CHEMICAL REVIEWS

Review

Silver-Catalyzed C#H and C#Si Bond Transformations and Related Processes

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Chem. Rev., **2008**, 108 (8), 3199-3222 • DOI: 10.1021/cr078359u • Publication Date (Web): 09 July 2008

Silver-Catalyzed C_{sp}−H and C_{sp}−Si Bond Transformations and Related Processes

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Received February 6, 2008

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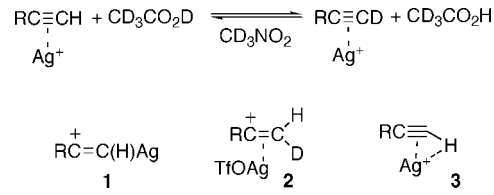
1. Introduction

Alkynes are extremely versatile unsaturated hydrocarbons,[1] which are ubiquitously found in functional materials,[2] supramolecules,[3] and natural products.[4] Further, they are also useful synthetic intermediates from which a wide variety of saturated and unsaturated compounds can be obtained via addition reactions across their C−C triple bonds.[5] In particular, recent advances in the transition-metal-catalyzed transformations of alkynes have provided rapid and concise access to complex molecular architectures.[6] Therefore, the development of a new preparative method of substituted alkynes promises to greatly expand the utility of the synthetic methodologies based on their transformations.

C_{sp^3}-substituted alkynes have conventionally been synthesized through the deprotonation of terminal alkyne precursors and subsequent reactions of the resultant metal acetylides with electrophiles such as alkyl halides and carbonyl compounds.[7] Since the acidity of acetylenic protons is higher than those of alkanes and alkenes (pK_a values of acetylene, ethylene, and ethane relative to water are 25, 44, and 50, respectively),[8] the deprotonation of terminal alkynes has been routinely performed using alkyllithiums or Grignard reagents in dry aprotic solvents under an inert gas atmosphere or alternatively with alkali metal amides in liquid ammonia. Because of their air and moisture sensitivities, acetylides formed in situ are directly used for further reactions without isolation. In contrast, silver acetylides can be readily prepared from terminal alkynes with ammoniacal silver salts, and they are isolable as precipitates.[9] The isolated silver acetylides, however, have been employed in a rather limited number of synthetically useful C−C bond formations.[9d] These involve the substitution reactions on acyl halides,[9a,10] aryldiazonium salts,[11] iminochlorides,[12] ribofuranosyl halides,[13] and alkyl halides[14] or additions to iminium[15] and pyridinium[16] salts, aldehydes,[17] and CO_2.[18] While the stoichiometric use of metal acetylides has been well established, a process that enables their catalytic generation and simultaneous transformation is ideal in terms of atom and step economies.[19,20] In addition, such a catalytic process has a significant merit according to which the direct handling of potentially explosive silver acetylides can be avoided.[9a] This review surveys the silver-catalyzed processes in which acetylenic C_{sp}−H as well as C_{sp}−Si bond transformations occur under the influence of silver mediators. To show the synthetic utility of silver-catalyzed C_{sp}−H and C_{sp}−Si bond functionalizations, relevant transformations of the resulting products are also outlined.

Scheme 1



2. Silver-Catalyzed Alkyne C_{sp}−H and C_{sp}−Si Bond Transformations

2.1. Mechanism of Alkyne C_{sp}−H Bond Activation

In 1980, Lewandos and co-workers reported the H/D exchange of several terminal alkynes in the presence of stoichiometric amounts of silver triflate (AgOTf) (Scheme 1).[21] A rapid exchange reaction took place when the 1:1 complexes of terminal alkynes and AgOTf were treated with one equivalent of CD_3COOD even in the absence of a base at ambient temperature. In the case of 1,7-octadiyne, H/D exchange equilibrium was attained after 10.2 min. This is contrary to the observation of only 17% H/D exchange for

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10.1021/cr078359u CCC: $71.00
Published on Web 07/09/2008

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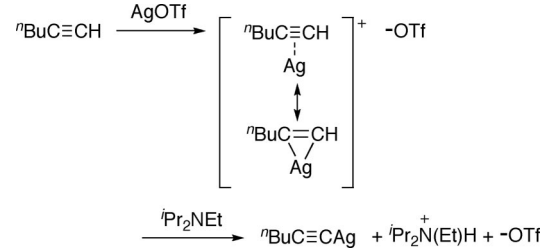
764 days in the absence of the silver salt. These facts show that the rate enhancement by silver coordination is estimated to be 1.1×10^5. The observed H/D exchange might be considered to proceed via silver acetylides, but no such species could be detected in the ^{1}H NMR measurements. Therefore, there were several intermediates **1**−**3** proposed on the basis of the literature precedents. The same authors further performed the kinetic analysis of the H/D exchange for the combinations of RC≡CH/CD_3CO_2D and RC≡CD/CH_3CO_2H to observe kinetic isotope effects of the order of 0.46 ± 0.07.[21b] They attributed such inverse isotope effects to the hybridization change in the terminal C_{sp} to $C_{sp^{\sim 2}}$ in transforming from reactants to activated complexes. They also found the correlation of the exchange rate with the terminal C−H stretching frequencies as well as the downfield chemical shifts of the terminal protons, leading to the consideration of 2-electron 3-center interaction of silver ions with the terminal C_{sp}−H bond as a cause of this activation (**3** in Scheme 1).

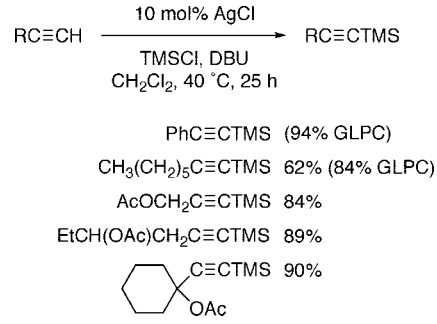
Quite recently, the in situ formation of silver acetylides was reinvestigated by Pale and co-workers.[22] They used ^{109}Ag NMR spectroscopy to elucidate the generation of a silver acetylide from a silver complex of 1-hexyne and a base (Scheme 2). First, they confirmed silver complex formation upon the treatment of 1-hexyne with AgOTf in various deuterated solvents by using the ^{1}H, ^{13}C, and ^{109}Ag NMR spectra as well as the ESI-MS spectrum. Then, upon the addition of ^{i}Pr$_2$NEt into the solution of the complex, they observed the formation of the expected acetylide and the concomitant precipitation of diisopropylethylammonium triflate. The obtained silver compound was identified by comparison of its ^{109}Ag NMR spectrum with that of the independently prepared hexynyl silver.

These observations provide a plausible mechanism of silver acetylide formation in the presence of a base as follows: (1) a silver cation coordinates to a terminal alkyne as a carbophilic Lewis acid, depriving the alkyne of a part of its electron density; (2) as a result, the acidity of its acetylenic proton is increased; and (3) finally, the base abstracts the terminal proton from the silver-coordinated alkyne, yielding a silver acetylide.

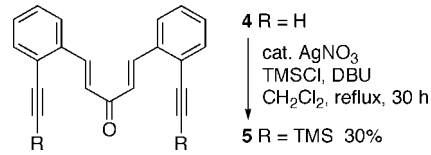
Scheme 2



Scheme 3



Scheme 4



2.2. Silylation and Desilylation

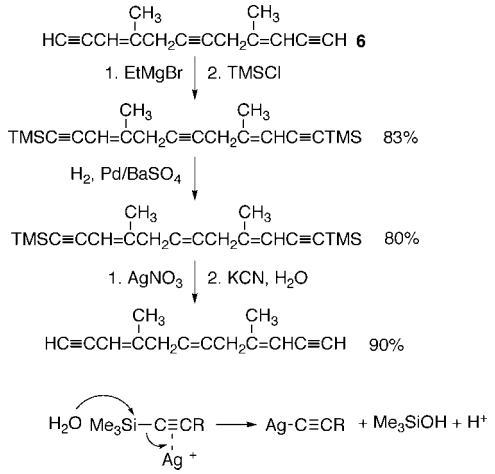
2.2.1. Silver-Catalyzed Silylation of Terminal Alkynes

The trimethylsilyl (TMS) group has been employed as a protecting group that avoids undesired reactions of terminal alkynes.[23] The silyl group is generally introduced onto the terminal carbon via deprotonation with strong bases such as *n*-butyllithium or Grignard reagents, and a subsequent treatment of the formed acetylide with chlorotrimethylsilane. A milder protocol is, hence, required for the trimethysilylation of terminal alkynes bearing functional groups reactive toward nucleophilic bases (e.g., an aldehyde, ester, or ketone). In 1981, Yamaguchi and co-workers reported that in the presence of a catalytic amount of AgCl or $AgNO_3$, the smooth silylation of terminal alkynes took place upon treatment with DBU in refluxing CH_2Cl_2 (Scheme 3).[24] The silylation of phenylacetylene also proceeded with CuCl in place of the silver salt, resulting in a lower yield. Triethylamine, which is less basic than DBU, was found to be an ineffective base. This intriguing method proved to be effective for several alkynes with an acetoxy group, thereby affording the corresponding silylation products in high yields. Although the substrate scope in terms of functional group compatibility remains to be examined further, silver-catalyzed silylation has been rarely applied to other terminal alkynes. Later, Acheson and Lee attempted the bissilylation of diyne **4** under Yamaguchi's conditions, but the desired adduct **5** was obtained only in 30% yield (Scheme 4).[25]

2.2.2. Silver-Promoted and -Catalyzed Desilylation of 1-(Trimethylsilyl)-1-alkynes

The trimethylsilylethynyl group (Me_3SiC≡C−) has been employed in the construction of highly conjugated molecular

Scheme 5

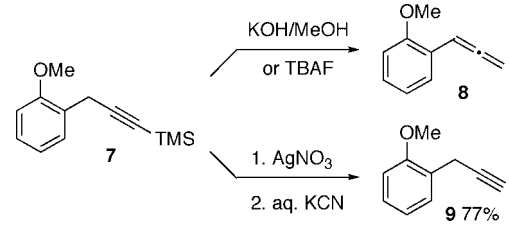


systems. It can be readily introduced and used for further C—C bond formations after the removal of the terminal TMS group. The deprotection of silylalkynes has been routinely carried out by treatment with weak bases in protic media. Undesired side reactions, however, might take place under such basic conditions. Alternatively, fluoride ions have been used for desilylation, but nonselective deprotection possibly occurs in the presence of other silyl-protecting groups. Therefore, a judicious choice of desilylation conditions is critical for the synthesis of complex molecules with base sensitive groups and/or multifunctionality. Schmidt and Arens successfully performed the selective hydrogenation of the central C—C triple bond of dienetriyne **6** after protecting both the alkyne termini with TMS groups; however, they encountered the isomerization of the obtained product to undesired allenic compounds when they attempted desilylation with potassium hydroxide in alcohol (Scheme 5).[26] They solved this problem by carrying out deprotection using a two-step protocol. The silylalkyne was first treated with an aqueous alcoholic solution of silver nitrate, and then the deargentation of the resulting silver acetylide was carried out by treatment with concentrated aqueous solution of potassium cyanide to afford the expected terminal alkyne in a good yield. The C—Si bond cleavage was considered to occur because of the attack of a water molecule to the silyl group of the silver-coordinated substrate. The importance of Ag(I) ion was shown by the inability of sodium nitrate to promote desilylation. Later, Pale and co-workers reported that silver acetylides were obtained from the reaction of trimethylsilylalkynes with $AgNO_3$ or AgOTf in MeOH at room temperature.[27]

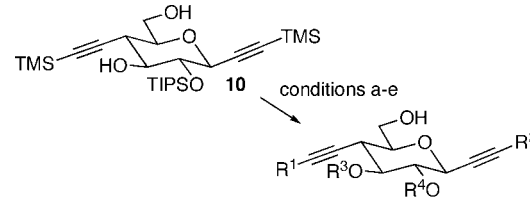
Since their first report in 1967, Ag(I)-promoted desilylation has been successfully applied to the syntheses of naturally occurring polyenes,[28] polyenynes,[29] artificial enediyne antibiotics,[30] carbohydrates,[31] and others.[32] The advantage of the Ag(I)-promoted method over the base- or fluoride-mediated protocols was clearly demonstrated again by Jung and Hagenah.[32e] The treatment of base-sensitive benzylic alkyne **7** with 10% KOH in methanol or less basic tetrabutylammonium fluoride (TBAF) afforded allene **8** instead of terminal alkyne **9** (Scheme 6). Required product **9** was obtained selectively in a good yield under Schmidt's conditions.

Alzeer and Vasella examined several desilylation conditions toward dialkynylglycoside **10** (Scheme 7).[31b] The selective removal of one of the two TMS groups was

Scheme 6

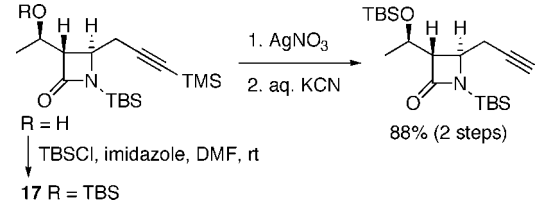


Scheme 7



(a) $AgNO_3$, aq. MeOH, 24 °C, 3 h; sat. KCN, 0 °C
11 R^2 = TMS, R^1 = R^3 = H, R^4 = TIPS: 96%
(b) ^{n}BuLi, THF, -78 °C, then rt, 48 h
12 R^1 = TMS, R^2 = R^3 = H, R^4 = TIPS: 70%
13 R^1 = TMS, R^2 = R^4 = H, R^3 = TIPS: 20%
(c) 0.5 N NaOH, MeOH, 25 °C, 6 h
14 R^1 = R^2 = R^3 = H, R^4 = TIPS: 95%
(d) $Bu_3NF{\cdot}3H_2O$, THF, 0 °C, 6 h
15 R^1 = R^2 = R^3 = R^4 = H: 94%
(e) 0.1 N HCl, MeOH, reflux, 48 h
16 R^1 = R^2 = TMS, R^3 = R^4 = H: 87%

Scheme 8

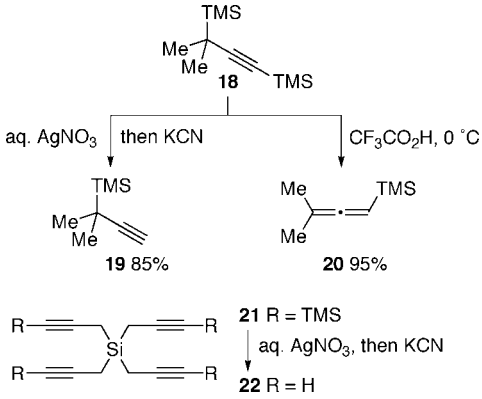


achieved using $AgNO_3$/KCN to give **11** with the triisopropylsilyl (TIPS) ether intact in an excellent yield (conditions a). Although monodesilylation occurred in the anomeric alkyne upon treatment with ^{n}BuLi, the concomitant migration of the TIPS group also took place, yielding a mixture of **12** and **13** (conditions b). On the other hand, usual desilylation methods using NaOH/MeOH or TBAF resulted in the complete removal of both the TMS groups (conditions c and d). In contrast, the TMS groups survived under acidic conditions (e), while the TIPS group was removed.

