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Trihaloethenes as versatile building blocks for organic synthesis

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This review highlights the chemistry of trihaloethene building blocks with a special focus on commercially available 1,1,2-trichloroethene. The topics surveyed herein include the use of trihaloethenes as C_2-building blocks for transition metal-catalyzed coupling reactions, addition, elimination and cycloaddition reactions as well as natural product syntheses.

1. Introduction

Within the family of commercially available trihaloethene derivatives, 1,1,2-trichloroethene (**1**, TCE, b.p. 87 °C) is by far the most commonly used reagent. Dr E. Fischer (not Hermann Emil Fischer) achieved the first synthesis of **1** in 1864 by reductive dehalogenation of hexachloroethane with hydrogen.[1] Since then, TCE (**1**) has gained major importance in various industrial applications.[2] The ease of preparation of large quantities of this non-flammable, volatile organic compound led to a staggering global consumption of 428.6×10^3 t in 2011. Of this, 84% of the total production volume in the USA were used as an intermediate for manufacturing the refrigerant 1,1,1,2-tetrafluoroethane (HFC-134a) and 15% as a solvent for metal degreasing.[2,3] The preparation of HFC-134a from **1** occurs by addition of hydrogen fluoride to the alkene, followed by halogen-exchange reactions to afford 2-chloro-1,1,1-trifluoroethane (HCFC-133a) (eqn (1)). By further treatment with hydrogen fluoride, HCFC-133a is then converted into HFC-134a (eqn (2)). These transformations can be mediated by several catalysts, which are typically derived from chromium salts.[4] TCE (**1**) is classified as human carcinogen, and its

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Thomas Magauer

Thomas Magauer was born in Linz, Austria in 1983. He grew up in Steyr and moved to Vienna in 2002 to study chemistry at the University of Vienna. In 2007, he joined the laboratories of Prof. Johann Mulzer and under his guidance he developed enantioselective syntheses of the complex polyketide kendomycin and the sesquiterpenoid echinopines A and B. After graduating in 2009, he moved to Harvard University, USA, to begin postdoctoral studies with Prof. Andrew G. Myers. At Harvard University he worked on carbohydrates, chiral silicon protecting groups and developed a synthesis of natural and diverse unnatural antiproliferative trioxacarcins. In 2012, he started his independent research as a Liebig-junior research group leader at the LMU Munich. Since 2013, his group has been supported by an Emmy Noether fellowship of the DFG.

toxicity has been investigated and discussed in detail.[3,5] Amongst other factors, the toxicity associated with **1** has led to continuously decreasing production rates in the industry.[2,6]

$$CCl_2{=}CHCl + 3HF \xrightarrow[200-400\ ^\circ C]{\text{Cr-catalyst}} CF_3CH_2Cl + 2HCl \quad (1)$$

$$CF_3CH_2Cl + HF \xrightarrow[250-450\ ^\circ C]{\text{Cr-catalyst}} CF_3CH_2F + HCl \quad (2)$$

In the field of synthetic organic chemistry, TCE (**1**) serves as a chlorinated C_2-building block[7,8] that found very interesting applications beyond cross coupling reactions.[9]

The corresponding bromo- and fluoro-derivatives, 1,1,2-tribromoethene (**2**, TBE, b.p. 163 °C) and 1,1,2-trifluoroethene (**3**, TrFE, b.p. −51 °C), respectively, have received much less attention from synthetic chemists. Although tribromoethene (**2**) has been known for over 150 years, its use in synthesis has been relatively limited.[10] Trifluoroethene (**3**), on the other hand, has found application in the synthesis of copolymers in combination with polyvinylidene fluoride (PVDF). This copolymer, named P(VDF-TrFE), is a very important organic ferroelectric material.[4a,11] The addition of TrFE (**3**) to the polymer, usually in a composition of P(VDF-TrFE) 70 : 30, enhances the all-*trans* conformation associated with the crystalline β-phase. This conformation and the dipole moment generated thereby, have a strong influence on the ferroelectric and also piezoelectric properties.[11]

Since the preparation of **1** and **3** has been extensively studied over the years, we will provide the reader only with a selection of approaches. There are several feedstock chemicals that can be used to synthesize TCE (**1**). One such feedstock is acetylene, which is converted to **1** *via* a chlorination–dehydrochlorination pathway.[2] A different approach is the oxychlorination of ethene to afford **1**. In this reaction, the chlorine source is hydrogen chloride, which is oxidized according to the Deacon process.[2,12,13] Tetrachloroethene can also be converted into TCE (**1**) *via* hydrogenolysis with transition metal catalysts.[14] TrFE (**3**) has also been prepared using various approaches: 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) can be used as starting material in a vapor-phase reduction,[4a] hydrodechlorination[15] or direct controlled-potential (bulk) electrolysis.[16] Alternatively, chlorotrifluoroethene (CTFE) has been used in hydrodechlorinations,[17] and 1,1,1,2-tetrafluoroethane in dehydrofluorination reactions.[18] In contrast, the preparation of TBE (**2**) has received less attention and one of the very few examples is based on the elimination of hydrogen bromide from 1,1,2,2-tetrabromoethane *via* phase-transfer conditions (PTC).[19]

A selection of further commercially available trihaloethenes is depicted in Fig. 1, although their use is less prevalent compared to TCE (**1**) or TrFE (**3**). Some trihaloethenes are used as monomers for the synthesis of halogenated polymers (2-bromo-1,1-difluoroethene (**4**, BDFE)),[20] or for radical addition reactions (2-chloro-1,1-difluoroethene (**6**)).[21]

Although trihaloethenes are generally available from commercial sources, iodine containing derivatives are far less

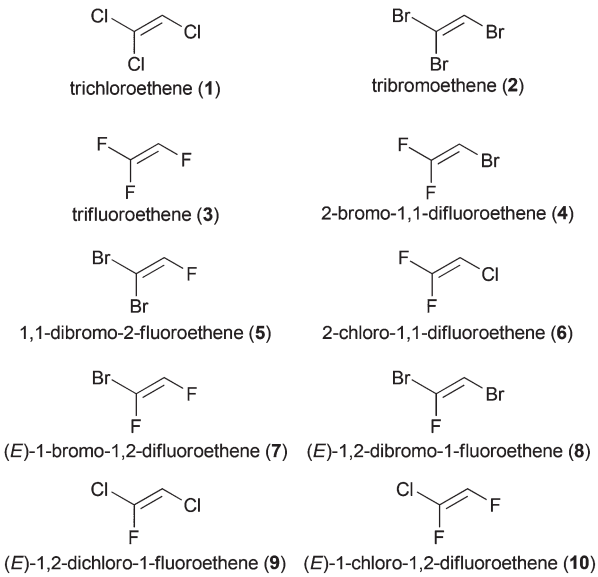
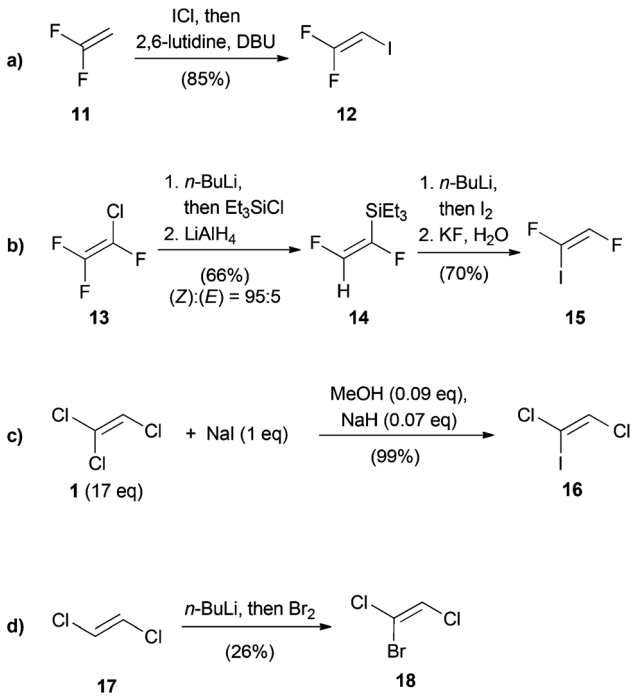


Fig. 1 A selection of commercially available trihaloethene derivatives.



