CHEMICAL REVIEWS

REVIEW

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Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems

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Received: May 11, 2011
Published: November 15, 2011

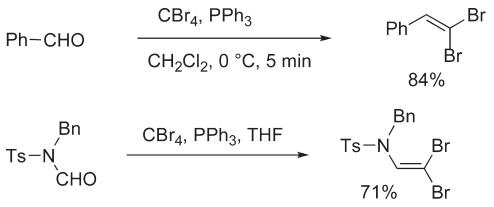
dx.doi.org/10.1021/cr200165q | *Chem. Rev.* 2012, 112, 1344–1462

1. INTRODUCTION

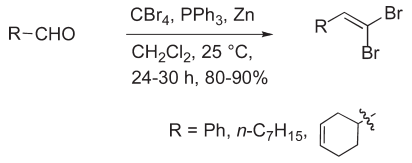
1,1-Dihalo-1-alkenes are valuable synthetic tools in organic chemistry and serve as interesting synthetic intermediates in a variety of non-metal-assisted chemical transformations.[1−10] Moreover, the vinyl dihalide functionality is an attractive and versatile bidentate electrophile for organometallic chemistry.[11] The presence of two geminal halogen atoms bonded to one alkenyl carbon renders these compounds more reactive toward oxidative addition of metal complexes than the corresponding monohaloalkenes, thereby making their metal-catalyzed cross-couplings facile. In 1987, three research groups reported the first examples of selective metal-catalyzed reactions of 1,1-dihalogenolefins. Minato and Suzuki described the palladium-catalyzed *trans*-selective monoalkylation and monoarylation of 1,1-dichloro-1-alkenes with organomagnesium and organozinc derivates,[12] and also some examples of a further substitution catalyzed by palladium and nickel complexes of the chlorine atom on the initially formed 1-chloroalkenes with alkyl or aryl groups.[13] On the other hand, Linstrumelle and co-workers reported that 1,1-dichloroethylene reacted under Pd catalysis with acetylenes or vinylalanes to afford selectively 2-chloro-1-en-3-ynes or 2-chloro-1,3-dienes, respectively.[14] At the same time, Trost and Walchli showed the first case where a 1,1-dibromovinyl group undergoes a selective Pd-catalyzed monosubstitution intramolecularly.[15] After these pioneering works, an impressive number of subsequent papers have reported metal-catalyzed selective monosubstitution and stepwise cross-coupling reactions between 1,1-dihaloalkenes and a variety of reagents. The *gem*-dihalovinyl moiety has also represented a very attractive key unit for metal-catalyzed syntheses of alkynes, carbocycles, heterocycles, etc. by a judicious selection of the coupling partners and well-designed starting materials.

This review provides a systematic summary of methods for the synthesis of 1,1-dihaloolefins and a deep overview of metal-catalyzed reactions involving these compounds and leading to the formation of new C−C, C−H, C−N, etc. bonds, by an effective replacement of one or both dihalides with other elements. The present review is organized in two parts; the former is dedicated to the synthetic procedures used to prepare 1,1-dihaloolefins, while the latter is devoted to a discussion on metal-catalyzed processes leading to defined products. Regarding the second part, each of these processes is arranged, where possible, according to the category of the organometallic reagent used, namely, organoboron, -zinc, -tin, etc. As a matter of interest, this review restricts its scope to reactions of 1,1-dihalo-1-alkenes involving only the vinylic carbon linked to both the *gem*-halogens.

Scheme 1



Scheme 2



2. SYNTHESIS OF *GEM*-DIHALOVINYL SYSTEMS

2.1. Synthesis of 1,1-Dibromo-1-alkenes

2.1.1. Wittig-type Reactions. In 1962, Ramirez and co-workers presented a simple and straightforward procedure for the 1,1-dibromoalkene synthesis.[16] Thus, β,β-dibromostyrene was formed in 84% yield and in only 5 min by reaction of benzaldehyde (1 equiv) with (dibromomethylene)triphenylphosphane ($Ph_3P{=}CBr_2$), generated in situ from a mixture of carbontetrabromide (2 equiv) and triphenylphosphine (4 equiv) in CH_2Cl_2 at 0 °C (Scheme 1). Recently, this procedure has been also successful to prepare a β,β-dibromoenamide from the parent formamide (Scheme 1).[17]

Ten years later, Corey and Fuchs reported a modified Ramirez method by developing a procedure that requires the addition of an aldehyde (1 equiv) to a reagent prepared by reaction of zinc dust, PPh_3 (2 equiv), and CBr_4 (2 equiv) in CH_2Cl_2 at room temperature (Scheme 2).[18] This system in which zinc was used to reduce the initially produced Br_2PPh_3 with formation of $ZnBr_2$ and generation of PPh_3 can be preferred; since less phosphine is required, the isolation procedure is simpler and the yields of dibromoolefins are somewhat higher.

The ylide $Ph_3P{=}CBr_2$, generated in situ from CBr_4 and PPh_3, was also used with light modifications, to obtain the dibromomethylenation of ketones.[19] The main changes to the Ramirez procedure concerned the substitution of CH_2Cl_2 with hydrocarbon (heptane) or aromatic (benzene or toluene) solvents at reflux temperature and the use of different CBr_4/PPh_3 ratios. Thus, Posner and co-workers converted a variety of ketones such as cycloheptanone, 2-octanone, *trans*-2-decalone and 4-*tert*-butylcyclohexanone in low to good yields (28%, 35%, 80%, and 81%, respectively) by using benzene as the solvent at reflux temperature and with a ketone/CBr_4/PPh_3 ratio of 1/2.5/5.[19a] On the other hand, sterically hindered ketones were dibromomethylenated in good yields (80−82%) carrying out the reaction in heptane at reflux temperature and with a ketone/CBr_4/PPh_3 ratio of 1/1.5/3.[19c] Some representative examples are described in Scheme 3.

A convenient variant of the Ramirez and Corey−Fuchs procedures was next developed since the presence of the reactive Lewis acidic byproduct, Br_2PPh_3 or $ZnBr_2$, in the reaction

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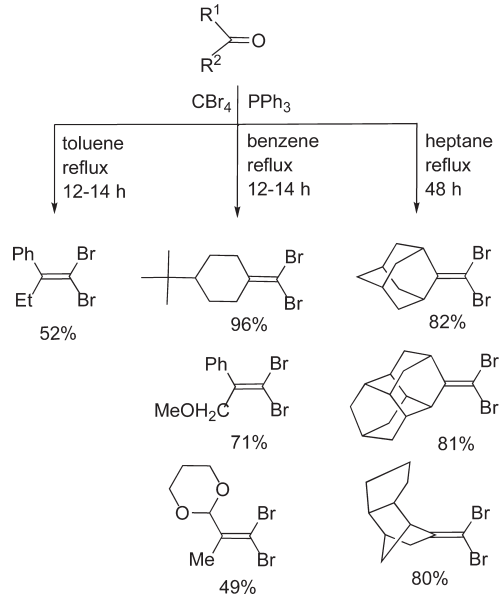
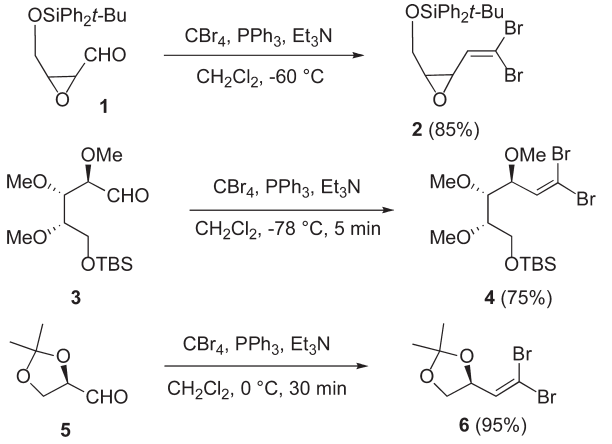
Scheme 3



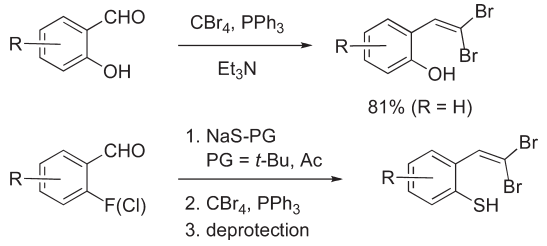
Scheme 4



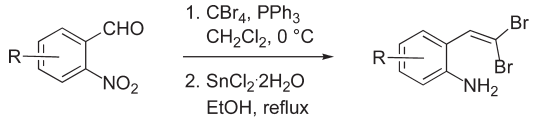
mixture could be in some cases incompatible with other functional groups present in the aldehyde substrate.[20] It was found that treatment of the reaction mixture with 1 equiv of Et_3N before the addition of the 2,3-epoxyaldehyde **1** to the reagent prepared from PPh_3 (2 equiv) and CBr_4 (2 equiv) in CH_2Cl_2 at −60 °C, allowed the dibromide **2** to be obtained with good yield (85%) (Scheme 4). Analogously, the synthesis of other dibromoalkenes, such as compounds **4**[21a] and **6**,[21b] was reported in this and other papers (Scheme 4).

The Ramirez olefination has been recently pursued to prepare substituted 2-(2,2-dibromovinyl)-phenols, -thiophenols, and -anilines. For the synthesis of the first type of compounds, protecting group-free conditions were established (Scheme 5).[22] Slow addition of Et_3N (6 equiv), followed by salicylaldehyde, to the active ylide $Ph_3P{=}CBr_2$ formed from 3 equiv of CBr_4 and 6 equiv of PPh_3 provided 2-(2,2-dibromovinyl)phenol in 81%. The use of excess ylide and slow addition of reagents were necessary for high yields. This procedure was also found be

Scheme 5



Scheme 6



R	yield (%)	R	yield (%)
H	88	4-CO_2Me	88
3-Me	69	4-OBn-5-OBn	41
3-F	81	5-OBn	82
3-OBn-4-OMe	72	5-F	80
4-F	76	5-CF_3	78
4-OBn	76	4-CO_2Me	63

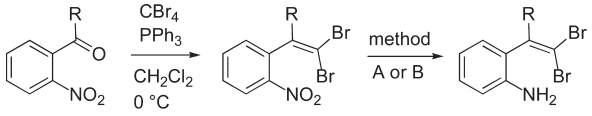
successfully applicable to other α-hydroxybenzaldehyde substrates containing Lewis basic moieties. 2-(2,2-Dibromovinyl)thiophenols were obtained by nucleophilic substitution of 2-fluoro(chloro)-benzaldehydes with sodium 2-methylpropane-2-thiolate or ethanethioate, followed by Ramirez olefination and finally by deprotection of thiophenol group (Scheme 5).[22]

Since the Ramirez olefination is sensitive to amine or amide functionalities, Lautens and Fang used *o*-nitrobenzaldehydes as starting materials for obtaining 2-(2,2-dibromovinyl)anilines.[23] A one-pot, two-step procedure that implies the reaction between 2-nitrobenzaldehydes and CBr_4/PPh_3, followed by reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ in refluxing ethanol, provided in good yields *gem*-dibromovinylanilines bearing either an electron-donating or an electron-withdrawing group at the C-3, C-4, or C-5 position (Scheme 6). On the other hand, iron powder in the presence of a catalytic amount of $FeCl_3 \cdot 6H_2O$ provided a useful system to reduce sterically hindered nitro groups such as in 1-(2,2-dibromovinyl)-3-methyl-2-nitrobenzene (95% yield) and 2-(2,2-dibromovinyl)-1-nitronaphthalene (88% yield). The reagent $SnCl_2 \cdot 2H_2O$ proved also effective for the preparation of dibromovinylanilines from ketones, but with substrates bearing sensitive groups, the reduction was best performed with H_2 and 1 mol % vanadium-doped platinum on carbon, which gave excellent selectivity for the nitro group, leaving double bonds, triple bonds, and halogens intact (Scheme 7).

Triethylamine has been occasionally replaced with success by other amines, as in the synthesis of the dibromide **7**, where 2,6-dimethylpyridine (2 equiv) was used with PPh_3 (4 equiv) and CBr_4 (2 equiv) in CH_2Cl_2 at 0 °C (96% yield) (Scheme 8).[24]

Since the significant amount of triphenylphosphine oxide waste generated in the Ramirez dibromomethylenation is difficult to remove, resulting in a tedious and solvent-consuming purification process, a simpler procedure that uses triisopropylphosphite

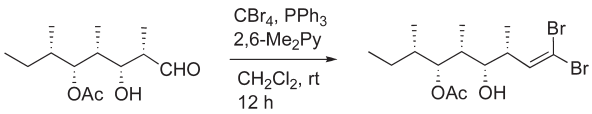
Scheme 7



R	**nitro** yield (%)	**amine** yield (%)
CF_3	88	82[a] or 89[b]
Ph—≡	54	59[a] or 0[b]

[a]method A: H_2, 1% Pt-C[V], MeOH, rt
[b]method B: $SnCl_2{\cdot}2H_2O$, EtOH, reflux

Scheme 8



7 (96%)

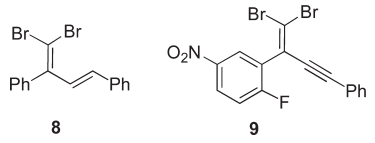
instead of PPh_3 has been recently developed.[25] In this case, the byproduct triisopropyl phosphonate is an oil and therefore, in many cases, the *gem*-dibromoolefinated products can be easier to separate, for instance, by crystallization. Alternatively, the triisopropyl phosphonate can be eliminated by simple treatment of the crude reaction mixture with an acid, which hydrolyzes it into nonhazardous phosphoric acid and isopropanol. In general, the reactivity of triisopropyl phosphite toward *gem*-dibromoolefination is comparable to PPh_3 with aldehydes and higher than PPh_3 with ketones. For instance, the two *gem*-dibromides **8** and **9** (Figure 1) were obtained from the related aldehydes in <5% and 69% yields with PPh_3, whereas they were formed in 44% and 98% yields with $P(Oi\text{-}Pr)_3$.[25]

The addition of 2.5 equiv of hexamethylphosphorous triamide $[P(NMe_2)_3]$ to a cooled (−78 °C) solution of an aldehyde and CBr_4 was another procedure performed to obtain dibromomethylenation with satisfactory yields (54−70%) (Scheme 9).[26] Fluorenone, the only reported ketone, gave fluoren=Br_2 in 70% yield.

Two *gem*-dibromovinyl systems were obtained by reaction of benzaldehyde or benzophenone with the ylide $Ph_3P{=}CBr_2$ produced from bromoform and PPh_3 in the presence of KO*t*-Bu (Scheme 10).[27] Unfortunately, (2,2-dibromovinyl)benzene and (2,2-dibromoethene-1,1-diyl)dibenzene were obtained in low yields (42% and 9%, respectively). On the other hand, the dibromide **4** could be conveniently prepared from the aldehyde **3** by this protocol[28] (Scheme 10).

Savignac and Mori groups reported the transformation of aldehydes and ketones to the related 1,1-dibromoalkenes using diethyl dibromomethanephosphonate.[29] This reagent in THF and in the presence of LiBr was treated with lithium diisopropylamide (LDA) at −70 °C and then with the carbonyl compound. In this way, sterically hindered ketones afforded the related alkenes in fairly good yields (50−70%), whereas aldehydes gave lower yields (40−61%). A representative example is depicted in Scheme 11.

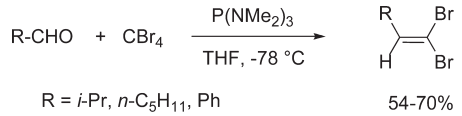
A convenient entry to 1,1-dibromoalkenes was obtained by condensation of aldehydes with $Ph_3P{=}CBr_2$, generated *in situ* from $Ph_3P(Br)CHBr_2$ and KO*t*-Bu (Scheme 12).[30]



8 **9**

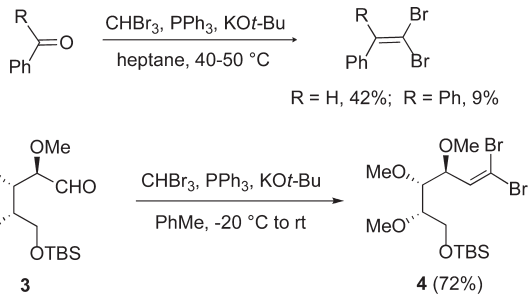
Figure 1

Scheme 9



R = *i*-Pr, *n*-C_5H_{11}, Ph 54-70%

Scheme 10



This method was also effective in the dibromoolefination of lactones.[32] Thus, eight lactones were converted into the related dibromoalkenes in moderate to high yields (32−87%) by using $Ph_3P{=}CBr_2$, generated from an excess of $Ph_3P(Br)CHBr_2$ (4 equiv) and KO*t*-Bu (4 equiv) in refluxing THF for 0.5−2 h. In Scheme 13, one of the substrates used in this paper is shown.

Seven partially or unprotected aldoses were reacted with a large excess (4 equiv) of $Ph_3P{=}CBr_2$, generated *in situ* from $Ph_3P(Br)CHBr_2$ and Zn (4 equiv), to give *gem*-dibromides in good yields (44−90%).[33] A representative example is shown in Scheme 14.

Taylor and co-workers have recently developed a practical one-pot synthesis of 1,1-dibromoalkenes from primary alcohols via manganese dioxide-mediated oxidation and the subsequent Wittig reaction.[34] Thus, for instance, 1,1-dibromo-2-(4-nitrophenyl)ethene was obtained in 86% yield by heating under reflux a mixture of *p*-nitrobenzyl alcohol (1 equiv), active MnO_2 (10 equiv), $Ph_3P(Br)CHBr_2$ (3.5 equiv), 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (1.5 equiv), and molecular sieves in CH_2Cl_2 for 17 h (Scheme 15). Under these conditions, a range of benzyl alcohols with electron-neutral, electron-deficient, and electron-rich substituents and heterocyclic, allylic, and propargylic substrates were converted into the related 1,1-dibromoalkenes in good to excellent yields (46−86%). An aliphatic case, 2-phenylethanol, was also studied, but the reaction was slow and low yielding (14% yield), indicating a limitation to this methodology.

More recently, the same group has employed their tandem oxidation/olefination protocol to obtain β,β-dibromoenones in 30−66% yields from α-hydroxyketones (Scheme 16).[31] The only difference with the previous procedure was the use of KO*t*-Bu as the base and THF as the solvent instead of MTBD and CH_2Cl_2, respectively.

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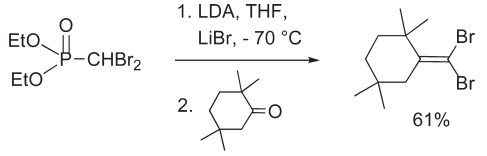
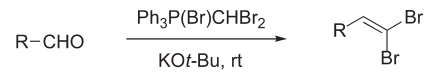
Scheme 11

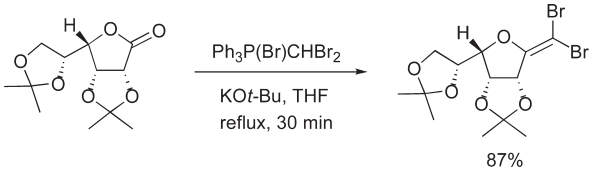


Scheme 12

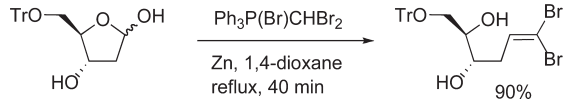


R	yield (%)	R	yield (%)
(*E*)-PhCH=CH	98		
4-$Me_2NC_6H_4$	68		87

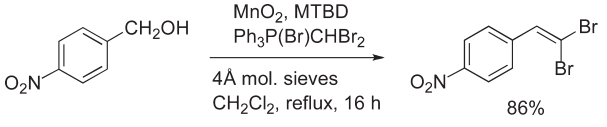
Scheme 13



Scheme 14



Scheme 15

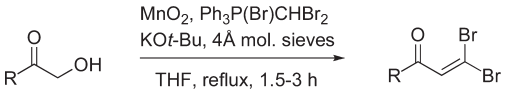


2.1.2. Elimination-Based Reactions. Normant and Rezaei reported a three-step process for converting aliphatic ketones into the homologous *gem*-dibromoalkenes (Scheme 17).[35] In the first step, $LiCBr_3$ was added at −100 °C to ketones **10**, followed by $BF_3 \cdot OEt_2$. Then, the formed alcohols **11** were treated with prop-1-en-2-yl ethanoate to give the trihaloesters **12**, which were finally submitted to an elimination reaction by ethyl magnesium bromide to afford the desired alkenes **13** in 60−95% yields.

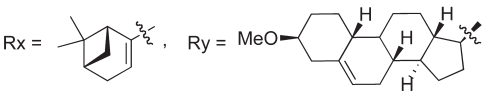
Mesylates of aryl-substituted tribromomethyl carbinols were also reduced to the corresponding vinylidene dibromides by indium metal in very good yields (Scheme 18).[36]

The Lautens group, because benzophenone showed no reactivity under Ramirez olefination conditions, pursued an alternative route to obtain the desired *gem*-dibromoalkene **17** from the diarylketone **14**. The strategy involved Wittig olefination

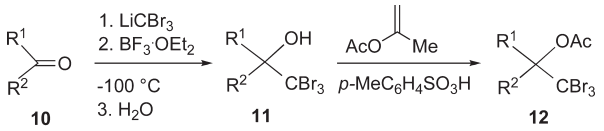
Scheme 16

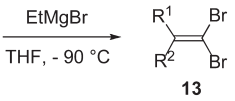


R	yield (%)	R	yield (%)
Ph	59	2-thienyl	66
4-$MeOC_6H_4$	46	Rx	54
4-$O_2NC_6H_4$	30	Ry	51
2-naphthyl	43		



Scheme 17





R^1	R^2	**13** yield (%)
i-Pr	*i*-Pr	95
Ph	Et	84
-$(CH_2)_7$-		60

followed by sequential bromine addition/dehydrobromination/bromination reactions (Scheme 19).[23]

Zweifel and co-workers described the synthesis of 1,1-dibromoalkenes starting from alkynes (Scheme 20).[37] Thus, treatment of boronic ester derivatives **19a,b**, formed by hydroboration of 1-bromo-1-alkynes **18a,b**, with Br_2 followed by debromohalogenation with NaOMe afforded the related 1,1-dibromoalkenes in 62−67% yields. Alternatively, the same and other dibromoalkenes were obtained in 76−89% yields by desilicohalogenation with NaOMe of 1-bromo-1-alkenylsilanes **21b−d**, obtained by hydroalumination of 1-trimethylsilylalkynes **20b−d**.[38]

Two alternative procedures for the preparation of β-dibromomethylenated nitroalkanes have been recently reported.[39] Addition of bromoform to conjugated nitroalkenes in the presence of Mg provided β-tribromomethyl nitroalkanes in good to excellent yields and with high diastereoselectivites. These Michael adducts formed under radical conditions underwent elimination of HBr in the same pot under reflux to afford β-dibromomethylenated nitroalkanes in good yields (method A, Scheme 21). Alternatively, a one-pot high yielding synthesis of the same dibromides was possible under anionic conditions via LDA-mediated addition of bromoform to nitroalkenes (method B, Scheme 21).

Addition of Br_2 to a CCl_4 solution of 2-bromoethenyl butyl ether afforded 1-(1,2,2-tribromoethoxy)butane, which underwent elimination of HBr by treatment with Et_3N at 60 °C for 2 h to give 2,2-dibromoethenyl butyl ether in 91% yield (Scheme 22).[40]

Some examples of 2,2-disubstituted 1,1-dibromo-1-alkenes in which a substituent in the β-position is an OR group (R = 4-methylbenzenesulfonate, 4-methylbenzenesulfonate and acetyl) were reported (two cases in Scheme 23).[41,42] This kind of

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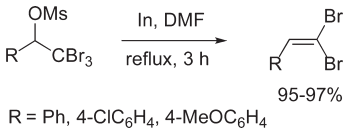
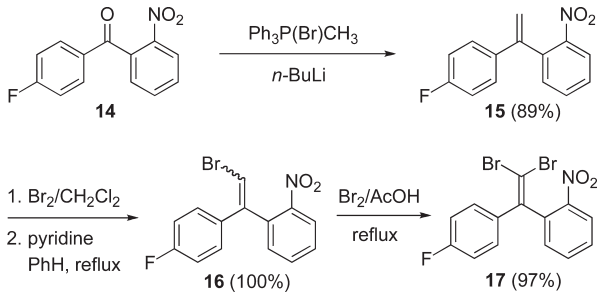
Scheme 18



Scheme 19



compound was prepared from a 1,1-dibromo-2-one by treatment with a base, followed by an electrophile.

Vinyl halides **24** and **25** were prepared from the tribromoromethyl carbinol **23**, obtained in turn by reaction of benzo[*b*]-thiophene-2-carboxaldehyde with the tribromomethane anion[43] generated in situ from 2,2,2-tribromoethanoic acid in DMSO (Scheme 24).[44] The intermediate **23** was treated with $SOCl_2$ or Et_2NSF_3 to give the vinyl halides **24** (33% yield) or **25** (32% yield) through halogenation followed by dehydrobromination.

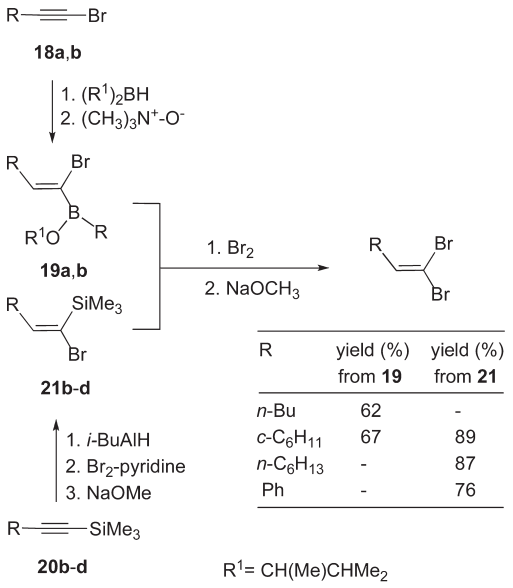
2.1.3. Substitution Reactions. Although the most common source for *gem*-dibromoalkenes are carbonyl compounds, there are some examples in which alkene and alkyne derivatives have been used as starting materials. Reaction of longifolene **26** and camphene **29** with $Hg(OAc)_2$/NaCl resulted in the isolation of vinylic dimercurichlorides **27** and **30**, respectively (Scheme 25). These organometallics by treatment with Br_2 in pyridine afforded the related *gem*-dibromoalkenes **28** and **31** in very high yields.[45]

Recently, 1,1-dibromo-2-arylethenes have been readily obtained in good yields (66−90%) via double *ipso*-bromo desilylation with *N*-bromosuccinimide (NBS) of 1,1-bis(trimethylsilyl)-2-arylethenes, which were in turn easily obtained in high yields by Heck coupling of aryliodides with ethene-1,1-diylbis(trimethylsilane) (Scheme 26).[46] Interestingly, 1,1-bis(trimethylsilyl)-2-alkenylethenes, for example, 1,1-bis(trimethylsilyl)-4-phenylbuta-1,3-diene, under the same reaction conditions led to the selective formation of the dibrominated products containing 1,3-diene fragments.

A variety of *gem*-dibromides were prepared from stannyl acetylenes (Scheme 27). These compounds by treatment with 1.4 equiv of $Cp_2Zr(H)Cl$ generated the related 1,1-heterobimetallic species of tin and zirconium, which by brominolysis with 2.5 equiv of Br_2 in CCl_4 or 3.0 equiv of *N*-bromosuccinimide at room temperature gave the corresponding dibromides in 53−83% yields.[47]

2.1.4. Miscellaneous Reactions. Nenajdenko and co-workers reported an efficient one-pot transformation of a wide range of aldehydes and ketones into the corresponding dibromoalkenes via intermediate formation of the related hydrazones (Scheme 28).[48] Thus, these carbonyl compounds were treated with hydrazine hydrate, and when the starting materials disappeared, CBr_4 and catalytic CuCl were added to give the target

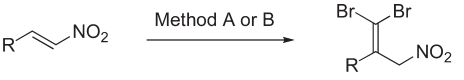
Scheme 20



R	yield (%) from **19**	yield (%) from **21**
n-Bu	62	-
c-C_6H_{11}	67	89
n-C_6H_{13}	-	87
Ph	-	76

R = **a**: *n*-Bu, **b**: *c*-C_6H_{11}, **c**: *n*-C_6H_{13}, **d**: Ph

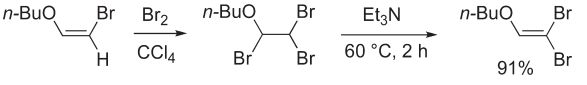
Scheme 21



R	yield (%) method A	yield (%) method B
4-$MeOC_6H_4$	58	64
3,4-$(MeO)_2C_6H_3$	51	66
3,4-$(OCH_2O)C_6H_3$	75	72
4-$Me_2NC_6H_4$	72	77
4-$O_2NC_6H_4$	62	76
3-furyl	60	88
3-thienyl	58	77

Method A: $CHBr_3$ (22 equiv), Mg (8 equiv), THF, 0 °C to rt 0.5 h, then reflux, 24 h; Method B: LDA (6 equiv), $CHBr_3$ (1.1 equiv), THF, -78 °C, 3 h, then rt (12 h)

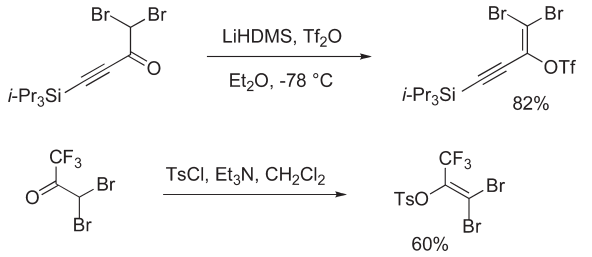
Scheme 22



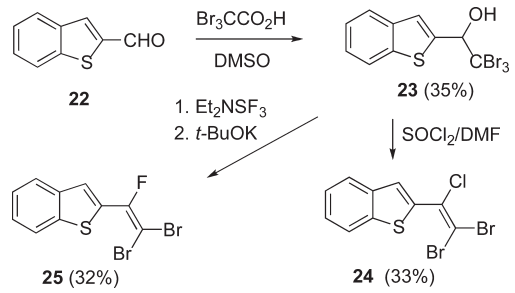
products in 43−97% yields from aldehydes[48a] and 43−97% yields from linear, cyclic, and caged ketones,[48a] depending on the steric hindrance of the staring material. Analogously, a wide range of hydrazones of (hetero)aryl alkyl ketones (electron-rich and electron-poor) was converted into the related dibromoalkenes in 23−92% yields.[48b] The proposed mechanism of the reaction starts from the oxidation of CuCl with CBr_4 to give a Cu(II) salt, which in turn oxidizes the hydrazone to the diazoalkane (Scheme 28). Decomposition of the diazoalkane generates a copper−carbene complex, which by interaction with CBr_4 finally leads to the dibromoalkene.

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

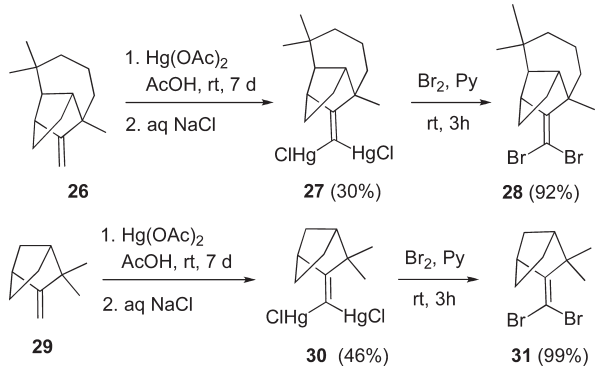
Scheme 23



Scheme 24



Scheme 25

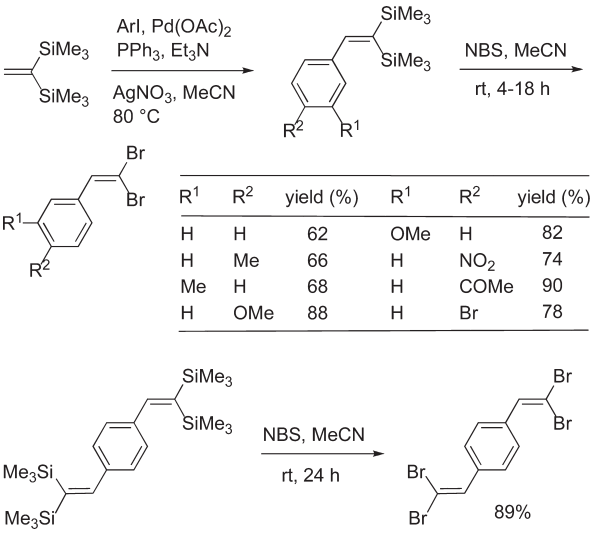


The synthesis and a study of the chemical properties of 2,2-dibromovinyl trifluoromethyl ketone have been reported.[49] This compound was prepared in 75% yield by trifluoroacetylation of 1,1-dichloroethene in the presence of aluminum bromide (Scheme 29).

2.2. Synthesis of 1,1-Dichloro-1-alkenes

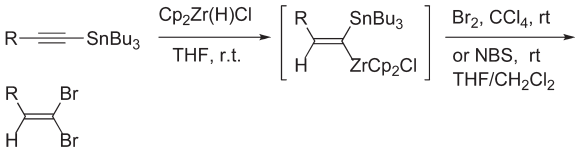
2.2.1. Wittig-type Reactions. The synthesis of β,β-dichlorostyrene by reaction of benzaldehyde with (dichloromethylene)triphenylphosphane ($Ph_3P{=}CCl_2$), generated in situ from tetrachloromethane and PPh_3 was reported, but the yield was only 35% because of the concomitant formation of α,α-dichlorotoluene in equal quantities (Scheme 30).[50] Besides benzaldehyde, other aldehydes (quinoline-2-carboxaldehyde and 3-benzyloxypropanal)[51] and ketones[52] [benzophenone, 1-phenylpropan-1-one, 2-methyl-1-phenylpropan-1-one,[52a] and cyclopentanone (61%), cycloheptanone (40%), acetophenone (45%), norcamphor, (76%), and cholestan-3-one (80%)[52b]] were converted into the related *gem*-dichloroolefins following this method. Light modification of this procedure, namely, slow addition of CCl_4 to a THF solution containing PPh_3 and formamides at reflux temperature, allowed also the synthesis of β,β-dichloroenamides in high yields (81−92%) (Scheme 31).[17]

Scheme 26



R^1	R^2	yield (%)	R^1	R^2	yield (%)
H	H	62	OMe	H	82
H	Me	66	H	NO_2	74
Me	H	68	H	COMe	90
H	OMe	88	H	Br	78

Scheme 27



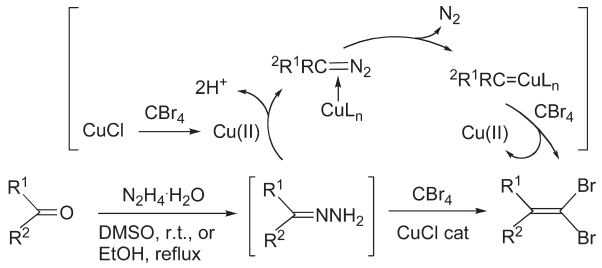
R	Ph	*n*-Bu	*n*-C_6H_{13}	$BnOCH_2$	$Cl(CH_2)_3$	$HOCH_2$	*c*-C_6H_{11}
yield (%)	78	53	83	81	73	55	70

An improvement of this method was obtained by adding activated magnesium to the reaction mixture, thus decreasing or eliminating the formation of side products.[55] The role of Mg is to remove from the mixture Ph_3PCl_2 (by formation of $MgCl_2$ and generation of PPh_3) that reacts with benzaldehyde to give the byproduct α,α-dichlorotoluene. In this way a number of aliphatic aldehydes were converted into the related *gem*-dichloroolefins in good yields (Scheme 33).