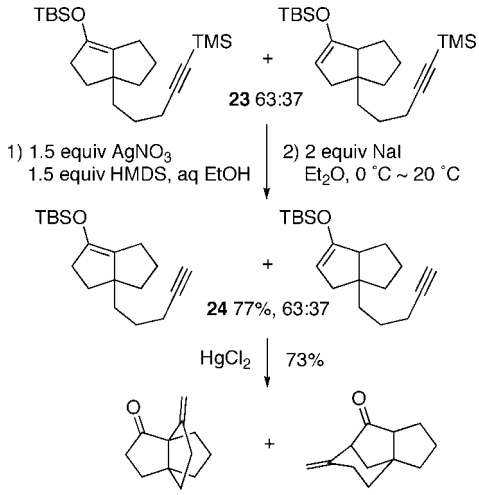
The Schmidt desilylation procedure is also compatible with strained β-lactam rings, which are important components of antibiotic carbapenems.[33] Ikegami and co-workers succeeded in the selective removal of the TMS group on the alkyne moiety of **17**, which is an intermediate for the synthesis of (±)-thienamycin (Scheme 8).[33a] The Schmidt desilylation effectively tolerated not only the azetidinone ring but also the *tert*-butyldimethylsilyl (TBS) groups protecting the lactam nitrogen as well as the secondary alcohol side chain. Similarly, the Schmidt desilylation procedure was utilized in the synthesis of β-lactam-fused enediynes.[30c–i]

By using the reliable desilylation selectivity in favor of C_{sp}—Si bonds over C_{sp^3}—Si bonds, propargyl silanes have been obtained from 1,3-bissilylpropyne derivatives.[34] Then, 3,3-dimethyl-3-(trimethylsilyl)propyne **19** was obtained in a good yield via the selective desilylation of **18** (Scheme 9).[34a] The yield was lower under the conventional basic

Scheme 9



Scheme 10

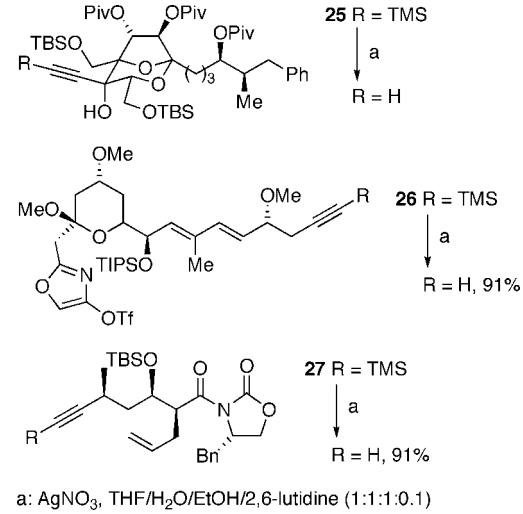


conditions (70%, NaOEt/EtOH). On the other hand, the protodesilylation of **18** exclusively gave allenylsilane **20** in a high yield because of the removal of the propargylic TMS group. Tetrapropargylsilane **22** was also obtained albeit in a moderate yield of 45% from **21** without affecting the quaternary silicon center.[34b]

One of the disadvantages of the Schmidt procedure is obviously the requirement of excess amounts of poisonous KCN for the deargentation process. Hence, there have been several modifications reported in the literature. Russian researchers carefully carried out the deprotection of trimethylsilylated conjugated enynes, which are polymerizable under basic conditions.[35] The silylenynes were allowed to react with $AgNO_3$ to give rise to silver acetylides, which were then isolated and treated with the calculated amount of diluted HCl, resulting in the desired enynes in approximately 70% yield.

The C_{sp}−Si bond cleavage in the presence of silyl enol ether is obviously incompatible with conventional desilylation conditions using highly nucleophilic hydroxide or fluoride anions. Drouin and Boaventura carried out the desilylation of the alkyne moiety of **23** by treatment with $AgNO_3$ in the presence of hexamethyldisilazane (HMDS) to avoid acidifying the reaction conditions (Scheme 10).[36a] A subsequent treatment of the resulting silver acetylide with NaI in place of KCN in ether led to formation of **24** in a good yield, which further underwent Hg(II)-promoted cyclization between the intact TBS enol ether and the terminal alkyne. The protonation of a silver acetylide also proceeds

Scheme 11



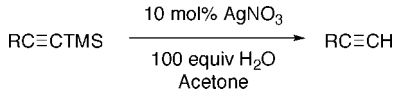
with aqueous LiBr.[37] Desilylation with Ag(I)/KI was used for the synthesis of complex natural product frameworks.[36b,c]

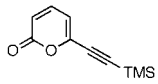
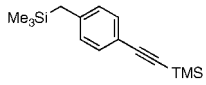
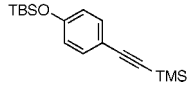
In the total synthesis of (+)-zaragozic acid, Carreira and Du Bois accomplished the desilylation of **25** in the presence of $AgNO_3$/2,6-lutidine (Scheme 11).[38a,b] Their protocol requires no extra steps to decompose silver acetylides with aqueous KCN or NaI. This method was also successfully employed in the deprotection of intermediates **26** and **27** in the construction of the complex frameworks of natural products such as (+)-phorboxazole A and (+)-8-*epi*-xanthatin, respectively, as shown in Scheme 11.[38c,d] A similar combination of $AgNO_3$ with pyridine also proved to be effective for the selective removal of a TMS group in the total synthesis of calicheamicinone by Clive and co-workers.[39]

In 2004, Rossi, and co-workers devised a new method by developing a catalytic version of the silver-promoted desilylation in their synthetic study of (−)-nitidon.[40a] They employed a stoichiometric amount of CF_3CO_2H to protonate the intermediary silver acetylide, resulting in the effective restoration of the silver promoter. The apparent disadvantage of the method using the strong acid is, however, the lack of general applicability toward acid-sensitive substrates. The same research group further investigated the catalytic desilylation of silylalkynes in more detail by carefully examining several silver salts as catalysts, solvents, and additives.[40b] They revealed that $AgNO_3$, $AgOCOCF_3$, AgOTf, and $AgBF_4$ were effective promoters with loadings of 5−10 mol %, while Ag_2O, Ag_2CO_3, $AgHF_2$, and AgI totally failed to catalyze the desilylation process. As a solvent, acetone containing 10−160 equivalents of water or dry methanol proved to be effective. The addition of one equivalent of acetic acid or trifluoroacetic acid facilitated the desilylation process. Typical examples are compiled in Table 1. The new conditions effectively tolerated a benzylic trimethylsilyl group, and a phenolic-TBS ether was also preserved when 0.3 equivalents of pyridine were added as an acid scavenger. On the other hand, an aliphatic TBS ether was incompatible with this protocol even in the absence of an acid additive, although the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether remained unaffected (Scheme 12). The deprotection of the TBS ether was ascribed to the concomitantly formed HNO_3 under the desilylation conditions.

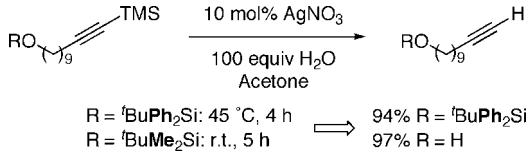
Meanwhile, Pale and co-workers also reported their own catalytic protocol that uses $AgNO_3$ or AgOTf in a mixed solvent of $MeOH/CH_2Cl_2/H_2O$ at room temperature.[41] Their

Table 1. Ag(I) Catalyed Selective Desilylation of Trimethylsilylalkynes

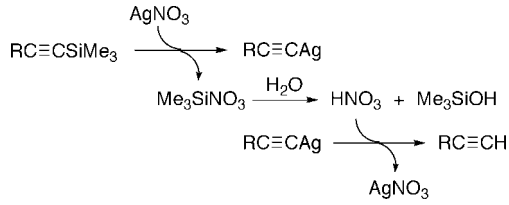


alkynes	conditions	yield (%)
PhC≡CTMS	20 °C, 31 h	91
	20 °C, 21 h	87
$CH_3(CH_2)_9C{\equiv}CTMS$	20 °C, 24 h, 55 °C, 24 h	92
	20 °C, 43 h	94
	pyridine (0.3 equiv) 40 °C, 33 h	97

Scheme 12



Scheme 13

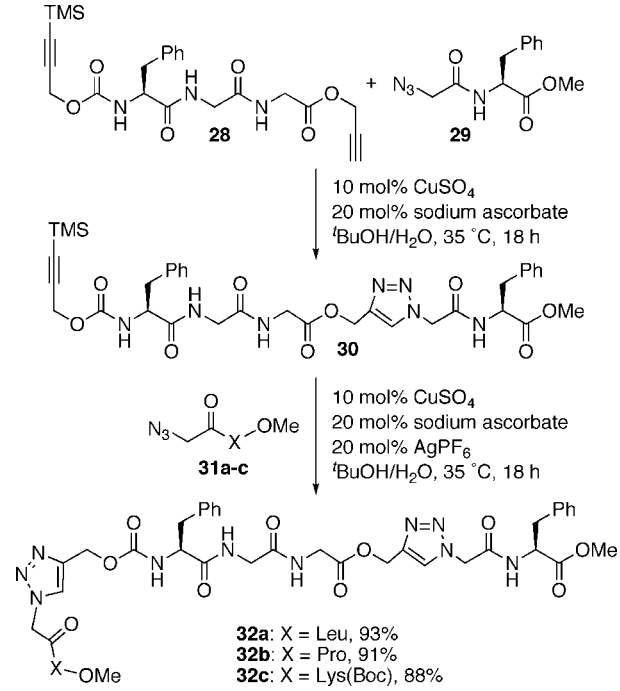


conditions effectively tolerate various functional groups including TBS, TBDPS, and TIPS ethers of secondary alcohols, methoxymethyl and benzyl ethers, and pivaloate. The silver-catalyzed desilylation of trimethylsilylalkynes has been applied to the synthesis of pharmaceutically intriguing molecules.[42]

The proposed mechanism for catalytic desilylation is outlined in Scheme 13. The $AgNO_3$-promoted cleavage of the C_{sp}—Si bond is accompanied by the concomitant formation of trimethylsilyl nitrate, which is hydrolyzed to give rise to trimethysilanol and HNO_3. The silver acetylide formed at this stage then reacts with HNO_3 to furnish a terminal alkyne, and as a result, $AgNO_3$ is restored.

The copper(I)-catalyzed [3 + 2] cycloaddition of terminal alkynes with azides, the so-called "click" chemistry, has received enormous attention because of its wide applicability.[43] The reaction proceeds via copper acetylide intermediates, and hence TMS-protected alkynes are anticipated to remain intact. On the other hand, in the presence of both Cu(I) and Ag(I) promoters, the click products would be obtained as a result of the in situ deprotection of the silylalkynes. Taking advantage of such useful chemoselectivity, a successive click—click process was realized by Aucagne and Leigh (Scheme 14).[44] They first carried out

Scheme 14



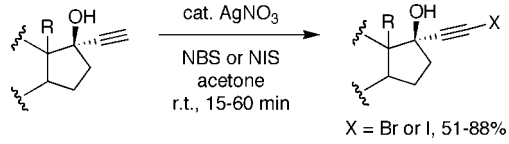
the click reaction of monosilylated diyne **28** with azide **29** under the standard click conditions. The second click reaction of resulting **30** was then executed separately with three azides **31a—c** in the presence of copper and silver salts to obtain three triazole peptides in excellent yields.

2.3. Halogenation

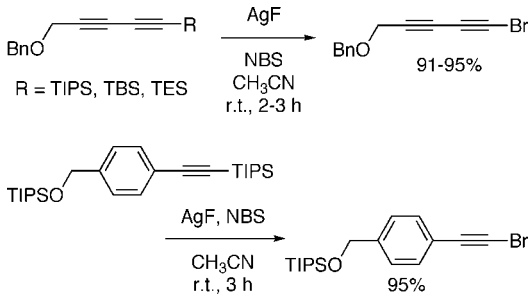
2.3.1. Silver-Catalyzed Halogenation of Terminal and 1-(Trialkylsilyl)-1-alkynes

1-Haloalkynes in which halogen atoms are directly bound to the acetylenic sp carbons are valuable synthetic intermediates in organic synthesis. Transition-metal-catalyzed C—C bond formations via the oxidative addition of their C_{sp}—X bonds have been developed. For example, copper-catalyzed cross coupling with terminal alkynes, the Cadiot—Chodkiewicz heterocoupling, has been employed to obtain unsymmetrical conjugated diynes,[45] and the platinum-catalyzed carbonylation of 1-iodooctyne in methanol was reported to yield a nonynoate.[46] Recently, several transition-metal-mediated and -catalyzed transformations of 1-haloalkynes, where C_{sp}—X bonds were preserved, have received increasing interest, because the resultant halogenated products can be utilized in further transformations.[47] 1-Haloalkynes also undergo partial hydrogenation to give haloalkenes,[48] which are utilized as coupling partners in transition-metal-catalyzed cross couplings.[49] 1-Haloalkynes have been prepared by the direct halogenation of terminal alkynes with hypohalides[50] or deprotonation of terminal alkynes followed by the treatment of the resulting acetylides with appropriate halogen sources.[50d,51] These conventional methods, however, have limitations in terms of the product yields, substrate scope, and experimental simplicity. Thus, various procedures that directly convert terminal alkynes into 1-haloalkynes have been developed: for example, I_2/liquid NH_3,[52a] I_2/morpholine,[52b] *N*-chlorosuccinimide (NCS)/HMPT,[52c] $BrCCl_3$/DBU,[52d] CBr_4/PPh_3,[52e] MX_n (M = Cu, Zn; n = 1, 2; X = Cl, Br, I)/$(Me_3SiO)_2$,[52f] CCl_4/TBAF,[52g] $(collidine)_2I^+PF_6^-$,[52h] CBr_4/KOH/18-*crown*-6/benzene,[52i,j] NaI/anodic oxidation,[52k]

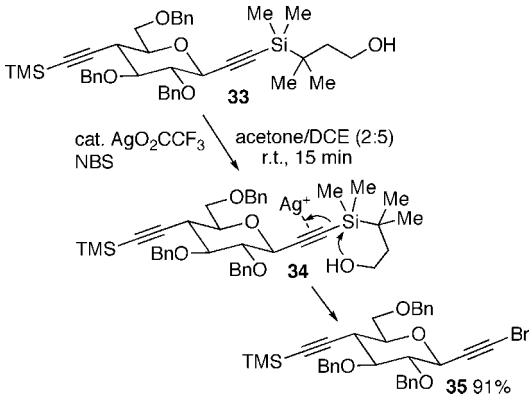
Scheme 15



Scheme 16



Scheme 17

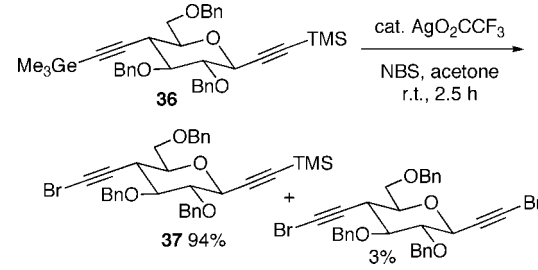


and $PhI(OAc)_2$/KI/CuI/Et_3N.[52l] 1-Bromo- and 1-iodoalkynes were also obtained from 3-arylpropiolic acids via decarboxylative halogenation using NBS or NIS as a halogen source.[52m]

Isolable silver(I) acetylides have been frequently utilized as the precursors of 1-haloalkynes,[53] while those of mercury(II) and copper(I) have rarely been used for this purpose.[54,55] In 1984, Hofmeister and co-workers devised the silver-catalyzed bromination and iodination of 17α-ethynyl steroids (Scheme 15).[56] They used silver nitrate as a catalyst with *N*-bromo- and *N*-iodosuccinimides (NBS and NIS, respectively) as the halogen sources in acetone at ambient temperature to obtain the desired bromoethynyl and iodoethynyl derivatives in 51−88% yields. Solvents except for DMSO such as THF, ethanol, and *N*-methyl-2-pyrrolidone were reported to be suitable for this method. In contrast, the use of NCS failed to give rise to the corresponding chloride under their conditions. Both the halogen source and the solvent are critical for the selective formation of 1-haloalkynes under catalytic conditions. The reaction of several terminal alkynes with I_2 in the presence of $AgNO_3$ in methanol gave rise after aqueous treatment to diiodoalkenes and α,α-diiodoketones together with 1-iodoalkynes.[57]

Furthermore, Nishikawa and co-workers found that 1-(trimethylsilyl)-1-alkynes were directly converted into the corresponding 1-bromo- and 1-iodoalkynes under essentially the same conditions.[58] The monoiodination of bis(trialkylsilyl)acetylenes was also accomplished using ICl, but this method was confined to the preparation of (iodoethynyl)trialkylsilanes.[59] In contrast, bistrimethylsilylated polyalkynes

Scheme 18



were successfully transformed into bisiodinated products by means of silver catalysis.[60] The silver-catalyzed protocol is also applicable to electron-deficient alkynes such as tosyl ethynyl sulfone.[61] Selected examples are compiled in Figure 1. When slight excess amounts of AgF were used instead of $AgNO_3$ in acetonitrile, alkynes protected with TIPS, TBS, and triethylsilyl (TES) groups also gave bromoalkynes in high yields (Scheme 16).[62]

Cai and Vasella reported the selective monobromination of dialkynylglycosides **33** and **36** (Schemes 17 and 18).[63] They carried out this reaction in a mixed solvent system of acetone/1,2-dichloroethane (DCE) in a ratio of 2:5 using silver trifluoroacetate as the catalyst to obtain **35** with the anomeric bromoalkyne in a high yield with excellent selectivity. The 1,1-dimethyl-3-hydroxypropyldimethylsilyl group is considered to be selectively removed due to the internal attack of the pendant hydroxy group (see **34**). Diminished selectivity was observed when the reaction was executed in acetone. On the other hand, the germyl alkyne moiety of **36** selectively underwent bromination to give **37** in 94% yield along with a small amount of dibromination side product.

