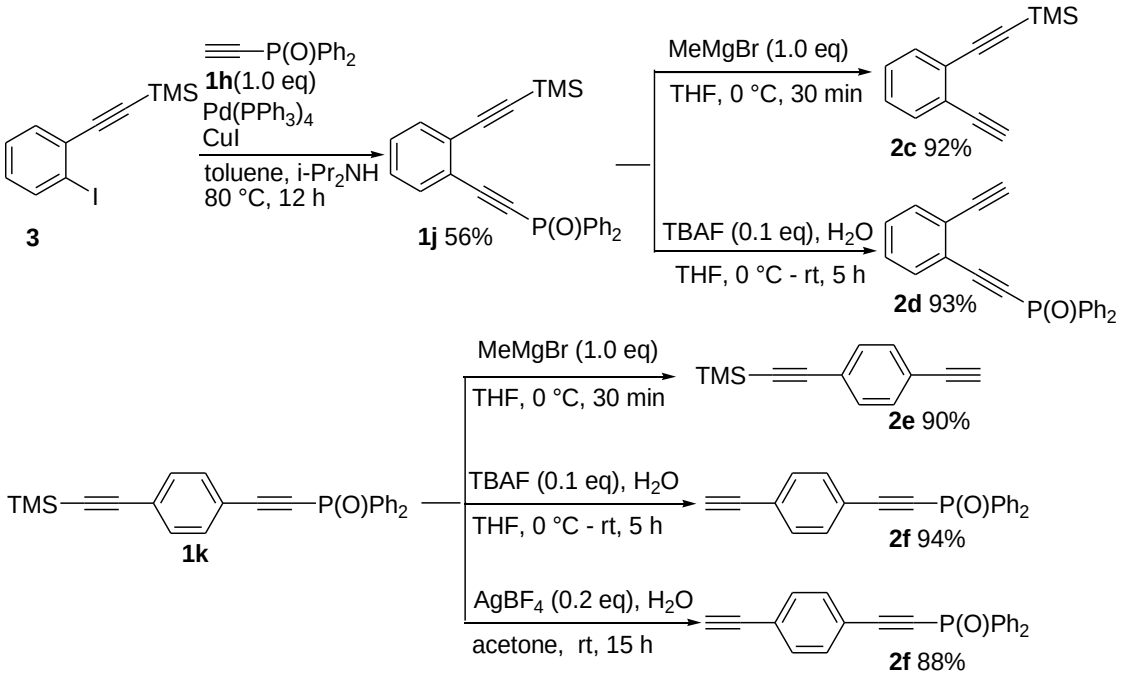


98% (recovered)

Scheme 2.10 Stability of TMS under MeMgBr

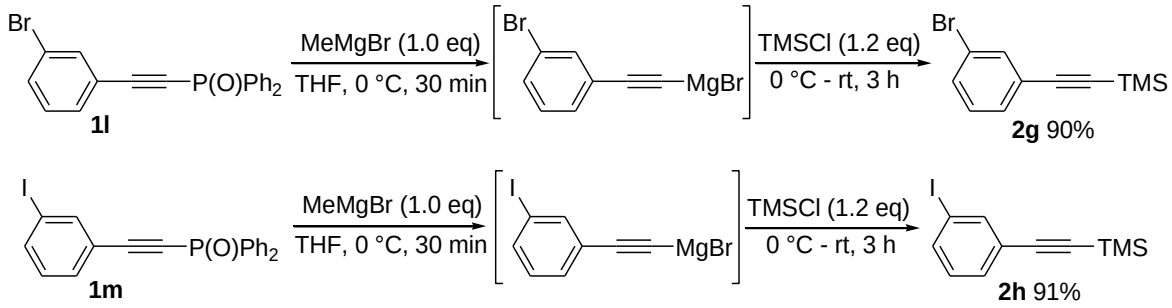
Facile selective deprotection of TMS and $Ph_2P(O)$ group was achieved by changing deprotecting reagent. In the presence of TMS group, selective deprotection of $Ph_2P(O)$ was achieved by using MeMgBr as a deprotecting reagent. While TBAF enabled selective deprotection of TMS group. Sonogashira coupling between iodide **3** and phosphorylethyne **1h** gave ortho-substituted TMS- and $Ph_2P(O)$-protected diyne **1j** in 56% yield. Treatment of **1j** with MeMgBr afforded ortho-substituted mono-TMS- protected diyne **2c** in 92% yield. Subjection of **1j** to TBAF and small amount of water gave ortho-substituted

mono-$Ph_2P(O)$-protected diyne **2d** in 93% yield. Similarly, treatment of para-substituted TMS- and $Ph_2P(O)$-protected diyne **1k** with MeMgBr afforded mono-TMS- protected diyne **2e** in 90% yield. In the presence of TBAF and small amount of water, desilylation of **1k** proceeded and gave mono-$Ph_2P(O)$-protected diyne **2f** in 94% yield. Specially, treatment of **1k** with catalytic amount of $AgBF_4$ and small amount of water also afforded **2f** in 88% yield (Scheme 2.11).



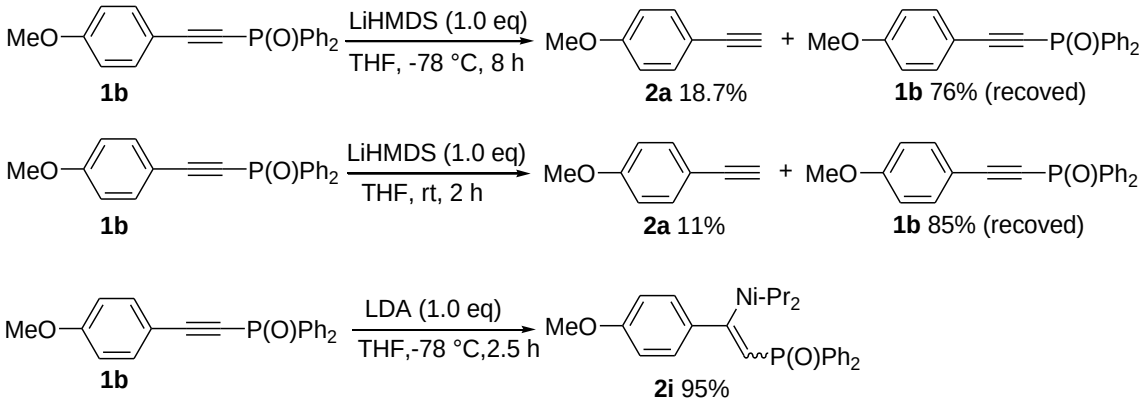
Scheme 2.11 Selective deprotection of $Ph_2P(O)$ and TMS

One-pot transformation of $Ph_2P(O)$ group to TMS group was succeeded by treatment of $Ph_2P(O)$-protected ethynes with MeMgBr followed by addition of TMSCl. Treatment of phosphorylethyl-substituted bromide **1l** with MeMgBr afforded magnesium acetylide. Addition of TMSCl into this newly formed THF solution of magnesium acetylide afforded trimethylsilylethyl-substituted bromide **2g** in 90% yield. We obtained trimethylsilyethyl-substituted iodide **2h** in 91% yield by the same procedure (Scheme 2.12).



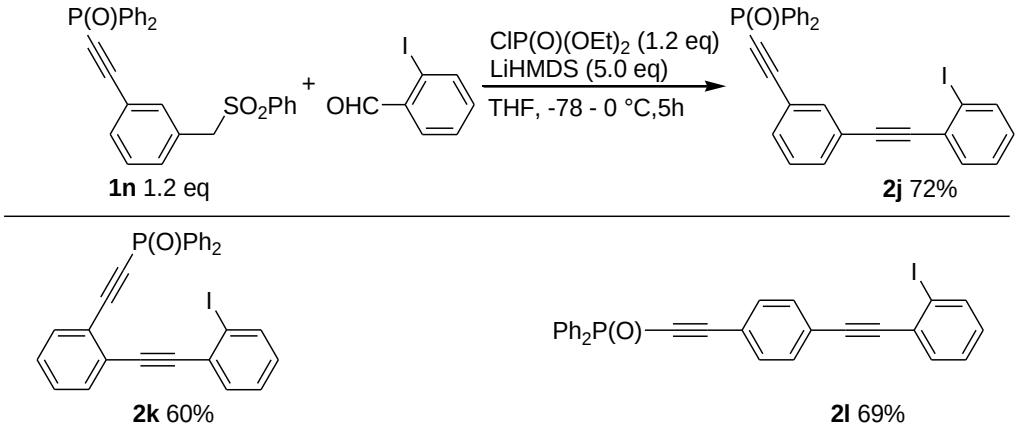
Scheme 2.12 One-pot Transformation of $Ph_2P(O)$ Group to TMS Group

However, large amount of phosphorylethyne **1b** remained unchanged in THF solution of LiHMDS at -78 °C or rt, and over 75% of **1b** was recovered. Treatment of **1b** with LDA at -78 °C gave the β-addition product vinylphosphine oxide **2i** in 95% yield (Scheme 2.13).



Scheme 2.13 Treatment of Phosphorylethyne with LiHMDS and LDA

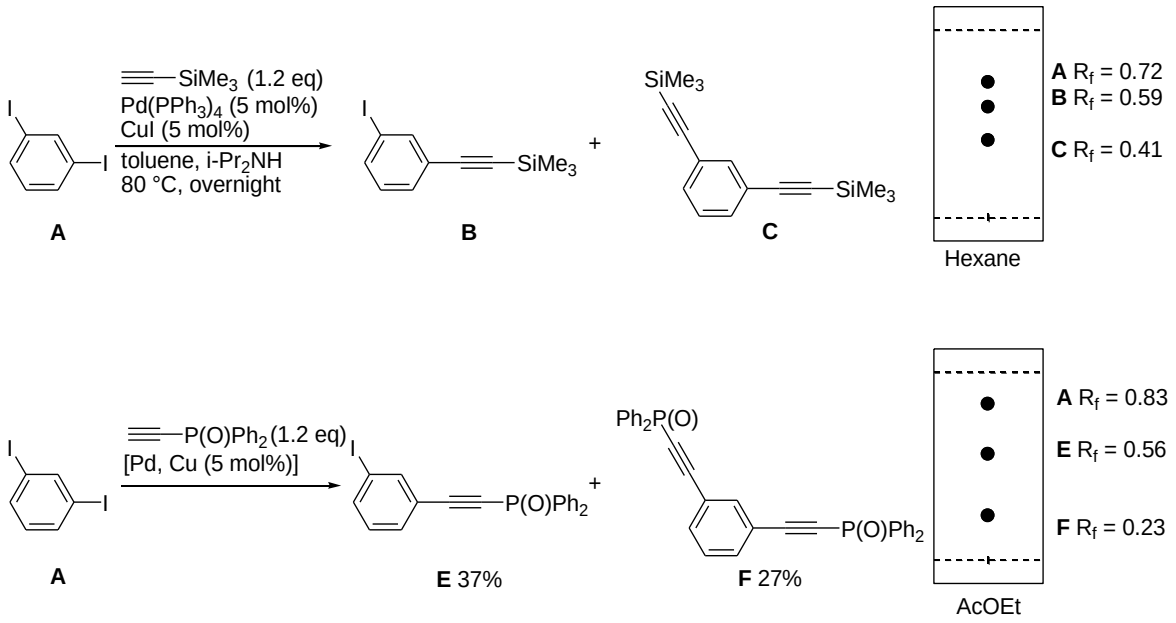
In the presence of LiHMDS, Phosphorylethyl-substituted sulfonylbenzene **1n** could be used as a starting compound in double elimination protocol. Treatment of **1n** with 2-iodobenzaldehyde, $ClP(O)(OEt)_2$ and LiHMDS afforded the desired product meta-phosphorylethyl-substituted iodide **2j** in 72% yield. We obtained ortho- and para-phosphorylethyl-substituted iodide derivatives **2k** and **2l** in moderate yields by the same procedure (Scheme 2.14).



Scheme 2.14 Double Elimination of Phosphorylethyl-substituted Sulfonylbenzene and 2-Iodobenzaldehyde

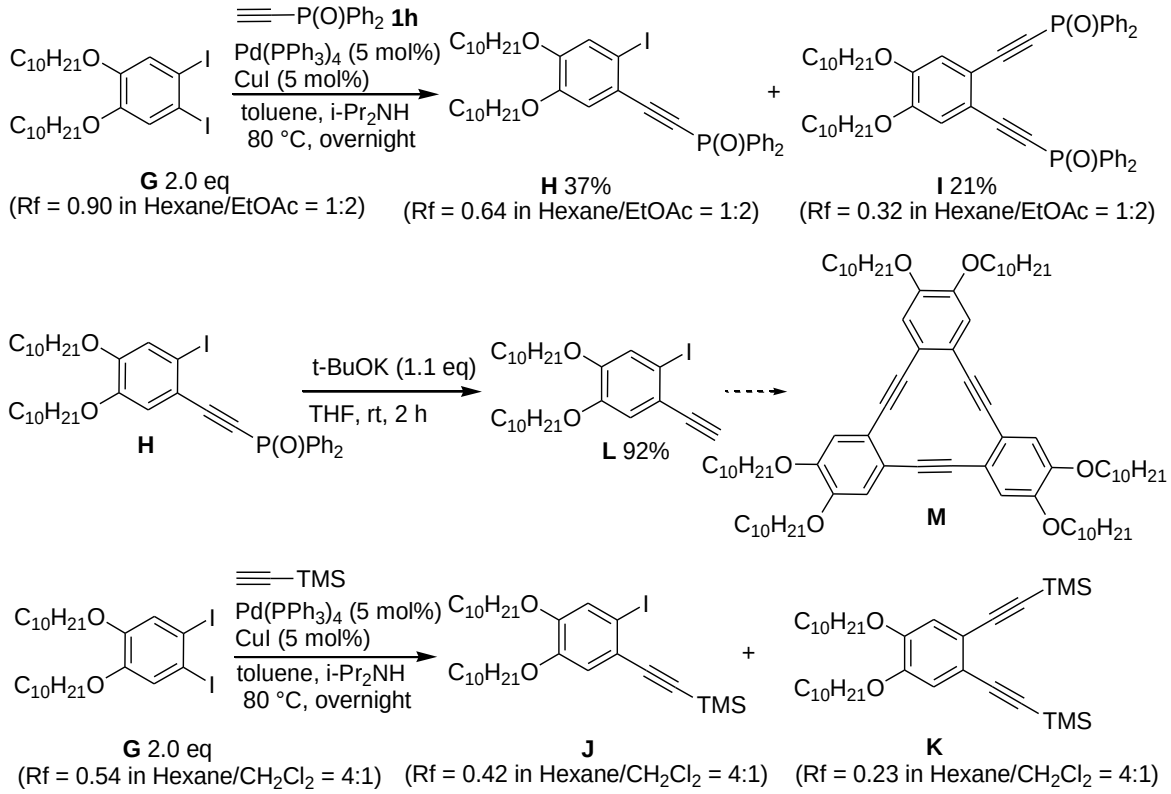
Facile isolation of mono- and bis$Ph_2P(O)$-protected acetylenes

The diphenylphosphoryl-ethyne bond remained intact in Sonogashira coupling. In Sonogashira coupling between 1,3-diiodobenzene and phosphorylethyne, a thin layer chromatography (TLC) analysis indicated formation of mono- and bis-adducts **E** and **F**. As we expected, high polarity of phosphine oxide enables easy separation of **E** and **F** by a column chromatography on silica gel: R_f = 0.56 for mono-adduct **E** and R_f = 0.23 for bis-adduct **F** in AcOEt. For instance, in 10 mmol scale of coupling reaction, 140 g of silica gel, 30 times weight of the crude product, enabled isolation of **E** in a pure form, while the same scale of coupling reaction between **A** and trimethylsilylethyne required 260 g of silica gel, 70 times weight of the crude product, for separation of mono- and di(silylethynyl)adducts which showed R_f = 0.59 and 0.41 in hexane, respectively (Scheme 2.15).[5]



Scheme 2.15 Facile Isolation of Mono- and Bis-adducts Using $Ph_2P(O)$ as a Protecting Group for Terminal Acetylenes

By taking advantage of this highly polar protecting group, the key intermediate iodo-substituted terminal acetylene **L** was prepared easily from diiodide **G**. Sonogashira coupling between $Ph_2P(O)$-protected acetylene **1h** and 1,2-bis(decyloxy)-4,5-diiodobenzene **G** provided a mixture of mono- and bis-adducts **H** and **I**. High polarity of $Ph_2P(O)$ enabled easy separation of **H** and **I** by a column chromatography on silica gel: R_f = 0.64 for mono-adduct **H** and R_f = 0.31 for bis-adduct **I** in Hexan/AcOEt = 1:2. Treatment of **H** with t-BuOK gave iodo-substituted terminal acetylene **L** in 92%. Hexadehydrotribenzoannulene **M** was prepare from **L** by copper-catalyzed cyclotrimerization.[6] While Sonogashira coupling between TMS-acetylene and 1,2-bis(decyloxy)-4,5-diiodobenzene **G** provided a mixture of mono- and diadducts **J** and **K**. The mono-diadducts **J** was kind of difficult to separate from the mixture of diiodode **G** and bis-adduct **K** because their similar R_f values (R_f = 0.42 for mono-adduct **J** and R_f = 0.23 for bis-adduct **K)** (Scheme 2.16).



Scheme 2.16 Facile Isolation of Products Using $Ph_2P(O)$ as Protecting Group for Terminal Acetylenes

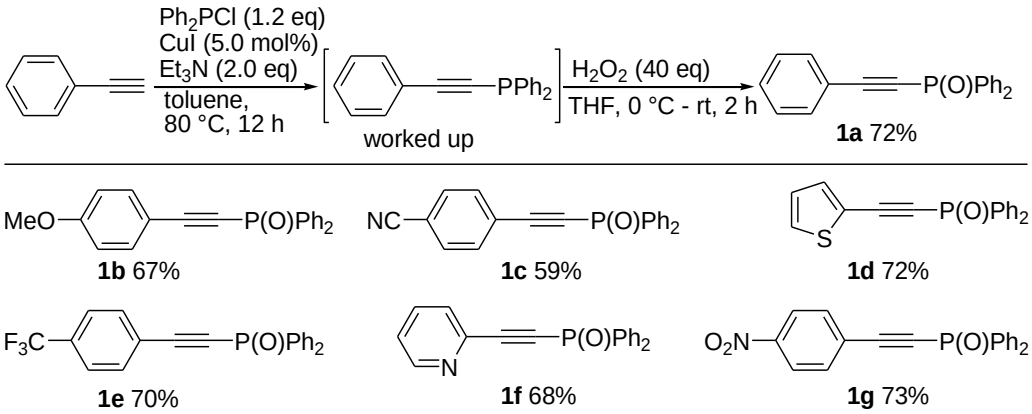
2.4 Conclusion

$Ph_2P(O)$ group was an idea protecting group for terminal acetylenes. The $Ph_2P(O)$ group was introduced readily to terminal acetylenes by CuI-catalyzed phosphination and subsequent oxidation with H_2O_2 or by lithium acetylide involved one-pot process. $Ph_2P(O)$-protected ethynes remained intact in Sonogashira coupling, and their high polarity enabled easy separation of the desired coupling product from byproducts. By treatment with t-BuOK or MeMgBr, $Ph_2P(O)$-protected ethynes were transformed to the corresponding terminal ethynes.

2.5 Experimental Section

General. All reactions were carried out under an atmosphere of argon with freshly distilled solvents, unless otherwise noted. Toluene was distilled from sodium. Diisopropylamine and triethylamine were distilled from CaH_2. DMF was distilled from $Ca(OH)_2$. Dry tetrahydrofuran (THF) was purchased from Wako Chemicals. $Pd(PPh_3)_4$ was prepared according to the reported method. Silica gel (Daiso gel IR-60) was used for column chromatography. The other materials were purchased from commercial sources and used without additional purification. NMR spectra was recorded at 25 °C on JEOL Lambda 300 and JEOL Lambda 500 instruments in $CDCl_3$ and calibrated with tetramethysilane (TMS) as an internal reference. Mass spectra were recorded on JEOL MStation JMS-700 and Shimadzu/Kratos MALDI 4 and Platform II single quadrupole (Micro-mass, Altrinchan, UK) mass spectrometers. Elemental analyses were performed by the Perkin-Elmer PE 2400. Melting points (m.p.) were measured on a GTO-250RS instrument.

Synthesis of 1a, 1b, 1c, 1d, 1e, 1f and 1g by CuI-catalyzed phosphination and subsequent oxidation (representative procedure for 1a):



A toluene solution (5.0 mL) of ethynylbenzene (109.8 μL, 1.0 mmol), CuI (19.0 mg, 0.1 mmol), Ph_2PCl (220.6 μL, 1.2 mmol) and Et_3N (277.2 μL, 2.0 mmol) was stirred under nitrogen at 80 °C for 8 h. After usual workup with CH_2Cl_2 and

NH_4Claq, the combined organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was used for next step without purification. To a THF solution (10.0 mL) of the crude diphenyl(phenylethynyl)phosphine was added H_2O_2aq (30%, 2.5 mL, 20.0 mmol) slowly at 0 °C, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and water, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford diphenyl(phenylethynyl)phosphine oxide **1a** in a pure form (226.7 mg, 75% yield).

1a:[5] white powder; m.p. 94-96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.48-7.52 (m, 4H), 7.56 (t, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.89-7.93 (m, 4H).

1b:[5] white powder; m.p. 125-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.49-7.56 (m, 8H), 7.88-7.92 (m, 4H).

1c:[5] pale yellow powder; m.p. 163-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.55 (m, 4H), 7.57-7.62 (m, 2H), 7.69 (br, 4H), 7.84-7.92 (m, 4H).

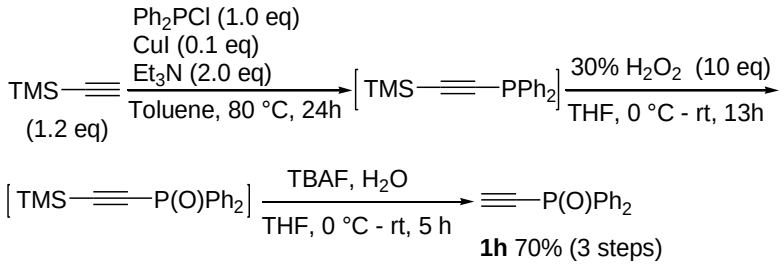
1d: white powder, m.p. 79-82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (t, *J* = 3.7 Hz, 1H), 7.45 (d, *J* = 4.6 Hz, 1H), 7.48-7.52 (m, 5H), 7.56-7.58 (m, 2H), 7.87-7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.77 (d, *J* = 168.2 Hz), 98.64 (d, *J* = 30.4 Hz), 119.5 (d, *J* = 4.7 Hz), 127.38, 128.62 (d, *J* = 13.4 Hz), 130.60, 130.92 (d, *J* = 10.9 Hz), 132.26 (d, *J* = 2.5 Hz), 132.68 (d, *J* = 122.2 Hz), 135.77. ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.02; HRMS (FAB) calcd for $C_{18}H_{13}OPS$ ($M+H^+$): 309.0425, found 309.0128.

1e:[5] pale yellow powder, m.p. 146-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.54 (m, 4H), 7.58-7.60 (m, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.88-7.92 (m, 4H).

1f: white powder, m.p. 125-127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.39 (m, 1H), 7.49-7.52 (m, 4H), 7.56-7.58 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.91-7.95 (m, 4H), 8.67 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.99 (d, *J* = 162.3 Hz), 102.75 (d, *J* = 27.9 Hz), 124.70, 128.56 (d, *J* = 14.0 Hz), 130.84 (d, *J* = 11.4 Hz), 132.12 (d, *J* = 122.5 Hz), 132.30, 136.31, 140.44 (d, *J* = 4.2 Hz), 150.25, 150.27. ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.19; HRMS (FAB) calcd for $C_{19}H_{14}NOP$ ($M+H^+$): 304.0813, found 304.0957.

1g: white powder, m.p. 165-167 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.55 (m, 4H), 7.59-7.62 (m, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.87-7.92 (m, 4H), 8.26 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 87.53 (d, *J* = 160.7 Hz), 101.82 (d, *J* = 27.9 Hz), 123.62, 126.31 (d, *J* = 3.8 Hz), 128.72 (d, *J* = 13.7 Hz), 130.84 (d, *J* = 11.2 Hz), 131.97 (d, *J* = 122.3 Hz), 132.54 (d, *J* = 2.8 Hz) 133.34, 148.31. ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.02; HRMS (FAB) calcd for $C_{20}H_{14}NO_3P$ ($M+H^+$): 348.0711, found 348.0810.

Synthesis of 1h:

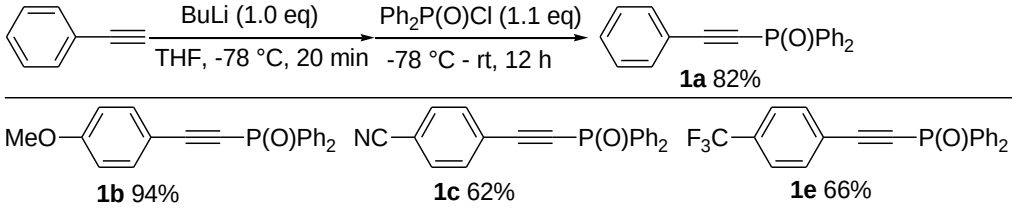


To a flask were added CuI (190.4 mg, 1.0 mmol), Ph_2PCl (1.8 mL, 10.0 mmol), trimethylsilylacetylene (1.7 mL, 12.0 mmol), triethylamine (2.8 mL, 20.0 mmol) and toluene (30.0 mL), and the mixture was stirred under nitrogen at 80 °C for 24 h. After workup with AcOEt/water, the organic layer was washed with aqueous NH_4Cl and brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was used for next step without purification. To the crude product were added THF (20.0 mL) and then 30% H_2O_2 (5.0 mL) at 0 °C, and the mixture was stirred under air at rt for 13 h. After workup with

CH_2Cl_2/water, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was used for next step without purification. To the crude product were added water (0.5 mL) and THF (50.0 mL), and then TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) at 0 °C, and the mixture was stirred under air at rt for 5 h. After the solvents were evaporated, the crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to give **1h** in a pure form (1.63 g, 72% yield in 3 steps).

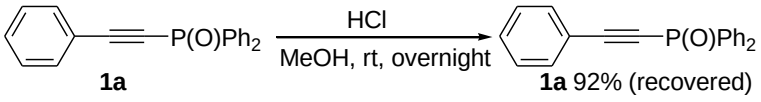
1h:[5,7] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.33 (d, *J* = 9.8 Hz, 1H), 7.48-7.52 (m, 4H), 7.56-7.59 (m, 2H), 7.83-7.87 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.78 (d, *J* = 159.7 Hz), 93.96 (d, *J* = 27.4 Hz), 128.67 (d, *J* = 13.4 Hz), 130.90 (d, *J* = 11.4 Hz), 131.53, 132.50.

Synthesis of 1a, 1b, 1c and 1e by lithium acetylide involved one-pot process (representative procedure for 1a):



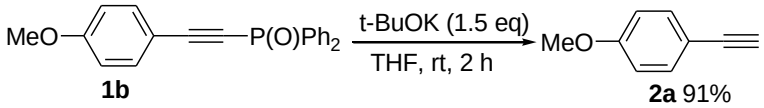
To A THF solution (5.0 mL) of ethynylbenzene (109.8 μL, 1.0 mmol) was added BuLi (1.6M in hexane, 625.0μL, 1.0 mmol) at -78 °C. After stirred for 20 min at -78 °C, $Ph_2P(O)Cl$ (209.9 μL, 1.1 mmol) was added at -78 °C, and then the reaction mixture was stirred for 12 h at rt. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **1a** in a pure form (247.9 mg, 82% yield).

Treatment of Phenylethynylphosphine Oxide with HClaq:



To a MeOH solution (10 mL) of **1a** (151.2 mg, 0.5 mmol) was added HClaq (12 M, 0.08 mL, 1 mmol) at rt, and the mixture was stirred at rt overnight. After workup with CH_2Cl_2 and water, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/EtOAc, 1:1) to recover **1** in a pure form (139.1 mg, 92%).

Treatment of 4-Methoxyphenylethynylphosphine Oxide with t-BuOK:

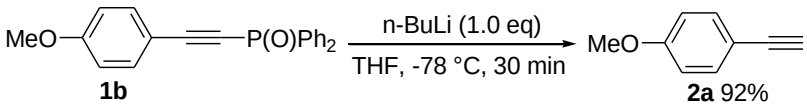


1b **2a** 91%

To a THF solution (10 mL) of **1b** (166.2 mg, 0.5 mmol) was added t-BuOK (84.0 mg, 0.75 mmol) at rt, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **2a** in a pure form (60.1 mg, 91%).

2a:[5] pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 1H), 3.81 (s, 3H), 6.84 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H).

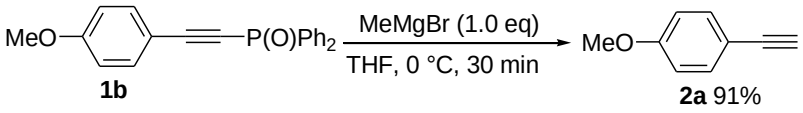
Treatment of 4-Methoxyphenylethynylphosphine Oxide with n-BuLi:



1b **2a** 92%

To a THF solution (10 mL) of **1b** (166.2 mg, 0.5 mmol) was added n-BuLi (1.6 M in hexane, 312.5 μL, 0.5 mmol) at -78 °C, and the mixture was stirred at -78 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **2a** in a pure form (60.8 mg, 92%).

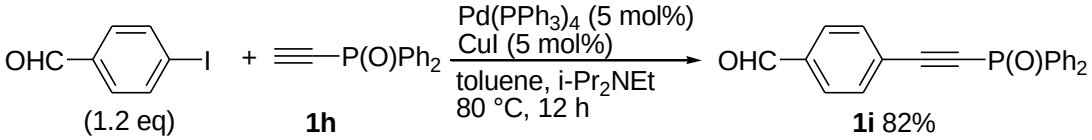
Treatment of 4-Methoxyphenylethynylphosphine Oxide with MeMgBr:



1b **2a** 91%

To a THF solution (10 mL) of **1b** (332.3 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **2a** in a pure form (120.3 mg, 91%).

Synthesis of 1i:

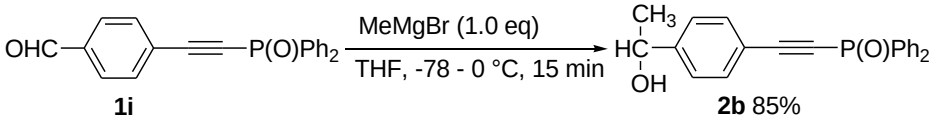


(1.2 eq) **1h** **1i** 82%

A toluene solution (5.0 mL) of 4-iodobenzaldehyde (278.4 mg, 1.2 mmol), **1h** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylethylamine (0.5 mL) was stirred under nitrogen at 80 °C for 12 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:2) to afford **1i** in a pure form (270.8 mg, 82% yield).

1i: white powder; m.p. 148-149 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.54 (m, 4H), 7.57-7.61 (m, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.88-7.92 (m, 6H), 10.05 (s, 1H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 86.35 (d, *J* = 163.7 Hz), 103.34 (d, *J* = 29.0 Hz), 125.72 (d, *J* = 4.1 Hz), 128.73 (d, *J* = 13.4 Hz), 129.51, 130.94 (d, *J* = 11.4 Hz), 132.41 (d, *J* = 122.0 Hz), 132.47, 133.06 (d, *J* = 1.6 Hz), 137.03, 191.05; HRMS (FAB) calcd $C_{21}H_{15}O_2P$ for ($M+H^+$): 331.0810; found 330.9758.

Treatment of 1i with MeMgBr:

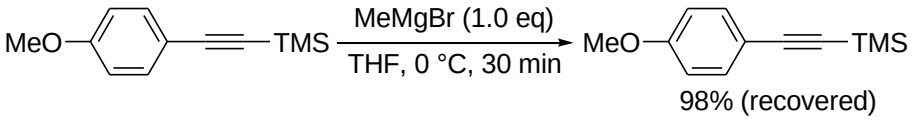


1i **2b** 85%

To a THF solution (10 mL) of **1i** (330.3 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at -78 °C, and the mixture was stirred at 0 °C for 15 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1.5) to afford **2b** in a pure form (294.4 mg, 85%).

2b: white powder; m.p. 98-99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (d, *J* = 6.4 Hz, 3H), 2.01 (s, 1H), 4.92-4.94 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.48-7.52 (m, 4H), 7.54-7.59 (m, 4H), 7.88-7.92 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 25.26 (d, *J* = 4.6 Hz), 69.24 (d, *J* = 7.3 Hz), 81.94 (d, *J* = 172.0 Hz), 105.90 (d, *J* = 30.5 Hz), 117.96 (d, *J* = 3.6 Hz), 125.59 (d, *J* = 4.6 Hz), 128.58 (d, *J* = 13.4 Hz), 130.80 (d, *J* = 11.4 Hz), 132.44 (d, *J* = 1.6 Hz), 132.46, 132.71 (d, *J* = 122.4 Hz), 149.83; HRMS (FAB) calcd $C_{22}H_{19}O_2P$ for ($M+H^+$): 347.1123; found 347.0099.

Treatment of TMS-protected ethyne with MeMgBr:

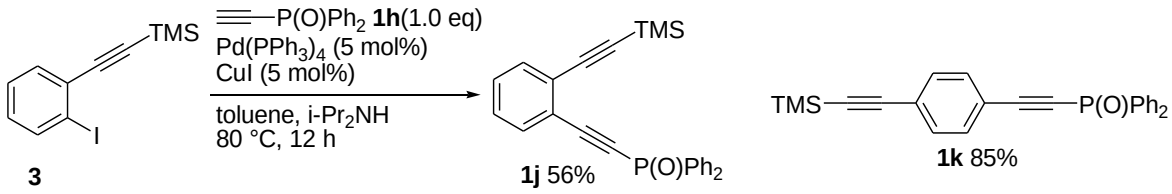


To a THF solution (10 mL) of ((4-methoxyphenyl)ethynyl)trimethylsilane (204.3 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford ((4-methoxyphenyl)ethynyl)trimethylsilane in a pure form (200.2 mg, 98%).

((4-methoxyphenyl)ethynyl)trimethylsilane:[8] pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (s, 9H), 3.81 (s, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 9.2 Hz, 2H).

Synthesis of 1j and 1k by Sonogashira coupling (representative procedure for

1j):



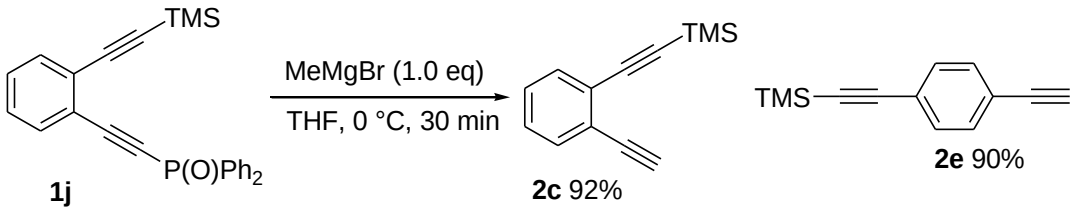
3 **1j** 56% **1k** 85%

A toluene solution (5.0 mL) of **3** (300.2 mg, 1.0 mmol), **1h** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 12 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **1j** in a pure form (223.2 mg, 56% yield).

1j: white powder, m.p. 122-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.13 (s, 9H), 7.31-7.34 (m, 1H), 7.37-7.40 (m, 1H), 7.47-7.50 (m, 4H), 7.52-7.56 (m, 3H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.93-7.97 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ -0.25 (d, *J* = 4.1 Hz), 86.04 (d, *J* = 167.9 Hz), 100.12, 102.24, 103.49 (d, *J* = 30.0 Hz), 122.47 (d, *J* = 4,1 Hz), 126.55 (d, *J* = 3.8 Hz), 128.27 (d, *J* = 5.8 Hz), 128.60 (d, *J* = 12.4 Hz), 130.14, 131.04 (d, *J* = 11.3 Hz), 132.14, 132.76, 133.13 (d, *J* = 122.0 Hz), 133.14; HRMS (FAB) calcd for $C_{25}H_{23}OPSi$ ($M+H^+$): 399.1256, found 399.1299.

1k: white powder, m.p. 174-175 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.49-7.54 (m, 6H), 7.55-7.58 (m, 2H), 7.87-7.91 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ -0.26 (d, *J* = 4.6 Hz), 84.48 (d, *J* = 167.9 Hz), 98.05, 103.78, 104.61 (d, *J* = 29.9 Hz), 119.59 (d, *J* = 4.0 Hz), 125.49, 128.61 (d, *J* = 13.4 Hz), 130.88 (d, *J* = 11.3 Hz), 131.88, 131.91, 132.23, 132.76 (d, *J* = 122.4 Hz); HRMS (FAB) calcd for $C_{25}H_{23}OPSi$ ($M+H^+$): 399.1256, found 399.1640.

Synthesis of 2c and 2e by selective deprotection of $Ph_2P(O)$ (representative procedure for 2c):



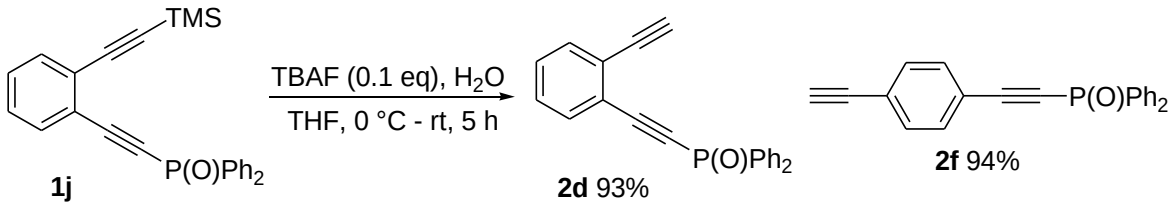
1j **2c** 92%

To a THF solution (10 mL) of **1j** (398.5 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **2c** in a pure form (182.5 mg, 92%).

2c:[4] ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.27 (s, 9H), 3.30 (s, 1H), 7.27-7.30 (m, 2H), 7.46-7.50 (m, 2H).

2e:[9] ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 3.16 (s, 1H), 7.41 (s, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ -0.13 (d, *J* = 4.1 Hz), 78.94 (d, *J* = 3.6 Hz), 83.18, 96.44, 104.32, 122.08, 123.55, 131.81, 131.90.

Synthesis of 2d and 2f by selective deprotection of TMS (representative procedure for 2d):



1j **2d** 93%

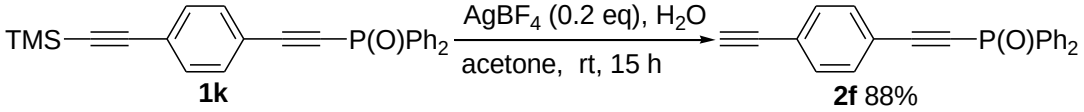
To a THF solution (10 mL) of **1j** (398.5 mg, 1.0 mmol) were added water (0.05 mL) and TBAF (1.0 M in THF, 0.1 mL, 0.1 mmol) at 0 °C, and the mixture was stirred under air at rt for 5 h. After the solvents were evaporated, the crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to give **2d** in a pure form (303.5 mg, 93%).

2d:[6] white powder; m.p. 121-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (s, 1H), 7.36 (t, *J* = 7.60 Hz, 1H), 7.41 (t, *J* = 7.65 Hz, 1H), 7.47-7.50 (m, 4H), 7.54-7.56

(m, 3H), 7.60 (d, *J* = 7.65 Hz, 1H), 7.94-7.99 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 81.34, 82.32, 86.36 (d, *J* = 167.8 Hz), 103.13 (d, *J* = 29.8 Hz), 123.07 (d, *J* = 3.7 Hz), 125.77 (d, *J* = 1.5 Hz), 128.52 (d, *J* = 13.6 Hz), 128.68, 130.24, 131.10 (d, *J* = 11.2 Hz), 132.19 (d, *J* = 3.1 Hz), 132.69, 132.85, 132.95 (d, *J* = 122.0 Hz).

2f: [6] white powder; m.p. 145-147 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.24 (s, 1H), 7.48-7.52 (m, 6H), 7.54-7.58 (m, 4H), 7.87-7.91 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 80.42, 82.57, 84.60 (d, *J* = 167.6 Hz), 104.36 (d, *J* = 29.4 Hz), 120.08, 120.13, 124.49, 128.66 (d, *J* = 13.7 Hz), 130.93 (d, *J* = 11.2 Hz), 132.15, 132.35, 132.69 (d, *J* = 121.9 Hz).

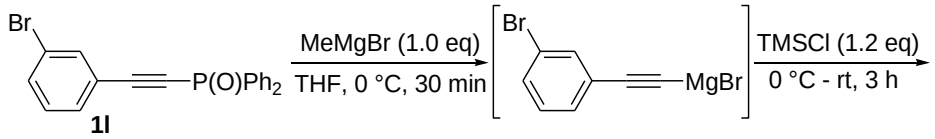
Synthesis of 2f by selective deprotection of TMS:



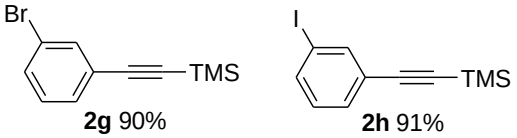
1k **2f** 88%

To a acetone solution (10 mL) of **1k** (398.5 mg, 1.0 mmol) were added water (2.1 mL) and $AgBF_4$ (38.9 mg 0.2 mmol) at rt, and the mixture was stirred under nitrogen at rt for 15 h in dark. After workup with CH_2Cl_2 and H_2O, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to give **2f** in a pure form (287.2 mg, 88%).

Synthesis of 2g and 2h by one-pot transformation of $Ph_2P(O)$ group to TMS group (representative procedure for 2g):



1l



2g 90% **2h** 91%

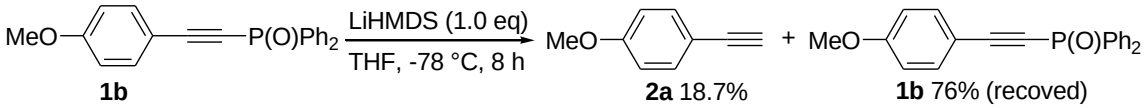
To a THF solution (10 mL) of **1l** (381.2 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C. After the mixture was stirred for

30 min at 0 °C, TMSCl (152.3 μL, 1.2 mmol) was added at 0 °C. The mixture was stirred under nitrogen at rt for 3 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to give **2g** in a pure form (227.9 mg, 90% yield).

2g:[10] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (s, 9H), 7.16 (t, *J* = 7.88 Hz, 1H), 7.36-7.40 (m, 1H), 7.42-7.46 (m, 1H), 7.62 (t, *J* = 1.65 Hz, 1H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ -0.14, 95.85, 103.25, 121.99, 125.09, 129.59, 130.47, 131.61, 134.70.

2h:[11] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (s, 9H), 7.03 (t, *J* = 7.88 Hz, 1H), 7.40-7.43 (m, 1H), 7.62-7.66 (m, 1H), 7.82 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ -0.18, 93.50, 95.86, 103.11, 125.15, 129.64, 131.01, 137.46, 140.49.

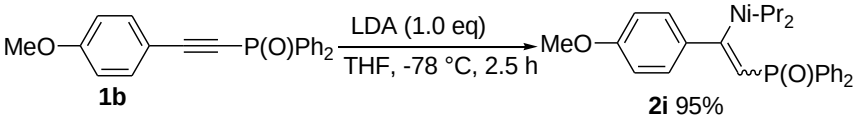
Treatment of 4-Methoxyphenylethynylphosphine Oxide with LiHMDS:



1b **2a** 18.7% **1b** 76% (recoved)

To a THF solution (10 mL) of **1b** (166.2 mg, 0.5 mmol) was added LiHMDS (1.3 M in THF, 384.6 μL, 0.5 mmol) at -78 °C, and the mixture was stirred at -78 °C for 8 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2a** (12.3 mg, 18.7%) and **1b** in pure forms (126.3 mg, 76%).

Treatment of 4-Methoxyphenylethynylphosphine Oxide with LDA:



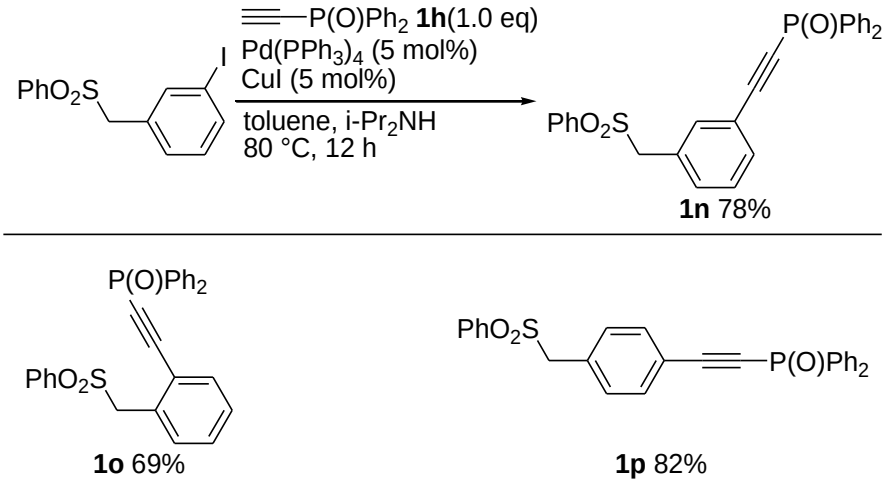
1b **2i** 95%

To a THF solution (10 mL) of **1b** (166.2 mg, 0.5 mmol) was added LDA (1.0 M in

THF, 500.0 μL, 0.5 mmol) at -78 °C, and the mixture was stirred at -78 °C for 2.5 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to recrystallization (THF/hexane) to afford **2i** in a pure form (227.1 mg, 95%)

2i: white powder; m.p. 165-166 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (d, *J* = 6.4 Hz, 12H), 3.50 (br, 2H), 3.72 (s, 3H), 6.60 (d, *J* = 17.7 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 2H), 7.05-7.07 (m, 2H), 7.34-7.38 (m, 4H), 7.40-7.43 (m, 2H), 7.68-7.72 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 21.66, 46.56, 54.98 (d, *J* = 2.5 Hz), 94.22 (d, *J* = 118.9 Hz), 113.3 (d, *J* = 7.3 Hz), 127.68-127.80 (m), 128.70 (d, *J* = 8.3 Hz), 130.59-130.64 (m), 132.24 (d, *J* = 8.8 Hz), 132.62(dd, *J* = 4.4 Hz, *J* = 10.0 Hz), 134.12 (d, *J* = 102.9 Hz), 142.82 (dd, *J* = 8.73 Hz, *J* = 24.31 Hz), 157.96 (d, *J* = 2.0 Hz); HRMS (FAB) calcd $C_{27}H_{32}NiO_2P$ for ($M+H^+$): 478.1493; found 478. 2434.

Synthesis of 1n, 1o and 1p by Sonogashira coupling (representative procedure for 1m):



A toluene solution (5.0 mL) of 1-iodo-3-(phenylsulfonylmethyl)benzene (358.2 mg, 1.0 mmol), **1h** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 12 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic

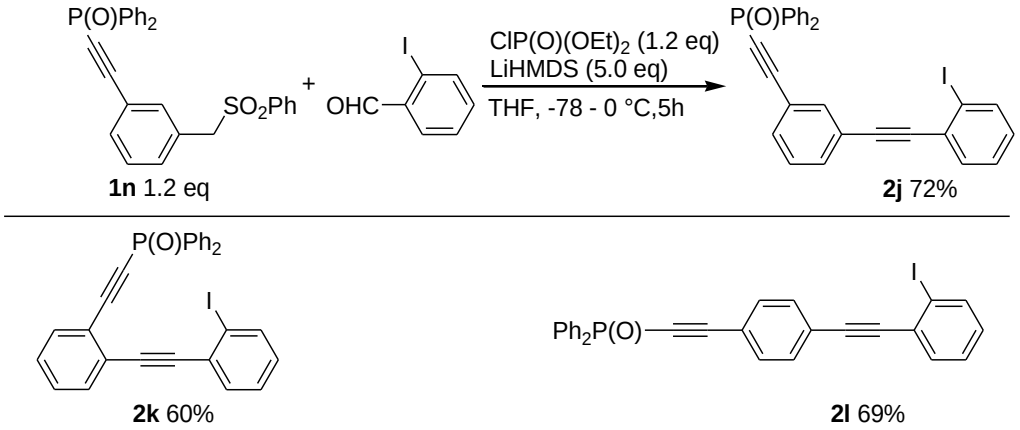
layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:2) to afford **1n** in a pure form (356.1 mg, 78% yield).

1n: white powder; m.p. 208-209 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.29 (s, 2H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.29-7.32 (m, 2H), 7.46-7.53 (m, 6H), 7.55-7.61 (m, 4H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.86-7.90 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 62.18, 83.59 (d, *J* = 167.0 Hz), 104.01 (d, *J* = 29.4 Hz), 120.42 (d, *J* = 4.1 Hz), 128.51, 128.65 (d, *J* = 14.4 Hz), 128.87, 129.05, 130.91 (d, *J* = 11.4 Hz), 132.33, 132.70 (d, *J* = 122.5 Hz), 132.83, 132.97, 134.02, 134.46, 134.55, 137.45; HRMS (FAB) calcd $C_{27}H_{21}O_3PS$ for ($M+H^+$): 457.0949; found 457.2547.

1o: white powder; m.p. 182-183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.53 (s, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.36-7.39 (m, 1H), 7.42-7.47 (m, 4H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.53-7.56 (m, 5H), 7.59-7.62 (m, 2H) , 7.89-7.94 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 60.40, 87.20 (d, *J* = 164.8 Hz), 101.99 (d, *J* = 29.0 Hz), 121.66 (d, *J* = 3.5 Hz), 128.46-128.48(m), 128.76 (d, *J* = 12.9 Hz), 128.96, 129.02, 130.76, 130.96 (d, *J* = 10.8 Hz), 131.59, 132.42, 132.68 (d, *J* = 121.9 Hz), 133.52, 133.84, 137.75; HRMS (FAB) calcd $C_{27}H_{21}O_3PS$ for ($M+H^+$): 457.0949; found 457.2533.

1p: white powder; m.p. 205-206 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 (s, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.46-7.53 (m, 8H), 7.56-7.59 (m, 2H), 7.62-7.65 (m, 3H), 7.87-7.91 (m, 4H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 62.60, 84.14 (d, *J* = 166.4 Hz), 104.33 (d, *J* = 29.5 Hz), 120.49, 128.54, 128.68 (d, *J* = 14.4 Hz), 129.06 (d, *J* = 3.0 Hz), 129.10, 130.85, 130.95 (d, *J* = 11.4 Hz), 132.34, 132.60 (d, *J* = 6.3 Hz), 132.76 (d, *J* = 122.4 Hz), 134.01, 137.52; HRMS (FAB) calcd $C_{27}H_{21}O_3PS$ for ($M+H^+$): 457.0949; found 457.2557.