The dichloromethylenation of lactones was successfully accomplished by Chapleur, who found that the complex formed by slow addition of $P(NMe_2)_3$ (2 equiv) to a dry THF solution containing CCl_4 (3 equiv) at −30/−40 °C reacted smoothly with several γ-lactones derived from carbohydrates to give dichloroolefins

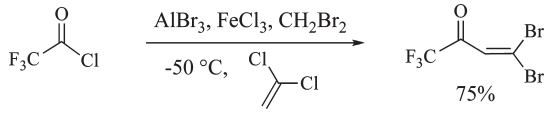
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 28

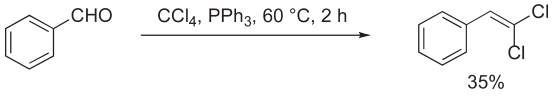


R^1	R^2	yield (%)	R^1	R^2	yield (%)
n-C_7H_{15}	H	83	4-MeC_6H_4	Me	52
$PhCH_2$	H	43	4-ClC_6H_4	Me	75
$PhCH_2CH_2$	H	70	4-$MeOC_6H_4$	Me	92
n-C_7H_{15}	Me	97	4-$O_2NC_6H_4$	Me	74
n-C_4H_9	*n*-C_4H_9	54	4-$MeSO_2C_6H_4$	Me	45
c-C_3H_5	Me	71	2-naphthyl	Me	41
-$CH_2(CH_2)_2CH_2$-		52	2-thienyl	Me	62
-$CH_2(CH_2)_3CH_2$-		68	Ph	Et	75
-$CH_2(CH_2)_4CH_2$-		73	-*o*-C_6H_4-$(CH_2)_2$-		51
-$CH_2(CH_2)_5CH_2$-		78	-*o*-C_6H_4-$(CH_2)_3$-		23
menthone		53			
adamantanone		43			
camphor		60			

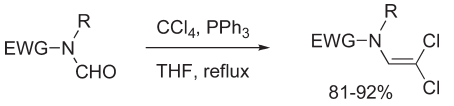
Scheme 29



Scheme 30



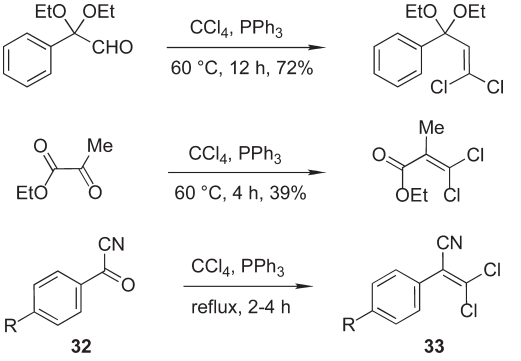
Scheme 31



EWG = Ts, R = 3-butenyl, $PhCH_2$, 4-$MeOC_6H_4$
EWG = $PhCH_2$, R = $(MeO)_2CHCH_2$

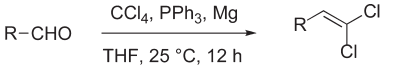
in good yields.[56] However, this procedure was found to be limited to lactones highly reactive, α-substituted, or having a bicyclo[3.3.0] structure, such as lactones **34** and **35** (Figure 2). The same author later found that a slow addition of a large excess of CCl_4 to a solution of the lactone and PPh_3 in refluxing THF allowed the transformation in high yields of less reactive lactones such as **36** and even esters such as **37**, tolerating a number of protecting groups such as ethers, acetals, and esters except

Scheme 32



R	**33** yield (%)	R	**33** yield (%)
H	67	OMe	60
Me	68	NO_2	0
Cl	20		

Scheme 33



R	yield (%)	R	yield (%)
$CH_3(CH_2)_3$	70	$CH_3(CH_2)_7$	75
$CH_3(CH_2)_5$	85	$CH_3(CH_2)_{10}$	80
$CH_3(CH_2)_6$	75	$CH_3OOC(CH_2)_7$	60

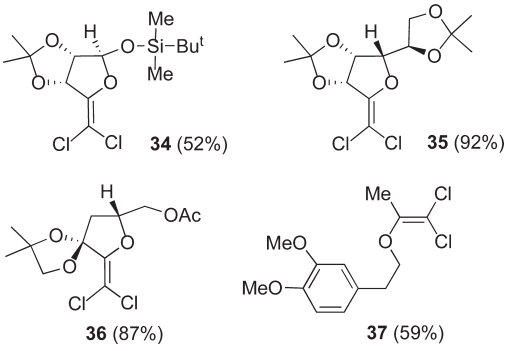


Figure 2

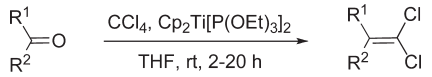
acetates and silyl ethers (Figure 2).[57] This procedure was also successful for the dichloromethylenation of 6-undecanone and 9-fluoroenone in good yields (88% and 89%, respectively).[35]

The dichloroolefination of ketones with organotitanium species formed from $Cp_2Ti[P(OEt)_3]_2$ and CCl_4 was explored.[58] The reaction produced 1,1-dichloroalkenes in good yields with both diaryl and dialkyl ketones (Scheme 34). The titanocene dichloromethylidene complex $Cl_2C{=}TiCp_2$ was suggested to be an active species of the reaction on the basis of the results obtained in an analogue reaction performed with $CDCl_3$ instead of CCl_4.

Burton and co-workers studied the dichloromethylenation of substituted cyclohexanones with $CXCl_3$ (X = Br or Cl) and

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

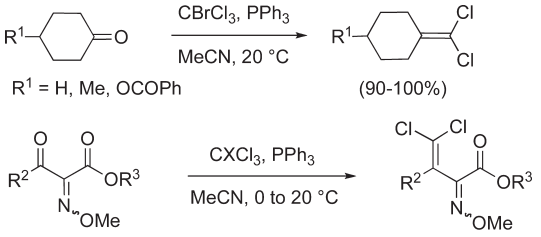
Scheme 34



R^1	R^2	yield (%)
Ph	Ph	22
1-naphthyl	Me	66
$PhCH_2CH_2$	$PhCH_2CH_2$	64
$PhCH_2CH_2$	$CH_3(CH_2)_3$	62
$R^3C(Me)=CHCH_2$	Me	72
$CH_3(CH_2)_4$	$CH_3(CH_2)_4$	58
$CH_3(CH_2)_{10}$	Me	74
$PhCH_2CH(CH_3)$	Et	20
$-(CH_2)_3CH(Ph)CH_2-$		61
$-(CH_2)_2CH(t\text{-Bu})(CH_2)_2-$		58

R^3: $Me_2=CHCH_2CH_2$

Scheme 35



X	R^2	R^3	yield (%)
Cl	Ph	Et	94
Br	CF_3	Et	80
Br	$MeOCH_2$	Me	71

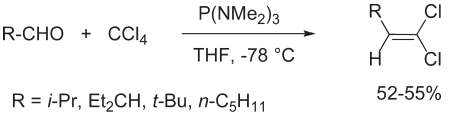
PPh_3 under a variety of conditions.[59] The best yields of 1,1-dichloromethylenes were obtained with $CBrCl_3$ in acetonitrile (Scheme 35). Some α-methoxyimino β-dichloromethylene esters were also prepared similarly in good yields (Scheme 35).

The addition of 2.5 equiv of $P(NMe_2)_3$ to a cooled (−78 °C) solution of CCl_4 containing aliphatic aldehydes has been another procedure performed to obtain dichloromethylenation with satisfactory yields (52−55%) (Scheme 36).[26] However, the reaction appeared to be dependent on the solvent. Thus, the reaction of benzaldehyde with fluorenone in THF gave trace amounts of olefination products, whereas in THF/CH_2Cl_2 the yield of the corresponding dichloromethylenes was 26% and 66%, respectively.

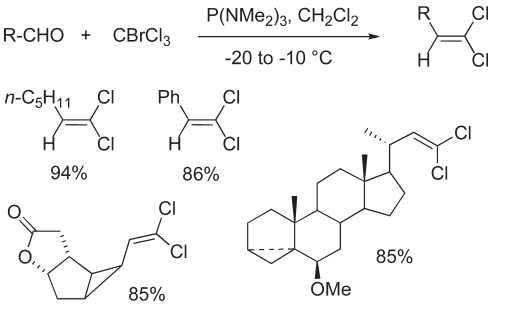
Next, Salmond described an improvement of this procedure that entails the addition of a CH_2Cl_2 solution containing $P(NMe_2)_3$ to a cooled (−15 °C) mixture of the aldehyde and $CBrCl_3$ (Scheme 37).[60] This method proved to be very effective for aliphatic, aromatic, cyclopropyl, and steroidal aldehydes.

Straightforward access to *gem*-dichlorovinyl systems consists in the reaction of carbonyl compounds with the ylide $Ph_3P{=}CCl_2$ produced from reaction of PPh_3 with dichlorocarbene, in turn generated in situ by reacting $CHCl_3$ with KO*t*-Bu. In this fashion, a number of 1,1-dichloroalkenes were prepared in 29−81% yields from a variety of aldehydes and ketones (Scheme 38).[27]

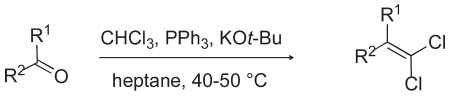
Scheme 36



Scheme 37



Scheme 38



R^1	R^2	yield (%)
Ph	Ph	59
H	$CH_3(CH_2)_9CH_2$	29
H	PhCH=CH	77
H	Ph	48
$4\text{-}O_2NC_6H_4$	$4\text{-}O_2NC_6H_4$	83
$4\text{-}Me_2NC_6H_4$	$4\text{-}Me_2NC_6H_4$	81
H	$2,6\text{-}Cl_2C_6H_3$	43
H	$3,4\text{-}Cl_2C_6H_3$	77
$-CH_2(CH_2)_4CH_2-$		33

This method is fairly good but needs the use of freshly prepared KO*t*-Bu from *t*-BuOH and potassium metal. In order to eliminate the hazardous K metal, a procedure that uses a KO*t*-Bu·*t*-BuOH adduct to replace KO*t*Bu has been reported. This base was simply prepared by heating commercially available KO*t*-Bu in anhydrous *t*-BuOH for 30 min before removal of the excess of *t*-BuOH under vacuum. This protocol was first described by Olah and Yamada who prepared 1-(2,2-dichlorovinyl)- and 1-(1,1-dichloroprop-1-en-2-yl)-2-nitrobenzene in 37% and 56% yields, respectively.[61] In more recent papers,[23,62] to ensure complete conversion of the starting material and to significantly increase the yield, the use of an excess of the ylide (1.5−2 equiv), instead of the stoichiometric amount employed in the original procedure, has been reported.[62] In Figure 3, a wide collection of dichlorovinyl systems obtained from the related aldehydes or ketones by this protocol are reported.[23,62]

The Wittig−Horner reactions between carbonyl compounds and $(EtO)_2P(O)CCl_2Li$, generated under different protocols, allow another preparation of 1,1-dichloroalkenes[63] (Scheme 39).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

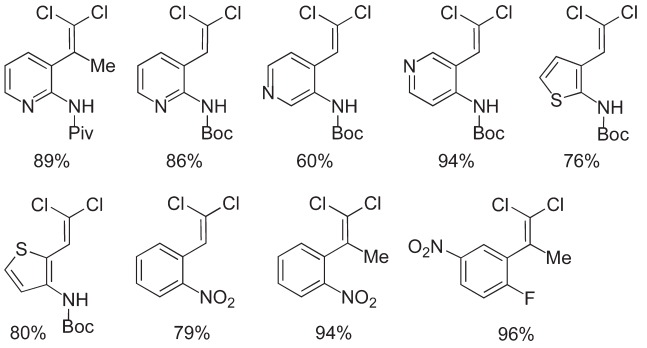
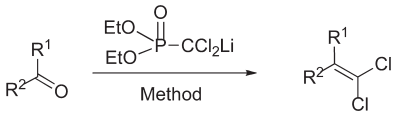


Figure 3

Scheme 39



Method
A: $(EtO)_2P(O)CCl_3$, *n*-BuLi, THF, -85 °C
B: $(EtO)_2P(O)CCl_3$, *n*-BuLi, THF/Et_2O, -100 °C
C: $(EtO)_2P(O)CHCl_2$, LiHDMS (or LDA), THF, -78 °C
D: $(EtO)_2P(O)CH_2Cl$, LiCl, *n*-BuLi, then CCl_4, THF, -75 °C
E: $(EtO)_2P(O)CH_3$, $PhSO_2Cl$, *n*-BuLi, THF, -78 °C

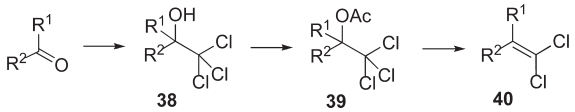
R^1	R^2	method	yield (%)	Ref.
t-Bu	H	A	55	64
n-C_9H_{19}	H	B	92	65
n-C_9H_{19}	H	C	60-80	69
$CH_3CH(Ph)CH_2$	H	C	60-80	69
n-C_7H_{15}	H	E	75	68
c-C_6H_{11}	H	B	84	65
Ph	H	E	82	68
4-ClC_6H_4	H	B	90	65
4-ClC_6H_4	H	D	67	66
4-ClC_6H_4	H	E	90	68
2-$MeOC_6H_4$	H	B	94	65
$CH_3CH=CH$	H	B	76	65
Me	Me	A	47	64
Ph	Ph	A	69	64
Ph	Me	E	85	68
Ph	Ph	E	82	68
-$CH_2(CH_2)_2CH_2$-		B	90	65
-$CH_2(CH_2)_2CH_2$-		D	77	66
-$CH_2(CH_2)_2CH_2$-		E	66	68
-$CH(CH_3)(CH_2)_2CH(CH_3)$-		D	71	66
pulegone		D	90	66
camphor		D	80	66

Only representative results are reported for each reference

With this reagent, obtained *in situ* from $(EtO)_2P(O)CCl_3$ and *n*-BuLi in THF at −85 °C, pivaldehyde, acetone, and benzophenone gave the related 1,1-dichloralkenes in 55%, 47%, and 69% yield, respectively.[64]

Next, the yield of this reaction was greatly increased by using a 60/40 mixture of THF/Et_2O instead of pure THF (Scheme 39).[65] In this way, alkyl, aryl, and alkenyl aldehydes gave 1,1-dichloroolefins in yields varying from 75% to 92%, and cyclohexanone was converted into the resultant dichlorovinyl system in 90% yield.

Scheme 40



In the same year, Savignac and co-workers reported the dichloromethylenation of carbonyl compounds by reaction with $(EtO)_2P(O)CCl_2Li$, generated *in situ* by treating $(EtO)_2(O)PCH_2Cl$ with 1 equiv of *n*-BuLi and then CCl_4 in THF at −75 °C.[66] Substituted benzaldehydes (4-F, 4-Cl, and 3,4-OCH_2O) gave dichloroolefins in 62−80% yields, whereas cyclic ketones (substituted cyclohexanones, carvone, pulegone, menthone, camphor, and fluorenone) afforded higher yields (70−90%) (Scheme 39). A 3,3-dichloro-2-propenylidene derivative was analogously prepared in 58% yield.[67]

More recently, Oh and co-workers reacted $(EtO)_2P(O)CCl_2Li$, formed *in situ* by treatment of $(EtO)_2P(O)CH_3$ with $PhSO_2Cl$ (2 equiv) in the presence of *n*-BuLi (3 equiv) in THF at −78 °C, with carbonyl compounds to obtain the related 1,1-dichloroolefins in good yields (Scheme 39).[68]

Finally, Savignac and co-workers in a study aimed to synthesize internal alkynes from carbonyl compounds, obtained a variety of unisolated 1,1-dichloralkenes in high yields (estimated on the formed final alkynes) by reaction of $(EtO)_2P(O)CCl_2Li$, generated in situ from $(EtO)_2P(O)CHCl_2$ and 1 equiv of LiHDMS (or LDA) in THF at −78 °C.[69]

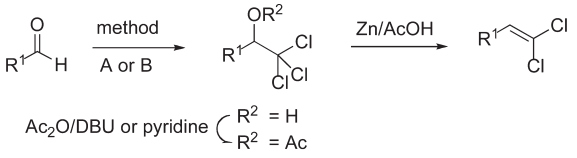
2.2.2. *β*-Elimination-Based Reactions. The dichloromethylenation of carbonyl compounds has been achieved by a three-step sequence: (i) reaction of aldehydes or ketones with $CHCl_3$ or CCl_4 to give the trichloromethyl carbinols **38**, (ii) transformation of the alcohol moiety of **38** into the related acetate **39** (other derivatives such as mesylates, tosylates, etc., were rarely used), and (iii) elimination of chloride and acetate from the trichloroacetates to generate the desired vinyl dichlorides **40** (Scheme 40).

In this approach, the key intermediates **38** have been generally prepared by base-promoted addition of $CHCl_3$ to aldehydes or ketones. Relatively strong bases have been employed.[70] Potassium *tert*-butoxide in liquid ammonia at −78 °C,[70a] sodium in liquid ammonia,[70b] and powdered potassium hydroxide in various solvents[70c,d,71] have been the most commonly used conditions. Among procedures employing bases, the most interesting ones appeared, however, to be those promoted in milder conditions and with less basic reagents such as cyclic amidines.[72] Thus, by use of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo [4.3.0] non-5-ene (DBN) and a slight excess of $CHCl_3$ without solvent, a number of carbonyl compounds (for instance, PhCHO, 2-ClC_6H_4CHO, 4-$O_2NC_6H_4CHO$, C_6H_{11}-CHO, cyclohexanone) were converted into the related carbinols **38** in high yields (75−98%), except in the case of mesitaldehyde and trimethylacetaldehyde, which afforded low yields (25% and 30%, respectively).

A method for generating trichloromethyl anion, avoiding the use of strong bases, has been reported. When trichloroacetic acid was mixed with sodium trichloroacetate in DMF, decarboxylation occurred at room temperature to generate the trichloromethyl anion, which in the presence of an aldehyde afforded the desired trichloromethyl carbinol **38**.[73] Under these conditions, a wide variety of aldehydes (PhCHO, *i*-PrCHO, *i*-BuCHO,

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

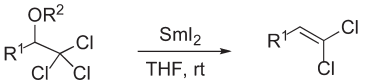
Scheme 41

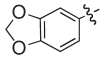


R^3	R^4	yield (%)
H	H	87[b]
H	OMe	93[a]
H	CO_2Me	80[a]
H	F	79[b]
OMe	OMe	75[b]

[a]method A, [b]Method B

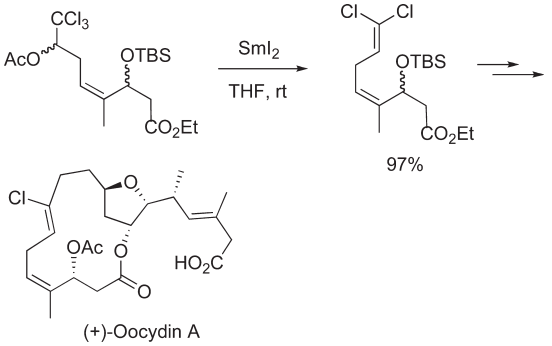
Scheme 42



R^1	R^2	yield (%)	R^1	R^2	yield (%)
Ph	H	85	Ph	Ac	81
4-ClC_6H_4	H	91	4-ClC_6H_4	Ac	90
2-ClC_6H_4	H	94	2-ClC_6H_4	Ac	96
4-$MeOC_6H_4$	H	85	4-MeC_6H_4	Ac	92
2-$MeOC_6H_4$	H	93	3-BrC_6H_4	Ac	85
2-furyl	H	78	4-HOC_6H_4	H	87
(*E*)-Ph-CH=CH	H	70			
t-Bu	H	75		Ac	85

Only representative examples are reported

Scheme 43



c-$C_6H_{11}CHO$, etc.) were converted into the related 1,1,1-trichloroalkan-2-ols in good yields.

Carbinols **38** were also obtained when a Pb/Al bimetal system was used to carry out the reductive addition of CCl_4 to aldehydes.[74] Thus, when a mixture of $PbBr_2$ (0.1 equiv) and finely cut aluminum foil (1.2−4 equiv) in DMF was added to a variety of aldehydes (aromatic, aliphatic, and α,β-unsaturated) and CCl_4 (2−4 equiv) at ambient temperature, trichloromethyl carbinols were directly obtained in high yields (75−98%).

The conversion of **38** into the corresponding vinyl chlorides **40** was obtained by acetylation to give acetates **39**, followed by treatment with acetic acid and zinc powder at 25−60 °C.[73b] Carbinols **38** could also be directly converted into **40** by AcOH/Zn, but in somewhat lower yield.

Vinyl chlorides **40** have been obtained from trichloromethyl carbinols **38** or alternatively from the related acetates **39** by reductive 1,2-elimination with a Pb/Al bimetal system.[74] Thus, treatment of a number of carbinols **38** with $PbBr_2$ (0.05 equiv) and aluminum (1.5 equiv) in methanol containing aqueous 35% hydrochloric acid (2 equiv) at 50−60 °C afforded the related 1,1-dichloroethenes **40** in 64−89% yield. On the other hand, acetates **39** were converted into **40** by treatment with $PbBr_2$ (0.1 equiv) and Al (1.2 equiv) in DMF at room temperature in similar yields.

Recently, in a study addressed to explore the application of the Suzuki−Miyaura protocol to the cross-coupling of 9-alkyl-9-borabicyclo[3.3.1]nonane with 1,1-dichloroalkenes, Roulland and co-workers prepared a variety of these compounds following the above-mentioned procedures (Scheme 41).[75] Thus, from nonenolizable aldehydes, the reaction with $CHCl_3$ in 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) led to 1,1,1-trichloroalkan-2-ols that were subjected to a subsequent one-pot acetylation followed by elimination promoted by zinc in acetic acid (method A).[72] From all other aldehydes, the 1,1,1-trichloroalkan-2-ols **38** were obtained under milder conditions utilizing the reaction of CCl_4 in the presence of Al and a catalytic amount of $PbBr_2$ in DMF (method B).[74] Subsequent acetylation and elimination steps gave 1,1-dichloroolefins.

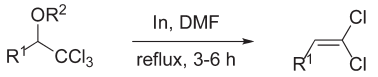
Samarium diiodide has been shown to promote the conversion of carbinols **38** or acetates **39** into *gem*-dichloroalkenes **40** under mild reaction conditions.[76] Thus, treatment of a variety of trichloromethyl carbinols with SmI_2 (2.2 equiv) in THF at room temperature for 3−8 h afforded the related 1,1-dichloroalkenes in high yields (70−94%) (Scheme 42). Interestingly, when the unsaturated carbinol (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol was used, the corresponding elimination took place as well, and the original double bond remained intact. The related acetates afforded very similar yields under identical reaction conditions. Roulland applied this methodology for generating in 97% yield (*Z*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-8,8-dichloro-4-methylocta-4,7-dienoate, a key intermediate in the total synthesis of (+)-oocydin A (Scheme 43).[77]

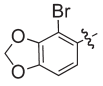
Ranu and co-workers, studying the reduction of trihalomethyl carbinols and their derivatives by indium metal, found that trichloromethyl carbinols produced a mixture of the corresponding dichloromethyl carbinols and vinylidene dichlorides, whereas their acetates, mesylates, and tosylates underwent clean reduction providing the respective vinylidene dichlorides only (Scheme 44).[36] High yields (71−95%) were obtained in the reduction of aromatic and heteroaromatic derivatives, whereas yields of nonaromatic substrates were lightly lowers (60−83%).

Reactions of Grignard reagents with tosylates of aryl-, alkyl-, and alkynyl(trichloromethyl) carbinols provided an attractive synthetic route to the related dichloroolefins (Scheme 45). The reaction occurs by a polar, ionic mechanism in which two $^{\bullet}MgBr$

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

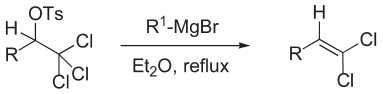
Scheme 44



R^1	R^2	yield (%)	R^1	R^2	yield (%)
Ph	Ac	76	1-naphthyl	Ts	98
PhCH=CH	Ac	83	3-$MeOC_6H_4$	Ms	92
2-pyridyl	Ac	71	3,4-$(MeO)_2C_6H_3$	Ms	91
4-allyl-OC_6H_4	Ac	73	3-MeC_6H_4	Ms	90
4-$MeOC_6H_4$	Ac	82	2-furyl	Ms	82
$CH_3(CH_2)_8$	Ac	60		Ms	87
4-ClC_6H_4	Ts	93			
4-$MeOC_6H_4$	Ms	92			

Only representative examples are reported

Scheme 45



R	R^1	yield (%)	R	R^1	yield (%)
Ph	*n*-Bu	56-78	4-BrC_6H_4	*n*-Bu	78
Ph	Ph	56-78	Et	*n*-Bu	33
Ph	$PhCH_2$	56-78	$CH_3(CH_2)_3C{\equiv}C$	*n*-Bu	73
4-$MeOC_6H_4$	*n*-Bu	64			

radicals serve as reducing agents to supply two electrons to the tosylate, which in this way is expelled as anion.[78]

Trichloromethyl carbinols (*i*-PrCH(OH)CCl_3 and EtOC-H_2CH(OH)CCl_3) were converted into the corresponding *gem*-dichloroalkenes, *i*-PrCH=CCl_2 and EtOCH_2CH=CCl_2, in 70% and 50% yield, respectively, by treatment with 2.5 equiv of $P(NMe_2)_3$ and an excess of CCl_4.[26]

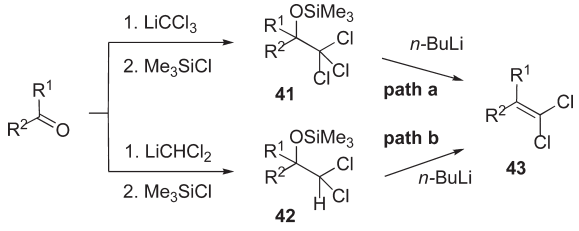
A procedure for the preparation of *gem*-dichloroalkenes **43** has been developed via formation of trichloromethyl and dichloromethyl silylethers **41** and **42**, obtained by addition of $LiCHCl_2$ or $LiCCl_3$ to aldehydes or ketones, followed by treatment of the intermediates with $MeSiCl_3$ (Scheme 46).[79] Compounds **41** and **42**, derived from ketones, when treated with one equiv of *n*-BuLi at −100 °C gave the related vinyl chlorides **43** in good yields.

Trichloromethyl carbinol **45** was obtained in good yield by addition of the benzothienylzinc reagent **44** to chloral (Scheme 47).[44] The alcohol **45** was halogenated with $SOCl_2$ followed by dehydrohalogenation to give the vinyl halide **46** (75% yield) or reduced with zinc/acetic acid to produce the 2,2-dichloroethenyl derivative **47** (50% yield).

Takai and co-workers found that the carbonate ester **48a**, derived from 1,1,1-trichloro-4-phenylbutan-2-ol reacted with nonanal in the presence of $CrCl_2$−DMF in THF affording stereoselectively the (*Z*)-2-chloroalk-2-en-1-ol **49** (77% yield). On the contrary, the related mesylate **48b** and the pyridine-2-carbonyloxy **48c** produced, under the same reaction conditions, (4,4-dichlorobut-3-enyl)benzene as the main product in very good yield (96% and 89%, respectively) (Scheme 48).[80]

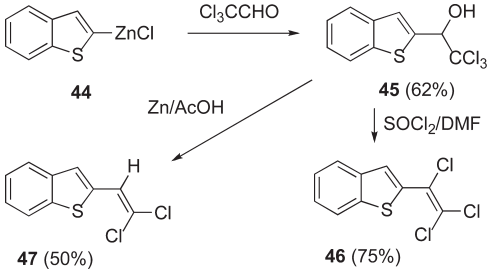
Various dichloroalkenes were prepared in moderate overall yields by reaction of α-lithiated dichloromethyltrimethylsilane

Scheme 46

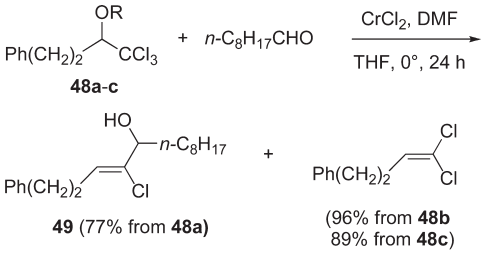


R^1	R^2	path	**43** yield (%)
Ph	Me	**a**	52
Me	Me	**b**	82
-$(CH_2)_5$-		**b**	73

Scheme 47



Scheme 48



a: R = CO_2Me, **b**: R = Ms, **c**: R = pyridine-2-carbonyl

with aldehydes at −100 °C, followed by careful hydrolysis at temperature lower than −80 °C of the intermediate β-hydroxysilanes (Scheme 49).[81]

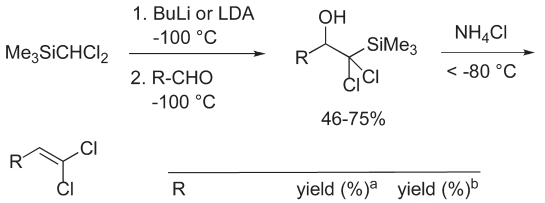
Thermolysis of a variety of 3,3-dichloro-4-aryloxetan-2-ones, prepared in 23−85% yields by cycloaddition between monosubstituted benzaldehydes and dichloroketene, afforded the related β,β-dichlorostyrenes in low to high yields (23−74%) (Scheme 50).[82] The rate of decarboxylation was enhanced by electron-donating substituents.

Finally, a preparation of *gem*-dichloroalkenes by dehydrochlorination was reported in 1950. In that circumstance, 1,1,2-trichloroethane **51**, prepared by chlorination of the chloroalkene **50**, was dehydrohalogenated in 72% yield by treatment with hot alcoholic KOH (Scheme 51).[83]

2.2.3. Miscellaneous Reactions. N-Unsubstituted hydrazones of aromatic aldehydes were converted into the related

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

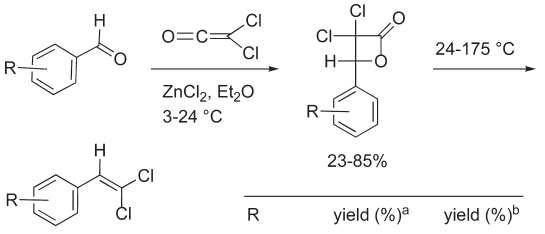
Scheme 49



R	yield (%)[a]	yield (%)[b]
Ph	77	58
n-C_5H_{11}	97	54
Me_2CHCH_2	80	49
$C_3H_7(Me)CH$	64	29
$Ph(CH_2)_2$	73	37
4-ClC_6H_4	85	39

[a]yield in the last step
[b]overall yield in two steps

Scheme 50



R	yield (%)[a]	yield (%)[b]
H	71	49
2-Me	73	28
2-NO_2	21	5
3-NO_2	73	39
3-OMe	74	29
4-OMe	23	18

[a]yield in the last step
[b]overall yield in two steps

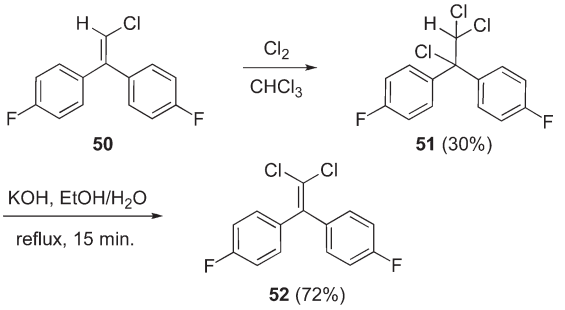
1,1-dichlorostyrenes by reaction with CCl_4 in the presence of copper(I) chloride as a catalyst (Scheme 52).[84] The authors investigated the factors affecting the reaction route and product yields that ranged from low to good depending on the nature of the substituents on the aromatic ring. The proposed mechanism for the formation of dichlorostyrenes implies the reaction of dichlorocarbene, resulting from oxidation of Cu(I) by CCl_4, with phenyldiazomethane, formed in turn by oxidation of benzylidenehydrazine with Cu(II) (Scheme 52).

The same authors later reported an efficient transformation of various hydrazones of (hetero)aryl alkyl ketones into 1,1-dichloroalkenes in moderate to good yields (31−82%) by reaction with CCl_4 in the presence of catalytic CuCl (Scheme 53).[48b] The mechanistic aspects of the ketone olefination were studied (Scheme 53).

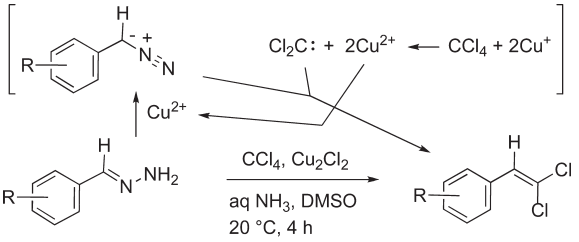
A convenient synthesis of 2-alkyl-substituted 1,1-dichloroalkenes was provided by Pd- or Ni-catalyzed cross-coupling of Grignard reagents with trichloroethylene (Scheme 54).[85] This reaction occurred at room temperature affording the coupled products in good yields.

On the other hand, 2-(hetero)aryl-substituted 1,1-dichloro-2-fluoro-1-alkenes were prepared by reaction of organolithium or

Scheme 51



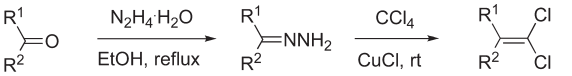
Scheme 52



R	yield (%)	R	yield (%)
H	27	2,6-Cl_2	79
4-NO_2	79	2,4-Cl_2	62
3-CN	70	4-Cl	86
4-Cl	74	2-Cl	64
3-Br	66	2-OH-5-NO_2	14

Only representative examples are reported.

Scheme 53



R^1	R^2	yield (%)	R^1	R^2	yield (%)
4-MeC_6H_4	Me	62	2-naphthyl	Me	31
4-$MeOC_6H_4$	Me	70	Ph	Et	57
4-ClC_6H_4	Me	82	2-thienyl	Me	42
4-$O_2NC_6H_4$	Me	58	-*o*-C_{64}-$(CH_2)_2$-		45
4-$MeSO_2C_6H_4$	Me	33	-*o*-C_6H_4-$(CH_2)_3$-		32

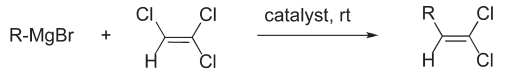
organomagnesium reagents with 1,1-dichloro-2,2-difluoroethylene.[86] Some representative results are reported in Scheme 55.[86c] This protocol was also pursued to obtain in good yields a number of 2-(2,2-dichloro-l-fluoroethenyl)benzo[*b*]thiophenes containing a variety of benzenoid ring substituents (Scheme 56).[44]

2.3. Synthesis of 1,1-Difluoro-1-alkenes

A variety of methods have been reported for the preparation of *gem*-difluoroalkenes, and two excellent reviews cover the literature until 1996.[87] Moreover, a book on "Organofluorine Chemistry"[88] and a recent review on the "C−F bond activation in organic synthesis"[89] deal partially this subject. This section

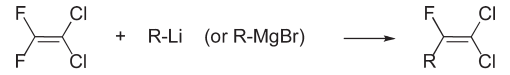
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 54



R	catalyst	yield (%)	R	catalyst	yield (%)
n-C_8H_{17}	$Pd(PPh_3)_4$	65	Me_2CHCH_2	$Ni(PPh_3)_4$	55
n-C_8H_{17}	$Ni(PPh_3)_4$	75	Me_2CH	$Ni(PPh_3)_4$	52
n-C_6H_{13}	$Pd(PPh_3)_4$	60	c-C_6H_{11}	$Pd(PPh_3)_4$	81
n-C_6H_{13}	$Ni(PPh_3)_4$	72			

Scheme 55



R	yield (%) *via* R-Li	yield (%) *via* R-MgBr
2-$MeOC_6H_4$	41	--
4-$MeOC_6H_4$	32	76
4-BrC_6H_4	--	50
1-naphthyl	31	82
2-furyl	53	--
2-thienyl	81	--
benzothiazol-2-yl	69	--
ferrocenyl	39	--

aims to provide an overview on the more recent results in this field, describing older ones only when necessary for a better understanding of the topic.

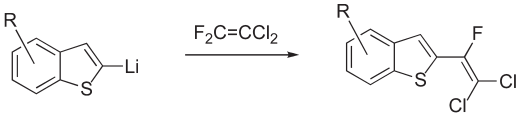
Recent methods on the synthesis of *gem*-difluoroalkenes can be classified as (i) Wittig-type and Reformatsky decarboxylation reactions, (ii) S_N2'-based reactions, (iii) β-elimination-based reactions, (iv) vinylmetal- or allylmetal-mediated reactions, and (v) Book rearrangement.

2.3.1. Wittig-type and Reformatsky Decarboxylation Reactions. The Wittig-type olefination has been extensively used for the conversion of aldehydes, ketones, and even lactones to the related difluoroalkenes, and a comprehensive review on fluorinated ylides has been reported.[87b]

Recent applications of the Wittig methodology to difluoroalkenes include the preparation of nucleosides. Chun and Jeong, in a study aimed to synthesize nucleoside **55**, examined the difluoromethylenation of the ketone **53** (Scheme 57).[90] The use of dibromodifluoromethane/zinc dust/triphenylphosphine in various solvents such as MeCN, DMF, or CH_2Cl_2 either failed to produce the desired compound **54** or resulted in disappointing yields. However, the exploitation of $P(NMe_2)_3$ instead of PPh_3 gave under refluxing conditions the key intermediate **54** in 47% yield.

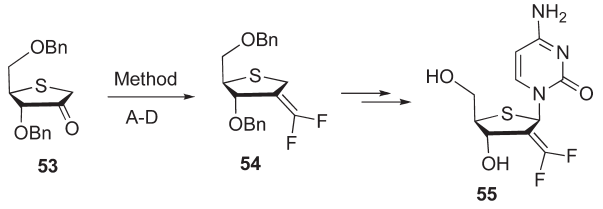
For the difluoromethylenation of 2′- or 3′-ketonucleosides, after initial efforts focused on conventional difluoromethylenation strategies, Serafinowski and co-workers found that the Wittig olefination with zinc and the reagent $[(Me_2N)_3PCBrF_2]Br$, generated *in situ* from CBr_2F_2 and $P(NMe_2)_3$ was partially successful.[91] However, they next found that if the quaternary phosphonium salt was prepared before the reaction, instead of being made *in situ*, much more reproducible and higher yielding results could be obtained (Scheme 58).[91]

Scheme 56



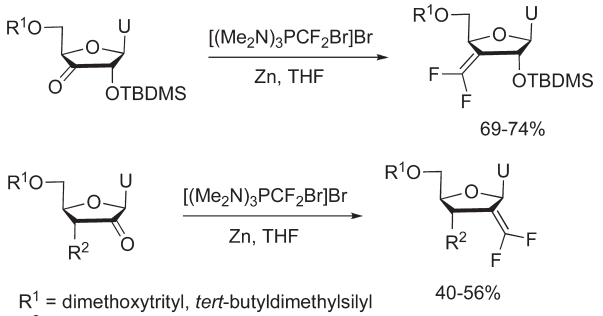
R = 4-Me, 3-Me, 7-Me, 4-Et, 4-Ph, 4-Cl, 5-Cl, 6-Cl

Scheme 57



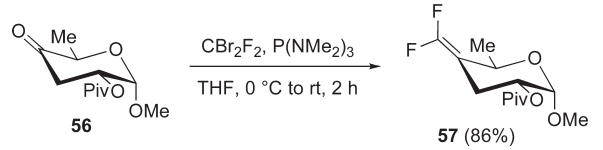
Method	**54** yield (%)
A: CBr_2F_2, PPh_3, Zn, THF, rt to reflux, 5 h	2
B: CBr_2F_2, PPh_3, Zn, DMF, rt then 60 °C, 15 h	decomposition
C: CBr_2F_2, PPh_3, Zn, CH_2Cl_2, rt, 60 h	no reaction
D: CBr_2F_2, $P(NMe_2)_3$, Zn, THF, reflux, 1 h	47

Scheme 58



R^1 = dimethoxytrityl, *tert*-butyldimethylsilyl
R^2 = tetraisopropyldisiloxan-1,3-diyl
U = Uracil-1-yl

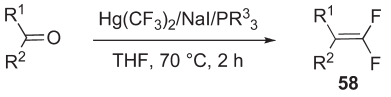
Scheme 59



In the synthesis of a deoxysugar dinucleotide containing an *exo*-difluoromethylene moiety,[92] Zao and Liu accomplished the incorporation of the difluoromethylene unit into the 4-ketosugar **56** by using a Wittig-type reagent generated *in situ* from $P(NMe_2)_3$ and CBr_2F_2 (Scheme 59). In this experiment, $P(NMe_2)_3$ was added dropwise to the solution of **56** and CBr_2F_2 in dry THF at 0 °C, followed by warming the reaction mixture to room temperature. This modified procedure not only gave a very

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 60



R^1	R^2	R^3	yield (%)
$Ph(CH_2)_2$	Me	Ph	67
1-naphthyl	H	Ph	67
2-naphthyl	Me	*n*-Bu	61
4-PhC_6H_4	Me	*n*-Bu	52
(*E*)-PhCH=CH	Ph	Ph	43
Ph	Ph	*n*-Bu	67
-*o*-$C_6H_4(CH_2)_3$-		*n*-Bu	61

Only representative examples are reported

clean reaction with high yield but also alleviated the requirement for zinc metal in the reaction.[91]

The use of difluoromethylene phosphorus ylides, generated by the $Hg(CF_3)_2/NaI/PR_3$ reagent combination, in the presence of aldehydes or ketones resulted in Wittig-type reactions giving *gem*-difluoroalkenes in moderate to good yields (Scheme 60).[93] Yields depended on the phosphine used. In most cases $P(n\text{-}Bu)_3$ promoted a better formation of difluoroalkenes than PPh_3, which was however more effective with aldehydes as substrates.