Scheme 1 Synthesis of the trihaloethenes **12**, **15**, **16** and **18**.

common. Scheme 1 outlines the four approaches involved in the stereoselective synthesis of differentially substituted trihaloethenes. The synthesis of 1,1-difluoro-2-iodoethene (**12**) is based on the addition of iodinemonochloride and subsequent elimination of hydrogen chloride (Scheme 1a).[22] This reaction could be conducted on a two mole scale without noticeable loss of yield. Burton published a selective synthesis of (*Z*)-1,2-difluoro-1-iodoethene (**15**) (Scheme 1b).[23] In the first two steps, silylation *via* chlorine–lithium exchange and

reduction with lithium aluminium hydride afforded **14** in a (*Z*) : (*E*) ratio of 95 : 5. Subsequent deprotonation and iodination followed by protodesilylation yielded isomerically pure **15**. The enrichment of the (*Z*)-isomer was explained due to decomposition of the lithiated (*E*)-isomer *via* elimination of lithium fluoride. In 2007, the group of Castanet reported the synthesis of (*Z*)-1,2-dichloro-1-iodoethene (**16**) from TCE (**1**) (Scheme 1c).[24] Since **1** is used as the solvent and the reaction proceeds *via* the intermediacy of the highly explosive dichloroacetylene (DCA, **41**), only substoichiometric quantities of base were used in order to avoid accumulation of large amounts of **41**. (*Z*)-1-Bromo-1,2-dichloroethene (**18**) was prepared in 1966 by Köbrich and Flory by lithiation of (*E*)-1,2-dichloroethene (**17**), followed by treatment with bromine (Scheme 1d).[25]

The following sections will focus on the chemistry of trihaloethenes, in particular TCE (**1**). Their functionalization *via* addition, elimination and transition metal-catalyzed reactions is presented, as well as their application in the synthesis of natural products.

2. Functionalization of trihaloethenes *via* addition and elimination reactions

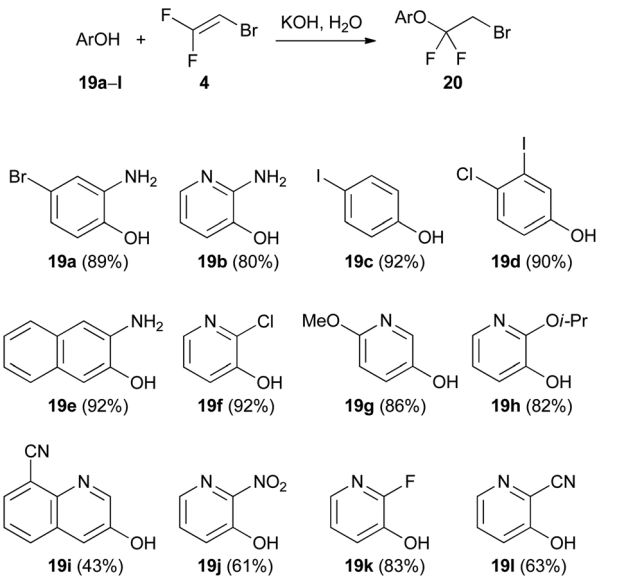
Addition reactions

Trihaloethenes are very versatile reagents for nucleophilic or electrophilic addition reactions. Additionally, the increased acidity of the vinylic proton (pK_a (1) = 27–29)[26] enables the simple use of lithiated trihaloethenes as valuable nucleophiles.

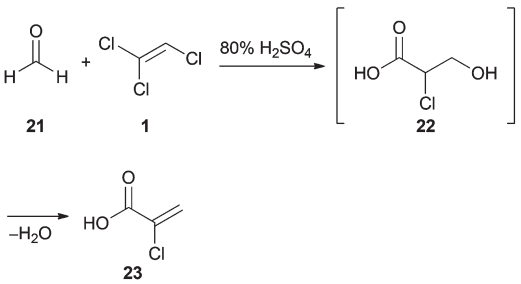
The Humphrey group reported an addition reaction to the C=C double bond as an efficient method to synthesize halogenated aryl and heteroaryl ethers.[27] A variety of phenols and 3-hydroxypyridines underwent nucleophilic addition to 2-bromo-1,1-difluoroethene (**4**) under basic conditions (Scheme 2). A small amount of water was a necessary additive to immediately protonate the initially formed anionic adduct and therefore prevent elimination of fluoride. In all reactions, less than 5% elimination was observed, except in the case of **19h**, where 14% elimination took place. In this instance, the authors suggested that the proton transfer might be hindered due to the presence of the sterically encumbered isopropoxy group.

Despite having three electron withdrawing chlorine substituents, TCE (**1**) is capable of nucleophilic addition to formaldehyde (**21**) under strongly acidic conditions (Scheme 3). This reaction was first reported by Prins in 1932, who claimed that the final product was 3,3′-oxybis(2-chloropropanoic acid).[28] However, in subsequent studies[29] the product was identified as 2-chloroacrylic acid (**23**). The putative intermediate **22** could not be isolated due to spontaneous dehydration under the reaction conditions.[30]

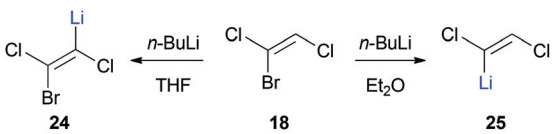
In 1966, Köbrich and Flory reported the reaction of (*Z*)-1-bromo-1,2-dichloroethene (**18**) with *n*-butyllithium and carbon dioxide (Scheme 4).[25] Surprisingly, depending on the reaction solvent, the differently lithiated products **24** or **25** were formed



Scheme 2 Addition reaction of hydroxy arenes and heteroarenes **19a–l** to 2-bromo-1,1-difluoroethene (**4**).



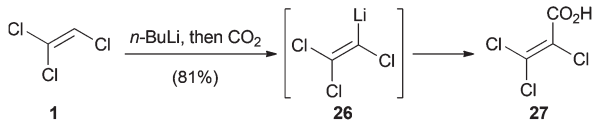
Scheme 3 Prins reaction of **1** with formaldehyde (**1**) under strongly acidic conditions.



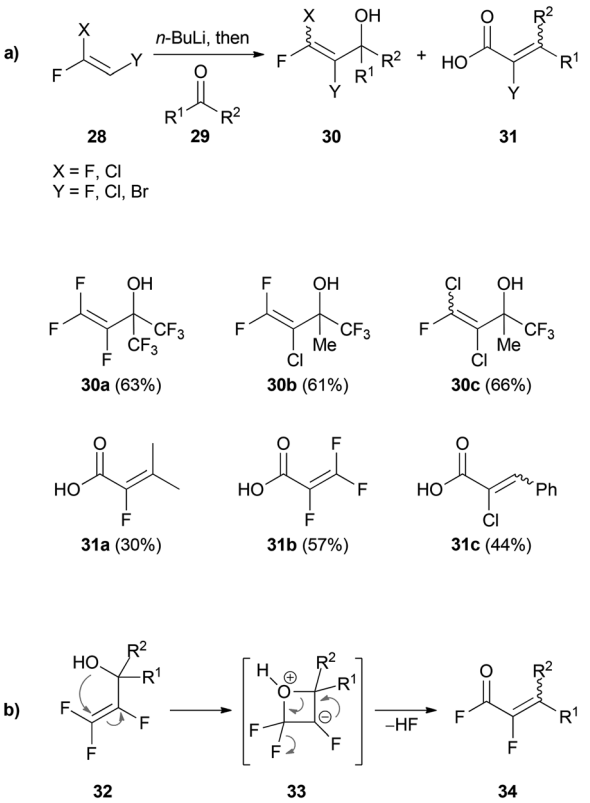
Scheme 4 Solvent effects on the regioselective lithiation of **18**.

in situ instead of the expected elimination products. While **24** is the product of vinylic deprotonation, halogen–lithium exchange leads to the formation of **25**. They proposed that deprotonation is quicker than the halogen–lithium exchange in the more polar and strongly coordinating solvent tetrahydrofuran.[25,31] Based on this discovery, various trihaloethenes could be metalated and used as nucleophiles in addition reactions with carbon dioxide to form the corresponding acids.