Synthesis of 2j, 2k and 2l by Double Elimination Procedure (representative procedure for 2j):



To a THF solution (10 mL) of **1n** (273.9 mg, 0.6 mmol) and 2-iodobenzaldehyde (116.0 mg, 0.5 mmol) was added $ClP(O)(OEt)_2$ (86.7 μL, 0.6 mmol) and LiHMDS (1.3 M in THF, 1923.1 μL, 2.5 mmol) at -78 °C, and the mixture was stirred at 0 °C for 5 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2j** in a pure form (190.2 mg, 72%).

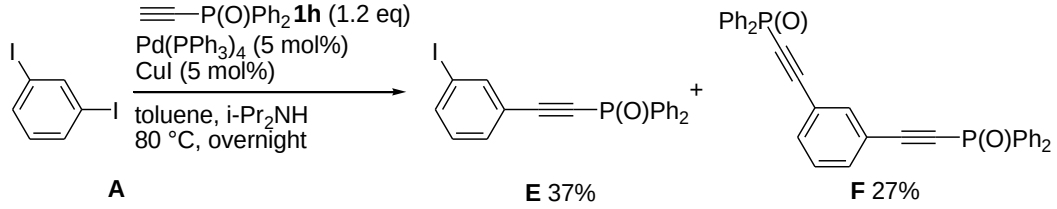
2j: colorless gel; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.50-7.53 (m, 5H), 7.56-7.59 (m, 3H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.88-7.93 (m, 5H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 83.53 (d, *J* = 167.4 Hz), 91.12, 92.83, 101.09, 104.08 (d, *J* = 29.5 Hz), 120.31 (d, *J* = 4.1 Hz), 123.65, 127.80 (d, *J* = 3.1 Hz), 128.62 (d, *J* = 13.9 Hz), 128.76, 129.02, 129.73 (d, *J* = 8.8 Hz), 130.89 (d, *J* = 11.3 Hz), 132.28, 132.45 (d, *J* = 4.1 Hz), 132.48, 132.70 (d, *J* = 122.5 Hz), 133.55, 135.13 (d, *J* = 2.1 Hz), 138.70; HRMS (FAB) calcd $C_{28}H_{18}IOP$ for ($M+H^+$): 529.0140; found 529.1348.

2k: white powder; m.p.72-74 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (dt, *J* = 7.4 Hz, *J* = 1.6 Hz, 1H), 7.20 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.24-7.25 (m, 1H), 7.33-7.39 (m, 5H), 7.45-7.48 (m, 3H), 7.65-7.68 (m, 2H), 7.84-7.86 (m, 1H), 7.90-7.95 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 86.44 (d, *J* = 168.5 Hz), 90.41, 96.17, 100.99, 103.46 (d, *J* = 30.0 Hz), 122.19 (d, *J* = 4.1 Hz), 126.50 (d, *J*

= 2.1 Hz), 127.76 (d, *J* = 6.2 Hz), 128.44-128.60 (m), 129.05, 129.78 (d, *J* = 9.3 Hz), 130.31, 130.97 (d, *J* = 10.8 Hz), 132.08, 132.39, 132.90 (d, *J* = 5.8 Hz), 132.91 (d, *J* = 122.0 Hz), 133.11, 138.63; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.65; HRMS (FAB) calcd $C_{28}H_{18}IOP$ for ($M+H^+$): 529.0140; found 529.1434.

2l: white powder; m.p. 96-97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (dt, *J* = 1.6 Hz, *J* = 7.1 Hz, 1H), 7.35 (dt, *J* = 1.0 Hz, *J* = 7.6 Hz, 1H), 7.50-7.55 (m, 5H), 7.56-7.60 (m, 6H), 7.88-7.93 (m, 5H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 84.62 (d, *J* = 167.4 Hz), 91.91, 94.72, 101.17, 104.70 (d, *J* = 30.0 Hz), 119.78 (d, *J* = 4.1 Hz), 125.37, 127.85, 128.66 (d, *J* = 13.4 Hz), 129.08, 129.82, 129.90, 130.95 (d, *J* = 11.4 Hz), 132.08 (d, *J* = 119.4 Hz), 132.31, 132.44 (d, *J* = 2.1 Hz), 133.28, 138.80; HRMS (FAB) calcd $C_{28}H_{18}IOP$ for ($M+H^+$): 529.0140; found 529.1630.

Sonogashira Coupling between 1,3-Diiodobenzene and Phosphorylethyne (1h):



A **E** 37% **F** 27%

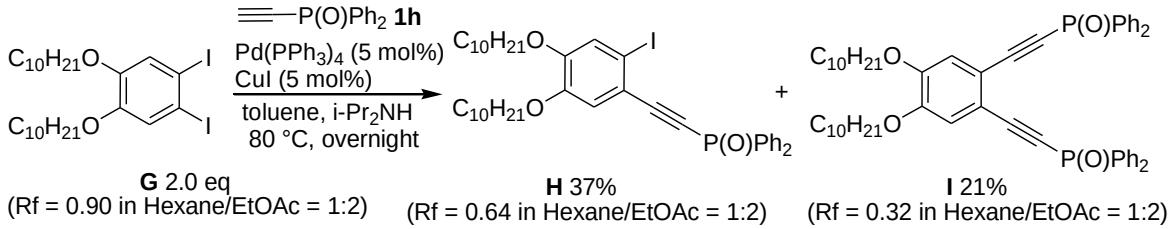
A toluene solution (5.0 mL) of 1,3-Diiodobenzene (329.9 mg, 1.0 mmol), **1h** (271.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt) to afford **E** in a pure form (158.4 mg, 37% yield) and **F** in a pure form (142.2 mg, 27% yield).

E:[5] white powder; m.p. 94-96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (t, *J* = 7.8 Hz, 1H), 7.49-7.53 (m, 4H), 7.56-7.59 (m, 3H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.86-7.91 (m, 4H), 7.94 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 83.98 (d, *J* = 165.7 Hz), 93.45,

102.89 (d, *J* = 29.2 Hz), 121.61 (d, *J* = 4.0 Hz), 128.51 (d, *J* = 13.4 Hz), 129.87, 130.70 (d, *J* = 11.2 Hz), 131.37, 132.20 (d, *J* = 2.8 Hz), 132.36 (d, *J* = 121.9 Hz), 139.46, 140.50; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.80.

F:[5] pale-yellow powder, m.p. 199-201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (t, *J* = 7.9 Hz, 1H), 7.50-7.53 (m, 8H), 7.57-7.60 (m, 4H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.83(s, 1H), 7.87-7.91 (m, 8H); ^{13}C NMR (75MHz, $CDCl_3$): δ 84.23 (d, *J* = 165.1 Hz), 103.01 (d, *J* = 29.1 Hz), 120.64 (d, *J* = 4.1 Hz), 128.64 (d, *J* = 13.7 Hz), 129.00, 130.81 (d, *J* = 11.5 Hz), 132.24 (d, *J* = 2.8 Hz), 132.34 (d, *J* = 121.9 Hz), 134.16, 136.03; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.90.

Sonogashira Coupling between 1,2-bis(decyloxy)-4,5-diiodobenzene and Phosphorylethyne (1h)



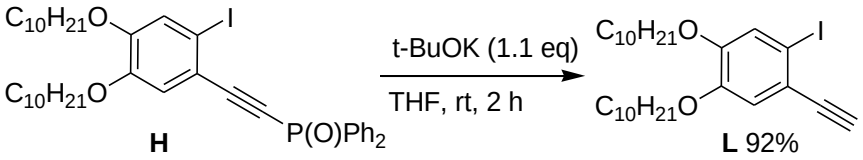
A toluene solution (5.0 mL) of 1,2-bis(decyloxy)-4,5-diiodobenzene **G** (642.4 mg, 1.0 mmol), **1h** (271.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt = 1:2) to afford **H** in a pure form (274.1 mg, 37% yield) and **I** in a pure form (176.2 mg, 21% yield) in a pure form.

H: white powder; m.p. 68-69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.89 (m, 6H), 1.27 (br, 24 H), 1.40-1.46 (m, 4H), 1.77-1.83 (m, 4H), 3.93 (t, *J* = 6.7 Hz, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 7.05 (s, 1H), 7.21 (s, 1H), 7.48-7.51 (m, 4H), 7.53-7.56 (m, 2H), 7.96-8.01 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.98, 22.54, 25.75, 28.79,

29.18, 29.40, 29.42, 29.44, 31.75, 69.20, 84.13 (d, *J* = 169.8 Hz), 90.09 (d, *J* = 2.5 Hz), 106.81 (d, *J* = 30.8 Hz), 117.73, 118.33 (d, *J* = 4.4 Hz), 122.42, 128.43 (d, *J* = 13.7 Hz), 130.99 (d, *J* = 11.5 Hz), 132.02 (d, *J* = 2.8 Hz), 132.95 (d, *J* = 122.0 Hz), 148.77, 151.55; HRMS (FAB) calcd $C_{40}H_{54}IO_3P$ for ($M+H^+$): 741.2855; found 741.6739.

I: white powder; m.p. 94-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.26-1.46 (m, 28 H), 1.82 (t, *J* = 7.2 Hz, 4H), 3.99 (t, *J* = 6.6 Hz, 4H), 7.05 (s, 2H), 7.35-7.38 (m, 8H), 7.45 (t, *J* = 7.0 Hz, 4H), 7.80-7.85 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.98, 22.53, 25.73, 28.72, 29.15, 29.18, 29.39, 29.42, 31.75, 69.25, 85.73 (d, *J* = 166.6 Hz), 102.98 (d, *J* = 29.8 Hz), 115.84 (q, *J* = 2.2 Hz), 116.58, 128.56 (d, *J* = 13.6 Hz), 130.77 (d, *J* = 11.2 Hz), 132.02 (d, *J* = 2.8 Hz), 132.64 (d, *J* = 121.9 Hz), 150.70; HRMS (FAB) calcd $C_{54}H_{64}O_4P_2$ for ($M+H^+$): 839.4280; found 839.8337.

Synthesis of L:



To a THF solution (10 mL) of **H** (370.4 mg, 0.5 mmol) was added t-BuOK (61.7 mg, 0.55 mmol) at rt, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **L** in a pure form (248.6 mg, 92%).

L:[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.27-1.44 (m, 28 H), 1.80 (q, *J* = 6.7 Hz, 4H), 3.28 (s, 1H), 3.95 (q, *J* = 6.8 Hz, 4H), 6.98 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.08, 22.64, 25.89, 28.97, 28.99, 29.30, 29.51, 29.54, 31.86, 69.23, 79.03, 85.41, 89.59, 117.53, 120.56, 122.65, 148.78, 150.26.

Reference

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Chapter 3 Application of $Ph_2P(O)$ in Carbon-carbon Bond Formation Reactions

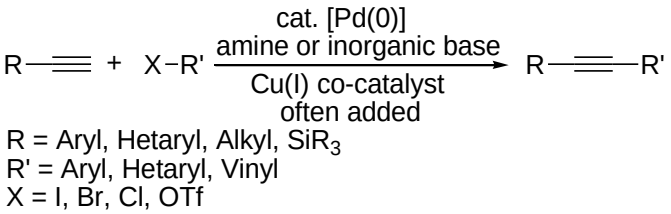
3.1 Abstract

$Ph_2P(O)$ is a promising protection group for terminal acetylene in carbon-carbon bond formation reactions such as Sonogashira coupling, Stille coupling, Suzuki coupling and oxidative homocoupling reactions. Highly polar feature of $Ph_2P(O)$ group allows facile separation of $Ph_2P(O)$-protected ethynes from byproducts which are difficult-to-separate when the trimethysilyl group is used instead of $Ph_2P(O)$. By taking advantage of this highly polar protecting group, a series of unsymmetrically substituted ethyne derivatives have been synthesized successfully.

3.2 Introduction

Transition metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a tremendously powerful synthetic tool, and the development has reached a level of sophistication that allows for a wide range of coupling partners to be combined efficiently.[1]

Sonogashira coupling reaction involves palladium catalyzed C–C bond formation process which is able to couple a terminal sp hybridized carbon from an alkyne with a sp^2 carbon of an aryl or vinyl halide (or triflate). The reaction name arises from the discovery in 1975 by Sonogashira, Tohda, and Hagihara that this process could be performed easily at room temperature using a palladium source such as $PdCl_2(PPh_3)_2$ as catalyst, combined with a co-catalytic amount of CuI in an amine as solvent (Scheme 3.1).[2]



Scheme 3.1 Sonogashira Coupling[2]

The mechanism of the palladium/copper-catalysed Sonogashira reaction is generally supposed to take place through two independent catalytic cycles (Fig. 3.1). The first ‘‘palladium-cycle’’ (cycle A) is classical from C–C cross-coupling formations and starts in the catalytically active species $Pd(0)L_2$. The first step in the catalytic cycle is initiated by oxidative addition of the aryl or vinyl halide. The formed [Pd(II)$R'L_2X$] adduct is then transformed into a [Pd(II)$L_2R'(CRCR_2)$] species after transmetalation with a copper acetylide formed in the ‘‘copper-cycle’’ (cycle B). This Adduct suffers reductive elimination, after cis/trans-isomerization, to the final alkyne, regenerating the catalyst [$Pd(0)L_2$] (Figure 3.1). [3]

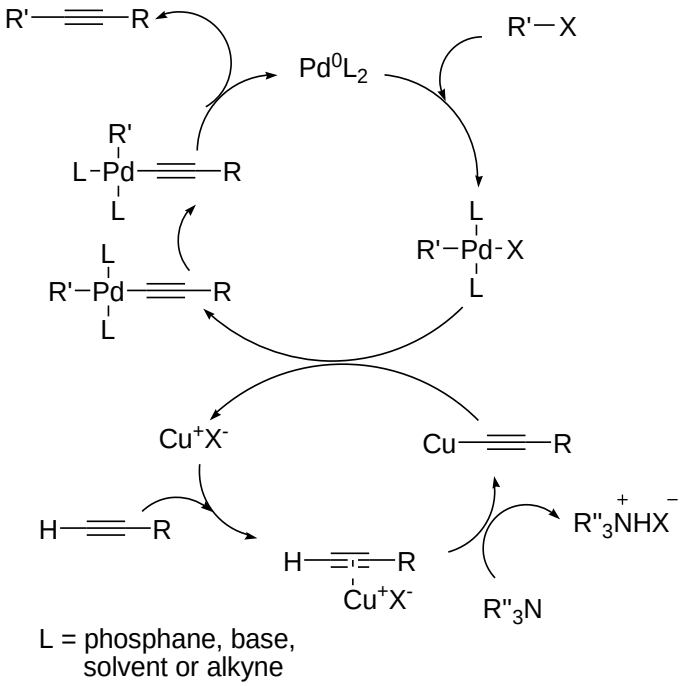
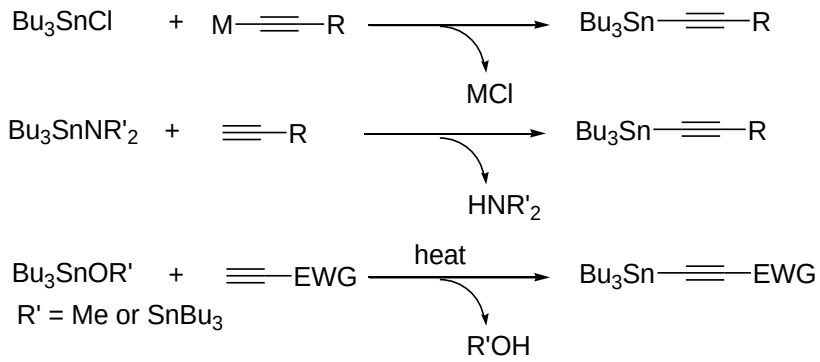


Figure 3.1 Supposed Mechanism for the Copper-cocatalyzed Sonogashira Reaction[3]

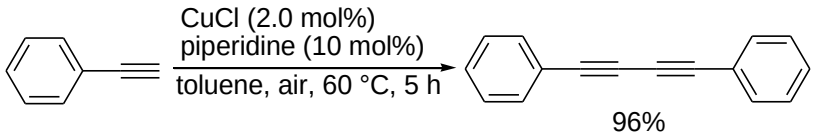
Alkynylstannanes, which have high stability, reactivity and functional group tolerance, are important reagents for introducing an alkynyl moiety into organic molecules. In particular, the Migita-Kosugi-Stille coupling using alkynylstannanes is widely used for the construction of C(sp)-C(sp^2) bonds in the synthesis of arylalkynes or conjugated enynes. Transmetalation between an organictin halide and an alkynyllithium or alkynylmagnesium compound is the most common route to alkynylstannanes. The direct reaction of a tin amide with a terminal alkyne is also employed for the synthesis of alkynylstannanes. The direct condensation reaction between a tin alkoxide and a terminal alkyne is regarded as a promising process that is mild because no strong base is required and an alcohol is the only by-product (Scheme 3.2).[4]



Scheme 3.2 Migita-Kosugi-Stille Coupling[4]

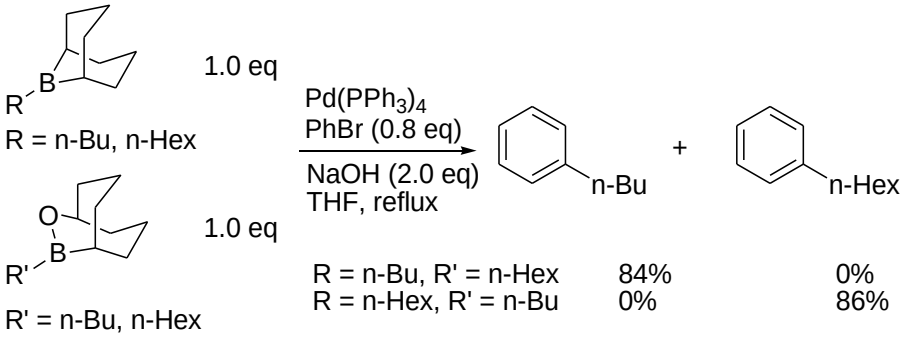
1,3-Diynes represent an important class of organic compounds, and the structural motif of 1,3-diyne has been recognized as an important functionality in molecular materials. A number of synthetic approaches have been developed for the synthesis of 1,3-diynes, including oxidative homocoupling reactions of terminal alkynes catalyzed by palladium, nickel complexes with the use of copper(I) as co-catalyst, Cu(I)/Cu(II)-mediated oxidative homocoupling reactions

of terminal alkynes and homocoupling reactions of alkynylsilanes, alkynylboronates and potassium alkynyl trifluoro- borates, and palladium-catalyzed homocoupling reactions of n-butyl alkynyltellurides.[5] Ruimao Hua demonstrated that CuCl with the use of a catalytic amount of piperidine as additive exhibits high catalytic activity in the oxidative homocoupling of terminal alkynes in air to afford 1,3-diynes with high yields (Scheme3.3).[6]



Scheme 3.3 Oxidative Homocoupling of Terminal Alkynes[6]

Suzuki-Miyaura coupling using organoboron compounds has emerged as a powerful tool due to its operational simplicity, environmentally benign nature, and the thermal stability of the transmetalating agents.[7] Since the first report in 1986 of the cross-coupling reaction between alkylboron reagents and aryl and alkenyl halides in the presence of Pd(0) and a base, the B-alkyl Suzuki-Miyaura cross-coupling has become one of the most popular cross-coupling protocols in organic synthesis.[8]



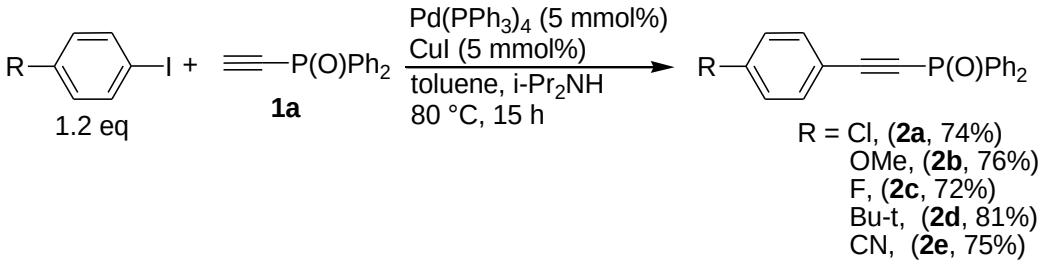
Scheme 3.4 Suzuki-Miyaura Coupling[8]

Herein, we report that $Ph_2P(O)$ serves as a protecting group for terminal acetylenes in Sonogashira coupling, Stille coupling, Suzuki coupling and oxidative homocoupling reactions.

3.3 Results and Discussion

Sonogashira coupling reactions between aryliodide and $Ph_2P(O)$-protected acetylene

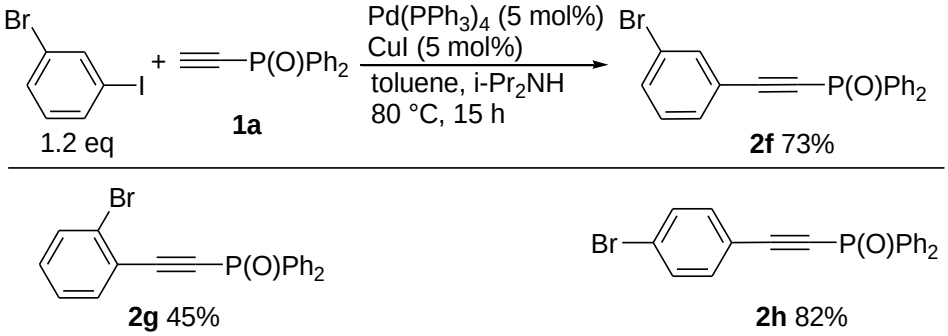
The diphenylphosphoryl-ethyne bond remained intact in Sonogashira coupling, and a coupling reaction of 1-chloro-4-iodobenzene with phosphorylethyne **1a** gave the desired 4-chlorophenylethynylphosphine oxide **2a** in 74% yield, and the chloro-moiety remained untouched. Similarly, 4-methoxylphenylethynylphosphine oxide **2b**, 4-fluorophenyl ethynyl phos- phine oxide **2c**, 4-tert-butylphenylethynylphosphine oxide **2d** and 4-cyano-phenylethynylphosphine oxide **2e** were obtained in 76%, 72%, 81% and 75% yields respectively (Scheme 3.5).



Scheme 3.5 Sonogashira Coupling of Aryliodide and Phosphorylethyne

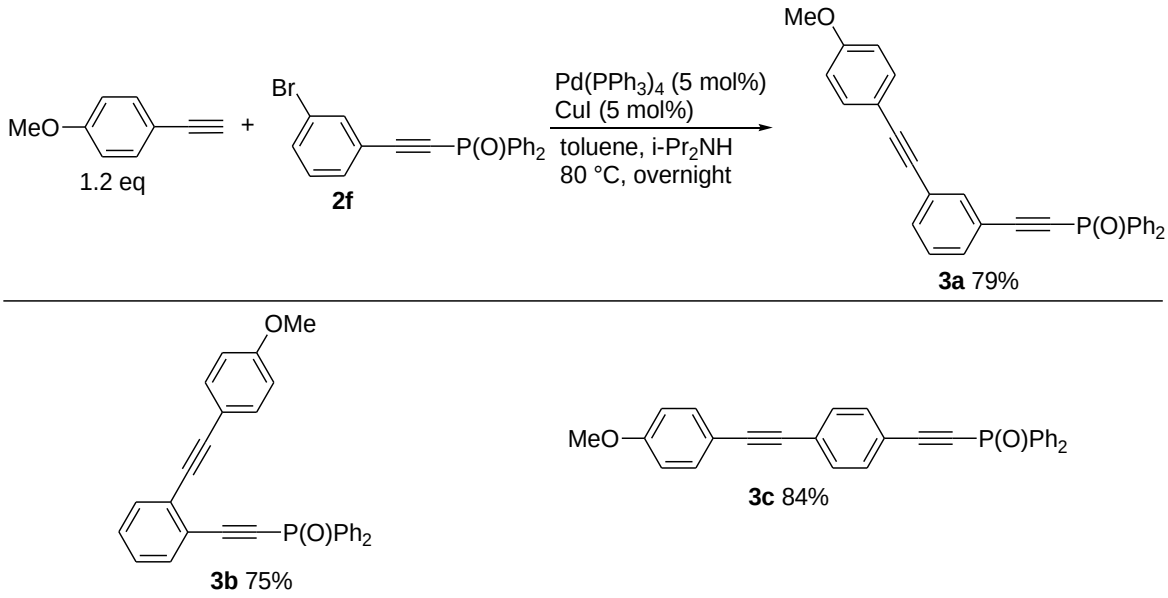
In order to discuss the reactivity of arylhalide with phosphorylethyne, Sonogashira coupling reaction of bromoiodide and phosphorylethyne was carried out. Sonogashira coupling reaction between 1-bromo-3-iodobenzene and phosphorylethyne **1a** proceeded smoothly and produced 3-bromophenyl-

ethynylphosphine oxide **2f** in 73% yield, and the bromo-moiety remained untouched. Similarly, 2-bromophenylethynyl phosphine oxide **2g** and 4-bromophenylethynyl phosphine oxide **2h** were obtained in 45% and 82% yield respectively (Scheme 3.6).



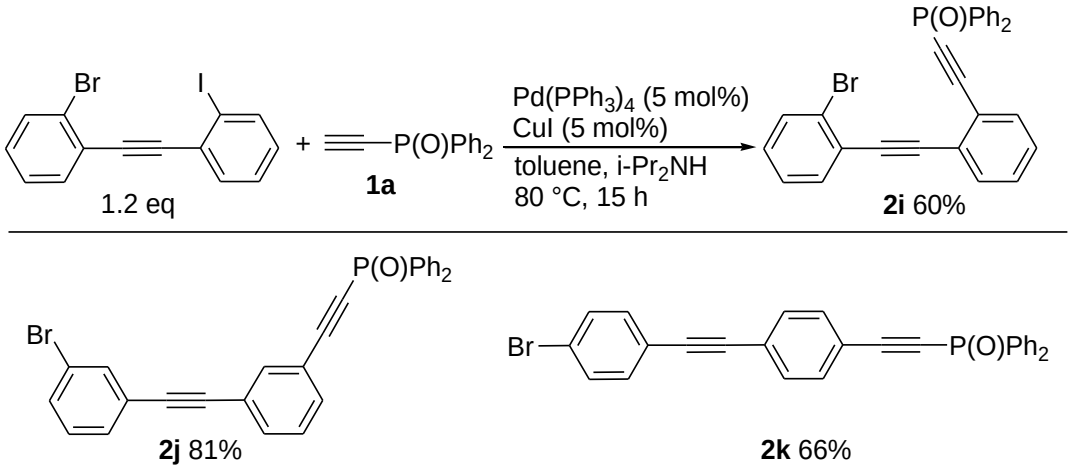
Scheme 3.6 Sonogashira Coupling of Bromoiodobenzene and Phosphorylethyne

With bromo-substituted phenylethynylphosphine oxide in hand, we prepared л-expanded phenylethynylphosphine oxide. Sonogashira coupling of 1-ethynyl-4-methoxybenzene and 3-bromophenylethynylphosphine oxide **2f** afforded the desired л-expanded phenylethynylphosphine oxide **3a** in 79% yield. л-Expanded phenylethynylphosphine oxide **3b** and **3c** were obtained in 75% and 84% yields respectively by the same procedure (Scheme 3.7).



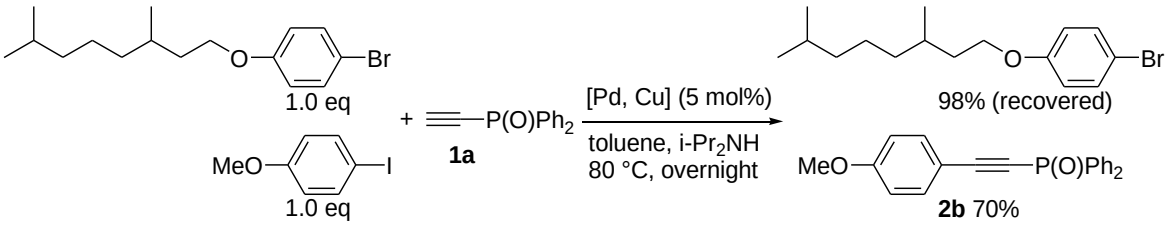
Scheme 3.7 Preparation of л-Expanded Phenylethynylphosphine Oxide by Sonogashira Coupling

When we used the л-expanded bromoiodide as a starting compound, Sonogashira coupling of 1-bromo-2-((2-iodophenyl)ethynyl)-benzene and phosphorylethyne **1a** proceeded smoothly and gave the desired product **2i** in moderate yield. Similarly, **2j** and **2k** were obtained in 81% and 66% yields respectively. And the bromo-moiety of the starting compounds remained untouched (Scheme 3.8).



Scheme 3.8 Sonogashira Coupling of л-Expanded Bromoiodobenzene and Phosphorylethyne

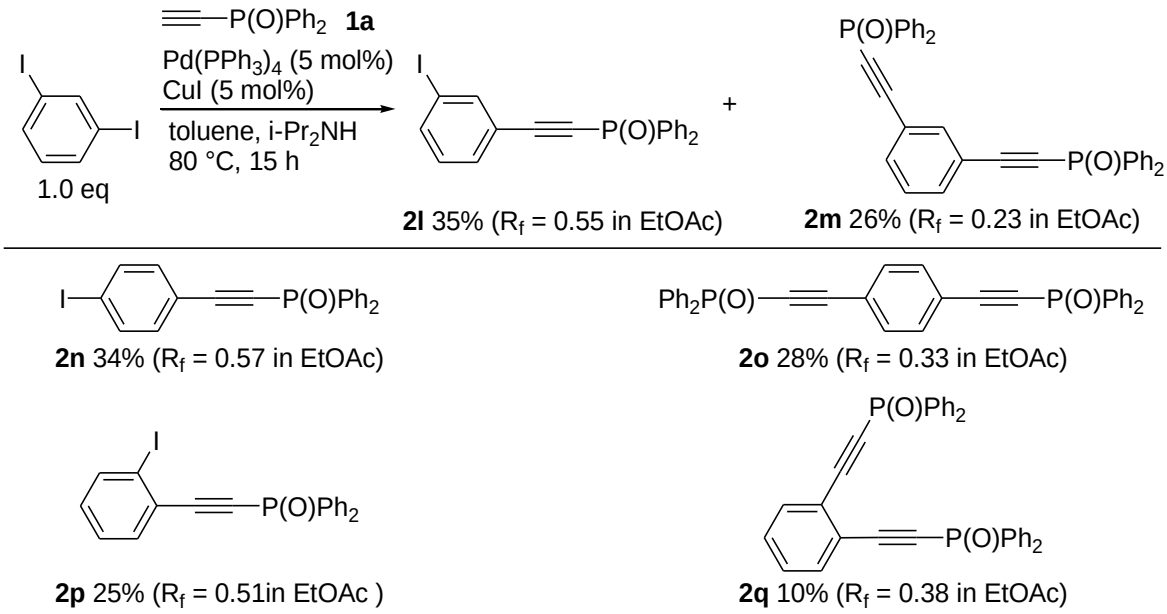
In order to study the reason why bromo-moiety remained untouched, we carried out the following competitive Sonogashira coupling reaction. Treatment of phosphorylethyne **1a** with 1.0 equivalent of 1-bromo-4-(3,7-dimethyloctyloxy)benzene and 1.0 equivalent of 1-iodo-4-methoxybenzene in Sonogashira coupling conditions gave 4-methoxy-phenylethynylphosphine oxide **2b** as a only product. Sonogashira coupling between 1-bromo-4-(3,7-dimethyloctyloxy)benzene and phosphorylethyne **1a** did not occur, and we recovered starting compound 1-bromo-4-(3,7-dimethyloctyloxy)benzene in 98% (Scheme 3.9). These results indicated that arylbromide did not react with phosphorylethyne **1a** in Sonogashira coupling.



Scheme 3.9 Competitive Sonogashira Coupling of Phosphorylethyne with Arylbromide and Aryiodide

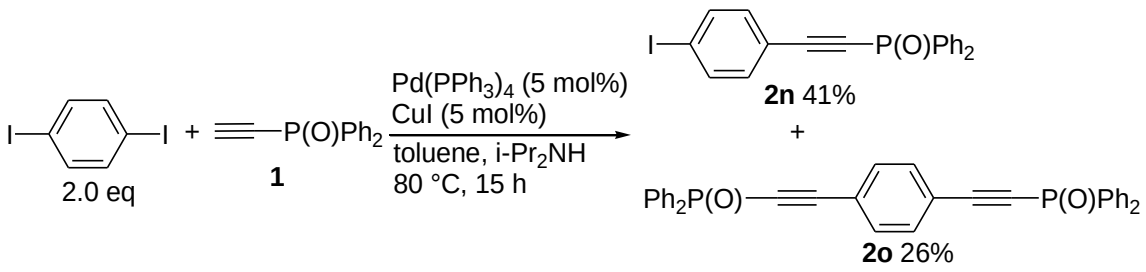
If we used diiodide as a starting compound in Sonogashira coupling, we could obtain mono- and bis-adduct. In Sonogashira coupling between 1,3-diiodobenzene and phosphorylethyne **1a**, a thin layer chromatography (TLC) analysis indicated formation of mono- and bis-adducts **2l** and **2m**. As we expected, high polarity of $Ph_2P(O)$ enables easy separation of **2l** and **2m** by a column chromatography on silica gel: R_f = 0.55 for mono-adduct **2l** and R_f = 0.23 for bis-adduct **2m** in AcOEt. By the same procedure, we obtained para-substitute

mono- and bis-sadducts **2n** and **2o** in 34% and 28% yields respectively, and ortho-substitute mono- and bis-adducts **2p** and **2q** in 25% and 10% yields respectively (Scheme 3.10).



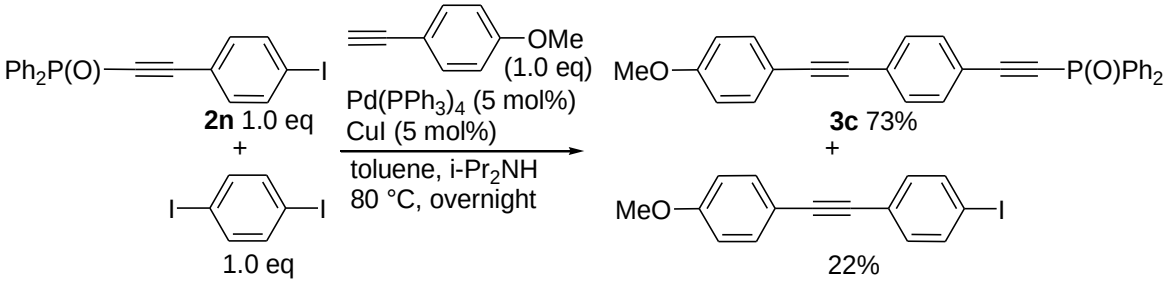
Scheme 3.10 Sonogashira Coupling of Diiodobenzene and Phosphorylethyne

2.0 Equivalents of 1,4-diiodobenzene was used to improve yield of the mono-adduct **2n**. However, we can not suppress the formation of bis-adduct even when 2.0 eq of 1,4-diiodobenzene was used (Scheme 3.11).



Scheme 3.11 Sonogashira Coupling of Phosphorylethyne with Excess Amount of Diiodobenzene

A competitive reaction was carried out to study the reason for the formation of bis-adduct. Competitive coupling of 1-ethynyl-4-methoxy- benzene with 1.0 equivalent of **2n** and 1.0 equivalent of 1,4-diiodobenzene gave product **3c** as a main product, and **2n** was more reactive than 1,4-diiodobenzene (Scheme 3.12).



Scheme 3.12 Competitive Sonogashira Coupling of Phosphorylethyne with Mono-adduct **2n** and Diiodobenzene

This experimental result showed fine agreement to LUMO energy values calculated at the B3LYP/6-31(d) level, which indicated -0.04564 for 1,4-diiodobenzene, -0.05968 for mono-adduct **2n**. Mono-adduct **2n** showed higher reactivity because of lower LUMO energy values, and Pd-catalyst inserted to the C-I bond in **2n** more easily (Figure 3.2).

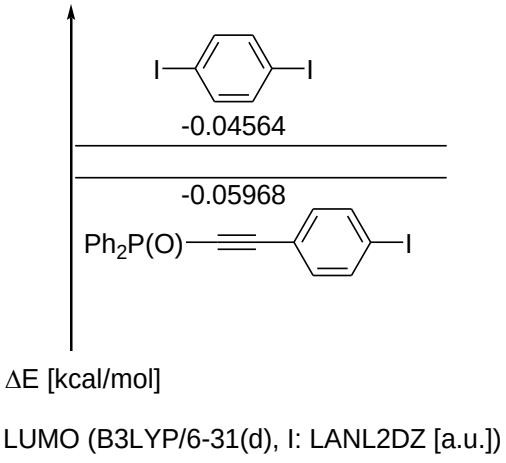
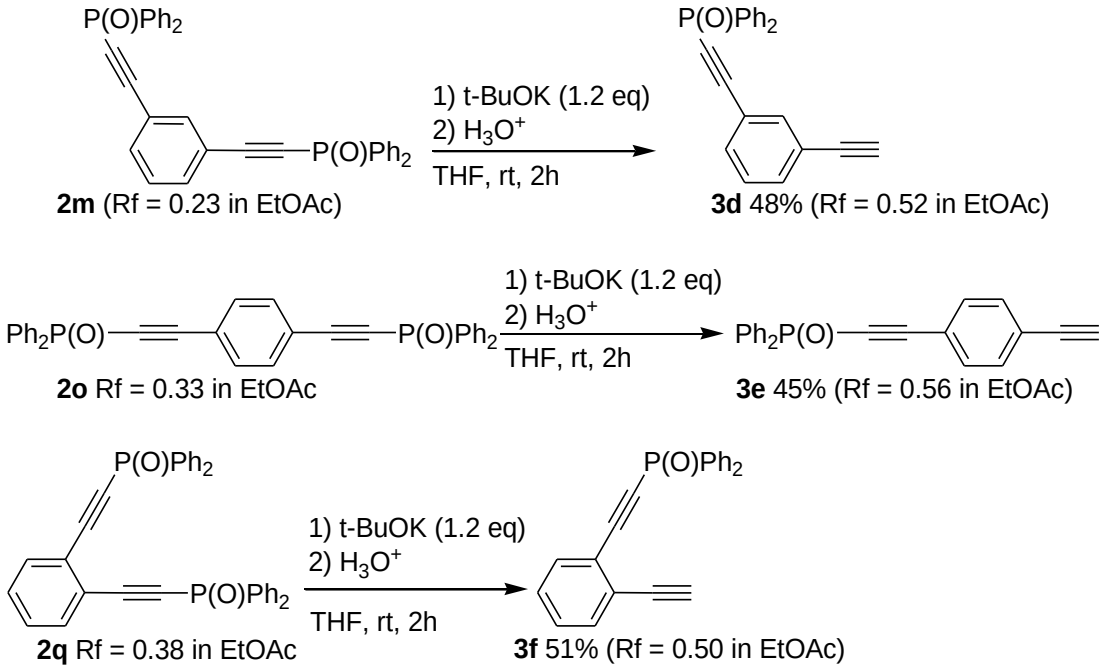


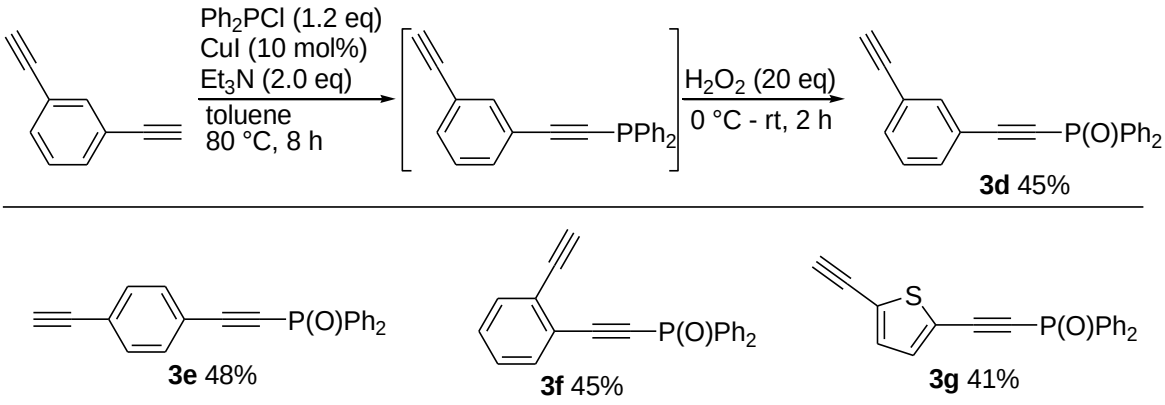
Figure 3.2 LUMO calculation

Mono-$Ph_2P(O)$-protected diynes were important intermediates in organic synthesis. With bis-adducts **2m**, **2o** and **2q** in hand, mono-$Ph_2P(O)$- protected diynes were prepared by selective deprotection of $Ph_2P(O)$. Treatment of **2m** with 1.2 equivalents of t-BuOK provided **3d** in 48% yield. High polarity of phosphine oxide enables easy separation of **3d** by a column chromatography on silica gel: R_f = 0.52 for **3d** and R_f = 0.23 for **2m** in AcOEt. Similarly, para- and ortho-substituted mono-$Ph_2P(O)$-protected diynes **3e** and **3f** were obtained in 45% and 51% yields respectively (Scheme 3.13).



Scheme 3.13 Selective Deprotection of Bis-$Ph_2P(O)$-Protected Diynes

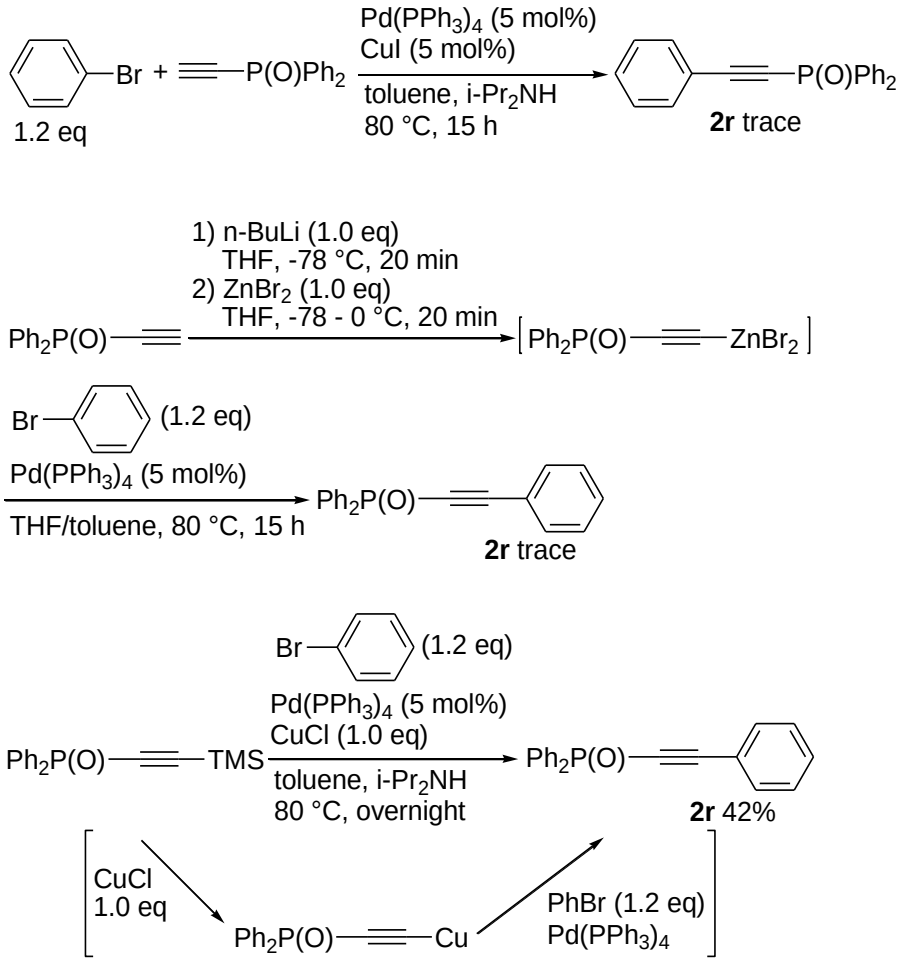
Mono-$Ph_2P(O)$-protected diynes could be prepared by selective protection of diethynylbenzene as well. Treatment of 1,3-diethynylbenzene with Ph_2PCl in the presence of a catalytic amount of CuI followed by oxidation with H_2O_2 gave the meta-substituted mono-$Ph_2P(O)$-protected diyne **3d** in 45%. Similarly, mono-$Ph_2P(O)$-protected diynes **3e**, **3f** and **3g** were obtained in 48%, 45% and 41% yields respectively (Scheme 3.14).



Scheme 3.14 Preparation of Mono-$Ph_2P(O)$-Protected Terminal Acetylenes by Selective Protection of Diethynylbenzene

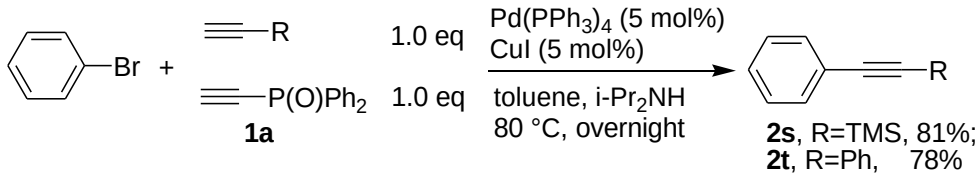
Coupling reactions between arylbromide and $Ph_2P(O)$-protected acetylene

In the previous case, aryliodide was always used in Sonogashira coupling. At here, we studied coupling reactions between arylbromide and phosphorylethyne. As shown in Scheme 3.15, Sonogashira coupling of bromobenzene and phosphorylethyne **1a** did not occur. Treatment of phosphorylethyne **1a** successively with BuLi and ZnBr afforded Zn-acetylide. Subjection of Zn-acetylide to Negishi coupling with bromobenzene gave trace amount of product. However, treatment of bromobenzene with TMS- phosphorylethyne **1b**, catalytic amount of $Pd(PPh_3)_4$ and 1.0 equivalent of CuCl provided the desired product **2r** in 42% yield. In this reaction, Cu-acetylide was formed from TMS-acetylene and CuCl.



Scheme 3.15 Coupling Reactions of Bromobenzene and Phosphorylethyne

In order to study why Sonogashira coupling of bromobenzene and phosphorylethyne did not occur, the following competitive reactions were carried out. Competitive Sonogashira coupling of bromobenzene with 1.0 equivalents of phosphorylethyne **1a** and 1.0 equivalents of TMS-acetylene or 1.0 equivalents of phenylacetylene just gave coupling products from TMS-acetylene or phenylacetylene, and no coupling product from phosphorylethyne was formed (Scheme 3.16). These results indicated that phosphorylethyne **1a** was much less reactive than TMS-acetylene or phenylacetylene.



Scheme 3.16 Competitive Sonogashira Coupling of Phenylbromide with Phosphorylethyne and TMS-acetylene or phenylacetylene

This experimental result showed fine agreement to HOMO energy values calculated at the B3LYP/6-31(d) level, which indicated -0.20496 for copper phenylacetylide, -0.23120 for copper TMS-acetylide and -0.23790 for copper $Ph_2P(O)$-acetylide. Phosphorylethyne showed lowest reactivity because $Ph_2P(O)$-substituted Cu-acetylide had the lowest HOMO energy value, and $Ph_2P(O)$-substituted Cu-acetylide was more difficult to form. $Ph_2P(O)$ decreased the reactivity of phosphorylethyne because of the electron- withdrawing effect of $Ph_2P(O)$ (Figure 3.3).

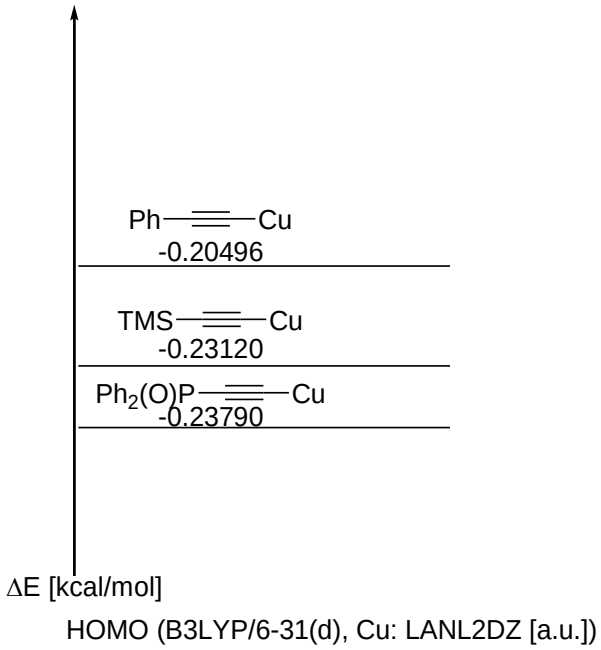
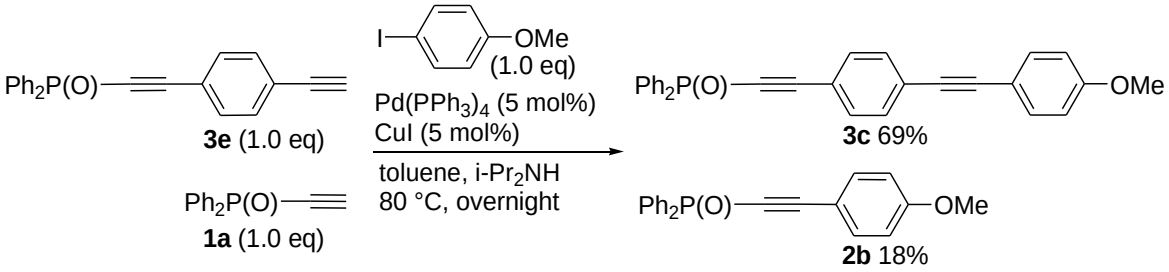


Figure 3.3 HOMO calculation

We also designed the following competitive reaction. As shown in Scheme

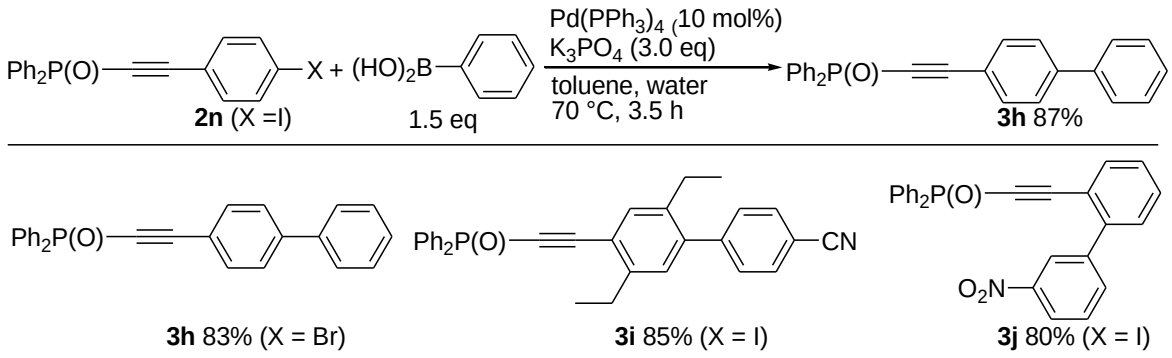
3.17, competitive Sonogashira coupling of 1-iodo-4-methoxybenzene with 1.0 equivalents of mono-$Ph_2P(O)$-protected diyne **3e** and 1.0 equivalents of phosphorylethyne **1a** gave ethynylphosphine oxide **3c** as a main product. This result indicated that mono-$Ph_2P(O)$-protected diyne **3e** was more reactive than phosphorylethyne **1a**. Mono-$Ph_2P(O)$-protected diyne **3e** showed higher reactivity because $Ph_2P(O)$ was far away from the reaction site in **3e**.