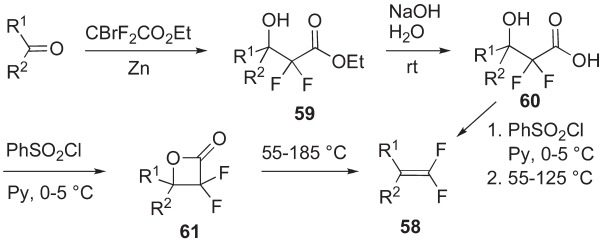
Dolbier and co-workers realized a formal difluoromethylenation of ketones via α,α-difluoro-β-lactones.[94] The procedure involved initial condensation of ketones with the Reformatsky reagent ethyl bromodifluoroacetate, hydrolysis of the first formed α,α-difluoro-β-hydroxy esters **59** to give α,α-difluoro-β-hydroxy acids **60**, followed by cyclization to make α,α-difluoro-β-lactones **61** (Scheme 61). Finally, lactones **61** were thermally decarboxylated to form 1,1-difluoroalkenes **58** in high yields. Interestingly, the presence of at least one aromatic ring in the β-position of acids **60** makes these products very prone to the *in situ* decarboxylation, thus allowing the conversion in high yields of β-aryl acids **60** into 2-aryl-substituted 1,1-difluoroolefins **58** in a one-pot lactonization−decarboxylation reaction sequence.

2.3.2. S_N2'-Based Reactions in Trihalomethyl Alkenes. Trifluoromethyl and bromodifluoromethyl alkene derivatives **62** with either electron-withdrawing or electron-donating substituents at the α-carbon smoothly underwent nucleophilic addition−elimination (via dehalogenation) reactions on reacting with carbon and heteroatom nucleophiles to give functionalized 1,1-difluoroalkenes **63** (Scheme 62). Thus, S_N2' reaction of organolithiums,[95] Grignard reagents,[95−97] N-lithiated amines,[98] lithium aluminum hydride,[96] ester enolates,[99] or silyl lithium reagents[100] with trifluoromethyl-substituted alkenes afforded the corresponding *gem*-difluoroalkenes (Scheme 63).

α-Trifluoromethylstyrene **64** proved to be a good substrate to react with a variety of organolithium reagents and N-lithiated amines to afford α-functionalized β,β-difluorostyrenes **65** in good yields (Scheme 64).[98] On the other hand, while the reaction of the alkyl alkene **66** with a reactive organolithium reagent such as butyllithium was successful to give the corresponding difluoroalkene **67**, no reaction was observed when the reaction was extended to the less reactive phenyllithium or LDA (Scheme 65).[98]

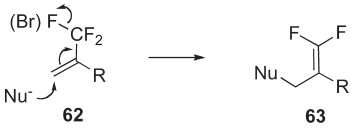
An interesting application of this protocol has been recently developed by Ichikawa and co-workers to obtain helicenes.[101] Symmetrical and nonsymmetrical 1,1-difluoroalkenes were prepared

Scheme 61

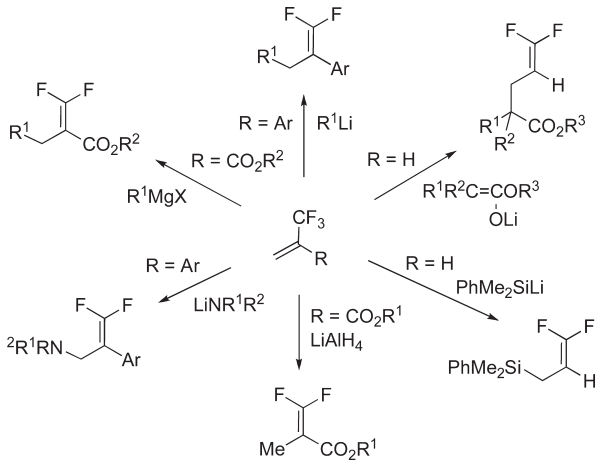


R^1	R^2	**58** (from **60**) yield (%)	**58** (from **61**) yield (%)
Me	Me	-	95
Et	Et	-	98
Bn	Bn	-	95
Ph	Bn	-	80
Ph	Me	-	90
4-ClC_6H_4	Me	-	85
4-$MeOC_6H_4$	Me	-	98
4-$F_3CC_6H_4$	Bn	63	-
Ph	Me	80	-
Ph	Me	85	-
4-MeC_6H_4	Me	81	-
4-ClC_6H_4	Me	65	-
Ph	Ph	88	-

Scheme 62



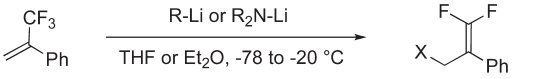
Scheme 63

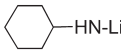
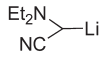
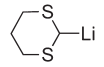


by S_N2' reactions of aryl methyl anions with the trifluoromethyl-substituted vinyl compound **66**, which was readily obtained from ethyl trifluoroacetate by a Grignard reaction followed by a Wittig olefination (Scheme 66). Compound **66** could also be prepared by alkylation with the benzyl bromide of 2-(trifluoromethyl)allylsilane **68**, derived from CF_3CO_2Et.

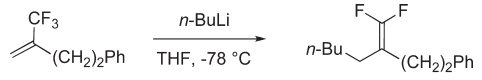
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 64



R -Li	**65** yield (%)	R_2N-Li	**65** yield (%)
Me-Li	90	*i*-Pr_2N-Li	90
Bu-Li	93	$(CH_2{=}CHCH_2)_2N$-Li	85
t-Bu-Li	92	(*S*)-PhCH(Me)NHLi	60
Ph-Li	90		66
$(EtO)_2P(O)CH_2$-Li	85		
$PhS(O)CH_2$-Li	83		90
$PhS(O_2)CH_2$-Li	80		
	86		
	90		

Scheme 65



Tellier and co-workers showed that 1-bromo-1,1-difluoro-2-alkenes **71** undergo S_N2' reactions as trifluoropropene derivatives.[103] Thus, brominated compounds **72**, obtained by reaction of thionyl bromide with 1,1-difluoro-l-alken-3-ols **71**, reacted with Grignard reagents in the presence of copper and lithium salts to give the related 1,1-difluoroalkenes **73** in good yields (Scheme 67).

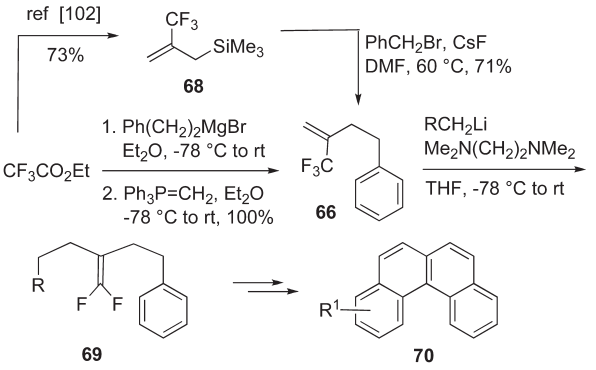
The S_N2' reaction of the dilithiated pivalanilide **74** with α-trifluoromethylstyrene was used to obtain 2-(3,3-difluoro-2-phenylallyl)aniline **75**, key intermediate in the synthesis of the fluoroindene **76** (Scheme 68).[104]

Scheme 69 illustrates an intramolecular version of the S_N2' reaction of the *ortho*-substituted CF_3-styrene derivative **77**, where the nitrogen nucleophile attacks the β-carbon in an S_N2' manner, forming in DMF the isoquinoline skeleton **78**.[105]

A catalytic alternative of the intramolecular S_N2' reaction of trifluoromethylated alkenes has been reported by Ichikawa and co-workers (Scheme 70).[106] Upon exposure to a catalytic amount of $Pd(PPh_3)_4$, *O*-pentafluorobenzoyloximes **79** underwent 5-*endo* mode of alkene insertion via oxidative addition of the N−O bond in **79**, followed by β-fluoride elimination to produce 4-difluoromethylene-1-pyrrolines **80**.

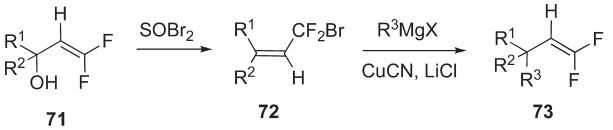
Cunico and Motta reported that the Si−C bond of *N,N*-dimethylcarbamoylsilane added regiospecifically to the C=C bond of electrophilically functionalized alkenes to afford β-silyl-β-functionalized amides. However, when α-trifluoromethylstyrene **64** was used as the alkene, concomitant defluorosilylation (β-elimination) occurred to give the difluoroalkene **81** in 64% yield (Scheme 71).[107]

Scheme 66



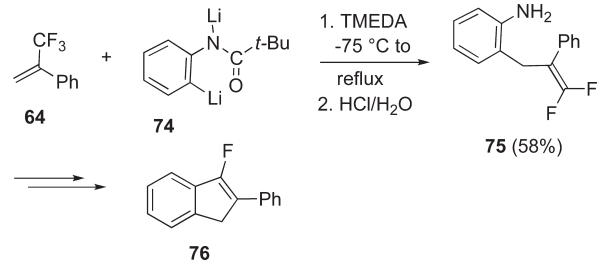
R	**69** yield (%)	R	**69** yield (%)
Ph	80	3-$MeOC_6H_4$	68
2-MeC_6H_4	74	4-Me-1-naphthyl	66
3-MeC_6H_4	76	2-naphthyl	62
4-MeC_6H_4	76	3-Me-2-naphthyl	41
2-$MeOC_6H_4$	73		

Scheme 67



R^1	R^2	R^3	**73** yield (%)	R^1	R^2	R^3	**73** yield (%)
n-C_6H_{13}	H	Me	70	*n*-C_6H_{13}	H	$PhCH_2$	80
n-C_6H_{13}	H	*n*-Bu	96	Ph	H	*i*-Pr	90
n-C_6H_{13}	H	*i*-Pr	92	Ph	H	*t*-Bu	85
n-C_6H_{13}	H	*t*-Bu	93	-$(CH_2)_5$-		*n*-Bu	87
n-C_6H_{13}	H	Allyl	80	-$(CH_2)_5$-		*i*-Pr	85

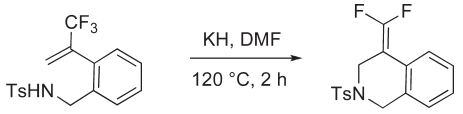
Scheme 68



In addition to strong nucleophilic reagents, organoboron compounds react with trifluoromethylated alkenes in the presence of rhodium complexes. Miura and Murakami reported the synthesis of *gem*-difluoroalkenes from reaction of α-(trifluoromethyl)styrenes with arylboronic esters in the presence of $[RhCl(cod)]_2$ and MeMgCl (Scheme 72).[108] The reaction proceeds through addition of arylrhodium(I) species across the electron-deficient carbon−carbon double bond, followed by β-fluoride elimination.

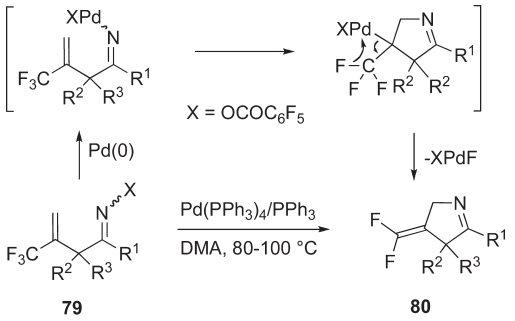
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 69



77 **78** (78%)

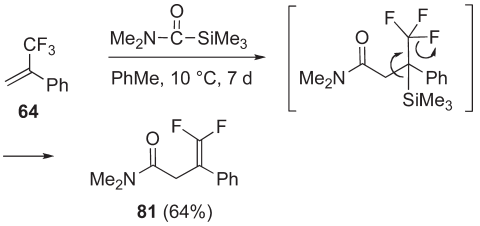
Scheme 70



79 **80**

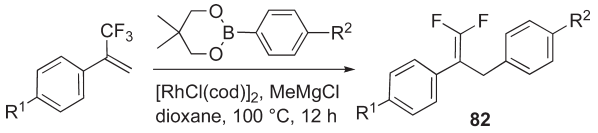
R^1	R^2	R^3	**80** yield (%)
Ph	H	H	60
Ph	$-CH_2)_2-$		65
$Ph(CH_2)_2$	H	H	20
Ph	$PhCH_2$	H	71

Scheme 71



81 (64%)

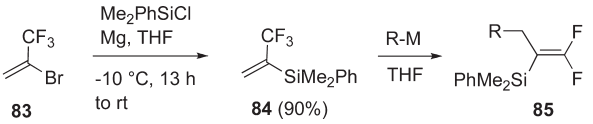
Scheme 72

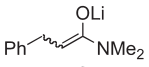
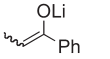
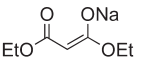


82

R^1	R^2	**82** yield (%)
F	H	60
Br	H	61
CN	H	54
H	CO_2Me	74

Scheme 73



R-M	**85** yield (%)	R-M	**85** yield (%)	R-M	**85** yield (%)
$LiAlH_4$	88		85		75
n-BuLi	93				
$n\text{-}C_{10}H_{21}Li$	99				
PhLi	85		59		89
i-Pr_2NLi	86				
i-BuNHLi	91		55		

The reactions of the silyl alkene **84**, readily prepared from 2-bromo-3,3,3-trifluoroprop-1-ene **83**, with a variety of nucleophiles, provided 3-substituted 1,1-difluoro-2-silylalkenes **85** (Scheme 73).[109] These compounds are useful difluoromethylene building blocks, which can be transformed to synthetically valuable compounds by several processes, such as bromodesilylation, desilylation, and fluoride-promoted desilylative alkylation with aldehydes (Scheme 74).[110]

Trifluoromethacrylic acid **86** and its esters are extremely strong nucleophile acceptors so that they participate in facile S_N2' reactions even at low temperature in aprotic solvents. Some results are summarized in Scheme 75.[96,97,110,111] Grignard and alkyl lithium reagents provide S_N2' products in moderate yields. Excess use of nucleophiles sometimes induces further addition−elimination reactions at the *gem*-difluoromethylene carbon of the initially formed products **87**, leading to the formation of β-substituted β-fluoroacrylic acids.

Because of the high reactivity of trifluoromethylated alkenes, even those substituted in the α-position with groups such as NMe_2[112] (Scheme 76) and OTs[113] (Scheme 77) undergo S_N2' reactions with a variety Grignard reagents, although they need a higher temperature or longer reaction times as compared with $CH_2{=}CH{-}CF_3$, $CH_2{=}C(Ph)CF_3$, and $CH_2{=}C(SiMe_2Ph)CF_3$, presumably because of the steric hindrance at the reaction sites.

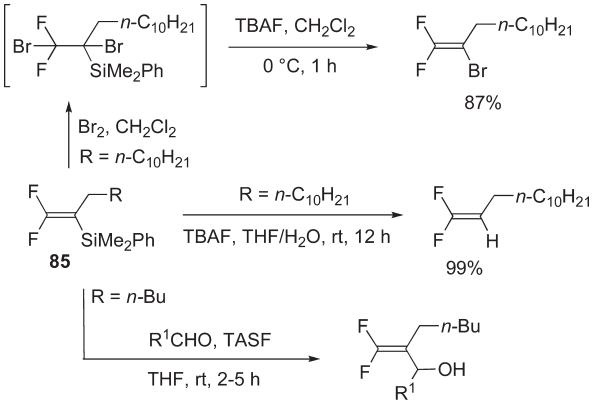
2.3.3. S_N2'-Based Reactions in Trifluoromethyl Iminoesters and Dithioesters. Unusual reaction selectivities were observed in the nucleophilic transformations of fluorinated iminoesters **90**[114] (Scheme 78) and dithioesters **92**[115] (Scheme 79) as compared with those of the corresponding carbonyl compounds. The carbon−heteroatom double bonds bearing a CF_3 group accept nucleophiles at the heteroatom site, leading to fluoroalkenes via formal S_N2' reactions.

2.3.4. Reductive-Type Reactions of Trifluoromethyl Group Bonded to π-Electron System. In previous sections, S_N2' reactions of organic fluorides have been introduced. Metaphorically, an electron can be regarded as the smallest nucleophile. In general, C−F bonds in organofluorine compounds are inert. Under electroreductive conditions, however, the bond breaking does rather easily occur when a CF_3 group is attached to a π-electron system such as aryl and carbonyl groups (**94**, Scheme 80), since electron acceptance into the π-system and subsequent extrusion of a fluoride ion may make large contributions to the net transformation.

Under reductive conditions, 2,2-difluoroenol ethers or 2,2-difluoroenamines could be profitably produced from trifluoromethyl ketones and imines. Electrochemical reductive defluorination of

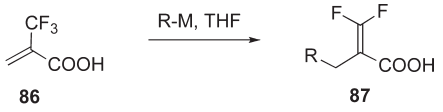
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 74



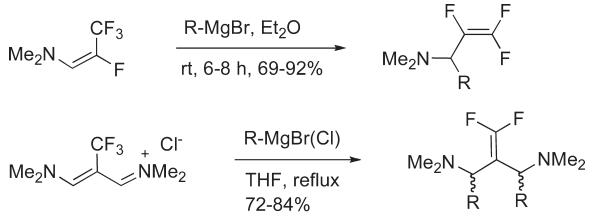
R^1	yield (%)	R^1	yield (%)
Ph	68	1-naphthyl	70
3-$MeOC_6H_4$	67	$Ph(CH_2)_2$	21

Scheme 75



R-M	R	**87** yield (%)	Ref.
$LiAlH_4$	H	54	96
PhMgBr	Ph	55	97
n-BuMgBr	*n*-Bu	48	97
$Bu_3SnCH_2OBn/BuLi$	$BnOCH_2$	54	110
CH_2=CHMgBr	CH_2=CH	30	111

Scheme 76



R = Ph, 4-$MeOC_6H_4$,4-MeC_6H_4,4-FC_6H_4, *n*-C_4H_9, *n*-C_8H_{17}
n-C_8H_{17}, 1-naphthyl, PhCH=CH, PhC≡C

trifluoromethyl ketones **95** in the presence of Me_3SiCl afforded the corresponding difluoroenol silyl ethers **96**. Combination of a lead cathode and Bu_4NBr as a supporting electrolyte gave enol ethers **96** in a high yields. A current density of ~10 mA/cm^2 or less was effective for the selective monodefluorination of **95** (Scheme 81).[116]

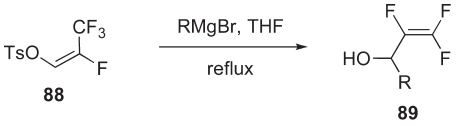
Similar electrolysis conditions could be applicable for the preparation of ketene silyl (O,S, O,N, and O,O) acetals. As demonstrated in Scheme 82, electrochemical reactions of thioesters **97** and the amide **99** afforded the corresponding difluoro ketene silyl acetals **98**[117] and **100**[17] in satisfactory yields. On the other hand, 1-trimethylsilyl-1,1-difluoroacetates **103** were formed selectively when the electrochemical reactions of esters **101** were carried out at 50 °C (Scheme 82).[118]

The electroreductive protocol worked well for selective monodefluorination of trifluoromethyl imines **104** to give the related difluoroenamines **105** (Scheme 83).[119] In addition, *N*-silyl enamines **105** fulfilled several important functions as difluoromethylated synthetic blocks.

In 1999, Amii and Uneyama reported that metallic magnesium, which serves as a convenient electron source, proved to be useful for the C−F bond breaking process of trifluoromethyl ketones **95** to provide a practical route to 2,2-difluoroenol silyl ethers **96** (Scheme 84).[120,121] The formation of **96** can be explained by assuming that the intermediate ketyl species **106** are generated in the reaction of Mg(0) with ketones **95**, which are further reduced to anion species **107** by Mg. The resultant β-fluorinated organomagnesium species **107** readily undergo β-elimination to afford difluoroenol ethers **96**.

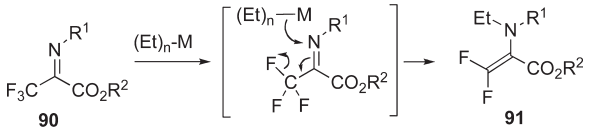
To demonstrate further synthetic utility of these C−F bond cleavage reactions, Uneyama and co-workers developed the fluorinated diene **108**, which is an analogue of the Danishefsky's diene, acting as one of the most fascinating C_4 building blocks.[122]

Scheme 77



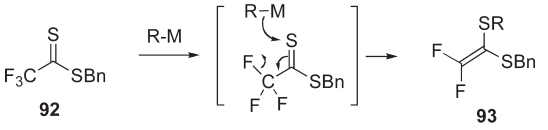
R	**89** yield (%)	R	**89** yield (%)
Ph	75	4-ClC_6H_4	72
4-MeC_6H_4	85	2-naphthyl	70
2-MeC_6H_4	25	$PhCH_2CH_2$	14

Scheme 78



R^1	R^2	$(Et)_n$-M	**91** yield (%)
3-$MeOC_6H_4$	Et	EtMgBr	50
3-$MeOC_6H_4$	Et	Et_2Zn	88
Ph	Et	Et_2Zn	80
3-ClC_6H_4	Et	Et_2Zn	84
PhCH(Me)	Bn	Et_2Zn	85

Scheme 79

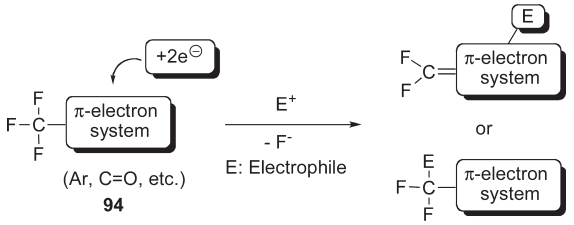


R-M = EtMgBr
R-M = *n*-BuLi

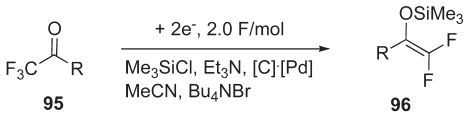
R	Et	*n*-Bu
93 yield (%)	86	69

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 80

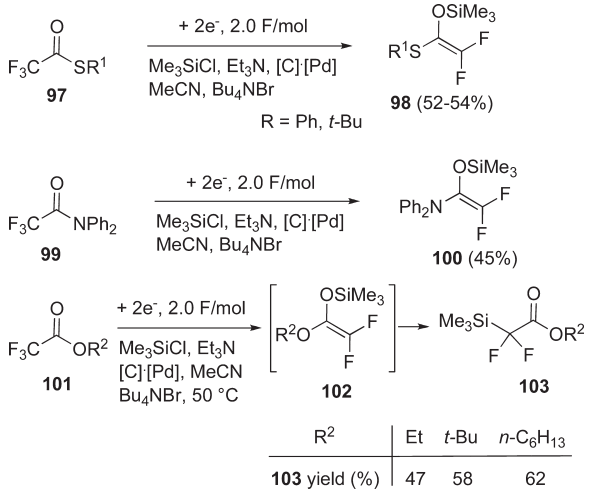


Scheme 81



R	**96** yield (%)	R	**96** yield (%)
Ph	80	EtO_2CCH_2	50
$PhCH_2$	44	2-pyridyl	70
$Ph(CH_2)_2$	74	2-furyl	55
n-C_6H_{13}	71	2-thienyl	74

Scheme 82



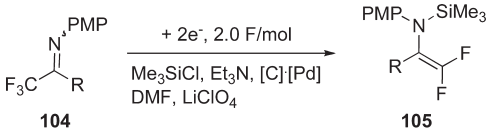
R^2	Et	*t*-Bu	n-C_6H_{13}
103 yield (%)	47	58	62

The process shown in Scheme 85 provided access to **108** in a simple and efficient fashion.

This protocol was also applicable for the selective defluorination of trifluoromethyl imines **109** to yield the corresponding N-silylated difluoroenamines **110** (Scheme 86).[123] Notably, the Cl-arene functionality in **109** (R = 4-ClC_6H_4) was perfectly compatible under the used reaction conditions.

When the trifluoromethyl iminoester **111** was subjected to reductive defluorination upon treatment with metallic magnesium and trimethylsilyl chloride, it led to the enaminoester **112** in 58% yield (Scheme 87).[123] Aminodifluoroacrylate **112** is a very interesting compound possessing both *N*-silyl-difluoroenamine and difluoroacrylate moieties. Because of the unique structure, the enamine **112** is a useful precursor to a wide repertoire of

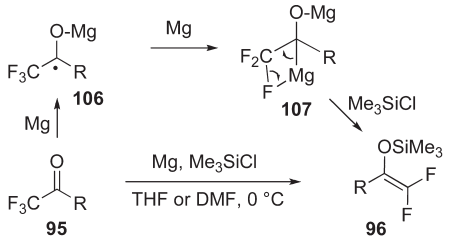
Scheme 83



R	**105** yield (%)	R	**105** yield (%)
H	47	4-ClC_6H_4	74
Et	50	2-furyl	57
Ph	75	CO_2Et	78
4-$MeOC_6H_4$	58	CO_2Et	50

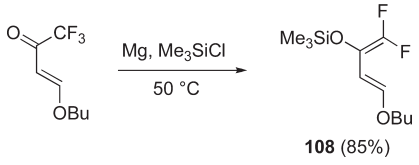
PMP = 4-$MeOC_6H_4$

Scheme 84



R	**96** yield (%)	R	**96** yield (%)
Ph	91	2-furyl	97
4-$MeOC_6H_4$	89	2-thienyl	97
4-$F_3CC_6H_4$	87	n-C_6H_{13}	56
4-ClC_6H_4	98	c-C_6H_{11}	62

Scheme 85



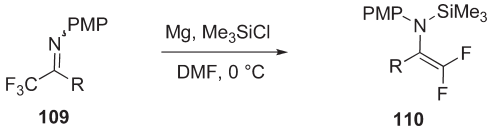
difluorinated α-amino acids, since it can react not only with electrophiles but also with nucleophiles and radical species at the β-position, regioselectively.[119]

A one-pot reaction sequence involving Mg(0)-promoted reductive C−F and C−Cl bond cleavage of trifluoroacetimidoyl chlorides **113** resulted in the selective formation of bis-silylated difluoroenamines **114** (Scheme 88).[124] When imidoyl chlorides **113** were treated with Mg metal and Me_3SiCl in THF at 0 °C for 30 min, the dehalogenative double silylation reactions proceeded smoothly to afford bis-silylated difluoroenamines **113** in high yields.

Shi and co-workers prepared the stable ethyl 3,3-difluoro-2-trimethylsiloxyacrylate **115** in 92% yield by heating methyl 2-benzyloxy-3,3-difluoropropenate with 1 equiv of trimethylsilyl iodide in CH_2Cl_2 (Scheme 89),[125] which was in turn obtained from ethyl 3,3,3-trifluoro-2-oxopropanoate.[126]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

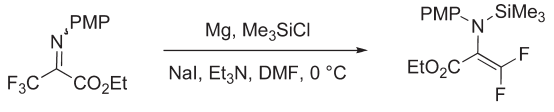
Scheme 86



109 **110**

R	**110** yield (%)	R	**110** yield (%)
H	47	4-ClCC$_6$H$_4$	88
n-C$_6$H$_{13}$	77	2-pyridyl	72
Ph	82	2-thienyl	63
4-MeOC$_6$H$_4$	99		

Scheme 87



111 **112** (58%)

Tius and co-workers described the preparation of the difluoromethylene compound **117**, as intermediate in the synthesis of a bifunctional cannabinoid ligand, by exposing the β-trifluoromethyl-α,β-unsaturated ester **116** to magnesium in MeOH (Scheme 90).[127] The reaction occurs via fluoride elimination from a β-anionic intermediate. A small amount (5−7%) of the saturated β-trifluoromethyl ester was also obtained.

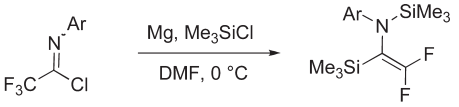
2.3.5. β-Elimination-Based Reactions. *2.3.5.1. Reductive Dehalogenation Reactions of Vicinal Dihalides.* Reductive dehalogenation of vicinal dihalides has been also used in the preparation of *gem*-difluoroalkenes. Upon treatment with low-valent metals such as magnesium, zinc, and aluminum, chloro- and bromoalkanes endowed with a trifluoromethyl group at the α-position partake in vicinal dehalodefluorination, resulting in the formation of *gem*-difluoroalkenes (Scheme 91).[128−131]

Ruthenium(II)- or copper(I)-induced regioselective radical reaction of the $CClF_2CCl_2^{\bullet}$ radical, derived from $CClF_2CCl_3$, to trimethylsilyl enol ethers **118** yielded (β,β,γ-trichloro-γ,γ-difluoropropyl)carbonyl compounds **119** as intermediates (Scheme 92).[132] Spontaneous dehydrochlorination afforded [β-chloro-β-(chlorodifluoromethyl)vinyl]carbonyl compounds **120**. Reductive dechlorination of **120** with zinc gave γ,γ-difluoroallyl ketones **122a**−**e** and an ester **122f**. In some cases, the nickel(0)-catalyzed reduction with zinc has proven to be superior to the simple dehydrochlorination.

In some cases, the use of additives has proved to facilitate 1,2-elimination reactions. Thus, the treatment of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate with 1.1 equiv of zinc dust in Et_2O at room temperature for 0.5 h did not provide the desired benzyl 2,3,3-trifluoroprop-2-enoate, which was instead formed in 76% yield after addition of Et_2AlCl (1.3 equiv) as Lewis acid (Scheme 93).[133] Similarly, the use of Zn in combination with a catalytic amount of CuI allowed the dechlorodefluorination of *O,Cl*-acetals to afford the corresponding difluoroenol ethers (a representative example is reported in Scheme 93).[125]

Reductive manipulations of CF_3CX_2 moieties allowed the formation of *gem*-difluorovinyl organometallic reagents. Treatment of

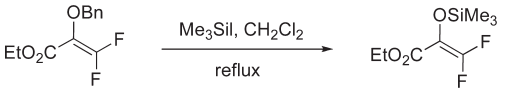
Scheme 88



113 **114** (80-85%)

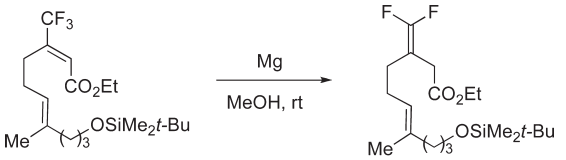
Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$

Scheme 89



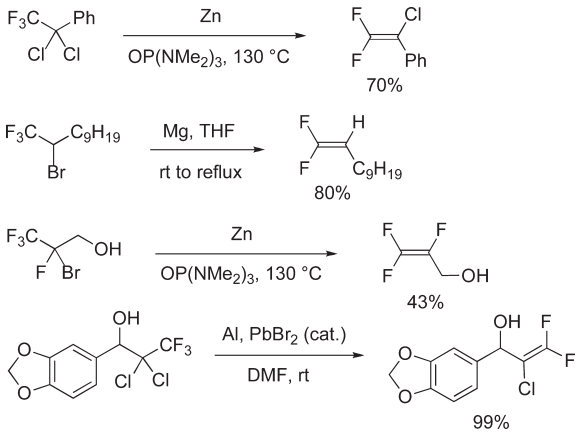
115 (92%)

Scheme 90



116 **117** (>90%)

Scheme 91

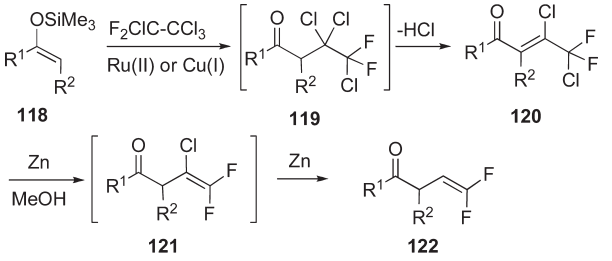


2,2-dibromohexafluoropropane **123** with 2 equiv of metallic zinc in DMF gave $CF_3(ZnX)C{=}CF_2$ **124**, which participates in allylation, acylation, halogenation, and oxidative dimerization to afford a variety of $CF_3(R)C{=}CF_2$ compounds (Scheme 94).[134] In a competition experiment, Zn reacted faster with the intermediate $CF_3CBr{=}CF_2$ than with $CF_3CBr_2CF_3$ **123**.

Tamura and Sekiya reported that 2,2-dichloro-1,1,1-trifluoroethane **128** reacted with zinc and catalytic CuI and aldehydes to afford under slightly different reaction conditions predominantly either 1-substituted 2-chloro-3,3-difluoro-2-propen-1-ols **131** or 1-substituted 2,2-dichloro-3,3,3-trifluoro-1-propanols **132**, formed from **131** by reductive 1,2-dehalogenation (Scheme 95).[135] The

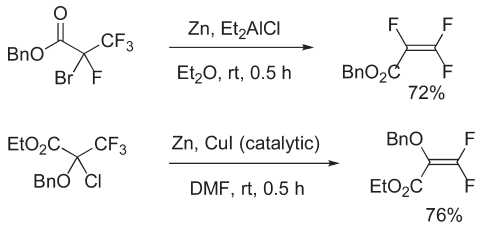
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 92



	R^1	R^2	**120** yield (%)	**122** yield (%)
a	Ph	H	80	67
b	(*E*)-PhCH=CH	H	40	34
c	-*o*-$C_6H_4(CH_2)_2$-		53	59
d	*n*-C_5H_{11}	H	53	58
e	-$(CH_2)_3$-		26	43
f	*n*-BuO	H	64	32

Scheme 93



reactions proceeded via 1,1-dichloro-2,2,2-trifluoroethylzinc chloride **130** as an organozinc intermediate.

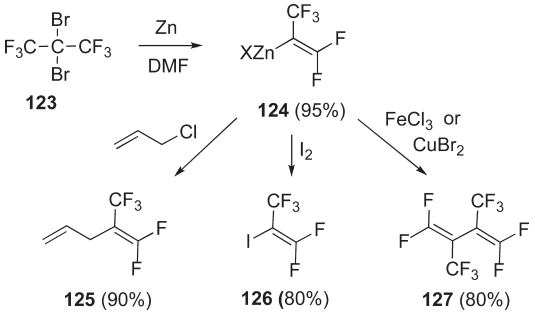
2.3.5.2. Desulfonylation and Desulfinylation Reactions. The selective introduction of a (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) into organic molecules with reagents such as $PhSO_2CF_2H$, $PhSO_2CF_2Br$, and $PhSO_2CF_2SiMe_3$ has attracted much attention since the $PhSO_2CF_2$ group can be readily transformed into difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) functionalities.[136]

Difluoromethyl phenyl sulfone and its derivatives have been employed to achieve a three-step synthesis of *gem*-difluoroalkenes via a reduction−desulfonation protocol.

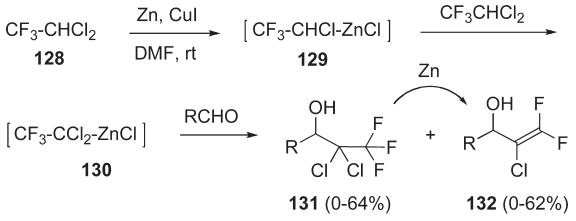
The use of the $PhSO_2CF_2H$ reagent was reported for the preparation of the 1,1-difluoroalkene **135**, in response to the failure of some conventional difluoromethylenation strategies such as the use of difluoromethyldiphenylphosphine oxide[87] or the couple $CBr_2F_2/P(NMe_2)_3$[87] (Scheme 96).[137] Addition of lithium hexamethyldisilazide to a mixture of the ketone **133** and $PhSO_2CF_2H$ afforded the alcohol **134**, which could be converted into compound **135** by treatment with methanesulfonyl chloride and then SmI_2 (36% overall yield from **133**).

A similar strategy was followed to obtain the difluoroalkene **136**, an intermediate in the total synthesis of F_2CBI, a difluorocyclopropane analog of the alkylation subunits of CC-1065 and the duocarmycins (Scheme 97).[138] In this case, however, the reductive elimination was effected in 77% yield by treatment of **137** with 6 equiv of Na(Hg) and 4 equiv of Na_2HPO_4.