2.3.2. Synthetic Applications of Silver-Catalyzed Halogenation

As already mentioned above, 1-haloalkynes are useful synthetic intermediates. This section briefly surveys the transformations of alkynes via silver-catalyzed halogenation and the subsequent reactions of the resulting 1-haloalkynes.

1-Bromoalkynes are the coupling components of Cadiot−Chodkiewicz heterocoupling with terminal alkynes.[45] This method is one of the most powerful tools to obtain unsymmetrical 1,3-diynes, and it has been employed in the synthesis

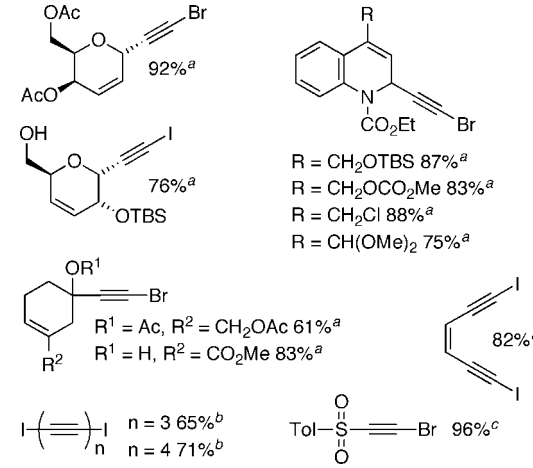
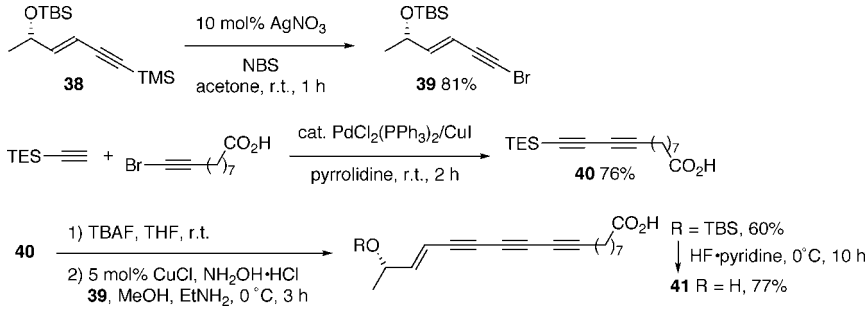


Figure 1. 1-Haloalkynes synthesized by silver-catalyzed halogenation of the corresponding trimethylsilylalkynes (a, ref 58; b, ref 60; c, ref 61).

Scheme 19



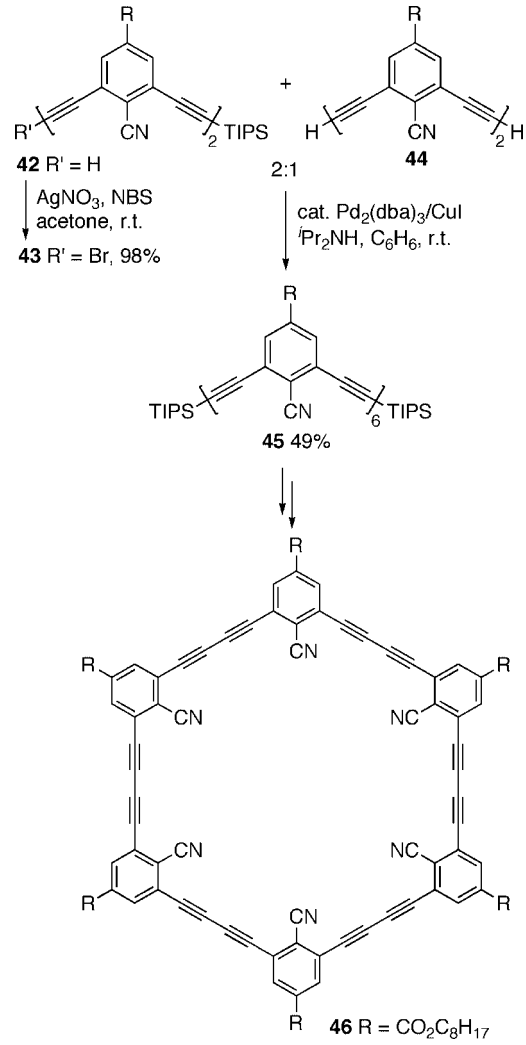
of several polyacetylene natural products.[64] For example, the total synthesis of *E*-15,16-dihydrominquartynoic acid (**41**) was accomplished by the Cadiot−Chodkiewicz coupling of **39** and **40** (Scheme 19).[64e] The former coupling partner was obtained from the silver-catalyzed bromination of **38**, where the C_{sp}−Si bond was selectively transformed into the C_{sp}−Br bond in the presence of TBS ether. The other precursor **40** was prepared by the Sonogashira-type coupling of 10-bromodec-9-ynoic acid and triethylsilylacetylene. The key heterocoupling of **39** was accomplished by directly using a terminal 1,3-diyne generated in situ from **40** and TBAF.

The combination of silver-catalyzed bromination and catalytic heterocouplings has also been a highly reliable tool in the construction of polyacetylene macrocycles.[65] Tobe and co-workers executed the twofold Sonogashira-type coupling of tetrayne **44** with two equivalents of bromoalkyne **43**, which was prepared by the silver-catalyzed bromination of **42** without the loss of TIPS protection, to obtain linear dodecayne **45** (Scheme 20).[65a] After the removal of the TIPS group, **45** was converted into macrocyclic dodecayne **46** via Glaser coupling cyclization.

Furthermore, silver-catalyzed halogenation was combined with transition-metal-catalyzed couplings other than Cadiot-Chodkiewicz and Sonogashira-type heterocouplings. Clive and co-workers treated diyne **47** with $AgNO_3$ and NIS to prepare diiododiyne **48** in a high yield (Scheme 21).[39] Palladium-catalyzed Stille coupling of **48** with *cis*-1,2-bis(trimethylstannyl)ethene successfully constructed a cyclic enediyne framework (**49**) of calicheamicinone. In the total synthesis of (+)-cylindricine C−E, trimethylsilylated 1,8-nonadiyne was subjected to silver-catalyzed bromination and then coupling with a Knochel-type zinc−copper reagent derived from serine to afford diynylamino acid **51** albeit in a moderate yield (Scheme 22).[66]

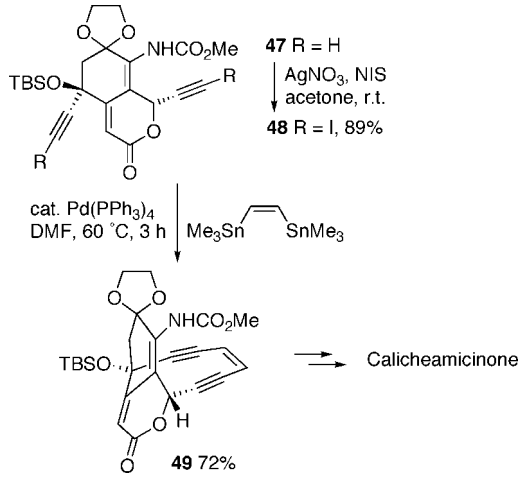
Chromium(II)-mediated addition of organohalides to aldehydes is a highly chemoselective C−C bond forming method in organic synthesis.[67] Takai and co-workers found that 1-alkynyliodides also added to aliphatic and aromatic aldehydes in the presence of $CrCl_2$ in DMF at 25 °C to afford propargyl alcohols in good yields.[68] The use of a catalytic amount of nickel(II) along with the stoichiometric chromium mediator, the Nozaki−Hiyama−Kishi (NHK) protocol, proved to be reliable in the total synthesis of natural products,[69] and later Fürstner et al. devised a highly useful variant that reduces the toxic chromium reagent to a catalytic amount.[70] The addition of acetylides to carbonyl compounds has been employed to obtain valuable synthetic intermediates, namely, propargyl alcohols. The NHK reaction of 1-iodoalkynes can be executed under mild reaction conditions, and it effectively tolerates a wide variety of functional groups that are amenable to the addition of highly reactive lithium acetylides or the corresponding Grignard reagents. Thus, this

Scheme 20

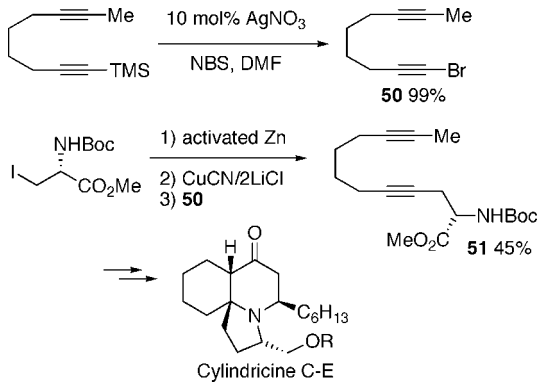


method is combined with silver-catalyzed alkyne iodination, providing remarkably mild access to highly labile structures.[71] Meyers and Finney used the silver catalysis and intramolecular NHK coupling to synthesize didehydro[10]annulene precursor **55**, which was found to be extremely sensitive toward basic conditions (Scheme 23).[71a] Cyclization precursor **54** was prepared via the silver-catalyzed iodination of **52** followed by the Dess−Martin oxidation of the resulting **53**. The researchers first attempted the intramolecular acetylide−aldehyde addition on a parent terminal alkyne related to **54** but failed to obtain the desired cyclization product **55**. In contrast, the intramolecular NHK coupling of **54** was carried out by treatment with 2.5 equivalents of $CrCl_2$ doped with 0.01% $NiCl_2$ in rigorously deoxygenated THF at 0 °C to obtain **55**, albeit in a moderate yield. Another

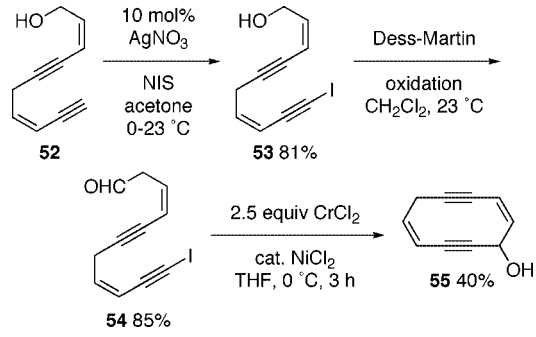
Scheme 21



Scheme 22



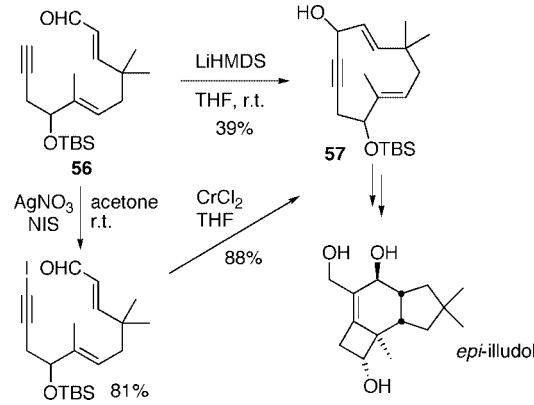
Scheme 23



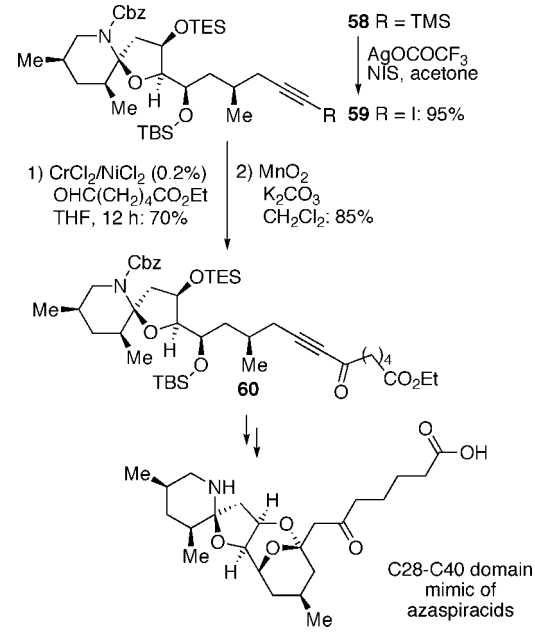
useful application is the synthesis of *epi*-illudol proposed by Malacria and co-workers (Scheme 24).[71b] The cyclization of acetylenic aldehyde **56** was carried out by dropwise addition of lithium hexamethydisilazide (LiHMDS) in THF at room temperature, resulting in the clean formation of **57**. The reaction was, however, incomplete, and 23% of **56** was recovered. An alternative two-step route consisting of Ag-catalyzed iodination and intramolecular NHK reaction with the slow-addition technique improved the overall yield of **57** up to approximately 70%.

As outlined in Scheme 25, the intermolecular NHK coupling strategy was also applied to the synthesis of a highly functionalized molecule.[71h] Upon treatment with silver trifluoroacetate and NIS, trimethylsilylalkyne **58** was directly converted into the corresponding iodoalkyne **59** without affecting the Cbz-protected spiro N,O-acetal moiety as well as the TES and TBS ethers. Subsequent intermolecular NHK coupling was followed by oxidation with MnO_2 to give ynone

Scheme 24



Scheme 25

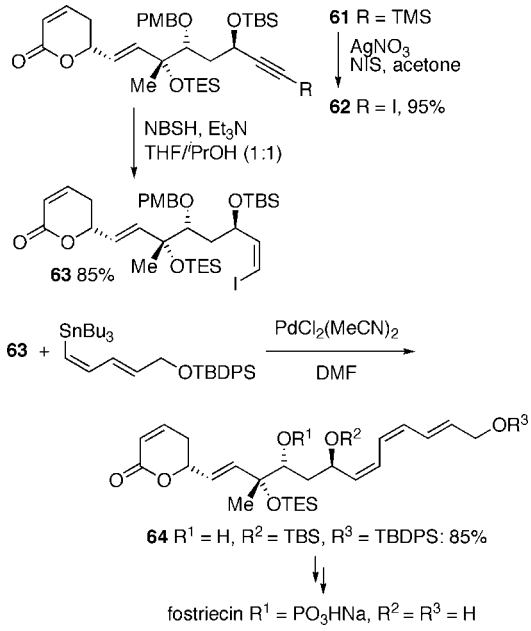


60, which was finally transformed into a hapten for the antibody toward natural toxin azaspiracids.