Scheme 3.17 Competitive Sonogashira Coupling of Iodomethoxybenzene with Phosphorylethyne **1a** and **3e**

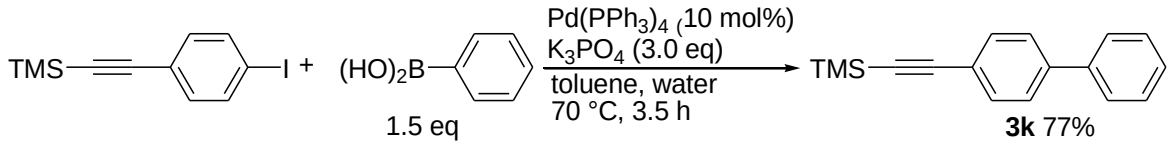
Application of ethynylphosphine oxide in Suzuki coupling

Phosphorylethyl-substituted halide could be applied in Suzuki coupling as well. Treatment of phosphorylethyl-substituted iodide with phenylboronic acid in Suzuki coupling conditions provided the desired product ethynylphosphine oxide **3h** in 87% yield. Similarly, Suzuki coupling products **3i**, and **3j** were obtained in 85% and 80% yields respectively. Suzuki coupling between phosphorylethyl-substituted bromide and phenylboronic acid proceeded smoothly and gave the **3h** in 83% yield (Scheme 3.18).



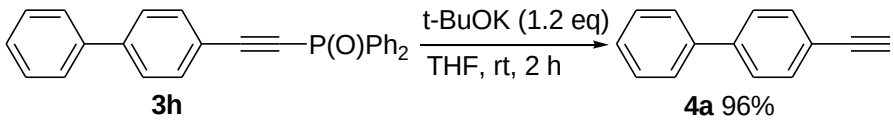
Scheme 3.18 Suzuki Coupling of Phosphorylethyl-substituted Halide and Aryllboronic Acid

Suzuki coupling between TMS-ethyl-substituted iodide and phenylboronic acid proceeded and gave the **3k** in 77% yield (Scheme 3.19).



Scheme 3.19 Suzuki Coupling of TMS-ethyl-substituted Iodide and Phenylboronic Acid

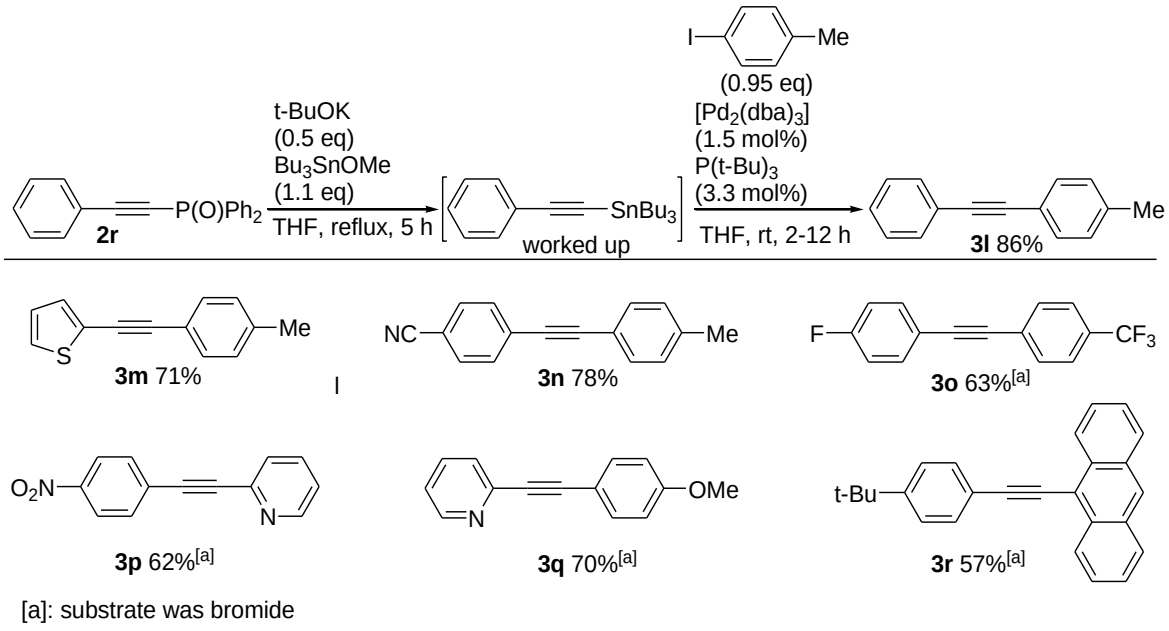
With the Suzuki coupling product **3h** in hand, biphenyl-substituted terminal acetylene **4a** was obtained in 96% yield by treatment of **3h** with t-BuOk (Scheme 3.20).



Scheme 3.20 Preparation of Biphenyl-substituted Terminal Acetylene by Deprotection of $P(O)Ph_2$

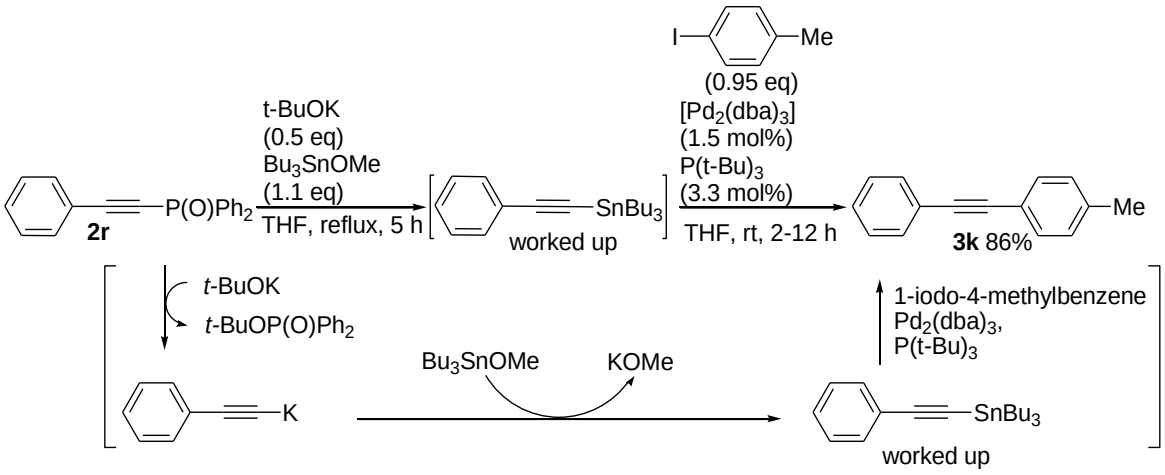
Application of ethynylphosphine oxide in Migata-Kosugi-Stille coupling

Phosphorylethynes could be applied to Migata-Kosugi-Stille coupling as well as Sonogashira coupling. Treatment of phosphorylethyne **2r** with t-BuOK and Bu_3SnOMe in refluxing temperature for 5 h, after workup with NH_4Faq/CH_2Cl_2, we obtained the crude product stannylethyne. Treatment of the crude stannylethyne with 1-iodo-4-methylbenzene under Stille coupling conditions gave the desired coupling product **3l** in 86% yield. Similarly, coupling products **3m**, **3n**, **3o**, **3p, 3q** and **3r** were obtained in moderate yields (Scheme 3.21).



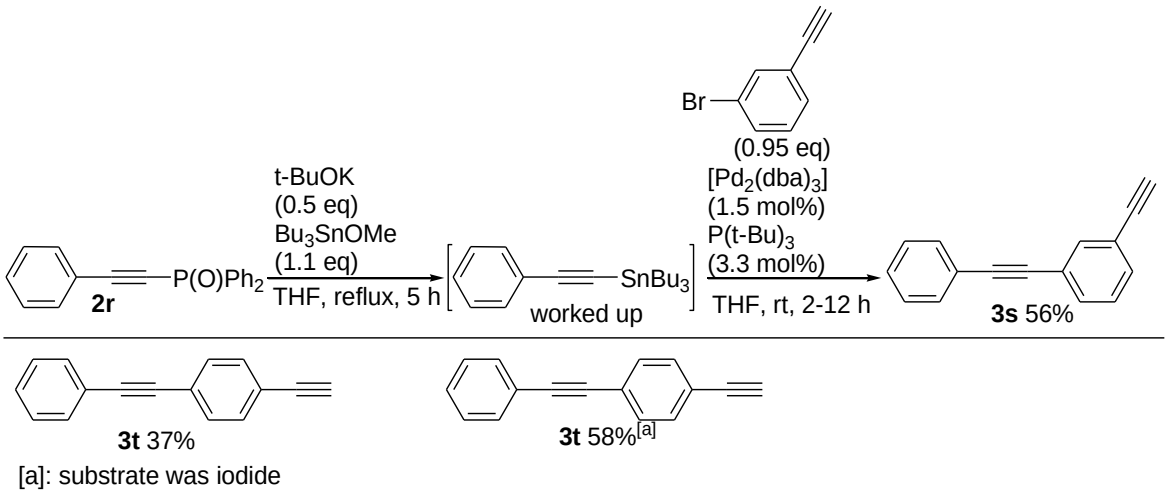
Scheme 3.21 Application of Phosphorylethynes in Migata-Kosugi-Stille Coupling

In this process, addition of 0.5 equivalent of t-BuOK enabled the complete deprotection of the $Ph_2P(O)$ group and the formation of stannylethyne because MeOK which was produced by stannylation of the resulting potassium acetylide with Bu_3SnOMe also served as a deprotection reagent (Scheme 3.22).



Scheme 3.22 Mechanism of Migata-Kosugi-Stille Coupling

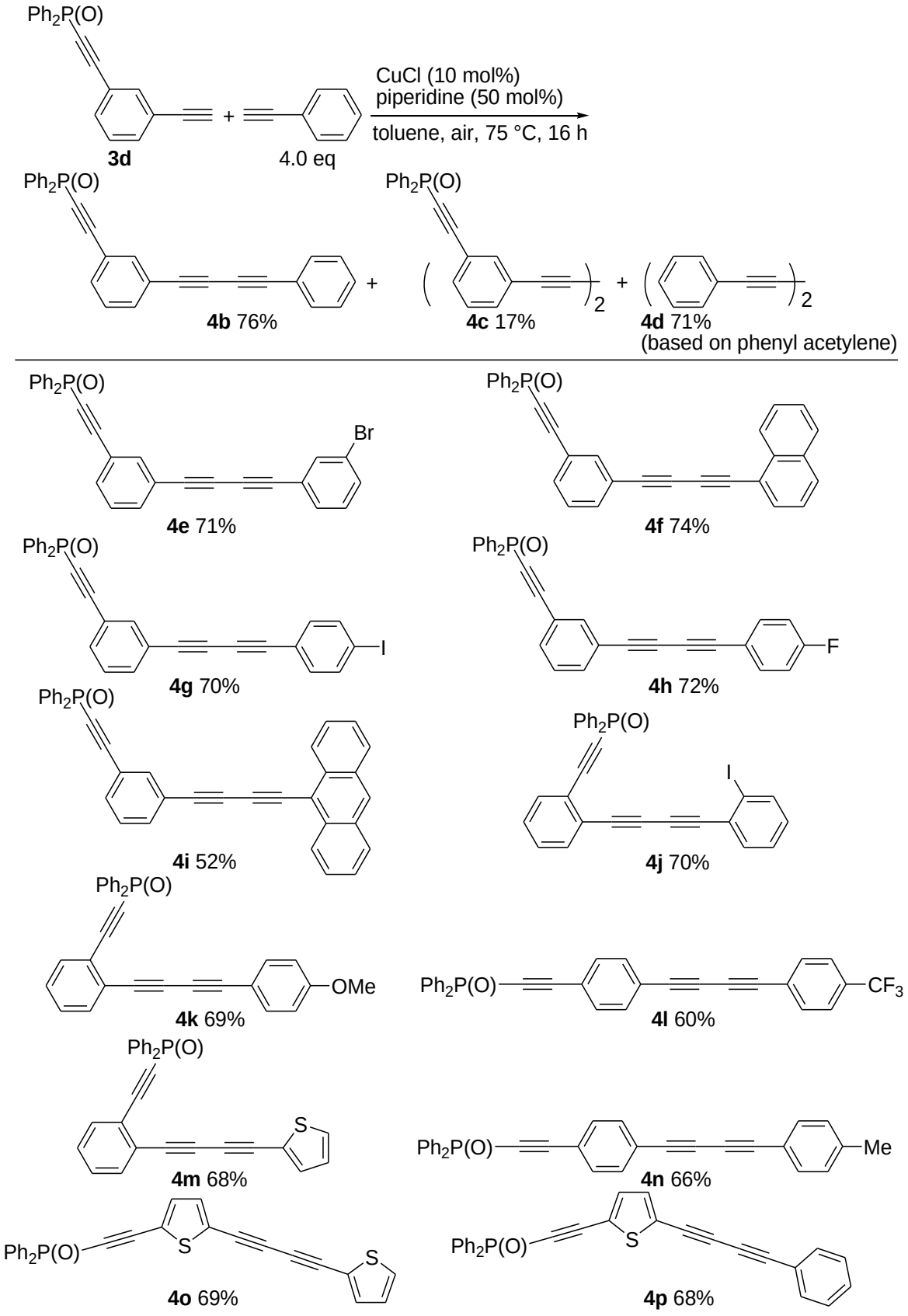
This deprotection/Migata-Kosugi-Stille coupling protocol proceeded smoothly in coupling between **2r** and 1-bromo-3-ethynylbenzene to provide **3s** in 56% yield. In this reaction, only stannylethyne reacted with phenyl bromide moiety of 1-bromo-3-ethynylbenzene, and terminal ethyne moiety of 1-bromo-3-ethynylbenzene remained untouched. Similarly, deprotection/ Migata-Kosugi-Stille coupling between **2r** and 1-bromo-4-ethynylbenzene or 1-ethynyl-4-iodobenzene proceeded smoothly and gave the desired product **3s** in 37% and 58% yield respectively (Scheme 3.23).



Scheme 3.23 Migata-Kosugi-Stille Coupling

Application of ethynylphosphine oxide in Hey coupling

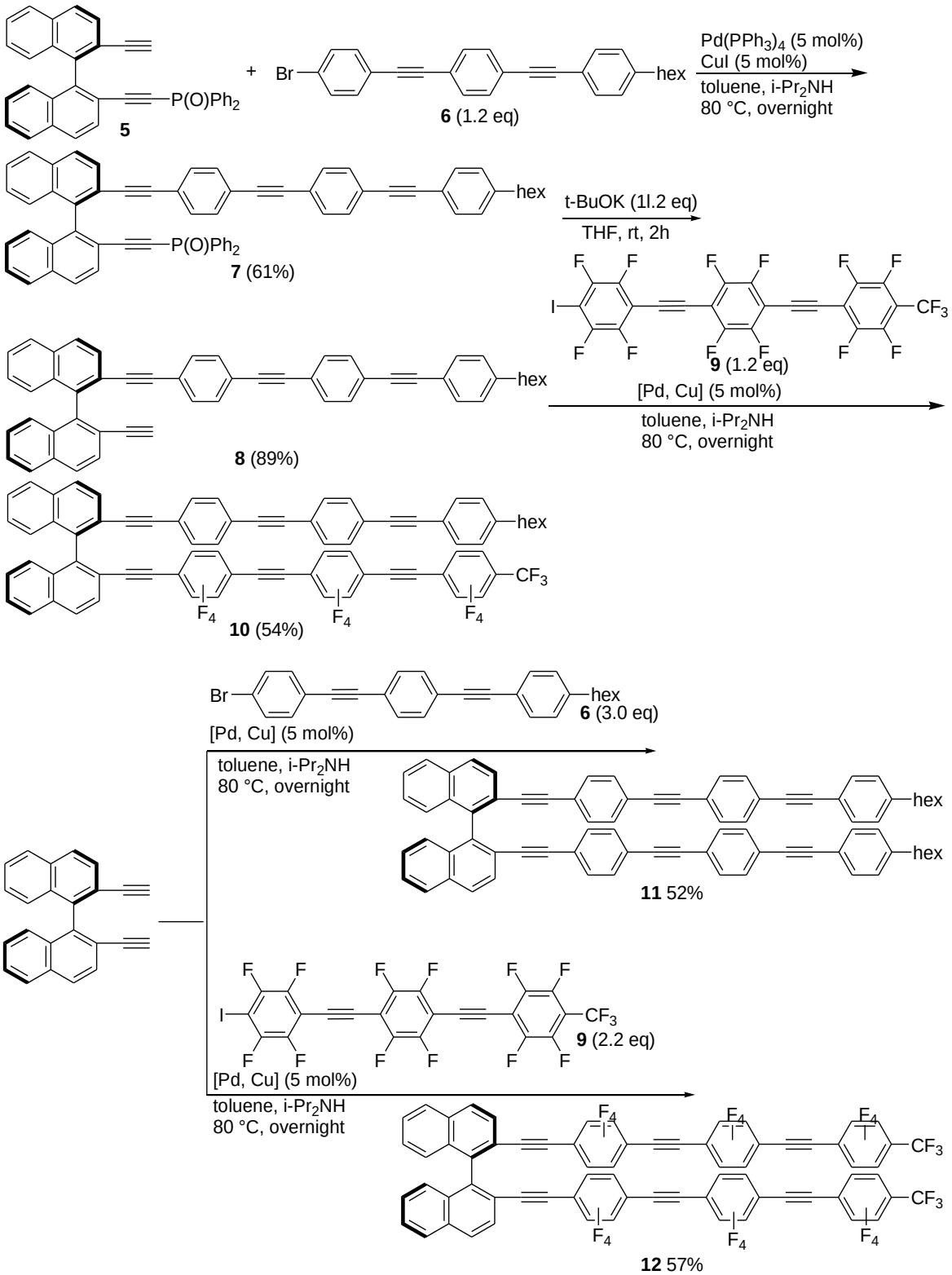
Mono-$Ph_2P(O)$-protected diynes could be applied in Hey coupling to prepare unsymmetrically substituted yne-diynes. When a toluene solution of mono-phosphoryl-protected diyne **3d** and phenylethyne was heated in the presence of CuCl and piperidine, **4b** was obtained in 76% yield. In this Hay coupling, homocoupling products **4c** and **4d** were produced as byproducts, but the high polarity of $Ph_2P(O)$ group enabled easy purification of the desired heterocoupling product **4b** by column chromatography on silica gel (R_f = 0.55 for **4b**, 0.24 for **4c**, and 0.97 for **4c** in AcOEt). Similarly, we obtained unsymmetrically substituted yne-diynes **4e** – **4p** in moderate yields (Scheme 3.24).



Scheme 3.24 Application of Phosphorylethynes in Hay Coupling

Preparation of Enantiopure 2,2'-diethynyl-1,1'-binaphthyl Derivatives 10, 11 and 12

In order to study the UV absorption spectra and Fluorescence emission spectra of binaphthyl derivatives, we designed and prepared 2,2'-diethynyl-1,1'-binaphthyl Derivatives **10**, **11** and **12**. Sonogashira coupling reaction between mono-$Ph_2P(O)$-protected 2,2'-diethynyl-1,1'- binaphthyl **5** and arylbromide **6** gave the desired product **7** in 61% yield. Treatment of **7** with t-BuOK afforded the terminal acetylene **8** in 89%. Sonogashira coupling reaction between **8** and **9** gave the desired product **10** in 54% yield. Using simple Sonogashira coupling, we synthesis binaphthyl derivatives **11** and **12** in moderate yields (Scheme 3.25).

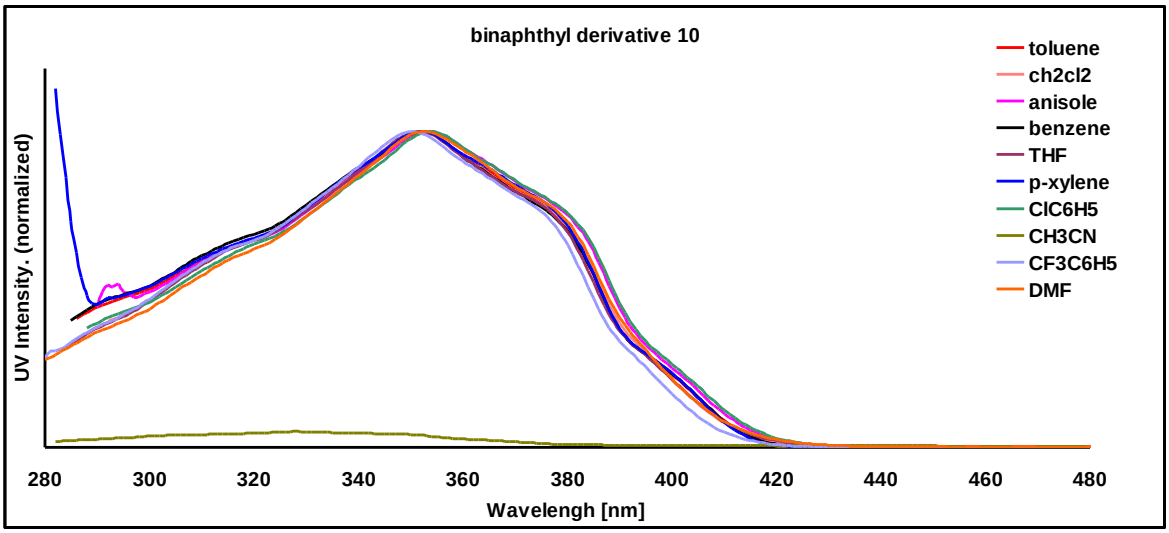


Scheme 3.25 Preparation of Enantiopure 2,2'-diethynyl-1,1'-binaphthyl Derivatives

UV absorption spectra of naphthyl derivatives 10, 11 and 12

UV absorption spectra of binaphthyl derivatives **10**, **11** and **12** were recorded in toluene, CH_2Cl_2, anisole, benzene, THF, p-xylene, ClC_6H_5, CH_3CN, $CF_3C_6H_5$ and DMF solution (1.0×10^{-4} M) at room temperature.

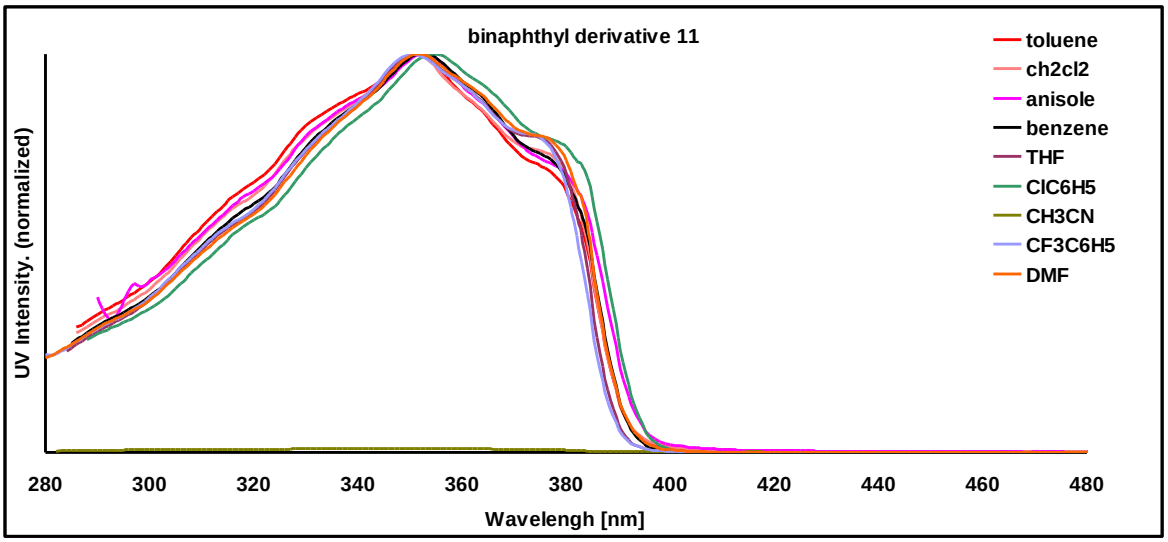
UV absorption spectrum of binaphthyl derivative **10** was shown in figure 3.4, polarities of different solvents did not affect the λ_{max}. In CH_3CN, binaphthyl derivatives **10** showed weak UV absorption because of its poor solubility in CH_3CN.



	$CH_3C_6H_6$	p-xylene	C_6H_6	$MeOC_6H_5$	ClC_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
λ_{max}	352	352	352	353	354	350	328	353	352	352(nm)

Figure 3.4 UV absorption spectrum of binaphthyl derivatives **10**

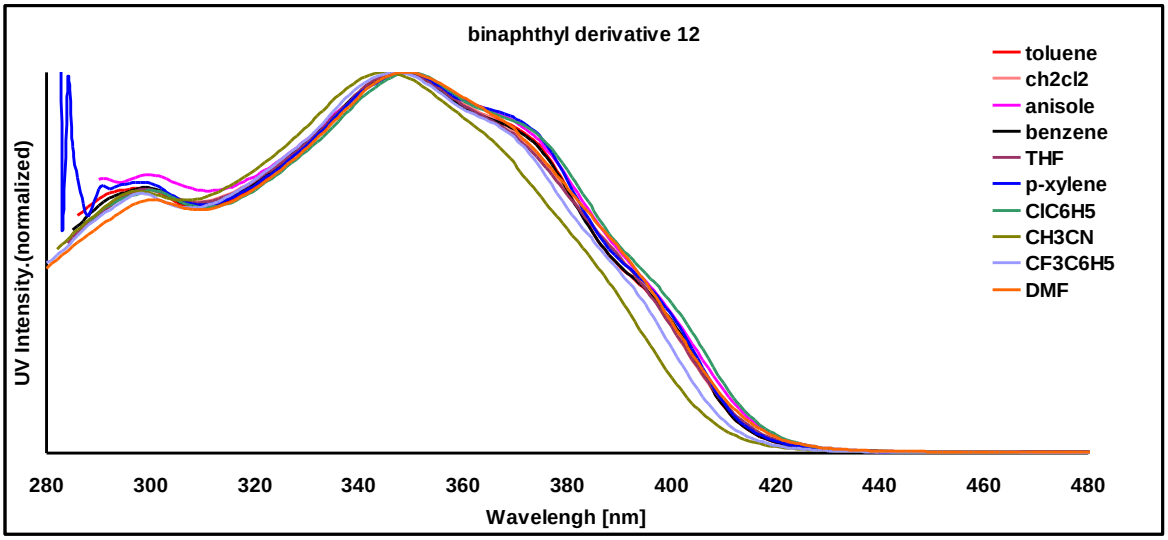
UV absorption spectrum of binaphthyl derivative **11** was showed in figure 3.5. The λ_{max} in all theses solvents is about 350 nm. Polarities of different solvents did not affect the λ_{max}. In CH_3CN, binaphthyl derivatives **11** showed weak UV absorption because of it's poor solubility in CH_3CN.



	$CH_3C_6H_6$	p-xylene	C_6H_6	MeO C_6H_5	Cl C_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
λ_{max}	352	351	353	353	355	351	348	352	351	351(nm)

Figure 3.5 UV absorption spectrum of binaphthyl derivatives **11**

Figure 3.6 is the UV absorption spectrum of binaphthyl derivative **12**. Polarities of different solvents did not affect the λ_{max}.



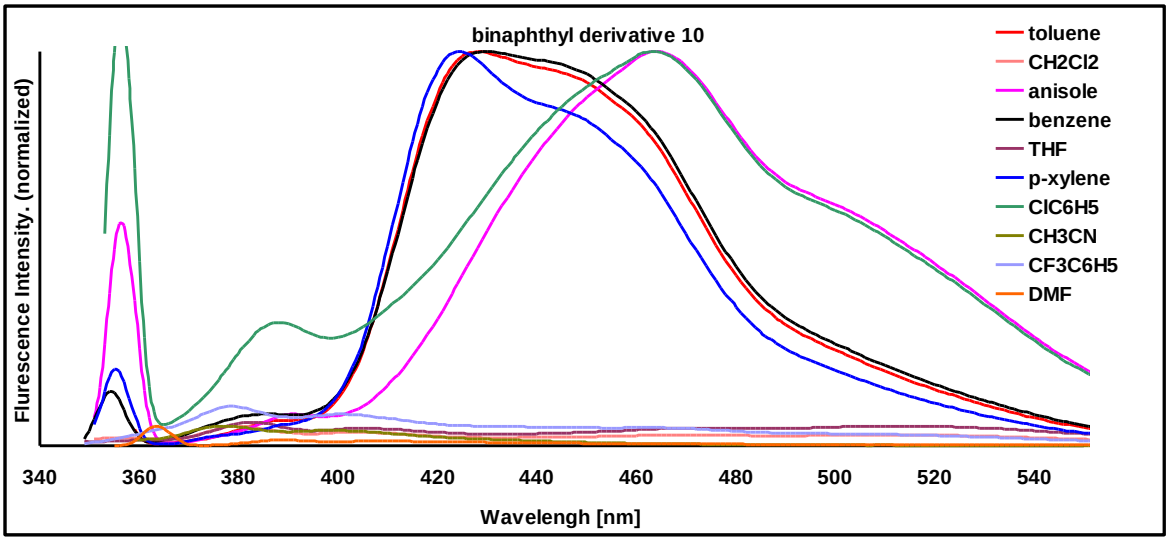
	$CH_3C_6H_6$	p-xylene	C_6H_6	MeO C_6H_5	Cl C_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
λ_{max}	349	349	348	350	350	347	345	349	348	348(nm)

Figure 3.6 UV absorption spectrum of binaphthyl derivatives **12**

Fluorescence emission spectra of binaphthyl derivatives

Fluorescence emission spectra of binaphthyl derivatives **10**, **11** and **12** were recorded in toluene, CH_2Cl_2, anisole, benzene, THF, p-xylene, ClC_6H_5, CH_3CN, $CF_3C_6H_5$ and DMF solution (1.0×10^{-4} M) at room temperature.

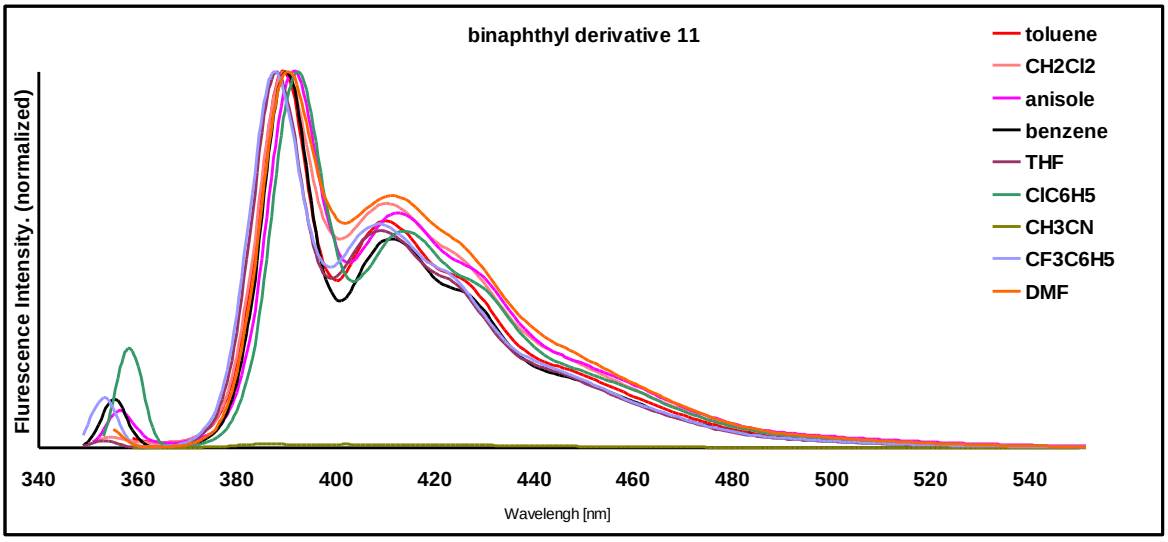
Fluorescence emission spectrum of binaphthyl derivative **10** was showed in figure 3.7, polarities of different solvents affected the λ_{max} of emission and excitation. Compared to polar aromatic solvents such as anisole and chlorobenzene, the λ_{max} of emission and excitation showed hypsochromic shift in less polar aromatic solvents such as toluene, p-xylene, and benzene. In non-aromatic solvents such as CH_3CN, DMF, dichloromethane and THF, the λ_{max} of emission and excitation showed larger hypsochromic shift. Binaphthyl derivatives **10** showed very weak fluorescence emission in trifluorobenzene, dichloromethane, THF, CH_3CN and DMF.



	$CH_3C_6H_6$	p-xylene	C_6H_6	$MeOC_6H_5$	ClC_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
Ex	354	355	354	356	356	332	342	364	345	345
Em	428	424	430	464	463	378	377	389	380	383(nm)

Figure 3.7 Fluorescence emission spectrum of binaphthyl derivatives **10**

Fluorescence emission spectrum of binaphthyl derivative **11** was showed in figure 3.8, polarities of different solvents did not affect the λ_{max} of emission and excitation. Binaphthyl derivatives **11** showed very weak fluorescence emission in CH_3CN.

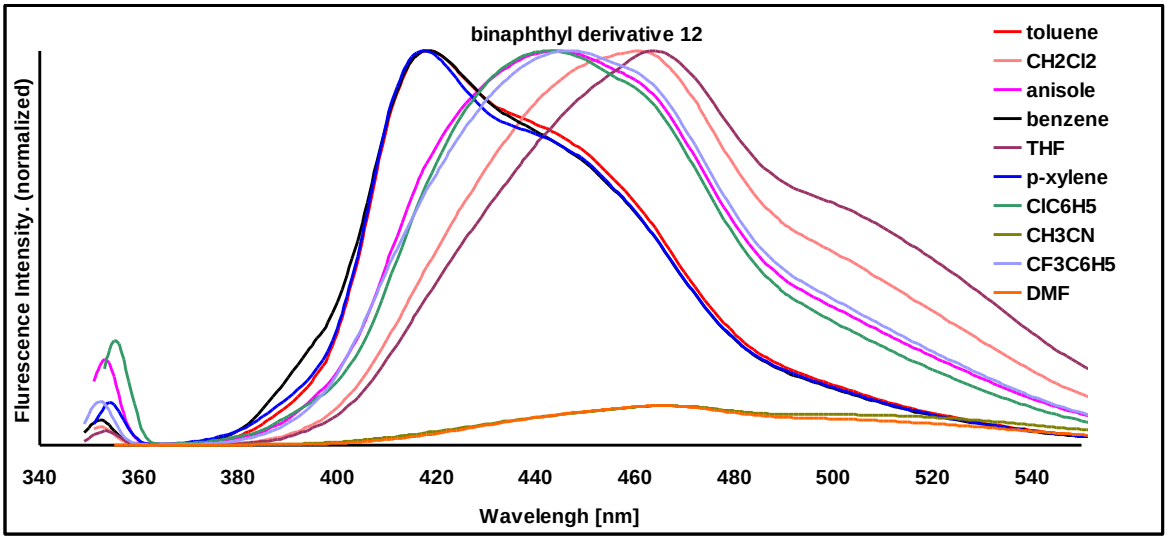


	$CH_3C_6H_6$	C_6H_6	$MeOC_6H_5$	ClC_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
Ex	355	355	356	358	353	347	354	354	353
Em	389	390	391	392	388	387	390	390	388(nm)

Figure 3.8 Fluorescence emission spectrum of binaphthyl derivatives **11**

Fluorescence emission spectrum of binaphthyl derivative **12** was showed in

figure 3.9, polarities of different solvents affected the λ_{max} of emission and excitation. Compared to polar aromatic solvents such as anisole chlorobenzene and trifluorobenzene, the λ_{max} of emission and excitation showed hypsochromic shift in less polar aromatic solvents such as toluene, p-xylene, and benzene. In non-aromatic solvents such as CH_3CN, DMF, dichloromethane and THF, the λ_{max} of emission and excitation showed larger bathochromic shift. Binaphthyl derivatives **12** showed very weak fluorescence emission in CH_3CN and DMF.



	$CH_3C_6H_6$	p-xylene	C_6H_6	MeO C_6H_5	Cl C_6H_5	$CF_3C_6H_5$	CH_3CN	DMF	CH_2Cl_2	THF
Ex	352	354	324	354	356	352	348	347	353	353
Em	418	417	418	443	443	447	466	465	460	464(nm)

Figure 3.9 Fluorescence emission spectrum of binaphthyl derivatives **12**

3.4 Conclusion

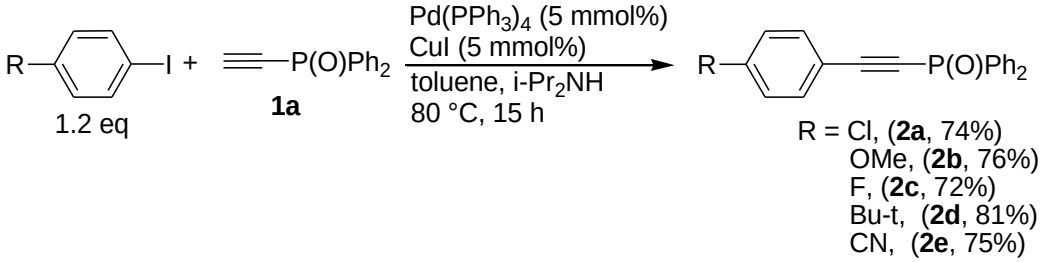
The diphenylphosphoryl-ethyne bond of ethynylphosphine oxide remained intact in Sonogashira coupling, Suzuki coupling and oxidative homocoupling, and

a series of arylethynylphosphine oxides were prepared in pure forms by taking advantage of high polarity of $Ph_2P(O)$. A number of arylethynes were synthesized by subjecting phosphorylethynes to Migata-Kosugi-Stille coupling.

3.5 Experimental Section

General. All reactions were carried out under an atmosphere of argon with freshly distilled solvents, unless otherwise noted. Toluene was distilled from sodium. Diisopropylamine and triethylamine were distilled from CaH_2. DMF was distilled from $Ca(OH)_2$. Dry tetrahydrofuran (THF) was purchased from Wako Chemicals. $Pd(PPh_3)_4$ was prepared according to the reported method. Silica gel (Daiso gel IR-60) was used for column chromatography. The other materials were purchased from commercial sources and used without additional purification. NMR spectra was recorded at 25 °C on JEOL Lambda 300 and JEOL Lambda 500 instruments in $CDCl_3$ and calibrated with tetramethysilane (TMS) as an internal reference. Mass spectra were recorded on JEOL MStation JMS-700 and Shimadzu/Kratos MALDI 4 and Platform II single quadrupole (Micro-mass, Altrinchan, UK) mass spectrometers. Elemental analyses were performed by the Perkin-Elmer PE 2400. Melting points (m.p.) were measured on a GTO-250RS instrument.

Synthesis of 2a, 2b, 2c, 2d and 2e by Sonogashira coupling (representative procedure for 2a):



A toluene solution (5.0 mL) of 1-chloro-4-iodobenzene (286.1 mg, 1.2 mmol),

phosphorylethyne **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2a** in a pure form (249.2 mg, 74% yield).

2a: white powder, m.p. 145-146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.49-7.59 (m, 8H), 7.87-7.91 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 83.87 (d, *J* = 166.9 Hz), 103.89 (d, *J* = 29.8 Hz), 118.24 (d, *J* = 4.0 Hz), 128.58 (d, *J* = 13.6 Hz), 128.91, 130.81 (d, *J* = 11.5 Hz), 132.24 (d, *J* = 3.1 Hz), 132.65 (d, *J* = 122.3 Hz), 133.60 (d, *J* = 1.9 Hz), 136.94; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.22; HRMS (FAB) calcd for $C_{20}H_{14}ClOP$ ($M+H^+$): 337.0471, found 336.9925.

2b:[9] white powder, m.p. 125-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, *J* = 9.05 Hz, 2H), 7.46-7.53 (m, 8H), 7.90-7.92 (m, 4H).

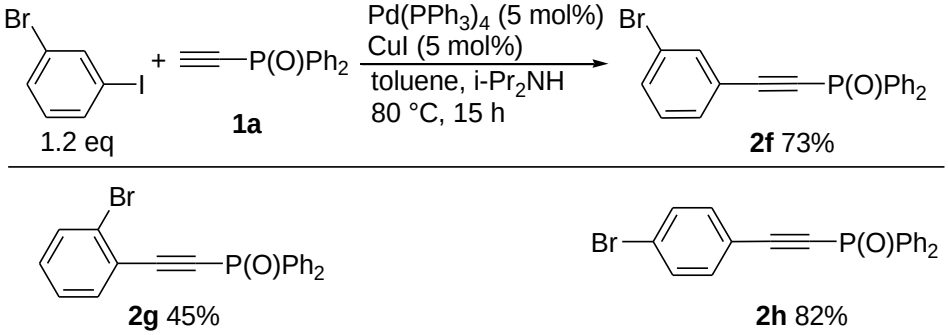
2c: white powder, m.p. 119-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (t, *J* = 8.7 Hz, 2H), 7.49-7.52 (m, 4H), 7.56 (dd, *J* = 1.5 Hz, 14.6 Hz, 2H), 7.59-7.62 (m, 2H), 7.87-7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 82.68 (d, *J* = 168.8 Hz), 104.16 (d, *J* = 30.1 Hz), 116.01 (d, *J* = 22.3 Hz), 128.58 (d, *J* = 13.4 Hz), 130.82 (d, *J* = 11.2 Hz), 132.22 (d, *J* = 3.1 Hz), 132.73 (d, *J* = 121.9 Hz), 134.62 (d, *J* = 1.5 Hz), 134.73 (d, *J* = 1.9 Hz), 163.72 (d, *J* = 252.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ -106.51. ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.07; HRMS (FAB) calcd for $C_{20}H_{14}FOP$ ($M+H^+$): 321.0766, found 321.0739.

2d: white powder, m.p. 120-121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 9H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.48-7.51 (m, 4H), 7.54-7.57 (m, 4H), 7.88-7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.88 (d, *J* = 4.7 Hz), 34.89, 82.09 (d, *J* = 171.3 Hz), 105.79 (d, *J* = 30.4 Hz), 116.67 (d, *J* = 4.3 Hz), 125.48, 128.48 (d, *J* = 13.4 Hz), 130.79 (d, *J* = 11.2 Hz), 132.04 (d, *J* = 3.1 Hz), 132.19, 133.03 (d, *J* = 122.6

Hz), 154.24. ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.27; HRMS (FAB) calcd for $C_{24}H_{23}OP$ ($M+H^+$): 359.1487, found 359.1686.

2e: [9] pale yellow powder, m.p. 163-165 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.54 (m, 4H), 7.57-7.60 (m, 2H), 7.66-7.70 (m, 4H), 7.88-7.92 (m, 4H).

Synthesis of 2f, 2g and 2h by Sonogashira coupling (representative procedure for 2f):



A toluene solution (5.0 mL) of 1-bromo-3-iodobenzene (339.5 mg, 1.2 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2f** in a pure form (278.3 mg, 73% yield).

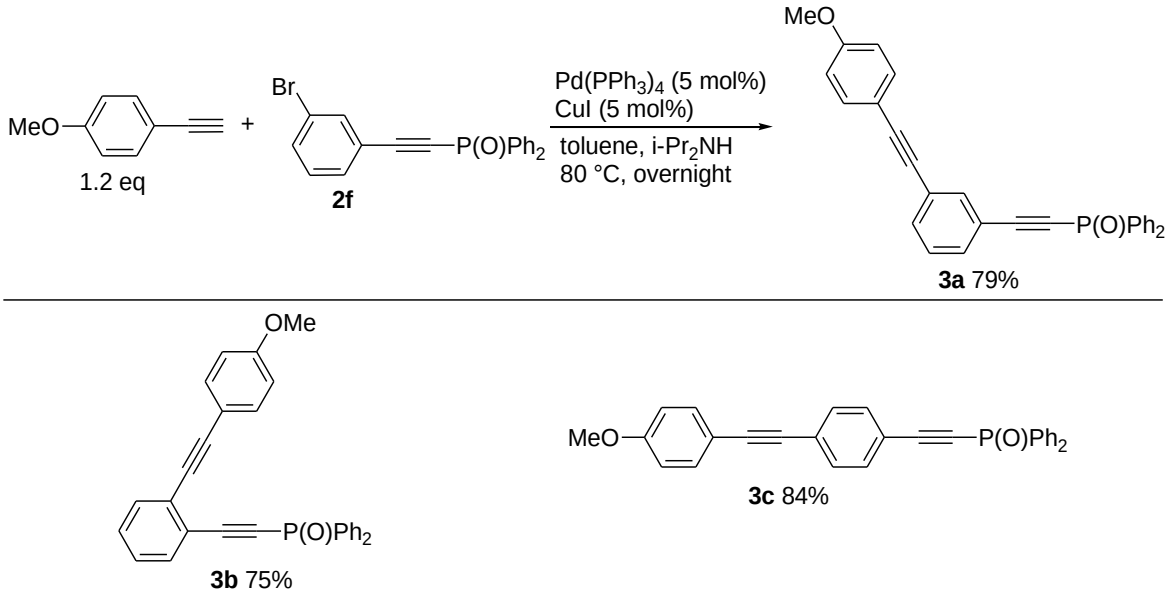
2f:[10] white powder; m.p. 98-99 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.0 Hz, 1H), 7.49-7.54 (m, 5H), 7.56-7.60 (m, 3H), 7.74 (s, 1H), 7.86-7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.06 (d, *J* = 165.7 Hz), 103.07 (d, *J* = 29.2 Hz), 121.69 (d, *J* = 3.7 Hz), 122.18, 128.60 (d, *J* = 13.7 Hz), 129.96, 130.80 (d, *J* = 11.2 Hz), 132.29 (d, *J* = 3.1 Hz), 132.45 (d, *J* = 121.9 Hz), 133.74, 134.84, 134.87.

2g: white powder, m.p. 88-89 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29-7.35 (m, 2H), 7.49-7.52 (m, 4H), 7.55-7.58 (m, 2H), 7.61-7.64 (m, 2H), 7.94-7.98 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 86.76 (d, *J* = 166.3 Hz), 102.63 (d, *J* = 29.5 Hz),

122.05 (d, *J* = 3.8 Hz), 125.87 (d, *J* = 2.1 Hz), 127.04, 128.39 (d, *J* = 13.7 Hz), 130.70 (d, *J* = 11.2 Hz), 131.54, 132.07 (d, *J* = 3.1 Hz), 132.40, 132.46 (d, *J* = 121.9 Hz), 134.16 (d, *J* = 1.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.08; HRMS (FAB) calcd for $C_{20}H_{14}BrOP$ ($M+H^+$): 380.9966, found 381.0261.

2h:[9] white powder; m.p. 154-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.6 Hz, 2H), 7.49-7.59 (m, 8H), 7.86-7.91 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 83.74 (d, *J* = 166.3 Hz), 103.60 (d, *J* = 29.4 Hz), 118.25 (d, *J* = 4.3 Hz), 125.02, 128.30 (d, *J* = 13.7 Hz), 130.44 (d, *J* = 11.2 Hz), 131.48, 131.97 (d, *J* = 2.8 Hz), 132.24 (d, *J* = 121.9 Hz), 133.35 (d, *J* = 1.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.88.

Synthesis of 3a, 3b and 3c by Sonogashira coupling (representative procedure for 3a):



A toluene solution (5.0 mL) of 1-ethynyl-4-methoxybenzene (158.6 mg, 1.2 mmol), **2f** (381.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel

(hexane/AcOEt, 1:1) to afford **3a** in a pure form (341.6 mg, 79% yield).

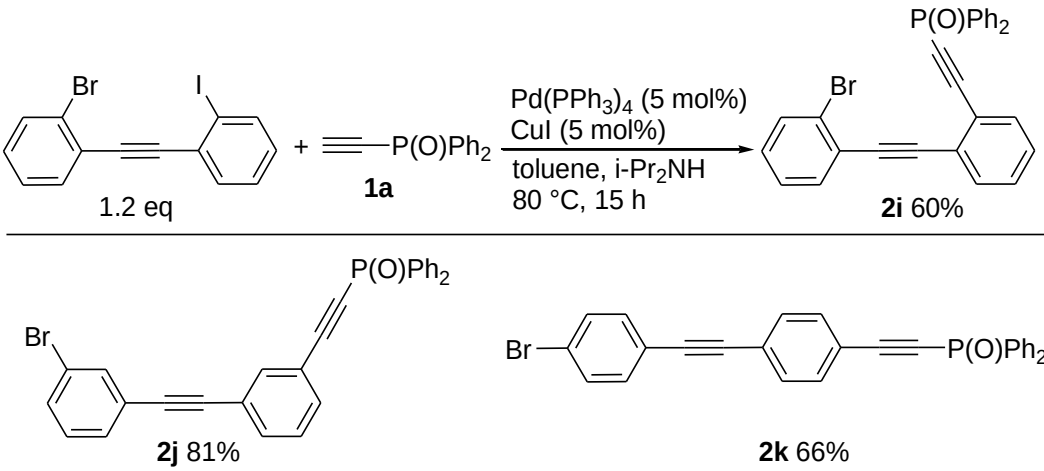
3a:[9] white powder, m.p. 151-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.49-7.54 (m, 5H), 7.56-7.58 (m, 3H), 7.74 (s, 1H), 7.88-7.93 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 55.28 (d, *J* = 4.1 Hz), 83.27 (d, *J* = 167.8 Hz), 86.48, 90.87, 104.36 (d, *J* = 29.5 Hz), 114.02 (d, *J* = 6.8 Hz), 114.58, 120.20 (d, *J* = 4.1 Hz), 124.37, 128.66 (d, *J* = 13.4 Hz), 130.93 (d, *J* = 11.3 Hz), 131.63, 132.28, 132.30, 133.13 (d, *J* = 4.2 Hz), 133.28, 133.43, 135.08, 159.86; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.78.

3b: yellow powder, m.p.140-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.26-7.34 (m, 3H), 7.35-7.44 (m, 5H), 7.47-7.50 (m, 2H)，7.56 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.94-7.97 (m, 4H) ; ^{13}C NMR (75MHz, $CDCl_3$): δ 55.18 (d, *J* = 4.6 Hz), 85.90, 85.98 (d, *J* = 169.1 Hz), 94.73, 103.82 (d, *J* = 30.1 Hz), 113.85, 114.37, 121.88 (d, *J* = 4.1 Hz), 127.21 (d, *J* = 1.9 Hz), 127.63, 128.54 (d, *J* = 13.4 Hz), 130.25, 130.84 (d, *J* = 11.2 Hz), 131.81, 132.03 (d, *J* = 2.8 Hz), 132.86 (d, *J* = 1.8 Hz), 132.91 (d, *J* = 121.6 Hz), 133.20, 159.81; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.86; HRMS (FAB) calcd for $C_{29}H_{21}O_2P$ ($M+H^+$): 433.1279, found 433.1562.