Similarly, Köbrich and Flory metalated **1** with *n*-butyllithium and treated the so generated vinyl lithium intermediate **26** with carbon dioxide to afford trichloroacrylic acid (**27**) (Scheme 5).[25]



Scheme 5 Carboxylation of **1** with carbon dioxide.



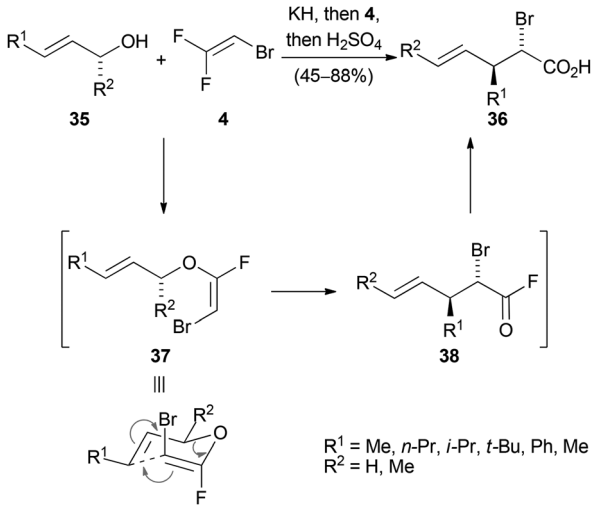
Scheme 6 (a) 1,2-Addition of trihalovinyllithium reagents to carbonyl compounds **29**. (b) Reaction mechanism for the 1,3-rearrangement of **32**.

Based on the results of Köbrich and Flory, Tarrant prepared fluorine-containing vinyllithium reagents using **28**. Treatment with a variety of carbonyl compounds **29** afforded the corresponding 1,2-addition products **30** (Scheme 6a).[32]

In the cases where the carbonyl compounds **29** did not have electron withdrawing CF_3-groups, subsequent rearrangement of the intermediate alcohols to **31** was usually observed. The postulated mechanism of the 1,3-rearrangement is illustrated in Scheme 6b. Attack of the hydroxyl group at the vinylic *gem*-difluoro group of **32** leads to formation of the oxetane intermediate **33**. Subsequent elimination of hydrogen fluoride gives rise to the acid fluoride **34** which is then hydrolyzed to give the acid **31**.

Addition–elimination reactions

Reactions wherein a nucleophilic addition to the trihaloethene followed by elimination of a halide anion takes place are

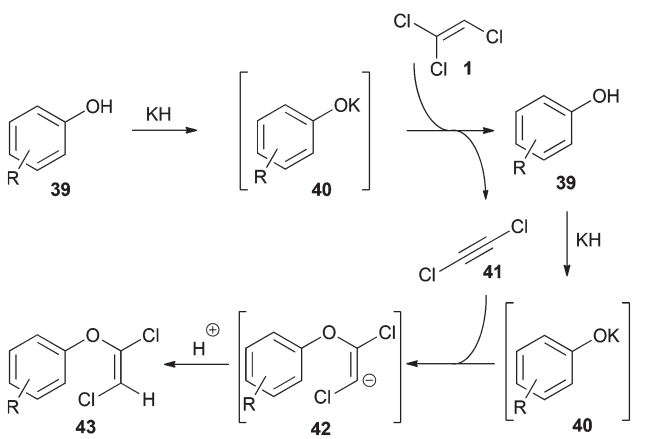


Scheme 7 Claisen rearrangements of halogenated allyl vinyl ethers.

designated as addition–elimination reactions. A useful application of this concept was demonstrated in 2000 by Tellier for the stereoselective synthesis of halogenated carboxylic acids (Scheme 7).[33] Various allylic alcohols **35** were treated with potassium hydride to form the corresponding alkoxides, which then reacted with 2-bromo-1,1-difluoroethene (**4**) at −90 °C to selectively form the *E*-enol ether **37**. At temperatures around −30 °C, **37** underwent a Claisen rearrangement to give the acid fluoride **38**, which afforded the *anti* substituted acid **36** upon aqueous workup.

Elimination–addition reactions

These transformations, in some cases referred to as condensation[34] or substitution[30,35] reactions, occur readily with TCE (**1**). Seminal studies concerning their mechanism were performed by Kende.[34] Based on these findings, Hultin described a detailed mechanism using phenols as nucleophiles (Scheme 8).[35]



Scheme 8 Mechanism of the elimination–addition reaction of **1** using potassium phenolates **40**.

In the first step DCA (**41**) is formed by deprotonation of **1** with the potassium phenolate **40**. Regeneration of **40** by a second equivalent of base then initiates the addition reaction to the *in situ* generated **41**. Finally, protonation of the vinyl anion **42** affords the 1,2-dichlorovinyl ether **43**. The addition step proceeds highly stereoselective and provides the *E*-configured vinyl ether as the main product.[35]

The dehydrochlorination of TCE (**1**) is a very common reaction that was also studied in more detail.[30] The β-elimination generally occurs by treatment of **1** with a strong base and leads to the formation of DCA (**41**).[36] In a procedure reported in 1961, a gaseous mixture of **1** in diethyl ether was passed through pyrex tubes containing a potassium hydroxide/calcium oxide mixture.[37] Two other reports describe the synthesis of **41** *via* phase-transfer catalysis (PTC).[36d,38] While Kende synthesized **41** by deprotonating **1** with lithium bis(trimethylsilyl)amide,[39] Greene employed potassium hydride and a catalytic amount of methanol for this transformation (Scheme 9).[36b]

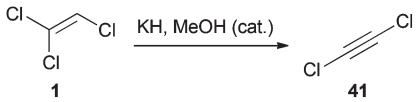
Preparing **41** as a solution in diethyl ether forms a rather stable diethyl ether–DCA (**41**) complex and proved to be a practical method for the handling of this reagent, as pure **41** is toxic and highly explosive.[30,56]

Kende employed an elimination–addition reaction with *in situ* generated **41** to prepare various dichlorovinyl ketones in up to 64% yield (Scheme 10a).[34] The same conditions were investigated for the reaction of **49** with 1,2-dichloro-1-fluoroethene (**9**). Although **9** was used as a 1 : 1 mixture of (*E*) and (*Z*)-isomers, only the (*E*)-isomer **50** was observed as the product (Scheme 10b). This result implies the formation of chlorofluoroacetylene as an intermediate, similar to the mechanism depicted in Scheme 8.

Greene reported a method based on a similar protocol (Scheme 11).[40] After the treatment of alcohols **51** with potassium hydride and TCE (**1**) to form the intermediate dichlorovinyl ethers, addition of excess *n*-butyllithium gave the corresponding chloro ynol ethers. Under the reaction conditions, a subsequent halogen–lithium exchange took place and the generated lithium acetylide is then either protonated or alkylated to yield the ynol ether **52**.