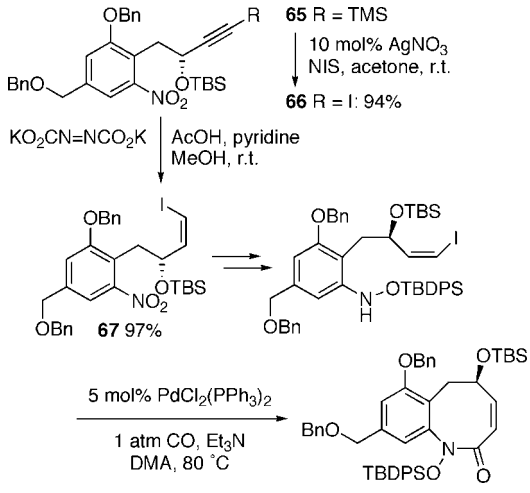
The partial hydrogenation of 1-haloalkynes produces *Z*-haloalkenes, which can be further used in cross-coupling reactions. Diimide reduction or hydroboration/protodeboration has been employed for this purpose.[72] In the asymmetric total synthesis of fostriecin, Jacobsen and Chavez prepared *Z*-alkenyl iodide **63** from trimethylsilylalkyne **61** via its Ag-catalyzed conversion into iodoalkyne **62** and the following diimide reduction with *o*-nitrobenzenesulfonylhydrazide (NBSH)/Et_3N (Scheme 26).[72b] Thereafter, obtained **63** was subjected to a ligand-free Stille coupling with a *Z*,*E*-dienylstannane to produce *Z*,*Z*,*E*-triene **64** that was further converted into fostriecin. Similarly, Trost and Ameriks prepared *Z*-alkenyl iodide **67** via the Ag-catalyzed iodination of chiral propargyl alcohol derivative **65** and the subsequent hydrogenation of iodide **66** with dipotassium azodicarboxylate/AcOH (Scheme 27).[72g] After the SmI_2 reduction of the nitro group and appropriate protection, **67** was converted into an 8-membered lactam relevant to FR900482 by palladium-catalyzed carbonylative cyclization.

An *E*-alkenyl halide was also obtained from a propargyl alcohol derivative (Scheme 28).[73] The silver-catalyzed bromination of chiral propargyl alcohol **68** was carried out on a 2.5-g scale to quantitatively afford bromination product

Scheme 26



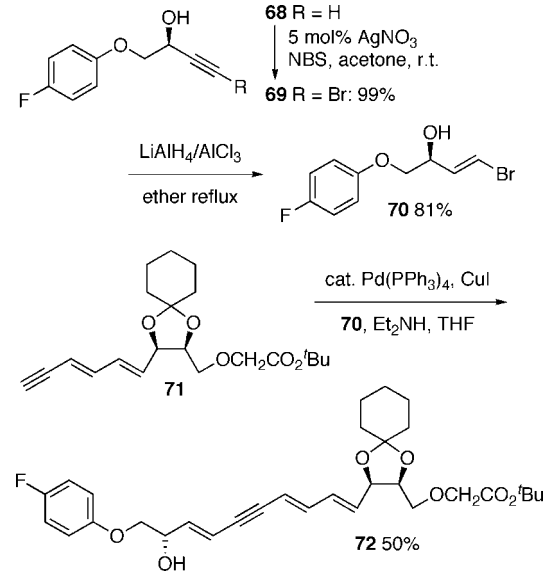
Scheme 27



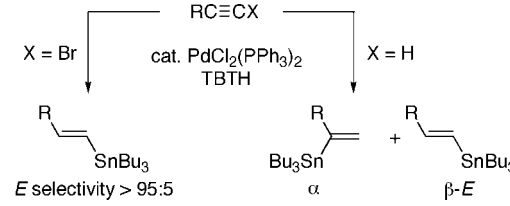
69. The subsequent treatment of **69** with $LiAlH_4/AlCl_3$ in refluxing ether resulted in the formation of *E*-bromoalkene **70** in a high yield. The Sonogashira coupling of **70** and dienyne **71** gave 3-oxa lipoxin A_4 analogue **72** albeit in a moderate yield. Although the aluminum hydride reduction of 1-haloalkynes selectively gives rise to *trans* haloalkenes, the substrates are limited to propargyl alcohol derivatives.[48b] Therefore, further investigations have focused on the selective synthesis of *trans* haloalkenes from alkynes with wide substrate scope (vide infra).

The hydrostannations of alkynes have been continuously investigated due to the potential utility of the alkenylstannane products in organic synthesis.[74] The control of regio- and stereoselectivities still remains to be improved, particularly in transition-metal-catalyzed hydrostannations. To address this issue, Chong and co-workers devised the palladium-catalyzed regioselective hydrostannation using bulky and electron-rich phosphine ligands.[74c] On the other hand, Guibé and co-workers reported in 1990 that the Pd-catalyzed hydrostannation of 1-bromoalkynes with tributylstannane (TBTH) provided β-*E* alkenylstannanes with excellent regio- and stereoselectivities as opposed to the corresponding terminal alkynes, giving rise to α-stannylated products along

Scheme 28



Scheme 29

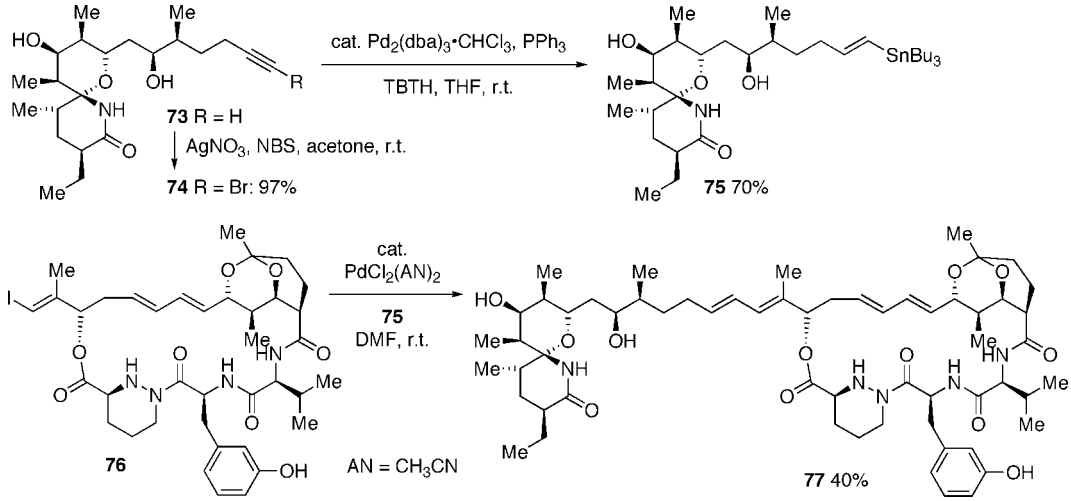


with β-*E* adducts with varied yields and ratios (Scheme 29).[75a] Later, the scope of this method was further extended to various functionalized alkynes and the resulting alkenylstannanes were used for subsequent Stille coupling by Pattenden and co-workers.[75b] Moreover, Maleczka Jr. et al. devised an intriguing hydrostannation process, in which TBTH was produced in situ by the reduction of tributyltin chloride with polymethylhydrosiloxane, thereby avoiding the undesired formation of hexabutylditin from hydrostannane.[75c]

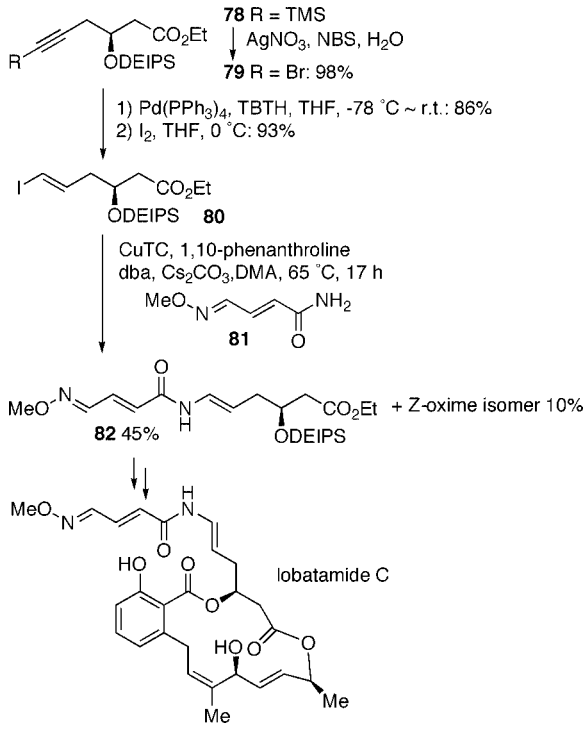
Selective hydrostannation has been combined with the silver-catalyzed formation of 1-bromoalkynes to provide a viable access to highly functionalized alkenylstannanes.[76] For example, Duan and Paquette synthesized the cyclic N,O-acetal unit **75** bearing a pendant *E* alkenylstannane by the Ag-catalyzed bromination of **73** and subsequent Pd-catalyzed hydrostannation of the obtained bromoalkyne **74** (Scheme 30).[76c] The Stille coupling between **75** and vinyliodide **76** was performed under palladium catalysis at room temperature to furnish **77**, which was finally transformed into sanglifehrin A via the hydrolysis of the acetal moiety. Protection-free hydroxy and phenoxy groups as well as a *N*-acyl-*N*,*O*-acetal were effectively tolerated in these transformations.

As referenced above, a general method to prepare haloalkenes from readily available terminal alkynes is of great importance in organic synthesis. Pattenden and co-workers revealed that *E* iodoalkenes were concisely prepared by the hydrostannation of 1-bromoalkynes and subsequent treatment of the formed *E* vinylstannanes with I_2.[75b] This method has been employed in several total syntheses of complex natural products.[77] Porco and co-workers synthesized enamide ester component **82** of lobatamide C via Cu-catalyzed coupling of *E* vinyl iodide **80** and oxime amide **81** (Scheme 31).[77a] The required *E* iodide **80** was prepared by the Pd-catalyzed hydrostannation of **79** and tin—iodine exchange. 1-Bro-

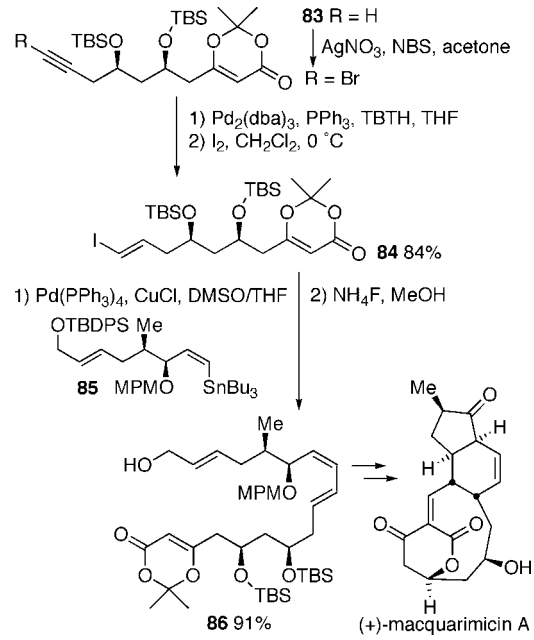
Scheme 30



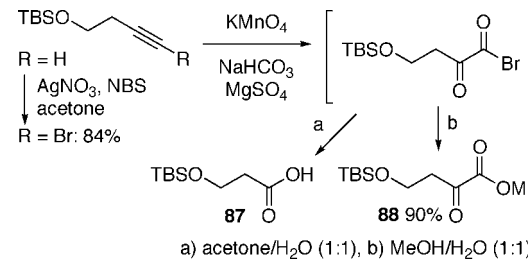
Scheme 31



Scheme 32



Scheme 33



moalkyne **79** was directly obtained from trimethylsilylalkyne **78** under silver catalysis in an excellent yield. Tadano and co-workers similarly converted alkyne **83** into *E* vinyliodide **84**, which was subjected to Stille coupling with *Z* vinylstannane **85** to afford *E*,*Z*-diene intermediate **86** in the bioinspired total synthesis of (+)-macquarimicin A (Scheme 32).[77b,c]

Li and Wu prepared 1-bromoalkyne by the silver-catalyzed bromination of the TBS ether of homopropargyl alcohol and subjected the resulting product to $KMnO_4$ oxidation in different mixed solvents (Scheme 33).[78a] When the oxidation was carried out in acetone−H_2O, carboxylic acid **87** was formed in low yield with a concomitant loss of CO_2. On the other hand, the reaction in MeOH−H_2O gave rise to α-ketoester **88** in a high yield. This method proved to be effective for phenylacetylene, several carbohydrate-derived alkynes, and a tetrahydrofuran derivative (Figure 2). Plet and Porter applied the Ag-catalyzed bromination/$KMnO_4$ oxidation to sugar alkyne **89** to obtain α-ketoester **90**, which was treated with hydrazine hydrate to give **91** bearing the bicyclic hemithioacetal framework relevant to tagetitoxin (Scheme 34).[78b]

Cyclization or cycloaddition of 1-haloalkynes might produce valuable halogenated compounds if their C_{sp}−halogen bonds are preserved during these reactions. This is the case for the Bergman−Masamune cyclization of *o*-bis(haloalkynyl)arenes.[79] Bowles and Anthony developed a fascinating iterative process that enables rapid access to acenes (Scheme 35).[79a] They prepared bis(bromoethynyl)benzene **93** from known diyne **92** upon treatment with NBS and $AgNO_3$ and subjected

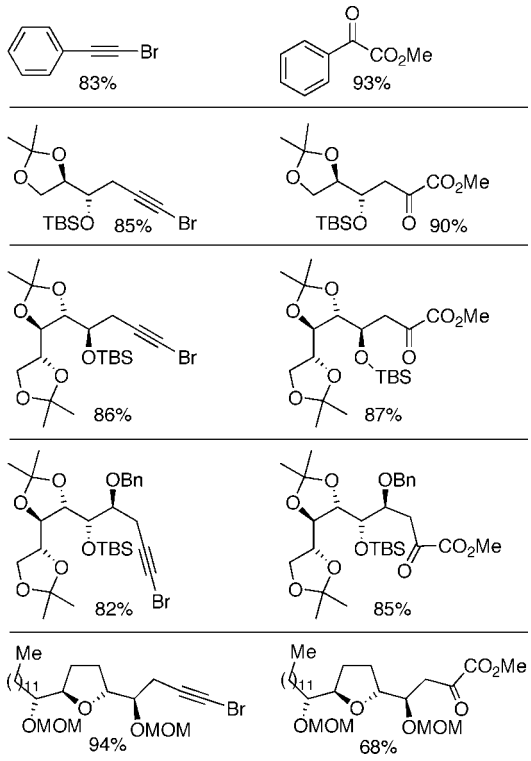
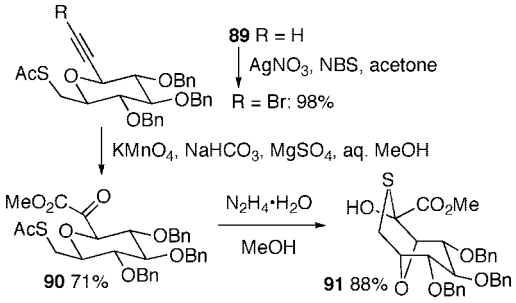


Figure 2. Synthesis of α-ketoesters via silver-catalyzed bromination of alkynes and $KMnO_4$ oxidation.

Scheme 34



it to thermolysis in the presence of 1,4-cyclohexadiene (CHD) to obtain 2,3-dibromonaphthalene **94** in a reasonable yield. The Negishi modification of the Sonogashira coupling with a zinc acetylide was applied to **94** to obtain bis(trimethylsilylethynyl)naphthalene **95** in a good yield. Repeating the same process with **92** converted **95** into the higher analogue **96** in a reasonable yield. A further elongation of the acene skeleton was, however, hampered by the insolubility of the intermediates. After desilylation, **96** was converted into naphthacene in 64% yield. A similar transformation was applied to dimethylnaphthalene derivative **98**, which was formed by the regioselective [2 + 2 + 2] cyclocoupling of trimethylsilylpenta-1,3-diyne with benzyne complex **97** generated in situ by the reduction of an arylnickel (Scheme 36).[79c] Consequently, 2,3-dibromo-9,10-dimethylanthracene was obtained albeit in a moderate yield. Since the starting nickel complex was prepared from *o*-dibromobenzene, this three-step sequence might be repeated to give higher acenes, although such an attempt was not reported. Interestingly, a Ni(II) porphyrin complex bearing a dibromoenediyne moiety also underwent Bergman−Masamune cyclization to give rise to dibromopicenoporphyrin complex **99** as a result of the cyclization of a biradical species onto the *meso*-phenyl substituents (Scheme 37).[79b] The corresponding diiododiyne failed to give the expected diiodopicenoporphyrin complex.