3c: pale-yellow powder, m.p. 187-189 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.46-7.53 (m, 8H), 7.56-7.57 (m, 4H), 7.88-7.93 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 55.25 (d, *J* = 4.9 Hz), 84.25 (d, *J* = 167.9 Hz), 87.36, 92.94, 104.94 (d, *J* = 30.1 Hz), 114.04, 114.54, 118.88 (d, *J* = 4.7 Hz), 126.15, 128.64 (d, *J* = 13.4 Hz), 130.90 (d, *J* = 10.8 Hz), 131.37, 132.26 (d, *J* = 2.8 Hz), 132.36 (d, *J* = 1.9 Hz), 132.83 (d, *J* = 121.9 Hz), 133.16, 159.96; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.78; HRMS (FAB) calcd for $C_{29}H_{21}O_2P$ ($M+H^+$): 433.1279, found 433.1655.

Synthesis of 2i, 2j and 2k by Sonogashira coupling (representative

procedure for 2i):



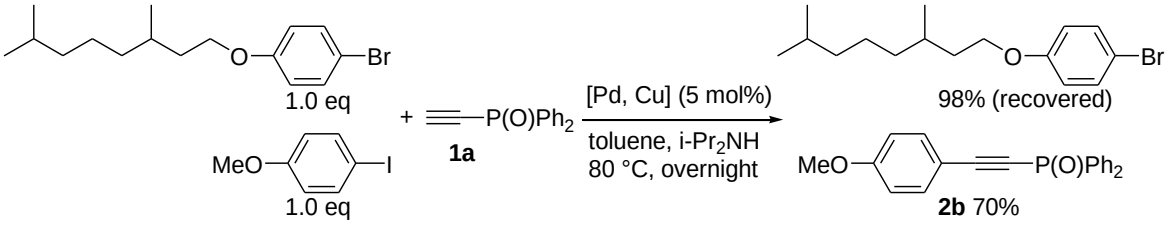
A toluene solution (5.0 mL) of 1-bromo-2-((2-iodophenyl)ethynyl)benzene (459.6 mg, 1.2 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2i** in a pure form (288.8 mg, 60% yield).

2i: pale-yellow powder, m.p. 126-129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.20 (m, 2H), 7.28-7.30 (m, 1H), 7.33-7.39 (m, 5H),7.44-7.48 (m, 3H), 7.58-7.60 (m, 1H), 7.64-7.67 (m, 2H), 7.90-7.95 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 86.33 (d, *J* = 168.6 Hz), 91.19, 92.66, 103.37 (d, *J* = 30.4 Hz), 122.15 (d, *J* = 4.1 Hz), 124.55, 125.50, 126.39 (d, *J* = 1.8 Hz), 126.94, 128.39, 128.44 (d, *J* = 13.7 Hz), 129.78, 130.28, 130.85 (d, *J* = 11.2 Hz), 132.04 (d, *J* = 2.8 Hz), 132.28, 132.32, 133.00 (d, *J* = 2.2 Hz), 132.79 (d, *J* = 121.9 Hz), 133.55; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.91; HRMS (FAB) calcd for $C_{28}H_{18}BrOP$ ($M+H^+$): 481.0279, found 481.0896.

2j: pale-yellow powder, m.p. 170-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.48-7.53 (m, 5H), 7.56-7.60 (m, 4H), 7.68 (s, 1H), 7.75 (s, 1H), 7.88-7.93 (m, 4H); ^{13}C NMR

(75MHz, $CDCl_3$): δ 83.47 (d, *J* = 166.3 Hz), 88.74, 88.96, 103.84 (d, *J* = 29.5 Hz), 120.15 (d, *J* = 3.7 Hz), 121.97, 123.30, 124.33, 128.51 (d, *J* = 13.3 Hz), 128.65, 129.66, 129.97, 130.71 (d, *J* = 11.2 Hz), 131.57, 132.16 (d, *J* = 3.1 Hz), 132.55 (d, *J* = 122.0 Hz), 133.43, 134.01, 135.06, 135.08; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.85; HRMS (FAB) calcd for $C_{28}H_{18}BrOP$ ($M+H^+$): 481.0279, found 481.0886.

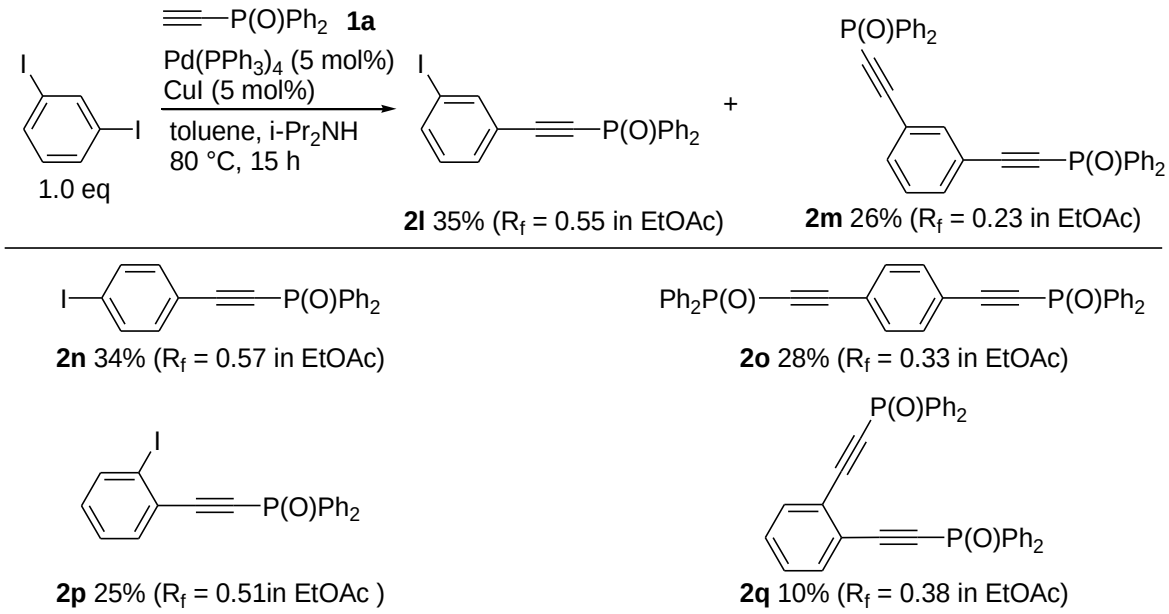
2k: pale-yellow powder, m.p. 222-224 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.2 Hz, 2H), 7.50-7.53 (m, 8H), 7.56-7.59 (m, 4H), 7.88-7.92 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 84.56 (d, *J* = 166.7 Hz), 89.50, 91.50, 104.60 (d, *J* = 29.5 Hz), 119.58 (d, *J* = 3.8 Hz), 121.45, 123.04, 125.31, 128.63 (d, *J* = 13.3 Hz), 130.88 (d, *J* = 11.2 Hz), 131.53, 131.64, 132.27 (d, *J* = 3.1 Hz), 132.39 (d, *J* = 2.2 Hz), 132.72 (d, *J* = 121.9 Hz), 133.00; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.80; HRMS (FAB) calcd for $C_{28}H_{18}BrOP$ ($M+H^+$): 481.0279, found 481.0733.



A toluene solution (10.0 mL) of 1-bromo-4-(3,7-dimethyloctyloxy)benzene (313.3 mg, 1.0 mmol), 1-iodo-4-methoxybenzene (234.0 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 10:1, and hexane/AcOEt, 1:1) to recover 1-bromo-4-(3,7-dimethyloctyloxy)benzene (307.0 mg, 98% yield) and afford **2b** in a pure form (232.6 mg, 70% yield).

Synthesis of 2l, 2m, 2n, 2o, 2p and 2q by Sonogashira coupling

(representative procedure for 2l and 2m):



A toluene solution (5.0 mL) of 1,3-Diiodobenzene (329.9 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt) to afford **2l** (149.9 mg, 35% yield) and **2m** in pure forms (136.9 mg, 26% yield).[6]

2l:[9] m.p. 94-96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (t, *J* = 8.0 Hz, 1H), 7.49-7.53(m, 4H), 7.56-7.59 (m, 3H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.86-7.91 (m, 4H), 7.94(s, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 83.98 (d, *J* = 165.7 Hz), 93.45, 102.89 (d, *J* = 29.2 Hz), 121.61 (d, *J* = 4.0 Hz), 128.51 (d, *J* = 13.4 Hz), 129.87, 130.70 (d, *J* = 11.2 Hz), 131.37, 132.20 (d, *J* = 2.8 Hz), 132.36 (d, *J* = 121.9 Hz), 139.56, 140.50; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.80.

2m:[9] pale-yellow powder, m.p. 199-201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (t, *J* = 8.0 Hz, 1H), 7.50-7.53(m, 8H), 7.26-7.34 (m, 3H), 7.57-7.60 (m, 4H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.83(s, 1H), 7.87-7.91 (m, 8H); ^{13}C NMR (75MHz, $CDCl_3$):

δ 84.23 (d, *J* = 165.1 Hz), 103.01 (d, *J* = 29.1 Hz), 120.64 (d, *J* = 4.1 Hz), 128.64 (d, *J* = 13.7 Hz), 129.00, 130.81 (d, *J* = 11.5 Hz), 132.24 (d, *J* = 2.8 Hz), 132.34 (d, *J* = 121.9 Hz), 134.16, 136.03; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.90.

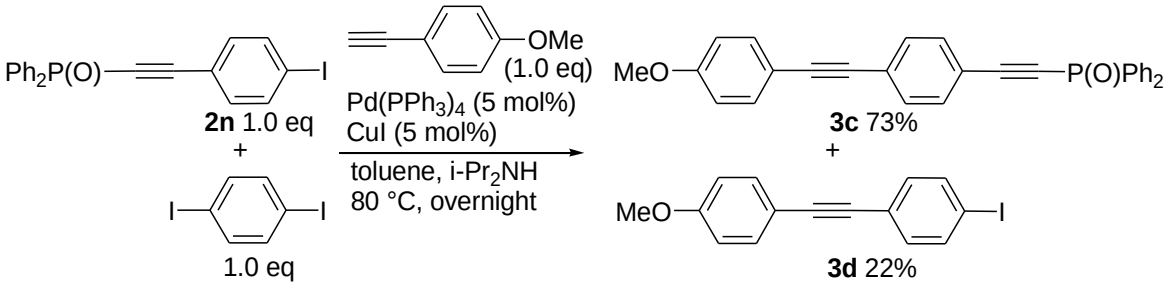
2n: yellow powder, m.p. 163-166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.49-7.52 (m, 4H), 7.56-7.59 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.86-7.91 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 83.94 (d, *J* = 167.0 Hz), 97.28, 103.74 (d, *J* = 29.4 Hz), 118.70 (d, *J* = 3.5 Hz), 128.27 (d, *J* = 13.4 Hz), 130.40 (d, *J* = 11.2 Hz), 131.94 (d, *J* = 3.1 Hz), 132.18 (d, *J* = 121.6 Hz), 133.19 (d, *J* = 1.8 Hz), 137.31; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.87; HRMS (FAB) calcd for $C_{20}H_{14}IOP$ ($M+H^+$): 428.9827, found 429.0385.

2o: white powder, m.p. 264-266 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.53 (m, 8H), 7.57-7.61 (m, 8H), 7.87-7.91 (m, 8H); ^{13}C NMR (75MHz, $CDCl_3$): δ 85.78 (d, *J* = 164.8 Hz), 103.54 (d, *J* = 28.9 Hz), 122.01 (d, *J* = 4.0 Hz), 128.67 (d, *J* = 13.4 Hz), 130.87 (d, *J* = 11.2 Hz), 132.39 (d, *J* = 3.2 Hz), 132.44 (d, *J* = 122.0 Hz), 132.46 (d, *J* = 1.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.88; HRMS (FAB) calcd for $C_{34}H_{24}O_2P_2$ ($M+H^+$): 527.1252, found 527.1783.

2p: pale-yellow powder, m.p. 112-114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.50-7.61 (m, 7H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.96-8.00 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 85.87 (d, *J* = 166.4 Hz), 100.29 (d, *J* = 2.2 Hz), 105.64 (d, *J* = 29.4 Hz), 126.52 (d, *J* = 4.3 Hz), 127.80, 128.41 (d, *J* = 13.4 Hz), 130.86 (d, *J* = 11.5 Hz), 131.44, 132.12 (d, *J* = 2.8 Hz), 132.45 (d, *J* = 123.1 Hz), 133.92 (d, *J* = 1.8 Hz), 138.74; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.96; HRMS (FAB) calcd for $C_{20}H_{14}IOP$ ($M+H^+$): 428.9827, found 429.0447.

2q: white powder, m.p. 158-160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.42 (m, 8H), 7.46-7.49 (m, 6H), 7.68 (dd, *J* = 2.4 Hz, 3.4 Hz, 2H), 7.82-7.87 (m, 8H); ^{13}C NMR (75MHz, $CDCl_3$): δ 87.47 (d, *J* = 163.5 Hz), 101.88 (d, *J* = 28.8 Hz), 122.97,

128.62 (d, *J* = 13.4 Hz), 130.34, 130.72 (d, *J* = 11.2 Hz), 132.16 (d, *J* = 3.2 Hz), 132.28 (d, *J* = 121.9 Hz), 133.56; ^{31}P NMR (121 MHz, $CDCl_3$): δ 10.06; HRMS (FAB) calcd for $C_{34}H_{24}O_2P_2$ ($M+H^+$): 527.1252, found 527.1912.

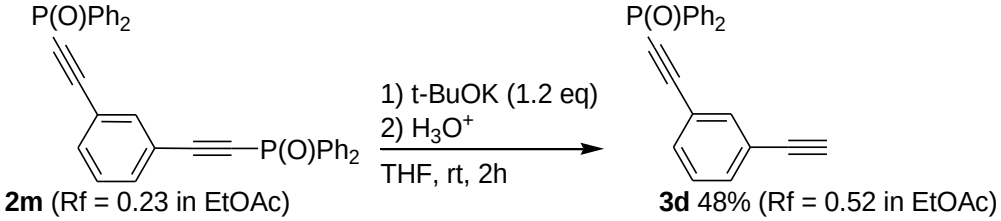


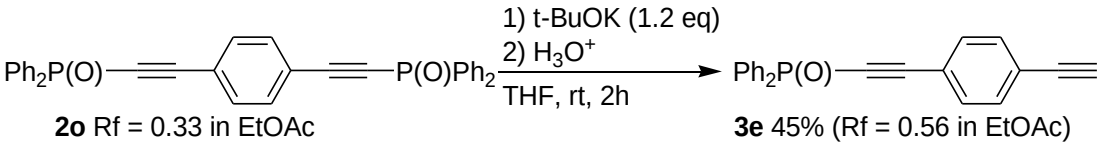
A toluene solution (5.0 mL) of 1,4-Diiodobenzene (329.9 mg, 1.0 mmol), **2n** (428.2 mg, 1.0 mmol), 1-ethynyl-4-methoxybenzene (132.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 10:1, and hexane/AcOEt, 1:1) to afford **3c** (315.7 mg, 73% yield) and **3d** in pure forms (73.5 mg, 22% yield).

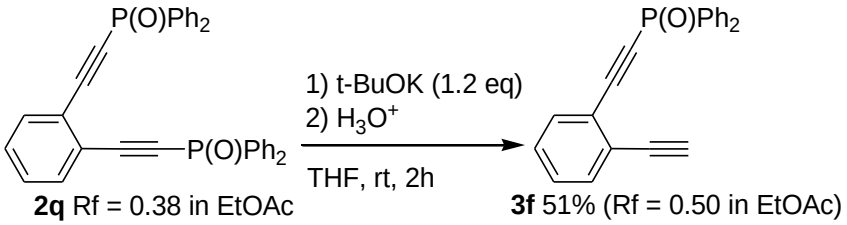
3c: pale-yellow powder, m.p. 187-189 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.46-7.53 (m, 8H), 7.56-7.57 (m, 4H), 7.88-7.93 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ 55.25 (d, *J* = 4.9 Hz), 84.25 (d, *J* = 167.9 Hz), 87.36, 92.94, 104.94 (d, *J* = 30.1 Hz), 114.04, 114.54, 118.88 (d, *J* = 4.7 Hz), 126.15, 128.64 (d, *J* = 13.4 Hz), 130.90 (d, *J* = 10.8 Hz), 131.37, 132.26 (d, *J* = 2.8 Hz), 132.36 (d, *J* = 1.9 Hz), 132.83 (d, *J* = 121.9 Hz), 133.16, 159.96; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.78; HRMS (FAB) calcd for $C_{29}H_{21}O_2P$ ($M+H^+$): 433.1279, found 433.1655.

3d:[11] white powder, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H).

Synthesis of 3d, 3e and 3f by Selective Deprotection (representative procedure for 3d):

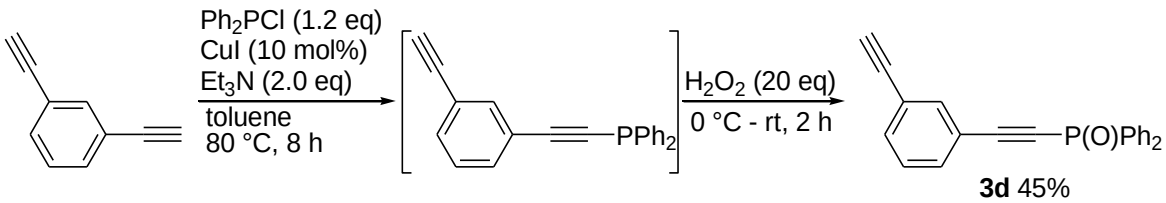


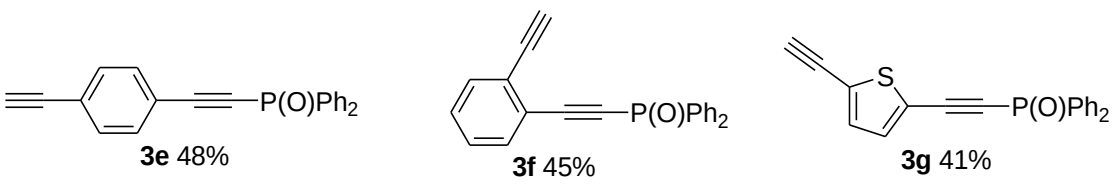




To a THF solution (10 mL) of **2m** (263.2 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6mmol) at rt, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3d** in a pure form (78.3 mg, 48%).

Synthesis of 3d, 3e, 3f and 3g by Selective Protection of Diethynylbenzene (representative procedure for 3d):





A toluene solution (10 mL) of 1,3-diethynylbenzene (126.2 mg, 1.0 mmol), CuI (19.0 mg, 0.1 mmol), Ph_2PCl (220.6 μL, 1.2 mmol) and Et_3N (277.2 μL, 2.0 mmol) was stirred under nitrogen at 80 °C for 8 h. After usual workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was used for next step without purification. To a THF solution (10.0 mL) of crude product was added H_2O_2aq (30%, 2.5 mL, 20.0 mmol) at 0 °C, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and water, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3d** in a pure form (146.8 mg, 45% yield).

3d:[9] white powder, m.p. 111-113 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.49-7.52 (m, 4H), 7.55-7.58 (m, 4H), 7.71 (s, 1H), 7.87-7.91 (m, 4H).

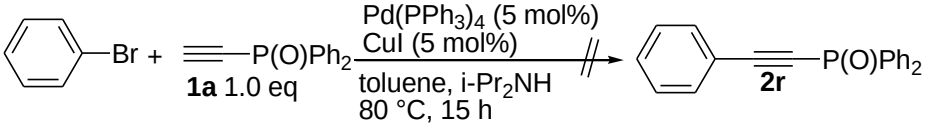
3e:[10] white powder; m.p. 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.24 (s, 1H), 7.48-7.52 (m, 6H), 7.54-7.58 (m, 4H), 7.87-7.91 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 80.42, 82.57, 84.60 (d, *J* = 167.6 Hz), 104.36 (d, *J* = 29.4 Hz), 120.08, 120.13, 124.49, 128.66 (d, *J* = 13.7 Hz), 130.93 (d, *J* = 11.2 Hz), 132.15, 132.35, 132.69 (d, *J* = 121.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.11.

3f:[10] white powder; m.p. 121-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (s, 1H), 7.36 (t, *J* = 7.60 Hz, 1H), 7.41 (t, *J* = 7.65 Hz, 1H), 7.47-7.50 (m, 4H), 7.54-7.56 (m, 3H), 7.60 (d, *J* = 7.65 Hz, 1H), 7.94-7.99 (m, 4H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 81.34, 82.32, 86.36 (d, *J* = 167.8 Hz), 103.13 (d, *J* = 29.8 Hz), 123.07 (d, *J* = 3.7 Hz), 125.77 (d, *J* = 1.5 Hz), 128.52 (d, *J* = 13.6 Hz), 128.68, 130.24, 131.10 (d, *J* = 11.2 Hz), 132.19 (d, *J* = 3.1 Hz), 132.69, 132.85, 132.95 (d, *J* = 122.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.65.

3g: white powder; m.p. 75-76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.44 (s, 1H),

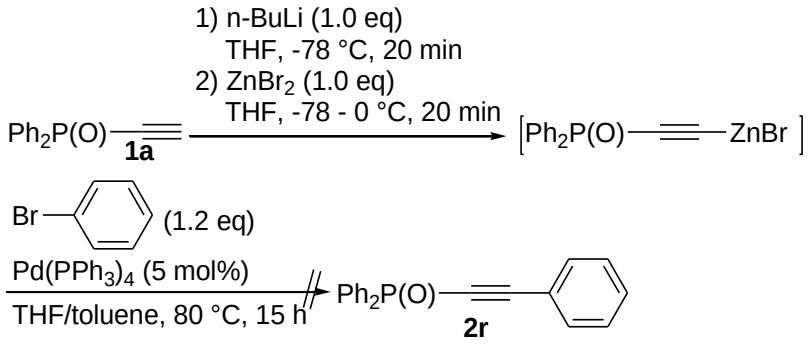
7.17 (d, *J* = 4.0 Hz, 1H), 7.31 (d, *J* = 4.0 Hz, 1H) 7.49-7.53 (m, 4H), 7.56-7.60 (m, 2H), 7.85-7.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.60, 83.72 (d, *J* = 6.2 Hz), 87.58 (d, *J* = 163.2 Hz), 97.34 (d, *J* = 30.0 Hz), 120.80 (d, *J* = 4.6 Hz), 126.67, 128.67 (d, *J* = 13.6 Hz), 130.92 (d, *J* = 11.5 Hz), 132.38 (d, *J* = 2.8 Hz), 132.41 (d, *J* = 122.3 Hz), 132.82, 135.22; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.99; HRMS (FAB) calcd for $C_{20}H_{13}OPS$ ($M+H^+$): 333.0425, found 333.0241.

Sonogashira Coupling Reaction between Bromobenzene and 1a



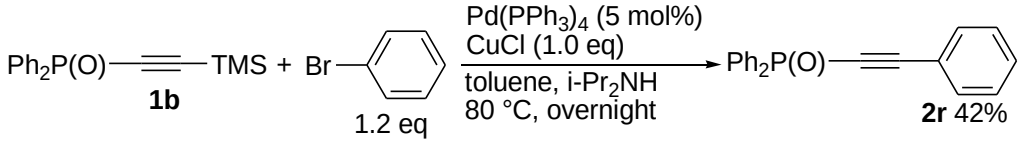
A toluene solution (5.0 mL) of bromobenzene (157.0 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford the desired product **2r** in 0% yield.

Negishi Coupling Reaction between Bromobenzene and 1a



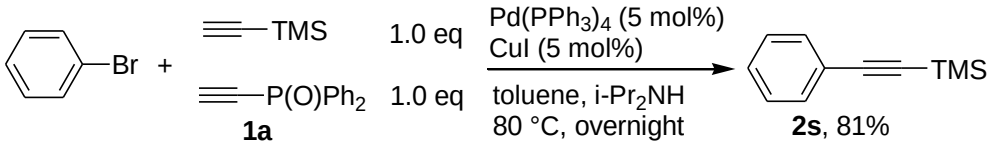
To a THF solution (10 mL) of **1a** (226.2 mg, 1.0 mmol) was added n-BuLi (1.6 M in hexane, 625 μL, 1.0 mmol) at -78 °C, and the mixture was stirred at -78 °C for 20 min, and then $ZnBr_2$ (221.8 mg, 1.0 mmol) was added to the reaction mixture at -78 °C, and the mixture was stirred at 0 °C for 20 min. To the reaction mixture

were added bromobenzene (188.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol) and toluene (10 mL), and the mixture was stirred at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford the desired product **2r** in 0% yield.



A toluene solution (5.0 mL) of bromobenzene (188.4 mg, 1.2 mmol), **1b** (298.4 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuCl (99.0 mg, 1.0 mmol) and diisopropylamine (0.5 mL) was stirred at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford the desired product **2r** (127.0 mg, 42% yield) in a pure form.

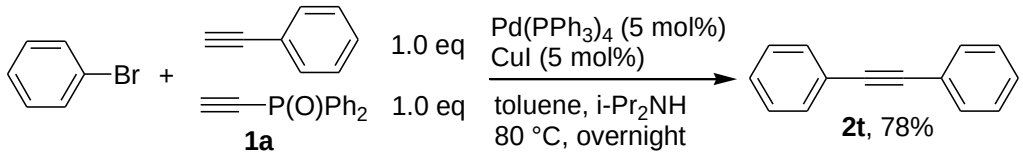
2r:[9] white powder; m.p. 94-96 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H), 7.48-7.52 (m, 4H), 7.56 (t, J = 7.3 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.89-7.93 (m, 4H).



A toluene solution (5.0 mL) of bromobenzene (157.0 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), trimethylsilyacetylene (141.9 μL, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **2s** in a pure form (141.2

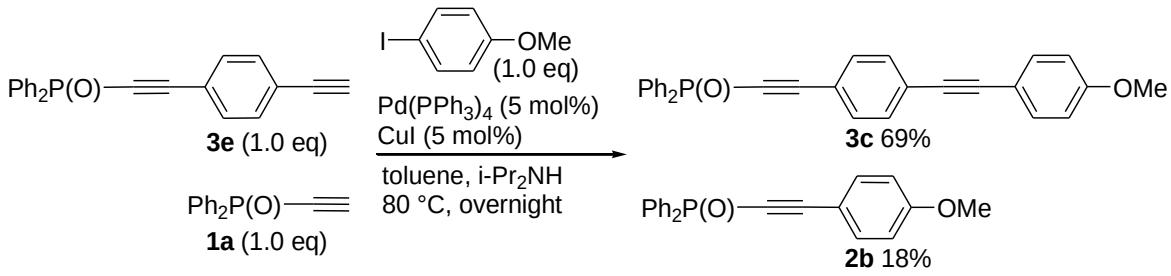
mg, 81% yield).

2s:[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.25 (s, 9H), 7.26-7.31 (m, 3H), 7.45-7.48 (m, 2H).



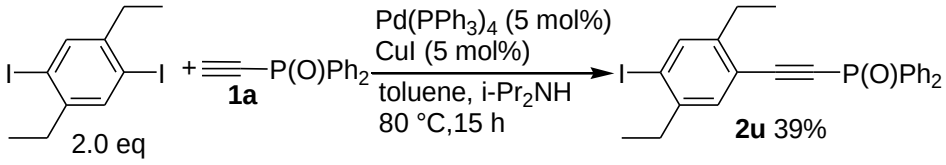
A toluene solution (5.0 mL) of bromobenzene (157.0 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), ethynylbenzene (102.1 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **2t** in a pure form (139.0 mg, 78% yield).

2s: [13] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.37 (m, 6H), 7.52-7.55 (m, 4H).



A toluene solution (5.0 mL) of 1-iodo-4-methoxybenzene (234.0 mg, 1.0 mmol), **1a** (226.2 mg, 1.0 mmol), **3e** (326.3 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1.5:1) to afford **3c** (298.4 mg, 69% yield) and **2b** in pure forms (59.8 mg, 18% yield).

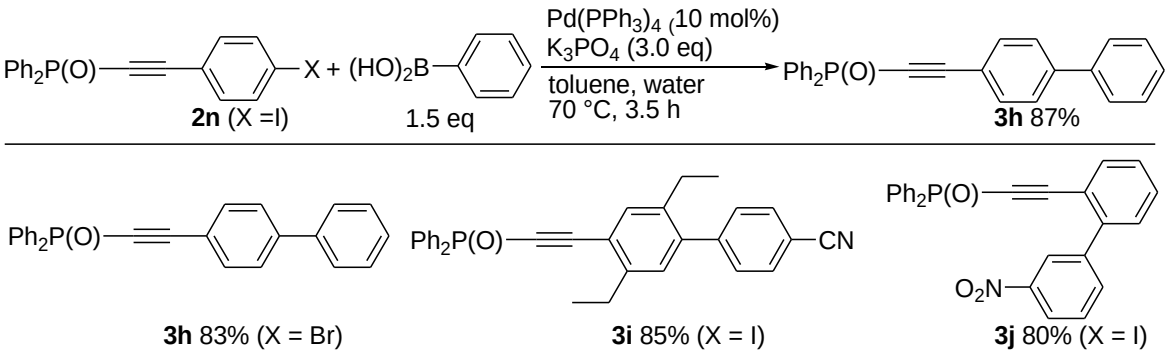
Synthesis of Starting Compound 2u for Suzuki Coupling



A toluene solution (5.0 mL) of 1,4-diethyl-2,5-diiodobenzene (772.0 mg, 2.0 mmol), **1a** (226.2 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2u** in a pure form (188.9 mg, 39% yield).

2u: white powder, m.p. 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.21 (m, 6H), 2.64-2.75 (m, 4H), 7.37 (s, 1H), 7.47-7.57 (m, 6H), 7.72 (s, 1H), 7.86-7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.20 (d, *J* = 5.0 Hz), 14.77 (d, *J* = 4.4 Hz), 26.75, 33.33, 86.92 (d, *J* = 168.5 Hz), 103.75 (d, *J* = 29.8 Hz), 104.14, 119.21 (d, *J* = 4.1 Hz), 128.54 (d, *J* = 13.6 Hz), 130.77 (d, *J* = 11.2 Hz), 132.16 (d, *J* = 3.2 Hz), 132.89 (d, *J* = 121.9 Hz), 139.08, 139.11, 146.41, 146.44; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.45; HRMS (FAB) calcd for $C_{24}H_{22}IOP$ ($M+H^+$): 485.0453, found 485.1412.

Synthesis of 3h, 3i, and 3j by Suzuki Coupling (representative procedure for 3h):



A toluene solution (10.0 mL) of **2n** (428.2 mg, 1.0 mmol), phenylboronic acid

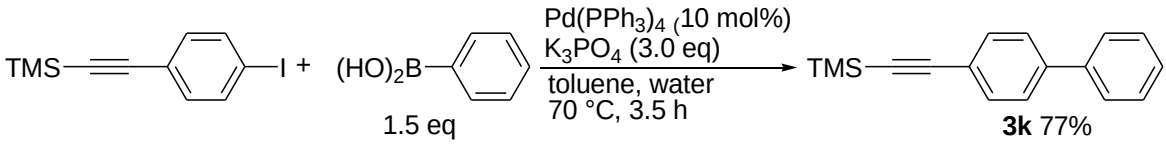
(182.9 mg, 1.5 mmol), $Pd(PPh_3)_4$ (115.6 mg, 0.10 mmol), K_3PO_4 (636.8 mg, 3.0 mmol) and H_2O (0.05 mL) was stirred under nitrogen at 70 °C for 3.5 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3h** in a pure form (329.2 mg, 87% yield).

3h: white powder, m.p. 151-152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.3 Hz, 1H), 7.45-7.52 (m, 6H), 7.56-7.62 (m, 6H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.90-7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.37 (d, *J* = 169.8 Hz), 105.37 (d, *J* = 30.10 Hz), 118.52 (d, *J* = 4.1 Hz), 127.01, 127.12, 128.09, 128.59 (d, *J* = 13.7 Hz), 128.88, 130.89 (d, *J* = 10.9 Hz), 132.16, 132.91 (d, *J* = 1.6 Hz), 132.98 (d, *J* = 119.1 Hz), 139.60, 143.38; HRMS (FAB) calcd for $C_{26}H_{19}OP$ ($M+H^+$): 379.1174, found 379.3200.

3i: white powder, m.p. 155-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, *J* = 7.5 Hz, 3H), 1.21 (t, *J* = 7.6 Hz, 3H), 2.51 (q, *J* = 7.5 Hz, 2H), 2.81 (q, *J* = 7.5 Hz, 2H), 7.04 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.48-7.58 (m, 7H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.89-7.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.98 (d, *J* = 4.3 Hz), 15.25 (d, *J* = 4.1 Hz), 25.37, 27.25, 86.59 (d, *J* = 169.1 Hz), 104.17 (d, *J* = 29.8 Hz), 111.22, 118.65, 119.16 (d, *J* = 4.0 Hz), 128.60 (d, *J* = 13.6 Hz), 129.44, 129.66, 130.87 (d, *J* = 11.5 Hz), 131.99, 132.20 (d, *J* = 2.5 Hz), 133.08 (d, *J* = 121.9 Hz), 133.60, 139.08, 142.24, 145.32, 145.67; HRMS (FAB) calcd for $C_{31}H_{26}NOP$ ($M+H^+$): 460.1752, found 460.3889.

3j: white powder, m.p. 141-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.48 (m, 7H), 7.52 (t, *J* = 7.0 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.62-7.66 (m, 4H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.52 (d, *J* = 166.3 Hz), 103.72 (d, *J* = 28.9 Hz), 118.7 (d, *J* = 3.8 Hz), 122.64, 123.93 (d, *J* = 5.3 Hz), 128.55 (d, *J* = 13.4 Hz), 129.20,

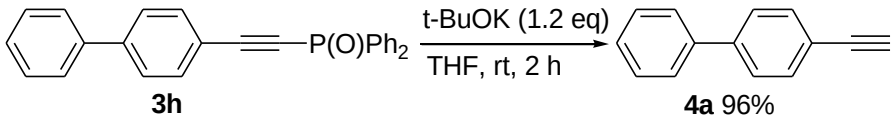
129.45, 130.70 (d, *J* = 11.2 Hz), 131.09, 132.25 (d, *J* = 2.5 Hz), 132.40 (d, *J* = 121.9 Hz), 134.27, 135.24, 141.12, 142.72, 147.92; HRMS (FAB) calcd for $C_{26}H_{18}NO_3P$ ($M+H^+$): 424.1024, found 424.2095.



A toluene solution (10.0 mL) of ((4-iodophenyl)ethynyl)trimethylsilane (300.2 mg, 1.0 mmol), phenylboronic acid (182.9 mg, 1.5 mmol), $Pd(PPh_3)_4$ (115.6 mg, 0.10 mmol), K_3PO_4 (636.8 mg, 3.0 mmol) and H_2O (0.5 mL) was stirred under nitrogen at 70 °C for 3.5 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3k** in a pure form (192.8 mg, 77% yield).

3k:[14] white powder; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.52-7.60 (m, 6H);

Synthesis of 4a

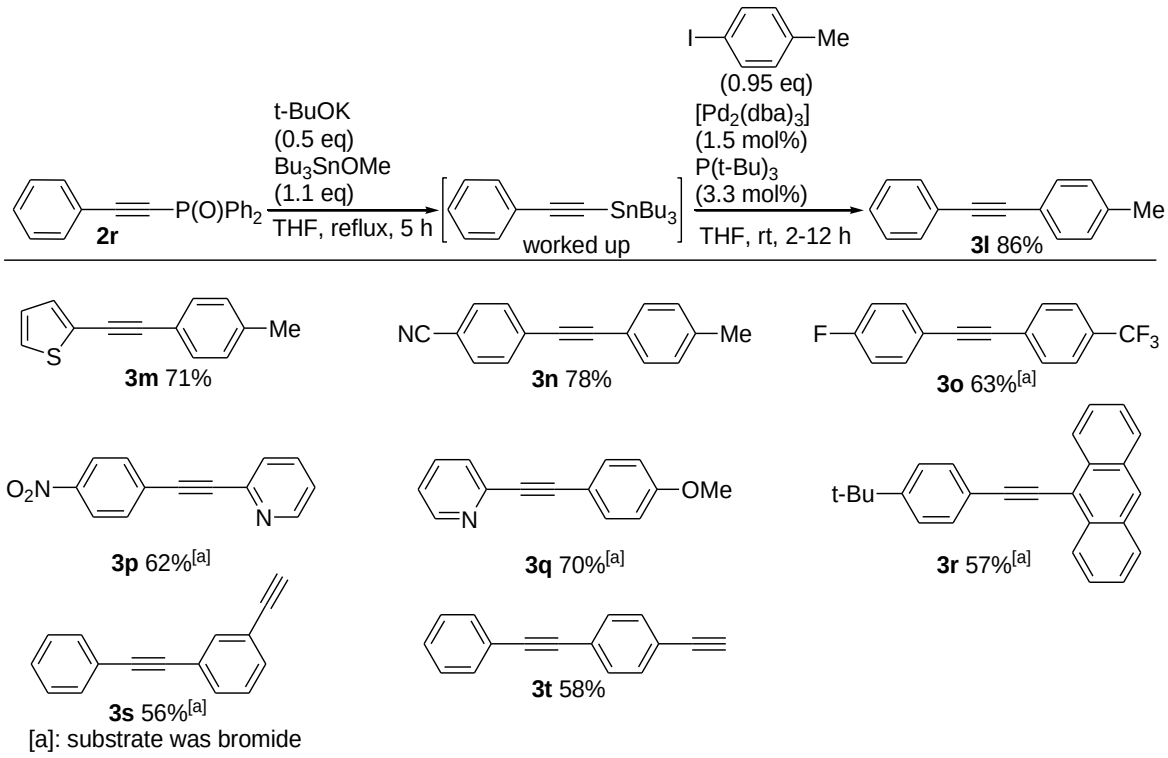


To a THF solution (10 mL) of **3h** (189.2 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6 mmol) at rt, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **4a** in a pure form (85.6 mg, 96%).

4a:[14] white powder; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.13 (s, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.56-7.61 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.71, 83.53, 120.94, 126.98, 127.03, 127.71, 128.85, 132.53, 140.22, 141.55.

Synthesis of 3l, 3m, 3n, 3o, 3p, 3q, 3r, 3s and 3t by Migata-Kosugi-Stille

coupling (representative procedure for 3g):



To a THF solution (5.0 mL) of **2r** (302.3 mg, 1.0 mmol) were added Bu_3SnOMe (353.2 mg, 316.8 μL, 1.1 mmol) and t-BuOK (56.1 mg, 0.5 mmol). The mixture was stirred for 5 h under nitrogen at refluxing temperature, and then quenched with H_2O (10.0 mL). The mixture was extracted with diethyl ether (3 × 10.0 mL). The collected organic layers were dried ($MgSO_4$). The solvent was evaporated to give a crude product, which was used in the Migata-Kosugi-Stille coupling without purification. To a THF solution (5.0 mL) of the crude product was added 1-iodo-4-methylbenzene (207.1 mg, 0.95 mmol), $P(t\text{-}Bu)_3$ (0.1 M in THF, 330.0 μL, 0.033 mmol) and $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol) sequentially. The mixture was stirred under nitrogen at rt for 4 h, and then quenched with NH_4Faq (10%, 10.0 mL). The mixture was extracted with diethyl ether (3 × 10.0 mL). The collected organic layers were dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **3l** in a pure form (165.3 mg, 96% yield, based on iodide).

3l:[15] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.30-7.36 (m, 3H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.52-7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.49, 88.68, 89.52, 120.10, 123.39, 128.05, 128.29, 129.09, 131.45, 131.50, 138.35.

3m:[16] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.01 (t, *J* = 3.7 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.26-7.28 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.51, 81.89, 93.17, 119.75, 123.48, 126.98, 127.03, 129.11, 131.26, 131.61, 138.57.

3n:[17] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.58-7.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.57, 87.17, 94.07, 111.15, 118.58, 119.06, 128.42, 129.25, 131.65, 131.94, 131.98, 139.43.

3o:[18] white powder; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04-7.10 (m, 2H), 7.51-7.56 (m, 2H), 7.62 (bs, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -110.41, -63.28; ^{13}C NMR (75 MHz, $CDCl_3$): δ 87.65, 90.63, 115.79 (d, *J* = 22.3 Hz), 118.64 (d, *J* = 3.4 Hz), 123.91 (q, *J* = 272.0 Hz), 125.29 (q, *J* = 3.8 Hz), 126.91, 129.95 (d, *J* = 32.5 Hz), 131.73, 133.63 (d, *J* = 8.4 Hz), 162.79 (d, *J* = 250.1 Hz).

3p:[19] white powder; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.35 (m, 1H), 7.59 (dt, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.72-7.78 (m, 3H), 8.25 (d, *J* = 9.0 Hz, 2H), 8.66-8.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.66, 93.10, 123.56, 123.59, 127.48, 129.05, 132.71, 136.31, 142.35, 147.41, 150.28.

3q:[20] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.20-7.23 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.67 (dt, *J* = 1.8 Hz, 7.6 Hz, 1H), 8.61 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR (125.65 MHz, $CDCl_3$): δ 55.29 (d, *J* = 4.1 Hz), 87.54, 89.45, 114.02 (d, *J* = 7.3 Hz), 114.23, 122.38, 126.86, 133.58 (d, *J* = 3.6 Hz), 136.09, 143.71, 149.99, 160.10.

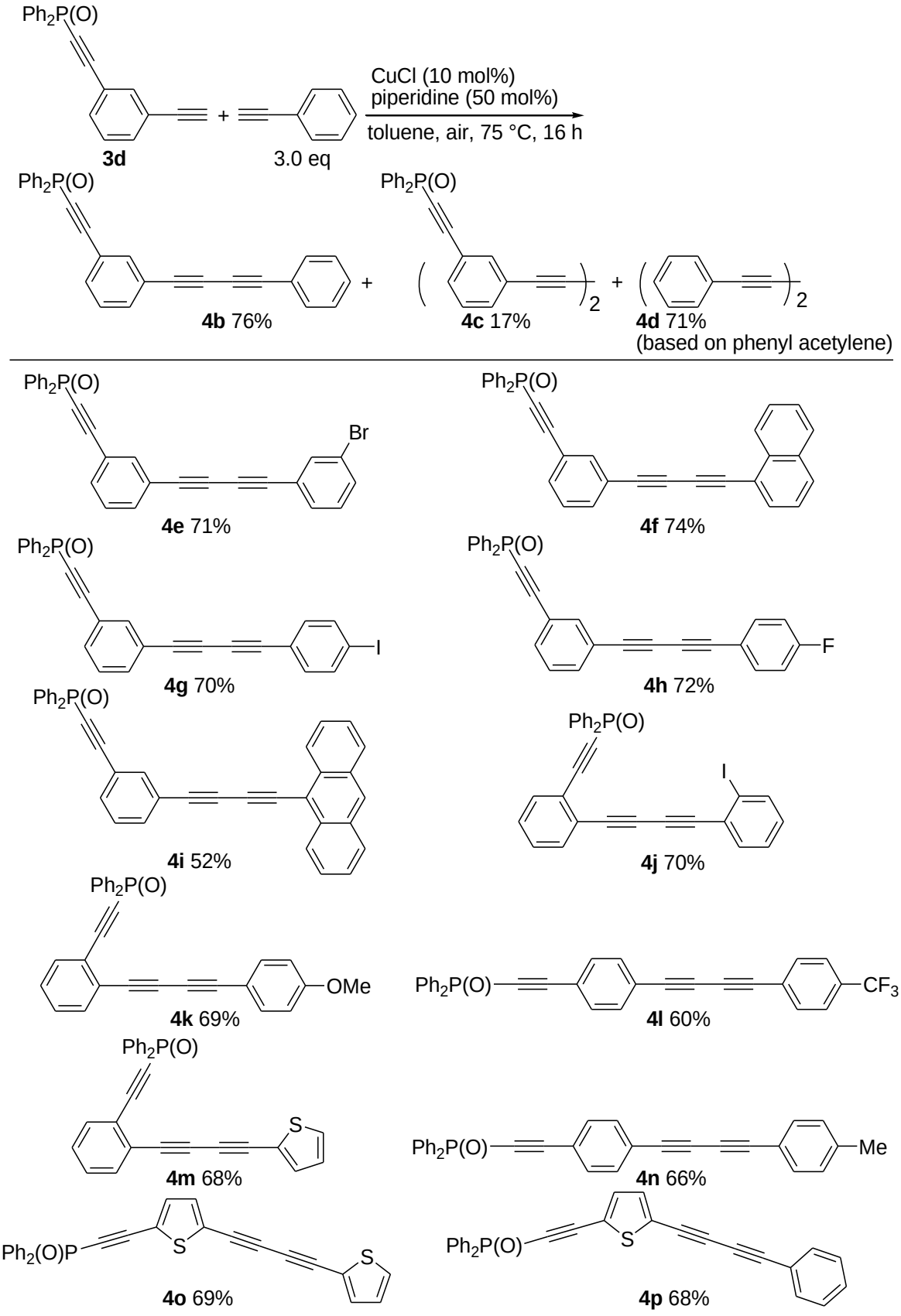
3r:[21] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 9H), 7.48 (d, *J* = 8.6

Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.60 (dt, *J* = 1.2 Hz, 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.6 Hz, 2H), 8.43 (s, 1H), 8.66 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 31.27, 34.90, 85.66, 100.95, 117.56, 120.60, 125.55, 125.66, 126.52, 126.83, 127.46, 128.68, 131.20, 131.42, 132.56, 151.85.

3s:[22] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.35-7.36 (m, 3H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.50-7.54 (m, 3H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.82, 82.73, 88.27, 90.04, 122.39, 122.84, 123.58, 128.36, 128.41, 128.48, 131.61, 131.75, 131.81, 135.05.

3t:[22] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (s, 1H), 7.35-7.36 (m, 3H), 7.46-7.50 (m, 4H), 7.52-7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.86, 83.24, 88.79, 91.33, 121.79, 122.85, 123.71, 128.38, 128.52, 131.44, 131.60, 132.04.

Synthesis of 4b, 4e, 4f, 4g, 4h, 4i, 4j, 4k,4l, 4m, 4n, 4o, and 4p by Hey coupling (representative procedure for 4b):



A mixture of **3d** (326.3 mg, 1.0 mmol), ethynylbenzene (329.5 μL, 3.0 mmol),

CuCl (9.9 mg, 0.1 mmol), piperidine (50.0 μL, 0.5 mmol) and toluene (10 mL) in an atmosphere of air was stirred at 75 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt) to afford **4b** in a pure form (319.8 mg, 75% yield), **4c** in a pure form (55.3 mg, 17%) and **4d** in a pure form (215.4 mg, 71% (based on **20**)).

4b:[10] pale-yellow powder; m.p. 166-167 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.41 (m, 4H), 7.49-7.54 (m, 6H), 7.56-7.59 (m, 4H), 7.74 (s, 1H), 7.87-7.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 73.44, 75.32, 79.58, 82.40, 83.83 (d, *J* = 167.0 Hz), 103.74 (d, *J* = 29.4 Hz), 120.53 (d, *J* = 4.1 Hz), 121.37, 122.70, 128.43 (d, *J* = 5.2 Hz), 128.69 (d, *J* = 13.4 Hz), 128.86 (d, *J* = 8.8 Hz), 129.45 (d, *J* = 3.1 Hz), 130.93 (d, *J* = 11.3 Hz), 132.35, 132.53, 132.71 (d, *J* = 121.9 Hz), 132.82, 134.33, 136.06; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.36.

4c:[10] pale-yellow powder; m.p. 198-201 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.8 Hz, 2H), 7.48-7.61 (m, 16H), 7.75 (s, 2H), 7.86-7.94 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.82, 80.40, 83.94 (d, *J* = 166.0 Hz), 103.57 (d, *J* = 29.2 Hz), 120.59 (d, *J* = 4.0 Hz), 122.32, 128.68 (d, *J* = 13.4 Hz), 128.90, 130.91 (d, *J* = 11.5 Hz), 132.35 (d, *J* = 2.8 Hz), 132.65 (d, *J* = 122.2 Hz), 133.05, 134.36, 136.11; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.90.

4d:[23] white powder; m.p. 83-84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.39 (m, 6H), 7.52-7.54 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 73.87, 81.52, 121.76, 128.43, 129.19, 132.48.

4e: 76% yield, white powder, m.p. 105-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.49-7.53 (m, 5H), 7.56-7.60 (m, 4H), 7.67 (s, 1H), 7.74 (s, 1H), 7.88-7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.69, 74.91, 80.36, 80.52, 83.94 (d, *J* = 166.0 Hz),

103.62 (d, *J* = 29.1 Hz), 120.62 (d, *J* = 4.0 Hz), 122.22, 122.41, 123.45, 128.70 (d, *J* = 13.6 Hz), 128.91, 129.89, 130.95 (d, *J* = 11.5 Hz), 131.07, 132.36 (d, *J* = 3.1 Hz), 132.62, 132.70 (d, *J* = 122.2 Hz), 133.04 (d, *J* = 1.8 Hz), 134.38, 135.10, 136.12 (d, *J* = 1.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.38; HRMS (FAB) calcd for $C_{30}H_{18}BrOP$ ($M+H^+$): 505.0279, found 505.2509.

4f: 76% yield, white powder, m.p. 92-93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.51-7.54 (m, 4H), 7.55-7.64 (m, 6H), 7.79-7.80 (m, 2H), 7.87-7.93 (m, 6H) , 8.35 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.47, 78.02, 80.62, 80.78, 83.81 (d, *J* = 166.3 Hz), 103.72 (d, *J* = 29.5 Hz), 118.97, 120.50 (d, *J* = 4.0 Hz), 122.67, 125.11, 125.87, 126.67, 127.24, 128.41, 128.66 (d, *J* = 13.6 Hz), 128.86, 129.96, 130.89 (d, *J* = 11.2 Hz), 132.14, 132.32 (d, *J* = 2.8 Hz), 132.66 (d, *J* = 122.2 Hz), 132.79 (d, *J* = 1.9 Hz), 132.97, 133.78, 134.29, 136.01; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.20; HRMS (FAB) calcd for $C_{34}H_{21}OP$ ($M+H^+$): 477.1330, found 477.2258.

4g: 76% yield, white powder, m.p. 180-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.49-7.53 (m, 4H), 7.56-7.60 (m, 4H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.74 (s, 1H), 7.87-7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.83, 75.08, 80.32, 81.33, 83.91 (d, *J* = 166.3 Hz), 95.82, 103.65 (d, *J* = 29.2 Hz), 120.61 (d, *J* = 4.1 Hz), 120.90, 122.51, 128.70 (d, *J* = 13.6 Hz), 128.91, 130.95 (d, *J* = 11.2 Hz), 132.37 (d, *J* = 2.8 Hz), 132.69 (d, *J* = 122.3 Hz), 132.99, 133.83, 134.34, 136.09, 137.69; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.26; HRMS (FAB) calcd for $C_{30}H_{18}IOP$ ($M+H^+$): 553.014, found 553.3327.