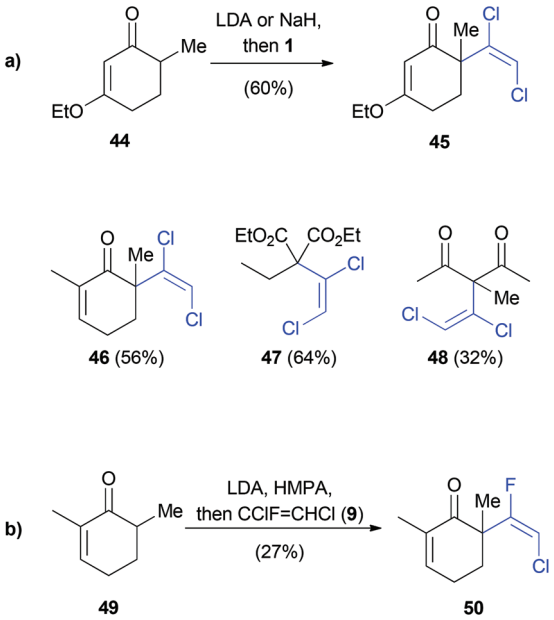
In 1995, Greene expanded the one-pot methodology for the synthesis of ynol ethers to the preparation of ynethiol ethers **58** by implementing the corresponding thiols **57** (Scheme 12).[41] Primary, secondary and tertiary thiols served as substrates in this reaction and the obtained yields ranged from 69–98%.

Pielichowski reported the reaction of TCE (**1**) with secondary amines **59** to obtain glycinamides **60** (Scheme 13a).[38,42]



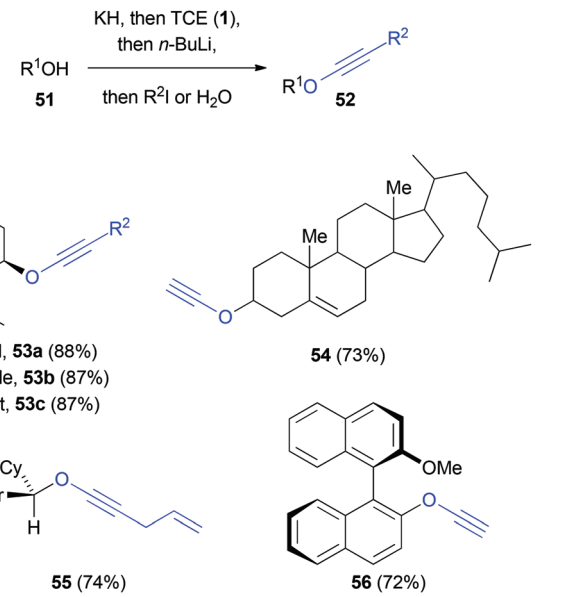
1 **41**

Scheme 9 Synthesis of DCA (**41**) from **1**.

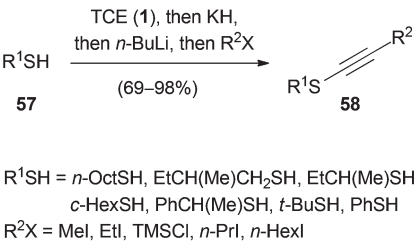


44 **45** **46** (56%) **47** (64%) **48** (32%) **49** **50**

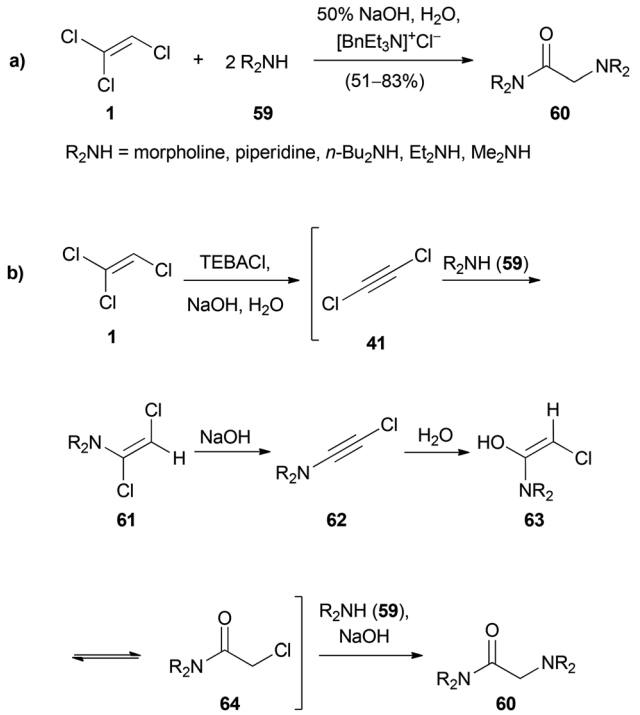
Scheme 10 α-Vinylation of ketones.



Scheme 11 Preparation of ynol ethers.



Scheme 12 Synthesis of ynethiol ethers.



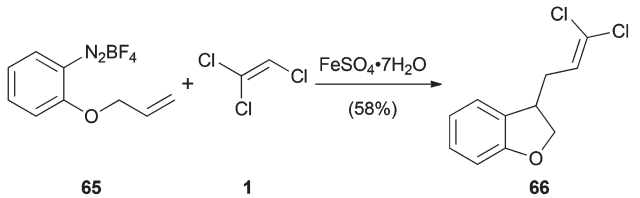
Scheme 13 (a) Synthesis of substituted glycinamides **60**. (b) Proposed mechanism.

The proposed reaction mechanism is depicted in Scheme 13b. DCA (**41**) is formed by deprotonation with sodium hydroxide under PTC conditions. The secondary amine **59** adds to **41** and the resulting enamine **61** undergoes a further elimination to the ynamide **62**. Addition of water to **63** and replacement of the α-chloro ketone in **64** with the second equivalent of amine leads to the glycinamide **60**.

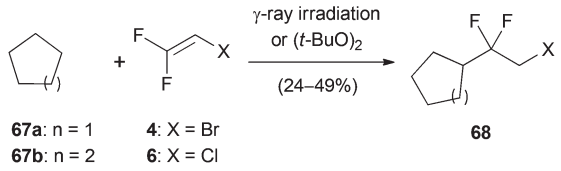
Radical addition reactions

Trihaloethenes can not only undergo nucleophilic addition reactions but also radical addition reactions (Scheme 14).[43] Iron(II) sulfate reduces the diazonium salt **65** to generate an aryl radical, which undergoes a 5-*exo*-*trig* cyclization followed by addition to **1**. Subsequent elimination of chlorine leads to **66** in 58% yield.

A related reaction reported by the Sandford group relies on the radical hydroalkylation of fluorinated trihaloethenes with cyclopentane (**67a**) and cyclohexane (**67b**) (Scheme 15).[21] The alkyl radicals, generated by γ-ray irradiation or treatment with



Scheme 14 Radical cyclization and addition of diazionium salt **65** to **1**.



Scheme 15 Free radical addition of trihaloethenes **4** and **6**.

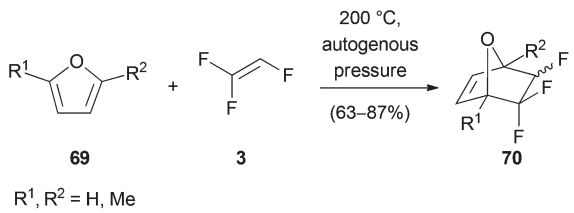
di-*tert*-butyl peroxide, regioselectively substitute the *gem*-difluoro carbon atom. The authors suggest that the regioselectivity is governed by the little sterical hindrance and the increased electrophilicity of this position.

3. Cycloadditions

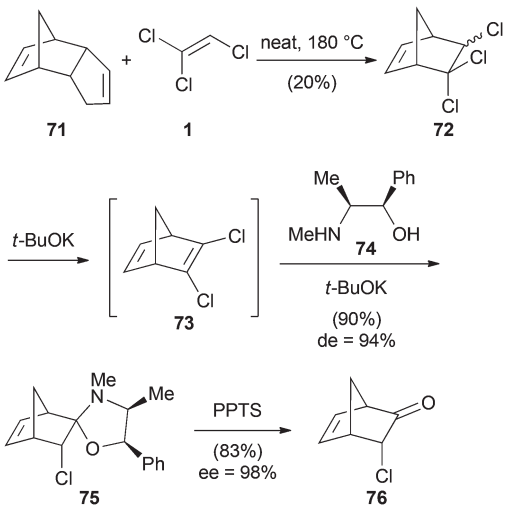
[4 + 2] cycloadditions

Trihaloethenes have also found application as dienophiles in cycloaddition reactions. Chambers reported Diels–Alder reactions between trifluoroethene (**3**) and various substituted furan derivatives **69** (Scheme 16).[44] The reactions were carried out in an autoclave at 200 °C under autogenous pressure to yield fluorinated oxabicyclo[2.2.1]hept-2-enes **70**.