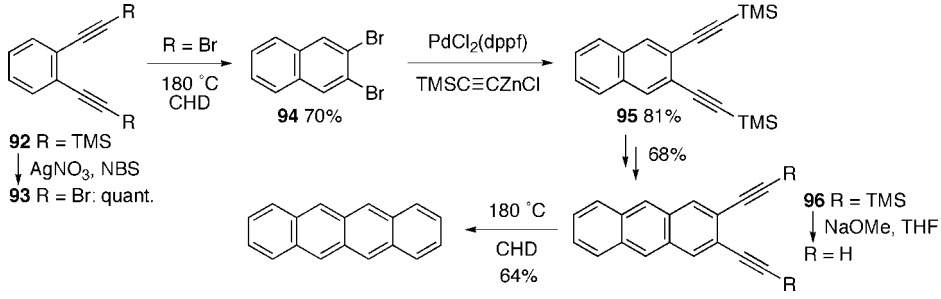
Low-valent transition metals are capable of undergoing oxidative addition toward the C_{sp}−I bond in iodoalkynes, resulting in the formation of transition metal acetylides,[80] which might serve as intermediates for the catalytic couplings of iodoalkynes. In contrast, Iwasawa and co-workers found that TBS enol ether **100** bearing a pendant iodoalkyne was allowed to react with a stoichiometric amount of $W(CO)_5$-THF to give rise to cyclization product **102** with 1,2-migration of the iodine atom (Scheme 38).[81a,b] This cyclization is considered to proceed via iodovinylidene species **101**, resulting in the formation of the zwitterionic species. The requisite substrate was prepared by the silver-catalyzed iodination of the parent terminal alkyne without affecting the TBS enol ether moiety. The generality of this remarkable transformation was established as summarized in Figure 3. Various 5- and 6-membered cycloalkenyliodides were obtained from alkynyl enol ethers in two steps.

As opposed to the above examples, a cationic gold complex catalyzed a similar cyclization of **103** without the transposition of the iodine atom (Scheme 39).[81c] Toste and co-workers utilized this method for the construction of iodobicyclo[4.3.0]nonenone **104**, which underwent Suzuki−Miyaura coupling with an azadienylboronic ester, resulting in dienylhydrazone **105**. They completed the asymmetric total synthesis of (+)-lycopladine A by conducting the isomerization/6π-electrocyclization of **105**.

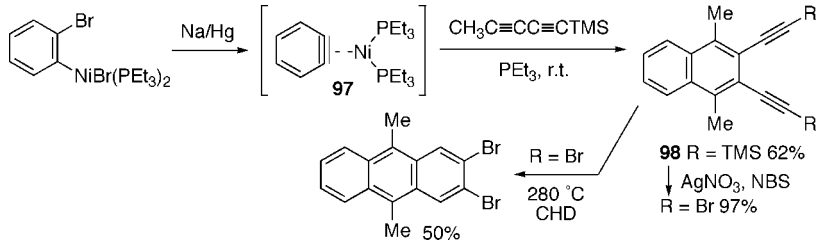
Iodobenzenes are highly valuable intermediates in organic synthesis. Although chloro- and bromobenzenes have been conventionally prepared by means of electrophilic aromatic halogenation, the direct iodination of aromatic precursors is problematic due to the low electrophilicity of molecular iodine. Therefore, aromatic iodination requires a Lewis acid activator or oxidative and/or acidic reaction conditions, which hamper the synthesis of iodobenzenes bearing labile functionalities. Yamamoto and co-workers have recently developed a novel two-step strategy to assemble *p*-diiodobenzenes as outlined in Scheme 40.[82a] In this process, 1,6-diynes **106** were converted into diiododiynes **107** via the silver-catalyzed C_{sp}−H iodination, and then the [2 + 2 + 2] cycloaddition of **107** with acetylene was carried out in 1,2-dichloroethane (DCE) at room temperature using an organoruthenium catalyst, Cp*RuCl(cod) (Cp* = η^5-pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene). Overall, this two-step procedure enables the catalytic assembly of bicyclic *p*-diiodobenzenes **108** with the exact control of the substitution pattern. This method effectively tolerated malononitrile, an ether, or a sulfonamide tether on the diyne, resulting in the formation of diiodobenzenes over 60% overall yields. Protecting groups such as an acid labile ketal or benzyl ether were also compatible with the present method. This two-step process also effected the selective synthesis of polyaromatic compounds, while the electrophilic iodination of substrates possessing multiple benzene rings would result in a mixture of several products. Diynes bearing a single terminal alkyne moiety were also transformed into unsymmetrical iodobenzenes.

Taking advantage of the Ru(II)-catalyzed cyclotrimerization technology, hexa-*p*-phenylene **114** was synthesized from linear polyyne substrates (Scheme 41).[82a] The silver-catalyzed iodination of tetrayne **109** afforded diiodide **110**, and the subsequent ruthenium-catalyzed twofold cycloaddition of **110** with acetylene gave diiodobiphenyl component

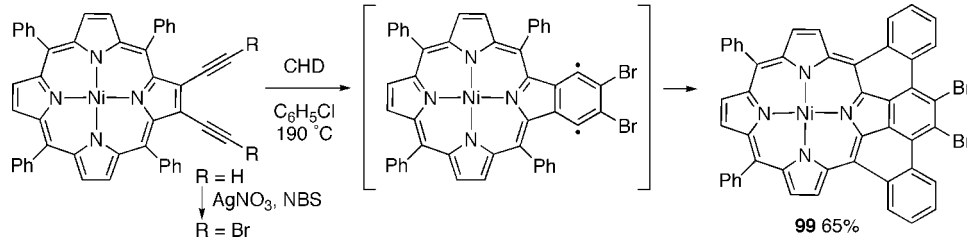
Scheme 35



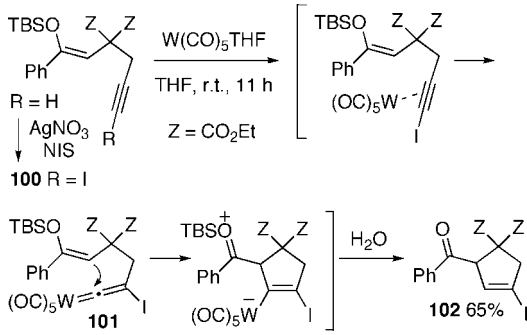
Scheme 36



Scheme 37



Scheme 38



111 in a good overall yield. The other coupling partner biphenylboronate **113** was also prepared by the ruthenium-catalyzed cycloaddition of diynylboronate **112**. Finally, twofold Suzuki−Miyaura coupling of **111** with **113** furnished the desired hexa-*p*-phenylene **114** albeit in a moderate yield.

The monoalkyne component is not limited to acetylene. The cycloaddition of a diiododiyne derived from dipropargyl ether and 1-hexyne uneventfully furnished unsymmetrical *p*-diiodobenzene **115** in a high yield (Scheme 42). This product was further utilized for the synthesis of an oligo(*p*-phenylene ethynylene) by the iterative Sonogashira coupling strategy.[82b] A mild Sonogashira protocol was applied to the coupling of **115** with phenylacetylene, resulting in the regioselective alkynylation at the sterically less hindered C−I bond. Consequently, **116** was obtained in a high yield. The coupling with trimethylsilylacetylene at the more hindered site was then accomplished at 120 °C under microwave heating, and the subsequent desilylation of the adduct gave diyne **117** in an excellent overall yield. Its coupling with **115** was, however, found problematic due to the undesired homo coupling of **117**. To suppress this particular side

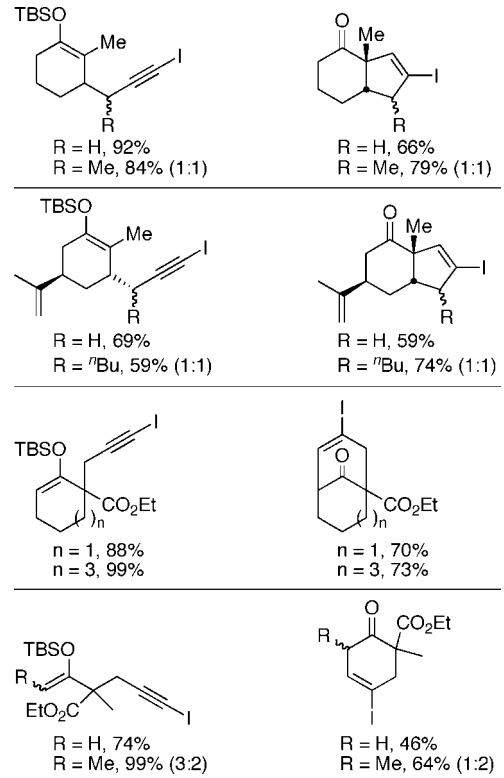
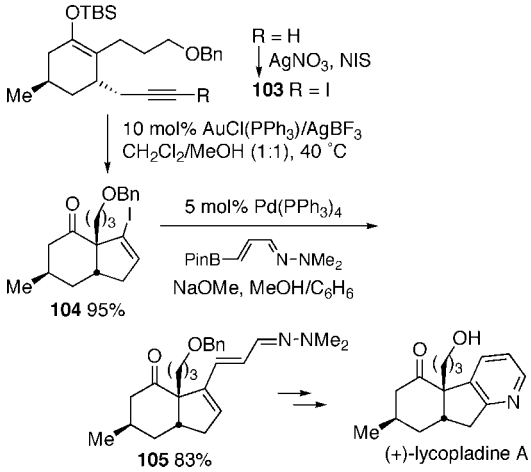
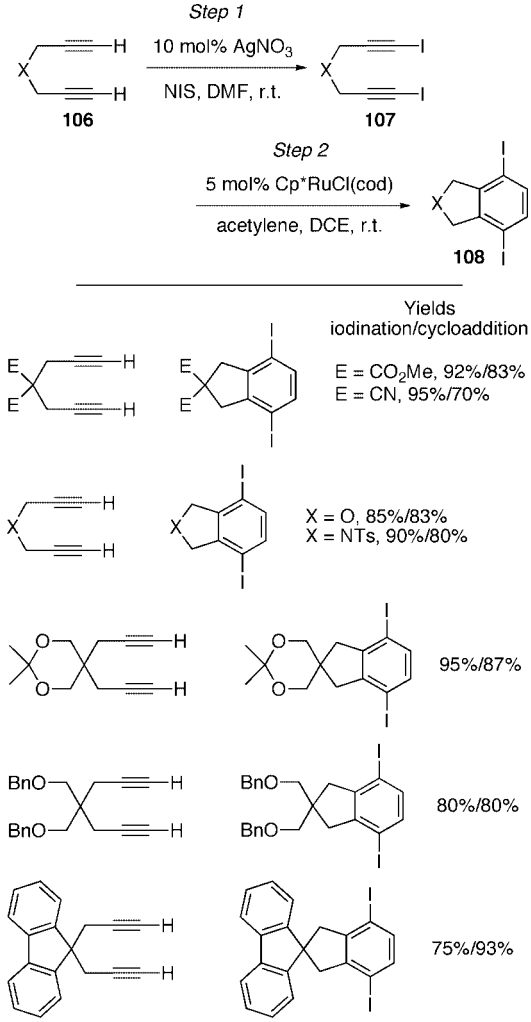


Figure 3. Products and yields of Ag-catalyzed iodination and W-mediated cyclization.

Scheme 39



Scheme 40



reaction, the loading of CuI was reduced to one-half the amount of the palladium catalyst, leading to the selective formation of **118**. The final coupling with phenylacetylene was again carried out with microwave heating to afford **119** in a high yield.

Another demonstration of the silver-catalyzed iodination/ruthenium-catalyzed cycloaddition/palladium-catalyzed cross coupling sequential process is the divergent synthesis of spirocyclic *C*-arylribosides relevant to the natural product family of the papulacandins (Scheme 43).[82c,d] The lithium

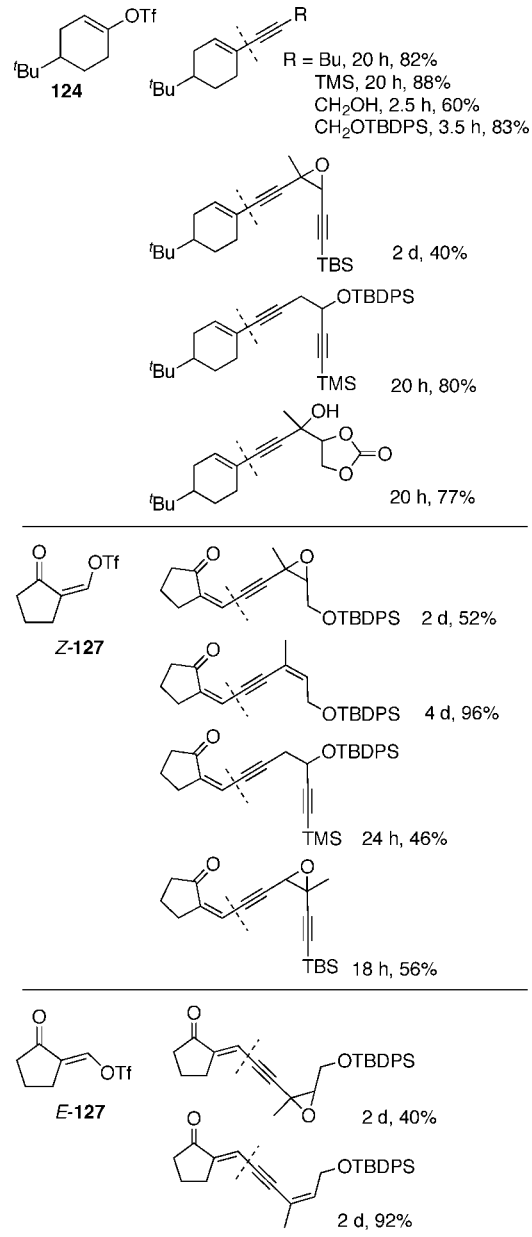


Figure 4. Sonogashira coupling of alkynes with enol triflates using silver cocatalyst.

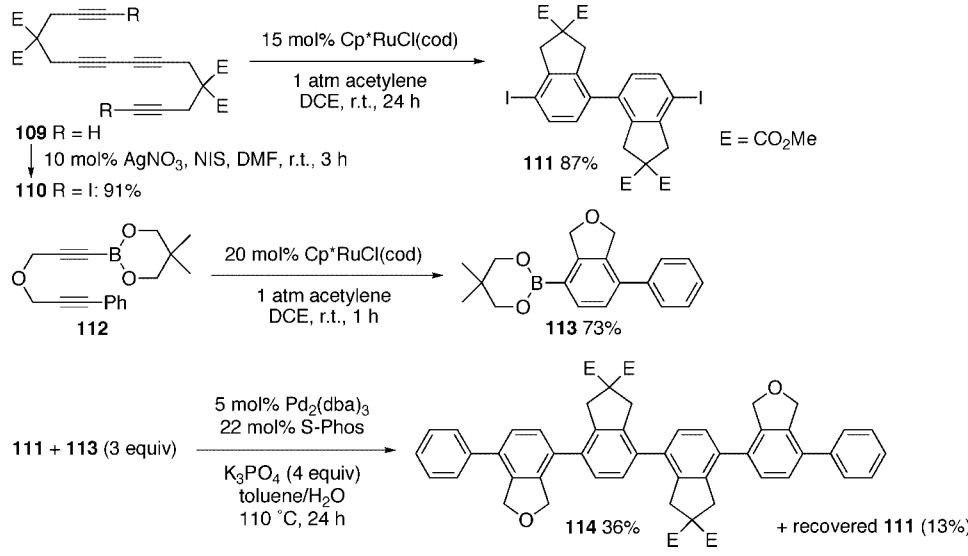
acetylide addition to δ-ribonolactone **120** was followed by the glycosilation with trimethylsilyl propargyl alcohol promoted montmorillonite K10 to give diyne **121**. The direct C_{sp}—Si iodination was carried out in the presence of $AgNO_3$ to obtain iododiyne **122** as a single anomer. The ruthenium-catalyzed cycloaddition with acetylene converted **122** into the iodobenzene platform **123**, which underwent several palladium- and copper-catalyzed coupling reactions to furnish variously functionalized ribosides in good yields.