4h: 76% yield, white powder, m.p. 154-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (t, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.49-7.54 (m, 6H), 7.56-7.59 (m, 4H), 7.74 (s, 1H), 7.87-7.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.25, 75.14, 79.57, 81.26, 83.86 (d, J_{C-P} = 166.3 Hz), 103.67 (d, J_{C-P} = 29.4 Hz), 115.90 (d, J_{C-F} = 22.4 Hz), 117.49 (d, J_{C-F} = 3.8 Hz), 120.54 (d, J_{C-P} = 4.0 Hz), 122.57, 128.67 (d,

J_{C-P} = 13.3 Hz), 128.86, 130.92 (d, J_{C-P} = 11.2 Hz), 132.33 (d, J_{C-P}= 3.1 Hz), 132.69 (d, J_{C-P} = 122.6 Hz), 132.86, 134.30, 134.58 (d, J_{C-F} = 8.7 Hz), 136.03, 163.10 (d, J_{C-F} = 251.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ -108.53; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.05; HRMS (FAB) calcd for $C_{30}H_{18}FOP$ ($M+H^+$): 445.1079, found 445.1496.

4i: 76% yield, white powder, m.p. 94-95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.50-7.54 (m, 6H), 7.56-7.64 (m, 5H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.84 (s, 1H), 7.90-7.94 (m, 4H), 8.03 (d, *J* = 8.2 Hz, 2H), 8.48 (s, 1H), 8.56 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.78, 79.78, 82.44, 83.89 (d, *J* = 166.3 Hz), 84.22, 103.79 (d, *J* = 29.5 Hz), 115.16, 120.64 (d, *J* = 4.0 Hz), 122.87, 125.91, 126.43, 127.36, 128.73 (d, *J* = 13.4 Hz), 128.90, 128.96, 129.19 (d, *J* = 3.5 Hz) , 130.92 (d, *J* = 11.2 Hz), 131.01, 132.38 (d, *J* = 2.8 Hz), 132.76 (d, *J* = 122.3 Hz), 132.88 (d, *J* = 2.2 Hz), 134.11, 134.30, 136.05; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.50; HRMS (FAB) calcd for $C_{38}H_{23}OP$ ($M+H^+$): 527.1487, found 527.4655.

4j: [10] yellow powder; m.p. 129-131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (dt, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H) 7.32 (t, *J* = 7.6 Hz, 1H), 7.36-7.41 (m, 1H), 7.42-7.44 (m, 2H), 7.48-7.50 (m, 6H), 7.60-7.62 (m, 2H), 7.85 (d, *J* = 7.9 Hz 1H), 8.00-8.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 76.91, 78.48, 80.67, 84.57, 86.90 (d, *J* = 166.5 Hz), 100.81, 102.60 (d, *J* = 29.4 Hz), 123.57 (d, *J* = 4.1 Hz), 125.25 (d, *J* = 2.1 Hz), 127.86, 128.17, 128.71 (d, *J* = 12.4 Hz), 129.16, 130.27, 130.45, 130.52, 131.05 (d, *J* = 11.4 Hz), 132.14, 132.80 (d, *J* = 122.0 Hz), 133.05 (d, *J* = 6.6 Hz), 133.94, 138.88; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.60.

4k: 70% yield, white powder, m.p. 204-205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.40-7.43 (m, 3H), 7.48-7.49 (m, 6H), 7.56-7.61 (m, 2H), 8.00-8.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.36 (d, *J* = 4.6 Hz), 72.70, 78.69, 79.21, 83.82, 86.72 (d, *J* = 167.0 Hz), 102.86 (d, *J* = 29.5 Hz), 113.23, 114.21, 114.30, 123.49 (d, *J* = 4.1 Hz),

125.78 (d, *J* = 2.0 Hz), 128.68 (d, *J* = 12.9 Hz), 130.21 (d, *J* = 2.6 Hz), 131.08 (d, *J* = 11.3 Hz), 132.10, 132.97(d, *J* = 12.8 Hz), 132.98 (d, *J* = 122.0 Hz), 134.15, 134,21, 160.63; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.41; HRMS (FAB) calcd for $C_{31}H_{21}O_2P$ ($M+H^+$): 457.1279, found 457.1753.

4l:[10] white powder; m.p. 253-255 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.54 (m, 6H), 7.56-7.59 (m, 4H), 7.60-7.64 (m, 4H), 7.87-7.91 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 75.70, 76.42, 81.38, 81.44, 85.38 (d, J_{C-P} = 166.4 Hz), 104.12 (d, J_{C-P} = 29.4 Hz), 120.74, 120.77, 123.64 (q, J_{C-F} = 272.0 Hz), 123.75, 125.24 (d, J_{C-F} = 1.5 Hz), 125.42 (d, J_{C-F}= 3.1 Hz), 128.71 (d, J_{C-P} = 13.4 Hz), 130.95 (d, J_{C-P} = 10.8 Hz), 130.98 (q, J_{C-F} = 32.5 Hz), 132.38, 132.52 (d, J_{C-P} = 8.9 Hz) , 132.63 (d, J_{C-P} = 122.0 Hz), 132.75; ^{19}F NMR (121 MHz, $CDCl_3$): δ -94.03; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.51.

4m: 68% yield, white powder, m.p. 169-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (t, *J* = 4.4 Hz, 1H), 7.34 (d, *J* = 3.4 Hz, 1H), 7.36-7.39 (m, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.51-7.52 (m, 6H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.98-8.03 (m, 4H); ^{13}C NMR (125MHz, $CDCl_3$): δ 76.49, 77.80, 78.56, 81.24, 86.95 (d, *J* = 166.4 Hz), 102.64 (d, *J* = 28.9 Hz), 121.60, 123.54 (d, *J* = 4.1 Hz), 125.38 (d, *J* = 2.0 Hz), 127.31 (d, *J* = 11.9 Hz), 128.70 (d, *J* = 11.8 Hz), 129.04 (d, *J* = 5.6 Hz), 129.22 (d, *J* = 11.3 Hz), 130.25 (d, *J* = 5.6 Hz), 131.07 (d, *J* = 11.3 Hz), 132.16, 132.89 (d, *J* = 121.9 Hz), 133.03 (d, *J* = 12.9 Hz), 134.65, 134,74; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.08; HRMS (FAB) calcd for $C_{28}H_{17}OPS$ ($M+H^+$): 433.0738, found 433.1571.

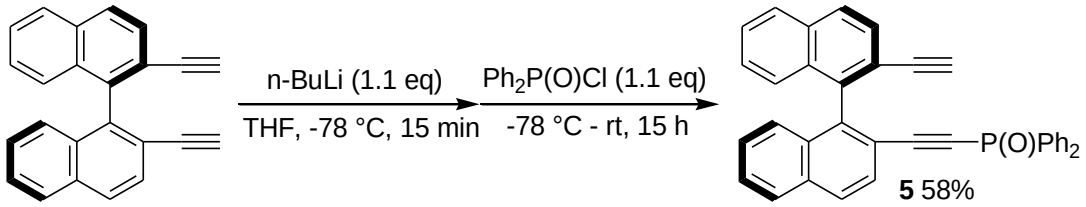
4n: 66% yield, white powder, m.p. 265-266 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.49-7.52 (m, 6H), 7.55-7.58 (m, 4H), 7.87-7.91 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.64 (d, *J* = 7.8 Hz), 72.94, 77.30, 79.99, 83.72, 85.16 (d, *J* = 166.4 Hz), 104.41 (d, *J* = 28.9 Hz), 118.26, 120.27 (d, *J* = 4.1 Hz), 124.46, 128.70 (d, *J* = 13.9 Hz), 129.23,

129.31, 130.97 (d, *J* = 11.3 Hz), 132.35, 132.45, 132.52, 132.79 (d, *J* = 121.9 Hz), 144.00; ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.21; HRMS (FAB) calcd for $C_{31}H_{21}OP$ ($M+H^+$): 441.1330, found 441.3852.

4o: 62% yield, white powder, m.p. 136-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01-7.03 (m, 1H), 7.22 (d, *J* = 3.7 Hz, 1H), 7.32 (d, *J* = 3.6 Hz, 1H), 7.36-7.38 (m, 2H), 7.49-7.53 (m, 4H), 7.56-7.59 (m, 2H), 7.85-7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 75.10, 77.34, 78.22, 80.02, 88.15 (d, *J* = 163.8 Hz), 97.08 (d, *J* = 30.0 Hz), 121.31, 121.79 (d, *J* = 4.6 Hz), 126.54, 127.30 (d, *J* = 8.8 Hz), 128.72 (d, *J* = 13.9 Hz), 129.49 (d, *J* = 8.3 Hz), 130.98 (d, *J* = 11.4 Hz), 132.38 (d, *J* = 122.5 Hz), 132.44, 133.91 (d, *J* = 9.8 Hz), 134.93 (d, *J* = 8.3 Hz), 135.44 (d, *J* = 10.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.19; HRMS (FAB) calcd for $C_{26}H_{15}OPS_2$ ($M+H^+$): 439.0302, found 439.0049.

4p: white powder; m.p. 141-144 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 4.0 Hz, 1H), 7.32-7.37 (m, 3H), 7.39-7.40 (m, 1H), 7.39-7.54 (m, 6H), 7.56-7.60 (m, 2H), 7.85-7.89 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 73.01, 73.29, 80.26, 85.17, 88.04 (d, *J* = 164.4 Hz), 97.27 (d, *J* = 29.4 Hz), 121.11, 121.62 (d, *J* = 4.1 Hz), 126.74, 128.51, 128.73 (d, *J* = 13.4 Hz), 129.69, 131.00 (d, *J* = 11.3 Hz), 132.28, 132.40 (d, *J* = 122.5 Hz), 132.50 (d, *J* = 12.4 Hz), 133.85 (d, *J* = 10.3 Hz), 135.44 (d, *J* = 12.4 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.12; HRMS (FAB) calcd for $C_{28}H_{17}OPS$ ($M+H^+$): 433.0738, found 433.1170.

Preparation of binaphthyl Derivatives 10, 11 and 12

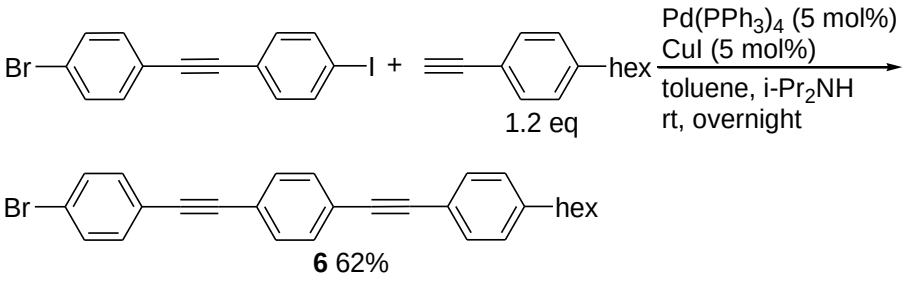


5 58%

To A THF solution (5.0 mL) of (R)-2,2'-diethynyl-1,1'-binaphthyl (302.4 mg, 1.0 mmol) was added BuLi (1.6 M in hexane, 687.5 μL, 1.1 mmol) at -78 °C. After stirred for 15 min at -78 °C, $Ph_2P(O)Cl$ (209.9 μL, 1.1 mmol) was added at -78 °C,

and then the reaction mixture was stirred for 12 h at rt. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **5** in a pure form (291.5 mg, 58% yield).

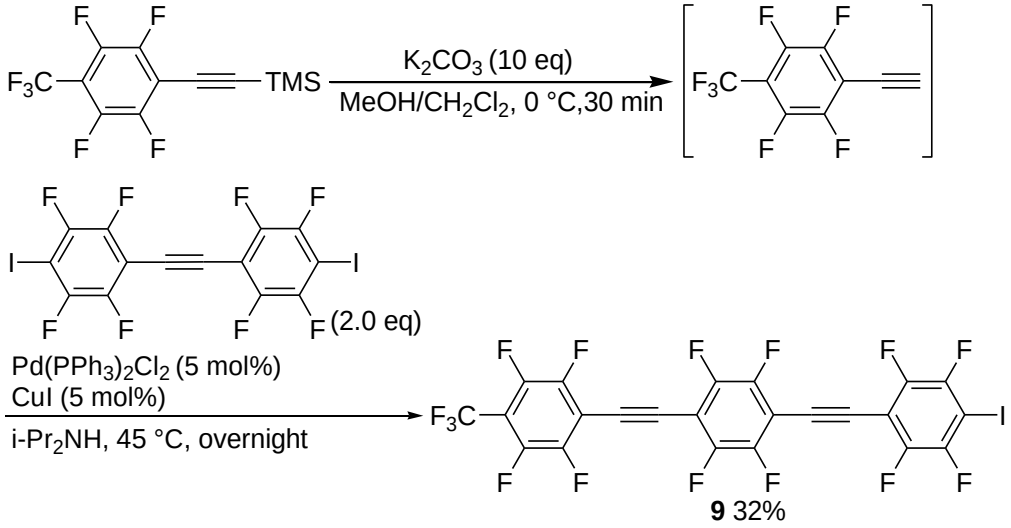
5:[9] white powder; ^1H NMR (500 MHz, $CDCl_3$): δ 2.81 (s, 1H), 7.04-7.08 (m, 2H), 7.11-7.16 (m, 3H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.32-7.36 (m, 5H), 7.38-7.45 (m, 3H), 7.53-7.55 (m, 2H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.90-7.98 (m, 4H).



A toluene solution (5.0 mL) of 1-bromo-4-((4-iodophenyl)ethynyl)benzene (383.0 mg, 1.0 mmol), 1-ethynyl-4-hexylbenzene (223.6 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **6** in a pure form (273.7 mg, 62% yield).

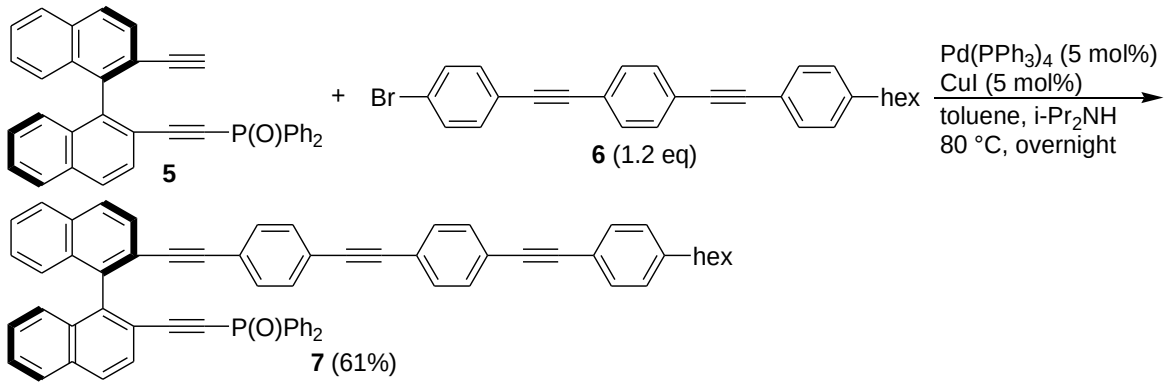
6: white powder; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.30-1.31 (m, 6H), 1.55-1.63 (m, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.48-7.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.08, 22.58, 28.90, 31.19, 31.68, 35.93, 88.39, 90.00, 90.27, 91.70, 120.04, 122.02, 122.43, 122.67, 123.63, 128.48, 128.55, 131.48, 131.55, 131.66, 133.01, 143.76; HRMS (FAB) calcd for $C_{28}H_{25}Br$ (M^+): 440.1140,

found 440.2717.



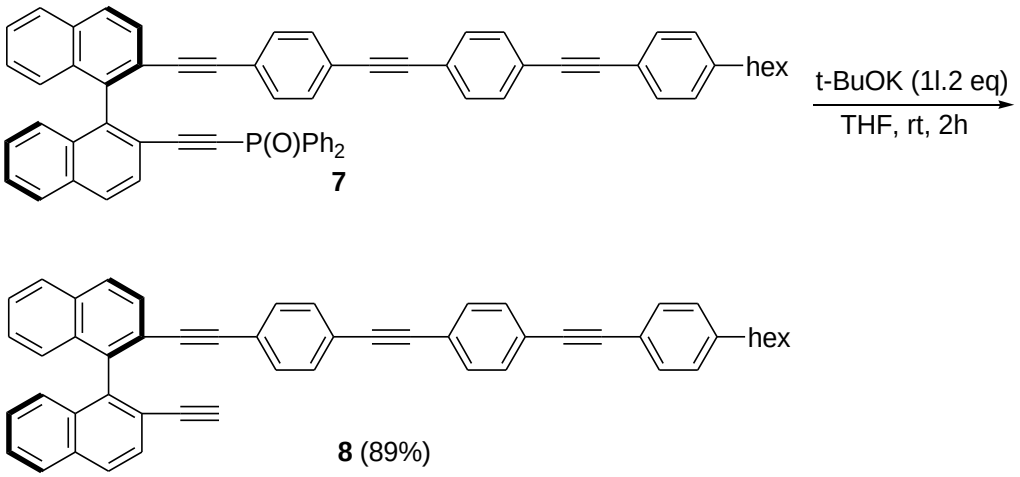
To a flask was added trimethyl((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)ethynyl)silane (314.3 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), THF (5.0 mL) and methanol (5.0 mL), and the reaction mixture was stirred at 0 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was used for next step without purification. A i-Pr_2NH solution (20.0 mL) of crude product, 1,2-bis-(2,3,5,6-tetrafluoro-4-iodophenyl)ethyne (1147.9 mg, 2.0 mmol), $Pd(PPh_3)_2$- Cl_2 (35.0 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) was stirred under nitrogen at 45 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to recrystallization (hexane/CH_2Cl_2) to afford **9** in a pure form (220.2 mg, 32% yield).

9: white powder; ^{19}F NMR (282.6 MHz, $CDCl_3$): δ -140.09- -139.98 (m, 2F), -134.83- -134.69 (m, 4F), -133.70- -133.62 (m, 2F), -133.10- -133.07 (m, 2F), -119.44- -119.36 (m, 2F), -56.92- -56.77 (m, 3F),



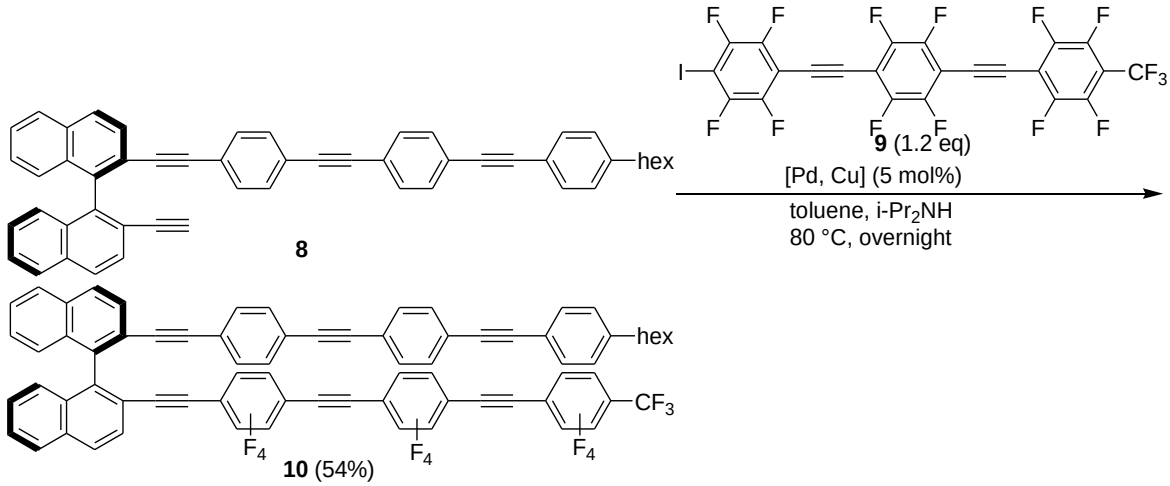
A toluene solution (10.0 mL) of **5** (502.5 mg, 1.0 mmol), 1-bromo-4-((4-iodophenyl)ethynyl)benzene (529.7 mg, 1.2mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **7** in a pure form (526.4 mg, 61% yield).

7: white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.29-1.31 (m, 6H), 1.59-1.62 (m, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 7.08-7.17 (m, 6H), 7.24-7.28 (m, 7H), 7.34-7.49 (m, 11H), 7.53-7.57 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.95-8.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.07, 22.56, 28.88, 31.17, 31.66, 35.90, 85.53 (d, *J* = 171.6 Hz), 88.41, 90.65, 90.75, 91.02, 91.68, 93.94, 104.40 (d, *J* = 30.5 Hz), 118.56 (d, *J* = 4.1 Hz), 120.03, 121.66, 122.49, 122.69, 122.74, 123.53, 126.32, 126.69, 126.94, 127.32, 127.78, 128.13, 128.16 (d, *J* = 12.9Hz), 128.27-128.32 (m), 128.46, 128.50, 128.52, 130.35, 130.48, 130.54, 131.16 (d, *J* = 11.8 Hz), 131.26, 131.45 (d, *J* = 2.6 Hz), 131.53, 131.71 (d, *J* = 4.1 Hz), 132.22, 132.43, 132.63, 132.80 (d, *J* = 122.0 Hz), 132.96, 133.59, 133.92, 139.16, 142.27 (d, *J* = 2.0 Hz), 143.72; HRMS (FAB) calcd for $C_{64}H_{47}OP$ ($M+H^+$): 863.3365, found 863.6748.



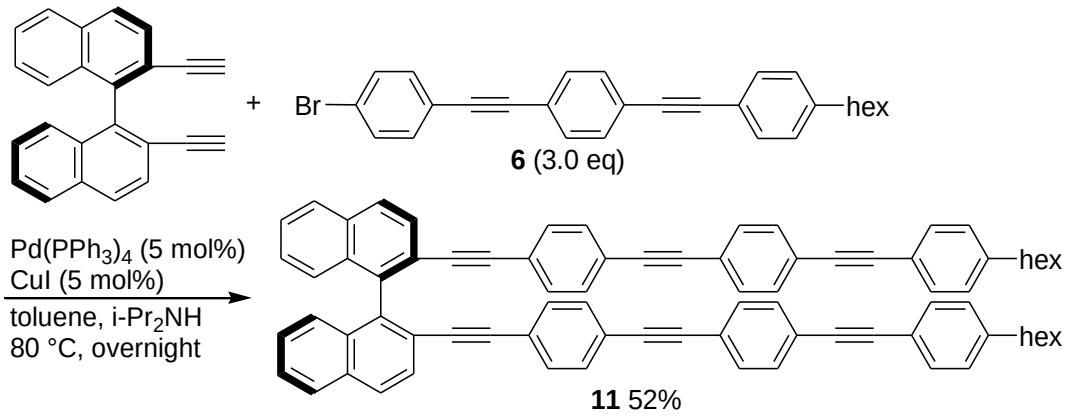
To a THF solution (10 mL) of **7** (431.5 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6mmol) at rt, and the mixture was stirred at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 6:1) to afford **8** in a pure form (295.0 mg, 89%).

8: white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.26-1.30 (m, 6H), 1.58-1.62 (m, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.79 (s, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.27-7.33 (m, 5H), 7.43-7.50 (m, 8H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.93-7.98 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 80.68 (d, *J* = 8.8 Hz), 82.80, 88.44, 90.84, 90.88, 91.20, 91.65, 93.23, 120.06, 120.54, 121.28, 122.44, 122.58, 123.13, 123.49, 126.35, 126.55, 126.60, 126.77, 126.82, 127.99, 128.05, 128.08, 128.17, 128.47, 128.55, 128.90, 131.14, 131.22, 131.44, 131.45, 131.49, 131.55, 132.45, 132.48, 133.01, 133.14, 140.07, 140.72, 143.73; HRMS (FAB) calcd for $C_{52}H_{38}$ (M^+): 662.2974, found 662.6219.



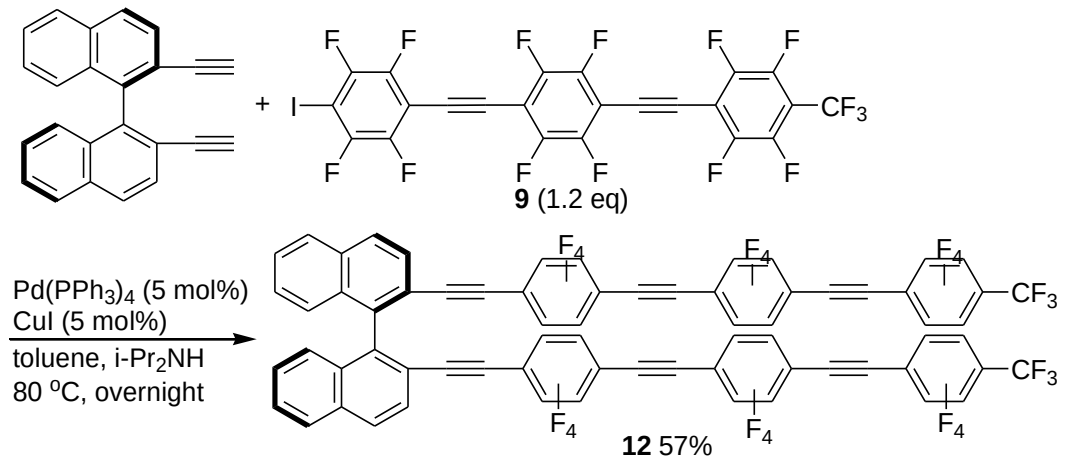
A toluene solution (10.0 mL) of **8** (662.8 mg, 1.0 mmol), **9** (825.8 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to recrystallization (hexane/CH_2Cl_2) to afford **10** in a pure form (691.3 mg, 54% yield).

10: white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.30-1.32 (m, 6H), 1.58-1.62 (m, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.26-7.28 (m, 3H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.35-7.37 (m, 2H), 7.42-7.52 (m, 7H), 7.56 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.96-8.05 (m, 4H); ^{19}F NMR (282.6 MHz, $CDCl_3$): δ -140.18- -140.07 (m, 2F), -136.87- -136.75 (m, 2F), -136.52- -136.41 (m, 2F), -134.97 (br, 4F), -133.23- -133.12 (m, 2F), -56.88 (t, *J* = 44.1 Hz, 3F).



A toluene solution (10.0 mL) of (R)-2,2'-diethynyl-1,1'-binaphthyl (302.4 mg, 1.0 mmol), **6** (1324.2 mg, 3.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **11** in a pure form (532.1 mg, 52% yield).

11: white powder; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 6H), 1.30-1.31 (m, 12H), 1.60-1.62 (m, 4H), 2.61 (t, J = 7.6 Hz, 4H), 6.71 (d, J = 8.6 Hz, 4H), 7.16 (d, J = 8.2 Hz, 4H), 7.23-7.24 (m, 2H), 7.32-7.38 (m, 5H), 7.42-7.52 (m, 15H), 7.78 (d, J = 8.6 Hz, 2H), 7.96-8.00 (m, 4H); HRMS (FAB) calcd for $C_{80}H_{62}$ (M^+): 1022.4852, found 1022.3471.



A toluene solution (10.0 mL) of (R)-2,2'-diethynyl-1,1'-binaphthyl (302.4 mg, 1.0

mmol), **9** (825.8 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for overnight. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to recrystallization (hexane/CH_2Cl_2) to afford **12** in a pure form (876.2 mg, 57% yield).

10: white powder; ^{1}H NMR (500 MHz, $CDCl_3$): 7.08-7.15 (m, 1H), 7.27 (s, 1H), 7.33-7.36 (m, 2H), 7.50-7.54 (m, 2H), 7.83 (d, *J* =7.5 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 2H).

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Chapter 4 One-pot Transformation of $Ph_2P(O)$-protected Ethynes: Deprotection Followed by Transition Metal-catalyzed Coupling or Nucleophilic Addition

4.1 Abstract

$Ph_2P(O)$-protected ethynes were successfully transformed to arylethynes in one-pot manner through t-BuOK-catalyzed or MeMgBr-catalyzed deprotection followed by Sonogashira coupling with aryl halide. Arylethynes were obtained similarly by $Ph_2P(O)$-deprotection, stannylation of the resulting terminal ethynes and Migita-Kosugi-Stille coupling. Deprotection followed by intramolecular Eglinton coupling could be carried out in one-pot to provide cyclic butadiynes. Phenyl-substituted prop-2-yn-1-ols were prepared by one-pot transformation through MeMgBr-catalyzed deprotection followed by nucleophilic addition to aldehyde.

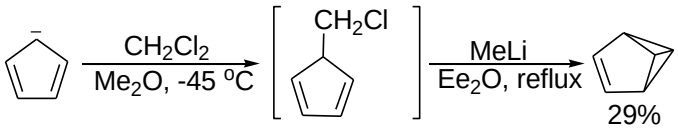
4.2 Introduction

Integration of multistep reactions into a one-pot manner is of great importance today, owing to the enormous potential for combinatorial applications and their economical and environmental significance of one-pot operation.[1]

Forming three to six bonds effectively in one reaction vessel clearly represents an extremely severe challenge due to the multiplicity of reaction pathways available to reactive polyfunctional molecules and to several monofunctional

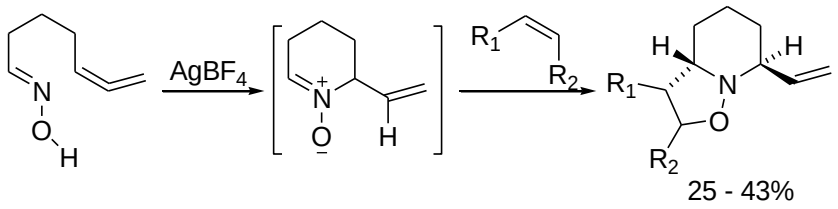
molecules in the same reaction vessel; success, however, would provide rapid and efficient means for transforming simpler molecules into structurally much more complex, nonpolymeric, useful compounds. Over the years, various different procedures have been developed for constructing three to six bonds in one-pot annulation reactions.[1]

Several examples by different research groups have been reported in which non-benzenoid 4n + 2 aromatic anions react with methylene chloride to give tricyclic products having three new bonds and a new bicyclobutane ring (Scheme 4.1).[2]



Scheme 4.1 Preparation of Tricyclic Compound by One-pot Manner[2]

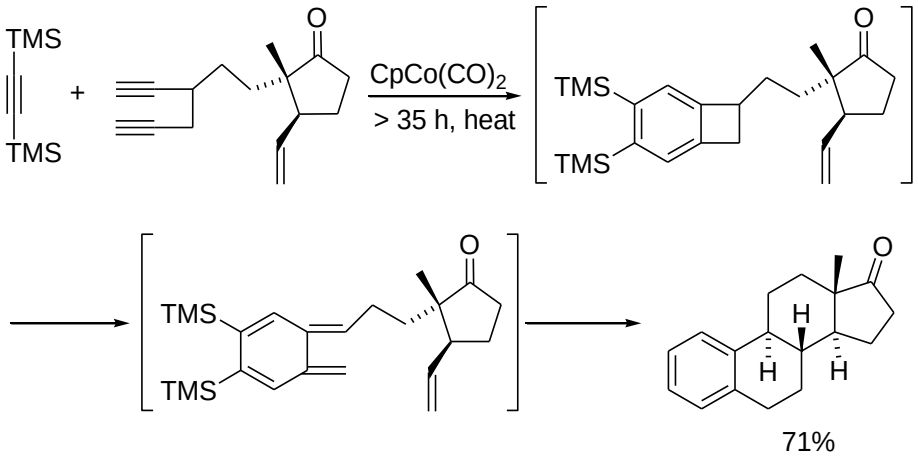
Certain allenic oximes undergo a silver(I)-catalyzed ene-type cyclization to give nitrones which are trapped in situ by various 1,3-dipolarophiles producing overall three new bonds and new six- and five-membered rings (Scheme 4.2).[3]



Scheme 4.2 Formation of Six- and Five-membered Rings by One-pot Manner[3]

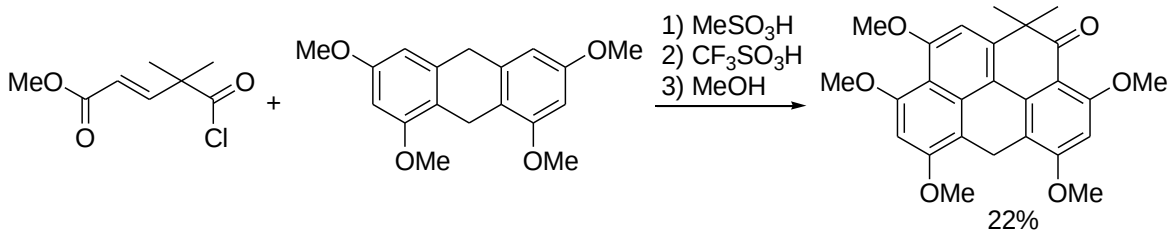
Vollhardt has pioneered the use of cobalt templates to organize α, ω-diynes and acetylenes in order to promote their 2 + 2 + 2 annulation leading to regiospecifically substituted aromatic compounds having three new bonds; such systems have been used as the key components in various short, intramolecular

Diels-Alder total syntheses of estrone steroids involving (2 + 2 + 2) + (0 + 4) formation of crucial benzocyclobutene intermediates (Scheme 4.3).[4]



Scheme 4.3 One-pot Diels-Alder total syntheses of estrone steroids[4]

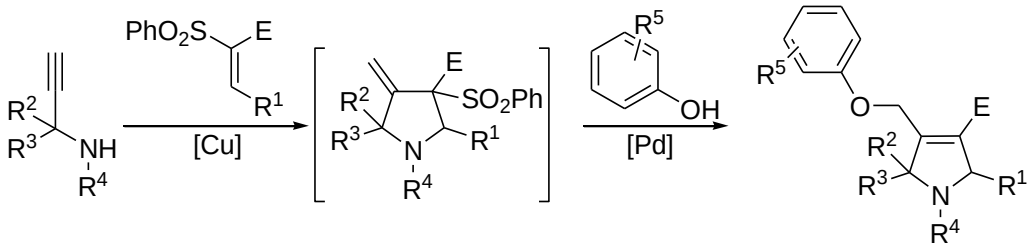
Kelly has recently used a two-component, one-pot, (3 + 3) + (3 + 3) annulation involving probably sequential Friedel-Crafts reactions for construction of the fourth and fifth six-membered rings of the antibiotic resistomycin containing the benzo[cd]-pyrene ring system (Scheme 4.4).[5]



Scheme 4.4 Preparation of Benzo[cd]-pyrene Ring by One-pot Annulation [5]

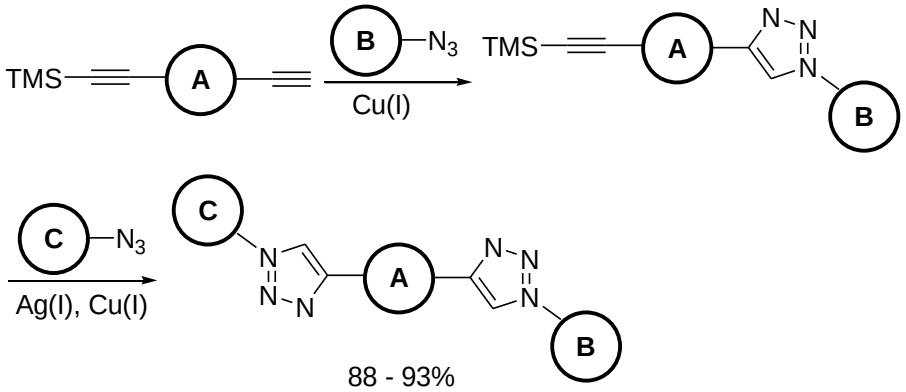
Polysubstituted 4-(phenoxymethyl)-3-pyrrolines and their isomeric 4-(phenoxymethylene)pyrrolidines have been prepared by sequential one-pot coupling of three components: a propargylamine, a vinyl sulfone (or nitroalkene) and a phenolic derivative. The methodology is based on the sequential

integration of a Cu-catalysed cycloaddition and a Pd-catalysed allylic substitution reaction (Scheme 4.5).[6]



Scheme 4.5 Preparation of Polysubstituted 4-(phenoxymethyl)-3-pyrrolines by Sequential One-pot Coupling of Three Components [6]

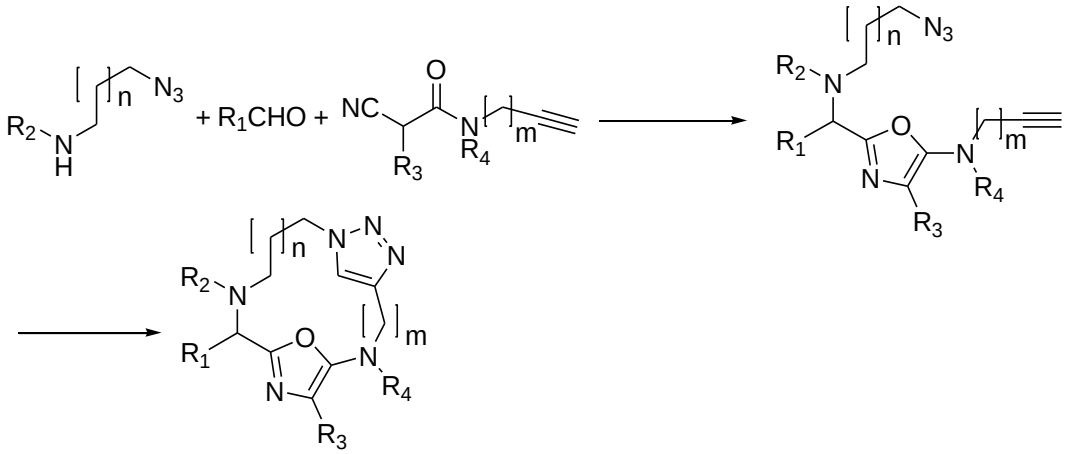
Vinecent Aucagne has reported a methodology for the successive regiospecific "clicking" together of three components in one-pot via two triazole linkages. The protocol utilizes copper(I)-mediated alkyne-azide cycloaddition reactions combined with a silver(I)-catalyzed TMS-alkyne deprotection under mild hydroalcoholic conditions (Scheme 4.6).[7]



Scheme 4.6 Chenoselective Formation of Successive Triazole Linkages in One Pot: "Clicking- Clicking" Chemistry[7]

One-pot procedure has also developed for preparation of complex macrocycles. By combining three appropriately designed simple substrates, a programmed

sequence involving an α-isocyano acetamide-based three component reaction followed by a copper-catalyzed intramolecular [3+2] cycloaddition of alkyne and azide took place to afford complex macrocycles in moderate to good yields. One macrocycle and two heterocycles were produced with concurrent formation of five chemical bonds in this operationally simple process (Scheme 4.7).[8]



Scheme 4.7 Preparation of Macrocycles by One-pot Procedure[8]

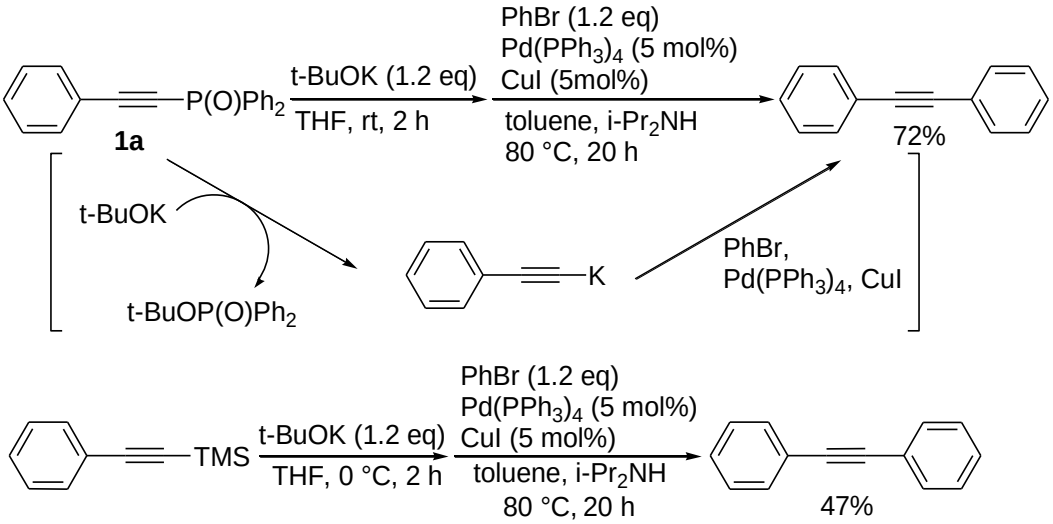
Herein, we report one-pot $Ph_2P(O)$-deprotection/Sonogashira coupling, $Ph_2P(O)$-deprotection/stannylation/Migita-Kosugi-Stille, $Ph_2P(O)$-deprotection/Pd-catalyzed coupling, and $Ph_2P(O)$-deprotection/nucleophilic addition.

4.3 Results and Discussion

One-pot t-BuOK-catalyzed Deprotection/Sonogashira Coupling

Firstly, we tried deprotection of **1a** followed by Sonogashira coupling of the resulting terminal ethyne with phenyl bromide in one-pot (Scheme 4.8). When a THF solution of **1a** was treated with 1.2 equivalent of t-BuOK at rt for 2 h, TLC analysis indicated that **1a** was deprotected completely to give phenylethyne. After PhBr, $Pd(PPh_3)_4$, CuI, i-Pr_2NH and toluene had been added to the THF

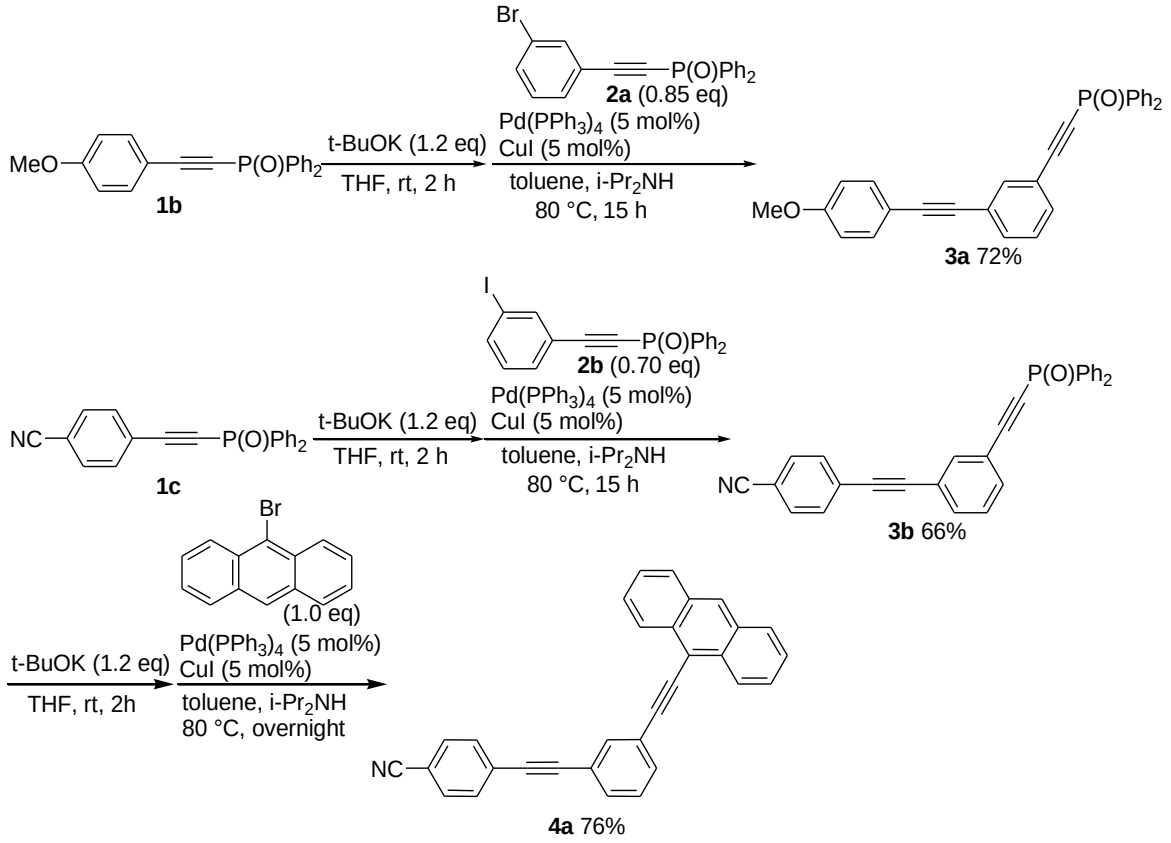
solution, the mixture was heated at 80 °C for 20 h to give diphenylethyne in 72% yield. In deprotection of this protocol, t-BuOP(O)Ph_2 was formed as a byproduct, but it did not disturb the following Sonogashira coupling. While Me_3Si-protected phenylethyne was used for this one-pot deprotection/Sonogashira coupling instead of **1a**, diphenylethyne was obtained in 47% yield.



Scheme 4.8: One-pot t-BuOK-catalyzed Deprotection and Sonogashira Coupling

Subjection of **1b** to t-BuOK-catalyzed deprotection followed by Sonogashira coupling with **2a** gave $Ph_2P(O)$-protected ethyne **3a** in 72% yield. In this one-pot reaction, the addition of stoichiometric amount of t-BuOK enabled selective $Ph_2P(O)$-deprotection of **1b** while the $Ph_2P(O)$-protection of **2a** remained untouched. For complete deprotection of **1b**, 1.2 equivalent of t-BuOK were used, although **2a** would undergo also deprotection by an excess amount of t-BuOK. In order to consume phosphoryl bromide **2a** completely in the coupling stage, 0.85 equivalent of **2a** was used for the Sonogashira coupling. Otherwise the remaining phosphoryl-ethyne **1b** and bromide **2a** would prevent easy isolation of **3a** because of similar R_f values of **1b**, **2a** and **3a** (R_f = 0.30 for **1b**, 0.32 for **2a** and 0.29 for **3a**, hexane/AcOEt (1:1)). Similarly, one-pot reaction of **1c** with **2b** provided **3b** in

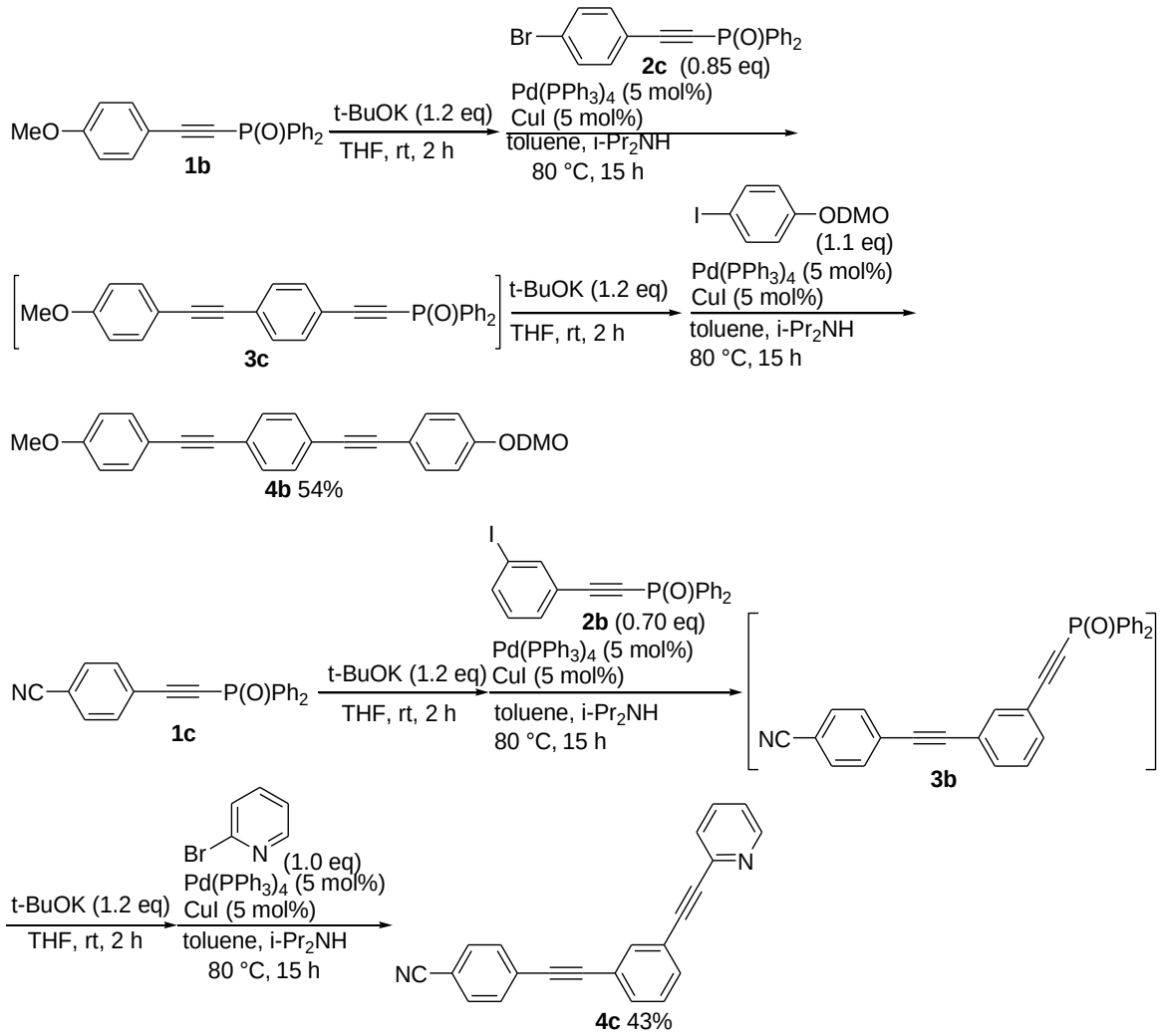
66% yield, and no decomposition of cyano group was observed in spite of the treatment of t-BuOK in the deprotection step. $Ph_2P(O)$-protected ethyne **3b** could be applied to one-pot $Ph_2P(O)$-deprotection/Sonogashira coupling with 9-bromo-anthracene to afford **4a** in 76% yield (Scheme 4.9).