Another example of a [4 + 2] cycloaddition was published by Borsato (Scheme 17).[45] They synthesized 3-chloronorbornenone



Scheme 16 [4 + 2] Cycloaddition with TrFE (**3**).



Scheme 17 [4 + 2] Cycloaddition with TCE (**1**).

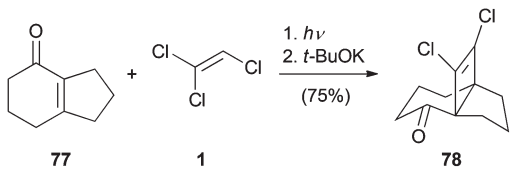
(**76**) *via* a three-step synthesis starting with a Diels–Alder reaction between TCE (**1**) and cyclopentadiene. The formed trichloronorbornene **72** was converted to the dichloronorbornadiene **73** under basic conditions and subsequently desymmetrized with the chiral auxiliary (−)-ephedrine (**74**). Hydrolysis with pyridinium *p*-toluenesulfonate (PPTS) then afforded bicyclic ketone **76**.

[2 + 2] cycloaddition

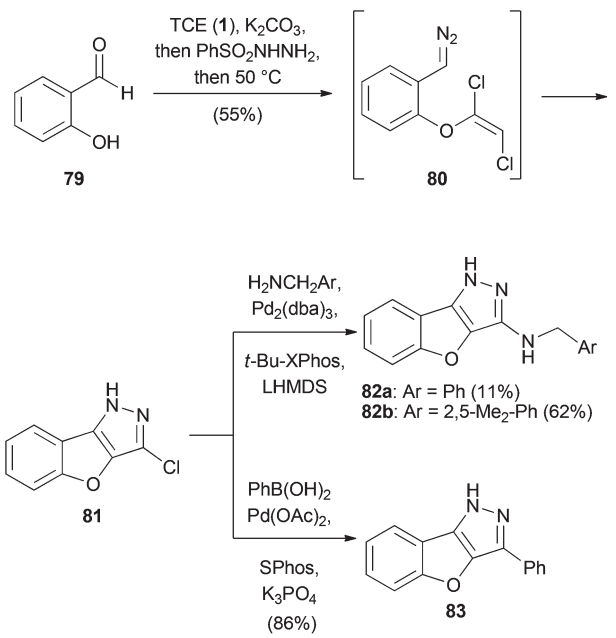
A photochemical [2 + 2] cycloaddition reaction with TCE (**1**) was reported by Tobe (Scheme 18).[46] The bicyclic enone **77** was dissolved in **1** and irradiated with a 500 W high-pressure mercury lamp. The following elimination of hydrochloric acid under basic conditions allowed isolation of the cyclobutene **78**.

1,3-Dipolar cycloaddition

Mani and Sales discovered an intramolecular 1,3-dipolar cycloaddition one-pot protocol for the concise synthesis of benzofuropyrazoles (Scheme 19).[47] Starting from salicylaldehyde (**79**), the corresponding dichlorovinyl ether was generated and treated with benzenesulfonyl hydrazide to form the corresponding hydrazine. Raising the temperature to 50 °C afforded aryldiazomethane **80**, which spontaneously cyclized to form



Scheme 18 [2 + 2] Cycloaddition of an enone with **1**.



Scheme 19 A one-pot protocol for the synthesis of benzofuropyrazoles.

chloropyrazole **81** in 55% overall yield. The product could be further functionalized by Buchwald–Hartwig or Suzuki–Miyaura cross-coupling reactions.

4. Transition metal-catalyzed reactions

Since the reactivities of the three C–Cl bonds of TCE (**1**) differ significantly from each other, it can be used as versatile reagent for cross-coupling reactions. Hultin reported detailed studies concerning the different possibilities to sequentially and selectively functionalize **1** using traditional palladium(0)-catalyzed transformations such as Suzuki–Miyaura, Negishi, and Sonogashira cross-coupling reactions (Fig. 2).[48]

Hultin exploited the unique reactivity of **1** which enabled the preparation of highly substituted ethene derivatives in a controlled fashion (Scheme 20).[48] In each case, the first step involves formation of a (*E*)-1,2-dichlorovinyl ether **84** by an elimination–addition reaction. As depicted in route A, deprotonation of the C(2)–H group in **84** followed by subsequent addition of an electrophile allows the preparation of substituted 1,2-dichlorovinyl ether **85**. In route B, the C(1)–Cl group of **84** is able to participate in cross-coupling reactions just as the C(2)–Cl group in the ensuing step (route C). The trisubstituted alkene **87** can be obtained *via* route C. Route D starts from **86** as well, but the following step involves the deprotonation of C(2)–H and replacement with an electrophile. A further cross-coupling reaction of the C(2)–Cl group of **88** then gives rise to the tetrasubstituted alkene **89**.

However, there are limitations to the reaction pathways depicted in route A and C. While Suzuki–Miyaura cross coupling reactions at the C(1)–Cl group of product **85** (route A) were not stereoselective, Sonogashira cross-couplings proved to be unsuccessful at all. In route C, deprotonation of the C(2)–H group of **87** was problematic and generation of a tetrasubstituted alkene was not possible *via* this route.[48]

Suzuki–Miyaura coupling

Hultin and Geary[35,49] expanded the Suzuki–Miyaura cross-coupling reactions to include 1,2-dichlorovinylaryl ethers **90**.

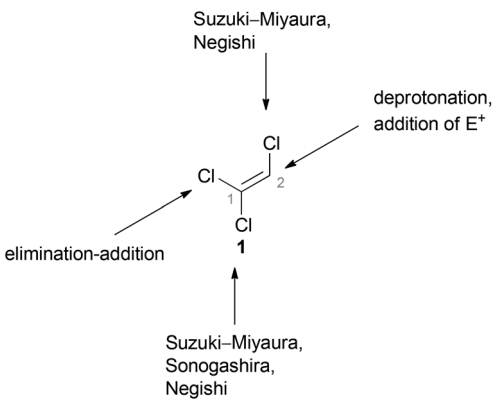
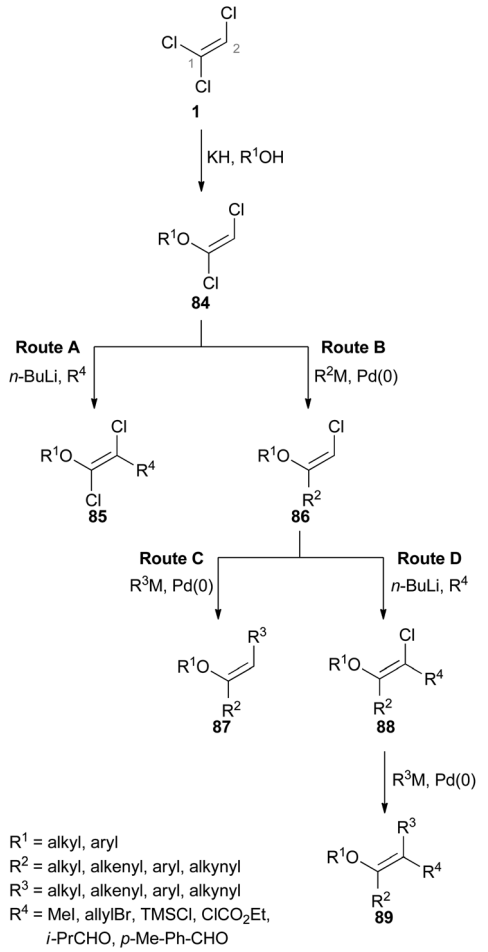


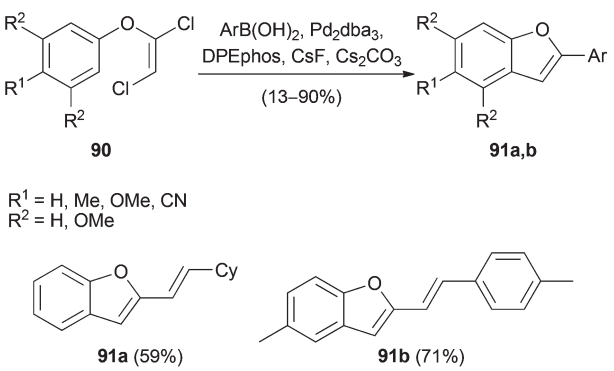
Fig. 2 Overview of the different functionalization possibilities of **1**.