2.4. Carbon—Carbon Bond Formations

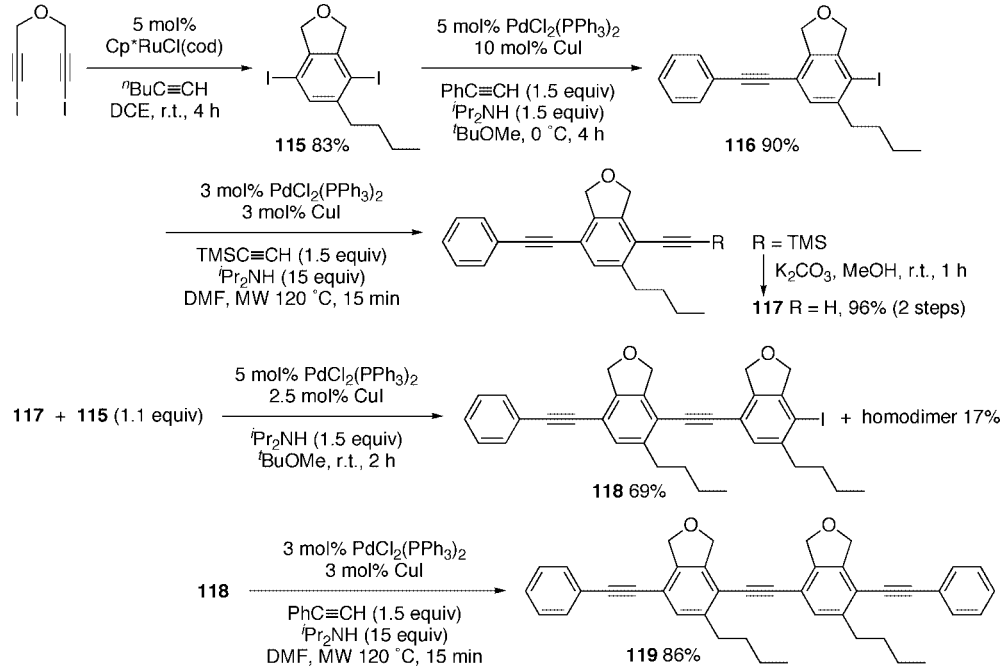
2.4.1. Sonogashira-Type Coupling Reactions Mediated by Silver

Without a doubt, transition-metal-catalyzed cross-coupling reactions are indispensable tools in modern synthetic organic chemistry.[49] Among them, Sonogashira coupling has been one of the most fascinating methods to construct C_{sp^2}—C_{sp} bonds under palladium catalysis.[83] This mild and efficient

Scheme 41



Scheme 42

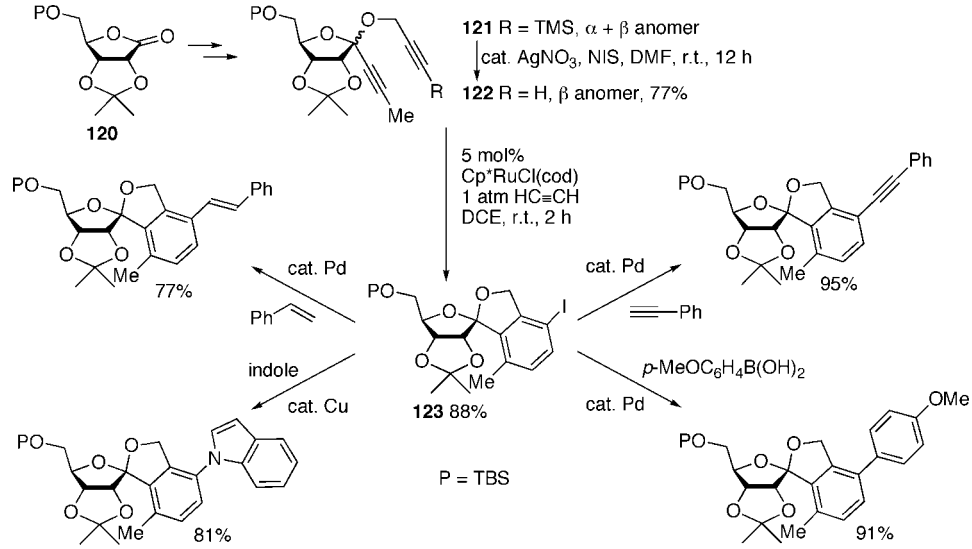


method provides concise and rapid access to arylalkyne and enyne frameworks.

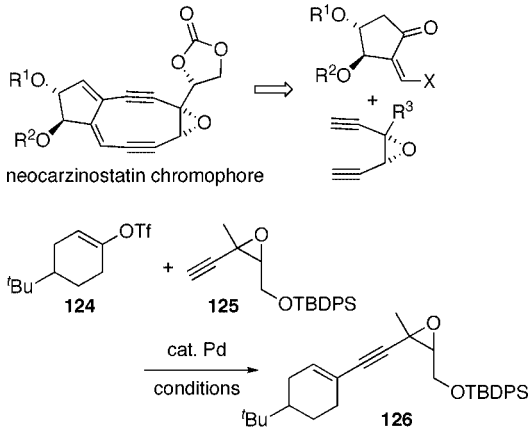
A potentially useful application of this method is the construction of the epoxy enediyne core of the neocarzinostatine chromophore via the coupling of enol triflate **124** and epoxyalkyne **125** (Scheme 44).[84] Sonogashira coupling usually requires a copper salt, typically CuI, as a cocatalyst, together with a base additive, and copper acetylides are believed to be involved in the catalytic cycle. The standard Sonogashira conditions (a), however, gave unsatisfactory results. The diminished yield of **126** was attributed to the decomposition of acid labile epoxyalkyne **125** under the reaction conditions. Thus, a slow addition of **125** enabled an increase in the yield up to 54% (conditions b). With hope for further improvement, Pale and Bertus examined several silver salts as cocatalysts in place of CuI. The use of AgI led to the formation of **126** in a comparable yield without recourse to the slow addition technique (conditions c). The best result was obtained by increased catalyst loadings (conditions d). Other silver salts, $AgNO_3$ and Ag_2CO_3, proved to be less effective (conditions e and f), while AgOTf gave a significant decrease in the yield due to its electrophilicity having a deleterious effect on the epoxyalkyne substrate (conditions g). The substrate scope of Sonogashira coupling using the silver cocatalyst is shown in Figure 4. Simple alkynes such as 1-hexyne and trimethylsilylacetylene gave the coupling products in higher yields. Unprotected hydroxy and epoxy groups diminished the product yields. In addition to **124**, methylenecyclopentanone derivatives *E*- and *Z*-**127** could be used as enol triflates, resulting in the stereoselective formations of coupling products.

Later in 2000, Mori and co-workers reported that the Sonogashira coupling of terminal alkynes with iodobenzenes proceeded in the absence of base additives if a stoichiometric amount of Ag_2O was used together with the palladium catalyst (Scheme 45).[85] The reactions of trimethylsilylacetylene, aliphatic alkynes, and phenylacetylene with iodobenzene and its derivatives bearing methoxy or acetyl substit-

Scheme 43



Scheme 44



conditions:

(a) 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI, 2 equiv $^iPr_2NEt$, DMF, r.t., 1 h: 25%

(b) 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI, 2 equiv $^iPr_2NEt$, DMF, r.t., 1 h (slow addition of **125**): 54%

(c) 5 mol% $Pd(PPh_3)_4$, 10 mol% AgI, 1.5 equiv $^iPr_2NEt$, DMF, r.t., 24 h: 51%

(d) 10 mol% $Pd(PPh_3)_4$, 20 mol% AgI, 1.25 equiv $^iPr_2NEt$, DMF, r.t., 20 h: 78%

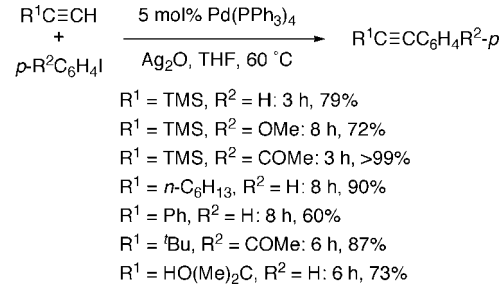
(e) 10 mol% $Pd(PPh_3)_4$, 20 mol% $AgNO_3$, 1.25 equiv $^iPr_2NEt$, DMF, r.t., 15 h: 52%

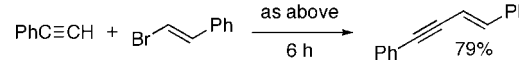
(f) 10 mol% $Pd(PPh_3)_4$, 20 mol% Ag_2CO_3, 1.25 equiv $^iPr_2NEt$, DMF, r.t., 15 h: 61%

(g) 10 mol% $Pd(PPh_3)_4$, 20 mol% AgOTf, 1.25 equiv $^iPr_2NEt$, DMF, r.t., 15 h: 40%

uents at the para position proceeded in THF at 60 °C to give the coupling products in moderate to quantitative yields. On the other hand, *p*-anisyl bromide and triflate failed to undergo coupling with phenylacetylene under the same reaction conditions. This is in contrast to *E*-*β*-bromostyrene giving rise to the corresponding enyne in 79% yield. As these authors claimed, their method is less efficient than standard Sonogashira coupling, but it has a practical advantage that omits procedures to remove base additives as well as ammonium salts. The exact role of Ag_2O has not been revealed. The palladium-catalyzed cross coupling of terminal alkynes with arylboronic acids was also accomplished using

Scheme 45

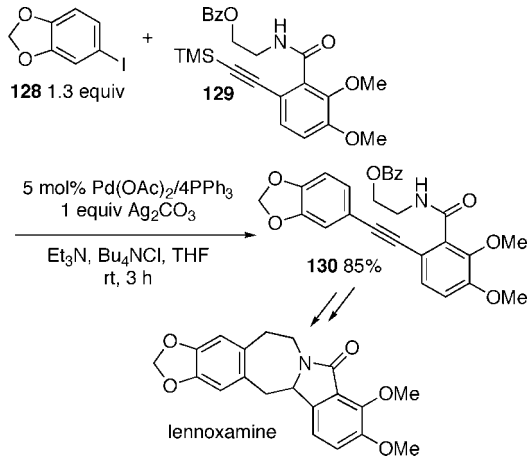




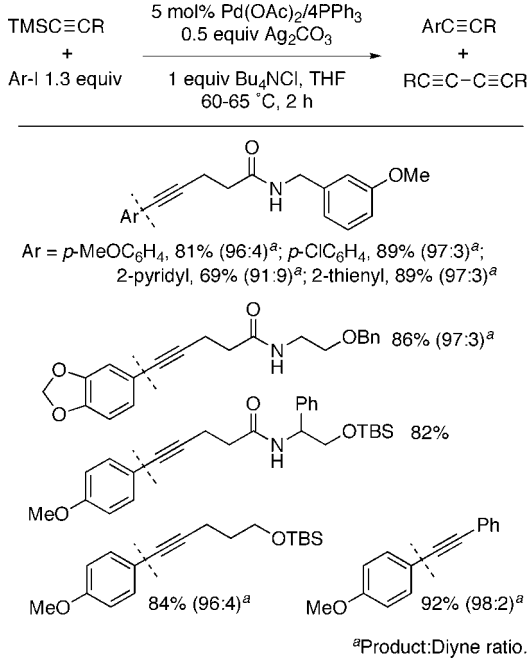
excess amounts of Ag_2O and K_2CO_3 in CH_2Cl_2 at room temperature.[86a] In this case, on the basis of the previous findings, Ag_2O is considered to be an activator of boronic acids.[86b]

Trimethylsilylalkynes are frequently used as protected terminal alkynes. A catalytic process enabling their direct coupling is undoubtedly of practical significance in terms of atom and step economies as compared to usual stepwise desilylation/coupling procedures. In addition, the use of trimethylsilylalkynes results in the suppression of the undesired Glaser-type homocoupling reactions leading to 1,3-diynes.[45] In this context, the direct Sonogashira couplings of trimethylsilylalkynes have been successfully executed in the presence or absence of copper salts in protic media under basic conditions.[87] Similarly, trimethylsilylalkynes also underwent Sonogashira couplings in aprotic solvents such as DMF, 1,3-dimethylimidazolidin-2-one, or *N*,*N*-dimethylacetamide at 80−120 °C, and copper additives play a critical role in the desilylation process.[88] Recently, the copper-free Sonogashira coupling under microwave irradiation was also reported by Sørensen and Pombo-Villar.[89] In the formal total synthesis of lennoxamine, Koseki and Nagasaka executed the coupling reaction of aryl iodide **128** and trimethylsilylalkyne **129** in the presence of a palladium(triphenylphosphine) catalyst as well as stoichiometric amounts of Bu_4NCl and Ag_2CO_3 in place of a copper salt otherwise under standard conditions (Scheme 46).[90a] Consequently, the desired Sonogashira product **130** was obtained in 85% yield. It is noteworthy that the Sonogashira coupling of the parent

Scheme 46



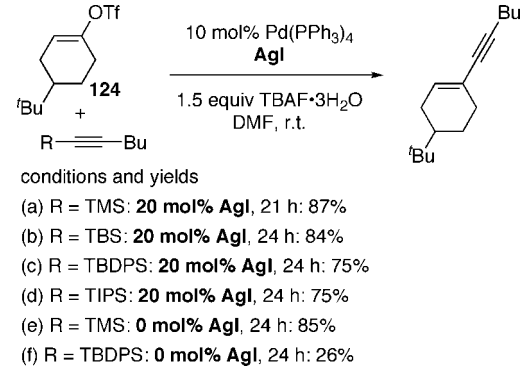
Scheme 47



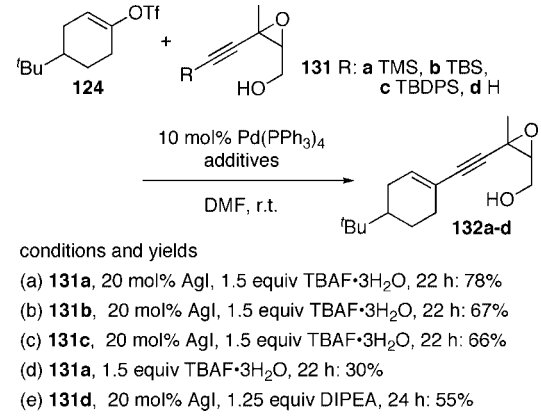
terminal alkyne of **129** failed to give **130**. Later, the same research group examined the generality of their own protocol (Scheme 47).[90b] They attempted the reaction of various aryl iodides and trimethylsilylated alkynes bearing a pendant amide moiety with a reduced amount of Ag_2CO_3 (0.5 equivalent) in the absence of a base at 60−65 °C to obtain the desired coupling products in good yields together with trace amounts of homocoupling side products. In addition to the amide derivatives, simple trimethylsilylated pentyne possessing a silyloxy group and phenylacetylene also gave the corresponding coupling products with similar efficiency and selectivity. The use of an aryl bromide, however, led to the exclusive homo coupling of the alkyne. The authors tentatively attributed the successful Sonogashira coupling to the formation of silver acetylides from the trimethylsilylalkynes.