Scheme 4.9: One-pot Synthesis of Arylethynes through t-BuOK-catalyzed $Ph_2P(O)$-Deprotection and Sonogashira Coupling

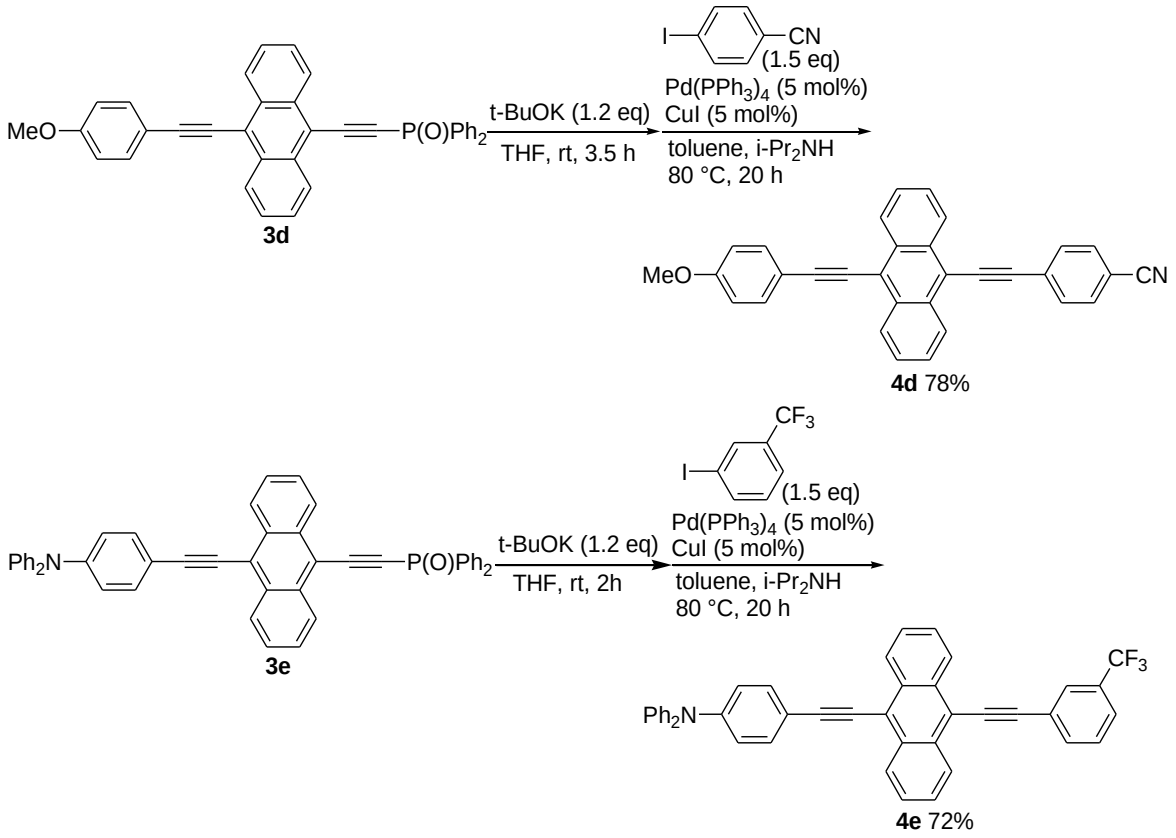
We succeeded synthesis of phenyleneethynylene having expanded л-system such as **4a** by repeating one-pot deprotection/Sonogashira coupling protocol. The synthetic process for phenyleneethynylene could be further compacted by subjection of crude product of the first one-pot protocol to the second. When phosphorylethyne **1b** was treated successively with t-BuOK and with aryl bromide **2c** and Pd and Cu catalysts, phosphorylethyne **3c** was provided, and subjection of

the crude product **3c** to the second deprotection/coupling with 4-(3,7-dimethyloctyloxy)phenyl iodide afforded **4b** in 54% yield (based on **2c**). In this synthetic process, a filtration of the crude product **3c** by a thin pad of silica gel was required. Otherwise the second one-pot protocol was disturbed by the remaining oxidized transition metal catalyst(s) to provide **4b** in a low yield. This compacted process of successive one-pot protocols could be applied to synthesis of **4c**: subjection of the phosphorylethyne **1c** to deprotection/coupling protocols with **2b** and 2- bromopyridine provided **4c** in 43% yield (Scheme 4.10).



Scheme 4.10: Compacted One-pot Synthesis of Arylethynes through t-BuOK-catalyzed $Ph_2P(O)$-Deprotection and Sonogashira Coupling

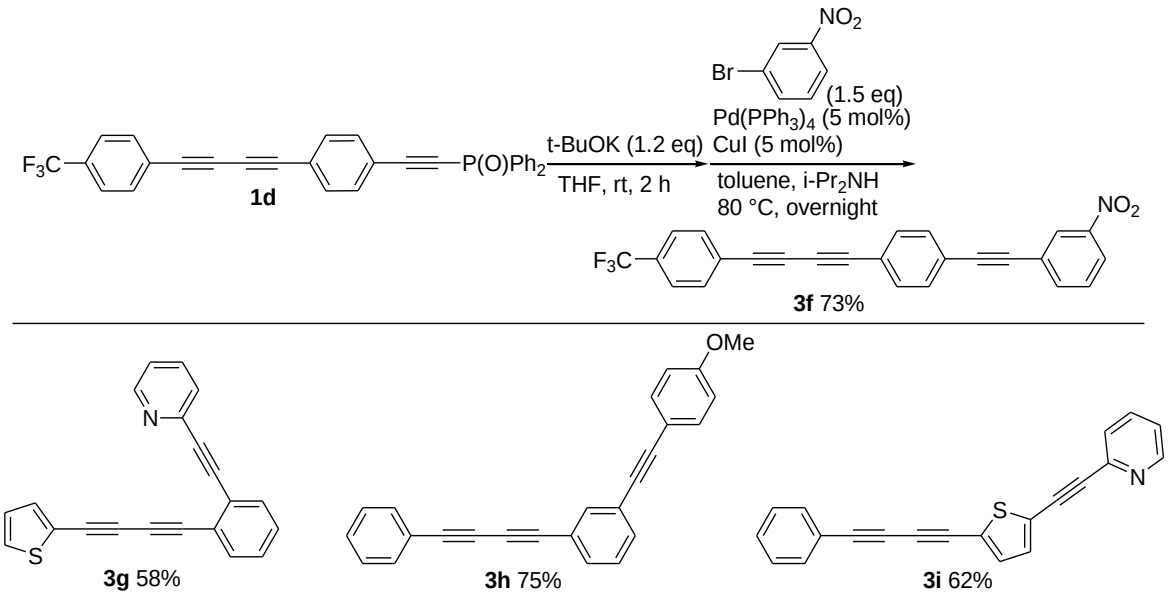
This one-pot deprotection/Sonogashira coupling protocol could be applied to synthesize unsymmetrically substituted anthracen derivatives. When phosphorylethyne **3d** was treated successively with t-BuOK and with 4-iodobenzonitrile and Pd and Cu catalysts, 4-((10-((4-methoxyphenyl)ethynyl) anthracen-9-yl)ethynyl)benzonitrile **4d** was provided in 78% yield. Similarly, unsymmetrically substituted anthracen derivative **4e** was obtained in 72% yield (Scheme 4.11).



Scheme 4.11: Synthesis of Unsymmetrically Substituted Anthracen Derivatives through One-pot t-BuOK-catalyzed $Ph_2P(O)$-Deprotection and Sonogashira Coupling

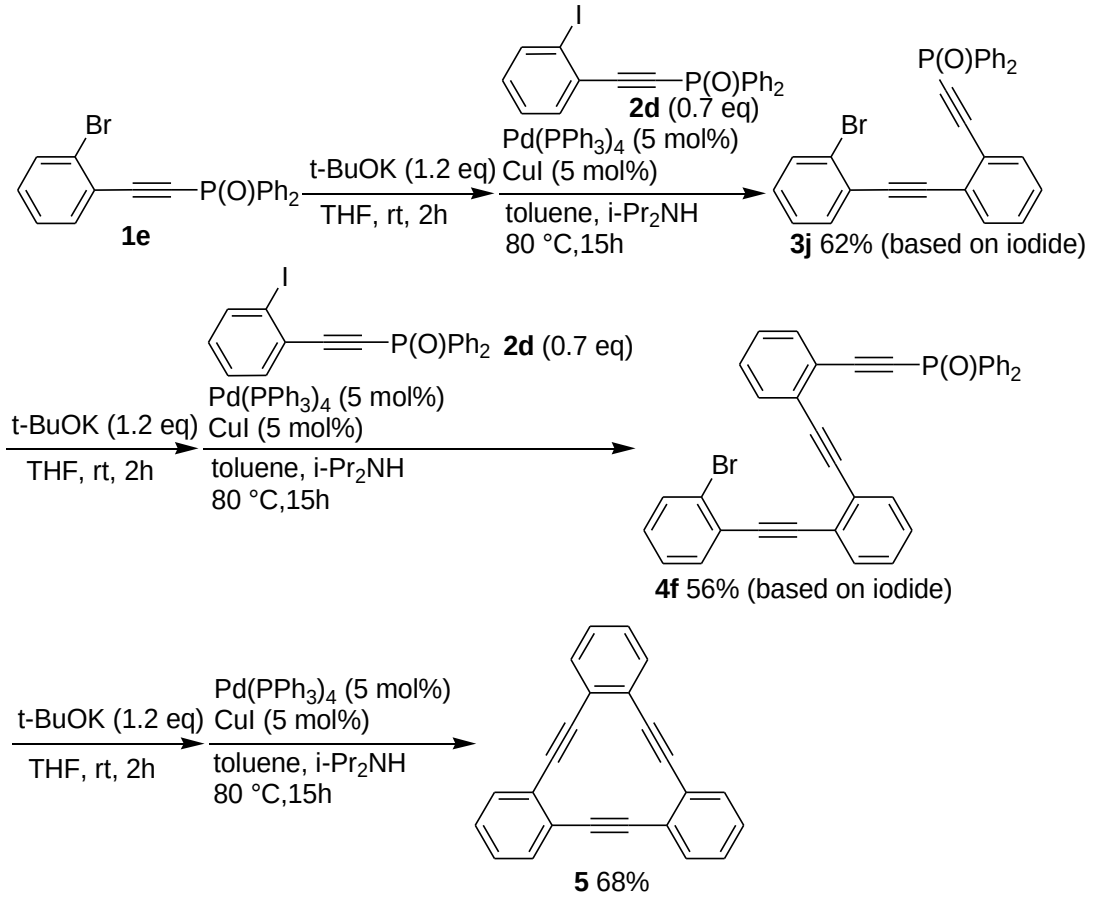
Subjection of Hay coupling product **1d** to deprotection and Sonogashira coupling with 1-bromo-3-nitrobenzene furnished yne-diyne **3f** in 73% yield. The similar

deprotection/Sonogashira coupling protocol also afforded yne-diyne **3g**, **3h** and **3i** in 58%, 75% and 62% yields, respectively (Scheme 4.12).



Scheme 4.12: Synthesis of Yne-diyne by One-pot Deprotection/Sonogashira Coupling

Cyclic triyne **5** could be synthesized by repeating one-pot deprotection/Sonogashira coupling protocol. When phosphorylethyne **1e** was treated successively with t-BuOK and with aryliodide **2d** and Pd and Cu catalysts, phosphorylethyne **3j** was provided in 62% yield. Subjection of product **3j** to one-pot deprotection/Sonogashira coupling with **2d** again produced expanded phosphorylethyne **4f**. When **4f** was subjected to t-BuOK-catalyzed deprotection followed by intramolecular Sonogashira coupling, the expected cyclization occurred to gave cyclic triyne **5** in 68% yield (Scheme 4.13).



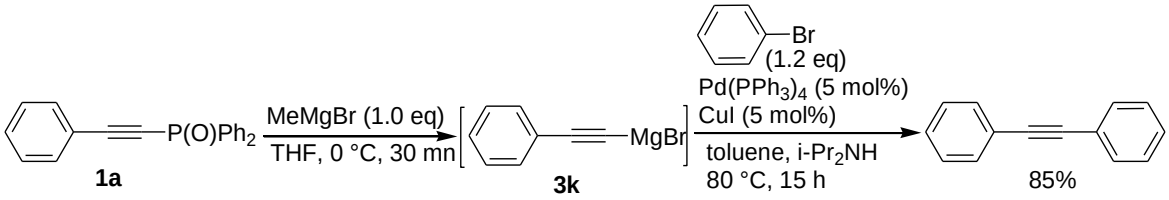
Scheme 4.13: Synthesis of Cyclic Triyne by Repeating One-pot Deprotection/Sonogashira Coupling Protocol

One-pot MeMgBr-catalyzed Deprotection/Sonogashira Coupling

We succeeded in preparation of expanded л-system and yne-diynes by One-pot t-BuOK-catalyzed Deprotection/Sonogashira coupling. And then we are intrigued by One-pot MeMgBr-catalyzed Deprotection/Sonogashira coupling.

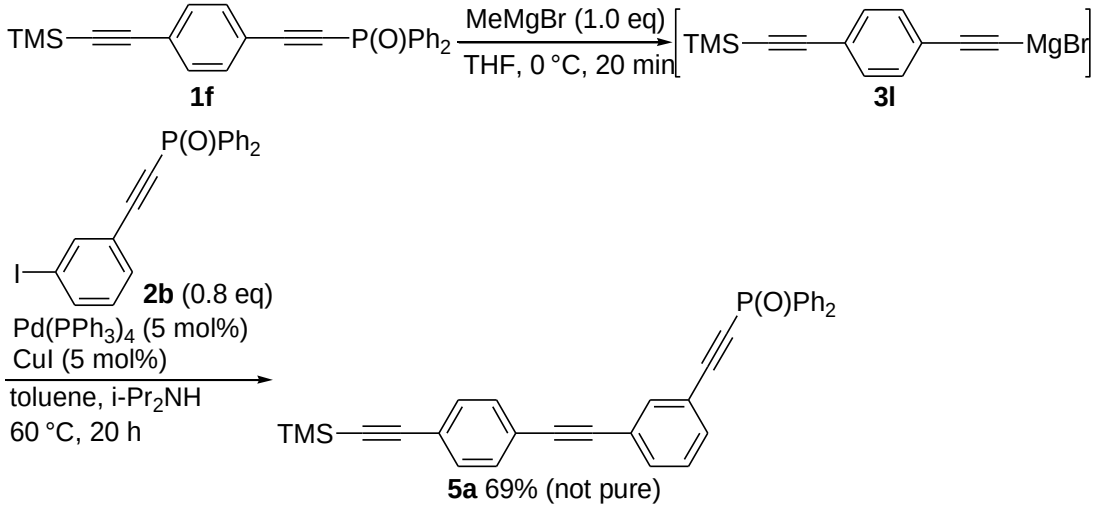
At the beginning, we tried MeMgBr-catalyzed deprotection of **1a** followed by Sonogashira coupling of the resulting terminal ethyne with phenyl bromide in one-pot (Scheme 4.14). Treatment of **1a** with 1.0 equivalent of MeMgBr at 0 °C for 30 min, TLC analysis indicated that **1a** was deprotected completely to give magnesium acetylide. After PhBr, $Pd(PPh_3)_4$, CuI, i-Pr_2NH and toluene had been added to the result THF solution of crude magnesium acetylide, the mixture was

heated at 80 °C for 15 h to give diphenylethyne in 85% yield. In deprotection of this protocol, $MeP(O)Ph_2$ was formed as a byproduct, but it did not disturb the following Sonogashira coupling.



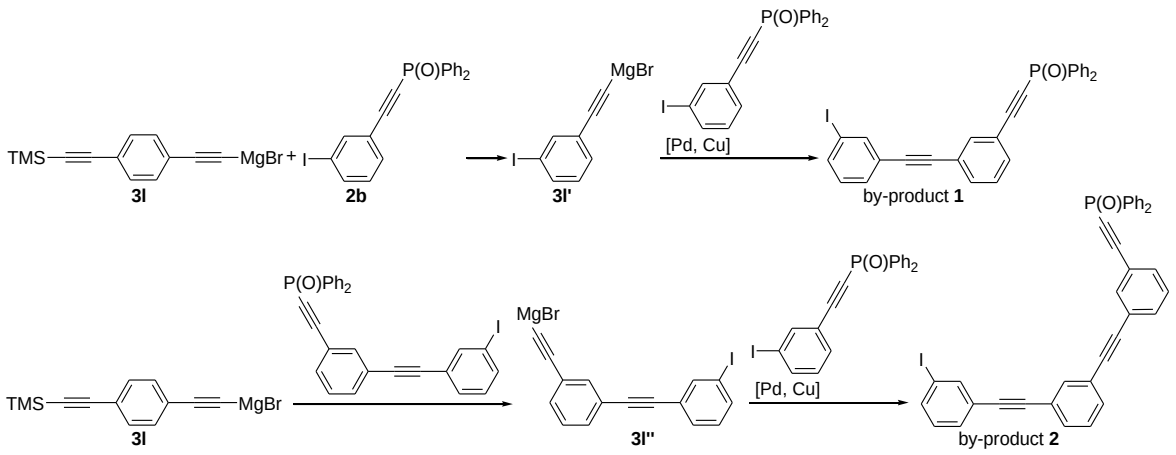
Scheme 4.14: One-pot MeMgBr-catalyzed Deprotection/Sonogashira Coupling

In order to prepare л-expanded TMS and $Ph_2P(O)$-protected ethyne **5a**, we carried out MeMgBr-catalyzed deprotection of **1f** followed by Sonogashira coupling of the resulting TMS-substituted magnesium acetylide with **2b** in one-pot. When a THF solution of **1f** was treated with 1.0 equivalents of MeMgBr at 0 °C for 20 min, TLC analysis indicated that **1f** was $Ph_2P(O)$-deprotected completely to give TMS-substituted magnesium acetylide. After **2b**, $Pd(PPh_3)_4$, CuI, i-Pr_2NH and toluene had been added, the mixture was heated at 80 °C for 20 h to gave a mixture of the desired product and by-products in 69%, and the desired product was very difficult to separate from the by-products (Scheme 4.15).



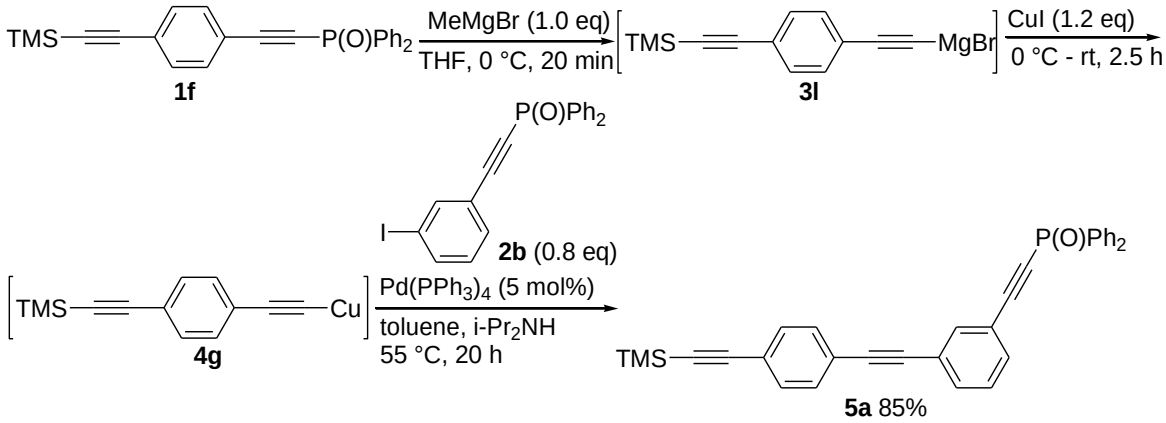
Scheme 4.15: Preparation of л-Expanded TMS and $Ph_2P(O)$-protected Ethyne by MeMgBr-catalyzed Deprotection and Sonogashira coupling

One possible reason for the failure was that reaction between magnesium acetylide **3l** and **2b** occurred to form magnesium acetylide **3l'**. Sonogashira coupling between **3l'** and **2b** provided by-product **1**. By-product **2** would be formed through Sonogashira coupling of **2b** and **3l''** which was formed by reaction between magnesium acetylide **3l** and by-product **1** (Scheme 4.16).



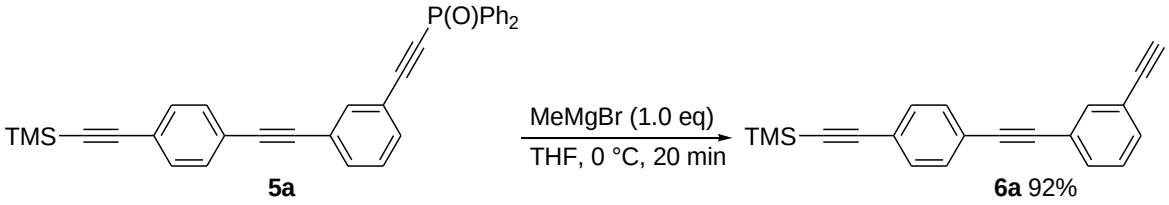
Scheme 4.16: Formation of By-products

Then we tried to prevent the $Ph_2P(O)$-deprotection of **2b** by transformation of magnesium acetylide to copper acetylide. When phosphorylethyne **1f** was treated successively with MeMgBr and CuI, copper acetylide **4g** was provided, and direct subjection of copper acetylide **4g** to Sonogashira coupling with phosphorylethyne **2b** afforded **5a** in 85% yield (based on **2b**) (Scheme 4.17).



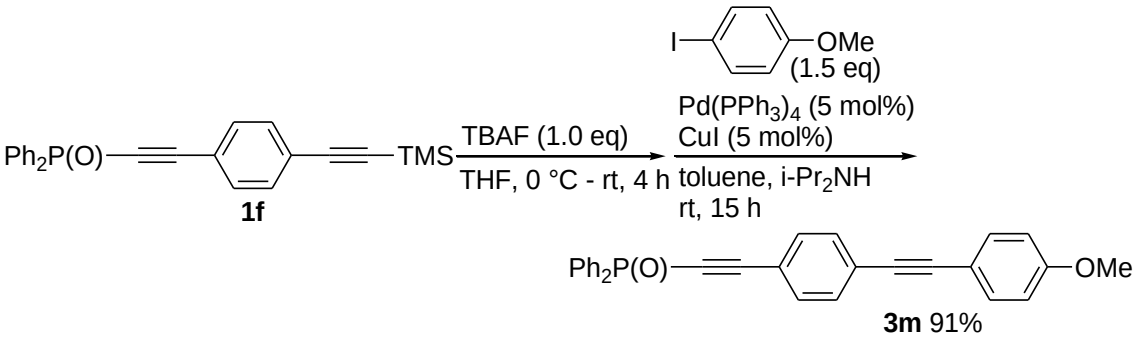
Scheme 4.17: Preparation of л-Expanded TMS and $Ph_2P(O)$-protected Ethyne by One-pot MeMgBr-catalyzed Deprotection/Transformation of Magnesium Acetylide to Copper Acetylide/Sonogashira Coupling

With TMS and $Ph_2P(O)$-protected ethyne **5a** in hand, we prepared mono-TMS-protected terminal acetylene successfully. Treatment **5a** with 1.0 equivalent of MeMgBr provided mono-TMS-protected terminal acetylene **6a** in excellent yield (Scheme 4.18).



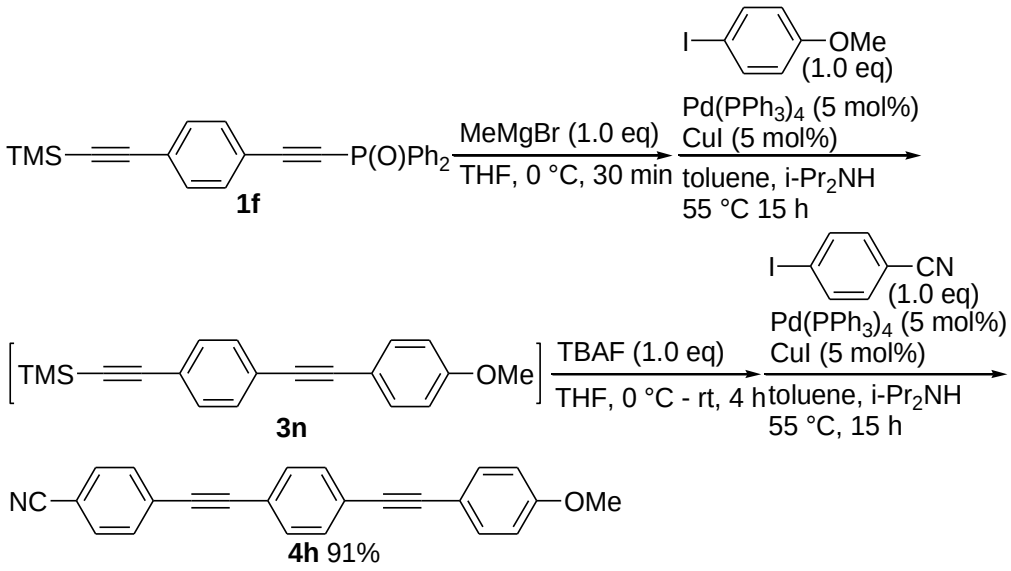
Scheme 4.18: Selective Deprotection of $Ph_2(O)P$

Phosphorylethyne **1f** could be applied to one-pot TBAF-catalyzed desilylation/Sonogashira coupling. When phosphorylethyne **1f** was treated successively with TBAF and with 1-iodo-4-methoxybenzene and Pd and Cu catalysts, phosphorylethyne **3m** was provided in 91% yield (Scheme 4.19).



Scheme 4.19: One-pot TBAF-catalyzed Desilylation/Sonogashira Coupling

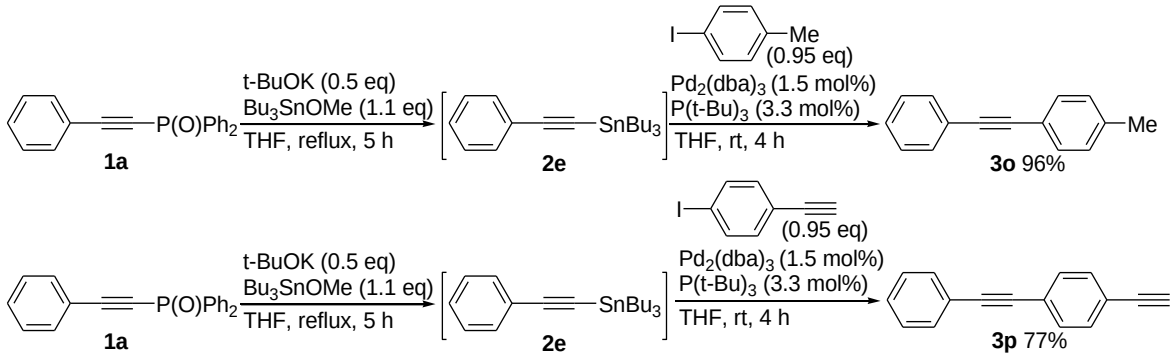
We succeeded synthesis of unsymmetrcally substituted phenyleneethynylene **4h** by combination of one-pot MeMgBr-catalyzed dephosphination/Sonogashira coupling and TBAF-catalyzed desilylation/ Sonogashira coupling protocol. When TMS and $Ph_2P(O)$-protected ethyne **1f** was treated successively with MeMgBr and with 1-iodo-4-methoxy- benzene and Pd and Cu catalysts, TMS-protected phenyleneethynylene **3n** was provided, and subjection of the crude product **3n** to TBAF-catalyzed desilylation/Sonogashira coupling with 4-iodobenzonitrile afforded **4h** in 91% yield. In this synthetic process, a filtration of the crude product **3n** by a thin pad of silica gel was required. Otherwise the second one-pot protocol was disturbed by the remaining oxidized transition metal catalyst(s) to provide **4h** in a low yield (Scheme 4.20).



Scheme 4.20: Synthesis of Phenyleneethynylene by Combination of One-pot MeMgBr-catalyzed Dephosphination/Sonogashira Coupling and TBAF-catalyzed Desilylation/Sonogashira Coupling

One-pot t-BuOK-catalyzed Deprotection/Stannylation/Migata-Kosugi- Stille coupling

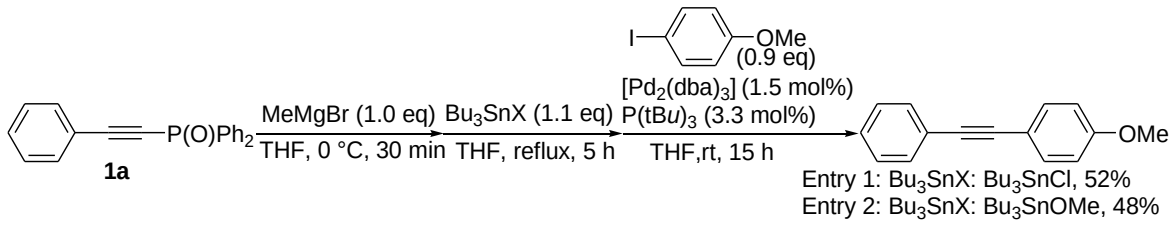
One-pot deprotection/coupling reaction protocol could be applied to Migata-Kosugi-Stille coupling as well as Sonogashira coupling. When phosphorylethyne **1a** was subjected to deprotection (t-BuOK), stannylation (Bu_3SnOMe) and Migata-Kosugi-Stille coupling with 1-iodo-4-methyl- benzene ($Pd_2(dba)_3$ and t-Bu_3P), each step proceeded smoothly to give **3o** in 96% yield This deprotection/Migata-Kosugi-Stille coupling protocol proceeded smoothly in coupling between **1a** and 1-ethynyl-4-iodobenzene to provide **3p** in 77% yield. In this reaction, only stannylethyne **2e** reacted with phenyl iodide moiety of 1-ethynyl-4-iodobenzene, and terminal ethyne moiety of 1-ethynyl-4-iodobenzene remained untouched (Scheme 4.21).



Scheme 4.21: One-pot t-BuOk-catalyzed Deprotection/Stannylation/Migata-Kosugi-Stille Coupling

One-pot MeMgBr-catalyzed Deprotection/Stannylation/Migata-Kosugi- Stille coupling

When phosphorylethyne **1a** was subjected to deprotection (MeMgBr), stannylation (Bu_3SnOMe) and Migata-Kosugi-Stille coupling with 1-iodo-4-methoxybenzene ($Pd_2(dba)_3$ and t-Bu_3P), the stannylation step did not proceed completely when tributylchlorostannane or tributyl(methoxy)stannane was used. And we obtained the desired product in moderate yields in both cases (Scheme 4.22).

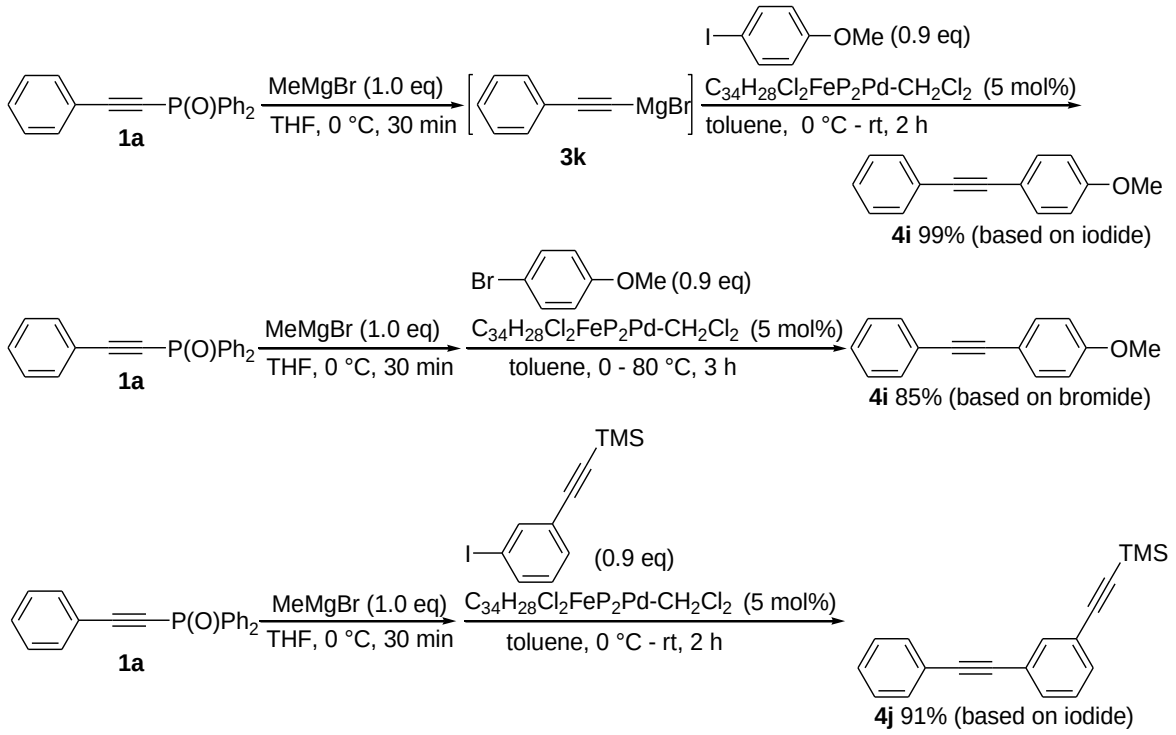


Scheme 4.22: One-pot MeMgBr-catalyzed Deprotection/Stannylation/Migata-Kosugi-Stille Coupling

One-pot MeMgBr-catalyzed Deprotection/Pd-catalyzed Coupling

We succeeded in one-pot MeMgBr-catalyzed deprotection/Pd-catalyzed

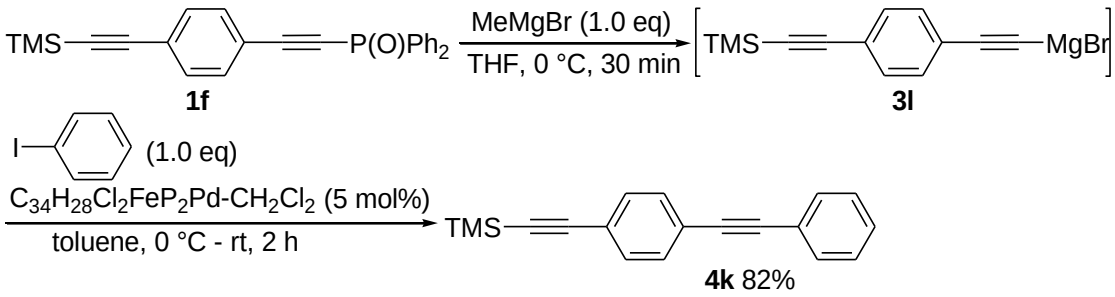
coupling protocol. When phosphorylethyne **1a** was treated with MeMgBr, magnesium acetylide **3k** was provided, and direct subjection of magnesium acetylide **3k** to Pd-catalyzed coupling with 1-iodo-4-methoxybenzene at room temperature afforded **4i** in 99% yield (based on iodide). Higher temperature was required when arylbromide was used as a coupling substrate. Subjection of **1a** to MeMgBr-catalyzed deprotection followed by Pd-catalyzed coupling with 1-bromo-4-methoxybenzene at 80 °C gave **4i** in 85% yield (based on bromide). This one-pot procedure proceeded smoothly in coupling between **1a** and ((3-iodophenyl)ethynyl)trimethylsilane to provide **4j** in 91% yield (based on iodide), TMS group in ((3-iodophenyl)ethynyl)- trimethylsilane remained untouched (Scheme 4.23).



Scheme 4.23: One-pot MeMgBr-catalyzed Deprotection/Pd-catalyzed Coupling

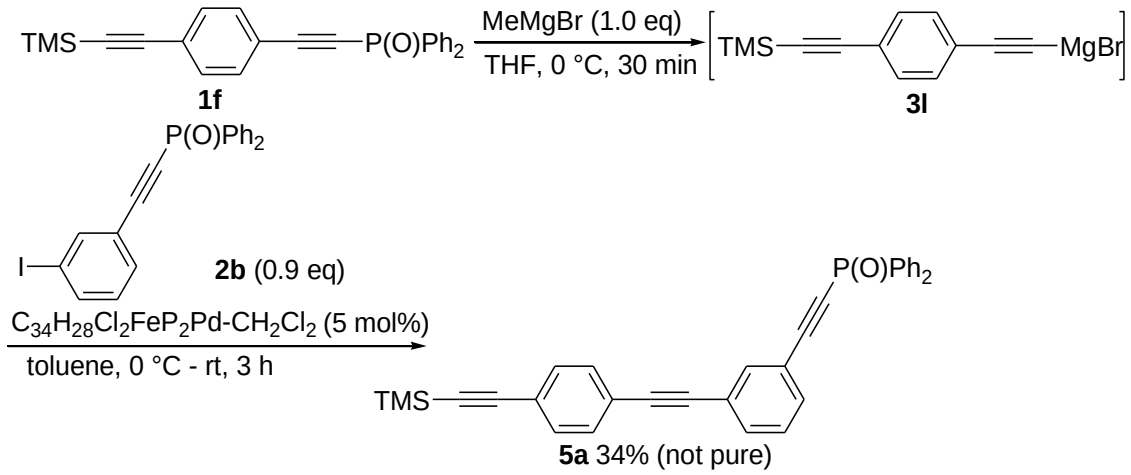
TMS and $Ph_2P(O)$-protected ethyne could be applied to this one-pot MeMgBr-catalyzed deprotection/Pd-catalyzed coupling protocol as well.

Treatment of TMS and $Ph_2P(O)$-protected ethyne **1f** with MeMgBr afforded TMS-substituted magnesium acetylide **3l**. Subjection of **3l** to Pd-catalyzed coupling with iodobenzene provided TMS- protected ethyne **4k** in 82% yield (Scheme 4.24).



Scheme 4.24: Application of TMS and $Ph_2P(O)$-protected Ethyne to One-pot MeMgBr-catalyzed Deprotection/Pd-catalyzed Coupling

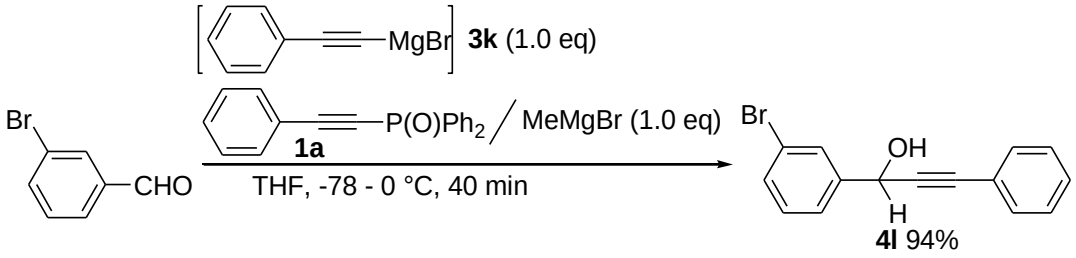
However, we failed to prepare TMS and $Ph_2P(O)$-protected ethyne **5a** by this one-pot MeMgBr-catalyzed deprotection/Pd-catalyzed coupling protocol. Treatment of **1f** with MeMgBr afforded TMS-protected magnesium acetylide **3l**. Addition of **2b** together with Pd catalysis to the reaction mixture provided a mixture of **5a** and by-products in 34% yield. And the desired product **5a** was very difficult to isolate from the by-products (Scheme 4.25). This was also because $Ph_2P(O)$-deprotection of **2b** occurred by reaction between magnesium acetylide **3l** and **2b** (Scheme 4.25).



Scheme 4.25: Preparation of Expanded TMS and $Ph_2P(O)$-protected Ethyne by One-pot MeMgBr-catalyzed Deprotection/Pd-catalyzed Coupling

One-pot MeMgBr-catalyzed Deprotection/Nucleophilic Addition to Aldehyde

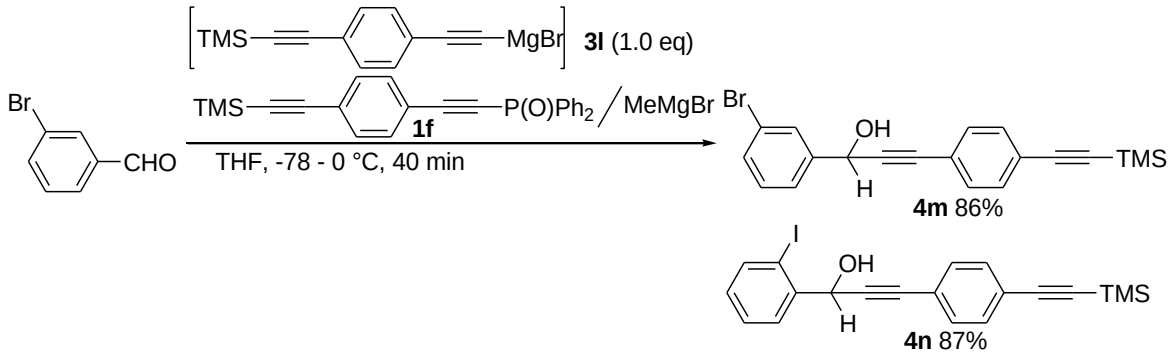
It was facile to obtain phenylprop-2-yn-1-ol derivatives by one-pot MeMgBr-catalyzed deprotection/nucleophilic addition to aldehyde. Treatment of $Ph_2P(O)$-protected ethyne **1a** with MeMgBr provided MeMgBr acetylide **3k**. Nucleophilic addition of **3k** to aldehyde group in 3-bromobenzaldehyde afforded the desired product Phenylprop-2-yn-1-ol **4l** in excellent yield. And the bromo group in 3-bromobenzaldehyde remained untouched (Scheme 4.26).



Scheme 4.26: Preparation of Phenylprop-2-yn-1-ol Derivatives by One-pot MeMgBr-catalyzed Deprotection/Nucleophilic Addition

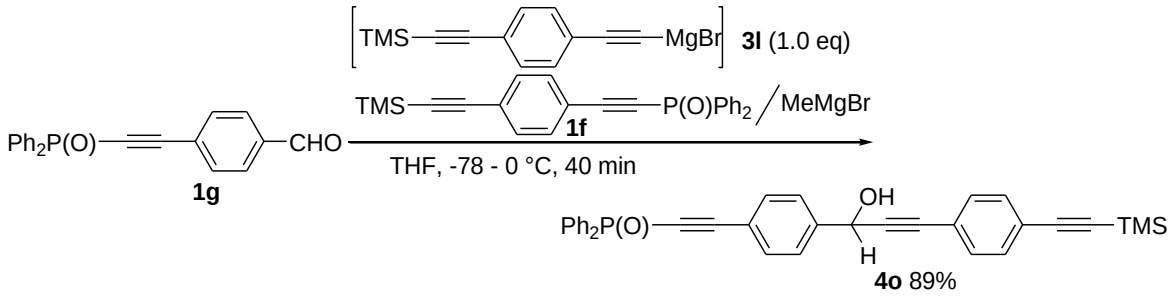
TMS- and $Ph_2P(O)$-protected ethyne **1f** could be applied to this one-pot

MeMgBr-catalyzed deprotection/nucleophilic addition as well. TMS-ethynyl-substituted phenylprop-2-yn-1-ol **4m** was provided in 86% yield by nucleophilic addition between 3-bromobenzaldehyde and magnesium acetylide **3l**, which was formed by treatment of **1f** with MeMgBr. In this procedure, TMS group in **1f** remained untouched. Iodo- and TMS- ethynyl-substituted phenylprop-2-yn-1-ol **4n** was obtained in 87% yield by the similar procedure, and iodo group in 2-iodobenzaldehyde remained untouched (Scheme 4.27).



Scheme 4.27: Preparation of TMS-ethynyl-substituted phenylprop-2-yn-1-ol Derivatives by One-pot MeMgBr-catalyzed Deprotection/Nucleophilic Addition

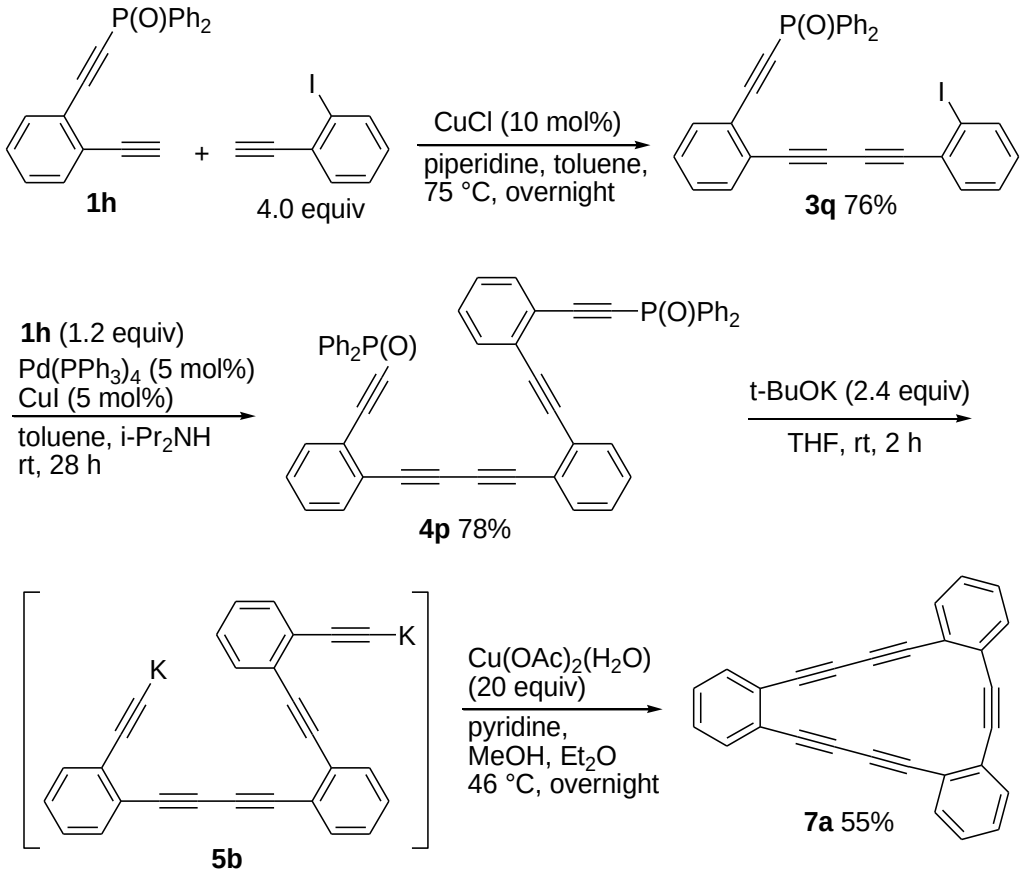
This one-pot protocol could be applied to synthesize TMS-ethynyl and $Ph_2P(O)$-ethynyl-substituted phenylprop-2-yn-1-ol **4o** as well. Nucleophilic addition of **3l** to aldehyde group in $Ph_2P(O)$-ethynyl-substituted aldehyde **1g** afforded the desired product **4o** in excellent yield. In this nucleophilic addition $Ph_2P(O)$-protected ethynyl group in **1g** remained untouched (Scheme 4.28).



Scheme 4.28: Preparation of TMS-ethynyl and $Ph_2P(O)$-ethynyl-substituted Phenylprop-2-yn-1-ol Derivatives by One-pot MeMgBr-catalyzed Deprotection/Nucleophilic Addition

One-pot Deprotection/Eglington cyclization

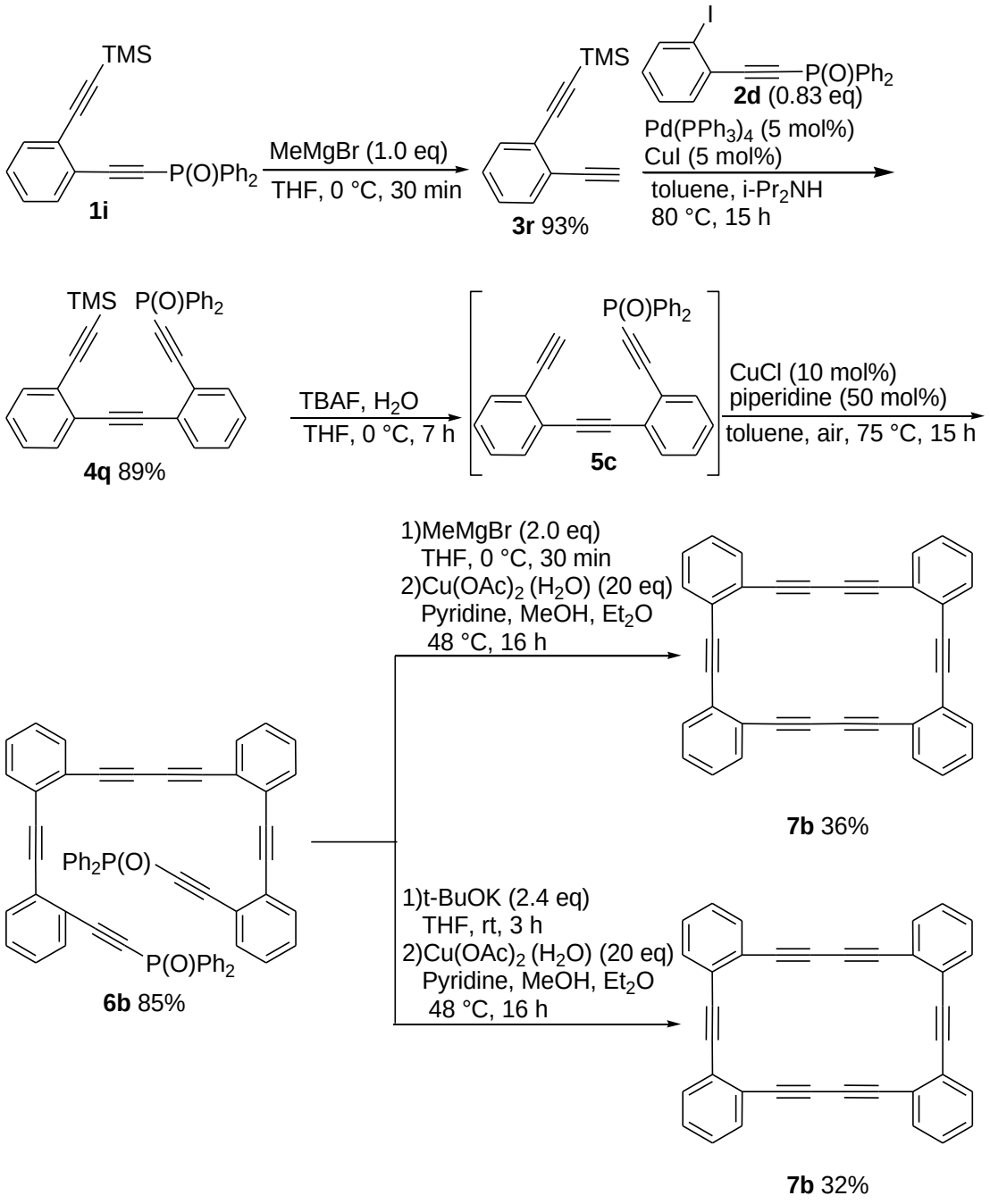
By invoking the $Ph_2P(O)$-assisted purification of the intermediate and copper-catalyzed butadiyne formation, we succeeded in synthesis of cyclic pentayne **7a** (Scheme 4.29). Hay coupling between mono-protected diyne **1h** and 1-ethynyl-2-iodobenzene gave iodotriyne **3q** in 77% yield, and Sonogashira coupling of the resulting iodide **3q** with **1h** provided bis-$Ph_2P(O)$-protected pentayne **4p** in 78% yield. When **4p** was subjected to t-BuOK-catalyzed deprotection followed by $Cu(OAc)_2$-catalyzed Eglington coupling, the expected cyclization occurred to produce cyclic pentayne **7a** in 55% yield. The final *in situ* deprotection/Eglington cyclization proceeded smoothly without isolation of deprotected-terminal ethyne **5b**.