Scheme 20 Reaction sequences for the functionalization of **1**.

The latter were derived from symmetrical phenols and **1**, and enabled the synthesis of 2-substituted benzofurans **91a,b** (Scheme 21).

The cross-coupling occurred selectively at the C(1)–Cl group of the electrophile and gave a single regio- and stereoisomer in all cases. This is due to the oxidative addition of palladium to the most electrophilic carbon atom. The authors also observed



Scheme 21 One-pot preparation of benzofurans from symmetrical phenols.

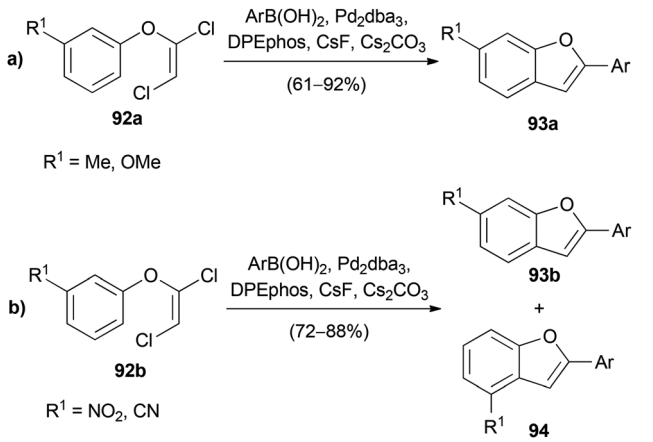
spontaneous cyclization to the benzofuran upon prolonged heating after completion of the Suzuki coupling. However, if the cross-coupling was incomplete, the subsequent cyclization did not occur and thus limited the utility of the one-pot protocol. Hultin and Geary further employed this method for the synthesis of indoles with substituents in C(2)-position. However, yields were generally lower for these substrates (29–47% yield).[49]

In further experiments it was demonstrated that 1,2-dichlorovinyl ethers **92a**, derived from unsymmetrical electron rich phenols, afforded substituted benzofurans **93a** as single regioisomers (Scheme 22a).[35] However, with electron deficient phenol derivatives **92b**, a mixture of the regioisomers **93b** and **94** was obtained (Scheme 22b).

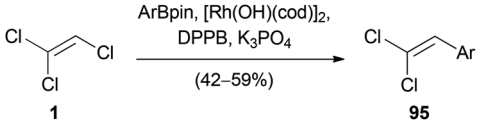
After further experimentation, the authors suggested four mechanistic possibilities: electrophilic aromatic substitution, σ-bond metathesis and two different assisted intermolecular palladations. Finally, the data were found to be consistent with a C–H metathesis as well as with an assisted palladation pathway. However, further discrimination was not possible so far.

Stereoselective Suzuki–Miyaura cross coupling reactions are also possible with TCE (**1**) itself. Matsuda reported the synthesis of (2,2-dichlorovinyl)arenes **95** by a rhodium(I)-catalyzed cross-coupling reaction of **1** with arylboronic esters (Scheme 23).[50] The reaction occurred selectively at the C(2)–Cl bond and a variety of β,β-dichlorostyrenes were synthesized.

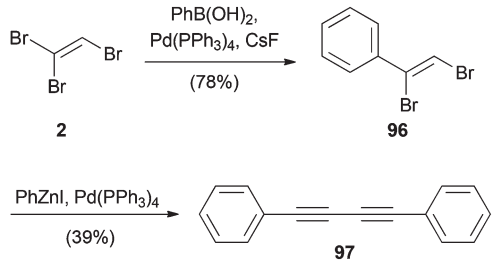
The observed selectivity differed significantly from the analogous rhodium(I)-catalyzed reaction using TBE (**2**), since a



Scheme 22 Synthesis of benzofurans from unsymmetrical phenols.



Scheme 23 Rhodium(I)-catalyzed Suzuki–Miyaura cross-coupling with TCE (**1**).



Scheme 24 Suzuki–Miyaura cross-coupling with TBE (**2**) and subsequent homocoupling under Negishi cross-coupling conditions.

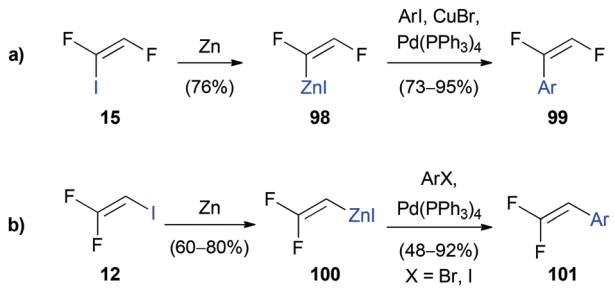
3 : 1 mixture of 2-(2,2-dibromovinyl)-naphthalene and (*Z*)-(1,2-dibromovinyl)naphthalene was obtained in low yield.[50]

An alternative Suzuki–Miyaura coupling with TBE (**2**) using a palladium(0) catalyst was reported by the group of Organ. For this reaction, the (*Z*)-isomer of 1,2-dibromovinyl benzene (**96**) was formed in good yield (Scheme 24).[51] Unfortunately, all attempts to further diversify bromide **96** by cross-coupling reactions, even under mild Negishi conditions, failed. Instead, elimination and homocoupling resulted in the formation of **97**.

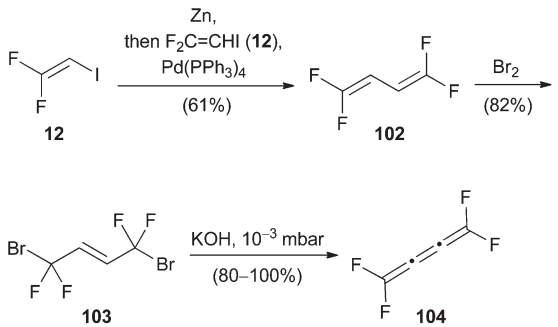
Negishi coupling

Burton and Liu reported the stereoselective preparation of (*Z*)-1,2-difluoro-1-iodoethane (**15**), which can undergo stereospecific Negishi cross-coupling reactions to obtain (*E*)-1,2-difluorostyrene derivatives **99** (Scheme 25a).[23] The metalation of **15** with activated zinc dust afforded exclusively the (*E*)-isomer **98**. The best yields were obtained by using *N*,*N*-dimethylacetamide, while the formation of several side products was observed when the reaction was conducted in *N*,*N*-dimethylformamide. By using substoichiometric amounts of copper(I) bromide as an additive for the Negishi cross-coupling, the reaction rate could be increased and full conversion was achieved within less than six hours. In an analogous reaction reported by Burton 1,1-difluoro-2-iodoethene (**12**) was used to prepare the metalated species **100** (Scheme 25b).[52] Palladium (0)-catalyzed coupling with various substituted aryl halides gave the corresponding 2,2-difluorostyrenes **101** in up to 92% yield without the need for an additional copper(I) additive.

Another Negishi coupling was reported by Lentz and coworkers in 2010 (Scheme 26).[22] The organozinc compound was



Scheme 25 Negishi cross-coupling with **15** and **12**.