Fluoride reagents such as TBAF and KF have been used for the C−Si bond activation, because the fluoride ion attacks organosilanes to form pentacoordinated silicates.[91] Taking advantage of the transmetalation activity of the silicates, Hiyama and Hatanaka developed the transition-metal-catalyzed cross coupling of organosilanes with organic

Scheme 48



Scheme 49

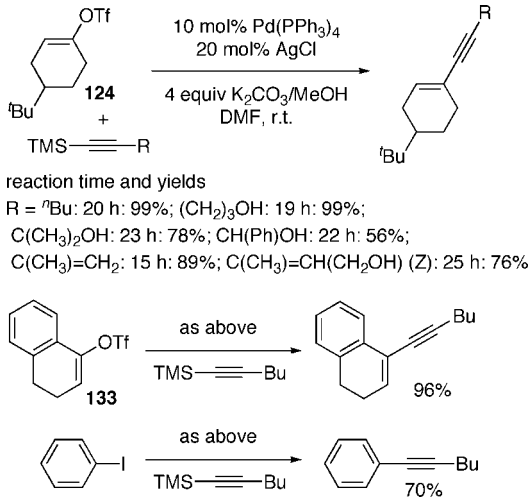


halides.[92a] They used tris(diethylamino)sulfonium difluorotrimethylsilicate as a fluoride mediator to accomplish the cross coupling of alkenyl and allyl trimethylsilanes with organic iodides and bromides. In this report, they also revealed that trimethylsilylalkynes participated into the palladium-catalyzed cross coupling with *E*-β-bromostyrene to afford enynes in high yields. Since their findings, the fluoride-promoted Sonogashira couplings of trimethylsilylalkynes with alkenyl and aryl halides have been developed.[92b–f] Pale and coworkers further found that the combination of a catalytic amount of silver salt and TBAF•$3H_2O$ effectively promoted the direct Sonogashira coupling of various trialkylsilylalkynes with an enol triflate (Scheme 48).[93a] The coupling of 1-hexyne derivatives possessing TMS, TBS, TBDPS, or TIPS groups with triflate **124** proceeded in the presence of 10 mol% $Pd(PPh_3)_4$ and 20 mol % AgI even at room temperature to give the desired enyne in 75−87% yields (conditions a−d). In the case of the trimethylsilylhexyne, a comparable yield was obtained in the absence of AgI (conditions e), while the yield dropped dramatically to 26% for the more robust TBDPS derivative (conditions f).

The advantage of fluoride-assisted Pd/Ag-catalyzed coupling is clearly illustrated by the results obtained with labile epoxyalkynyl alcohols **131a−d** (Scheme 49).[93a,b] Different silylated alkynes **131a−c** underwent Sonogashira coupling with triflate **124** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and AgI as well as 1.5 equivalent of TBAF•$3H_2O$ to give epoxyenynes **132** in 66−78% yields (conditions a-c). On the other hand, the couplings of TMS analogue **131a** in the absence of AgI or of the parent terminal alkyne **131d** under the previous conditions without TBAF diminished the yield to 30% and 55%, respectively (conditions d and e).

As described above, fluoride-assisted Pd/Ag-catalyzed Sonogashira coupling provides straightforward access to

Scheme 50

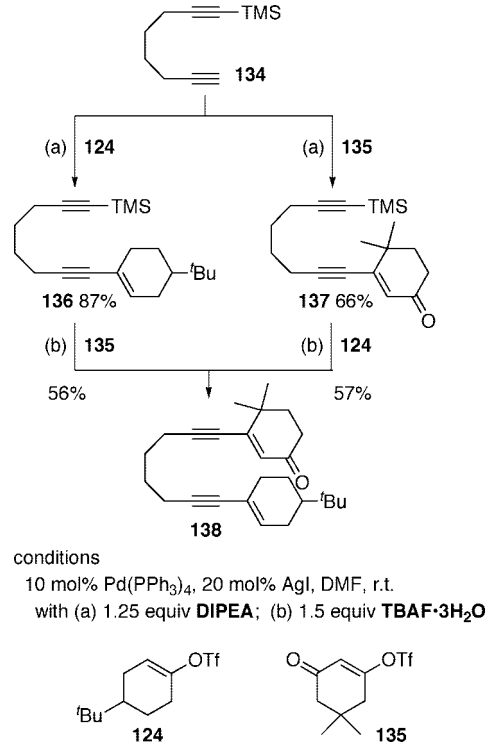


disubstituted alkynes from trialkylsilylalkynes without the desilylation step. This method, however, is not applicable to substrates bearing multiple silyl groups due to unselective desilylation. To address this issue, Halbes and Pale devised a modified protocol to selectively activate the TMS group.[94] They attempted the coupling of trimethylsilylalkynes with trilfate **124** using four equivalents of K_2CO_3/MeOH instead of TBAF·$3H_2O$ to successfully obtain the desired enynes in moderate to high yields (Scheme 50). The yields were lower with alkynes bearing tertiary or secondary hydroxy groups. This modified method also proved to be applicable to conjugated enol triflate **133** as well as iodobenzene. The yield was again slightly diminished for the latter. The authors proposed that the methoxide ion plays a role of the activator of the TMS group as is the case with the fluoride ion.

Taking advantage of the difference in the reactivities of silylated and terminal alkynes, the concise introductions of terminal groups onto polyynes were investigated.[95] As outlined in Scheme 51, monosilylated 1,7-octadiyne **134** was subjected to Sonogashira coupling conditions in favor of the C_{sp}—H terminus to afford monocoupling products **136** and **137** in 87% and 66% yields from triflates **124** or **135**, respectively.[95a] Then, their subsequent coupling with these triflates at the silylated termini under fluoride-assisted conditions furnished unsymmetrically functionalized diyne **138** in approximately 60% yield. The Sonogashira coupling of triyne bearing TMS and TIPS groups **139** with enol triflate **124** was carried out using $Pd(PPh_3)_4$/AgCl catalyst system in favor of the unprotected alkyne terminal to give **140** in a high yield, and hence, the silyl groups remained unaffected (Scheme 52).[95b] To secure the selective coupling at the TMS-bound termini, the next coupling with conjugated triflate **133** was executed in the presence of K_2CO_3/MeOH to furnish the required **141** with the TIPS group intact. Finally, the fluoride-assisted Pd/Ag-catalyzed protocol promoted the coupling with iodobenzene at the TIPS-protected alkyne carbon to afford **142** in 72% yield.

In Scheme 53, a readily available bissilylated 1,3-butadiyne was treated with MeLi·LiBr to result in selective monodesilylation.[96a] The obtained **143** was subjected to sequential Pd/Cu- and Pd/Ag-catalyzed Sonogashira couplings with different alkenylbromides, leading to unsymmetrical dienediyne **144** in a good overall yield. Interestingly, the vinylic silane moiety was untouched in the second coupling. This desymmetrization strategy was elegantly

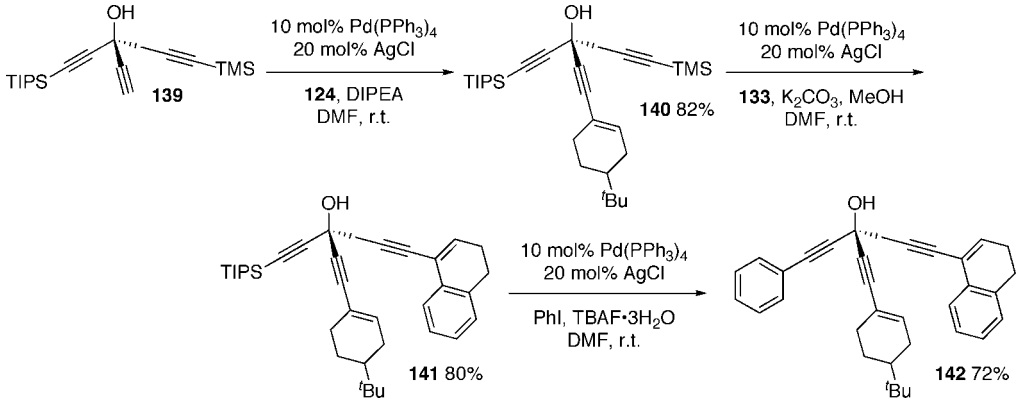
Scheme 51



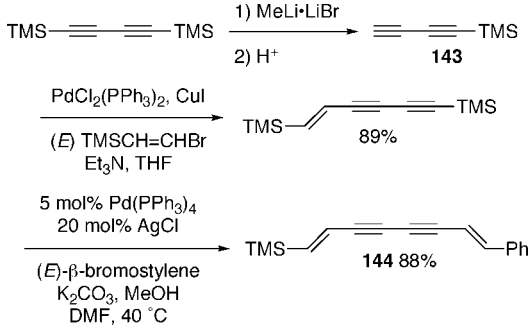
applied to the asymmetric total synthesis of (*S*)-1-dehydroxyvirol A (Scheme 54).[96b]

As described in the former section (see 2.2.2), silver-promoted desilylations are considered to proceed via silver acetylide intermediates. In fact, Pale and co-workers confirmed the silver acetylide formations upon treatment of trimethylsilylalkynes with $AgNO_3$ or AgOTf in MeOH at room temperature.[27] Silver acetylides are also believed to be involved in the above Pd/Ag-catalyzed Sonogashira couplings. Pale and co-workers demonstrated that the isolated silver acetylides actually participated in the palladium-catalyzed coupling with enol triflates (Scheme 55).[97] Salt complex **145** derived from 1-hexyne and $AgNO_3$ with the standard procedure, however, turned out to be totally ineffective toward the palladium-catalyzed coupling with enol triflates. Hence, they modified the procedure to obtain salt-free acetylide **146**, which gave rise to the expected coupling product upon treatment with triflates **124** and **135** in the presence of substoichiometric amounts of $Pd(PPh_3)_4$ in aprotic polar solvents such as DMF, MeCN, or ether. In the absence of the palladium complex, no coupling product was observed. High-yield formations of the enynes required 0.5 equivalent of $Pd(PPh_3)_4$ as opposed to the previous Pd/Ag-catalyzed Sonogashira reactions, giving coupling products with a less catalyst loading of 10 mol%.[84,93] In stark contrast, Li and Wang recently reported that the Sonogashira coupling of aryl and aliphatic terminal alkynes with aryl iodides and bromides took place under the influence of a catalytic amount of silver salts such as AgI, $AgNO_3$, AgCl, AgBr, Ag_2O, and AgOTf in the absence of a palladium catalyst.[98] The best result was obtained by carrying out the reaction with 10 mol % AgI, 30 mol % PPh_3, and two equivalents of K_2CO_3 in DMF at 100 °C (Scheme 56). The use of equal amounts of terminal alkynes and aryl halides gave the desired coupling products in good to excellent yields. These results obviously show that silver acetylides can participate in catalytic coupling with or without the Ag to Pd transmetalation,

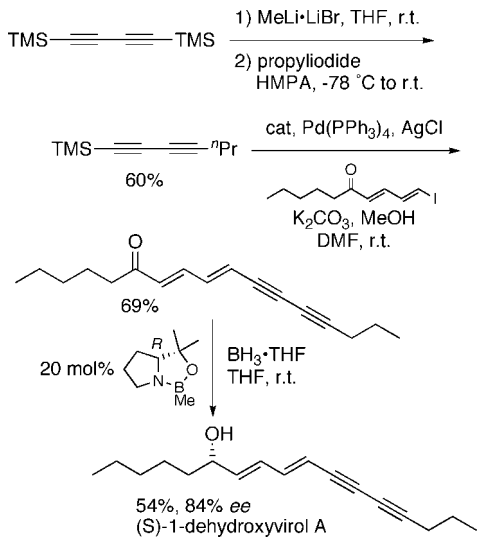
Scheme 52



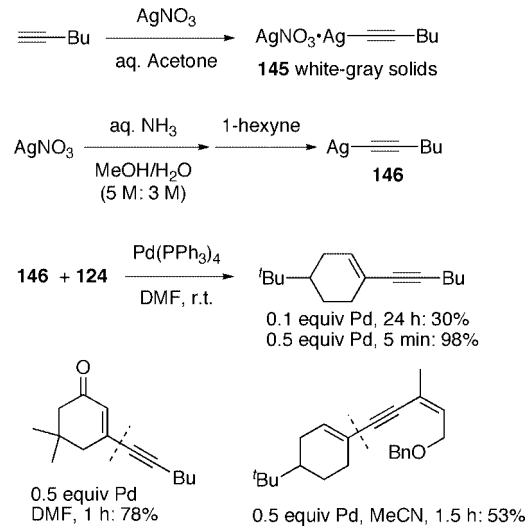
Scheme 53



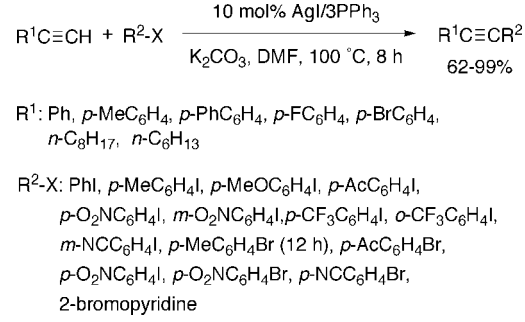
Scheme 54



Scheme 55



Scheme 56

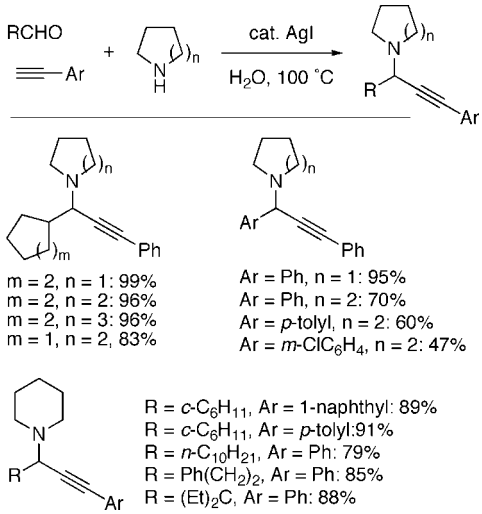


although the detailed understanding of the entire mechanism requires further investigation.

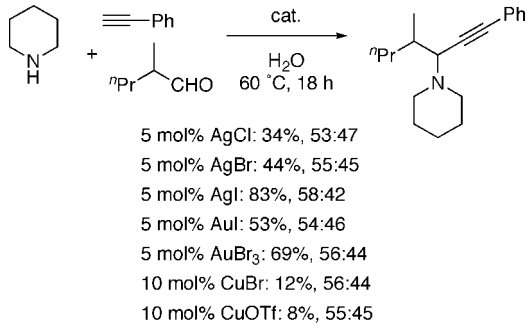
2.4.2. Silver-Catalyzed Addition of Terminal Alkynes to Carbonyl Compounds

While the isolated silver acetylides have been known to react with carbonyl and related compounds such as acyl halides,[10] iminochlorides,[12] iminium[15] and pyridinium[16] salts, aldehydes,[17] and CO_2,[18] the catalytic versions of these reactions have been hardly developed. One major example of such silver catalysis is the Mannich-type three-component condensation of aldehydes, amines, and terminal alkynes, leading to propargyl amines.[99] Because of the importance of the resulting propargyl amine derivatives, catalytic aldehyde−alkyne−amine couplings (A^3-couplings) have been extensively studied recently, and efficient methods have been developed using catalysts based on transition-metal elements including Cu, Ru−Cu, Ir, and Au.[100] In 2003, Li and co-workers reported the first silver-catalyzed A^3-coupling (Scheme 57).[101a] The most significant point in their method is that the reaction proceeds in water, although Mannich-type reactions are categorized as dehydrative condensation, usually requiring the removal of generated water. Among the silver salts tested (AgOTf, $AgBF_4$, Ag_2O, Ag_2SO_4, $AgNO_3$, AgF, AgCl, and AgBr), AgI exhibited the best catalytic performance. In the presence of 1.5−3 mol % AgI, aliphatic and aromatic aldehydes and cyclic secondary amines reacted with arylacetylenes at 100 °C to afford propargyl amines in 47−99% yields. The unwanted trimerization of aldehydes, which is a notable limitation for Cu- and Au-catalyzed conditions, was suppressed under silver catalysis.

Scheme 57



Scheme 58



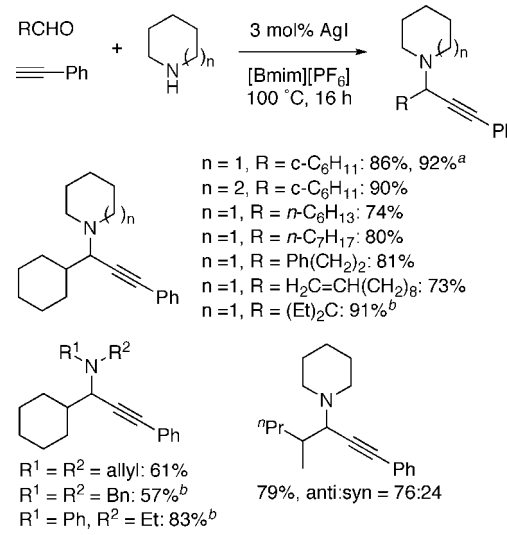
No example of an aliphatic alkyne was reported, while triethylsilylacetylene gave a similar adduct in a moderate yield. When A^3-coupling was examined toward an α-substituted aliphatic aldehyde, the corresponding product was also obtained in a high yield, but almost no diastereoselectivity was observed (Scheme 58).[101c] Other examined catalysts also exhibited no stereoselectivity, and the yields were lower than that obtained with AgI.