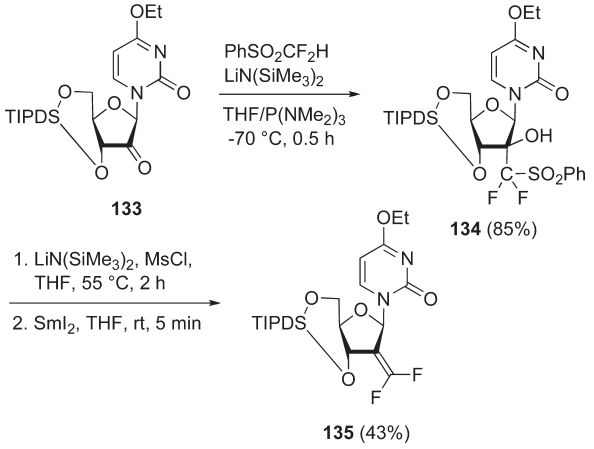
Scheme 94



Scheme 95



Scheme 96

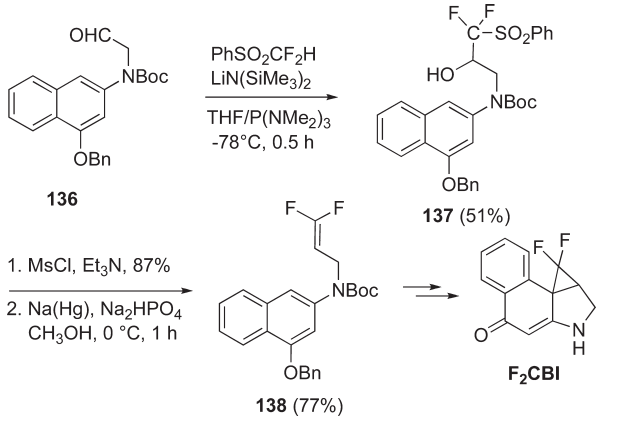


(Phenylsulfonyl)difluoromethyl alcohols such as **134** and **137** have been obtained not only with $PhSO_2CF_2H$[139] but also by reaction of aldehydes and ketones with $PhSO_2CF_2SiMe_3$[140] or $PhSO_2CBrF_2$.[141] Thus, the combination of $PhSO_2CBrF_2$ and tetrakis(dimethylamino)ethylene (TDAE) as a nucleophilic (phenylsulfonyl)difluoromethylating reagent, converted aldehydes into aryl and alkyl alcohols **139** (Scheme 98).[141] The reaction of these alcohols with methanesulfonyl chloride gave the corresponding mesylates, which underwent reductive elimination by treatment with Na(Hg)/Na_2HPO_4 to afford 1,1-difluoro alkenes in good yields.

(Phenylsulfonyl)difluoromethyl alcohols **139** have been also used in the preparation of 2,2-difluoro enol esters **141** and the 2-(1-chloro-2,2-difluorovinyl)naphthalene **143** (Scheme 99).[142]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 97



Deprotonation of **139** followed by benzoylation with benzoyl chloride afforded benzoates **140**, which by treatment with LiHDMS at room temperature gave enol esters **141** in moderate to good yields.

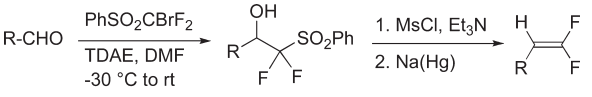
The $PhSO_2CF_2$-containing alkanes **144** were obtained in satisfactory yields by nucleophilic (phenylsulfonyl)difluoromethylation of primary alkyl iodides with the $PhSO_2CF_2^-$ anion, *in situ* generated from $PhSO_2CF_2H$ and KO*t*-Bu at −50 °C (Scheme 100).[143] Products **144** were subjected to base-mediated dehydrosulfonylation (KO*t*-Bu at −20 °C to room temperature) to give 1,1-difluoroalkenes in 55−88% yields. The one-pot conversion of alkyl iodides to 1,1-difluoro alkenes by using $PhSO_2CF_2H$ and KO*t*-Bu was also possible, but the isolation of alkenes from unreacted alkyl iodides was problematic due to their similar polarity.

Hu and co-workers have recently reported that difluoromethyl 2-pyridyl sulfone **145** is an efficient one-pot *gem*-difluoroolefination reagent. Thus, a variety of aldehydes and ketones by reaction with **145** and KO*t*-Bu in 1/1.2/1.8 molar ratio gave the corresponding *gem*-difluoroalkenes in good yields (Scheme 101).[144] A mechanism for the process was proposed as shown in the scheme.

Hu and co-workers have successfully carried out an efficient nucleophilic fluoroalkylation of cyclic sulfates **146** and sulfamidates **149** with the $PhSO_2CF_2H/LiN(SiMe_3)_2/P(NMe_2)_3$ system (Scheme 102).[145] These regioselective reactions afforded the related β-(phenylsulfonyl)-β,β-difluoromethylated products **147** and **150** in excellent yields. Upon selective desulfonylation, compounds **147** with R = $PhOCH_2$ and **150** with R = $PhCH_2$ were subjected to base-mediated α,β-elimination of a molecule of phenylsulfinic acid to give the corresponding β-difluoromethylenated alcohol **148** and amine **151** in 82% and 70% yield, respectively.

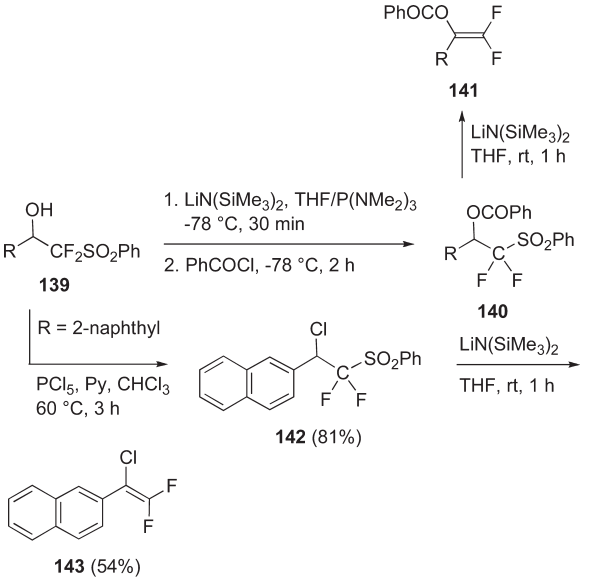
Pohmakotr and co-workers demonstrated that α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane **152** (Scheme 103) can serve as useful synthetic equivalent of α,α-difluoro-α-phenylsulfanylmethyl carbanion ($PhSCF_2^-$).[146] Both aldehydes and ketones underwent facile α,α-difluorophenylsulfanylmethylation with **152** in the presence of 10 mol % tetra-*n*-butylammonium fluoride (TBAF) in THF, providing *gem*-difluoro-substituted alcohols **153** in moderate to good yields (39−90%) (Scheme 103). Alcohols **153** were then oxidized with 3-chloroperbenzoic acid (MCPBA) to sulfoxides **154**, which were finally converted in

Scheme 98



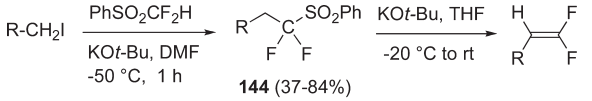
R	yield (%)
Ph	60
4-BrC_6H_4	70
$PhCH_2CH_2$	84

Scheme 99



R	**141** yield (%)	R	**141** yield (%)
2-naphthyl	65	2-$MeOC_6H_4$	25
Ph	54	4-*t*-BuC_6H_4	74
4-$MeOC_6H_4$	74	2-furyl	57
4-$Me_2NC_6H_4$	68		

Scheme 100



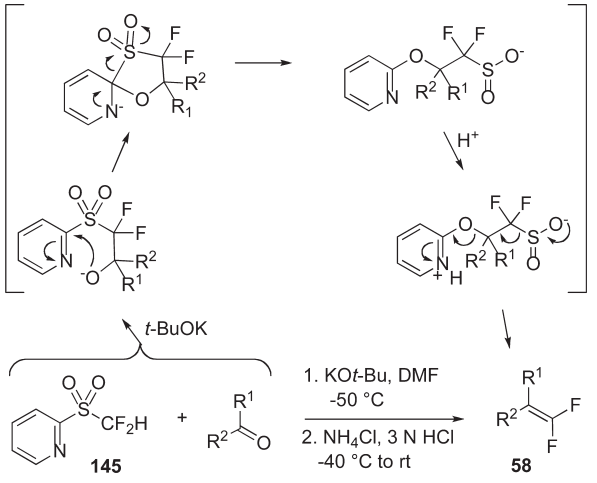
R	yield (%)	R	yield (%)
$Ph(CH_2)_3$	85	$Ph_2CH(CH_2)_2$	84
$Ph(CH_2)_4$	71	4-$MeOC_6H_4(CH_2)_4$	55
$Ph(CH_2)_5$	82	$PhO(CH_2)_3$	88
$Ph(CH_2)_6$	80	$PhO(CH_2)$	87

moderate to good yields to the related *gem*-difluoroalkenes **58** by neat pyrolysis at 200 °C under reduced pressure (0.05 mmHg) or flash vacuum pyrolysis (FVP).

The same research group prepared *gem*-difluoroalkenes by using bromodifluorophenylsulfanylmethane **155** as a *gem*-difluoromethylene (CF_2) building block (Scheme 104).[147] Reaction of

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

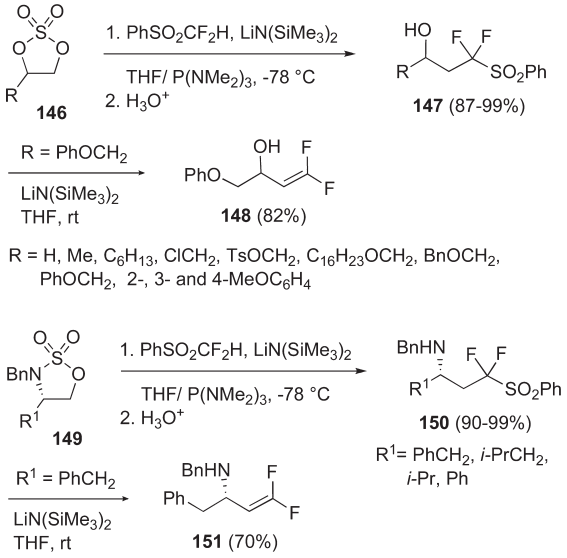
Scheme 101



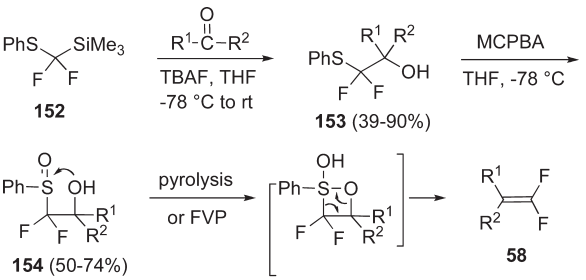
R^1	R^2	**58** yield (%)	R^1	R^2	**58** yield (%)
4-$MeOC_6H_4$	H	86	(*E*)-PhCH=CH	H	62
4-*t*-BuC_6H_4	H	74	$PhCH_2CH_2$	H	40
3-$O_2NC_6H_4$	H	72	4-PhC_6H_4	Me	81
3-ClC_6H_4	H	72	(*E*)-PhCH=CH	Me	80
2-naphthyl	H	92	$PhCH_2CH_2$	Me	72

Only representative examples are reported

Scheme 102



Scheme 103



R^1	R^2	**58** yield (%)	
		pyrolysis	FVP
4-$MeOC_6H_4$	H	79	82
2,4-$(MeO)_2C_6H_3$	H	74	70
3,4-$(MeO)_2C_6H_3$	H	71	68
C_6H_4CH=CH	H	70	60
2-$MeOC_6H_3CH$=CH	H	78	70
Ph	Ph	0	80
-*o*-$CH_2C_6H_4CH_2CH_2$-		0	41

various alkenes with the difluorophenylsulfanylmethyl radical **156**, generated from **155** under three complementary procedures [(SmI_2/THF/*i*-PrOH), (Et_3B/*n*-Bu_3SnH/O_2) or (AIBN/*n*-Bu_3SnH/benzene)], gave low to moderate yields of the adducts **157** (Scheme 104). Oxidation with MCPBA of **157** to sulfoxides **158** (75−92% yields), followed by vacuum pyrolysis, gave the corresponding *gem*-difluoroalkenes **58** in high yields (68−81%).

A methodology has been developed for the conversion of carboxylic acids to 1,1-difluoroolefins **58** via α,α-difluorothioethers **161** (Scheme 105).[148] Oxidation of **161** with MCPBA afforded sulfoxides **162**, which by neat pyrolysis at 160−200 °C underwent β-elimination to afford alkyl 1,1-difluoroolefins **58** in good yields.

2.3.5.3. Miscellaneous β-Elimination-Based Reactions. Another β-elimination reaction that converts thioethers to 1,1-difluoroolefins has been reported. In this case, the reaction of 1,1-bis(phenylthio)perfluoroalkyl aromatics or alkanes **163** with a mixture of 2 equiv of $TiCl_4$ and 4 equiv of $LiAlH_4$ in THF at reflux temperature for 3 h afforded α-aryl(alkyl)-β,β-difluorovinyl sulfides **164** in good yields (Scheme 106).[149]

Dehydroiodination of the (difluoroiodomethyl)cyclopentane derivative **166** proceeded by simply treating with DBU to give the difluoromethylene compound **167** in 90% yield (Scheme 107).[150] The compound **166** was in turn obtained in 58% yield by iodocarbocyclization of 2-(5,5-difluoropent-4-enyl)malonate **165**, mediated by I_2, $SnCl_4$, and 2,6-lutidine.

Shi and Huang studied the fluoride-mediated nucleophilic reactivity toward aromatic aldehydes of the CF_2-containing reagent **171**, obtained according to Scheme 108.[151] The mixed malonate ester **168** was treated successively with sodium hydride and CF_2Br_2 to afford the product **169**, which was directly subjected to decarboxylative halide elimination to provide the difluoroacrylate **170** in 80% yield. DIBAL reduction of **170**, followed by acetylation completed the synthesis of **171**.

The reaction of 1,3-dichloro-4,4,4-trifluorobut-2-ene **172** with magnesium gave 2-chloro-1,1-difluorobuta-1,3-diene **173** in 34% yield (Scheme 109).[152] The reaction was postulated to proceed via 1,4-elimination of the allylic magnesium chloride **174** or 1,2-elimination of **175**, which is generated by 1,3-Mg migration of **174** due to the anion-stabilizing effect of the trifluoromethyl group.

When chlorodifluoromethyl ketones **176** were reacted with diazomethane, epoxides **177** were formed, which upon treatment with *n*-BuLi underwent ring-opening (via lithium halogen

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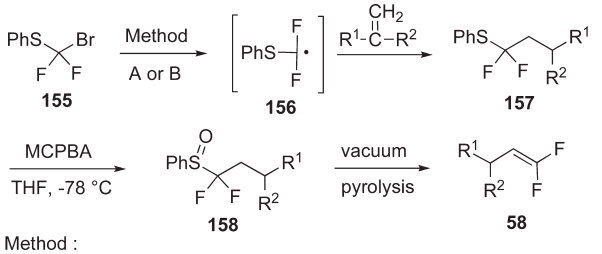
Scheme 104



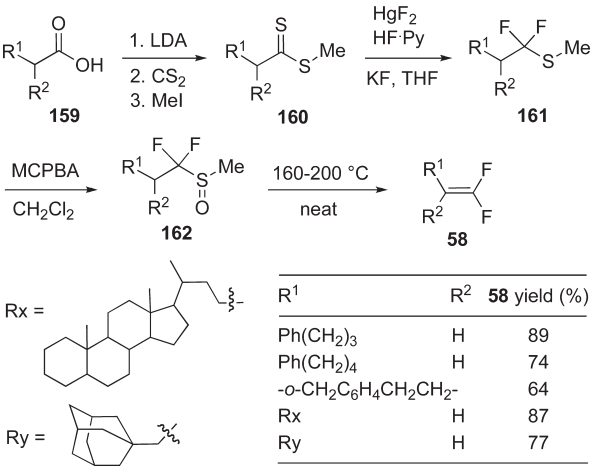
Method :

A: 1.5 equiv. SmI_2/THF/*i*-PrOH, 0 °C 20 min and then r.t., 2 h

B: 1.0 equiv. AIBN and 2.0 equiv. *n*-Bu_3SnH/benzene/reflux, 10 h

R^1	R^2	**157** yield (%)	**158** yield (%)	**58** yield (%)
Ph	H	53	92	81
$H_2C{=}CHCH_2O_2C$	Me	47	79	71
PhO_2S	H	49	77	68
$3,4\text{-}(MeO)_2C_6H_3CH_2$	H	12	75	80
$HO(CH_2)_8CH_2$	H	10	81	62

Scheme 105



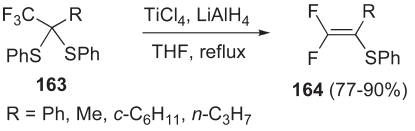
R^1	R^2	**58** yield (%)
$Ph(CH_2)_3$	H	89
$Ph(CH_2)_4$	H	74
$\text{-}o\text{-}CH_2C_6H_4CH_2CH_2\text{-}$		64
Rx	H	87
Ry	H	77

exchange) to afford in high yields *gem*-difluoroallylic alcohols **178** as suitable substrates for sigmatropic rearrangements (Scheme 110).[153] A similar approach was followed to obtain (3,3-difluoro-2-ethoxy)allylic alcohols **181** from the ethylacrylate derivative **179** (Scheme 110).[154]

2.3.6. Vinylmetal-Mediated Reactions. A general approach to *gem*-difluoroalkenes may be found in the reactions of difluorovinyl organometallic reagents with electrophiles.[155] Most reported difluorovinyl metals incorporate in the α-position electron-withdrawing groups such as aryl- or oxygen-containing groups, in order to enhance their thermal stability against the β-elimination of the metal fluoride (Figure 4). Few *gem*-difluorovinyl metals without a stabilizing substituent have been described. The unstable *gem*-difluorovinyl lithium ($CF_2{=}CHLi$) has been obtained by metalation with *s*-BuLi of 1,1-difluoroethylene at very low temperature (−110 °C), but its reaction with electrophiles was limited to carbonyl compounds.[155,156]

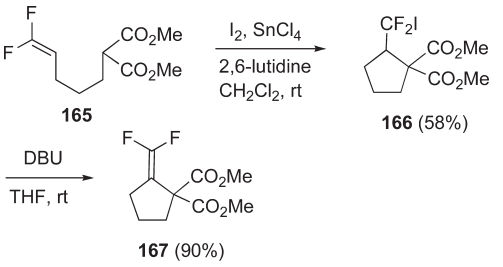
The use of the related stable zinc, boron, and copper reagents has shown to be of wider application. (2,2-Difluorovinyl)zinc(II)

Scheme 106

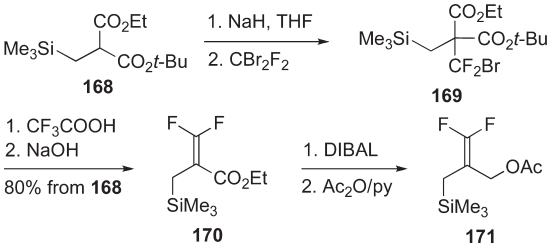


R = Ph, Me, *c*-C_6H_{11}, *n*-C_3H_7

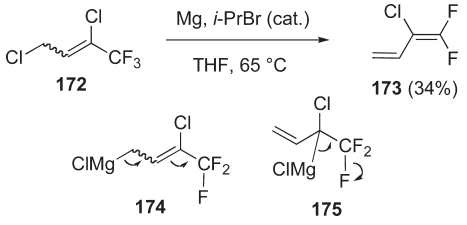
Scheme 107



Scheme 108



Scheme 109



chloride **183** was prepared by metalation of 1,1-difluoroethylene with *s*-BuLi at −110 °C to form a vinyl lithium intermediate, which undergoes exchange with $ZnCl_2$ at low temperature (Scheme 111). This stable zinc reagent readily couples with 2-iodopyridine in the presence of a catalytic amount of Pd-$(PPh_3)_4$ to afford 2-(2,2-difluorovinyl)pyridine **184** in 50% yield.[157]

An alternative and more convenient method to obtain a (2,2-difluoroethenyl)zinc reagent has been more recently described by Burton and Nguyen.[158] Treatment of 2,2-difluoroiodoethylene **185** with zinc at 50−60 °C in DMF afforded (2,2-difluorovinyl)zinc(II) iodide **186** in 60−80% yields after 1 h (Scheme 112). This zinc reagent was coupled with aryl iodides or bromides in the presence of $Pd(PPh_3)_4$ in DMF to give the corresponding 2,2-difluorostyrenes **187** in 48−92% yields.[158]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 110

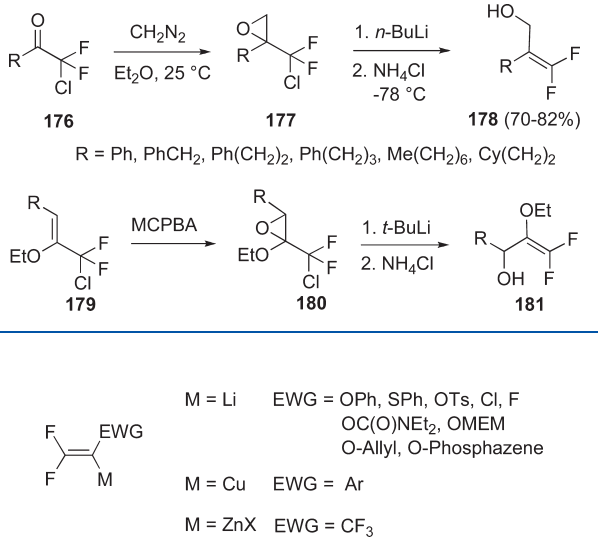


Figure 4

In a similar way, α-bromo-β,β-difluorostyrenes were prepared from $F_2C{=}CBrZnX$ (X = I, Br) and aryl iodides.[159]

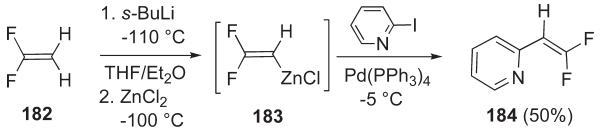
Ichikawa[160] developed a complementary procedure to a *gem*-difluorovinyl anion equivalent by a zirconium-mediated method from 2,2-difluorovinyl *p*-toluenesulfonate **190**,[161] readily obtained from 2,2,2-trifuoroethyl *p*-toluenesulfonate **189** (Scheme 113). Treatment of **190** with the zirconocene equivalent "Cp_2Zr" (prepared *in situ* from Cp_2ZrCl_2 and 2 equiv of *n*-BuLi) generated **192**, which in turn underwent palladium-catalyzed coupling with aryl iodides, via transmetalation with ZnI_2, leading to α-unsubstituted β,β-difluorostyrene derivatives in high yields.[162] Coupling reactions with alkenyl and alkynyl iodides also readily proceed to afford 1,1-difluoro-1,3-dienes and -1,3-enynes (Scheme 113).[160]

Two examples of nonstabilized *gem*-difluorovinyl metals are α-alkylated difluorovinyl boranes and coppers, which are described below.

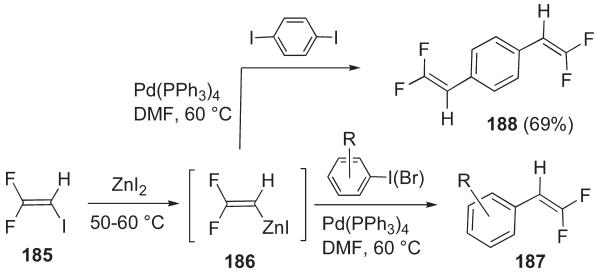
gem-Difluorovinyl metals with a stabilizing substituent in the α-position are easily obtainable from trifluoroethyl compounds,[163] which when treated with strong bases undergo dehydrofluorination via deprotonation of the proton on the carbon attached to the CF_3 group giving α-substituted *gem*-difluoroalkenes (such as, the alkene **190** from the tosylate **189**, Scheme 113).[160] In the presence of an excess amount of base, these difluoroalkenes afford *gem*-difluorovinyl lithium intermediates, which can be trapped by reactive electrophiles affording functionalized tetrasubstituted *gem*-difluoroalkenes (Scheme 114). It should be remarked that the stabilization of these alkenyl lithium reagents is important for an effective synthetic utilization. Some typical reactions of *gem*-difluorovinyl lithiums stabilized by oxygen- and phosphorus-containing groups with electrophiles are summarized in Scheme 115.[164−167]

A variety of 1-substituted 1-chloro(fluoro)-2,2-difluoroalkenes[168] have been synthesized by treatment of (1,2,2-trifluorovinyl)lithium and (1-chloro-2,2-difluorovinyl)lithium, generated from CF_3CH_2F and CF_3CH_2Cl by *n*-BuLi at −78 °C in Et_2O, with aldehydes,[168a,b] ketones,[168c] CO_2,[168d] I_2,[168d] Me_3SiCl,[168d] and main-group or transition metal halides (Bu_3SnCl, $HgCl_2$, $PtCl_2(PPh_3)_2$, etc.)[168e] (Scheme 116).

Scheme 111

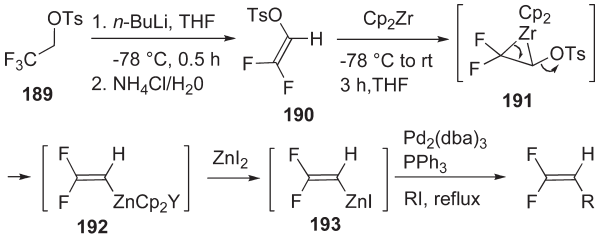


Scheme 112



R	**187** yield (%)	R	**187** yield (%)
H	81	3-NO_2	92
2-Me	71	4-NO_2	86
3-Me	78	2-F	69
4-Me	75	3-CF_3	62
3-OMe	88	4-CF_3	80
4-C(O)Me	78	Ph	81

Scheme 113



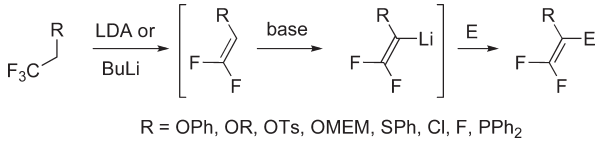
R	yield (%)	R	yield (%)
Ph	71	1-naphthyl	67
3-$O_2NC_6H_4$	81	3-*t*-$BuC_6H_4CH_2$	82
3-$EtO_2CC_6H_4$	80	PhCH=CH	85
3-$MeOCC_6H_4$	77	$Ph(CH_2)_2C{\equiv}C$	81

On the other hand, 1-aryl-substituted 1-fluoro-2,2-difluoroalkenes **195** were synthesized by Pd-catalyzed cross-coupling of bromo(iodo)benzenes **194** with (1,2,2-trifluorovinyl)zinc(II) bromide, derived from bromotrifluoroethylene (Scheme 117).[169] The analogue trifluoromethyl derivative **196** was obtained in a similar way from **194a** and $CF_2{=}C(CF_3)ZnBr$, generated by treatment of $CF_3CBr_2CF_3$ and zinc (Scheme 117).

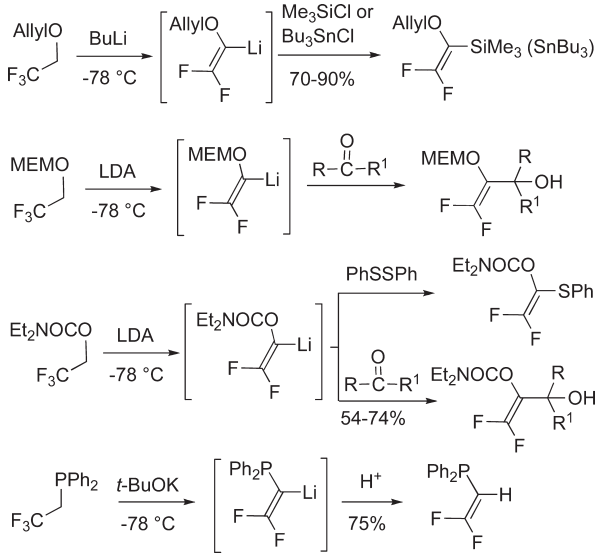
Since the reaction of the metalated enol carbamate **197** with alkyl halide electrophiles, including activated species, failed to result in carbon−carbon bond formations, Percy and co-workers developed a new procedure based on a transmetalation strategy (Scheme 118).[168b] Thus, the stable stannane **198** was initially

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 114



Scheme 115



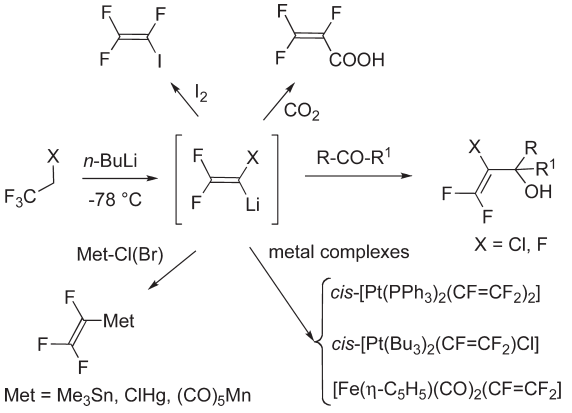
prepared by reaction of **197** with Bu_3SnCl. The addition at −78 °C of the CuI/2LiCl reagent to a solution of **198** (generated by tin−lithium exchange from stannane **198**) afforded the thermally stable vinyl copper reagent **199**, which was reacted with activated haloalkanes and acid chlorides to give in moderate to high yields products **200** and **201**, respectively.

2,2,2-Trifuoroethyl *p*-toluenesulfonate **189** merits particular attention, since it was converted into 2,2-alkenylboranes **203**, which are reactive and versatile building blocks for a wide range of difluoroalkenes. The treatment of **189** with *n*-BuLi at −78 °C generates the difluorovinyllithium tosylate **202**, which by reaction with trialkylboranes induces ate-complex formation and subsequent migration of the alkyl group from boron onto the vinylic carbon to afford **203** (Scheme 119).[171] Scheme 120 shows a selection of products that can be obtain from alkenylboranes **203**.[172]

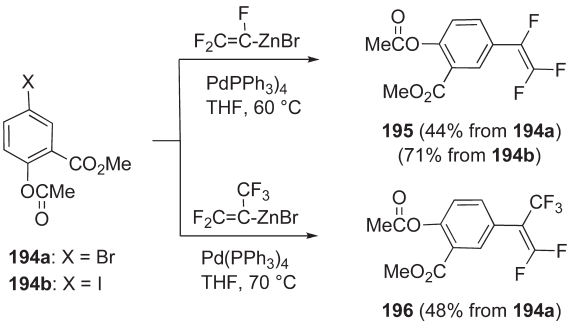
An interesting application of the difluorovinyl borane protocol has been recently developed by Ichikawa and co-workers in order to obtain helicenes **206** (Scheme 121).[101] The key intermediate, symmetrical 1,1-difluoroalkenes **205**, was synthesized in a one-pot operation from tosylate **189** and trialkyl boranes. Thus, the tosylate **189** was reacted with *n*-BuLi and then with trialkyl boranes to give vinyl boranes **204** (according to Scheme 119), which by treatment with $NaOCH_3$ and then with Br_2 underwent the second 1,2-migration of a β-alkyl group to yield symmetrically disubstituted 1,1-difluoro-1-alkenes in good yields (41−75%).

2.3.7. Brook-type Rearrangement. Trifluoromethyl ketones can originate 2,2-difluoroenol silyl ethers through the Brook-type rearrangement,[173] which involves the migration of

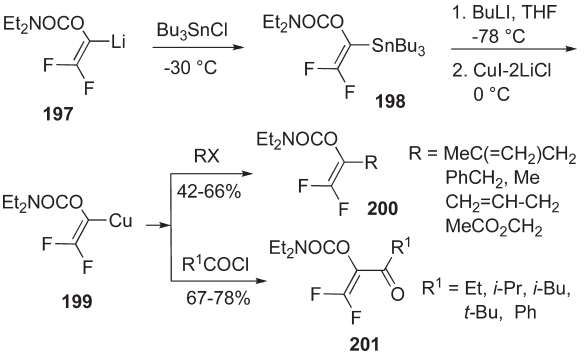
Scheme 116



Scheme 117



Scheme 118

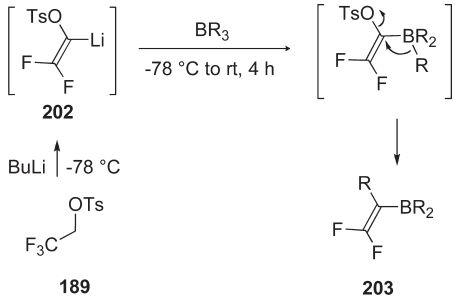


organosilyl groups from carbon to oxygen atoms (Scheme 122). This transposition is favored by the increased bond strength of the Si−O bond (110 kcal/mol) compared with the Si−C bond (76 kcal/mol).

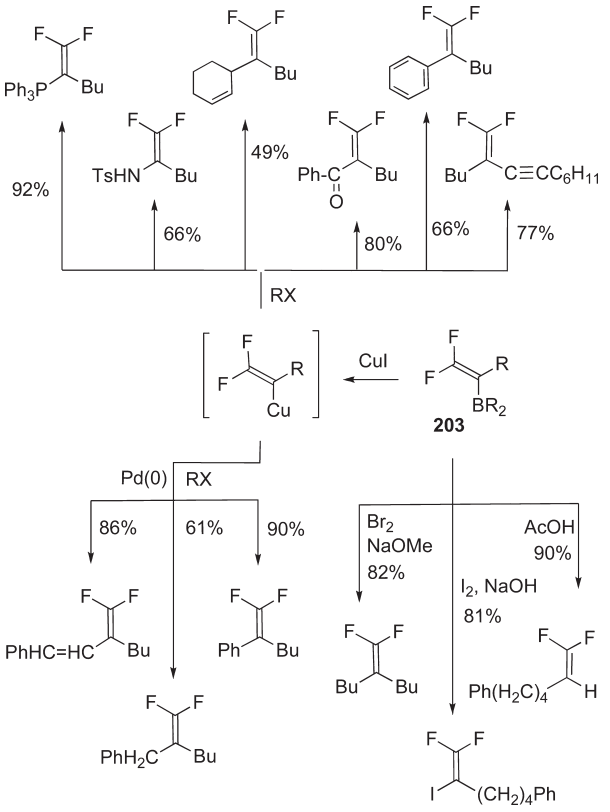
When trifluoromethyl ketones **95** are treated with trialkylsilyl anions,[174a,175] the intermediate α-silyl-α-trifluoromethylalkoxylates **207** are formed (Scheme 122). These intermediates undergo the Brook-type rearrangement with concomitant desilylative defluorination to generate 2,2-difluoroenol silyl ethers **208**. Alternatively, intermediates **207** can be obtained by reaction of acyl silanes **209** with CF_3SiMe_3[176] or trifluoroacetyl silanes **210**

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 119



Scheme 120

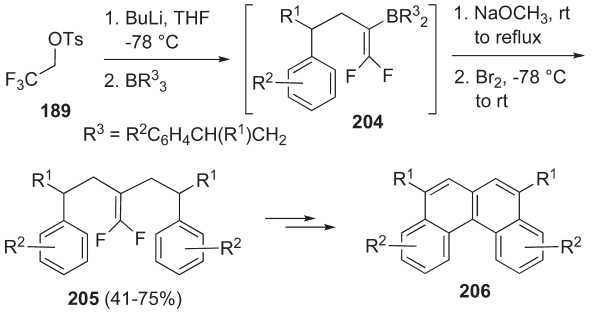


with alkyl metals[174] (Scheme 122). Examples of these transformations are given in Scheme 123.[174−177] 2,2-Difluoroenol silyl ethers obtained by reaction of acylsilanes with CF_3SiMe_3 were utilized by Portella and co-workers in the synthesis of difluorinated monoterpenes such as difluoroegomaketone,[177] difluorodehydro-*ar*-curcumene,[178] difluoro-*ar*-tumerone[178] and *gem*-difluoro-*C*-disaccharides.[179]

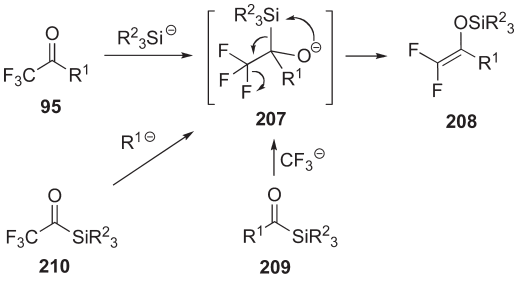
2.4. Synthesis of 1,1-Diiodo-1-alkenes

2.4.1. Wittig-type Reactions. Aldehydes have been converted into the related 1,1-diiodoalkenes in good yields by adding them to a CH_2Cl_2 solution of the reagent formed from tetraiodomethane and triphenylphosphine (Scheme 124).[180] On the other hand, ketones were unable to react with this reagent. The reactivity of aldehydes toward CI_4/PPh_3 depended on the nature of the substituent. Thus, substituents with electron-withdrawing

Scheme 121



Scheme 122



groups clearly activate the reaction, while the reverse was found with electron-donating ones. The presence of a phenolic group on the starting material stopped the reaction by preventing the formation of the ylide, while a hydroxy group on an aliphatic aldehyde was first converted into the related iodo derivative and then the aldehyde functionality underwent diiodomethylenation ($HOCH_2(CH_2)_7CHO \rightarrow ICH_2(CH_2)_7CHO \rightarrow ICH_2(CH_2)_7CH{=}CI_2$).

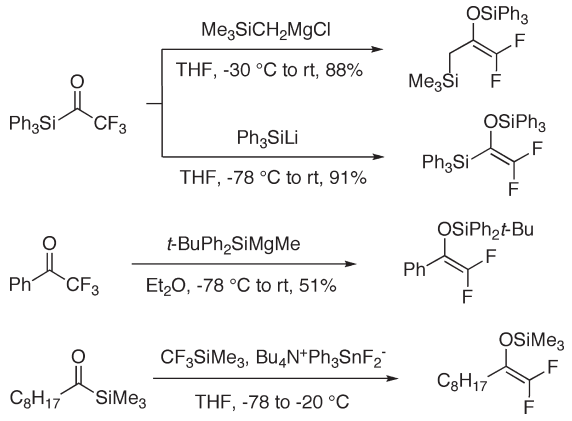
Recently, in a study aimed to stereoselectively synthesize (*Z*)-1-iodo-1-alkenes, seven 1,1-diiodoalkenes were prepared from the corresponding aldehydes following this procedure.[181] Some of them are described in Figure 5.

Straightforward access to *gem*-diiodovinyl systems consists in the reaction of aldehydes with the ylide $Ph_3P{=}CI_2$ produced by reaction of CHI_3 and PPh_3 in the presence of KO*t*-Bu (Scheme 125).[182] By this method, 4-(2,2-diiodovinyl)-*N*,*N*-dimethylaniline, not obtained when the ylide $Ph_3P{=}CI_2$ was generated from CI_4 and PPh_3,[180] was prepared in 80% yield. It was also possible to not isolate these diidoalkenes but to directly convert them into the related 1-iodoalkynes in good yields by treatment with KO*t*-Bu at −78 °C.