Scheme 26 Negishi cross-coupling with 1,1-difluoro-2-iodoethene (**12**) and formation of tetrafluorobutatriene (**104**).

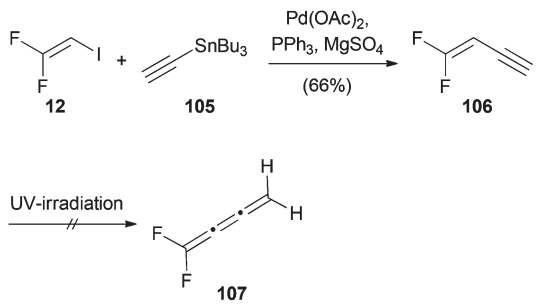
prepared from **12** using activated zinc powder and gave rise to the homocoupled product 1,1,4,4-tetrafluorobuta-1,3-diene (**102**), which was brominated in a 1,4-fashion to yield **103**. Intermediate **103** was then converted to tetrafluorobutatriene (**104**) *via* a double elimination reaction using potassium hydroxide.

Stille coupling

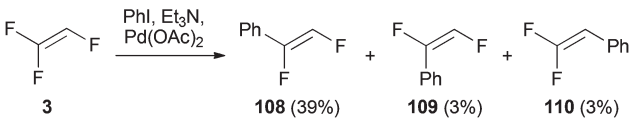
Lentz also reported a palladium(II)-catalyzed Stille cross-coupling reaction of **12** with tributyl(ethynyl)stannane (**105**) (Scheme 27).[22] Attempts to convert product **106** to the corresponding butatriene **107** using UV-irradiation were unsuccessful.

Heck reactions

To the best of our knowledge, only one report is detailing a Heck reaction using a trihaloethene. As shown in Scheme 28, TrFE (**3**) was treated with iodobenzene, triethylamine and a catalytic amount of palladium(II) acetate to obtain (*Z*)-(1,2-difluorovinyl)benzene **108** in 39% yield.[53] The other reaction products **109** and **110** were also formed in low yields. The formation of **108** is consistent with a β-fluoride elimination of



Scheme 27 Stille cross-coupling with **12**.



Scheme 28 Heck reaction with TrFE (**3**).

the palladium(II) intermediate. To support the mechanistic proposal, which involves attack of the arylpalladium(II) intermediate at the higher substituted carbon atom, MNDO-calculations (Modified Neglect of Diatomic Overlap) were conducted. The calculated net atomic charges of both C-atoms differ considerably (C(1) = +0.28; C(2) = +0.09), which indicates a charge controlled insertion reaction to **3**.

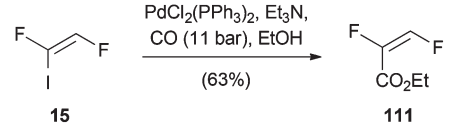
Pd-catalyzed CO insertion

A palladium-catalyzed carboalkoxylation of (*Z*)-1,2-difluoro-1-iodoethene (**15**) was published by Burton (Scheme 29).[54] Based on the modification of a former procedure of Burton and Wesolowski,[55] ethyl (*E*)-2,3-difluoroacrylate (**111**) could be prepared in 63% yield.

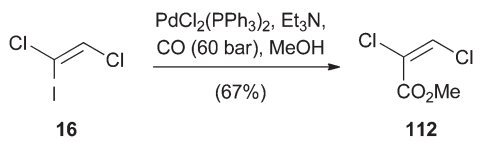
A very similar procedure was used by Castanet for the palladium(0)-catalyzed alkoxycarbonylation of (*Z*)-1,2-dichloro-1-iodoethene (**16**) (Scheme 30).[24] It was not possible to obtain the reaction product **112** by direct methoxycarbonylation of TCE (**1**). Therefore, the mono-iodo analogue **16** was synthesized to increase the rate of oxidative addition. In this manner, **112** could be obtained in moderate yield.

Kumada coupling

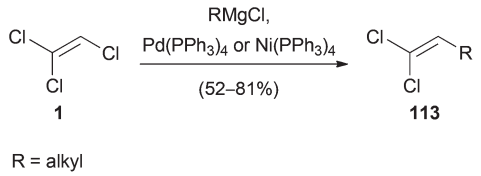
The palladium or nickel-catalyzed reaction of a Grignard reagent with **1** was reported in 1985.[56] Under mild conditions, **1** reacts with primary and secondary alkyl magnesium chlorides to yield 1,1-dichloroalkenes **113** in up to 81% yield (Scheme 31). The proposed mechanism, oxidative addition of the transition metal to **1**, transmetalation with the Grignard reagent and reductive elimination, is consistent with the general mechanism of Kumada cross-coupling reactions.[57]



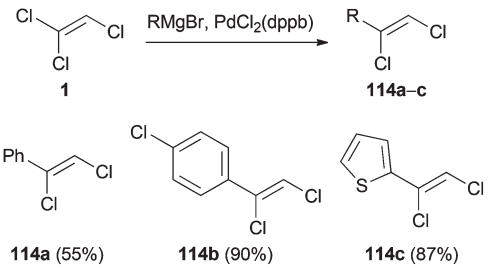
Scheme 29 Palladium(0)-catalyzed carboalkoxylation of **15**.



Scheme 30 Palladium-catalyzed methoxycarbonylation of **16**.



Scheme 31 Palladium- and nickel-catalyzed coupling of Grignard reagents with **1**.



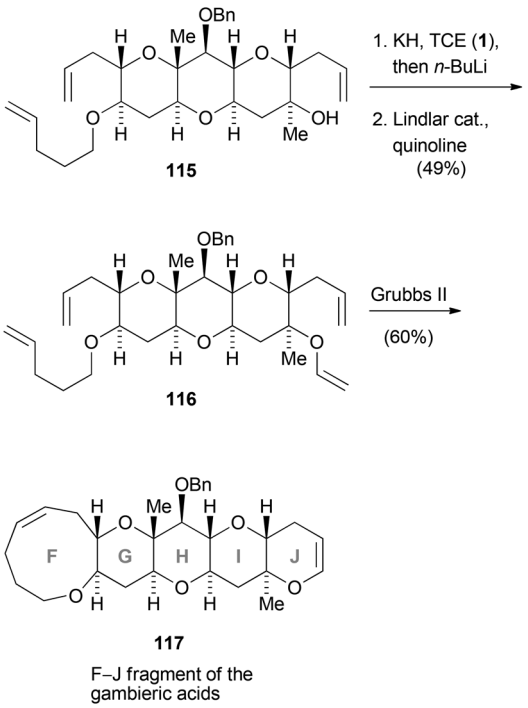
Scheme 32 Regioselective palladium(0)-catalyzed Kumada coupling.