Scheme 4.29: Synthesis of Cyclic Pentayne **7a** by Invoking Hay, Sonogashira and Eglinton Couplings

Cyclic hexayne **7b** was prepared successfully by taking advantage of selective deprotection of $Ph_2P(O)$ and TMS group. Subjection of **1i** to MeMgBr-catalyzed deprotection produced mono-TMS-protected diyne **3r** in 93% yield. Sonogashira coupling between mono-TMS-protected diyne **3r** and iodide **2d** gave TMS- and $Ph_2P(O)$-protected triyne **4q** in 89% yield. Treatment of **4q** with TBAF provided mono-$Ph_2P(O)$-protected triyne **5c**. And a short chromatography provided **5c** in a sufficient pure form for the next Hay coupling. Intermolecular Hay coupling of **5c** gave bis-$Ph_2P(O)$- protected hexayne **6b** in 85% yield. Subjection of **6b** to MeMgBr-catalyzed deprotection followed by $Cu(OAc)_2$-catalyzed Eglington coupling produced cyclic hexayne **7b** in 36% yield. t-BuOK could be also used as a deprotecting reagent for

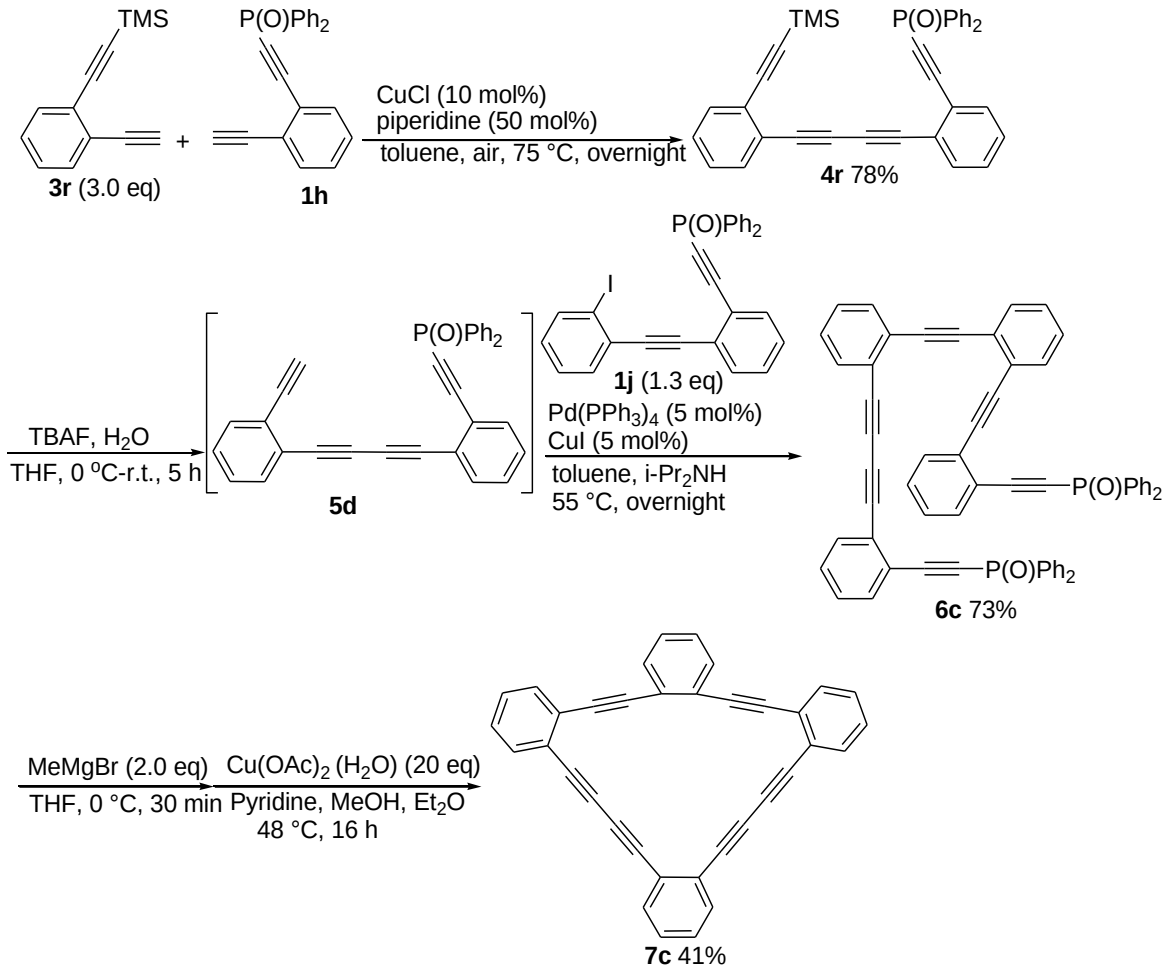
preparation of cyclic hexayne **7b** (Scheme 4.30).



Scheme 4.30: Synthesis of Cyclic hexaynes **7b** by Invoking Hay, Sonogashira and Eglinton Couplings

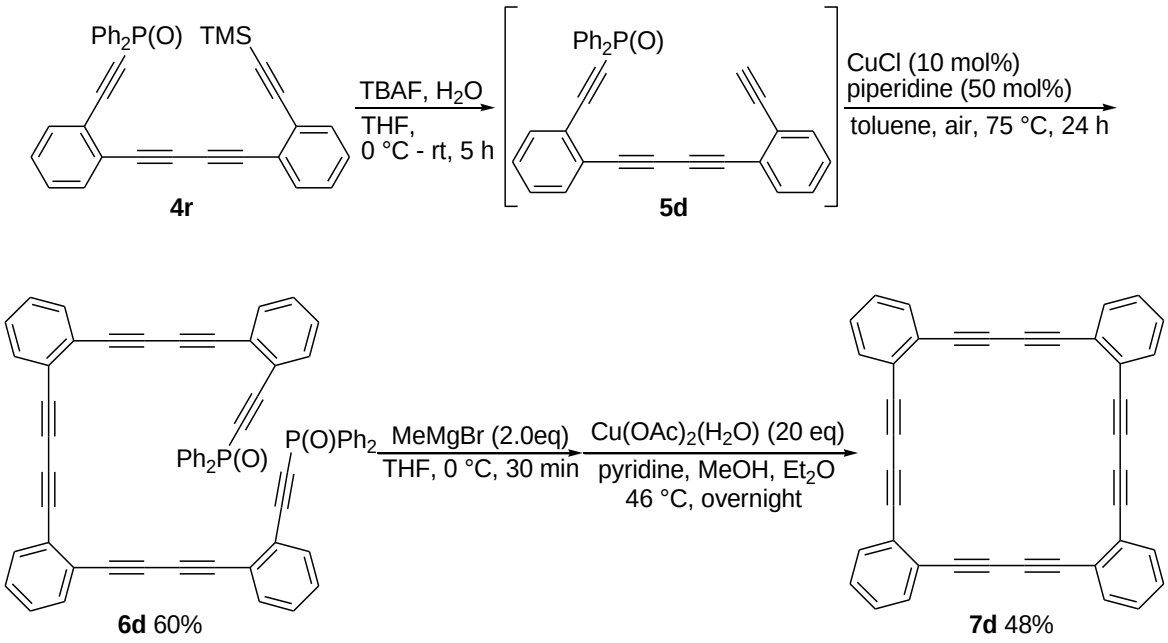
Mono-TMS-protected diyne **3r** could be applied to synthesize cyclic hexayne

7c as well. Hay coupling between mono-TMS-protected diyne **3r** and mono-$Ph_2P(O)$-protected diyne **1h** gave TMS- and $Ph_2P(O)$-protected butayne **4r** in 78% yield. Treatment of **4r** with TBAF provided mono-$Ph_2P(O)$-protected butayne **5d**. And a short chromatography provided **5d** in a sufficient pure form for the next Sonogashira coupling. Sonogashira coupling between **5d** and **1j** afforded bis-$Ph_2P(O)$-protected hexayne **6c** in 73% yield. Subjection of **6c** to MeMgBr-catalyzed deprotection followed by $Cu(OAc)_2$-catalyzed Eglington coupling produced cyclic hexayne **7c** in 41% yield (Scheme 4.31).



Scheme 4.31: Synthesis of Cyclic hexaynes **7c** by Invoking Hay, Sonogashira and Eglinton Couplings

TMS- and $Ph_2P(O)$-protected butayne **4r** was also a key intermediate to prepare cyclic octayne **7d**. Treatment of **4r** with TBAF provided mono-$Ph_2P(O)$-protected butayne **5d**. After a short chromatography, we obtained the crude product **5d**. Hey coupling of **5d** afforded bis-$Ph_2P(O)$- protected octayne **6d** in 60% yield. Subjection of **6d** to MeMgBr-catalyzed deprotection followed by $Cu(OAc)_2$-catalyzed Eglington coupling produced cyclic octayne **7d** in 48% yield (Scheme 4.32).



Scheme 4.32: Synthesis of Cyclic octayne **7d** by Invoking Hay, Sonogashira and Eglinton Couplings

Although Haley has synthesized successfully the cyclic pentayne **7a**, hexayne **7b** and hexayne **7c** by invoking the similar deprotection and cyclization of TMS-protected pentayne,[9] our protocol is more convenient to some extent than his process, which requires transformation of $Ar\text{-}N_3Et_2$ to Ar-I by heating in a pressure bottle and *in situ* desilylation of TMS-proptected butadiyne/Sonogashira coupling of the terminal butadyne moiety with aryl iodide under strictly controlled

reaction conditions.

4.4 Conclusion

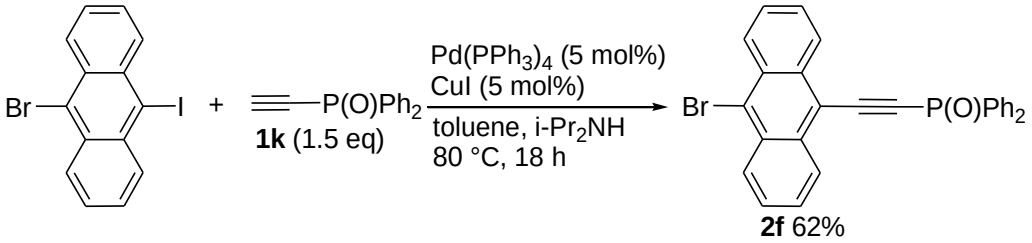
In summary, we have established a new methodology of C-C bond formation by invoking *in situ* deprotection of $Ph_2P(O)$ group/transition metal-catalyzed coupling or nucleophilic addition of the resulting terminal ethyne. In one-pot deprotection/Sonogashira coupling protocol, unsymmetrically substituted aryleneethynylenes were obtained easily. When a stoichiometric amount of t-BuOK was used for deprotection, aryl halide having $Ph_2P(O)$-protected ethyne could be employed as a coupling counterpart, and the corresponding aryleneethynylene having $Ph_2P(O)$-protected ethyne was obtained. Transformation of magnesium acetylide to copper acetylide was needed, when aryl halide having $Ph_2P(O)$-protected ethyne employed as a coupling counterpart in a stoichiometric amount of MeMgBr-deprotection. By compaction of deprotection, stannylation and palladium-catalyzed coupling, one-pot deprotection/Migata-Kosugi-Stille coupling was realized. In this coupling protocol, *in situ*-prepared stannylethyne reacted preferentially with aryl iodide, while unprotected terminal ethyne moiety of aryl iodide remained intact. Phenylprop-2-yn-1-ol derivatives were obtained by one-pot MeMgBr- catalyzed deprotection/nucleophilic addition. *In situ* deprotection of $Ph_2P(O)$ groups/intramolecular Eglington coupling proceeded smoothly to give a cyclic pentayne, hexayne and octaynes.

4.5 Experimental Section

General. All reactions were carried out under an atmosphere of argon with

freshly distilled solvents, unless otherwise noted. Toluene was distilled from sodium. Diisopropylamine and triethylamine were distilled from CaH_2. DMF was distilled from $Ca(OH)_2$. Dry tetrahydrofuran (THF) was purchased from Wako Chemicals. $Pd(PPh_3)_4$ was prepared according to the reported method. Silica gel (Daiso gel IR-60) was used for column chromatography. The other materials were purchased from commercial sources and used without additional purification. NMR spectra was recorded at 25 °C on JEOL Lambda 300 and JEOL Lambda 500 instruments in $CDCl_3$ and calibrated with tetramethysilane (TMS) as an internal reference. Mass spectra were recorded on JEOL MStation JMS-700 and Shimadzu/Kratos MALDI 4 and Platform II single quadrupole (Micro-mass, Altrinchan, UK) mass spectrometers. Elemental analyses were performed by the Perkin-Elmer PE 2400. Melting points (m.p.) were measured on a GTO-250RS instrument.

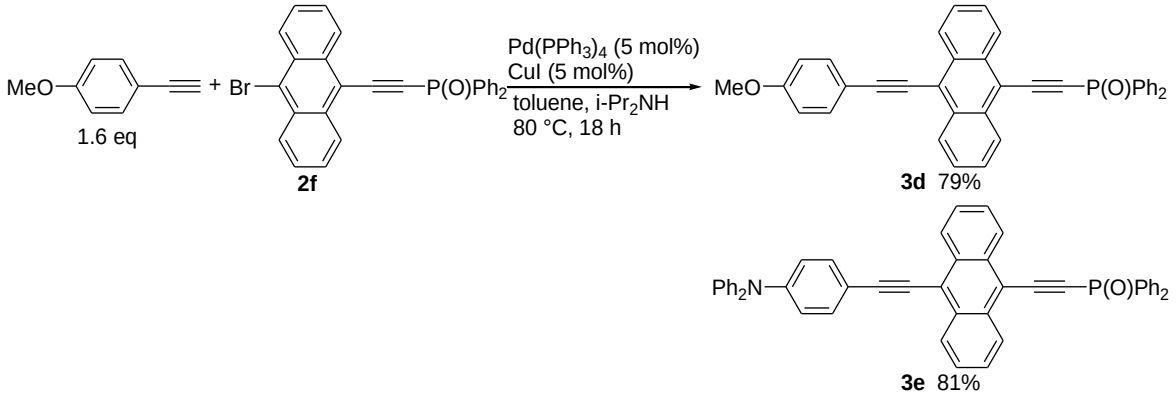
Synthesis of 3d and 3g:



A toluene solution (20.0 mL) of 9-bromo-10-iodoanthracene (383.0 mg, 1.0 mmol), **1k** (339.3 mg, 1.5 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 18 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **2f** in a pure form (298.4 mg, 62% yield).

2f: white powder, m.p. 195-196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.58 (m, 4H), 7.60-7.67 (m, 6H), 8.03-8.07 (m, 4H), 8.47 (d, *J* = 8.6 Hz, 2H), 8.59 (d, *J* =

8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 94.87 (d, *J* = 165.8 Hz), 102.44 (d, *J* = 29.5 Hz), 113.90 (d, *J* = 4.1 Hz), 126.42, 127.65, 127.83, 128.05, 128.50, 128.79 (d, *J* = 12.9 Hz), 129.99, 131.06 (d, *J* = 11.4 Hz), 132.41, 133.05 (d, *J* = 121.9 Hz), 133.94 (d, *J* = 2.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.33; HRMS (FAB) calcd for $C_{28}H_{18}BrOP$ ($M+H^+$): 481.0279, found 481.0703.

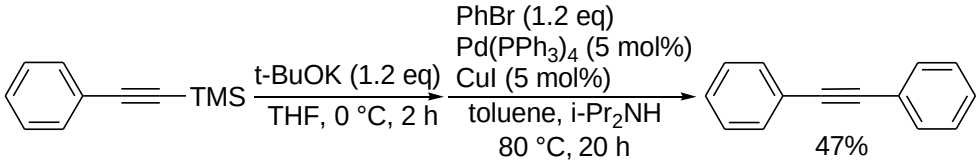


A toluene solution (20.0 mL) of 1-ethynyl-4-methoxybenzene (211.4 mg, 1.6 mmol), **2f** (481.3 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol) and diisopropylamine (0.5 mL) was stirred under nitrogen at 80 °C for 18 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3d** in a pure form (420.7 mg, 79% yield).

3d: white powder, m.p. 180-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.54-7.58 (m, 4H), 7.60-7.65 (m, 6H), 7.53 (d, *J* = 8.8 Hz, 2H), 8.04-8.08 (m, 4H), 8.45-8.47 (m, 2H), 8.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.36 (d, *J* = 4.6 Hz), 84.94, 94.89 (d, *J* = 167.5 Hz), 103.14 (d, *J* = 29.4 Hz), 104.35, 113.22 (d, *J* = 4.6 Hz), 114.22 (d, *J* = 8.3 Hz), 114.94, 122.28, 126.40, 126.78, 127.53 (d, *J* = 3.6 Hz), 127.94, 128.76 (d, *J* = 13.4 Hz), 131.07 (d, *J* = 11.3 Hz), 131.40, 132.35, 133.21 (d, *J* = 122.0 Hz), 133.24 (d, *J* = 1.5 Hz), 133.32, 160.26; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.31; HRMS (FAB) calcd for $C_{37}H_{25}O_2P$ ($M+H^+$): 533.1592, found 533.1822.

3e: white powder, m.p. 249-150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (t, *J* = 7.3 Hz, 4H), 7.17 (d, *J* = 7.6 Hz, 4H), 7.32 (t, *J* = 7.8 Hz, 4H), 7.54-7.58 (m, 4H), 7.60-7.64 (m, 8H), 8.04-8.08 (m, 4H), 8.45-8.47 (m, 2H), 8.68-8.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.51, 94.92 (d, *J* = 167.5 Hz), 103.20 (d, *J* = 29.5 Hz), 104.84, 113.19, 115.27, 121.94 (d, *J* = 8.2 Hz), 122.38, 123.87 (m), 125.22 (m), 126.46, 126.82, 127.59 (d, *J* = 5.2 Hz), 127.98, 128.78 (d, *J* = 13.3 Hz), 129.48 (m), 131.10 (d, *J* = 11.3 Hz), 131.46, 132.78 (d, *J* = 3.0 Hz), 132.84 (d, *J* = 121.0 Hz), 133.31, 133.72, 146.93, 148.70; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.26; HRMS (FAB) calcd for $C_{48}H_{32}NOP$ (M^+): 669.2222, found 669.4063.

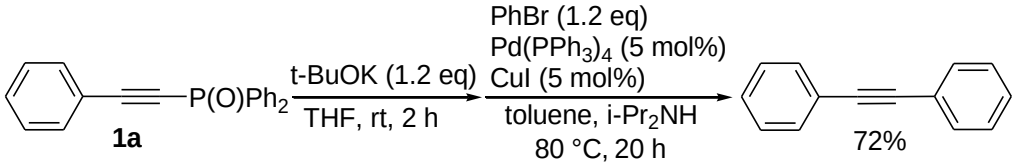
Syntheses of diphenylethyne: One-pot TMS-deprotection/Sonogashira coupling:



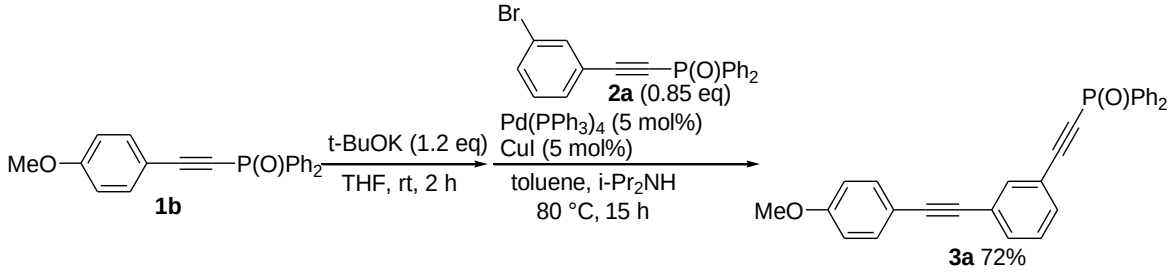
To a THF solution (10.0 mL) of trimethyl(phenylethynyl)silane (174.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, bromobenzene (188.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to give diphenylethyne in a pure form (83.8 mg, 47% yield).

Diphenylethyne:[10] white powder; m.p. 59-61 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.37 (m, 6H), 7.52-7.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 89.33, 123.22, 128.24, 128.33, 131.58.

Syntheses of diphenylethyne, 3a, 3b, 4a, 4b and 4c: One-pot t-BuOK-catalyzed $Ph_2P(O)$-deprotection/Sonogashira coupling:

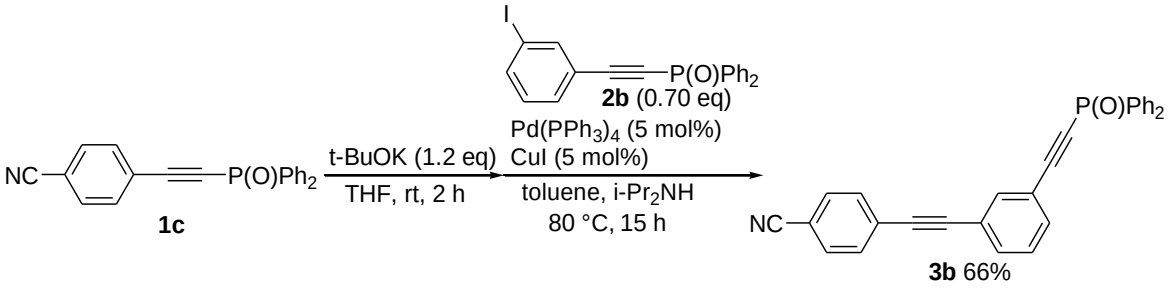


To a THF solution (10.0 mL) of **1a** (302.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, bromobenzene (188.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to give diphenylethyne in a pure form (128.3 mg, 72% yield).



To a THF solution (10.0 mL) of **1b** (332.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, **2a** (324.0 mg, 0.85 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 2:1) to give **3a** in a pure form (264.6 mg, 72% yield, based on bromide).

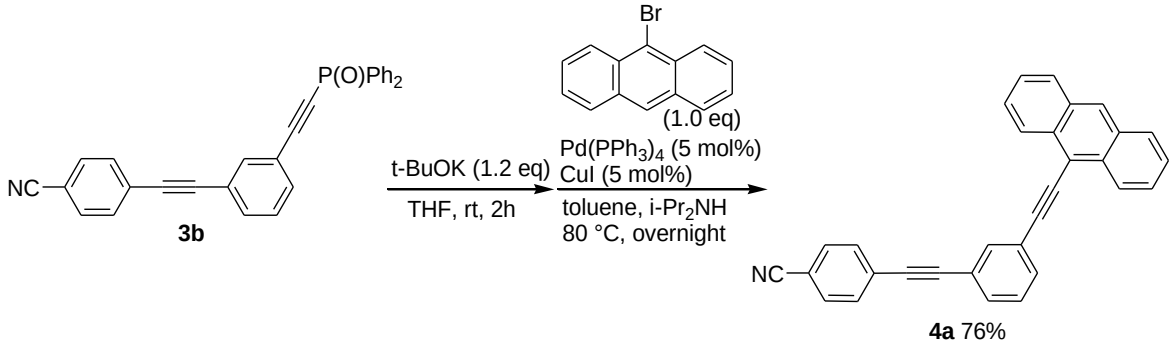
3a:[11] white powder; m.p. 151-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89(d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.49-7.54 (m, 5H), 7.56-7.58 (m, 3H), 7.74 (s, 1H), 7.88-7.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.28 (d, *J* = 4.1 Hz), 83.27 (d, *J* = 167.8 Hz), 86.48, 90.87, 104.36 (d, *J* = 29.5 Hz), 113.99, 114.04, 114.58, 120.20 (d, *J* = 4.1 Hz), 124.37, 128.66 (d, *J* = 13.4 Hz), 130.93 (d, *J* = 11.3 Hz), 131.63, 132.28, 132.79 (d, *J* = 122.4 Hz), 133.13 (d, *J* = 4.2 Hz), 133.43, 135.08, 159.86; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.78.



To a THF solution (10.0 mL) of **1c** (327.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, **2b** (299.7 mg, 0.7 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 2:1) to give **3b** in a pure form (197.5 mg, 66% yield, based on iodide).

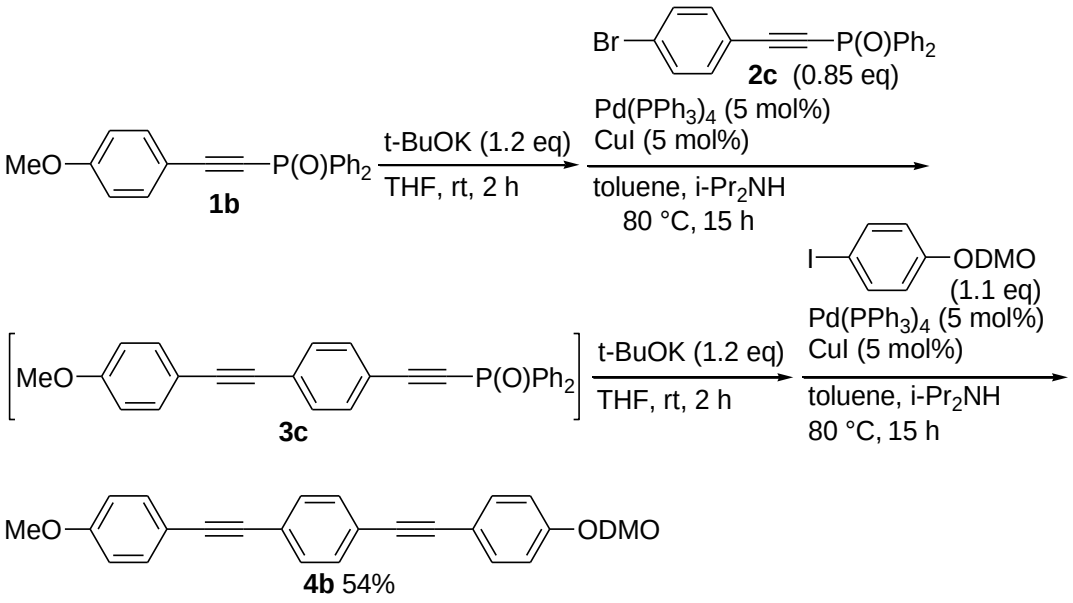
3b:[12] white powder; m.p. 174-176 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.49 - 7.53 (m, 4H), 7.56-7.61 (m, 6H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.77 (s, 1H), 7.88-7.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 83.86 (d, *J* = 166.4 Hz), 88.90, 91.84, 103.80 (d, *J* = 29.4 Hz), 111.93, 118.32, 120.57 (d, *J* = 3.5 Hz),

123.03, 127.49, 128.68 (d, *J* = 13.4 Hz), 128.87, 128.94, 130.94 (d, *J* = 11.3 Hz), 132.10 (d, *J* = 6.8 Hz), 132.35, 132.71 (d, *J* = 121.9 Hz), 132.76, 133.67, 135.42.



To a THF solution (10.0 mL) of **3b** (213.7 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6 mmol). After the mixture was stirred for 2 h under nitrogen at rt, 9-bromoanthracene (128.6 mg, 0.5 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), toluene (16.0 mL) and diisopropylamine (0.25 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 4:1) to give **4a** in a pure form (153.3 mg, 76% yield).

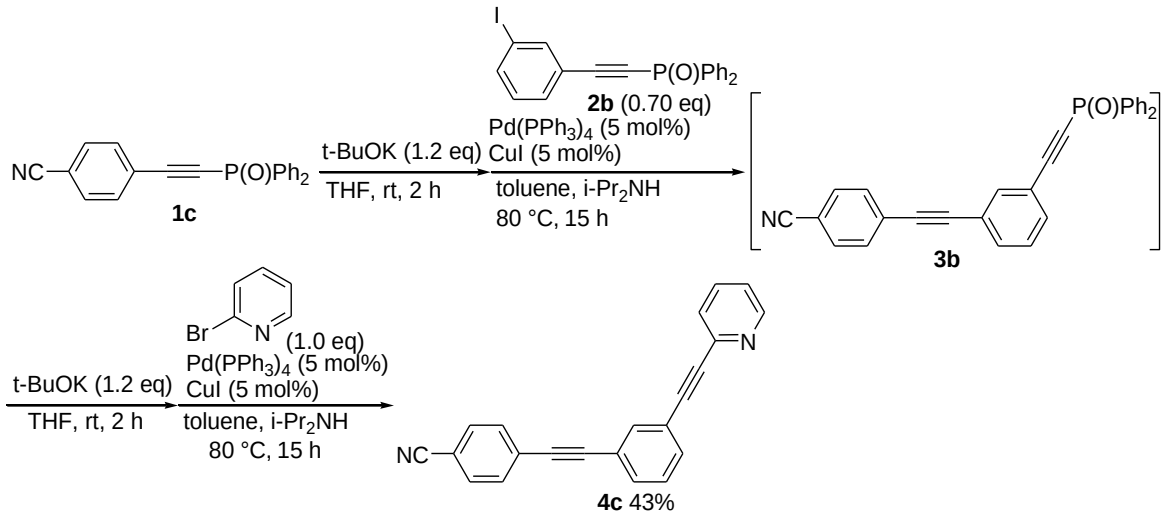
4a:[12] yellow powder; m.p. 215-218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (t, *J* = 7.65 Hz, 1H), 7.54 (t, *J* = 7.05 Hz, 2H), 7.58(d, *J* = 7.95 Hz, 1H), 7.60-7.64 (m, 2H), 7.64-7.68 (m, 4H), 7.78 (d, *J* = 7.65 Hz, 1H), 7.96 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 2H), 8.47 (s, 1H), 8.64 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 87.29, 88.37, 92.86, 99.49, 111.73, 116.71, 118.45, 122.78, 124.22, 125.72, 126.57, 126.62, 126.78, 127.92, 128.10, 128.16, 128.78, 131.17, 131.55, 132.08, 132.12, 132.69, 134.65 (d, *J* = 2.5 Hz).



To a THF solution (10.0 mL) of **1b** (332.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, **2c** (324.0 mg, 0.85 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/AcOEt, 1:1) to give the product **3c** in sufficiently pure form for further reaction. To a THF solution (10 mL) of crude product **3c** was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, 4-(3,7-dimethyloctyloxy)phenyl iodide (396.3 mg, 1.1 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 5:1) to afford **4b** in a pure form (213.3 mg, 54% yield,

based on bromide).

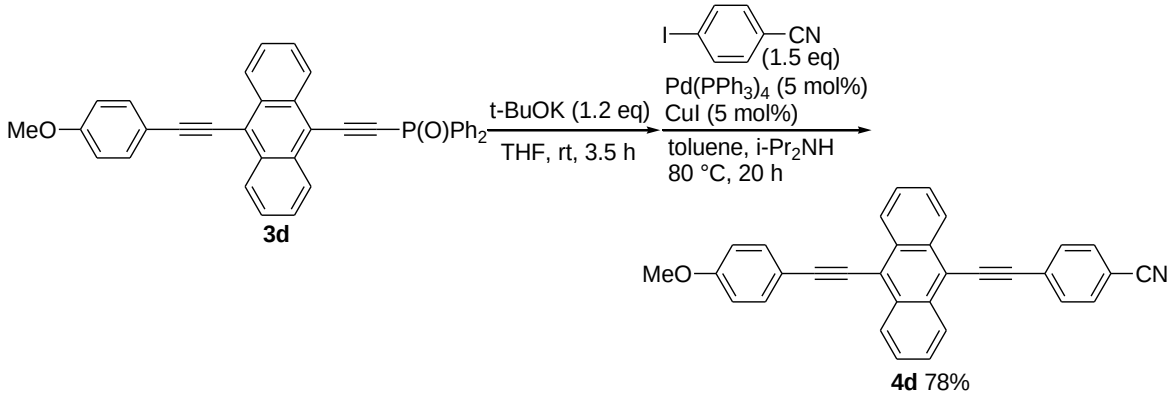
4b:[12] white powder; m.p. 151-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.75 Hz, 6H), 0.95 (d, *J* = 6.45 Hz, 3H), 1.15-1.35 (m, 6H), 1.51-1.62 (m, 2H), 1.67-1.68 (m, 1H), 1.80-1.86 (m, 1H), 3.83 (s, 3H), 3.97-4.05 (m, 2H), 6.86-6.89 (m, 4H), 7.45-7.48 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.63, 22.59, 22.63, 24.64, 27.96, 29.81, 36.08, 37.25, 39.20, 55.24, 66.39, 87.84, 87.94, 91.11, 91.27, 114.01, 114.55, 114.85, 115.16, 122.99, 123.10, 131.29, 133.04, 133.06, 159.32, 159.71.



To a THF solution (10.0 mL) of **1c** (327.3 mg, 1.0 mmol) was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, **2b** (299.7 mg, 0.70 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/AcOEt, 1:1) to give the product **3b** in sufficiently pure form for further reaction. To a THF solution (10.0 mL) of crude product **3b** was added t-BuOK (134.6 mg, 1.2 mmol). After the mixture was stirred for 2 h under nitrogen at rt, 2-bromopyridine (158.0

mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 5:1) to afford **4c** in a pure form (91.6 mg, 43% yield, based on iodide).

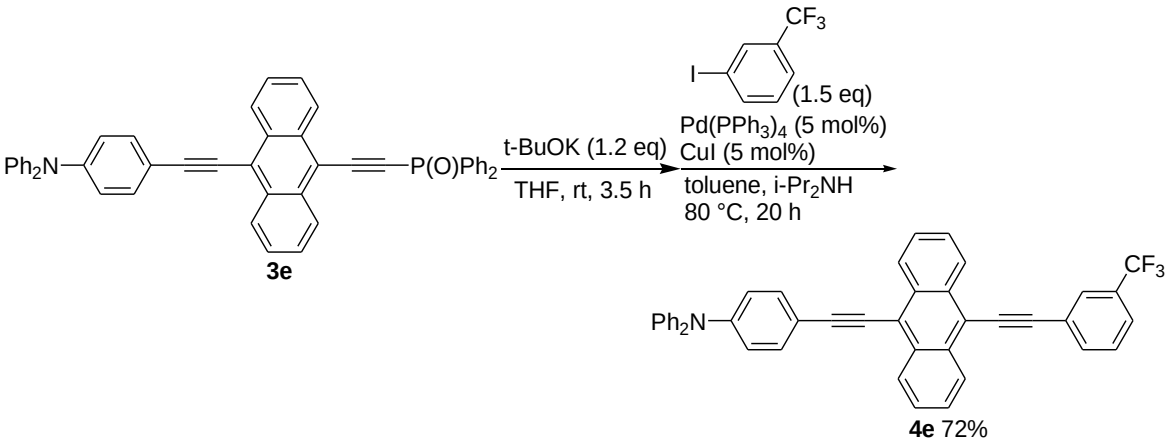
4c:[12] white powder; m.p. 154-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.29 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 2H), 7.60-7.62 (m, 3H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.71 (dt, *J* = 1.8 Hz, *J* = 7.9 Hz, 1H), 7.79 (s, 1H), 8,64 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 87.83, 88.31, 89.35, 92.57, 111.64, 118.44, 122.62, 122.82, 122.99, 127.20, 127.80, 128.65, 128.67, 132.04, 132.10, 132.44, 135.06, 136.21, 143.02, 150.14.



To a THF solution (15.0 mL) of **3d** (266.3 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6 mmol). After the mixture was stirred for 3.5 h under nitrogen at rt, 4-iodobenzonitrile (171.8 mg, 0.75 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), toluene (20.0 mL) and diisopropylamine (0.25 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 20 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel

(hexane/CH_2Cl_2, 4:1) to give **4d** in a pure form (169.1 mg, 76% yield).

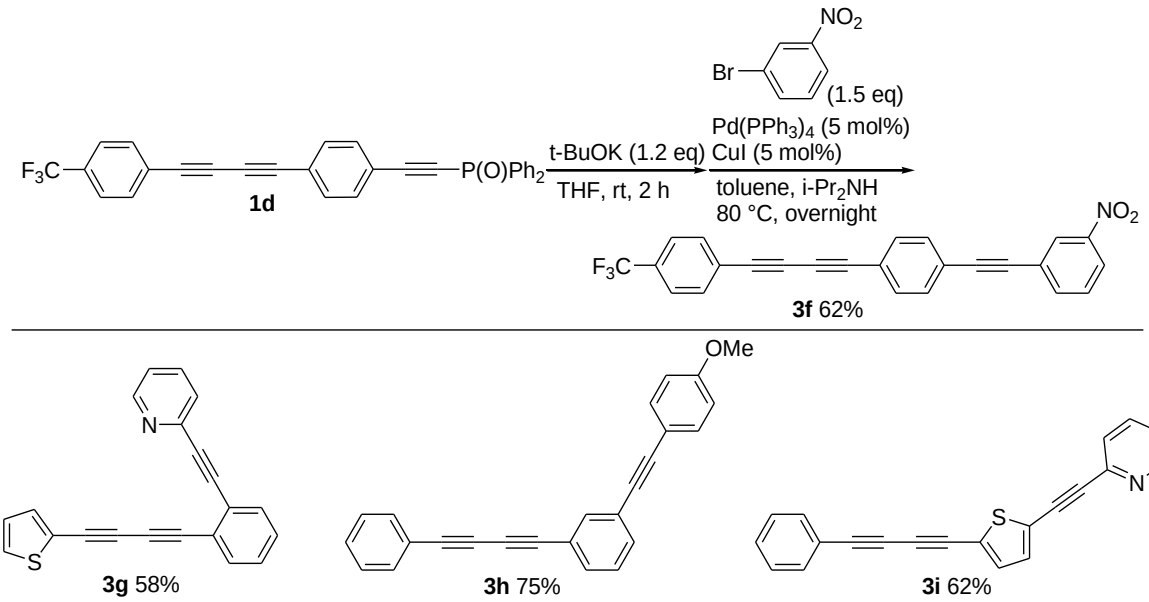
4d: white powder, m.p. 234-235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.60-7.66 (m, 4H), 7.69-7.72 (m, 4H), 7.80 (d, *J* = 8.2 Hz, 2H), 8.56-8.60 (m, 2H), 8.65-8.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.36, 85.17, 91.02, 100.17, 103.40, 111.55, 114.23, 115.28, 116.35, 118.58, 120.28, 126.71, 127.18, 127.48, 128.26, 131.75, 131.98, 132.18, 132.28, 133.24, 160.13; HRMS (FAB) calcd for $C_{32}H_{19}NO$ (M^+): 433.1467, found 433.3122.



To a THF solution (15.0 mL) of **3e** (334.9 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6 mmol). After the mixture was stirred for 3.5 h under nitrogen at rt, 1-iodo-3-(trifluoromethyl)benzene (204.0 mg, 0.75 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), toluene (20.0 mL) and diisopropylamine (0.25 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 20 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 4:1) to give **4e** in a pure form (220.9 mg, 72% yield).

4e: white powder, m.p. 190-191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09-7.12 (m, 4H), 7.18 (d, *J* = 7.6 Hz, 4H), 7.32 (t, *J* = 7.9 Hz, 4H), 7.58-7.69 (m, 8H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.02 (s, 1H), 8.65-8.67 (m, 2H), 8.69-8.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.77, 88.09, 100.28, 103.42, 115.84, 116.82, 119.71, 122.15,

122.20, 123.75, 123.76 (q, *J* = 272.3 Hz), 124.38, 125.11 (q, *J* = 2.1 Hz), 126.66, 126.92, 127.02, 127.41, 128.26 (q, *J* = 3.6 Hz), 129.07, 129.46 (m), 131.12 (d, *J* = 32.5 Hz), 131.79, 132.20, 132.67, 134.69, 147.04, 148.39; HRMS (FAB) calcd for $C_{43}H_{26}F_3N$ ($M+H^+$): 613.2017, found 613.1503.



To a THF solution (20.0 mL) of **1d** (247.2 mg, 0.5 mmol) was added t-BuOK (67.3 mg, 0.6 mmol). After the mixture was stirred for 2 h under nitrogen at rt, THF solvent was evaporated under vacuum. To the concentrated reaction mixture were added 1-bromo-3-nitrobenzene (151.5 mg, 0.75 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), toluene (10.0 mL) and diisopropylamine (0.25 mL), and the mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 7:1) to give **3f** in a pure form (128.8 mg, 62% yield).

3f:[12] white powder; m.p. 159-161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.57 (m, 5H), 7.62 (q, *J* = 8.6 Hz, 4H), 7.83 (d, *J* = 7.9 Hz, 1H), 8.19-8.21 (m, 1H), 8.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 75.58, 75.96, 80.94, 82.03, 89.49, 91.14, 121.94, 123.24, 123.28, 123.69 (q, $J_{C\text{-}F}$ = 272.1 Hz), 124.65, 125.42 (q, $J_{C\text{-}F}$ = 2.9

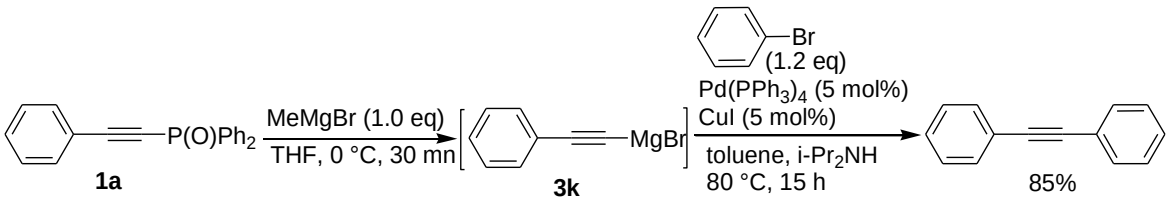
Hz), 126.40, 126.46, 129.43, 130.89 (q, J_{C-F} = 32.8 Hz), 131.78, 132.58, 132.72, 137.20, 148.16; ^{19}F NMR (282 MHz, $CDCl_3$) : δ -63.49.

3g: green powder, m.p. 77-78 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.02 (t, *J* = 4.1 Hz, 1H), 7.25-7.27 (m, 2H), 7.33-7.38 (m, 4H), 7.56 (d, *J* = 6.7 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.71 (dt, *J* = 1.0, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 75.84, 77.79, 78.02, 82.04, 87.32, 93.06, 121.90, 122.94, 124.69, 125.89, 127.18, 127.85, 128.64, 128.86, 128.96, 132.31, 132.70, 134.35, 136.13, 143.18, 150.00; HRMS (FAB) calcd for $C_{21}H_{11}NS$ (M^+): 309.0612, found 309.2251.

3h: [12] white powder; m.p. 126-128 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.29-7.40 (m, 4H), 7.45-7.50 (m, 4H), 7.54 (d, *J* = 6.7 Hz, 2H), 7.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.32 (d, *J* = 4.1 Hz), 73.80, 74.37, 80.71, 81.81, 86.94, 90.38, 114.01, 114.11, 114.94, 121.69, 122.13, 124.19, 128.49, 129.28, 131.74, 132.05, 132.52, 133.15 (d, *J* = 8.3 Hz), 135.18 (d, *J* = 3.1 Hz), 159.85.

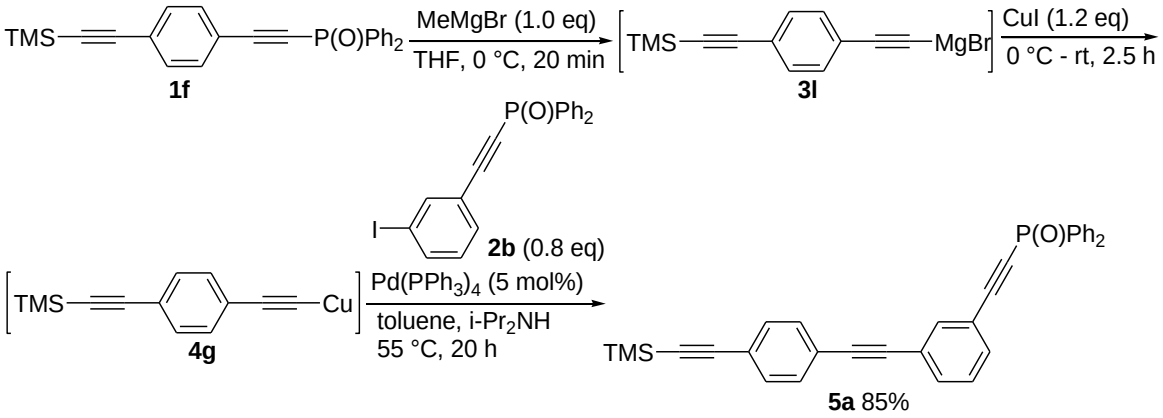
3i: white powder; m.p. 90-92 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23-7.28 (m, 3H), 7.33-7.40 (m, 3H), 7.52-7.54 (m, 3H), 7.70 (t, *J* = 7.0 Hz, 1H), 8.63 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 73.54, 73.80, 79.29, 81.93, 84.59, 93.39, 121.36, 123.16, 124.34, 124.68, 127.16, 128.48, 129.52, 132.51, 133.09, 134.04, 136.27, 142.68, 150.22; HRMS (FAB) calcd for $C_{21}H_{11}NS$ ($M+H^+$): 309.0612, found 309.0723.

Syntheses of diphenylethyne and 5a by one-pot MeMgBr-catalyzed Deprotection/Sonogashira Coupling



To a THF solution (10.0 mL) of **1a** (302.3 mg, 1.0 mmol) was added MeMgBr

(333.3 μL, 1.0 mmol). After the mixture was stirred for 30 min under nitrogen at rt, bromobenzene (188.4 mg, 1.2 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to give diphenylethyne in a pure form (151.5 mg, 85% yield).

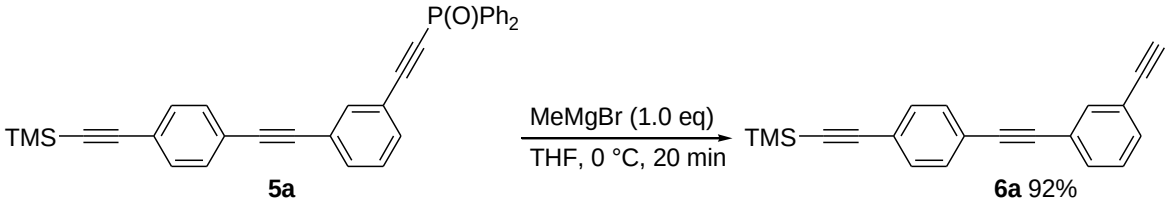


To a THF solution (10.0 mL) of **1f** (398.5 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol). After the mixture was stirred for 30 min under nitrogen at rt, CuI (228.5 mg, 1.2 mmol) was added at 0 °C. After the mixture was stirred for 2.5 min under nitrogen at rt for 2.5 h, **2b** (342.6 mg, 0.8 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to give **5a** in a pure form (339.1 mg, 85% yield, based on iodide).

5a: white powder; m.p. 133-134 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.45 (br, 4H), 7.49-7.53 (m, 4H), 7.55-7.59 (m, 4H), 7.75

(s, 1H), 7.88-7.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.13 (d, *J* = 4.6 Hz), 83.58 (d, *J* = 167.5 Hz), 89.52, 90.38, 96.60, 104.11 (d, *J* = 29.5 Hz), 104.42, 120.39, 120.42, 122.59, 123.37, 123.81, 128.68 (d, *J* = 13.4 Hz), 130.96 (d, *J* = 11.3 Hz), 131.44, 131.92, 132.18, 132.32 (d, *J* = 2.6 Hz), 132.83 (d, *J* = 122.5 Hz), 133.57, 135.27; HRMS (FAB) calcd for $C_{33}H_{27}OPSi$ ($M+H^+$): 499.1569, found 499.2264.

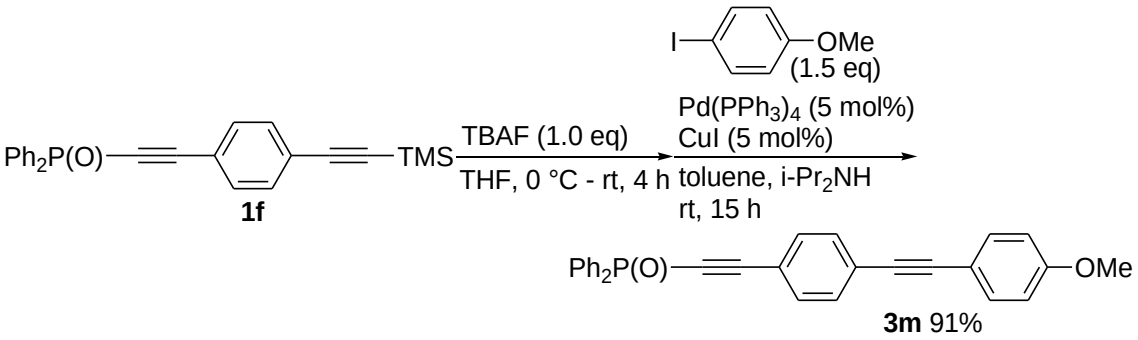
Syntheses of 6a by MeMgBr-catalyzed Deprotection



To a THF solution (10 mL) of **5a** (498.6 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **6a** in a pure form (274.6 mg, 92%).

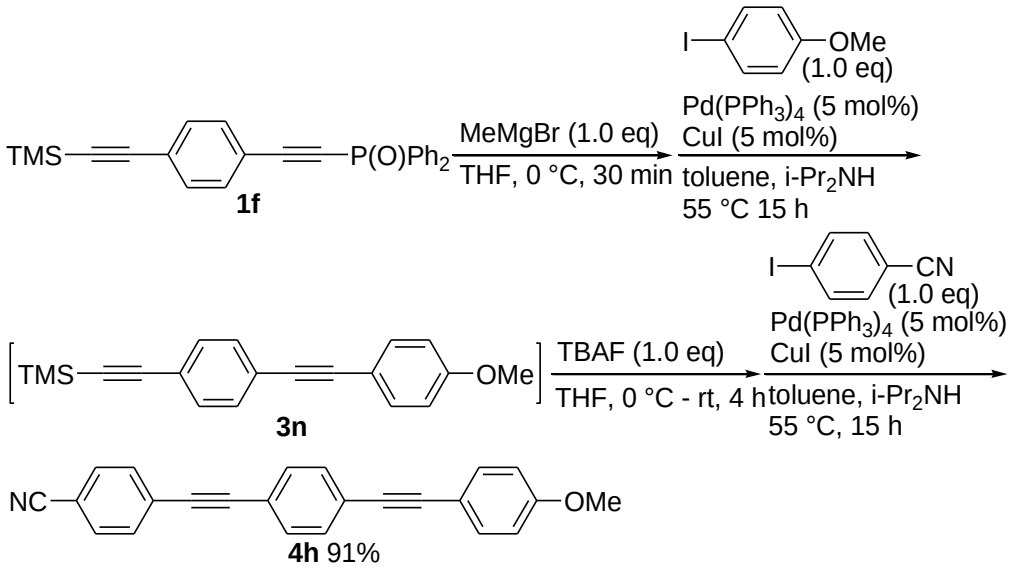
6a: white powder; m.p. 93-94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 3.10 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.45-7.50 (m, 6H), 7.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.11 (d, *J* = 4.1 Hz), 77.86 (d, *J* = 4.6 Hz), 82.68, 89.68, 90.15, 96.42, 104.52, 122.50, 122.92, 123.14, 123.35, 128.44, 128.48 (d, *J* = 4.0 Hz), 131.41, 131.82, 131.90, 135.07 (d, *J* = 3.1 Hz); HRMS (FAB) calcd for $C_{21}H_{18}Si$ (M^+): 298.1178, found 298.1330.