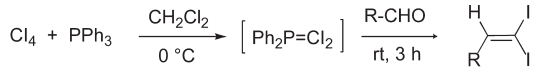
Duhamel and co-workers reported an efficient and general synthesis of a number of 1,1-diiodoalkenes by condensation of carbonyl compounds with diethyl diiodomethylphosphonate prepared *in situ* from (i) diethyl iodomethylphosphonate and KHDMS (method A) or LiHDMS (method B) and (ii) diethyl methylphosphonate and LiHDMS (method C) (Scheme 126).[183] As deduced from Scheme 126, methods A and B gave successful results starting from aldehydes as well as aliphatic, aromatic, and functionalized ketones. On the other hand, the method C presented some limitations, giving in all cases lower yields. Method B was later used to synthesize in excellent yield (88%) ethyl 3,3-diiodo-2-phenylprop-2-enoate from ethyl 2-oxo-2-phenylethanoate (Scheme 127).[184]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 123



Scheme 124



R	yield (%)	R	yield (%)
n-Bu	75%	3,4-(-OCH_2O-)C_6H_3	60%
Ph	87%	3,4-$(HO)_2C_6H_3$	0
4-ClC_6H_4	80%	PhCH=CH	70%
4-$O_2NC_6H_4$	98%	4-$(OHC)C_6H_4$	98%
4-$Me_2NC_6H_4$	0	*n*-C_8H_{17}	70%
3,4-$(MeO)_2C_6H_3$	72%	$HOCH_2(CH_2)_7$	68%
3-MeO-4-HOC_6H_3	52%		

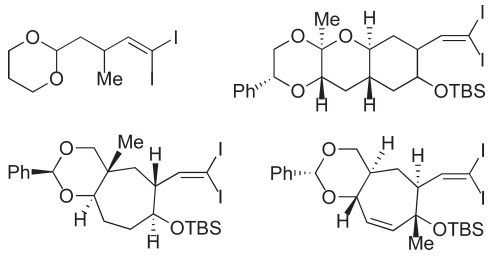


Figure 5

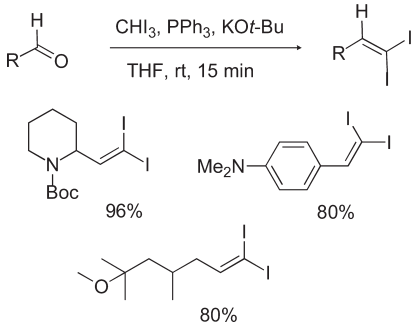
Charette and Cloarek,[185] in a study aimed to synthesize the *gem*-diiodoalkanes, prepared a wide range of 1,1-diiodoalkenes from aldehydes following five protocols or their modifications: A,[180] B,[182] C,[183] D,[183] and E[183] (Scheme 128). Protocol D, involving the use of preformed diiodomethyldiethylphosphonate,[183] was particularly useful for the synthesis of sensitive α-aryl *gem*-diiodoalkenes, which were unstable toward the conversion into iodinated triple bonds under protocols B and C.

2.4.2. Addition Reactions. Several 1,1-diiodoalkenes containing a functional group in the 2-position were prepared from 1-iodoacetylenes.[186,187] When iodophenylacetylene was stirred with iodine and I_2O_5 in MeOH for 34 h at room temperature, 2,2-diiodo-1-methoxyvinylbenzene was formed in 41% yield (Scheme 129).[186] The active species in this oxidation were oxides of iodine in combination with molecular iodine leading to iodonium-like species, which could attack the triple bond to form vinyl cations, captured subsequently by the solvent.

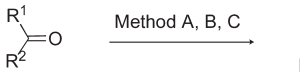
On the other hand, exploiting the fact that the reagent bis(pyridine)iodine(I) tetrafluoroborate adds I^+Nu^- to internal acetylenes,[187] Barluenga and co-workers were able to obtain a number of 2-substituted 1,1-diiodoalkenes in good yields when this iodinate reagent was reacted with 1-iodoacetylenes and a wide variety of nucleophiles (Scheme 130).[188]

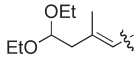
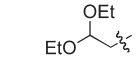
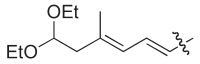
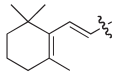
McNelis and co-workers reported that when 4-iodo-2-phenylbut-3-yn-2-ol was treated with stoichiometric amounts of iodine and iodic acid in refluxing methanol, 4,4-diiodo-3-phenylbut-3-en-2-one

Scheme 125



Scheme 126



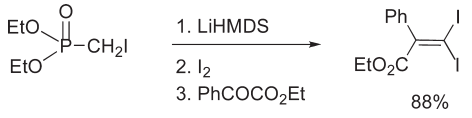
R^1	R^2	method	yield (%)
H	C_5H_{11}	B	71
H	C_6H_{13}	A	60
H		A	60
		B	70
H	2-thienyl	A	78
-$(CH_2)_5$-		A	74
Me		C	63
		B	84
Me		A	40
Me		A	70
		C	53
Me	Ph	B	64
Ph	Ph	B	51
Me	Me_2CHCH_2	B	89

Method: A = **y**, KHMDS (0.5 equiv), THF, -70 °C, 2 h, then carbonyl compound (0.4 equiv), THF, -70 to 0 °C.
B = **y**, LiHMDS (2 equiv), I_2 (1 equiv), THF, -0 °C, 30 min, then carbonyl, compound (1 equiv), THF, -70 °C to rt
C = **z**, HMDS (2 equiv), BuLi (3 equiv), THF, -0 °C, 30 min then I_2 (2 equiv), THF, -70 °C, 90 min, finally carbonyl compound (2 equiv), THF, -70 °C to rt

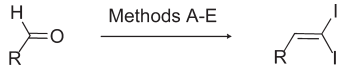
x: $(EtO)_2P(O)CHI_2$, **y**: $(EtO)_2P(O)CH_2I$, **z**: $(EtO)_2P(O)CH_3$

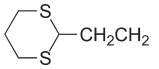
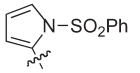
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 127



Scheme 128



R	method	R	method
n-C_6H_{13}	C	$PivO(CH_2)_4$	B
$Ph(CH_2)_2$	C	$TIPSO(CH_2)_4$	C
c-C_6H_{11}	C	Ph	D
$BnO(CH_2)_2CMe_2$	C	4-ClC_6H_4	D
$BnO(CH_2)_3$	A, B, C, E	thienyl	D
$BzHNCH_2$	B	$I(CH_2)_3$	F
$Cl(CH_2)_4$	C	$O_2N(CH_2)_2CMe_2$	B
p-$TolO_2S(CH_2)_2$	C		B
$EtO_2C(CH_2)_4$	B		
$NC(CH_2)_4$	F		
	C, E	$HO(CH_2)_4$	F
			D

Method:
A = CI_4, Ph_3, CH_2Cl_2, r.t., 2.5 h (87%).
B = CHI_3, Ph_3, KO*t*-Bu, PhMe, -20 °C, 10-30 min (37-69%).
C = $(EtO)_2P(O)CH_2I$, I_2, LiHMDS, THF, -78 °C, 10 min, (33-79%).
D = $(EtO)_2P(O)CHI_2$, LiHMDS, THF, -78 °C, 10 min (62-87%).
E = $(EtO)_2P(O)CH_3$, I_2, LiHMDS, THF, -78 °C, 10 min (46%).
F = Multistep routes

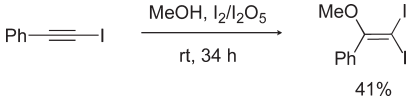
was formed in 75% yield via phenyl shift of a vinyl cationic intermediate (Scheme 131).[189]

2.4.3. Substitution Reactions. Two successful cases of 1,1-diiodoalkene preparation making use of a bromine−iodine exchange reaction have been described.[190] Thus, when hexamethylphosphoramide solutions of (2,2-dibromovinyl)cyclohexane or (dibromomethylene)cyclohexane were heated at 120 °C in the presence of the couple KI/CuI, the related *gem*-diiodoalkenes were obtained in 84% and 74% yield, respectively (Scheme 132). However, with *gem*-dibromoalkenes bearing a hydrogen atom on the double bond, the halogen exchange could be followed by loss of hydrogen halide and coupling of the resulting haloacetylene to a diacetylene. This reaction occurred quite readily when the double bond was conjugated with a phenyl group so that the related diiodo derivative was not obtained.

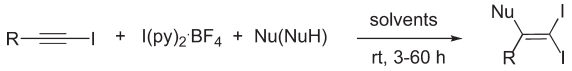
A single example of iododeboronation has been reported.[191] Thus, when bis(trimethylenedioxyboryl)methylenecyclohexane, obtained by treatment of cyclohexanone with lithium tri(trimethylenedioxyboryl)methide, was reacted with aqueous NaOH and then with I_2, (diiodomethylene)cyclohexane was formed in 71% yield (Scheme 133).

Two examples of preparation of *gem*-diiodoalkenes from alkenes were reported. Reaction of ICl in pyridine with vinylic dimercuriales **27** and **30**, prepared from longifolene and camphene (Scheme 25), afforded in very high yields the diiodo derivatives **211** and **212**, respectively (Scheme 134).[45]

Scheme 129



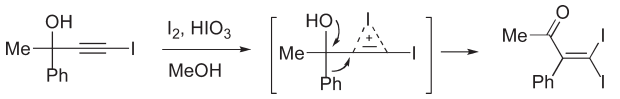
Scheme 130



Nu = $ClSiMe_3$, Br^-, I^-, NCS^-, pyridine, MeCOOH, HCOOH, *i*-PrOH anisole, PhSH

R	Nu	yield (%)	R	Nu	yield (%)
Ph	Cl	65	Ph	Br	65
Ph	NCS	75	Ph	pyridyl	57
H	HC(O)O	87	Ph	*i*-PrO	80
Ph	4-$MeOC_6H_4$	50	Ph	PhS	80
n-Bu	I	70	*n*-Bu	MeC(O)O	63

Scheme 131



A variety of *gem*-diiodides have been prepared from the related stannylacetylenes (Scheme 135). These compounds by treatment with 1.4 equiv of $Cp_2Zr(H)Cl$ generated the related 1,1-heterobimetallic species of tin and zirconium, which by iodonolysis with 2.15 equiv of I_2 in THF at room temperature gave the related diiodoakenes in 63−87% yields.[47]

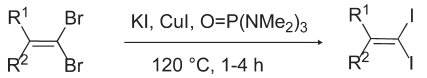
2.5. Synthesis of Mixed 1,1-Dihalo-1-alkenes

2.5.1. 1-Fluoro-1-bromo(chloro, iodo)-1-alkenes. 1-Fluorovinyl bromides or chlorides are readily available as mixtures of *E* and *Z* isomers by condensation of aldehydes and ketones with bromofluoromethylene and chlorofluoromethylene ylides (Ph_3P=CBrF and Ph_3P=CClF). Since an excellent review covers the literature on this field until 1996,[87b] only a quick guide on these ylides is given below. The ylide Ph_3P=CBrF can be generated from (i) CBr_3F and PPh_3 or (ii) (dibromofluoromethyl)triphenylphosphonium bromide by using PPh_3 or metals such as Zn, Zn(Cu), Hg, and Cd. The yields of bromofluoromethylene olefins were good with aromatic aldehydes and activated ketones but were often poor with aliphatic aldehydes, nonactivated ketones, and cyclic ketones.

A number of procedures have been developed for the generation of the ylide Ph_3P=CClF. These procedures can be classified according to the starting material and the method used to form the ylide: (i) $CHCl_2F$, PPh_3, and KO*t*-Bu; (ii) CCl_2FCO_2Me, PPh_3, and NaOMe; (iii) $PhHgCCl_2F$ and PPh_3; (iv) CCl_2FCO_2Na, and PPh_3; (v) $(Me_2N)_3P(Cl)CCl_2F$ and PPh_3 or $P(NMe_2)_3$; (vi) CCl_3F, PPh_3, and Zn; (vii) $(Me_2N)_3P(Cl)CCl_2F$, and Zn(Cu). In general, methodologies v, vi, and vii provide the best entry to chlorofluoromethylene olefins, whereas for cyclic ketone derivatives the organomercurial route iii appears to be the best one.

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 132



R^1	R^2	yield (%)
c-C_6H_{11}	H	84
Ph	H	0
-$(CH_2)_5$-		74

Scheme 133

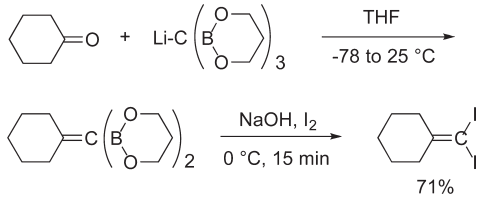
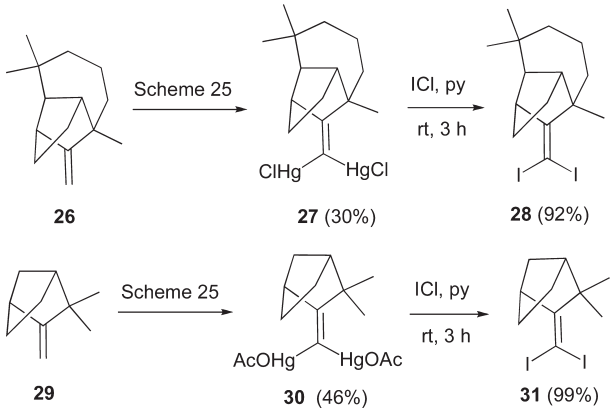


Table 1 shows the results obtained with these methods in the bromo- and chlorofluoromethylenation of benzaldehyde, trifluoromethylacetophenone, acetophenone, and cyclopentanone, taken as leading representatives of aromatic aldehydes, and activated, nonactivated, and cyclic ketones, respectively.[87b]

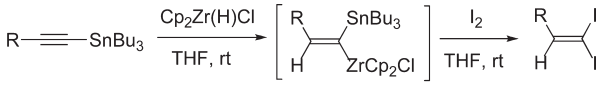
Pannecoucke and co-workers reported that diethylzinc could be used instead of Zn excess in the Wittig reaction. Diethylzinc acts as a debrominating agent on the phosphonium salt derived from CBr_3F and PPh_3 thus generating the reacting ylide ($Ph_3P(Br)CBr_2F + Et_2Zn \rightarrow Ph_3P{=}CBrF$).[192] Thus, under optimized conditions ($Et_2Zn/CBr_3F/PPh_3$ = 1.2/1.2/1.2; room temperature, 3 h) various aldehydes were converted to the related bromofluoroolefins in high yields, though the stereoselectivity never exceeded 70:30 (Scheme 136). The application of this protocol to aromatic and aliphatic ketones gave bromofluoroalkenes often in moderate to good yields but failed with easily enolizable substrates such as 2-oxocyclopentanecarboxylamide (Scheme 137). In these particular cases, the α-hydrogen is probably too acidic, and the ylide reacts first with it, instead of adding to the carbonyl group.

Highly stereoselective synthesis of (*E*)-bromodifluoro olefins **215** (*E*/*Z* > 10:1) was achieved in good yields via dehydrobromination of $RCHFCBr_2F$ **214** with lithium tetramethylpiperidide (LTMP) at −78 °C, whereas opposite selectivity (up to *E*/*Z* = 1/6.9) was obtained with other bases such as DBU or *n*-$Bu_4N(OH)$ (Scheme 138).[193] (*E*)-selectivity with LTMP was assumed to proceed via the transition state **219** involving a Li−F chelate, whereas elimination of HBr occurred with *n*-$Bu_4N(OH)$ from the transition state **220** wherein dipole−dipole repulsion of C−F bonds plays an important role. On the other hand, monofluoro olefins **217** were synthesized selectively by treatment of acetates **216** with a reagent consisting of EtMgBr and *i*-Pr_2NH (Scheme 138). (*E*)-Isomers **217** were predominantly obtained with aryl substrates **216**, whereas the alkyl substrate **216f** afforded the (*Z*)-isomer **217f** as the major product (*Z*/*E* = 2/1). The *Z*/*E* ratio of **217f** was improved up to 16/1 when the corresponding tosylate **218f** was reacted with Et_2Mg. The starting alcohols **213**, prepared by the reaction of $LiCBr_2F$ with aldehydes, were easily converted into

Scheme 134



Scheme 135



R	yield (%)	R	yield (%)
Ph	87%	$ClCH_2(CH_2)_2$	77%
n-C_4H_9	78%	$HOCH_2$	72%
n-C_6H_{13}	84%	cyclohexenyl	63%
$BnOCH_2$	84%		

substrates **214**, **216**, and **218** by fluorination, acetylation, or tosylation, respectively.

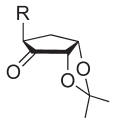
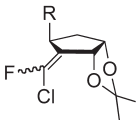
Eddarir and co-workers reported the synthesis of (*Z*)-1-bromo-1-fluoro-1-arylethylenes from (*Z*)-1-carboxyl-1-fluoro-2-arylethenes by addition of bromine followed by elimination (Scheme 139).[194,195] Bromination of the double bond was stereoselective, except for **221i** and **221j** that afforded, after stereospecific elimination, mixtures of diastereoisomers (*E*/*Z*). Attempts to prepare (*E*)-**217g** from (*E*)-**221a** failed because the bromination step was not selective.

Wnuk and Andrei[196] prepared a number of terminal dihaloalkenes **225**−**227** in high yields exploiting both the McCarthy's procedure for the stereospecific synthesis of 1-fluoroolefins[197] and the halodestannylation.[198] The global procedure involves (i) condensation of carbonyl compounds with the anion of diethyl fluoro(phenylsulfonyl)methylphosphonate to give (α-fluoro)-vinyl sulfones **223**, (ii) radical stannyldesulfonylation with Bu_3SnH/AIBN to yield (α-fluoro)vinyl stannanes **224**, and (iii) the halodestannylation with NIS, NBS, or Cl_2 to give 1-fluoro-1-iodoalkenes **225**, 1-fluoro-1-bromoalkenes **226**, or 1-fluoro-1-chloroalkene **227**, respectively (Scheme 140).

Shastin and co-workers proposed a new reaction for the conversion of N-unsubstituted hydrazones of carbonyl compounds to the related 1-bromo-1-fluoroalkenes by treatment with CBr_3F in the presence of catalytic amount of CuCl (Scheme 141).[199] Under optimal reaction conditions, the one-pot conversion of a number aromatic aldehydes containing electron-donating and electron-withdrawing groups into 1-bromo-1-fluorostyrenes was investigated. They found that reaction products could be prepared in good yields (48−95%) and

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Table 1. Preparation of Bromo(chloro)fluoroalkenes

substrate	PR_3	carbene source	base or metal	solvent	temp. (°C)	product	yield (%)	*Z*/*E*
PhCHO	PPh_3	CBr_3F	--	triglyme	70	PhCH=CBrF	64	54:46
PhCHO	PPh_3	$Ph_3P(Br)CBr_2F$	--	THF	70	PhCH=CBrF	70	55:45
PhCHO	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	PhCH=CBrF	64	55:45
$PhC(O)CH_3$	PPh_3	CBr_3F	--	triglyme	70	$PhC(CH_3)$=CBrF	18	53:47
$PhC(O)CH_3$	PPh_3	$Ph_3P(Br)CBr_2F$	--	THF	70	$PhC(CH_3)$=CBrF	45	46:54
$PhC(O)CH_3$	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	$PhC(CH_3)$=CBrF	55	51:49
$PhC(O)CF_3$	PPh_3	CBr_3F	--	CH_3CN	rt	$PhC(CF_3)$=CBrF	92	58:42
$PhC(O)CF_3$	PPh_3	$Ph_3P(Br)CBr_2F$	--	CH_3CN	rt	$PhC(CF_3)$=CBrF	97	56:44
$PhC(O)CF_3$	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	$PhC(CF_3)$=CBrF	86	52:48
c-C_6H_{10}=O	--	$Ph_3P(Br)CBr_2F$	Zn	triglyme	rt	*c*-C_6H_{10}=CBrF	18	--
PhCHO	PPh_3	$CCl_2FCO_2CH_3$	NaOMe	petr. ether	80	PhCH=CClF	40	--
PhCHO	PPh_3	$CHCl_2F$	KO*t*-Bu	heptane	0	PhCH=CClF	39	56:44
PhCHO	PPh_3	CCl_2FCO_2Na	--	triglyme	90	PhCH=CClF	49	56:44
PhCHO	PPh_3	$(Me_2N)_3P(Cl)CCl_2F$	--	PhCN	100	PhCH=CClF	60	56:44
PhCHO	PPh_3	CCl_3F	Zn	DMF	60	PhCH=CClF	64	52:48
PhCHO	--	$(Me_2N)_3P(Cl)CCl_2F$	Zn(Cu)	THF	60	PhCH=CClF	100	48:52
$PhC(O)CH_3$	PPh_3	$CCl_2FCO_2CH_3$	NaOMe	petr. ether	80	$PhC(CH_3)$=CClF	8	--
$PhC(O)CH_3$	$P(NMe_2)_3$	$(Me_2N)_3P(Cl)CCl_2F$	--	PhCN	55	$PhC(CH_3)$=CClF	56	52:48
$PhC(O)CH_3$	PPh_3	CCl_3F	Zn	DMF	60	$PhC(CH_3)$=CClF	17	43:57
$PhC(O)CH_3$	--	$(Me_2N)_3P(Cl)CCl_2F$	Zn(Cu)	THF	60	$PhC(CH_3)$=CClF	70	48:52
$PhC(O)CF_3$	PPh_3	$CCl_2FCO_2CH_3$	NaOMe	petr. ether	80	$PhC(CF_3)$=CClF	40	48:52
$PhC(O)CF_3$	PPh_3	$CHCl_2F$	KO*t*-Bu	heptane	0	$PhC(CF_3)$=CClF	31	56:44
$PhC(O)CF_3$	PPh_3	CCl_2FCO_2Na	--	triglyme	90	$PhC(CF_3)$=CClF	56	47:53
$PhC(O)CF_3$	PPh_3	$(Me_2N)_3P(Cl)CCl_2F$	--	THF	60	$PhC(CF_3)$=CClF	0	--
$PhC(O)CF_3$	PPh_3	CCl_3F	--	DMF	60	$PhC(CF_3)$=CClF	53	--
$PhC(O)CF_3$	--	$(Me_2N)_3P(Cl)CCl_2F$	--	DMF	60	$PhC(CF_3)$=CClF	100	48:52
c-C_5H_8=O	PPh_3	$CHCl_2F$	KO*t*-Bu	heptane	0	*c*-C_5H_8=CClF	27	--
c-C_5H_8=O	PPh_3	CCl_2FCO_2Na	--	triglyme	90	*c*-C_5H_8=CClF	9	--
c-C_5H_8=O	PPh_3	CCl_3F	Zn	DMF	60	*c*-C_5H_8=CClF	4	--
c-C_5H_8=O	--	$(Me_2N)_3P(Cl)CCl_2F$	Zn(Cu)	THF	60	*c*-C_5H_8=CClF	18	--
	PPh_3	$PhHgCCl_2F$	Zn(Cu)	benzene	80		82	--

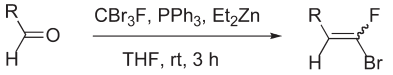
stereoselectivities with the most unhindered (*E*)-isomer prevailing.

2.5.2. 1-Chloro-1-bromo(iodo)-1-alkenes. Zweifel and co-workers found that mixed 1,1-dihaloalkenes can be prepared from 1-chloro-1-alkynes **228** (Scheme 142).[200] Thus, [(*E*)-1-chloro-1-alkenyl]alanates **229**, prepared by the highly stereo- and regioselective *trans* addition the Al−H moiety of $LiAlH_4$ to the triple bond of the related alkynes, were converted by reaction with acetone into the related triisopropoxyalumino derivatives **230**, which were not isolated, but by treatment with Br_2 at −78 °C afforded (*Z*)-1-bromo-1-chloroalkenes **231** in >97% isomeric purity and in good yields (61−87%). Alternatively, treatment of **230** with ICl at −30 °C afforded (*Z*)-1-iodo-1-chloroalkenes **232** in high yields (85−89%).

An alternative way to obtain (*Z*)-1-bromo-1-chloroalkenes **231** from the same precursor 1-chloro-1-alkynes **228**, via a hydoboration, bromination, and elimination sequence was later reported by the same author (Scheme 143).[201] Thus, when alkynes **228a**−**c** were submitted to hydroboration followed by oxidation, they gave boronic esters **233a**−**c**, which were treated sequentially with Br_2 and NaOMe/MeOH to give (*Z*)-**231a**−**c** in good yields (64−73%) and in high isomeric purities (97−98%). On the other hand, (*E*)-isomers of **231** were obtained from the 1-halo-1-vinylsilanes **236**[38] and **237**,[38] which by *trans*-halogenation (Br_2 or Cl_2) and *anti*-desilicohalogenation

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

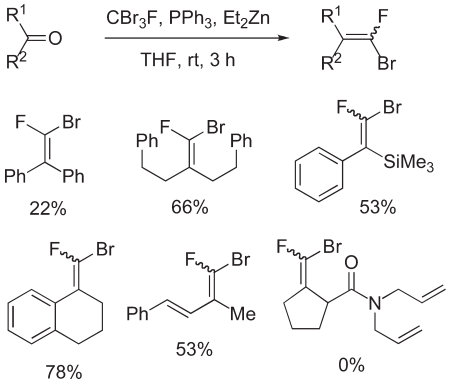
Scheme 136



R[a]	yield (%)	*E*/*Z*
$PhCH_2CH_2$	88	1/1.05
$TBDPSOCH_2CH_2$	90	1/0.88
$4\text{-}O_2NC_6H_4$	85	1/0.73
$4\text{-}MeOC_6H_4$	94	1/1.03
$4\text{-}FC_6H_4$	73	1/0.96

[a]Only representative examples are reported.

Scheme 137



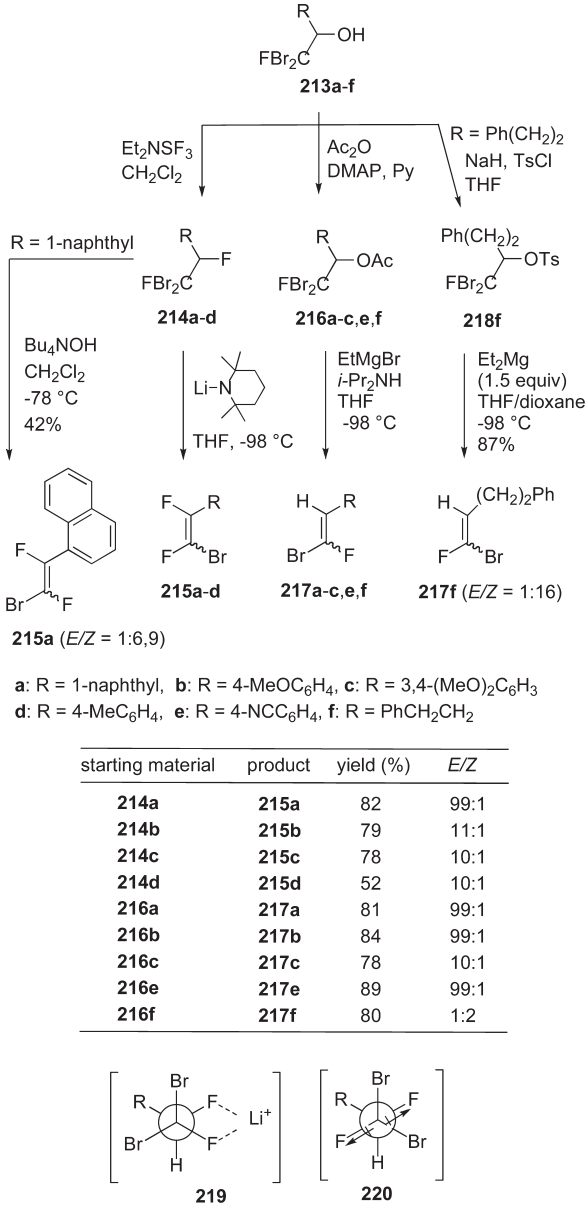
(NaOMe/MeOH) afforded (*E*)-**231a**−**d** in good yields (69−96%). The isomeric purities were better than 98% but were reduced with the increasing of the size of the alkyl substituent in **236** and **237** (57−73% with R = *t*-Bu and 91−95% with R = *c*-C_6H_{11}).

Barluenga and co-workers reported the electrophilic addition of bis(pyridine)iodine(I) tetrafluoroborate to 1-chloroacetylenes in the presence of 2 equiv of HBF_4 and different nucleophiles. This system added I^+Nu^- to 1-chloroacetylenes to give in good yields 2-functionalized 1-chloro-1-iodoalkenes **238** as single stereoisomers, except when NaI was used as the nucleophile for 1-chloro-2-phenylethyne, from which a mixture of stereoisomeric products was obtained (Scheme 144).[202]

1-Bromo-1-chloroalkenes were prepared from aliphatic ketones by Normant, following the same procedure employed to obtain *gem*-dibromoalkenes (Scheme 17), by replacing $LiCBr_3$ with $LiCBr_2Cl$ (Scheme 145).[35] In the first step, $LiCBr_2Cl$ was added to dodecan-6-one or cyclopentanone at −100 °C, followed by $BF_3 \cdot OEt_2$. Then, the formed alcohols **239** were converted to the related esters by treatment with prop-1-en-2-yl ethanoate to give the trihaloesters **240**, which were finally transformed into the desired alkenes **241** by treatment with ethylmagnesium bromide.

Linstrumelle and co-workers reported that (*E*)-chloroenynes **242**, easily obtainable in high stereoisomeric purity (≥99.9%) by reaction of 1-alkynes with (*E*)-1,2-dichloroethylenes,[203] were efficient precursors of mixed 1,1-dihaloenynes.[204] Thus, metalation of **242** with *n*-BuLi (1 equiv) at −100 °C generated α-chloroenyne lithium intermediates, which when treated at the same temperature with iodine or NBS afforded stereospecifically (*Z*)-1-chloro-1-bromo(iodo)enynes **243** in good yields (60−84%) (Scheme 146).

Scheme 138



a: R = 1-naphthyl, **b**: R = $4\text{-}MeOC_6H_4$, **c**: R = $3,4\text{-}(MeO)_2C_6H_3$
d: R = $4\text{-}MeC_6H_4$, **e**: R = $4\text{-}NCC_6H_4$, **f**: R = $PhCH_2CH_2$

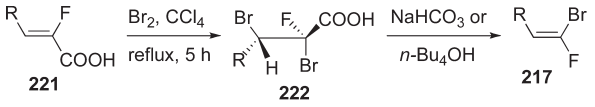
starting material	product	yield (%)	*E*/*Z*
214a	**215a**	82	99:1
214b	**215b**	79	11:1
214c	**215c**	78	10:1
214d	**215d**	52	10:1
216a	**217a**	81	99:1
216b	**217b**	84	99:1
216c	**217c**	78	10:1
216e	**217e**	89	99:1
216f	**217f**	80	1:2

Bromochloroalkenes were prepared with high geometrical purities by chlorination with $CClF_2CClF_2$ of (1-bromoalkenyl)lithiums, generated by slow addition at −95 °C of *n*-BuLi to THF solutions of a variety of dibromoalkenes (Scheme 147).[205] Under these reaction conditions, the (1-bromoalkenyl)lithium intermediate underwent a rapid geometrical isomerization by a mechanism involving Br/Li exchange, to give stereoselectively the thermodynamically favorable isomer.

2.5.3. 1-Bromo-1-iodo-1-alkenes. Barluenga and co-workers reported that the reaction of 1-bromo-1-alkynes with bis(pyridine)iodine(I) tetrafluoroborate in the presence of different nucleophiles and 2 equiv of tetrafluoroboric acid yielded 2-functionalized 1-bromo-1-iodoalkenes in high yields (Scheme 148).[206] These compounds were obtained as single stereoisomers, except

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

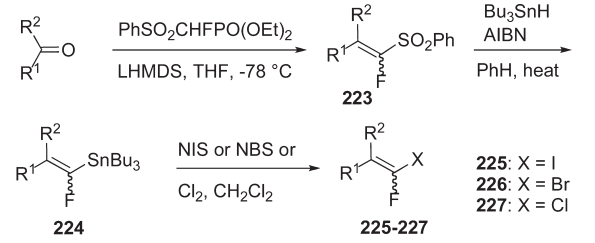
Scheme 139



	R	222 yield (%)	217 yield (%)
b	$MeOC_6H_4$	93	70[a]
g	Ph	84	82
h	$4\text{-}ClC_6H_4$	88	59
i	$4\text{-}O_2NC_6H_4$	82	83
j	$n\text{-}C_5H_{11}$	72	60[b]

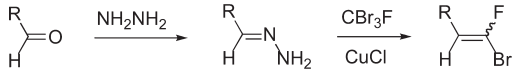
[a] *Z*/*E* = 63/27, [b] *Z*/*E* = 86/14

Scheme 140



	R^1	R^2	**224** *E*/*Z*	**225** yield (%) (*E*/*Z*)	**226** yield (%) (*E*/*Z*)	**227** yield (%) (*E*/*Z*)
a	Ph	H	95/25	95 (95/5)	97 (93/7)	70 (93/7)
b	$PhCH_2CH_2$	H	78/22	94 (78/22)	--	--
c	$PhCH_2OCH_2$	H	77/23	92 (67/33)	93 (77/23)	--
d	Ph	Me	45/55	94 (49/51)	--	--

Scheme 141



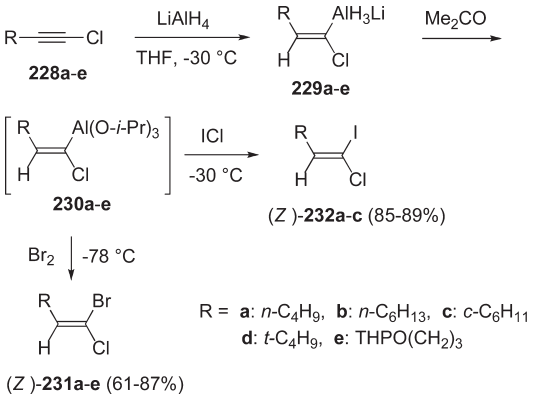
R[a]	yield (%)	*E*/*Z*
$4\text{-}NO_2C_6H_4$	87	3.5:1
$2\text{-}NO_2C_6H_4$	86	3.3:1
$4\text{-}ClC_6H_4$	86	6:1
2-Py	95	1.8:1
$2,6\text{-}Cl_2C_6H_3$	48	21:1

[a] Only representative examples are reported.

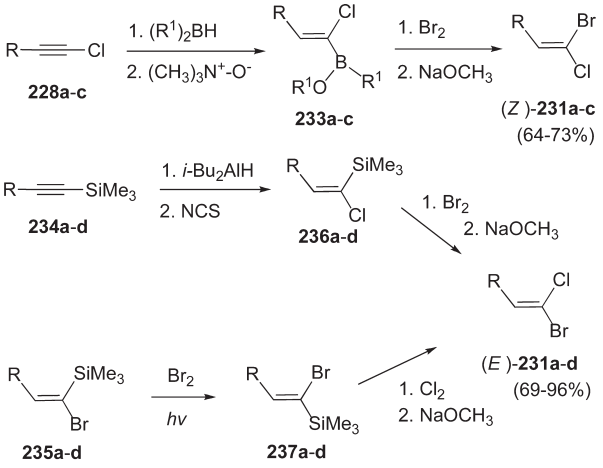
in the case of the bromoalkyne with R = Ph and I^- as the nucleophile, which afforded the product in a *Z*/*E* ratio of 3.3:1.

Both the geometric isomers of *gem*-bromoiodoalkenes **247** were prepared from the 1,1-heterobimetallic species of tin and zirconium **244**, obtained in turn from stannylacetylenes (Scheme 149).[47] By exploiting the fact that the reactions of electrophiles with C−Zr bonds are normally much faster than those with C−Sn bonds, the iodinolysis of **244** by using I_2 in THF at room temperature was performed to give the iodine products **245** exclusively. On the other hand, by using *N*-bromosuccinimide (NBS) in THF/CH_2Cl_2 at −78 °C to room

Scheme 142



Scheme 143



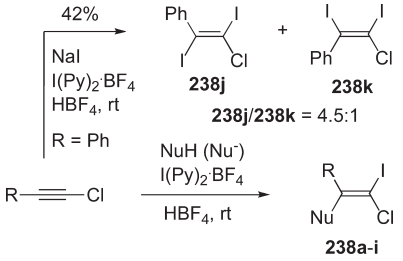
temperature, compounds **244** were converted into the bromine derivatives **246** in very high yields. The halogenolysis of the C−Sn bond in compounds **245** and **246** was next performed with NBS or I_2, under similar reaction conditions, to afford the isomeric compounds (*E*)- and (*Z*)-**246** with complete stereocontrol in good yields.