Another example of a palladium(0)-catalyzed coupling reaction of **1** with Grignard reagents was published in 1987 by Minato and Tamao (Scheme 32).[58]

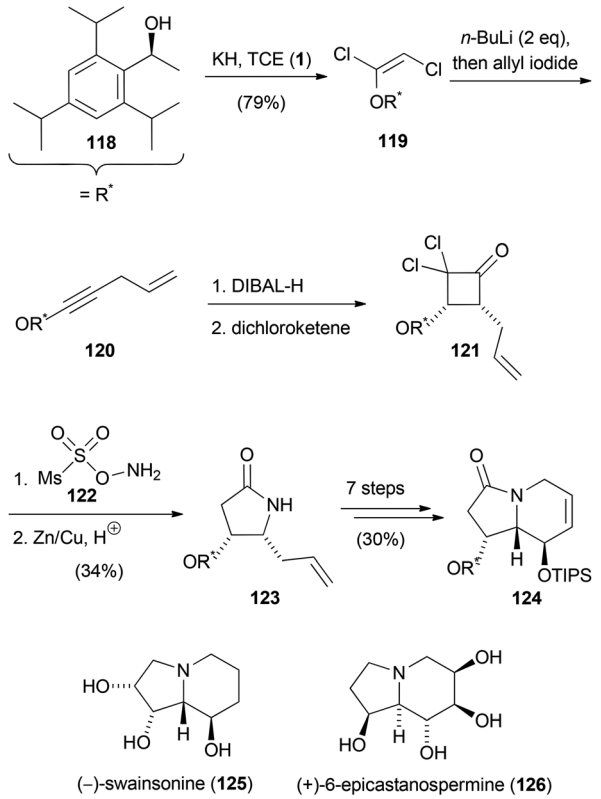
However, in contrast to the reaction depicted in Scheme 31, the arylation occurred at the C(1)–Cl group. This is remarkable, since former studies document that the oxidative addition generally takes place at the C(2)–Cl group.[59] It can be hypothesized that the regioselectivity of the reaction is dependent on the type of catalyst, but no explanation was given by the authors.[9a]

5. Application in natural product synthesis

The previously discussed reactions and methodologies have also been used for the synthesis of more complex molecules. In the following section, the synthesis of natural products



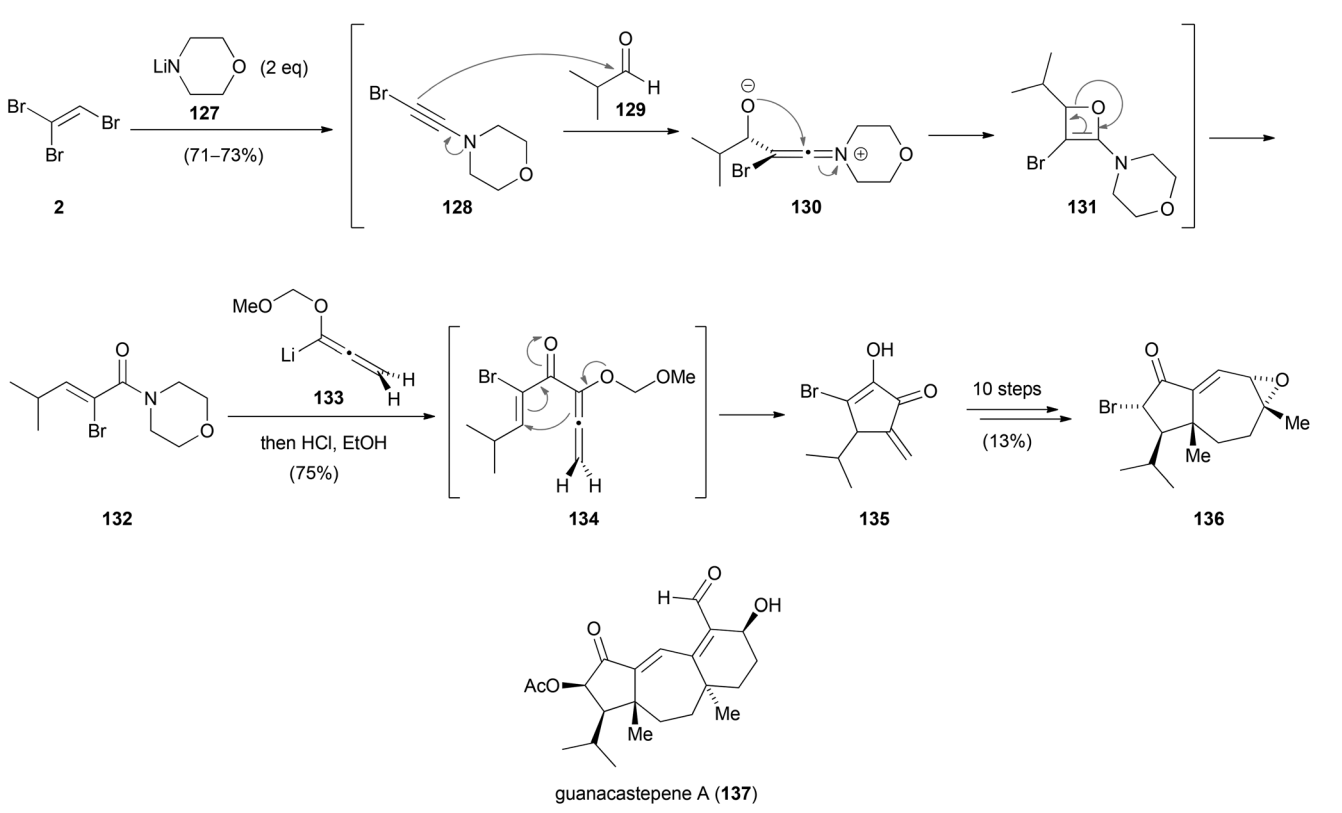
Scheme 33 Synthesis of the F–J fragment of the gambieric acids (**117**).



Scheme 34 Synthesis of an intermediate for the synthesis of (–)-swainsonine (**125**) and (+)-6-epicastanospermine (**126**).

involving transformations with trihaloethenes will be disclosed. Clark and co-workers conducted studies for the synthesis of gambieric acids A–D (Scheme 33).[60] For the synthesis of the F–J fragment **117**, **1** was employed to prepare enol ether **116**. In the first step, the 1,2-dichlorovinylether was formed which was treated with *n*-butyllithium to afford the corresponding ynol ether. Reduction with Lindlar catalyst then gave rise to **116**. The latter compound served as the substrate to simultaneously construct the six- and nine-membered cyclic ether **117** by ring-closing metathesis using Grubbs second generation catalyst.

Poisson's total syntheses of (–)-swainsonine (**125**) and (+)-6-epicastanospermine (**126**) started with the preparation of the chiral 1,2-dichloroenol ether **119** (Scheme 34).[61] Treatment of **119** with two equivalents of *n*-butyllithium gave rise to the corresponding acetylide, which was treated with allyl iodide to afford the ynol ether **120**. After selective reduction of the alkine moiety to the *Z*-double bond using DIBAL-H, a [2 + 2] cycloaddition with *in situ* generated dichloroketene took place, yielding cyclobutanone **121**. Tamura's reagent (**122**) was then used for the Beckmann ring expansion to yield a dichlorolactam, which was dechlorinated with zinc–copper couple in acidic medium. The so formed pyrrolidinone **123** was converted to the indolizidinone **124** in seven further steps. (–)-Swainsonine (**125**) and (+)-6-epicastanospermine (**126**) were prepared in eight and four steps, respectively, from this common indolizidinone precursor.



Scheme 35 Synthesis of the hydroazulene core **136** of the natural product guanacastepene A (**137**).

In the synthesis of the hydroazulene core **136** of guanacastepene A (**137**) by Tius, TBE (**2**) was used as the starting material (Scheme 35).[62] Reagent **2** was converted to 1-bromo-2-morpholinoacetylene (**128**) *via* an elimination–addition–elimination sequence. Nucleophilic addition to isobutyraldehyde (**129**) formed the zwitterionic ketene intermediate **130** which presumably rearranges *via* oxetane **131** to produce α-bromoamide **132** in up to 73% yield. In the following reaction, **132** was treated with a slight excess of allenylithium **133**. The *in situ* formed addition product **134** underwent an allenylithium/vinyl amide cyclopentannelation reaction (Nazarov cyclization) to afford the highly substituted cyclopentenone **135**, which was converted to the hydroazulene core **136** in ten steps.

7. Conclusions

In this review we outlined the chemistry of trihaloethenes in general and of TCE (**1**) in particular. The outstanding versatility of all these reagents was demonstrated for selected reactions. Trihaloethenes combine the properties of alkenes and halogenated compounds and can therefore participate in addition and elimination reactions or combinations thereof, as well as in transition metal-catalyzed reactions. Despite their versatile reactivity, trihaloethenes are only sparsely applied in the synthesis of natural products and their main application is the formation of vinyl or acetylenic ethers. By this review, we hope to turn more attention to this fascinating class of molecules and to extend their synthetic applications.

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