Li's group also performed A^3-coupling in ionic liquids.[101b] The reactions with aliphatic aldehydes gave good results in [Bmim][PF_6] or [Bmim][BF_4] (Scheme 59), while aromatic aldehydes were reported to give complex products. In addition to cyclic secondary amines, acyclic derivatives were able to undergo A^3-coupling to give coupling products in diminished yields. In contrast to the reaction in water, slight diastereoselectivity in favor of the anti-isomer was observed in the reaction employing 2-methylpentanal.

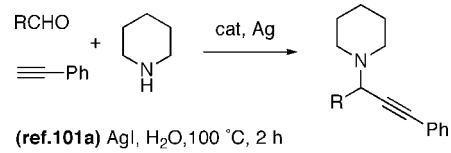
Since the first report by Li et al., A^3-coupling has been examined with other silver promoters such as [$Ag(MeCN)_4$]-[$B(C_6F_5)_4$],[102a] Ag-NaY zeolite,[102b,c] Ag nanoparticles in PEG (400 Da),[102d] Ag salt of 12-tungstophosphoric acid (AgTPA),[102e] and $AgNO_3$ under microwave irradiation (MWI).[102f] Scheme 60 summarizes the results obtained for the typical A^3-coupling reactions. Heterogeneous catalysts, Ag-NaY zeolite, Ag nanoparticles in PEG, and AgTPA could be recycled at least three times. The reactions with Ag-NaY zeolite and $AgNO_3$ under MWI were carried out without the solvent. In the latter case, both significant increase in the yield and shorter reaction time were realized as compared to the conventional heating (CH) conditions (Scheme 61).

A generally accepted mechanism of silver-catalyzed A^3-coupling is shown in Scheme 62. First, the terminal proton

Scheme 59

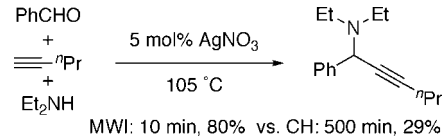


Scheme 60



(ref.101a) AgI, H_2O,100 °C, 2 h
R = Ph, 3% cat.: 70%
R = cyclohexyl, 1.5% cat.: 96%
(ref.101b) AgI, [Bmim][PF_6],100 °C, 16 h
R = cyclohexyl, 3% cat.: 86%
(ref. 102a) [$Ag(MeCN)_4$][$B(C_6F_5)_4$], PhMe, 75 °C
R = Ph, 3% cat.: 96%
R = cyclohexyl, 3% cat.: 98%
(ref. 102b,c) Ag-NaY zeolite, 100 °C, 15 h
R = Ph, 5% cat.: 81% (75% after 4th cycle)
R = *n*-hexyl, 5% cat.: 79%
(ref. 102d) Ag nanoparticles, PEG, 100 °C
R = Ph, 2% cat., 20 h: 77%
R = cyclohexyl, 1% cat., 10 h: 95%
(ref. 102e) AgTPA, MeCN, 80 °C
R = Ph, 6 h: 98% (96% after 4th cycle)
R = cyclohexyl, 3 h: 93%
(ref. 102f) $AgNO_3$, 105 °C (MWI), 10 min
R = Ph, 5% cat.: 90%

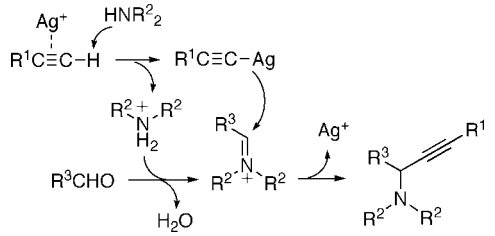
Scheme 61



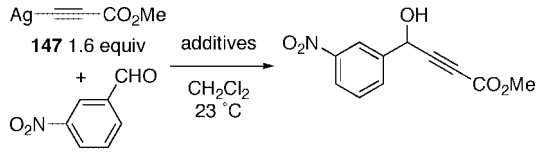
of a silver-coordinated alkyne is abstracted by the amine component to produce a silver acetylide and an ammonium ion. The condensation of the resulting ammonium ion with an aldehyde generates an iminium intermediate. Because of low nucleophilicity, the silver acetylide is allowed to react only with the positively charged highly electrophilic iminium ion even in the presence of the aldehyde. As a consequence, the desired propargyl amine is selectively produced, and H_2O is an exclusive side product.

In accordance with the above explanation, in 2004, Shahi and Koide reported that isolated acetylide **147** derived from methyl propiolate with $AgNO_3$ failed to react with *m*-

Scheme 62

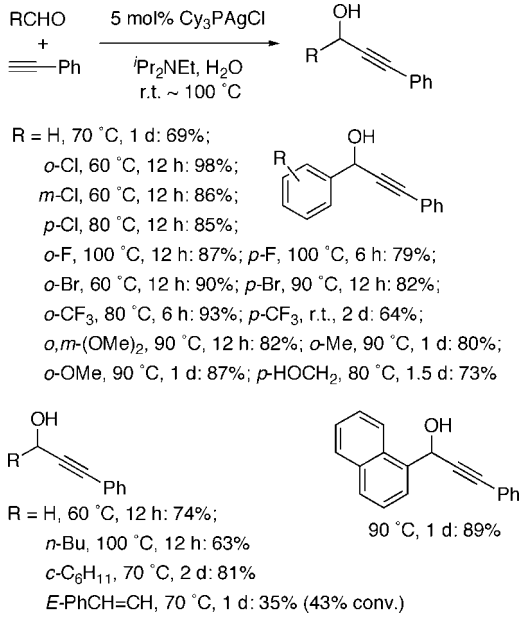


Scheme 63



additives and yields
(a) none, 30 h: 0%
(b) 1.2 equiv Cp_2ZrCl_2, 30 h: 73%
(c) 1.2 equiv Cp_2ZrCl_2, 0.2 equiv AgOTf, 5 h: 95%

Scheme 64



R = H, 70 °C, 1 d: 69%;
o-Cl, 60 °C, 12 h: 98%;
m-Cl, 60 °C, 12 h: 86%;
p-Cl, 80 °C, 12 h: 85%;
o-F, 100 °C, 12 h: 87%; *p*-F, 100 °C, 6 h: 79%;
o-Br, 60 °C, 12 h: 90%; *p*-Br, 90 °C, 12 h: 82%;
o-CF_3, 80 °C, 6 h: 93%; *p*-CF_3, r.t., 2 d: 64%;
o,m-$(OMe)_2$, 90 °C, 12 h: 82%; *o*-Me, 90 °C, 1 d: 80%;
o-OMe, 90 °C, 1 d: 87%; *p*-$HOCH_2$, 80 °C, 1.5 d: 73%

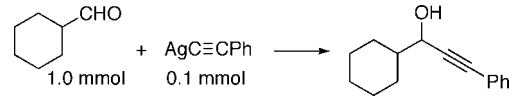
R = H, 60 °C, 12 h: 74%;
n-Bu, 100 °C, 12 h: 63%
c-C_6H_{11}, 70 °C, 2 d: 81%
E-PhCH=CH, 70 °C, 1 d: 35% (43% conv.)

90 °C, 1 d: 89%

nitrobenzaldehyde in the absence of additives (Scheme 63).[17] After screening promoters, they found that the use of 1.2 equivalents of Cp_2ZrCl_2 together with 0.2 equivalents of AgOTf as additives resulted in a high-yield formation of the expected alcohol. Although no mechanism was proposed, the transmetalation from Ag to Zr might be involved in this Zr-mediated addition of the silver acetylide.

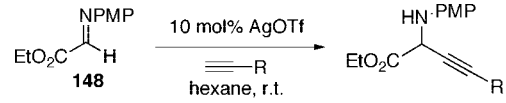
Silver acetylides have been known to form insoluble coordination polymers in which each alkyne component is σ-bonded to one silver atom and π-bonded to the other one.[9a] This polymeric nature might reduce their reactivity toward electrophiles. The addition of tertiary phosphines enables the depolymerization of silver acetylides to give rise to soluble monomeric species.[103] Yao and Li unveiled that the silver-catalyzed addition of phenylacetylene to aldehydes proceeded in the presence of phosphine additives (Scheme 64).[104] The best result was obtained using a tricyclohexylphosphine complex, Cy_3PAgCl, together with $^iPr_2NEt$ in water. Propargyl alcohol derivatives were obtained in 69−98% yields from aromatic aldehydes. The product yields were, however,

Scheme 65



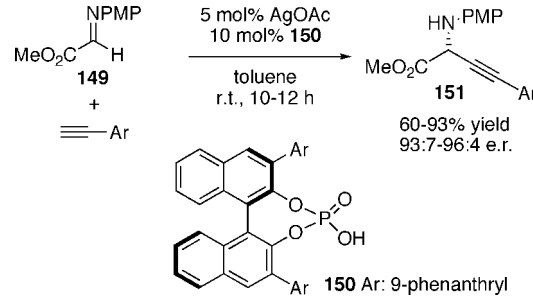
Conditions and yields based on AgC≡CPh.
(a) H_2O, 95 °C, overnight: NR
(b) toluene, 95 °C, overnight: NR
(c) 0.11 mmol Cy_3P, H_2O, 35 °C, overnight: 68%
(d) 0.11 mmol Cy_3P, toluene, 35 °C, 10 h: NR
(e) 0.11 mmol Cy_3P, 1.5 mmol phenylacetylene, H_2O, 95 °C, overnight: 86%
(f) 0.11 mmol Cy_3P, 1.5 mmol phenylacetylene, 0.2 mmol $^iPr_2NEt$, H_2O, 95 °C, overnight: 432%

Scheme 66



R = Ph, 0.5 h: 93%; $PhCH_2CH_2$, 0.5 h: 87%;
^{n}Bu, 0.5 h: 84%; $^nC_6H_{13}$, 0.5 h: 91%; $TMSCH_2$, 1 h: 79%

Scheme 67

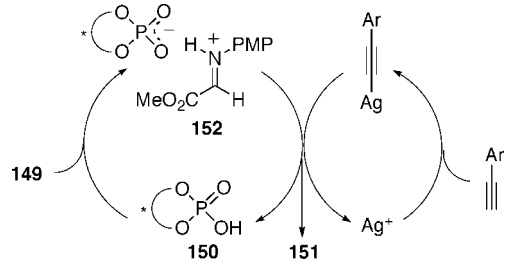


lower (35−81%) when aliphatic aldehydes were used. The reaction uneventfully proceeded with a benzaldehyde derivative possessing a free hydroxyl group. They also carried out stoichiometric reactions of the phenylacetylene-derived silver acetylide to show that all of Cy_3P, water solvent, and amine additive are essential for the catalytic conversion of alkynes (Scheme 65).

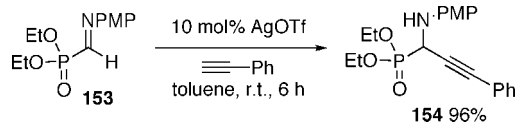
The catalytic three-component coupling of a glyoxalate, an amine, and an alkyne would give an alkynylglycinate, which is a versatile precursor of the other amino acids.[105] Yamamoto and co-workers realized such a three-component-coupling synthesis of alkynyl glycinates using $CuBr_2$ as a precatalyst.[106] Although the corresponding silver-catalyzed A^3-coupling remains to be investigated, Chan and co-workers developed an alternative method to catalytically access alkynylglycinates (Scheme 66).[107] In the presence of 10 mol % AgOTf, several terminal alkynes were added to *p*-methoxyphenyl-protected α-iminoester **148** at room temperature, resulting in high-yield formations of alkynylglycinates. In this case, no phosphine ligands as well as amine additives are required as opposed to the addition to aldehydes. The imino moiety might play a role as a base, and the protonation enhances the electrophilicity of the α-iminoester.

Further, this method was extended to an asymmetric version by Rueping and co-workers (Scheme 67).[108] They used chiral Brønsted acid **150** together with a silver salt, AgOAc, to realize the nonracemic synthesis of base-labile alkynylglycinates **151** in enantiomer ratios of 93:7−96:4. As shown in Scheme 68, the authors ascribed the observed

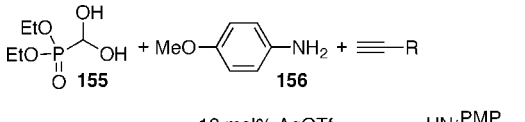
Scheme 68



Scheme 69



Scheme 70



R = Ph: 94%; *o*-BrC_6H_4: 86%: *p*-BrC_6H_4: 84%;
p-ClC_6H_4: 83%: *p*-FC_6H_4: 81%; 3,5-$F_2C_6H_4$: 69%;
p-$CF_3C_6H_4$: 78%; *m*-MeC_6H_4: 90%; *p*-MeC_6H_4: 89%;
p-$MeOC_6H_4$: 80%: 1-naphthyl: 61%; *n*-pentyl: 72%;
$PhCH_2CH_2$: 64%; $AcO(Me)_2C$: 55%

asymmetric induction to the formation of chiral ion pair **152** from iminoester **149** and Brønsted acid **150**. Nevertheless, an alternative pathway involving chiral silver species bearing the phosphonate ligand cannot be ruled out.

Similarly, AgOTf catalyzed the addition of phenylacetylene to α-iminophosphonate **153** in toluene at room temperature to give α-aminopropargylphosphonate **154** in 96% yield (Scheme 69).[109] The obtained α-aminophosphonate is a mimic of the corresponding glycinate. Dodda and Zhao further developed the three-component coupling of α-formylphosphonate hydrate **155**, *p*-anisidine **156**, and terminal alkynes as shown in Scheme 70. The reaction effectively proceeded in the presence of the silver catalyst and $MgSO_4$ as a drying agent at room temperature, and as a result, the desired α-aminopropargylphosphonates were obtained from both aromatic and aliphatic alkynes in 55−94% yields.

3. Summary

As a result of the carbophilic Lewis acid characteristic, silver cations are capable of depriving an alkyne of part of its electron density through coordination with a C−C triple bond. As a result, the acidity of its acetylenic proton is increased, and hence the silver-coordinated alkyne is easily converted into silver acetylide in the presence of a base to abstract the terminal proton. Similarly, trialkylsilylalkynes undergo desilylation more readily under the influence of silver salts. The in situ generated silver acetylides react with various electrophiles to give functionalized alkyne products. Thus, a judicious combination of silver promoters with electrophilic reagents allows the catalytic transformations of terminal or trialkylsilylalkynes. Along this line, various silver-catalyzed processes of practical importance have been developed to date. These include catalytic desilylation and halogenation, which have been extensively utilized in the construction of complex natural products and artificial materials. Catalytic A^3-coupling is also realized to provide access to propargylamines. The cocatalysis of palladium and silver operates very successfully in Sonogashira-type cross coupling reactions of alkynes with enol triflates or organohalides. In particular, the selective transformation of polyynes protected by different trialkylsilyl groups via Pd/Ag-catalyzed direct Sonogashira coupling provides a concise approach to highly functionalized polyalkyne materials.

The synthetic value of these silver catalyzed processes is further enhanced by the potential utility of the resulting functionalized alkyne products. For instance, haloalkynes are highly versatile precursors for transition-metal-catalyzed coupling reactions such as Cu-catalyzed Cadiot−Chodkiewicz reaction, Pd-catalyzed Sonogashira-type coupling, or Cr/Ni-catalyzed Nozaki−Hiyama−Kishi coupling. Haloalkynes can also undergo cyclization and cycloaddition across their C−C triple bonds in the presence or absence of catalysts to give unsaturated organohalides, which are capable of further transformations at the remaining carbon−halogen bonds.

In the future, further discoveries of unprecedented silver promoters as well as electrophilic reaction partners will significantly contribute to the progress of alkyne-based synthetic technologies.

4. References

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CR078359U