McNelis and co-workers reported that when iodine and [hydroxy(tosyloxy)iodo)]benzene (HTIB) were reacted in stoichiometric amounts with 3-bromo-1-phenylpropynol **248**, (*Z*)-3-bromo-3-iodo-2-phenylpropenal **249** was formed in 96% yield via phenyl shift of a vinyl cationic intermediate (Scheme 150).[207] Analogously, the tertiary alcohol **250** was converted into the ketone **251** by treatment with I_2 or *N*-iodosuccinimide (NIS) and HTIB in 89−96% yield (Scheme 150).[208] The application of this protocol (NBS or Br_2 were used instead of NIS or I_2) to the related iodine derivatives of **248** and **250** in order to obtain (*E*)-**249** and (*E*)-**251** failed.[207,208]

The stereospecific preparation of ethyl (*E*)-2,3-difluoro-3-iodoacrylate has been reported in 87% yield by treatment of ethyl (*E*)-2,3-difluoro-3-(tributylstannyl)acrylate[209] with iodine in ether (Scheme 151).[210]

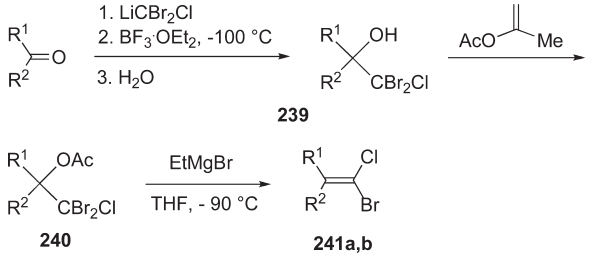
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 144

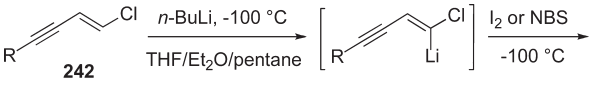


238	R	Nu	yield (%)
a	Ph	OAc	75%
b	Ph	OCHO	90%
c	Ph	Cl	60%
d	Ph	Br	57%
e	*n*-C_6H_{13}	OAc	63%
f	*n*-C_6H_{13}	OCHO	59%
g	*n*-C_6H_{13}	Cl	54%
h	*n*-C_6H_{13}	Br	51%
i	*n*-C_6H_{13}	I	35%

Scheme 145



Scheme 146

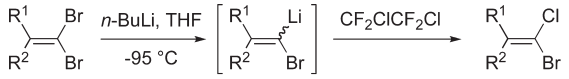


	R	X	**243** yield (%)
a	*n*-C_5H_{11}	Br	68
b	*n*-C_5H_{11}	I	84
c	Ph	I	60

2.5.4. Methods for Pure (*E*)- or (*Z*)-Isomers of *gem*-Bromofluoro-1-alkenes from Their *E*/*Z* Mixtures. Most literature describes the preparation of 1-bromo-1-fluoroalkenes as mixtures of (*Z*)- and (*E*)-isomers. Since these stereoisomers are difficult to separate by either simple distillation or chromatographic techniques,[211,212] several procedures have been developed to obtain pure (*E*)- or (*Z*)-isomers from their isomeric mixtures. A general approach to enrich *E*/*Z* mixtures of the (*E*)-isomers can be reached by exploiting the greater thermodinamic stability of these isomers with respect to *Z* ones. On the other hand, (*Z*)-isomers can be obtained taking advantage of the different reactivity of the bromine atom in (*Z*)- and (*E*)-1-bromo-1-fluoroalkenes.

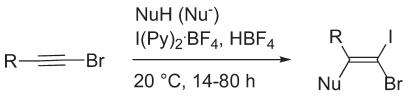
McCarthy and co-workers reported the isomerization of (*Z*)-1-bromo-1-fluoro-2-phenylethylene to an *E*/*Z* ratio of 92:8 by a

Scheme 147



R^1	R^2	yield (%)	*E*/*Z*
$Me(PhCH_2OCH_2)CH$	H	84	> 40:1
Ph	Et	88	5.2:1
Ph	$MeOCH_2$	94	1:10
$OCH_2CH_2CH_2OCH$	CH_3	94	10:1

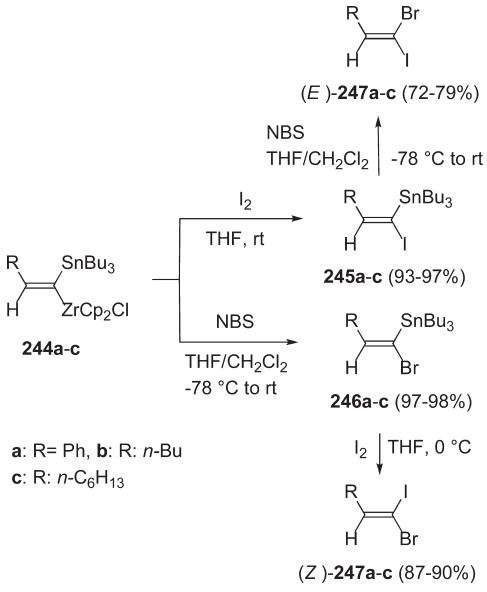
Scheme 148



R	Nu	yield (%)
Ph	AcO	79%
Ph	OHCO	80%
Ph	Cl	65%
Ph	Br	73%
n-C_6H_{13}	AcO	71%
n-C_6H_{13}	OHCO	80%
n-C_6H_{13}	Cl	79%
n-C_6H_{13}	Br	75%
n-C_6H_{13}	I	73%
Ph	I	66%[a]

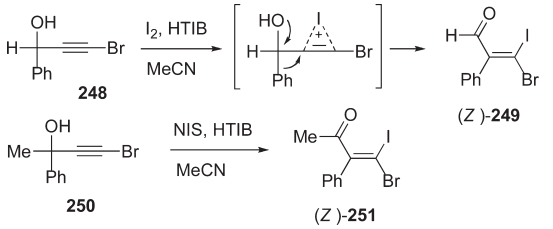
[a](*E*/*Z* = 3.3:1)

Scheme 149

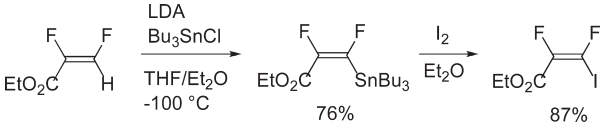


dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

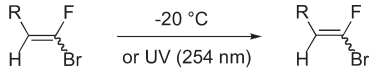
Scheme 150



Scheme 151



Scheme 152



R	*E/Z* starting alkene	yield (%) (*E/Z*) product
Ph	44:56	77 (82:18)
2-ClC_6H_4	48:52	67 (82:18)
4-$MeOC_6H_4$	66:34	62 (81:19)[a]
4-FC_6H_4	72:28	45 (87:13)
3-$O_2NC_6H_4$	63:37	53 (76:24)
1-naphthyl	49:51	46 (49:51)
PhCH(Me)	42:58	52 42:58)
n-C_7H_{15}	46:54	72 (46:54)

[a]Photolysis gave an *E/Z* ratio of 78:22

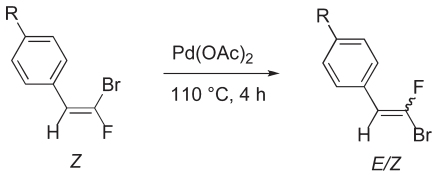
catalytic amount of bromine in chloroform.[211] However, Burton and Xu have recently experimented that this approach was only partially successful because of the prevailing formation of the saturated addition product, thus providing only a low yield (<20%) of 1-bromo-1-fluoro-2-phenylethylene with high *E*/*Z* ratio.[213]

The same research group found that in some cases *gem*-bromofluoroalkenes (*E*/*Z* ≈ 1:1) could be isomerized to high *E*/*Z* ratio (≥75:25) when stored at −20 °C for one week. Presumably, this isomerization was caused by a trace amount of bromine in the products. Alternatively, a similar isomerization was found to occur by photolysis at 254 nm for 1 h (Scheme 152).[23−214] Under these conditions, clean isomerization occurred for aryl-substituted alkenes (*E*/*Z* ratios >75:25 were successfully obtained) but not for alkenes with 1-naphthyl or alkyl groups.

Metal-catalyzed isomerization can be also pursued to obtain the more stable isomer. Thus, the isomerization catalyzed by $Pd(OAc)_2$ of some (*Z*)-1-bromo-1-fluoroalkenes occurred but was only partially successful (Scheme 153).[195]

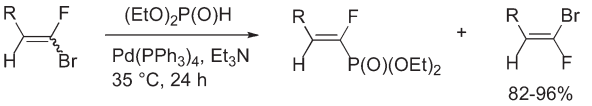
An interesting strategy to obtain stereo-defined 1-bromo-1-fluoroalkenes from their *E*/*Z* mixtures was inspired by the observation that (*E*)-isomers react faster than the corresponding

Scheme 153



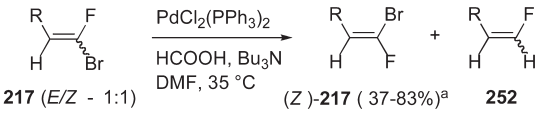
R	*E/Z*	R	*E/Z*
H	89:11	OMe	50:50
Cl	88:12		

Scheme 154



R = Me_2CH, Ph, C_7H_{15}, 2,3-$Me_2C_6H_3$, 3-ClC_6H_4, Ph(Me)CH

Scheme 155



217 (*E*/*Z* - 1:1) (*Z*)-**217** (37-83%)[a] **252**

[a]Yield based on the amount of the (*Z*)-isomer in the starting *E*/*Z* mixture

R = Ph, 2-ClC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, Ph(Me)CH, *n*-C_7H_{15}

(*Z*)-isomers in Pd-catalyzed coupling reactions. Thus, under proper reaction conditions, the (*E*)-isomer in an isomeric mixture reacts, leaving unchanged the *Z* one that, therefore, can be isolated.

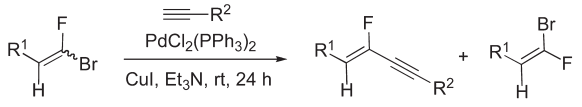
Burton and co-workers, by exploiting this peculiarity, reacted *E*/*Z* mixtures of 1-bromo-1-fluoroolefins with diethylphosphite and catalytic $Pd(PPh_3)_4$ to obtain predominately (*E*)-isomers of 1-fluorovinylphosphonates and unreacted (*Z*)-1-bromo-1-fluoroolefins, which could be recovered in 82−96% yields based on the amount of the (*Z*)-isomer present in the starting mixture (Scheme 154).[215]

Other conceptually similar approaches were later pursued by Burton and Pannecoucke. Selective reduction of the (*E*)-isomers in **217** was performed by using the system formed from formic acid, *n*-Bu_3N, and $PdCl_2(PPh_3)_2$ in DMF at 35 °C (Scheme 155).[213,216] Under these reaction conditions, all (*E*)-isomers (as well as a small amount of (*Z*)-isomers) were reduced and most of the (*Z*)-1-bromo-1-fluoroalkenes **217** remained unreacted and could be eventually isolated by repeated distillations. Alternatively, the mixture of **217** and **252** could remain unseparated and used in the Pd-catalyzed reactions because the hydrodebrominated products **252** generally do not participate in these reactions.

The Sonogashira reaction of *E*/*Z* mixtures of 1-bromo-1-fluoroolefins with 1-alkynes and catalytic $PdCl_2(PPh_3)_2$/CuI in Et_3N at room temperature gave (after 16−24 h) (*Z*)-monofluoroenynes in good yields and unreacted (*Z*)-1-bromo-1-fluoroolefins, which could be recovered and submitted to further couplings (Scheme 156).[217]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 156



E/*Z* [a] starting alkene	R^1	R^2	yield (%)(*Z*/*E*)[b] enyne	yield (%)[b] (*Z*)-alkene
6:5	Ph	Ph	38 (100:0)	100
3:2	Ph	acetal	54 (95:5)	100
1:1	Ph	$CH_3(OH)CH$	49 (95:5)	92
7:3	$Ph(CH_3)CH$	$CH_3(OH)CH$	53 (98:2)	100
1.1	4-ClC_6H_4	acetal	49 (99:1)	80
1.1	4-ClC_6H_4	$CH_3(OH)CH$	48 (99:1)	87

[a]Only representative results are reported.
[b]Yield based on the amount of olefin consumed

Pannecoucke and co-workers, by subjecting an isomeric mixture of 1-(2-bromo-2-fluorovinyl)-4-methoxybenzene to Negishi and Nozaki−Hiyama−Kishi reactions, found that in both cases only the (*E*)-isomer reacted to give a butylfluoroalkene and a 2-fluoroallyl alcohol, respectively, leaving unchanged the (*Z*)-isomer, which could be isolated in 89%[192] and 62%[218] yields, respectively (Scheme 157).

The same research group has recently described the synthesis of vinylic fluoride scaffolds via a Negishi coupling mediated by $Pd(OAc)_2/PPh_3$ of *gem*-bromofluoroolefins with alkoxyvinylzinc species (Scheme 158).[219] At 10 °C, only the (*E*)-isomers of *E*/*Z* mixtures of the substrates reacted to give, after hydrolysis, stereospecifically (*Z*)-α-fluoro-α,β-unsaturated ketones and, at the same time, the unreacted (*Z*)-isomers, which were recovered in high yields.

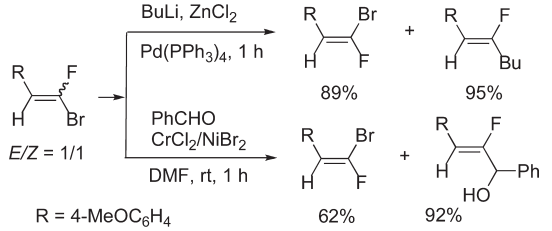
While Pd-mediated coupling reactions allow (*Z*)-isomers to be obtained, Pannecoucke and co-workers developed a method to obtain pure (*E*)-isomers from *E*/*Z* mixtures based on consuming chemoselectively one of the two isomers. Thus, stereoselective dehydrobromination of the (*Z*)-isomers, carried out with DBU in DMSO at 95 °C or $LiN(SiMe_3)_2$ in THF at room temperature, yielded pure (*E*)-isomers in good to excellent yields, based on the starting (*E*)-isomers in the mixtures (Scheme 159).[192]

3. METAL-CATALYZED REACTIONS OF *GEM*-DIHALOVINYL SYSTEMS

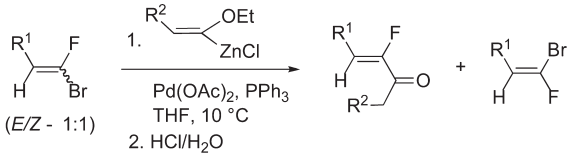
3.1. Selective Monosubstitution of Homo *gem*-Dihalovinyl Systems

3.1.1. Coupling with Alkenylmetal Reagents. In a study aimed at the synthesis of antibiotic subunits, Roush and co-workers reported the first two examples of stereoselective synthesis of (*Z*,*E*)-2-bromo-1,3-dienes via palladium(0)-catalyzed cross-coupling of 1,1-dibromoalkenes with vinylboronic acids and esters (Scheme 160).[220,221] They noted that the reaction of the dibromoalkene **253** with the catechol borane derivative **254** under standard Suzuki−Miyaura cross-coupling conditions [$Pd(PPh_3)_4$, aqueous NaOH, benzene, reflux][222] afforded the bromodiene **255** in only 36% yield, but a considerable improvement (65% yield) could be achieved by using thallium hydroxide as the base (Scheme 160).[220] Next, they found that the coupling reaction yields could be further improved when vinylboronic acids were employed rather than catechol borane derivatives.

Scheme 157



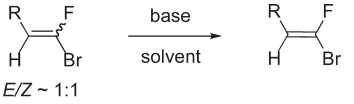
Scheme 158



R^1	R^2	yield (%)[a] (*Z*)-isomer	R^1	R^2	yield (%)[a] (*Z*)-isomer
4-$MeOC_6H_4$	H	86	$PhCH_2CH_2$	H	79
2-naphthyl	H	85	4-$MeOC_6H_4$	Ph	99
4-$O_2NC_6H_4$	H	90	4-$MeOC_6H_4$	Et	84

Only representative substrates are reported
[a]Based on the starting (*Z*)-isomer

Scheme 159



R^a	base/solvent	yield (%)[b] (*E*)-isomer
$PhCH_2CH_2$	$LiN(SiMe_3)_2$/THF	88
$TBDPSOCH_2CH_2$	$LiN(SiMe_3)_2$/THF	98
4-$O_2NC_6H_4$	DBU/DMSO	55
4-$MeOC_6H_4$	DBU/DMSO	85
4-FC_6H_4	$LiN(SiMe_3)_2$/THF	67

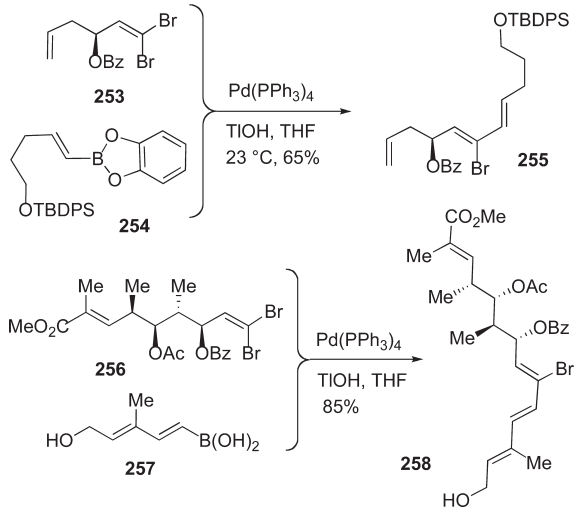
[a]Only representative examples are reported.
[b]Based on starting (*E*)-isomer.

Thus, the bromotriene **258** was formed in 85% yield from **256** and **257** (Scheme 160).[221]

Roush reported also additional examples and commented on the scope of this stereoselective synthesis of (*Z*,*E*)-2-bromo-1,3-dienes.[223] Some representative models are described in Scheme 161. The yields were generally high (75−87%), except in the cases of dienes **261a,b** and **263** (43−61%), where dicoupled trienes (for instance, **264** from **262**) were isolated in 5−10% yields. They supposed that the reluctance of (*Z*,*E*)-2-bromo-1,3-dienes to undergo a second cross-coupling could indicate that the triene formation derives from an initial cross-coupling at the (*Z*)-bromo unit of **259a,b** or **262**, with the resulting (*E*)-2-bromo-1,3-diene (which is presumably more reactive than the (*Z*)-diene isomer for steric reasons) then undergoing a second cross-coupling to give trienes. Moreover, they observed that the allylic alkoxy substituents of the most

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 160



efficient dibromoolefin substrates (such as **265** and **267a,b**) contribute both a steric and an electronic component that have a beneficial influence on the outcome of these modified Suzuki cross-coupling reactions.

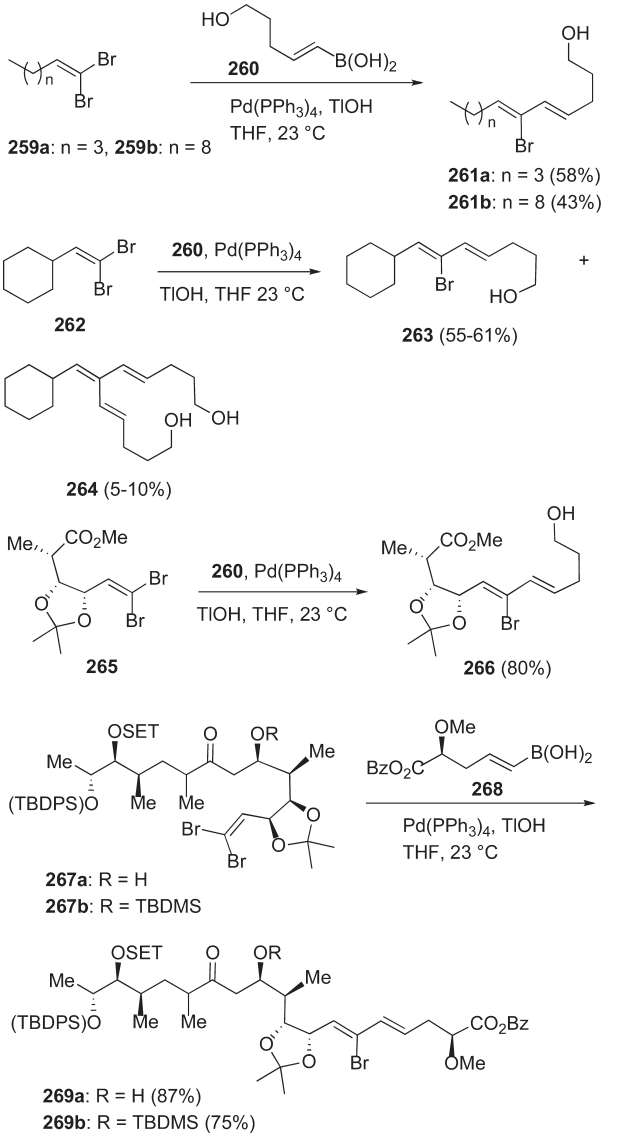
This protocol was later applied by Roush and co-workers to the stereoselective synthesis of a number of (*Z*,*E*)-2-bromo-1,3-dienes, which were synthons for subunits of a series of biologically active compounds.[224]

Other research groups also applied the Suzuki cross-coupling of vinylboronic acid derivatives with *gem*-dibromides in the presence of thallium or barium bases to prepare a variety of natural products (Schemes 162−164).[225]

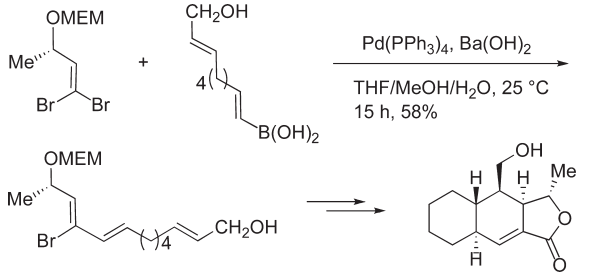
Brückner and Hanisch reported a strategy for the stereocontrolled synthesis of polyunsaturated butenolides.[226] In particular, they described the total synthesis of the α-alkenyl-γ-alkylidenebutenolide **274**, based on the selective formation of three sequential C−C bonds starting from the trihalodiene **270** (Scheme 165). In the presence of NaOH and catalytic $Pd(PPh_3)_4$, compound **270** underwent highly selective Suzuki couplings with alkenyl boronic acids. At 70 °C, the iodoolefin moiety coupled first with (*E*)-PhCH=CHB(OH)$_2$ and the (*E*)-bromoolefin moiety thereafter with (*E*)-cyclohexylCH=CHB(OH)$_2$. The resulting (*Z*)-bromolefin **272** was then transformed into the stereopure highly unsaturated compound **274** in three steps.

Shen demonstrated that when the soft ligand tris(2-furyl)phosphine (TFP) was used as the ligand for palladium in combination with aqueous Na_2CO_3 in 1,4-dioxane, (*E*)-dibromoalkenes were stereoselectively coupled with alkenyl and aryl boronic acids to give the corresponding (*Z*)-1-alkenyl(aryl)-1-bromoalkenes.[227] A variety of 1-aryl- and 1-alkyl-1,1-dibromoalkenes were coupled with (*E*)-β-styrylboronic acid to give trisubstituted (*Z*,*E*)-1,3-dienes in moderate to good yields (Scheme 166). The reactions were complete in 1−2 h, much faster than the corresponding arylboronic acids. The selectivity was also good; only in the case of (*S*)-4-[(1*Z*,3*E*)-2-bromo-4-phenylbuta-1,3-dienyl)]-2,2-dimethyl-1,3-dioxolane, the related (*E*,*Z*)-1,3-diene was isolated in 5% yield. This procedure was advantageous over the corresponding Stille and Suzuki reactions because it avoided the use of highly toxic organotin and thallium derivatives, respectively.

Scheme 161



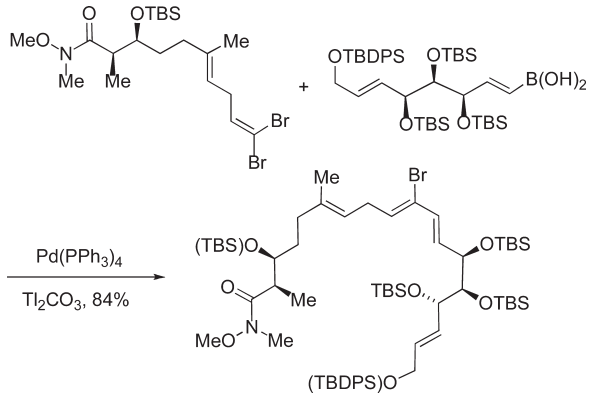
Scheme 162



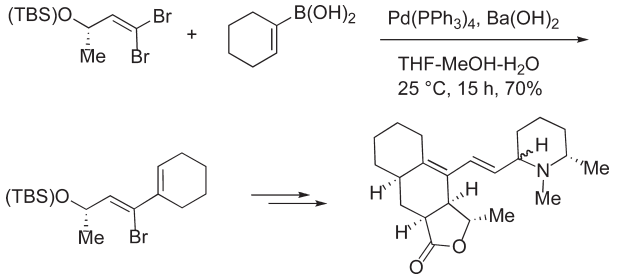
While the use of a variety of 1,1-dihaloalkenes in cross-coupling processes has been extensively studied, that of the simplest member of this family, namely, 1,1-dichloroethylene **275**, is more scarce. Linstrumelle and co-workers reported a single example of Pd-catalyzed coupling of **275** with a

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

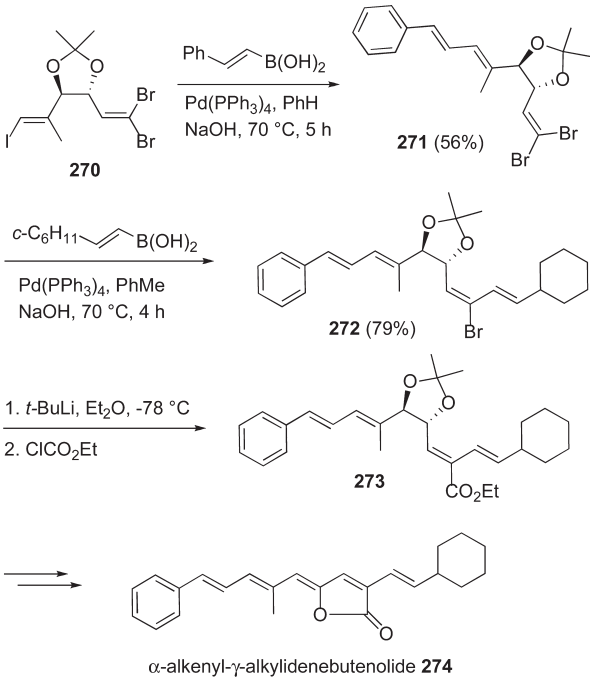
Scheme 163



Scheme 164

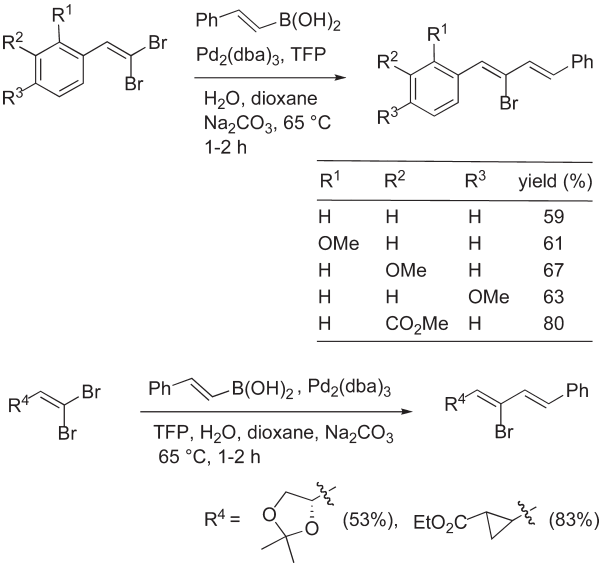


Scheme 165



vinylalane.[14] In this circumstance, **275** was coupled at room temperature with (*E*)-hex-1-enyldiisobutylaluminium in the presence of $Pd(PPh_3)_4$ to give (*E*)-2-chloroocta-1,3-diene in 70% yield (Scheme 167).

Scheme 166



R^1	R^2	R^3	yield (%)
H	H	H	59
OMe	H	H	61
H	OMe	H	67
H	H	OMe	63
H	CO_2Me	H	80

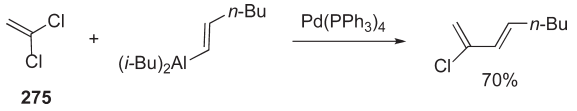
A breakthrough in this field has been recently made by Barluenga and co-workers, who described the usefulness of **275** in selective Suzuki−Miyaura couplings with boronic acids.[228] Thus, after an extensive study to develop suitable conditions for the coupling of **275** with (*E*)-1-octenylboronic acid, it was found that by use of $Pd_2(dba)_3$ (0.5 mol %) and XPhos (2 mol %) the monocoupled product could be obtained in 92% yield (Scheme 168). This protocol was then extended to a variety of alkenyl boronic acids that afforded moderate to good results of 2-chloro-1,3-butadienes **276** (Scheme 168). However, because in several cases XPhos afforded significant amounts of the dicoupled products, it was determined that in such instances the use of JohnPhos as supporting ligand provided better results. Interestingly, the reaction could be carried out in the presence of an arylic chlorine substituent on the boronic acid, which arose from the higher reactivity of vinyl chlorides over aryl chlorides toward palladium oxidative addition.

Willis and co-workers have recently reported, in a study addressed to the synthesis of 2-quinolones, two interesting examples of chemo- and stereoselective cross-coupling processes of a tribromide (Scheme 169).[229] Coupling of 1-bromo-2-(2,2-dibromovinyl)benzene with (*E*)-styrylboronic acid under Shen conditions afforded in 75% yield the (*Z*,*E*)-diene derived from *trans*-selective addition of the palladium complex on the C−Br bond of the alkene moiety (*Z*/*E* > 15:1), leaving unchanged that on the benzene ring.

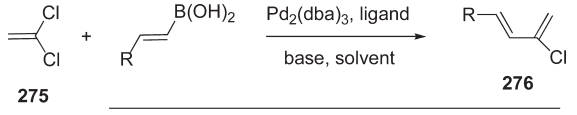
Panek and Hu reported an efficient method for the synthesis of configurationally pure (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*E*)-dienes bearing α- and α,β-stereogenic centers adjacent to a C−C double bond by Pd(0)-catalyzed cross-coupling reactions of (*E*)-trisubstituted vinylzinc intermediates with (*E*)- and (*Z*)-vinyl iodides under modified Negishi conditions.[230] One example regarded also the *gem*-dibromoalkene **277** that was coupled with the organozinc **278** to give the diene **279** in 55% yield as single stereoisomer (Scheme 170). Interestingly, in this one-pot sp^2-sp^2 coupling both the Pd(0) catalyst and the vinylzinc were generated in situ, the former by reduction of $PdCl_2(PPh_3)_2$ with DIBAL and the latter by hydrozirconation

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 167

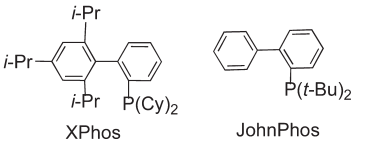


Scheme 168

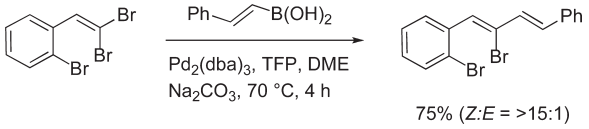


R	**276** yield (%)	R	**276** yield (%)
n-C_6H_{13}	92[a] or 86[b]	4-$MeOC_6H_4$	72[c]
$PhCH_2CH_2$	87[a]	4-ClC_6H_4	49[c]
Ph	76[c]	4-$F_3CC_6H_4$	61[c]

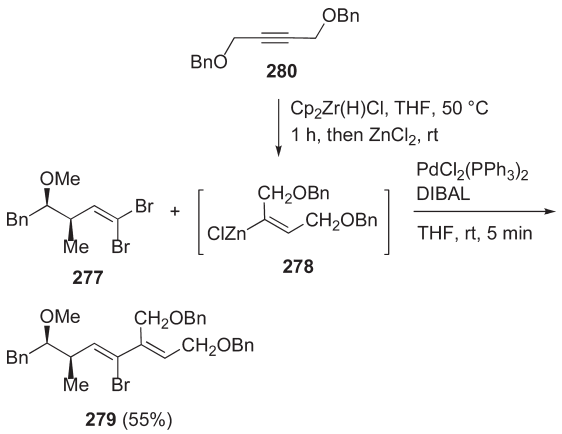
[a]Method A: XPhos, K_3PO_4, toluene, 100 °C
[b]Method B: XPhos, CsF, dioxane, 100 °C
[c]Method C: JohnPhos, CsF, dioxane, 70 °C



Scheme 169



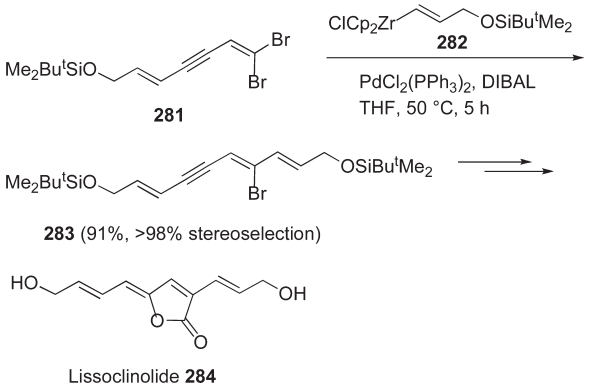
Scheme 170



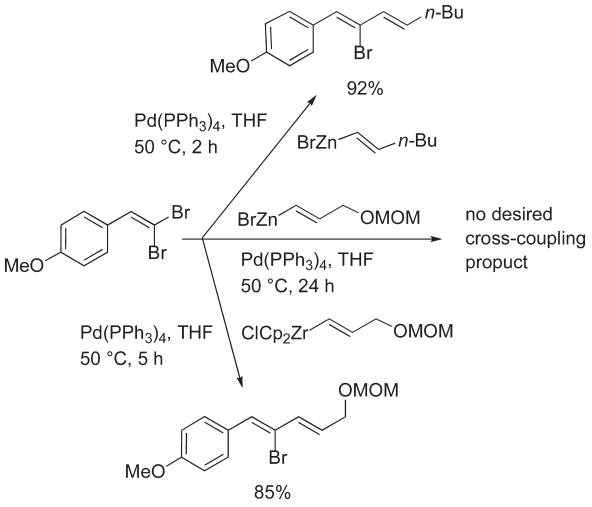
of the symmetrical alkyne **280** followed by treatment with anhydrous $ZnCl_2$.

Negishi and Xu synthesized the antibiotic lissoclinolide **284** from propargyl alcohol in 9 steps and 32% overall yield with nearly perfect degree of regio- and stereocontrol (Scheme 171).[231] In this synthesis, the key step was the unprecedented Pd-catalyzed

Scheme 171



Scheme 172

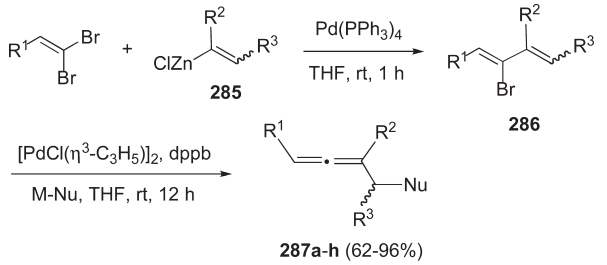


trans-selective cross-coupling of the 1,1-dibromoalkene **281** with the alkenylzirconium **282**. The reaction was highly satisfactory concerning both the yield (91%) and selectivity (>98% *trans*-isomer). The initial use of the zinc analogue of **282** failed. The results were puzzling, since a model experiment led to very satisfactory *trans*-selective cross-coupling, as shown in Scheme 172. The authors suspected that the inactivation of the alkenylzinc derivate occurs via a potential *E*-to-*Z* isomerization−chelation process.

A general and efficient new method for the Pd-catalyzed conversion of 1,1-dibromoalkenes into substituted functionalized allenes **287** has been recently reported (Scheme 173).[232] The key intermediates, (*Z*)-2-bromo-1,3-butadienes **286**, were readily available in 63−90% yields by Pd-catalyzed regio- and stereoselective cross-couplings of 1,1-dibromoalkenes with a series of vinylzinc reagents (Scheme 173). The choice of the organometallic reagent was important in this step. While $(CH_2{=}CH)ZnCl$ gave the coupling product in satisfactory yield, the less-reactive vinyltin reagent $(CH_2{=}CH)SnBu_3$ afforded the same product in very low yield (<20%). More basic Grignard reagents enhanced the elimination of HBr from **286**, giving considerable amounts of $R^1C{\equiv}C{-}CH{=}CH_2$ as byproduct. When R^1 was an alkyl substituent, a second cross-coupling proceeded to a certain extent to give a triene, $R^1CH{=}C{-}(CH{=}CH_2)_2$, as a byproduct (15% yield).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

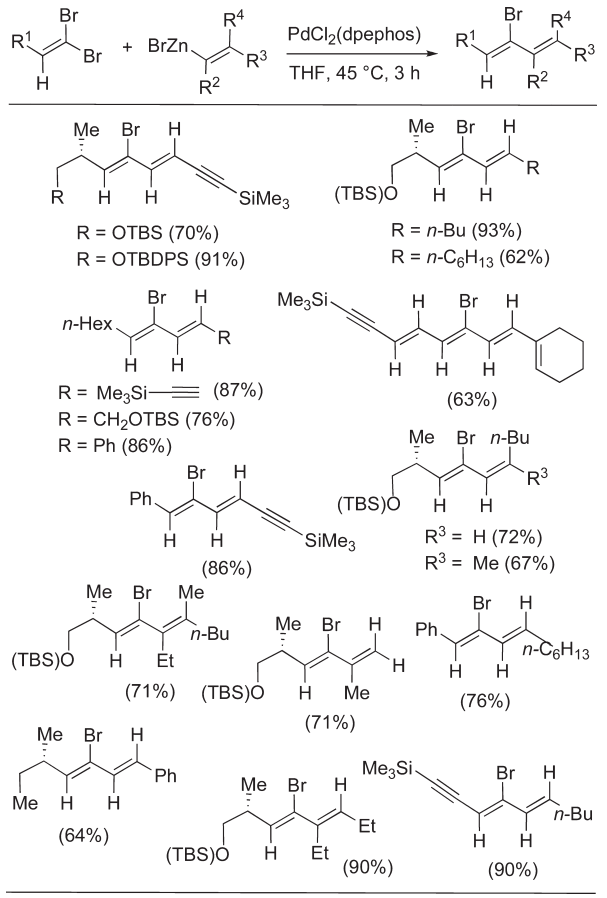
Scheme 173



287a: R^1 = Ph, R^2 = R^3 = H
287b: R^1 = $PhCH_2$, R^2 = R^3 = H
287c: R^1 = (*E*)-PhCH=CH, R^2 = R^3 = H
287d: R^1 = *i*-Pr, R^2 = R^3 = H
287e: R^1 = *n*-C_7H_{15}, R^2 = R^3 = H
287f: R^1 = Ph, R^2 = Me, R^3 = H
287g: R^1 = H, R^2 = Ph, R^3 = H
287h: R^1 = Ph, R^2 = H, R^3 = Me

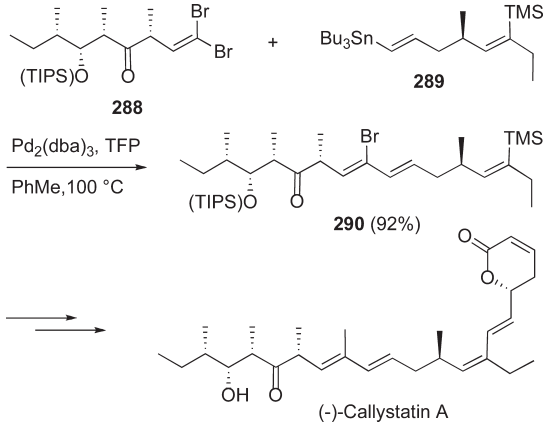
M-Nu:
Na[CMe(COOMe)$_2$]
Na[CH(COOMe)$_2$]
Na[CMe(COMe)(COOEt)
K[CMe(COMe)$_2$]
NaOPh
KN(Boc)$_2$
$LiPPh_2$

Scheme 174

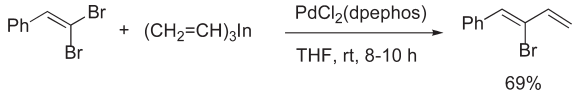


Negishi and co-workers, carrying out a splendid investigation of the sequential alkenylation−alkylation of 1,1-dibromoalkenes, obtained a number of stereoisomerically pure (≥98%) 2-bromo-1,3-dienes in 62−93% yields by cross-couplings between a variety of 1,1-dibromoalkenes and alkenylzinc derivatives catalyzed by 5 mol % $PdCl_2$(dpephos) (Scheme 174).[233,234]

Scheme 175



Scheme 176



In the synthesis of (−)-callystatin A, a polyketide-based natural product, the key step relied on the stereoselective cross-coupling between the *gem*-dibromoalkene **288** and the vinylstannane **289**. This Stille reaction was successfully carried out by using the couple $Pd_2(dba)_3$ and TFP as the catalytic system to give the (*E*,*Z*)-diene **290** as the only observed product in 92% yield (Scheme 175).[235]

Perez Sestelo and co-workers have recently studied the regio- and stereoselectivity of Pd-catalyzed cross-coupling reactions of triorganoindium reagents (R_3In, R = alkyl, alkenyl, aryl, and alkynyl) with haloalkenes.[236] Their paper reported a single example of *trans*-selective alkenylation, in which trivinylindium was successfully cross-coupled with (2,2-dibromovinyl)benzene in the presence of $PdCl_2$(dpephos, 2 mol %; Scheme 176).