Syntheses of 3m by one-pot TBAF-catalyzed Deprotection/Sonogashira Coupling



To a THF solution (20.0 mL) of **1f** (199.2 mg, 0.5 mmol) was added TBAF (1.0 M in THF, 500.0 μL, 0.5 mmol) at 0 °C. After the mixture was stirred for 4 h under nitrogen at rt, 1-iodo-4-methoxybenzene (175.5 mg, 0.75 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), toluene (10.0 mL) and diisopropylamine (0.25 mL) were added to the reaction mixture, and the mixture was stirred under nitrogen at rt for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to give **3m** in a pure form (196.8 mg, 91% yield).

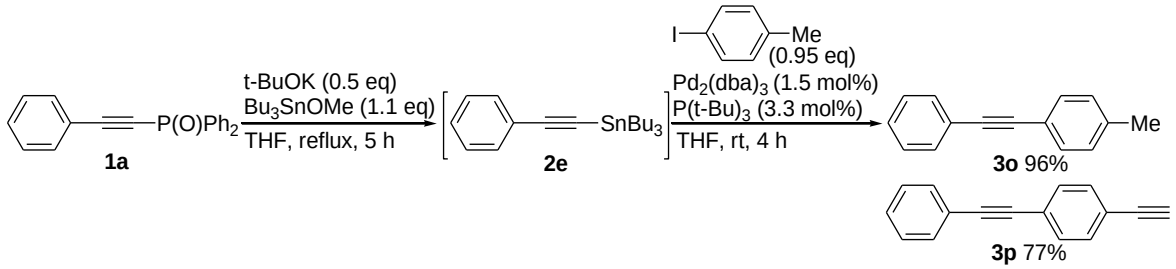
3m: pale-yellow powder, m.p. 187-189 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89(d, *J* = 8.8 Hz, 2H), 7.46-7.53 (m, 8H), 7.56-7.57 (m, 4H), 7.88-7.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.25 (d, *J* = 4.9 Hz), 84.25 (d, *J* = 167.9 Hz), 87.35, 92.94, 104.94 (d, *J* = 30.1 Hz), 114.04, 114.54, 118.88 (d, *J* = 4.7 Hz), 126.15, 128.64 (d, *J* = 13.4 Hz), 130.90 (d, *J* = 10.8 Hz), 131.37, 132.26 (d, *J* = 2.8 Hz), 132.34, 132.37, 132.83 (d, *J* = 121.9 Hz), 159.86; ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.78.



To a THF solution (10.0 mL) of **1f** (398.5 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol). After the mixture was stirred for 30 min under nitrogen at rt, 1-iodo-4-methoxybenzene (234.0 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 55 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/CH_2Cl_2, 6:1) to give the product **3n** in sufficiently pure form for further reaction. To a THF solution (10.0 mL) of crude product **3n** was added TBAF (1.0 M in THF, 1000.0 μL, 1.0 mmol) at 0 °C. After the mixture was stirred for 4 h under nitrogen at rt, 4-iodobenzonitrile (229.0 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), toluene (16.0 mL) and diisopropylamine (0.5 mL) was added sequentially. The mixture was stirred under nitrogen at 55 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 3:1) to afford **4h** in a pure form (303.4 mg, 91% yield).

4h: white powder, m.p. 226-227 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.89 (d, *J* = 7.4 Hz, 2H), 7.47-7.51 (m, 6H), 7.61-7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.33, 87.66, 89.26, 91.96, 93.52, 111.58, 114.03, 114.11, 114.90, 118.50, 121.48, 124.46, 128.03, 131.45, 131.68, 132.06, 133.14 (d, *J* = 6.2 Hz), 159.88; HRMS (FAB) calcd for $C_{24}H_{15}NO$ (M^+): 333.1154, found 333.1929.

Syntheses of 3o and 3p by One-pot t-BuOK-catalyzed Deprotection/ Stannylation/Migata- Kosugi-Stille coupling (representative procedure for 3o):



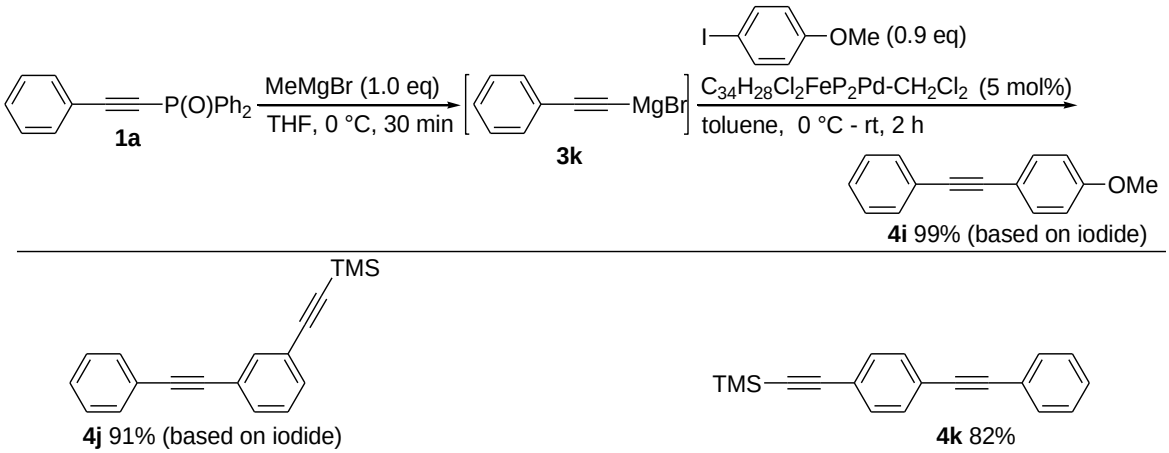
To a THF solution (5.0 mL) of **1a** (302.3 mg, 1.0 mmol) were added Bu_3SnOMe (353.2 mg, 316.8 μL, 1.1 mmol) and t-BuOK (56.1 mg, 0.5 mmol). The mixture was stirred for 5 h under nitrogen at refluxing temperature. After cooling, 1-iodo-4-methylbenzene (207.1 mg, 0.95 mmol), $P(t\text{-}Bu)_3$ (0.1 M in THF, 330.0 μL, 0.033 mmol) and $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol) was added into the reaction mixture sequentially. The mixture was stirred under nitrogen at rt for 4 h, and then quenched with NH_4Faq (10%, 10.0 mL). The mixture was extracted with diethyl ether (3 × 10.0 mL). The collected organic layers were dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to afford **3o** in a pure form (175.3 mg, 96% yield, based on iodide).

3o:[13] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.30-7.36 (m, 3H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.52-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.49, 88.68, 89.52, 120.10, 123.39, 128.05, 128.29, 129.09, 131.45, 131.50, 138.35.

3p:[14] white powder; m.p. 91-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (s, 1H),

7.35-7.36 (m, 3H), 7.46-7.50 (m, 4H), 7.52-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.86, 83.24, 88.79, 91.33, 121.79, 122.85, 123.71, 128.38, 128.52, 131.44, 131.60, 132.04.

Syntheses of 4i, 4j and 4k by One-pot MeMgBr-catalyzed Deprotection/ Pd-catalyzed Coupling (representative procedure for 4i):



To a THF solution (10.0 mL) of **1a** (302.3 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol). After the mixture was stirred for 30 min under nitrogen at 0 °C, 1-iodo-4-methoxybenzene (210.6 mg, 0.9 mmol), $C_{34}H_{28}Cl_2FeP_2Pd$-CH_2Cl_2 (40.8 mg, 0.05 mmol) were added at 0 °C. The mixture was stirred under nitrogen at rt for 2 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane) to give **4i** in a pure form (185.6 mg, 85% yield).

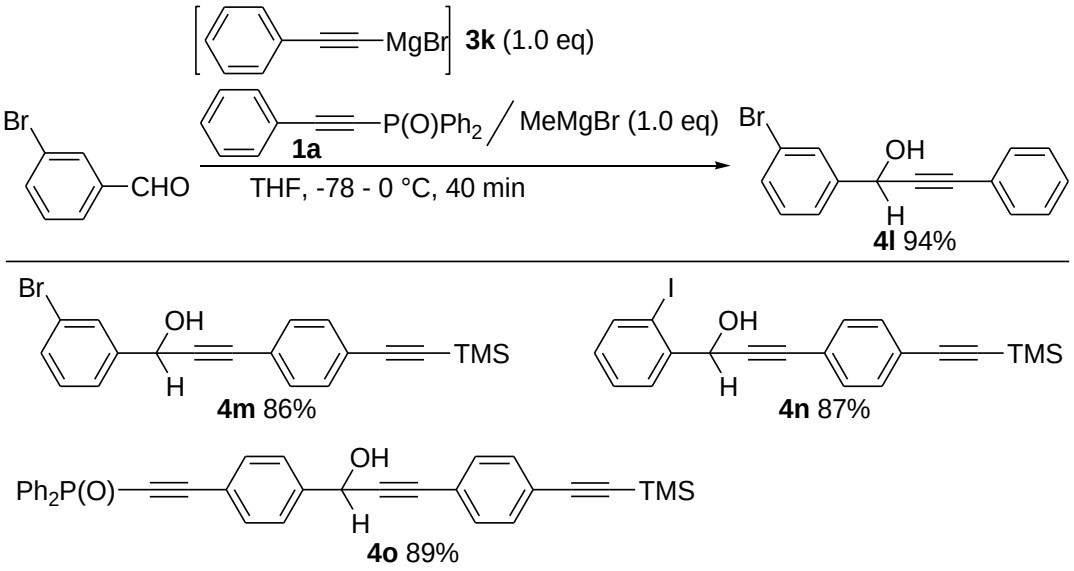
4i:[15] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.29-7.36 (m, 3H), 7.46-7.52 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.27 (d, *J* = 4.0 Hz), 88.04, 89.34, 113.96 (d, *J* = 9.8 Hz), 115.34, 123.56, 127.92, 128.25, 131.42, 133.03 (d, *J* = 6.2 Hz), 159.58.

4j: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.27-7.30 (m, 1H), 7.34-7.36 (m, 3H), 7.42 (dt, *J* = 1.4 Hz, 8.0 Hz, 1H), 7.46 (dt, *J* = 1.4 Hz, 7.6 Hz,

1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.52-7.53 (m, 1H), 7.65-7.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.09 (d, *J* = 4.1 Hz), 88.45, 89.91, 94.93, 104.12, 122.98, 123.43, 123.49, 128.28, 128.34, 128.36, 131.46-131.57(m), 131.61, 135.00 (d, *J* = 2.6 Hz); HRMS (FAB) calcd for $C_{19}H_{18}Si$ (M^+): 274.1178, found 274.1838.

4k:[16] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.34-7.36 (m, 3H), 7.43-7.47 (m, 4H), 7.51-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.09 (d, *J* = 4.1 Hz), 88.99, 91.26, 96.21, 104.61, 122.86, 122.96, 123.31, 128.37, 128.45, 131.37, 131.59, 131.87.

Syntheses of 4l, 4m, 4n and 4o by One-pot MeMgBr-catalyzed Deprotection/Nucleophilic Addition to Aldehyde (representative procedure for 4l):



To a THF solution (10.0 mL) of **1a** (302.3 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol), and the reaction mixture was stirred for 20 min under nitrogen at 0 °C. This reaction mixture was added to a THF solution (10.0 mL) of 3-bromobenzaldehyde (185.0 mg, 1.0 mmol) at -78 °C. And the mixture was stirred under nitrogen at 0 oC for 40 min. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$.

After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 8:1) to give **4l** in a pure form (269.9 mg, 94% yield).

4l: [17] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (d, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 6.1 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.31-7.37 (m, 3H), 7.47-7.49 (m, 3H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 64.34, 87.12, 87.91, 122.04, 122.66, 125.30, 128.33, 128.81, 129.79, 130.17, 131.44, 131.77, 142.72.

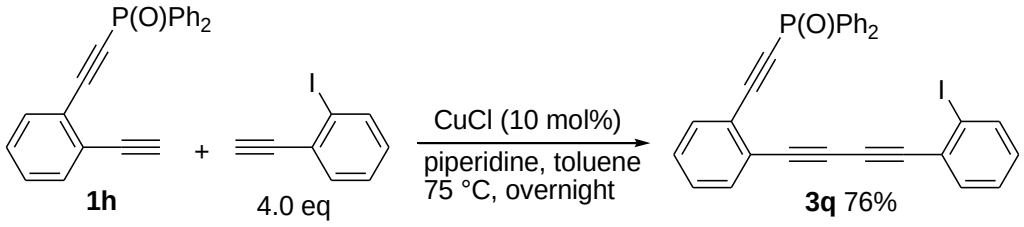
4m: white powder; m.p. 86-87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 2.61 (s, 1H), 5.63 (s, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.36-7.41 (m, 4H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.14 (d, *J* = 4.1 Hz), 64.25, 86.58, 89.74, 96.54, 104.34, 122.00, 122.65, 123.48, 125.21, 129.70, 130.16, 130.23, 131.52 (d, *J* = 4.6 Hz), 131.83, 142.48; HRMS (FAB) calcd for $C_{20}H_{19}BrOSi$ ($M\text{-}OH^+$): 365.0389, found 365.0703.

4n: colorless gel; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 2.49 (d, *J* = 5.5 Hz, 1H), 5.88 (d, *J* = 5.4 Hz, 1H), 7.05 (dt, *J* = 1.8 Hz, *J* = 7.6 Hz, 1H), 7.40-7.44 (m, 5H), 7.81 (dd, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.87 (dd, *J* = 0.9 Hz, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.13 (d, *J* = 4.1 Hz), 68.91 (d, *J* = 2.5 Hz), 86.41, 89.68, 96.39, 97.94, 104.42, 122.24, 123.28, 128.09, 128.69, 130.12 (d, *J* = 9.3 Hz), 131.50, 131.75, 139.68, 142.22; HRMS (FAB) calcd for $C_{20}H_{19}IOSi$ ($M\text{-}OH^+$): 413.0250, found 413.0812.

4o: white powder; m.p. 75-77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 2.65 (s, 1H), 5.72 (d, *J* = 6.1 Hz, 1H), 7.36-7.42 (m, 4H), 7.48-7.52 (m, 4H), 7.55-7.58 (m, 2H), 7.62 (br, 4H), 7.88-7.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.16 (d, *J* = 4.1 Hz), 64.01, 82.44 (d, *J* = 171.5 Hz), 85.76, 90.71, 96.27, 104.41, 105.62 (d, *J* = 30.4 Hz), 119.01 (d, *J* = 3.5 Hz), 122.46, 123.09, 126.78, 128.65 (d, *J* = 12.4 Hz), 130.85 (d, *J* = 11.3 Hz), 131.47, 131.68, 132.32, 132.49 (d, *J* = 122.9

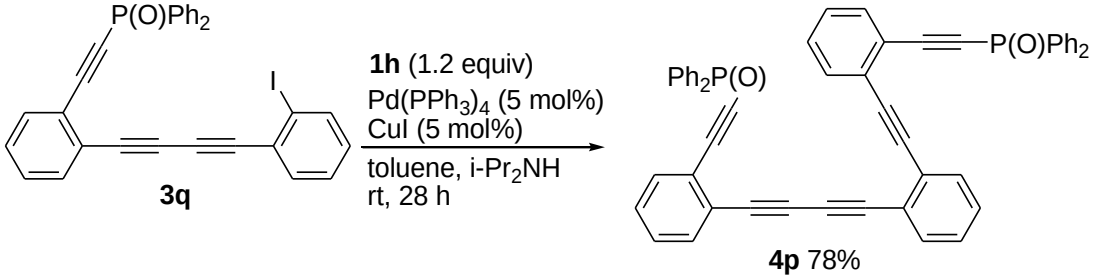
Hz), 132.63, 144.34; HRMS (FAB) calcd for $C_{34}H_{29}O_2PSi$ ($M\text{-}OH^+$): 511.1674, found 511.1711.

Synthesis of Cyclic Pentayne 7a by One-pot Deprotection/Eglington cyclization



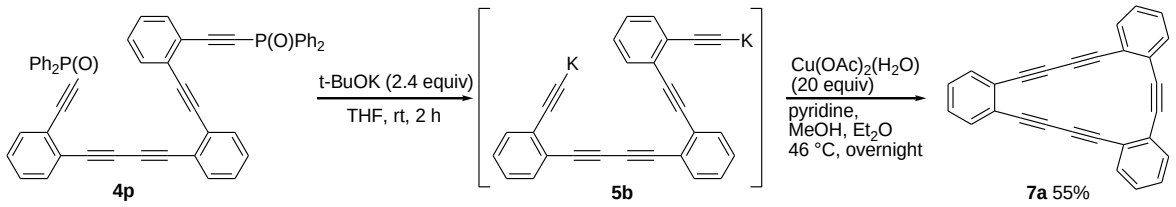
A mixture of **1h** (326.3 mg, 1.0 mmol), 1-ethynyl-2-iodobenzene (912.1 mg, 4.0 mmol), CuCl (9.9 mg, 0.1 mmol), piperidine (50.0 μL, 0.5 mmol) and toluene (10.0 mL) in an atmosphere of air was stirred at 75 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **3q** in a pure form (419.8 mg, 76% yield).

3q:[12] yellow powder; m.p. 129-131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (dt, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H) 7.32 (t, *J* = 7.6 Hz, 1H), 7.36-7.41 (m, 1H), 7.42-7.44 (m, 2H), 7.48-7.50 (m, 6H), 7.60-7.62 (m, 2H), 7.85 (d, *J* = 7.9 Hz 1H), 8.00-8.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 76.91, 78.48, 80.67, 84.57, 86.90 (d, *J* = 166.5 Hz), 100.81, 102.60 (d, *J* = 29.4 Hz), 123.57 (d, *J* = 4.1 Hz), 125.25 (d, *J* = 2.1 Hz), 127.86, 128.17, 128.71 (d, *J* = 12.4 Hz), 129.16, 130.27, 130.45, 130.52, 131.05 (d, *J* = 11.4 Hz), 132.14, 132.80 (d, *J* = 122.0 Hz), 133.05 (d, *J* = 6.6 Hz), 133.94, 138.88.



A toluene solution (10.0 mL) of **3q** (276.2 mg, 0.5 mmol), **1h** (195.9 mg, 0.6 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol) and diisopropylamine (0.25 mL) was stirred under nitrogen at rt for 28 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt) and recrystallization from THF/hexane to afford **4p** in a pure form (292.8 mg, 78% yield).

4p:[12] pale-yellow powder; m.p. 114-116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.24 (m, 2H), 7.30-7.34 (m, 3H), 7.35-7.39 (m, 5H), 7.40-7.48 (m, 11H), 7.59-7.63 (m, 3H), 7.92-7.98 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.61, 78.64, 80.44, 81.85, 86.41 (d, *J* = 167.9 Hz), 86.90 (d, *J* = 166.5 Hz), 91.93, 92.42, 102.59 (d, *J* = 29.4 Hz), 103.53 (d, *J* = 30.0 Hz), 122.14 (d, *J* = 3.6 Hz), 123.45 (d, *J* = 4.1Hz), 123.92, 125.28 (d, *J* = 2.0 Hz), 126.18, 126.44 (d, *J* = 2.0 Hz), 128.43 (d, *J* = 12.4 Hz), 128.46 (d, *J* = 11.9 Hz), 128.59, 128.61, 128.71, 129.12, 129.24, 130.28, 130.47, 130.90 (d, *J* = 11.3 Hz), 130.91 (d, *J* = 11.4 Hz), 132.11, 132.41, 132.55, 132.73 (d, *J* = 122.0 Hz), 132.86, 132.09, 132.98 (d, *J* = 122.0 Hz), 133.21.



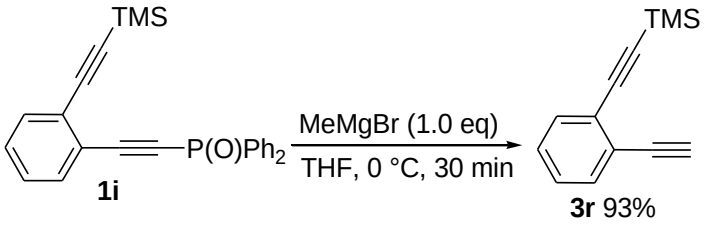
4p **5b** **7a** 55%

To a THF solution (4 mL) of **4p** (75.1 mg, 0.1 mmol) was added t-BuOK (26.9 mg, 0.24 mmol), and the mixture was stirred under nitrogen at rt for 4 h. Then this reaction mixture was diluted with pyridine (20.0 mL) and methanol (20.0 mL). This diluted reaction mixture was added to a 0.05 M solution consisting of $Cu(OAc)_2(H_2O)$ (399.3 mg, 2 mmol) in a 6:6:1 mixture of pyridine, methanol, and Et_2O at 46 °C via syringe over 7 hours. And the mixture was stirred under air for

overnight. After cooling, the mixture in the reaction flask was concentrated. The resultant sludge was diluted with CH_2Cl_2 and stirred vigorously with 10% HCl solution for 30 min. The organic layer was subsequently washed with dilute bicarbonate solution, water, and then brine, followed by drying over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 8:1) to afford **7a** in a pure form (19.2 mg, 55% yield).

7a:[9] pale-yellow powder; m.p.159 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.29 (m, 6H), 7.32-7.35 (m, 2H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.66, 80.81, 81.59, 82.16, 92.99, 123.20, 126.92, 128.13, 128.49, 129.05, 129.07, 130.47, 133.67, 134.48.

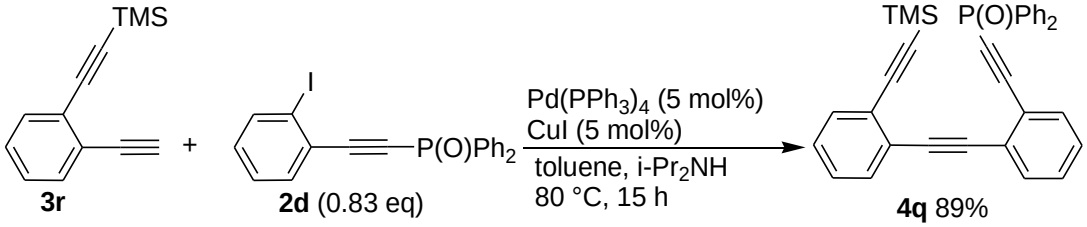
Synthesis of Cyclic Pentayne 7b by One-pot Deprotection/Eglington cyclization



1i **3r** 93%

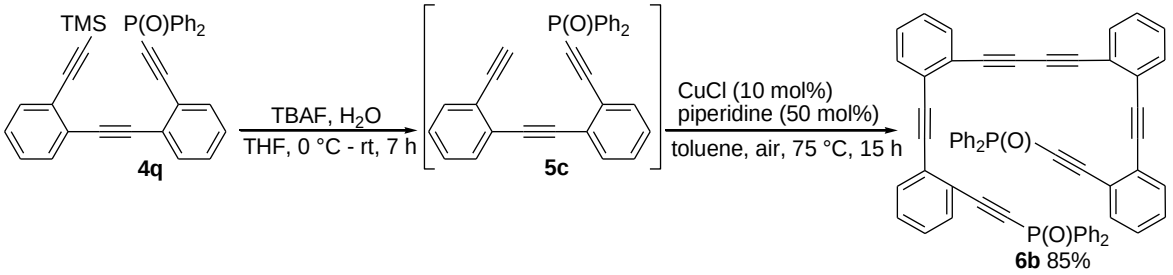
To a THF solution (10 mL) of **1i** (398.5 mg, 1.0 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 333.3 μL, 1.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane) to afford **3r** in a pure form (182.5 mg, 92%).

3r:[18] white powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.27 (s, 9H), 3.30 (s, 1H), 7.27-7.30 (m, 2H), 7.46-7.50 (m, 2H).



A toluene solution (10.0 mL) of **3r** (99.2 mg, 0.5 mmol), **2d** (179.8 mg, 0.42 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol) and diisopropylamine (0.25 mL) was stirred under nitrogen at 80 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt/EtOAc, 1:1) and recrystallization from THF/hexane to afford **4q** in a pure form (186.4 mg, 89% yield).

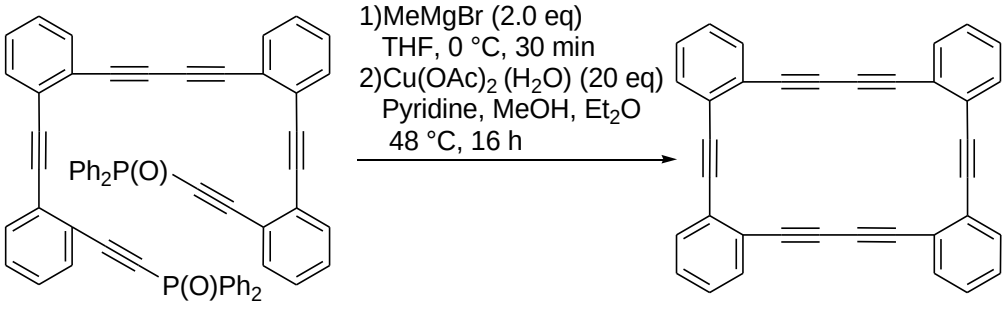
4q: white powder; m.p. 112-113 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.22 (s, 9H), 7.11-7.14 (m, 1H), 7.16-7.18 (m, 1H), 7.25-7.28 (m, 4H), 7.34-7.37 (m, 5H), 7.42-7.48 (m, 3H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.91-7.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.11 (d, *J* = 4.1 Hz), 86.33 (d, *J* = 168.4 Hz), 90.90, 93.09, 99.07, 103.17, 103.51 (d, *J* = 29.4 Hz), 122.26 (d, *J* = 3.6 Hz), 125.26, 125.76, 126.89 (d, *J* = 1.5 Hz), 128.11-128.27 (m), 128.46-128.62 (m), 130.20, 130.91 (d, *J* = 11.4 Hz), 132.02 (d, *J* = 2.0 Hz), 132.26, 132.99 (d, *J* = 122.0 Hz), 133.02; HRMS (FAB) calcd for $C_{33}H_{27}OPSi$ ($M+H^+$): 499.1569, found 499.2006.



To a THF solution (10.0 mL) of **4q** (249.3 mg, 0.5 mmol) was added (1.0 M in THF, 500.0 μL, 0.5 mmol) at 0 °C, the mixture was stirred for 7 h under nitrogen at

rt. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/AcOEt, 1:1) to give the product **5c** in sufficiently pure form for further reaction. A toluene solution (10.0 mL) of product **5c** (213.2 mg, 0.5 mmol), CuCl (5.0 mg, 0.05 mmol) and piperidine (24.8 μL, 0.25 mmol) in an atmosphere of air was stirred at 75 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (AcOEt) to afford **6b** in a pure form (361.6 mg, 85% yield).

6b: white powder; m.p. 227-228 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.2 Hz, 2H), 7.19 (dt, *J* = 1.3 Hz, *J* = 7.6 Hz, 2H), 7.21-7.25 (m, 3H), 7.28-7.32 (m, 3H), 7.37-7.40 (m, 8H), 7.45-7.49 (m, 4H), 7.54-7.59 (m, 6H), 7.93-7.97 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.02, 81.34, 86.38 (d, *J* = 168.5 Hz), 91.84, 92.58, 103.56 (d, *J* = 30.0 Hz), 121.99 (d, *J* = 4.1 Hz), 124.42, 126.28, 126.53 (d, *J* = 2.1 Hz), 128.28-128.42 (m), 128.52-128.65 (m), 128.97, 129.01, 130.34, 130.39, 130.94 (d, *J* = 11.3 Hz), 132.12, 132.67, 132.75 (d, *J* = 1.0 Hz), 133.04 (d, *J* = 122.9 Hz); HRMS (FAB) calcd for $C_{60}H_{36}O_2P_2$ ($M+H^+$): 851.2191, found 851.2702.

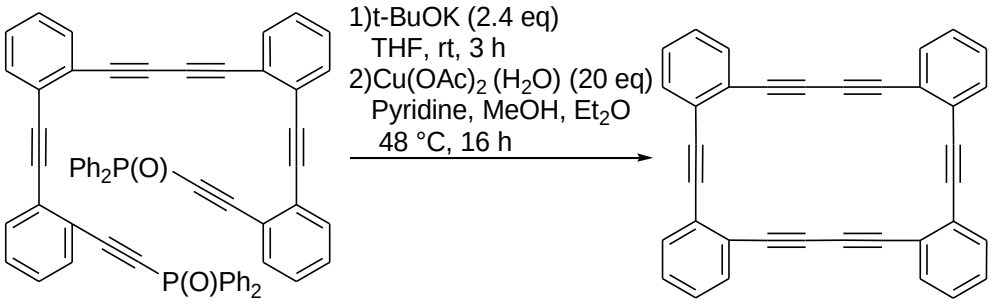


6b **7b** 36%

To a THF solution (5 mL) of **6b** (85.1 mg, 0.1 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 66.7 μL, 0.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for

30 min. Then this reaction mixture was diluted with pyridine (20.0 mL) and methanol (20.0 mL). This diluted reaction mixture was added to a 0.05 M solution consisting of $Cu(OAc)_2(H_2O)$ (399.3 mg, 2 mmol) in a 6:6:1 mixture of pyridine, methanol, and Et_2O at 48 °C via syringe over 7 hours. And the mixture was stirred under air for overnight. After cooling, the mixture in the reaction flask was concentrated. The resultant sludge was diluted with CH_2Cl_2 and stirred vigorously with 10% HCl solution for 30 min. The organic layer was subsequently washed with dilute bicarbonate solution, water, and then brine, followed by drying over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 8:1) to afford **7b** in a pure form (16.1 mg, 36% yield).

7b:[9] pale-yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.30 (m, 4H), 7.32-7.36 (m, 4H), 7.54 (br, 4H), 7.55 (br, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 78.09, 80.99, 91.59, 125.04, 126.44, 128.22, 128.67, 131.66, 133.21.

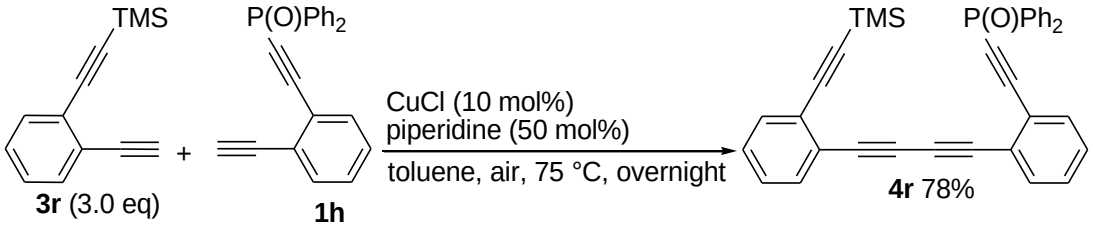


6b **7b** 32%

To a THF solution (5 mL) of **6b** (85.1 mg, 0.1 mmol) was added t-BuOK (26.9 mg, 0.24 mmol), and the mixture was stirred under nitrogen at rt for 3 h. Then this reaction mixture was diluted with pyridine (20.0 mL) and methanol (20.0 mL). This diluted reaction mixture was added to a 0.05 M solution consisting of $Cu(OAc)_2(H_2O)$ (399.3 mg, 2 mmol) in a 6:6:1 mixture of pyridine, methanol, and Et_2O at 48 °C via syringe over 7 hours. And the mixture was stirred under air for overnight. After cooling, the mixture in the reaction flask was concentrated. The resultant sludge was diluted with CH_2Cl_2 and stirred vigorously with 10% HCl

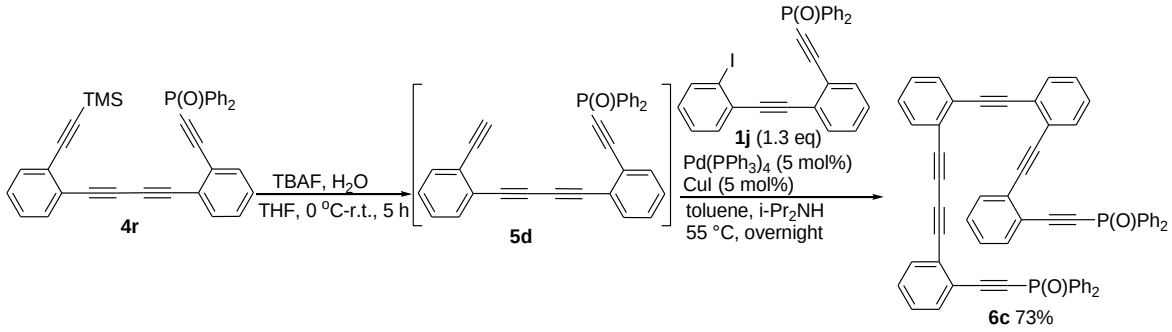
solution for 30 min. The organic layer was subsequently washed with dilute bicarbonate solution, water, and then brine, followed by drying over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 8:1) to afford **7b** in a pure form (14.4 mg, 32% yield).

Synthesis of Cyclic Pentayne 7c by One-pot Deprotection/Eglington cyclization



A mixture of **1h** (326.3 mg, 1.0 mmol), **3r** (595.0 mg, 3.0 mmol), CuCl (9.9 mg, 0.1 mmol), piperidine (50.0 μL, 0.5 mmol) and toluene (10.0 mL) in an atmosphere of air was stirred at 75 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/AcOEt, 1:1) to afford **4r** in a pure form (407.7 mg, 78% yield).

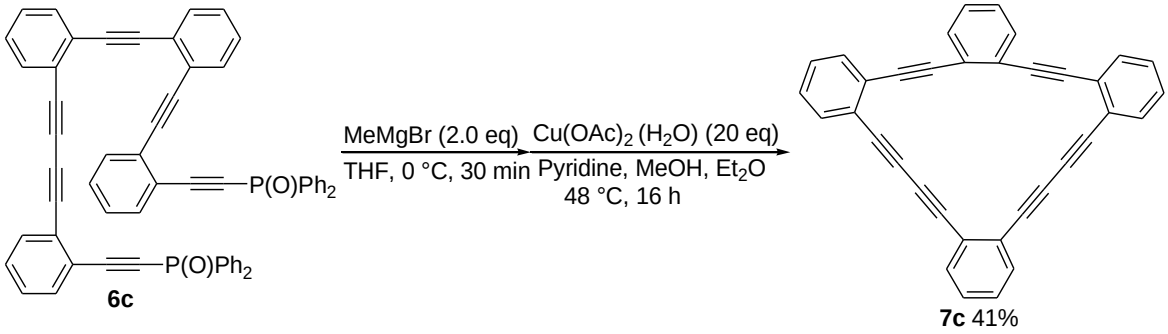
4r: yellow powder; m.p. 57-60 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 7.29-7.30 (m, 1H), 7.33-7.40 (m, 2H), 7.41-7.45 (m, 2H), 7.48-7.52 (m, 7H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H) 7.99-8.03 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -0.16 (d, *J* = 5.9 Hz), 77.21, 78.74, 80.10, 81.93, 86.76 (d, *J* = 166.9 Hz), 100.14, 102.68 (d, *J* = 29.5 Hz), 102.73, 123.49 (d, *J* = 4.1 Hz), 124.55, 125.48 (d, *J* = 2.2 Hz), 127.03, 128.22, 128.76 (d, *J* = 13.6 Hz), 129.02, 129.08, 130.26, 131.09, 131.74 (d, *J* = 119.7 Hz), 132.02, 132.15 (d, *J* = 2.8 Hz), 133.11, 133.15, 133.65; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.07; HRMS (FAB) calcd for $C_{35}H_{27}OPSi$ ($M+H^+$): 523.1569, found 523.2153.



To a THF solution (10.0 mL) of **4r** (261.3 mg, 0.5 mmol) was added (1.0 M in THF, 500.0 μL, 0.5 mmol) at 0 °C, the mixture was stirred for 5 h at rt. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/AcOEt, 1:1) to give the product **5d** in sufficiently pure form for further reaction. A toluene solution (10.0 mL) of product **5d** (225.2 mg, 0.5 mmol), **1j** (343.4 mg, 0.65 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol), CuI (4.8 mg, 0.025 mmol), and diisopropylamine (0.25 mL) was stirred under nitrogen at 55 °C for overnighy. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (EtOAc) to give **6c** in a pure form (310.6 mg, 73% yield).

6c: white powder; m.p. 91-93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13-7.16 (m, 1H), 7.22-7.36 (m, 12H), 7.41-7.49 (m, 10H), 7.51-7.54 (m, 3H), 7.56 (t, *J* = 4.6 Hz, 1H), 7.64 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H), 7.88-7.93 (m, 4H), 7.95-8.00 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.60, 78.75, 80.36, 82.01, 86.44 (d, *J* = 168.0 Hz), 86.79 (d, *J* = 167.0 Hz), 91.19, 91.76, 92.92, 93.09, 102.69 (d, *J* = 29.5 Hz), 103.59 (d, *J* = 29.9 Hz), 122.24 (d, *J* = 3.6 Hz), 123.36 (d, *J* = 3.6 Hz), 123.76, 124.90, 125.31 (d, *J* = 2.0 Hz), 125.38, 126.82, 128.24-128.39 (m), 128.46-128.67 (m), 128.74-128.76 (m), 129.04, 129.24, 130.26-130.32 (m), 130.90 (d, *J* = 11.4 Hz), 130.96 (d, *J* = 11.8 Hz), 132.08-132.14 (m), 132.29 (d, *J* = 3.1 Hz), 132.38 (d,

J = 1.0 Hz), 132.79 (d, *J* = 121.9 Hz), 132.93 (d, *J* = 121.9 Hz), 132.99, 133.01, 133.20, 133.22; HRMS (FAB) calcd for $C_{60}H_{36}O_2P_2$ ($M+H^+$): 851.2191, found 851.2945.

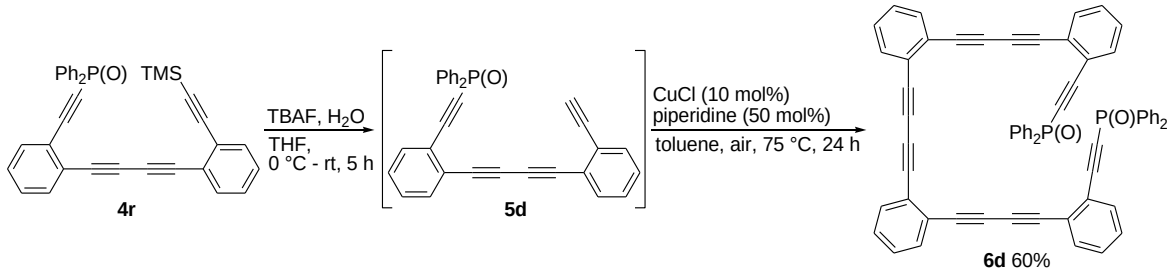


6c **7c** 41%

To a THF solution (5 mL) of **6c** (85.1 mg, 0.1 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 66.7 μL, 0.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then this reaction mixture was diluted with pyridine (20.0 mL) and methanol (20.0 mL). This diluted reaction mixture was added to a 0.05 M solution consisting of $Cu(OAc)_2(H_2O)$ (399.3 mg, 2 mmol) in a 6:6:1 mixture of pyridine, methanol, and Et_2O at 48 °C via syringe over 7 hours. And the mixture was stirred under air for overnight. After cooling, the mixture in the reaction flask was concentrated. The resultant sludge was diluted with CH_2Cl_2 and stirred vigorously with 10% HCl solution for 30 min. The organic layer was subsequently washed with dilute bicarbonate solution, water, and then brine, followed by drying over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 8:1) to afford **7c** in a pure form (18.4 mg, 41% yield).

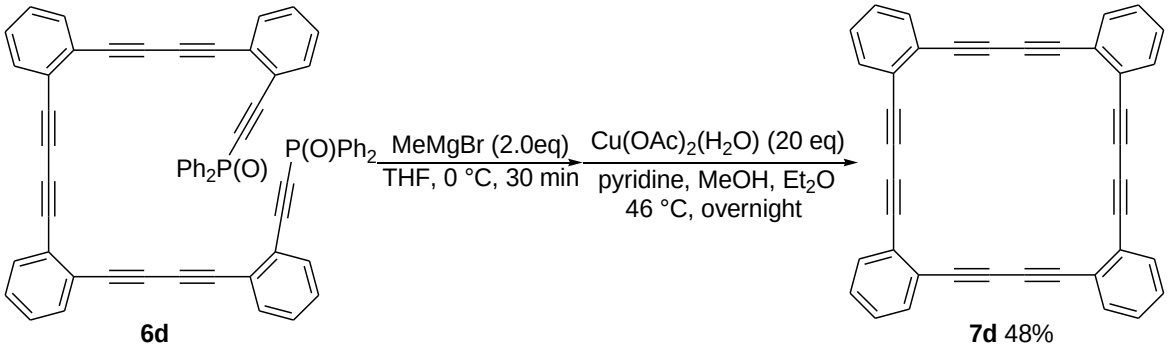
7c: [9] pale-yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.27-7.33 (m , 8H), 7.44-7.46 (m, 2H), 7.51-7.54 (m, 4H), 7.58-7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.40, 79.00, 80.26, 81.28, 90.29, 91.65, 124.33, 124.99, 126.79, 127.17, 127.99, 128.08, 128.68, 128.71, 131.38, 132.31, 132.77, 132.98.

Synthesis of Cyclic Pentayne 7d by One-pot Deprotection/Eglington cyclization



To a THF solution (10.0 mL) of **4r** (261.3 mg, 0.5 mmol) was added TBAF (1.0 M in THF, 500.0 μL, 0.5 mmol) at 0 °C, the mixture was stirred for 5 h at rt. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to a short column chromatography on silica gel (hexane/AcOEt, 1:1) to give the product **5d** in sufficiently pure form for further reaction. A toluene solution (10.0 mL) of product **5d** (225.2 mg, 0.5 mmol), CuCl (5.0 mg, 0.05 mmol) and piperidine (24.8 μL, 0.25 mmol) in an atmosphere of air was stirred at 75 °C for 15 h. After workup with CH_2Cl_2 and NH_4Claq, the organic layer was washed with brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (EtOAc) to give **6d** in a pure form (269.7 mg, 60% yield).

6d: red powder; m.p. 118-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.35 (m, 8H), 7.41-7.43 (m, 2H), 7.44-7.52 (m, 13H), 7.54-7.56 (m, 5H), 7.98-8.03 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.76, 78.18, 78.63, 80.78, 80.98, 81.26, 86.85 (d, J = 166.9 Hz), 102.60 (d, J = 29.4 Hz), 123.38 (d, J = 4.0 Hz), 124.77, 124.98, 125.20 (d, J = 2.0 Hz), 128.71 (d, J = 13.4 Hz), 129.02, 129.11, 129.18, 130.27, 130.97 (d, J = 11.3 Hz), 132.19, 132.72 (d, J = 121.9 Hz), 132.89, 133.17, 133.36, 133.46; ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.01; HRMS (FAB) calcd for $C_{64}H_{36}O_2P_2$ ($M+H^+$): 899.2191, found 899.4869.



6d **7d** 48%

To a THF solution (15 mL) of **6d** (89.9 mg, 0.1 mmol) was added MeMgBr (3.0 M in Ethyl Ether, 66.7 μL, 0.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min, THF solvent was evaporated under vacuum. The concentrated reaction mixture was diluted with pyridine (20 mL) and methanol (20 mL). This diluted reaction mixture was added to a 0.05 M solution consisting of $Cu(OAc)_2(H_2O)$ (399.3 mg, 2 mmol) in a 6:6:1 mixture of pyridine, methanol, and Et_2O at 46 °C via syringe over 6 hours. And the mixture was stirred under air for overnight. After cooling, the mixture in the reaction flask was concentrated. The resultant sludge was diluted with CH_2Cl_2 and stirred vigorously with 10% HCl solution for 30 min. The organic layer was subsequently washed with dilute bicarbonate solution, water, and then brine, followed by drying over $MgSO_4$. After filtration, the solvents were evaporated. The crude product was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 6:1) to afford **34** in a pure form (23.8 mg, 48% yield).[6)]

34:[9] pale-yellow powder; m.p.182 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.34 (m, 8H), 7.54-7.55 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 77.98, 80.67, 125.26, 128.86, 133.30.

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Chapter 5 Conclusion

In this thesis, a new protecting group, $Ph_2P(O)$ for terminal ethynes is developed. This protection group can be introduce to terminal acetylenes by treatment of phenylethynes with Ph_2PCl and CuI followed by H_2O_2-oxidation or by treatment of lithium acetylide with $Ph_2P(O)Cl$ in one-pot manner.

$Ph_2P(O)$ is stable under acidic conditions. While treatment of $Ph_2P(O)$-protected ethynes with strong bases such as t-BuOK, MeMgBr and BuLi enables facile deprotection to provide the corresponding ethynes. Facile selective deprotection of $Ph_2P(O)$ and TMS group is achieved by changing deprotecting reagent. By treatment with MeMgBr, $Ph_2P(O)$ was deprotected selectively in the presence of TMS group. While by treatment with TBAF, TMS group was deprotected selectively in the presence of $Ph_2P(O)$ group.

High polarity of $Ph_2P(O)$ group allows facile separation of $Ph_2P(O)$-protected ethynes from byproducts and remaining starting compouds which are inseparable or difficult-to-separate when the trimethysilyl group is used instead of $Ph_2P(O)$.

$Ph_2P(O)$-protected ethynes remain intact in Sonogashira coupling, Suzuki coupling and oxidative homocoupling, and a series of unsymmetrically substituted arylethynylphosphine oxides are prepared in pure forms easily by taking advantage of high polarity of $Ph_2P(O)$. A number of unsymmetrically substituted aryl-substituted acetylenes are synthesized by subjecting phosphorylethynes to deprotection, stannylation and Migata-Kosugi-Stille coupling.

We have established a new methodology of C-C bond formation by invoking *in situ* deprotection of $Ph_2P(O)$ group/transition metal-catalyzed coupling or nucleophilic addition of the resulting acetylide.

In one-pot deprotection/Sonogashira coupling protocol, unsymmetrically substituted aryleneethynylenes were obtained easily. When a stoichiometric

amount of t-BuOK was used for deprotection, aryl halide having $Ph_2P(O)$-protected ethyne could be employed as a coupling counterpart, and the corresponding aryleneethynylene having $Ph_2P(O)$-protected ethyne was obtained. When aryl halide having $Ph_2P(O)$-protected ethyne employed as a coupling counterpart in a stoichiometric amount of MeMgBr-catalyzed deprotection/ Sonogashira coupling, transformation of magnesium acetylide to copper acetylide is needed. Otherwise, the desired product is contaminated by the by-products. Unsymmetrically substituted diyne is prepared from TMS and $Ph_2P(O)$-protected diyne easily by one-pot de-$Ph_2P(O)$/Sonogashira coupling followed by one-pot de-TMS/Sonogashira coupling.

By compaction of deprotection, stannylation and palladium-catalyzed coupling, one-pot deprotection/Migata-Kosugi-Stille coupling was realized. In this coupling protocol, *in situ*-prepared stannylethyne reacted preferentially with aryl iodide, while unprotected terminal ethyne moiety of aryl iodide remained intact.

By taking advantage of nucleophilicity of magnesium acetylide and facile selective deprotection of $Ph_2P(O)$, a series of functionalized phenylprop- 2-yn-1-ol derivatives are prepared successfully through one-pot MeMgBr-catalyzed deprotection/nucleophilic addition to aldehyde.

In situ deprotection of $Ph_2P(O)$ group/intramolecular Eglington coupling proceeds smoothly to give cyclic pentayne, hexayne and octaynes in moderate yields.

Publications

Published Paper (doctoral thesis relative paper)

1. **L-F. Peng**, F. Xu, Y. Suzuma, A. Orita, J. Otera. One-Pot Transformation of $Ph_2P(O)$-Protected Ethynes: Deprotection Followed by Transition Metal-Catalyzed Coupling. *J. Org. Chem.*, **2013**, *78* (24), 12802–12808.

2. F. Xu, **L-F. Peng**, A. Orita, J. Otera. Dihalo-Substituted Dibenzopentalenes: Their Practical Synthesis and Transformation to Dibenzopentalene Derivatives. *Org. Lett.*., **2012**, *14*(15), 3970-3973.

3. S. Kawai, A. Sadeghi, F. Xu, **L-F. Peng**, R. Pawlak, T. Glatzel, A. Willand, A. Orita, J. Otera, S. Goedecker, E. Meyer. Obtaining Detailed Structural Information about Supramolecular Systems on Surfaces by Combining High-Resolution Force Microscopy with *ab Initio* Calculations. *ACS Nano*, **2013**, *7* (10), 9098–9105.

4. M. Muramatsu, T. Katayama, S. Ito, Y. Nagasawa, D. Matsuo, Y. Suzuma, **L-F. Peng**, A. Orita, J. Otera, H. Miyasaka. Photoinduced Charge-Transfer Dynamics of Sequentially Aligned Donor–Acceptor System in an Ionic Liquid. *Photochem. Photobiol. Sci.*, **2013**, *12*, 1885-1894.

Published Paper (other paper)

5. R-H. Qiu, X-H. Xu, **L-F. Peng**, Y-L. Zhao, N-B. Li, S-F. Yin. Strong Lewis Acids of Air-Stable Metallocene Bis(perfluorooctanesulfonate)s as High-Efficiency Catalysts for Carbonyl-Group Transformation Reactions. *Chem. Eur. J*. **2012**, *18*(20), 6172–6182.

6. H-N. Xu, W-Q. Liu, **L-F. Peng**, R-H. Qiu, Y-L. Zhao, J-G. Pan, X-H. Xu. Titanocene Perfluorooctanesulfonate-Catalyzed Reductive Cleavage of S-S Bond by Zinc in Commercial Tetrahedron and Its Application in Synthesis of Thioesters. *Chinese. J. Org. Chem.*, **2011**, *31*(10), 1719-1722.

7. P. Tan, X-H. Yin, A-H. Yu, R-H. Qiu, **L-F. Peng**, X-H. Xu, Y-L. Zhao, R-R. Tang. Highly Stereoselective Synthesis of 1,2-Diorganothio-1-alkenes via Hydrothiolation of Alkynyl Sulfides Catalyzed by Cesium Hydroxide. *Chinese. J. Org. Chem.*, **2011**, *29*(4), 765-768.

Presentation: (○:exhibitor)

1. One-Pot Transformation of $Ph_2P(O)$-Protected Ethynes: Deprotection/Transition Metal-Catalyzed Coupling
   A. Orita, ○**L-F. Peng**, F. Xu, K. Shinohara, J. Otera, K. Isozaki, H. Takaya, M. Nakamura.
   Proceeding of The International Symposium Organized by Institute for Chemical Research (ICRIS'14), Kyoto, Japan, 2014.3. (Poster)

2. Dihalo-Substituted Dibenzopentalenes: Their Practical Synthesis and Transformation to Dibenzopentalene Derivatives
   A. Orita, ○F. Xu, **L-F. Peng**, K. Shinohara, J. Otera, K. Isozaki, H. Takaya, M. Nakamura.
   Proceeding of The International Symposium Organized by Institute for Chemical Research (ICRIS'14), Kyoto, Japan, 2014.3. (Poster)

3. One-Pot $Ph_2P(O)$-Deprotection/Sonogashira Coupling
   A. Orita, ○**L-F. Peng**, Y. Suzuma, F. Xu, J. Otera.
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