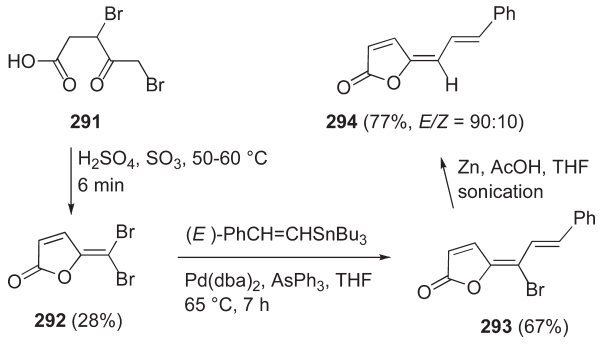
Notwithstanding cross-coupling reactions of fully substituted 1,1-haloalkenes show poor stereoselectivity due to the steric hindrance of the vicinal C−C bonds compared with the C−H bond of 2-substituted 1,1-dihaloalkenes, in some cases an excellent stereocontrol has been observed.

One of this circumstance occurred in the vinylation by Stille coupling of the γ-(dibromomethylene)-butenolide **292**, obtained from dibromolevulinic acid in a single step (Scheme 177).[237] In fact, the *gem*-dibromoolefin **292** underwent coupling with styryltributylstannane using the couple $Pd(dba)_2$ (6 mol %) and $AsPh_3$ (20 mol %) as the catalytic system to give the monobromobutenolide **293** with excellent stereocontrol and high yields (67−84%). Its stereochemistry was unambiguously determined by converting it into the bromine-free γ-alkylidenebutenolide **294** by replacing the bromine atom with hydrogen through sonication with Zn dust and a drop of AcOH in THF. Interestingly, this hydrodebromination proceeds with 90% retention of configuration.[238]

Ishihara and co-workers described the reaction of benzyl 2,3,3-trifluoroacrylate with various Grignard reagents in the presence of catalytic CuBr.[239] In particular, the use of 5.0 equiv of β-styrylmagnesium bromide and 0.25 equiv of CuBr allowed the corresponding β-vinylated product to be obtained in 45% yield with high *Z* selectivity (Scheme 178).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 177



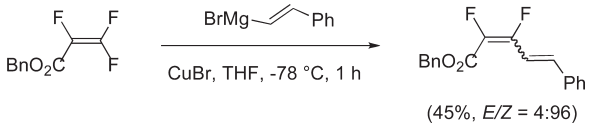
3.1.2. Coupling with (Hetero)arylmetal Reagents. Shen demonstrated that the soft ligand tris(2-furyl)phosphine is very effective in Pd-catalyzed coupling reactions of a wide variety of both 1,1-dibromoalkenes and arylboronic acids (Scheme 179).[227] By use of phenylboronic acid in the presence of catalytic $Pd_2(dba)_3$ and TFP, a number of (*Z*)-1-aryl-1-bromoalkenes were synthesized in moderate to good yields (40−89%). Good results were also obtained with both electron-rich and electron-deficient arylboronic acids by employing methyl 4-(2,2-dibromovinyl)benzoate as the starting material (73−87% yields). Most reactions gave the desired monobromides as the only products, though minor amounts (3−8%) of diarylalkenes were occasionally isolated. In some cases, low quantities (2−18%) of internal alkynes, derived from dehydrobromination of the initially formed monocoupled products, were isolated.

Barluenga and co-workers submitted 1,1-dichloroethylene **275** to cross-coupling reactions with a variety of arylboronic acids in the presence of $Pd_2(dba)_3$, JohnPhos, and CsF (Scheme 180).[228] Thus, under optimized reaction conditions a number of α-chlorostyrenes were obtained in high yields from boronic acids with electron-rich and electron-neutral substitutents (Scheme 180). However, the utilization of electron-poor arylboronic acids seemed to be a limitation of the reaction due to the undesired side reactions of the boronic acids.[240] In fact, when 3-acetylphenylboronic acid was used, the reaction proceeded with very low yield of the coupled product, with acetophenone, coming from the protodeborination of the boronic acid, being the main isolated product.

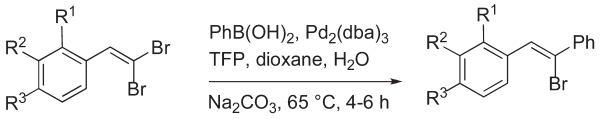
Cossy co-workers in a study aimed at the synthesis of disubstituted ynamides (Scheme 455) have recently prepared in good yields β-chloroenamides by Suzuki−Miyaura reaction of β,β-dichloroenamides with various boronic acids (Scheme 181).[17] The cross-couplings were carried out with $Pd(PPh_3)_4$ (5 mol %) as the catalyst and $Ba(OH)_2$ or NaOH as the base, to afford β-chloroenamides as almost exclusive geometric isomers (Z/E > 95/5). Notwithstanding the use of an excess of organoboron reagents (1.6 equiv), dicoupled products were not detected, in contrast with the corresponding dibromo counterpart that afforded under the same reaction conditions relevant amounts of the double cross-coupling products. Indeed, when β,β-dibromoenamide **295** was coupled with 2-methoxybenzeneboronic acid, a mixture of monocoupled **296** and dicoupled **297** products was produced in a 40:60 ratio (85%) (Scheme 182). However, by reduction of the amount of boronic acid to 1.05 equiv, (*Z*)-β-bromoenamide **296** was isolated in 74% yield with only traces of the dicoupled product **297** (4% yield).

Chelucci and co-workers have recently reported the chemo- and stereoselective synthesis of the bromoalkenes **299** as

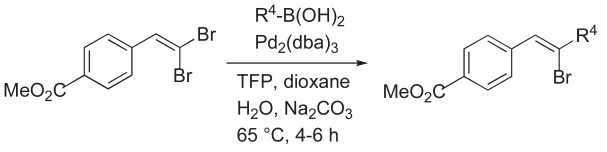
Scheme 178



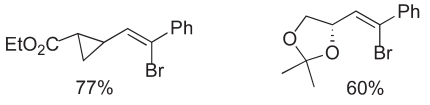
Scheme 179



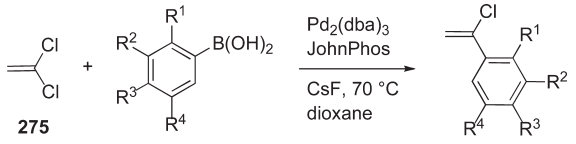
R^1	R^2	R^3	yield (%)
H	H	H	40
OMe	H	H	53
H	OMe	H	68
H	H	OMe	56
H	CO_2Me	H	89



R^4	yield (%)	R^4	yield (%)
4-$MeOC_6H_4$	84	3-$MeOC_6H_4$	87
2-$MeOC_6H_4$	73	2-$H(O)CC_6H_4$	75



Scheme 180



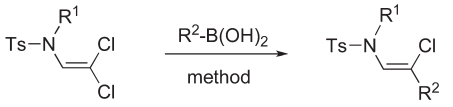
R^1	R^2	R^3	R^4	yield (%)
Me	H	H	H	64
H	Me	H	Me	87
H	OMe	H	H	66
H	-OCH_2O-		H	83
H	C(O)Me	H	H	21[a]

[a]chloroalkene/acetophenone = 31:69

intermediates in the total synthesis of 5-aryl-1,10-phenanthrolines (Scheme 183).[241] Thus, the tribromide **298** was coupled with a variety of organoboron reagents in the presence of $Pd_2(dba)_3$ (2.5 mol %) and TFP (15 mol %) to afford the monocoupled products **299** in 65−87% yields. Interestingly, in the cross-coupling process the palladium insertion occurred selectively on the C−Br bond of the alkene moiety rather than

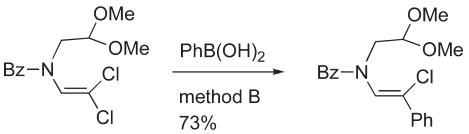
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 181



R^1	R^2	method	yield (%)
3-butenyl	Ph	A	76
3-butenyl	2-$MeOC_6H_4$	A	81
3-butenyl	4-FC_6H_4	B	89
$PhCH_2$	Ph	B	98
$PhCH_2$	2-$MeOC_6H_3$	B	91
$PhCH_2$	3,4-$Cl_2C_6H_4$	B	88
$PhCH_2$	(*Z*)-hexen-1-yl	B	65
4-$MeOC_6H_4$	Ph	B	94

method: A = $Pd(PPh_3)_4$, $Ba(OH)_2$, THF/MeOH/H_2O reflux
method: B = $Pd(PPh_3)_4$, aq NaOH, THF, reflux



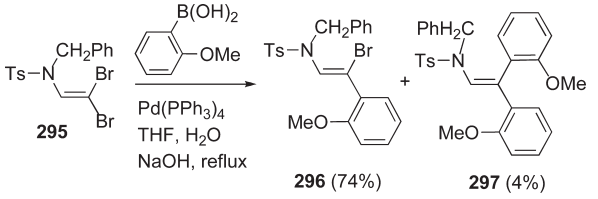
on that of the pyridine moiety with high electrophilicity (see Figure 7).

Another example of a chemo- and stereoselective cross-coupling process has been more recently reported by Willis co-workers, who in a study addressing the synthesis of 2-quinolones,[229] obtained selectively (*Z*)-1-bromo-2-(2-bromo-2-(4-methoxyphenyl)vinyl)benzene (*Z*/*E* = 15:1) by cross-coupling of 1-bromo-2-(2,2-dibromovinyl)benzene with 4-methoxyphenylboronic acid under Shen conditions (Scheme 184).

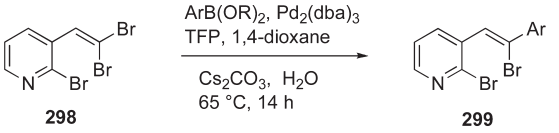
Shimizu and co-workers reported that the 3-fold Suzuki–Miyaura cross-coupling reaction of the 2-functionalized 1,1-dibromoalkene **300** with three kinds of aryl boronic acids provided a simple and straightforward approach to the synthesis of stereo-defined CF_3-substituted triarylethenes.[242] In the first step, coupling of **300** with various aryl boronic acids gave after extensive optimization, monocoupled products **301** in high yields and *Z*/*E* selectivities, ranging from 87:13 to 92:8 (Scheme 185). To gain insights into the effect of the CF_3 group on the reaction, the coupling of dibromoalkenes **302** with $PhB(OH)_2$ was carried out under these reaction conditions (Scheme 186). The reaction of nonfluorinated dibromoalkene **302a** resulted in a lower yield of isolated product and lower *Z*/*E* selectivity of the monocoupled product **303a**. Ethoxycarbonyl-substituted ethene **302b** gave **303b** in moderate yield together with fair amounts of the dicoupled product **304b** and acetylene **305** as byproduct. In the case of **302c**, diphenylated ethene **304c** was formed as the major product. Thus, these results appears to indicate that the high *Z* selectivity of **302** could be attributed to the presence of a CF_3 group (probably a Pd···F interaction in the oxidative addition step may be operative),[243] while both the CF_3 and tosyloxy groups are indispensable for suppressing the second coupling reaction.

Minato and Tamao described the first successful regio- and stereoselective mono(hetero)arylation and alkylation of 1,1-dichloroalkenes by organozinc and Grignard reagents (1 equiv) in the presence of $PdCl_2$(dppb, 1 mol %) as the catalyst to

Scheme 182

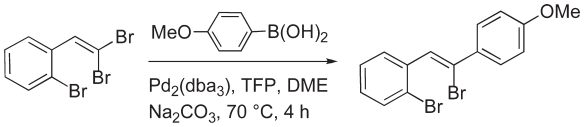


Scheme 183

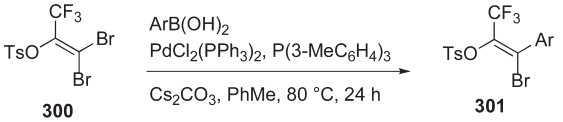


	Ar	**299** yield (%)		Ar	**299** yield (%)
a	Ph	87	**d**	2-Me-4-$MeOC_6H_3$	84
b	4-$O_2NC_6H_4$	68	**e**	3-pyridyl	70
c	3-ClC_6H_4	80	**f**	5-methylthien-2-yl	65

Scheme 184



Scheme 185

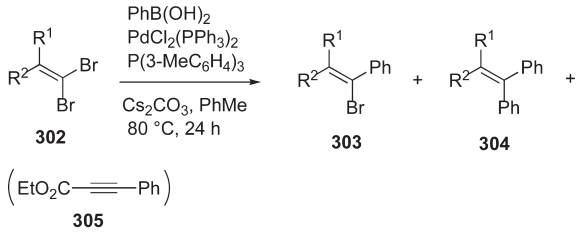


Ar	**301** yield (%)	*Z*/*E*
Ph	94	92:8
3-$MeOC_6H_4$	74	90:10
3-MeC_6H_4	73	89:11
3-$CF_3C_6H_4$	89	87:13
3-BrC_6H_4	85	88:12
4-PhC_6H_4	96	88:12
2-naphthyl	78	89:11
3-FC_6H_4	87	89:11
3-thienyl	80	90:10

produce 1-substituted (*Z*)-1-chloroalkenes in excellent yields (Scheme 187).[13] They observed that (i) the presence of the substituent R in the dichloroolefin skeleton was essential for the regio- and stereoselective monocoupling, since the parent 1,1-dichloroethene itself produced a comparable amount (ca. 25% yield) of diarylation product and no reaction took place with 1,1-dichloro-2,2-diphenylethene, (ii) the significant effect exerted by the vicinal *cis* substituent R may be steric, since the electronically different groups, such as alkyl, aryl, heteroaryl, and chlorine, are equally effective and (iii) the use of $PdCl_2$(dppb) as the catalyst was essential for the success of the reaction because the use of

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 186



	R^1	R^2	303 yield (%)(*Z*/*E*)	304 yield (%)	305 yield (%)
a	CH_3	OTs	70 (78:32)	0	--
b	CO_2Et	OTs	57 (96:4)	16	21
c	CF_3	$(CH_2)_2Ph$	15 (81:19)	47	--

$PdCl_2(PPh_3)_2$ resulted mainly in the formation of diarylation products. Some of the monocoupled products were subjected to further coupling to give trisubtituted alkenes (Schemes 355 and 356).[13]

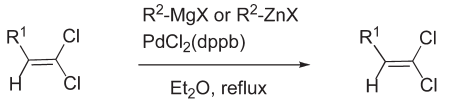
Minato next extended this protocol to the stereoselective mono(hetero)arylation of *cis*- and *trans*-(2,2-dihaloethenyl)-cyclopropanecarboxylates (Scheme 188).[244] The dichloroethenyl group was used in this work, except in one case where the dibromo analogue was employed. (*Z*)-Monocoupled products were obtained in high yields (61−100%) with a variety of aryl and heteroarylzinc reagents. With dichloroolefins, the resultant monocoupled products were quite resistant toward further metal-assisted couplings. On the other hand, with a dibromo analogue either monocoupling or dicoupling (Scheme 312) could be achieved selectively according to the stoichiometry of the organozinc reagent.

Recently, Negishi and Shi, in a project aiming to obtain an effective procedure for the Pd-catalyzed selective tandem arylation−alkylation of 1,1-dihaloalkenes with organozinc reagents, optimized first the *trans*-selective monoarylation process.[245] In the arylation of a variety of dibromides with phenyl-, 2-thienyl-, and 2-thiazolylzinc bromides, $PdCl_2$(dpephos) and THF appeared to be superior to the other examined catalysts [$Pd(PPh_3)_4$, $PdCl_2$(dppb), $PdCl_2$(dppf), $Pd(Pt\text{-}Bu_3)_2$] and solvents (Et_2O, toluene), although further survey of suitable solvents worked well in some cases (Scheme 189). Thus, in the reaction of 1,1-dibromo-1-octene with 2-thiazolylzinc bromide, toluene proved to be more satisfactory (84% yield) than either THF (73% yield) or Et_2O (<63% yield). Uniformly satisfactory results, combining both yields (>80%) and stereoselectivities (>99% *trans*-isomers) were obtained.

Alkenyl difluorides have been also used as substrates for Pd-catalyzed cross-coupling reactions. Selective cleavage of a C−F bond was observed in the cross-coupling of 1-(2,2-difluorovinyl)naphthalene with 4-methoxyphenylzinc chloride to form the (*Z*)-monofluoroalkene **206**, as the major product (70% yield), and the dicoupled product **207** (23% yield) (Scheme 190).[246]

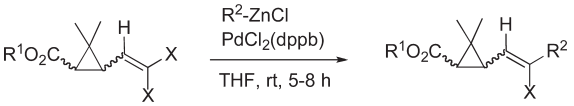
Shen and Wang reported the Stille reaction of 1,1-dibromoalkenes with aryl- and vinylstannanes (Scheme 191).[247] Depending on the reaction conditions, (*Z*)-1-aryl(alkenyl)-1-bromo-1-alkenes or internal alkynes (Scheme 418) were formed. After a systematic investigation to determine the optimal reaction conditions, it was found that $Pd_2(dba)_3$ (2.5 mol %) and TFP (15 mol %)

Scheme 187



R^2-ZnX or R^2-MgX	R^1	R^2	yield (%)
Ph-MgBr	Ph	Ph	98
Ph-ZnCl	Ph	Ph	94
4-ClC_6H_4-MgBr	Ph	4-ClC_6H_4	90
2-thienyl-MgBr	Ph	2-thienyl	80
Ph-MgBr	4-$MeOC_6H_4$	Ph	97
4-ClC_6H_4-MgBr	4-$MeOC_6H_4$	4-ClC_6H_4	81
Ph-MgBr	2-thienyl	Ph-	78
Ph-MgBr	Me	Ph	90
Ph-MgBr	Cl	Ph	55-78
4-ClC_6H_4-MgBr	Cl	4-ClC_6H_4	90
2-thienyl-MgBr	Cl	2-thienyl	87

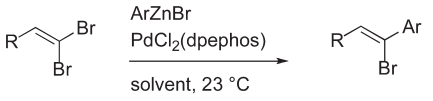
Scheme 188



X= Br, Cl; R^1 = Me, Et, 3-$PhOC_6H_4CH_2$

R^2 = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-thienyl, 2-furyl

Scheme 189



R	Ar	solvent	yield (%)
n-C_6H_{13}	Ph	THF	94
n-C_6H_{13}	2-thienyl	THF	84
n-C_6H_{13}	2-thiazolyl	toluene	84
(*S*)-$C_2H_5(CH_3)CH$	Ph	THF	86
(*S*)-$C_2H_5(CH_3)CH$	2-thienyl	THF	91
(*S*)-$C_2H_5(CH_3)CH$	2-thiazolyl	toluene	82

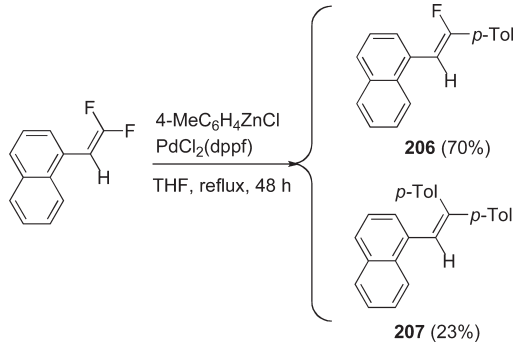
Only representative results are reported

allowed the coupling reaction with organostannanes (1.05 equiv) to be carried out in toluene at 100 °C for 20 h, giving the (*Z*)-1-aryl-1-bromoalkenes in good yields. Most 2-aryl- and 2-alkyl-1,1-dibromoalkenes gave monobromides in good yields with little or no dicoupled product (Scheme 191). The proposed mechanism for the reaction is depicted in Scheme 430.

While high stereoselectivity has been obtained in cross-coupling reactions of 2-substituted 1,1-dihaloalkenes, that of 2,2-disubstituted 1,1-haloalkenes has been generally poor. An example of high stereocontrol has been observed in the arylation of the γ-(dibromomethylene)butenolide **292** with phenyltributylstannane by the combination of $Pd(dba)_2$ (6 mol %) and $AsPh_3$ (20 mol %), affording the monobromobutenolide **298** with excellent stereocontrol

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 190



and high yield (84%) (Scheme 192). The stereochemistry of **298** was unambiguously determined by conversion into the bromine-free γ-alkylidenebutenolide **299** with Zn dust and a drop of AcOH in THF. It is noteworthy that this hydrodebromination occurred with 98% retention of configuration.[237]

The nickel-catalyzed coupling of a β,β-dibromoenol ether with a Grignard reagent has been described.[40] In that occasion, the reaction of 2,2-dibromoethenyl butyl ether with phenylmagnesium bromide catalyzed by nickel acetylacetonate in benzene afforded the related monocoupled product as single geometric isomer (Scheme 193). The yield was good (75%), but it was based on the converted starting material, which never exceeded 50%.

Ishihara and co-workers described the reaction of benzyl 2,3,3-trifluoroacrylate with various Grignard reagents (1.3 equiv) in the presence of catalytic CuBr (0.13 equiv) (Scheme 194).[239] By employing this amount of ArMgBr and catalyst, they generally obtained good yields of β-arylated products, but the use of 5.0 equiv of ArMgBr and 0.25 equiv of CuBr was required with less efficient Grignard reagents.

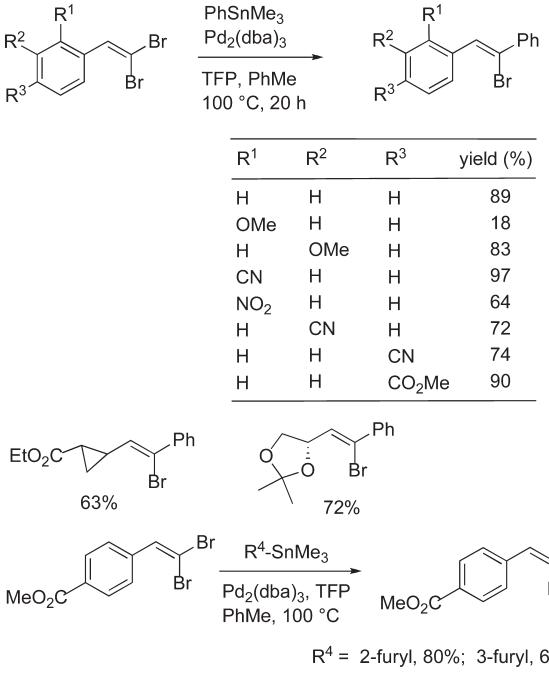
An anomalous Heck reaction was observed when the vinylidene difluoride **310** was used as a coupling partner in the arylation of alkenes. Under Heck reaction conditions, **310** underwent carbopalladation with aryl iodides to give α-fluorostyrenes **312** as main products, instead of the expected β,β-difluorostyrenes **311** (Scheme 195).[248] This result is due to the charge control in the Heck reaction that causes preferred arene addition to the F_2-carbon of **310**, followed by β-F elimination that leads to **312**. This finding was also exploited to introduce an α-fluorovinyl substituent into the 5-position of the indole **313** (Scheme 196).[249]

Two examples of *trans*-selective monoarylation with indium organometallics has been recently reported.[236] Thus, (2,2-dibromovinyl)benzene and 1,1-dibromonon-1-ene underwent the cross-coupling with triphenylindium in the presence of $PdCl_2$(dpephos) (2 mol %) and $Pd_2(dba)_3$/TFP (1:1, 2 mol %), respectively, to give the related monophenylated products in satisfactory yields (55−57%) (Scheme 197).

3.1.3. Coupling with Alkynylmetal Reagents. Linstrumelle and co-workers described for the first time the cross-coupling of *gem*-dihaloalkenes with acetylenes to afford enynes.[14] Thus, the coupling of 1,1-dichloroethylene (5 equiv) with a variety of 1-alkynes in the presence of $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.05 equiv), and *n*-$BuNH_2$ (1.5 equiv) afforded 2-chloroenynes **315** in high yields (72−90%) (Scheme 198).

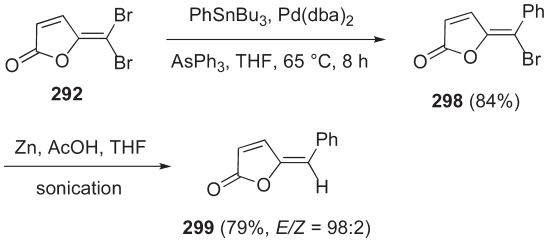
Kim and co-workers systematically investigated the reaction conditions for the Sonogashira cross-coupling[250] of

Scheme 191

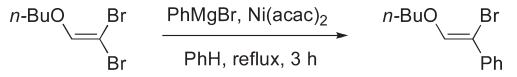


R^1	R^2	R^3	yield (%)
H	H	H	89
OMe	H	H	18
H	OMe	H	83
CN	H	H	97
NO_2	H	H	64
H	CN	H	72
H	H	CN	74
H	H	CO_2Me	90

Scheme 192



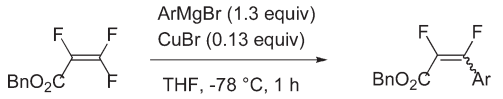
Scheme 193



2-aryl-1,1-dibromoethenes with 1-alkynes.[251] The coupling of the dibromide **316** with the alkyne **317**, chosen as a model substrate, was carried out under a variety of conditions, including Pd catalysts [$PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, $PdCl_2$, $Pd(PPh_3)_4$], phosphine ligands [PPh_3, TFP, $P(2\text{-}MeOC_6H_4)_3$, dppb, $P(4\text{-}MeOC_6H_4)_3$], solvents [benzene, toluene, $ClCH_2CH_2Cl$, TFP, AcOEt, acetone, MeCN, DMF, DMSO, NMP, *n*-BuOH], amines [Et_3N, piperidine, pyrrolidine, morpholine, *i*-Pr_2NH, Et_2NH, *t*-$BuNH_2$, *n*-$BuNH_2$], amount of the Pd catalyst, and reaction concentration (Scheme 199). The product ratio of 2-aryl-1-bromo-1-alkynylethene **318**, 2-aryl-1,1-dialkynylethene **319**, and 1-aryl-1,3-diyne **320** varied according to the reaction conditions. The coupling in benzene afforded **319** as the major product (75% yield), and no **320** was isolated. On the other hand, **320** was formed in DMF or DMSO in acceptable yields (58−62%). The ratio of the (*E*)- and (*Z*)-isomers of **318**

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

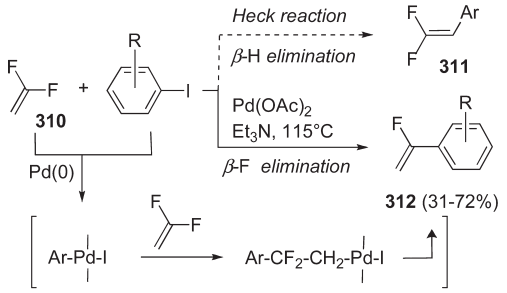
Scheme 194



Ar	yield (%)	*E*/*Z*
Ph	94	14:86
4-MeOC$_6$H$_4$	93	16:84
3-MeOC$_6$H$_4$	38 (56)[a]	12:88
2-MeOC$_6$H$_4$	0	--
4-MeC$_6$H$_4$	70 (97)[a]	14:86
4-(CH$_2$=CH)C$_6$H$_4$	97	12:88
1-Naphthyl	36 (74)[a]	5:95
2-Naphthyl	46 (98)[a]	8:92
4-F$_3$CC$_6$H$_4$	6	16:84

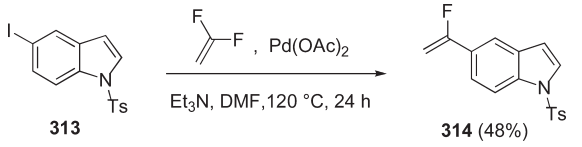
[a]5.0 equiv of RMgBr and 0.25 equiv of CuI were used.

Scheme 195

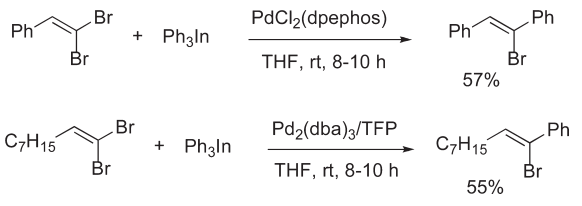


R = H, 4-MeO, 4-*i*-Pr, 4-F, 4-Me, 2-Me, 2-F, 4-C$_6$H$_4$, 4-NH$_2$

Scheme 196

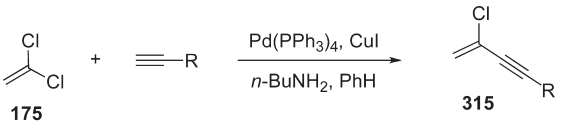


Scheme 197



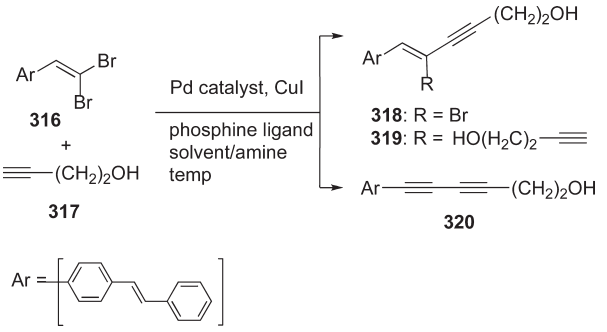
was between about 1:2 and 1:4 in other solvents than benzene and toluene, where (*Z*)-**318** was exclusively obtained. When amines were used as the solvent, the coupling gave **319** (20% yield) and **320** (68% yield) in *i*-Pr$_2$NH, whereas only **320** was isolated in piperidine (56% yield). Most of the Pd reagents catalyzed effectively the coupling in benzene to give **319** as the major product. However, Pd$_2$(dba)$_3$ was the most efficient catalyst in

Scheme 198

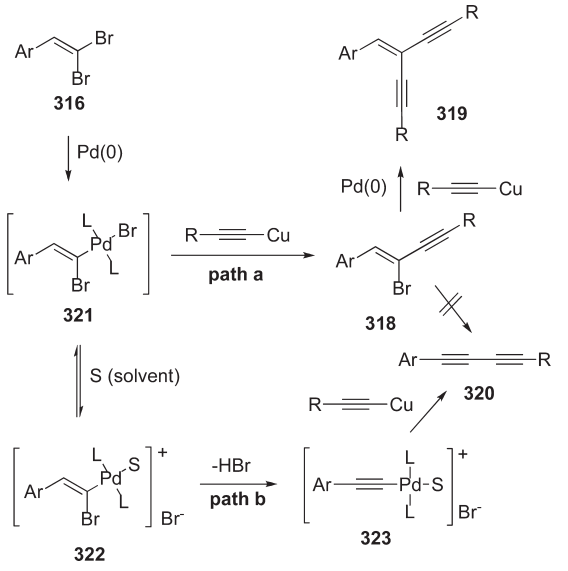


R	*n*-C$_5$H$_{11}$	Cl(CH$_2$)$_3$	AcO(CH$_2$)$_3$	Ph	Me$_3$Si
315 yield (%)	81	82	72	90	82

Scheme 199



Scheme 200

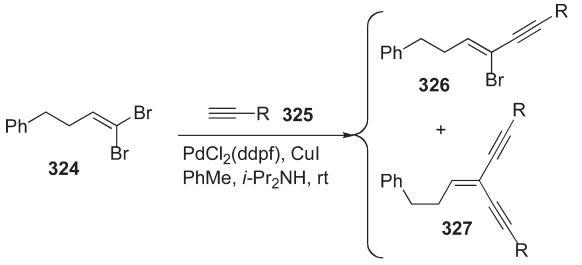


DMF in terms of yield and reaction rate for **320**. To explain the dependence of the products on the reaction conditions, the working hypothesis shown in Scheme 200 was proposed. The usual cross-coupling reaction is favored in nonpolar solvents such as benzene or toluene to give **318** or **319** after the oxidative addition of Pd(0) (path a). Highly polar and good coordinating solvents such as DMSO favor the solvated ionic complex **322**, which is converted into the alkynyl Pd intermediate **323** (path b).

Independently, Uenischi and co-workers also studied the reaction conditions for the Sonogashira cross-coupling of 1,1-dibromoalkenes with alkynes by using 1,1-dibromo-3-phenyl-1-butene **324** and terminal acetylenes **325a**−**e** as coupling partners

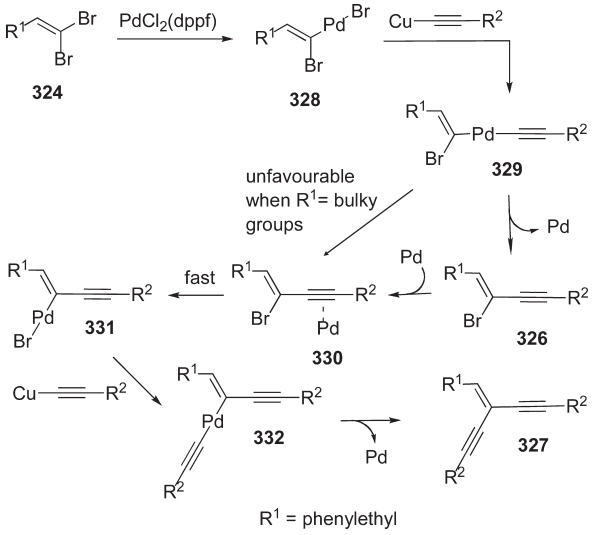
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 201



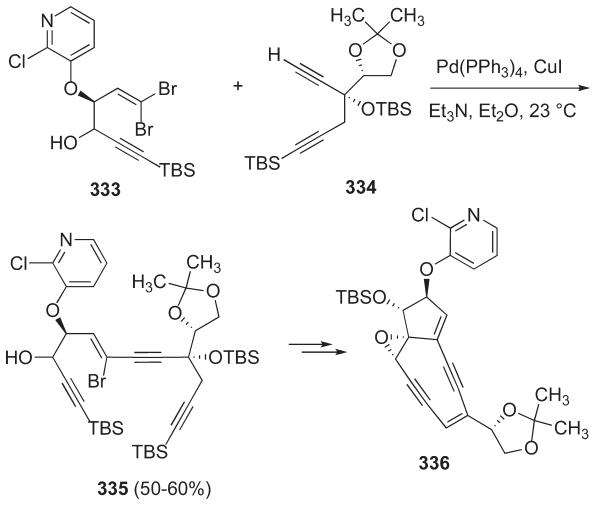
R	$SiMe_3$	$SiEt_3$	*t*-Bu	Ph	*n*-Bu
	a	**b**	**c**	**d**	**e**
324 yield (%)	0	0	0	24	0
326 yield (%)	68	61	56	24	17
327 yield (%)	13	13	11	42	61

Scheme 202

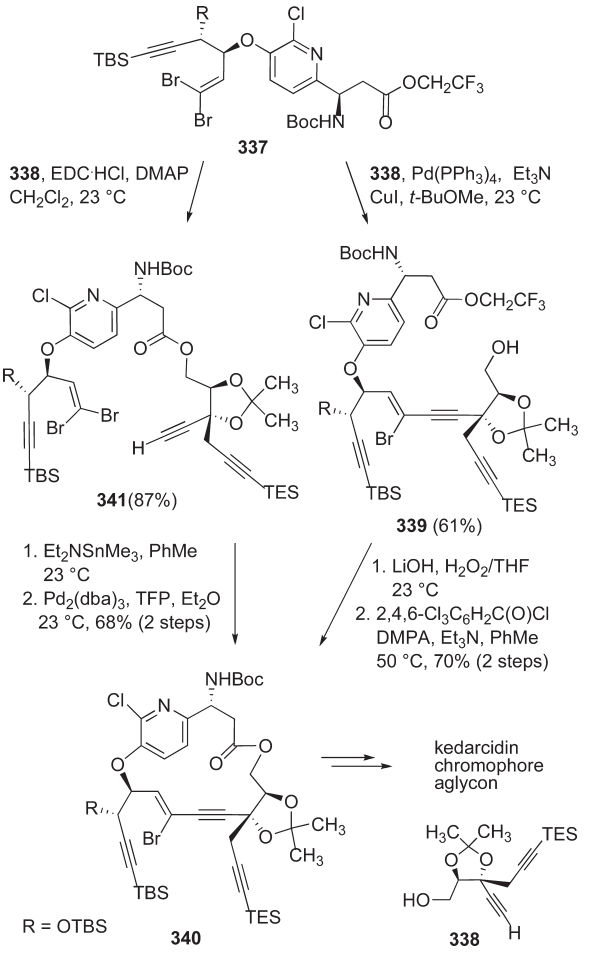


(Scheme 201).[252,253] Under standard Sonogashira conditions [$Pd(PPh_3)_4$, CuI, *i*-Pr_2NH, benzene, rt] the coupling of **324** with trimethylsilylacetylene **325a** was rather unselective giving the bromoenyne **326a** (20% yield), the enediyne **327a** (22% yield), and the recovered **324** (41% yield). Among other examined Pd catalysts [$PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(MeCN)_2$, Pd(dppe)$_2$, $PdCl_2$(dppf)], $PdCl_2$(dppf) was found to be very selective giving, after 15 min at room temperature, **326a** in 68% yield and **327a** in 13% yield. The coupling of **324** with other terminal acetylenes **325b**−**e** and $PdCl_2$(dppf) as the catalyst was then examined. The results indicated that the ratio **326**/**327** increased when alkynes bearing small substituents were used. Thus, for instance, with *t*-BuC≡CH the ratio of **326c**/**327c** was 56/11, whereas with *n*-BuC≡CH the ratio of **326e**/**327e** was 17/61 (Scheme 201). Based on the experimental results, a mechanism for the selectivity was proposed (Scheme 202). Reductive elimination of Pd from the initially formed intermediate **329** affords the bromoenyne **326** as the major reaction pathway. In the minor pathway, Pd stays bound to the enyne

Scheme 203



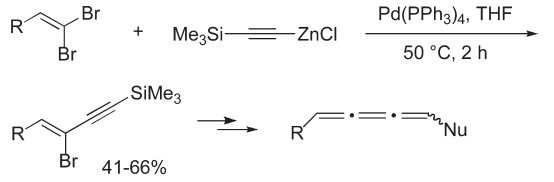
Scheme 204



after the reductive elimination, forming the Pd intermediate **230** with a tight or loose coordination. The transformation of **330** then occurs rapidly to give the intermediate **331**, which is

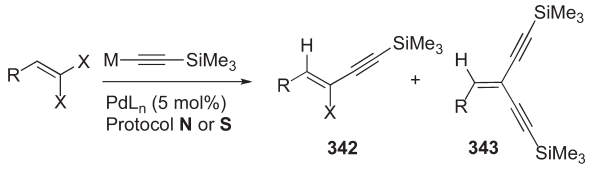
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 205



R = Ph, Naphthyl, 3-$CF_3C_6H_4$, 3-$MeOC_6H_4$, $PhCH_2$, $PhCH_2CH_2$

Scheme 206



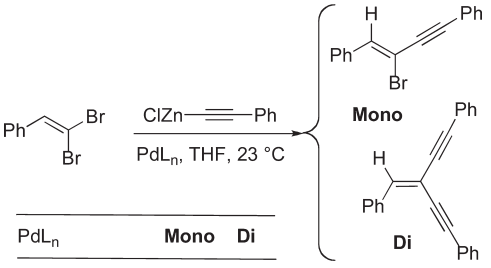
R	X	PdL_n	protocol and product yield (%)			
			N		S	
			342	343	342	343
Ph	Br	$Pd(PPh_3)_4$	84	14	15	18
Ph	Br	$PdCl_2$(TFP)	87	8	18	43
Ph	Br	$PdCl_2$(dppf)	89	3	78	3
Ph	Br	$Pd(DPEphos)Cl_2$	90	8	89	8
Ph	Cl	$Pd(PPh_3)_4$	61	12	--	--
Ph	Cl	$PdCl_2$(dppf)	87	10	33	18
Ph	Cl	$PdCl_2$(dpephos)	84	13	56	4
n-C_9H_{19}	Br	$PdCl_2$(dpephos)	94	3	92	6
n-C_6H_{13}	Br	$PdCl_2$(dpephos)	95	5	np	np
n-C_6H_{13}	Cl	$PdCl_2$(dpephos)	65	8	26	2
MeSi≡	Cl	$PdCl_2$(dpephos)	91	7	84	12
	Br	$PdCl_2$(dpephos)	96	2	np	np
TBSO 	Br	$PdCl_2$(dpephos)	87	13	90	10
TBSO 	Br	$PdCl_2$(dppf)	--	--	89	11
TBSO 	Br	$PdCl_2$(dpephos)	99	<1	np	np
TBSO 	Br	$PdCl_2$(dpephos)	99	<1	np	np

N: Negishi alkynylation with M = ZnCl, in THF, at 0-50 °C.
S: Sonogashira alkynylation with M = H , CuI (5 mol%), *i*-Pr_2NH (2 equiv) in benzene.
np: not performed

formally the product of the oxidative addition product of Pd to **326**. The reaction rate for the formation of **326** was higher with alkynes bearing bulky groups than with those with smaller ones, whereas a large substituent had a negative effect on the reaction rate during the second coupling, because the formation of the intermediate **330** is unfavorable. On the other hand, small groups at the terminal position of the acetylene favored the formation of the diyne **327**, through the alkyne-coordinated Pd complex **330** formed probably from **326**.

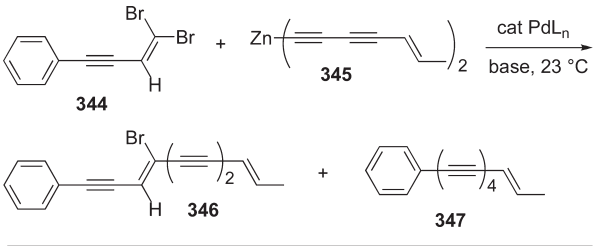
Myers and co-workers developing synthetic routes to kedarcidin, a chromoprotein enediyne antibiotic, described the preparation of the kedarcidin core structure[254] **336** (Scheme 203) and kedarcidin chromophore aglycon[255] (Scheme 204). Both syntheses share as common key steps the union of fragments containing

Scheme 207

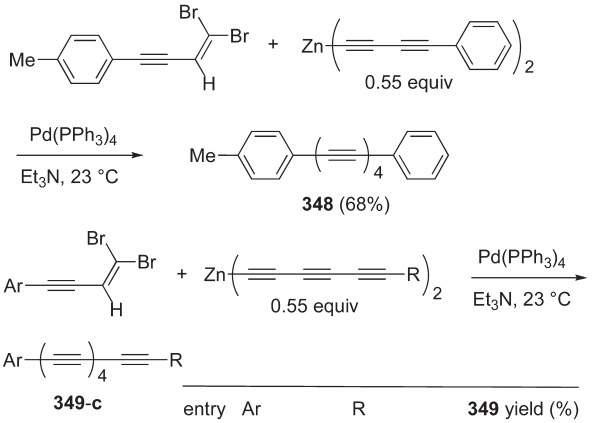


PdL_n	Mono	Di
$Pd(PPh_3)_4$	81%	8%
$PdCl_2$(dpephos)	66%	26%
$PdCl_2$(dpppf)	35%	40%

Scheme 208



345 (molar equiv)	added base	catalysts (%)	yield (%) 346	347	344
0.55	None	$PdCl_2$(dpephos)	<10	32	49
1.0	None	$PdCl_2$(dpephos)	<1	66	<1
0.55	Et_3N (1 equiv)	$Pd(PPh_3)_4$	<1	66	<1

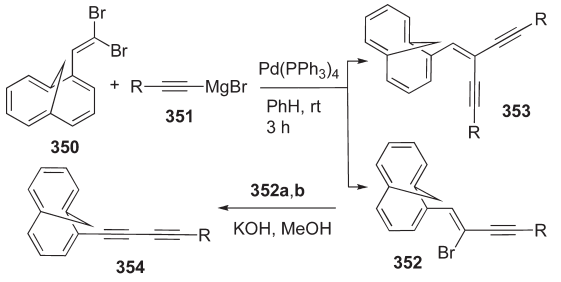


entry	Ar	R	**349** yield (%)
a	Ph	Me	43
b	Ph	(*E*)-MeCH=CH	48
c	4-MeC_6H_4	Ph	55

gem-dibromide and terminal acetylene moieties, respectively, by Pd-mediated cross-coupling reactions. In the synthesis of **336**, Sonogashira coupling [$Pd(PPh_3)_4$ (0.1 mol %) and CuI (0.3 equiv)] of **333** with the terminal alkyne moiety of **334** furnished bromoolefin **335** in 50−60% yields. Following the same procedure, compound **339** was synthesized in similar yield (61%) by coupling of **337** with **338** (Scheme 204). Both these couplings occurred by selective replacement of the *trans*-bromide to afford exclusively (*Z*)-vinyl bromides **335** and **339**. The absence of the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

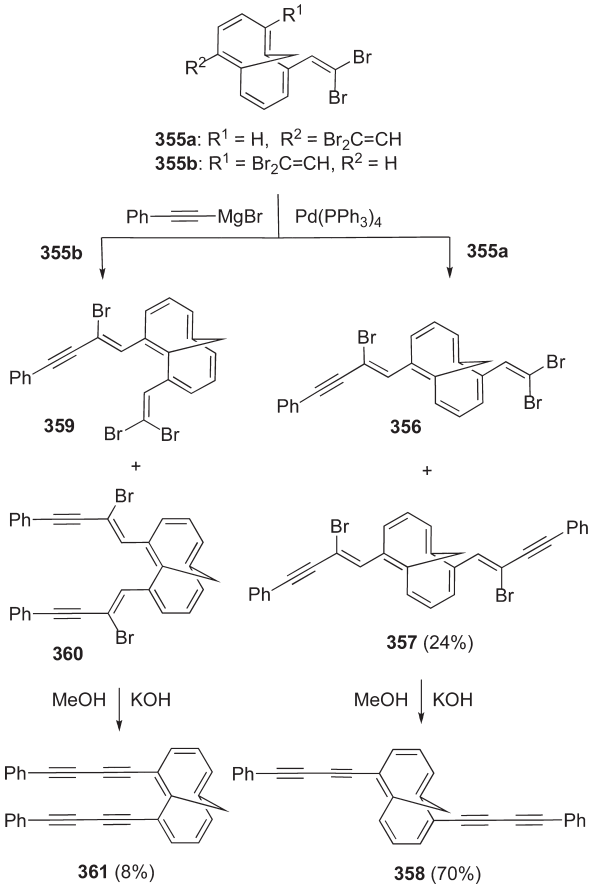
Scheme 209



	R	354 yield (%)
a	Ph	78
b	*t*-Bu	17

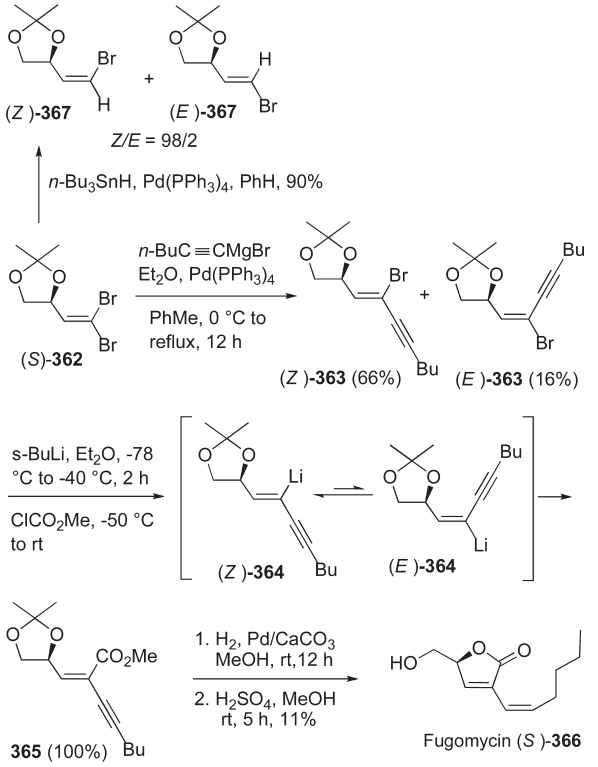
	R	352 yield (%)
a	Ph	59
b	*t*-Bu	28
c	TMS	57
d	TIPS	0

Scheme 210



(*E*)-isomers, whose formation was observed in related systems as a result of internal delivery of Pd(0) by prior coordination to a tethered terminal acetylene,[256] was ascribed in this case to the presence of the bulky *tert*-butyldimethylsilyl group, which may preclude such a directing effect. When the terminal acetylene function in compound **341** was submitted to intramolecular coupling with the *gem*-dibromide moiety under Sonogashira conditions, the desired macrolactone **340** was obtained, but the yields were low (<40%) and difficult to reproduce. Thus, activation of

Scheme 211



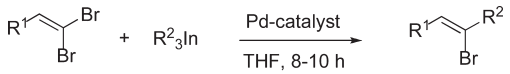
the terminal alkyne moiety prior to the cyclization was pursued by stannylation with the reagent Et_2NSnMe_3. Sequential addition of $Pd_2(dba)_3$ and TFP to the concentrated stannylation product then led to smooth formation of the macrolactone **340** within 12 h at 23 °C (68% yield from **337**).

Pd-catalyzed synthesis of functionalized butatrienes was achieved starting from a variety of 2-bromo-1-buten-3-ynes that were prepared in moderate yields (41−66%), but as sole (*Z*)-isomers, by coupling a number of 1,1-dibromoalkenes with trimethylsilylethynylzinc chloride in the presence of $Pd(PPh_3)_4$ (2 mol %) (Scheme 205).[257]

trans-Selective monoalkynylation of 1,1-dibromo(dichloro)-alkenes with $Me_3SiC{\equiv}CH$ or its zinc derivative was investigated in detail by Negishi and co-workers with $Pd(PPh_3)_4$, $PdCl_2$(TFP), $PdCl_2$(dppf), and $PdCl_2$(dpephos) as catalysts (Scheme 206).[258,259] The results depended significantly on (i) cross-coupling protocols, that is, Sonogashira alkynylation versus Negishi alkynylation, involving the use of different countercations (M), (ii) halogen leaving groups (X), that is, Br versus Cl, (iii) carbon substituents R, and (iv) catalysts. As long as 1,1-dibromo-1-alkenes and $PdCl_2$(dpephos) were used, both Negishi and Sonogashira protocols led to monoalkynylation products **342** in >87% yields and >99% stereoselectivities with no detectable sign of formation of the (*E*)-isomers, the dialkynylation products **343** being the main byproduct. On the other hand, substantial differences between the two protocols were observed when 1,1-dichloro-1-alkenes were used as substrates. Whereas the Negishi alkynylation with $PdCl_2$(dpephos) was generally satisfactory for monoalkynylation of 1,1-dichloro-1-alkenes as well, the Sonogashira alkynylation was rather unsatisfactory, except in the reaction of $Me_3SiC{\equiv}CCH{=}CCl_2$. Notwithstanding the very good results obtained in that study, these cannot be generalized to other alkynes. In fact, the results summarized in Scheme 207 clearly

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

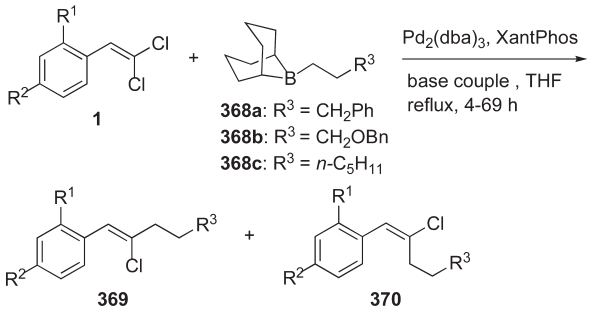
Scheme 212



R^1	R^2	yield (%)
n-C_7H_{15}	Me_3Si— ≡	76[a]
n-C_7H_{15}	Ph— ≡	70[a]
Ph	Me_3Si— ≡	62[b]
Ph	Ph— ≡	77[b]

[a] $Pd_2(dba)_3$/TFP (1:1, 2 mol%), 0°C
[b] $PdCl_2$(dpephos) (2 mol%), rt

Scheme 213



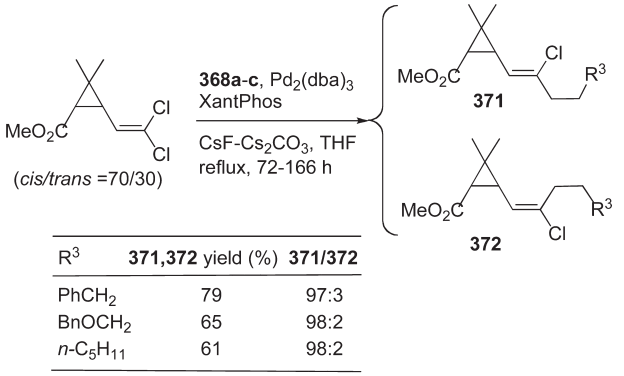
	R^1	R^2	R^3	**369,370** yield (%)	**369/370**
a	H	H	$PhCH_2$	80	97:3[b]
b	H	OMe	$PhCH_2$	88	93:7[b]
c	H	OMe	$BnOCH_2$	83	98:2[a]
c	H	OMe	n-C_5H_{11}	61	98:2[a]
e	H	CO_2Me	$PhCH_2$	65	94:6[a]
f	H	F	$PhCH_2$	65	98:2[b]
g	H	F	n-C_5H_{11}	65	93:7[a]
h	OMe	OMe	$PhCH_2$	82	94:6[a]
i	OMe	OMe	n-C_5H_{11}	79	95:5[b]

[a] Method A: KF-K_3PO_4 couple. [b] Method B: CsF-Cs_2CO_3 couple.

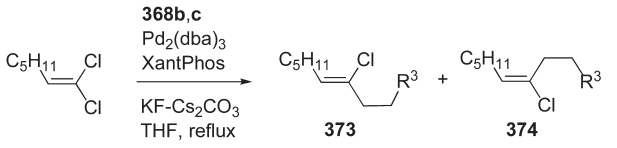
indicate that, at least in this case, $Pd(PPh_3)_4$ is superior to $PdCl_2$(dpephos) and $PdCl_2$(dppf) to form the monoalkynylation product.[258]

Negishi and co-workers reported some results for the development of iterative and convergent protocols for the synthesis of oligoynes. In the convergent approach, the critical step involves the Pd-catalyzed *trans*-selective monoalkynylation of 1,1-dibromoalkenes (Scheme 208).[260] Treatment of the dibromide **344** with the alkynylzinc derivative **345** (1.1 equiv) in the presence of $PdCl_2$(dpephos) (5 mol %) at 23 °C gave **346** and **347** in <10% and 32% yields, respectively, with 49% of the starting dibromide remaining unreacted. Only traces, if any, of the stereoisomer of **346** and dialkynylated product were present. Although the precise mechanism of formation of **347** was unclear, **345** should have been partially consumed as a mere base to neutralize HBr. As expected, the use of 2 equiv of **345** produced **347** in 66% yield along with only traces of **346** and the starting dibromide. Finally, a combination of **326** (0.55 mol equiv) and Et_3N (1 equiv) produced **347** in 66% yield. This procedure was successively applied to the synthesis of **348** in 68% yield as well as three conjugated pentaynes **349a**−**c** (Scheme 208).

Scheme 214



R^3	**371,372** yield (%)	**371/372**
$PhCH_2$	79	97:3
$BnOCH_2$	65	98:2
n-C_5H_{11}	61	98:2

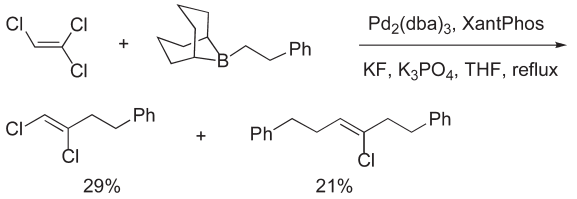


R^3	**373,374** yield (%)	**373/374**
$PhCH_2$	65	96:4
n-C_5H_{11}	74	94:6

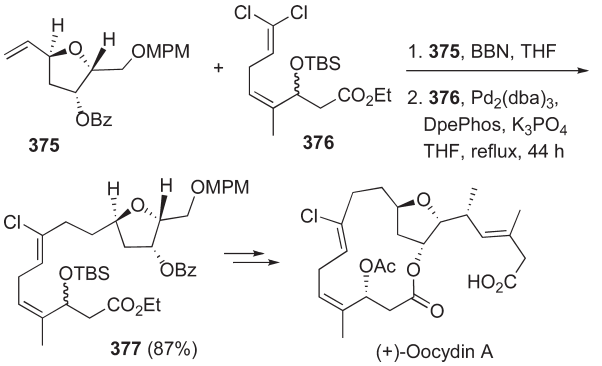
Neidlein and co-workers reported first the stereoselective Pd(0)-catalyzed coupling of 1,1-dibromoalkenes with alkynes to give enynes.[261] The initial use of the n-$BuNH_2$/CuI system, successfully employed in the preparation of 2-chloroenynes from dichloroethylene,[14] was not efficient in this system. Subsequently, they were able to accomplish the cross-coupling of the alkenyl bromide **350** by reaction with ethynylmagnesium bromides **351** in the presence of $Pd(PPh_3)_4$ in benzene (Scheme 209). In this way, enynes **352** were obtained in 28−59% yields with a small amount (<8% in all cases) of the disubstituted products **353**, whose formation was presumed to occur by an initial *cis*-coupling instead of a coupling of a second molecule of Grignard to the initially formed *trans*-substituted system. On the other hand, the coupling with triisopropylsilyl (TIPS) ethynylmagnesium bromides failed, probably because the TIPS group may be so sterically encumbered that the coupling event cannot take place. The coupling of phenylethynylmagnesium bromide with compounds **355** was also examined, but in this case a very complicated mixture of products was formed (Scheme 210). Compounds **351a,b**, **357**, and **360** were dehydrohalogenated with KOH/MeOH to give the related diynes in 8−78% yields (Schemes 209 and 210).

The antifungal butenolide fugomycin (*S*)-**366** was synthesized starting from the enantiomerically pure building block (*S*)-**362** (Scheme 211).[262] Its geminal dibromo substitution pattern permitted a sequential carbon−carbon bond formation in a stereoselective manner. The Pd(0)-catalyzed coupling of (*S*)-**362** with hexynylmagnesium bromide afforded an 8/2 mixture of (*Z*)- and (*E*)-**363** in 82% yield. This result contrasts with the highly selective replacement of bromine with hydrogen obtained using the system n-$Bu_3SnH/Pd(PPh_3)_4$, which afforded a 98/2 mixture of (*Z*)- and (*E*)-**367** in 90% yield (Scheme 211). Fortunately, treatment of a mixture of (*Z*)- and (*E*)-**363** with *n*-BuLi and then with chloroformate gave the carboxylic ester **365** in 100% crude yield. This result takes advantage of the fact that equilibration between the vinyllithium derivatives (*Z*)- and

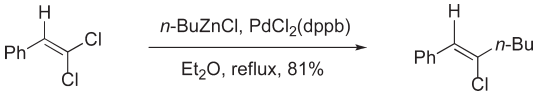
Scheme 215



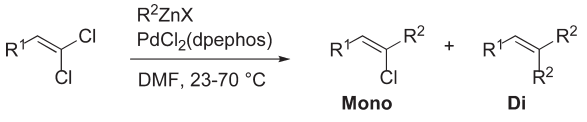
Scheme 216



Scheme 217



Scheme 218



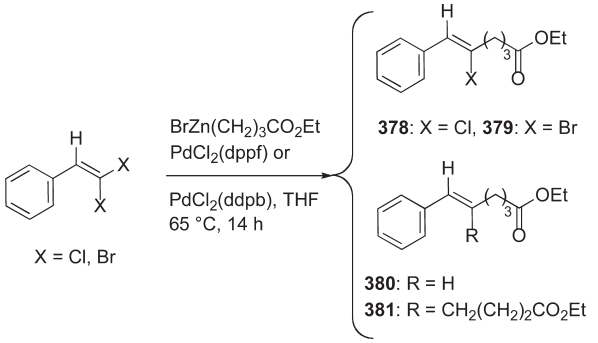
R^1	R^2ZnX (additive)	yield% Mono	yield% Di
n-C_6H_{13}	Me_2Zn-(NMI)	75	15
n-C_6H_{13}	Et_2Zn	76	13
n-C_6H_{13}	$C_8H_{17}CH(Me)CH_2ZnBr$	70	25
(TBS)OCH_2CHMe	Et_2Zn	85	5
(TBDPS)$O(CH_2)_2$	$C_8H_{17}ZnBr$	80	12
TMS ≡	Me_2Zn	90	5
TMS ≡	Me_2Zn	82	15
Ph	$C_8H_{17}ZnBr$	90	3

Only representative examples are reported

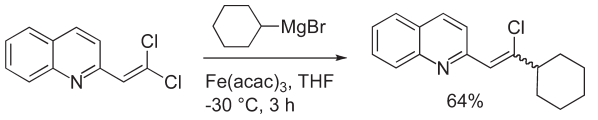
(*E*)-**364** occurs under the conditions employed and the thermodynamically favored isomer (*Z*)-**364** is formed preferentially.

trans-Selective monosubstitution of 1,1-dibromoalkenes by Pd-catalyzed cross-couplings with triorganoindium reagents (R_3In, R = alkyl, alkenyl, aryl, and alkynyl) has been examined.[236]

Scheme 219



Scheme 220

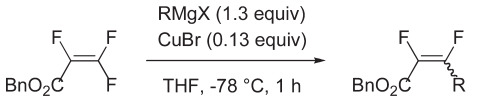


After careful inspection of different Pd complexes and reaction conditions, the best results for the monoalkynylation of 1,1-dibromonon-1-ene with $(RC{\equiv}C)_3In$ (R = Me_3Si and Ph) were obtained with $Pd_2(dba)_3$ and TFP (1:1, 2 mol %) as the catalytic system (Scheme 212). Unfortunately, the same reaction conditions applied to β,β-dibromostyrene were unsuccessful, but with the catalyst $PdCl_2$(dpephos) (2 mol %), alkynylindiums afforded the related monosubstituted products in good yields (62−77%) (Scheme 212).[236]

3.1.4. Coupling with Alkylmetal Reagents. Roulland and co-workers reported the selective Pd-catalyzed monoalkylation of 2-aryl- and 2-alkyl-substituted 1,1-dichloroalkenes with 9-alkyl-9-BBN (Schemes 213 and 214).[263] To establish the best reaction conditions to reach monoalkylated products, a broad range of phosphine ligands, Pd catalyst precursors, bases, and solvents were evaluated. Among solvents, those nonpolar and in particular THF appeared instrumental, while among ligands bidentate bisphosphines and, above all, those with large P−Pd−P bite angles, θ, appeared to be essentials. These results were in accord with those obtained by Negishi who demonstrated that dpePhos (θ = 102°) provided a good selectivity in the monocoupling of 1,1-dichloroalkenes with alkylzinc.[264] The best catalytic system was found to be $Pd_2(dba)_3$ (2.5 mol %) with XantPhos (5 mol %, θ = 111°) as the catalyst and KF−K_3PO_4 or CsF−Cs_2CO_3 as the couple F−base in refluxing THF. Yields were generally good, and the selectivity for the monocoupling was almost total in every case. The *Z*/*E* ratio was generally excellent, being in most cases greater than 95:5. Concerning substrates the higher reaction rates were observed with electron-poor styrenes, while negligible amounts of 2-fold coupled products were observed with electron-rich styrenes. When vinylidene chloride was used as the substrate, the reaction failed to give any coupling product, but trichloroethylene reacted under usual conditions with KF−K_3PO_4 as the F−base couple, to afford two products of *Z* configuration: the 1,2-dichloro-1-alkene (29%) resulting from the coupling of only one borane unit at C-1 and the chloroalkene (21%) formed by coupling of two borane units at C-1 and C-2 of the starting material (Scheme 215).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

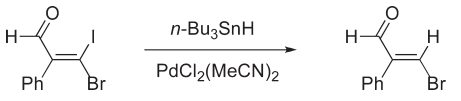
Scheme 221



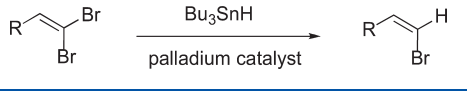
R	yield (%)	*E*/*Z*
n-Bu	92	14/86
$PhCH_2$	70 (84)[a]	31/69
4-pentenyl	43 (82)[a]	6/94
s-Bu	94	14/86
c-C_6H_{11}	91	9/91

[a]5.0 equiv of RMgBr and 0.25 equiv of CuI were used.

Scheme 222



Scheme 223



Next, Roulland applied this methodology to the total synthesis of (+)-oocydin A, a natural compound with cytotoxic and phytopathogenic properties.[265] The key step of this synthesis is the Suzuki−Miyaura cross-coupling between the 1,1-dichloro-1-alkene **376** and a 9-alkyl-9-BBN reagent prepared in situ by addition of BBN to the alkene **375** (Scheme 216). The initial use of their previously described optimal conditions[263] led to the compound **377** in only 34% yield along with degradation of the starting material. Reinvestigating the methodology revealed that the use of DpePhos (another large-bite-angle bisphosphine) in place of XantPhos in the absence of KF led to an effective cross-coupling of **376** to give **377** in a much improved yield (87%).

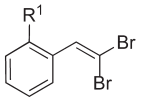
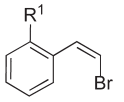
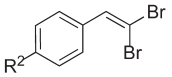
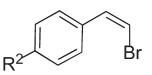
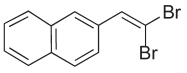
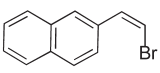
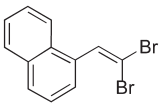
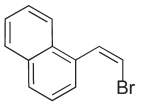
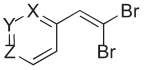
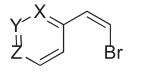
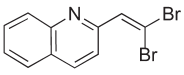
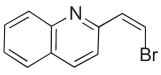
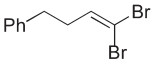
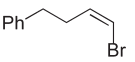
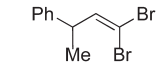
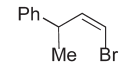
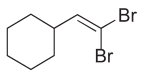
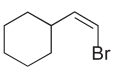
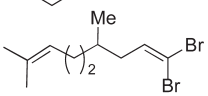
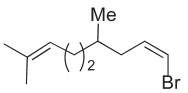
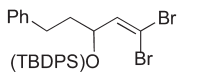
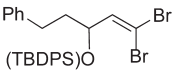
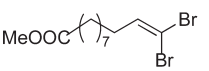
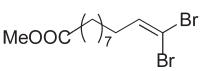
Minato and Tamao, in a study aimed at *trans*-selective Pd-catalyzed monosubstitution reactions of 1,1-dichloroalkenes by organozinc and magnesium reagents, reported an example of monoalkylation in which β,β-dichlorostyrene was coupled with *n*-BuZnCl (1 equiv) in the presence of $PdCl_2$(dppb) (1 mol %) to produce (*Z*)-(2-chlorohex-1-enyl)benzene in 81% yield (Scheme 217).[13] The use of the related Grignard reagent failed.

Since the application of the Minato protocol to alkyl-substituted 1,1-dibromo- and 1,1-dichloroalkenes produced only dialkylation products, Negishi conduced a systematic screening of Pd catalysts, additives, and solvents, which led to an optimized set of conditions.[264] Thus, with 5 mol % $PdCl_2$(dpephos), DMF, and in some cases one molar equivalent of *N*-methylimidazole relative to the zinc reagent, *trans*-selective monoalkylation of a variety of 1,1-dichloroalkenes, containing alkyl, aryl, alkenyl, and alkynyl groups, was satisfactorily achieved with alkyl zinc compounds. Some representative results are reported in Scheme 218.

Wnuk and Andrei investigated the differentiation of the two halogens in 1,1-dibromo- or 1,1-dichloroalkenes for selective monoalkylation with alkylzincs.[196] They found that β,β-dichlorostyrene reacted with $BrZn(CH_2)_3CO_2Et$ (1.7 equiv) in the presence of $PdCl_2$(dppf) (10 mol %) to give the (*Z*)-chloroalkene **378** (65% yield) in the addition to the monocoupled/reduced byproduct **380** (22% yield) (Scheme 219). Analogous coupling in the presence of $PdCl_2$(dppb) (10 mol %) produced **378** (53% yield), **380** (15% yield), and dialkylated product **381** (27% yield). A similar coupling with the more reactive β,β-dibromostyrene produced mainly dialkylated **381** (57−69% yields) and minor amounts of **380** (24−28% yields).

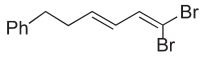
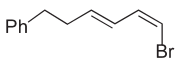
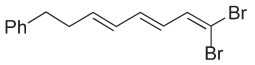
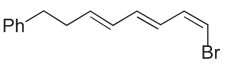
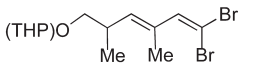
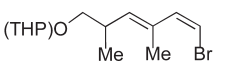
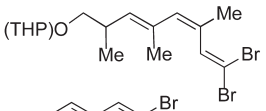
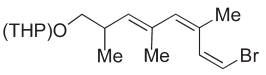
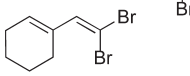
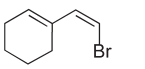
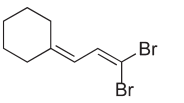
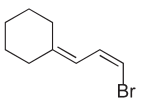
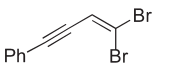
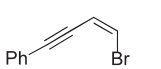
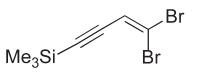
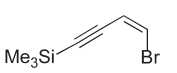
Figadère, Alami, and co-workers in a study aimed at the coupling of 1,1-dichloroalkenes with Grignard reagents under Fe catalysis, described that under optimal conditions the reaction of 1,1-dichloro-2-(2-quinolyl)ethylene with cyclohexylmagnesium bromide (3 equiv) and $Fe(acac)_3$ (10 equiv) led to a

Table 2. Stereoselective Hydrogenolysis of 1,1-Dibromoalkenes (Scheme 223)

dibromoalkene	(*Z*)-bromoalkene	yield (%)
		R^1 = H 76[a] R^1 = Me 79[a]
		R^2 = Me 79[a] R^2 = OAc 83[a] R^2 = OH 82[a] R^2 = NMe_2 90[a]
		86[b]
		87[b]
		X = N, Y = Z = CH 64[b] Y = N, X = Z = CH 62[b] Z = N, X = Y = CH 43[b]
		65[b]
		79[a]
		64[a]
		77[a]
		70[a]
		56[a]
		80[a]

[a] $Pd(PPh_3)_4$ was used as the catalyst. [b] Pd(0)-catalyst, generated in situ from $Pd(OAc)_2$ and $2PPh_3$, was used as the catalyst.

Table 3. Stereoselective Hydrogenolysis of Conjugated 1,1-Dibromoalkenes[a] (Scheme 223)

dibromoalkene	(*Z*)-bromoalkene	yield (%)
		82
		74
		82
		86
		85
		90
		68
		69

[a] $Pd(PPh_3)_4$ was used as the catalyst.

monocoupled product composed of a 5:1 mixture of undetermined *E*/*Z* isomers in 64% yield, with no dicoupled product (Scheme 220).[51]

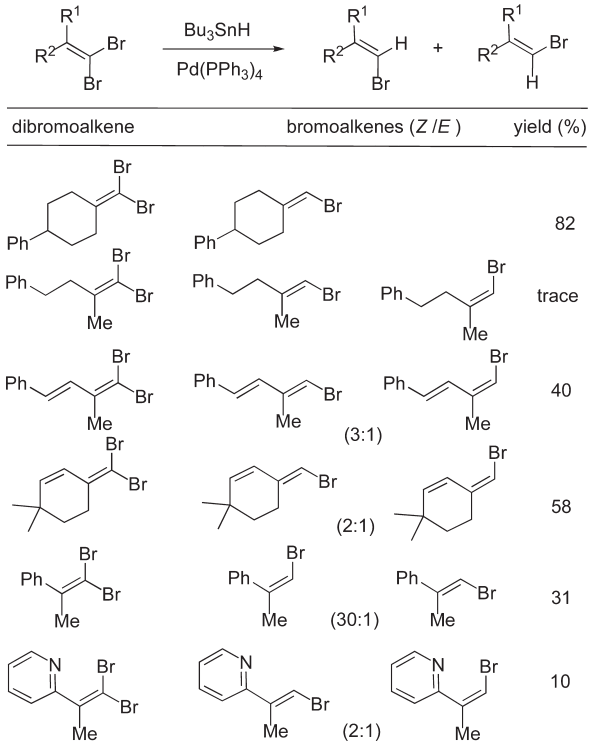
Ishihara and co-workers described the reaction of benzyl 2,3,3-trifluoroacrylate with various Grignard reagents (1.3 equiv) and catalytic CuBr (0.13 equiv) (Scheme 221).[239] Among these reagents, alkylmagnesium bromides gave the corresponding β-alkylated products in good to excellent yields with *Z* selectivity. However, the use of 5.0 equiv of Grignard reagent and 0.25 equiv of CuBr was necessary in some instances to improve the yields.

3.1.5. Hydrodehalogenation. McNelis and Bovonsombat reported that the reaction of (*Z*)-3-bromo-3-iodo-2-phenylprop-2-enal with Bu_3SnH in the presence of $PdCl_2(MeCN)_2$ caused the exchange of the vinyl iodine atom with a hydrogen atom to give the related (*E*)-1-bromoalkene (Scheme 222).[207] However, neither reaction conditions nor yield were reported.

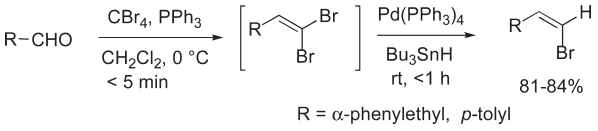
Next, Uenishi and co-workers developed a Pd-catalyzed hydrogenolysis of 1,1-dibromoalkenes with Bu_3SnH that occurred at room temperature to give stereoselectively (*Z*)-1-bromoalkenes (Scheme 223).[266,267]

A thorough investigation was carried out to determine the best reaction conditions, including the choice of the Pd catalyst [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2/2PPh_3$, $PdCl_2(CH_3CN)_2$, $PdCl_2$-$(dppf)_2$, $PdCl_2$, etc.], ligand, solvent, and hydride source. Among the catalysts, the most active were $Pd(PPh_3)_4$ and the Pd catalyst generated in situ from $Pd(OAc)_2$ and PPh_3. A number of phosphine and arsine ligands, with different steric and electronic demand, were examined in combination with $Pd(OAc)_2$ as catalysts. The results obtained showed that PPh_3 was the best ligand. Hindered and electron-deficient arylphosphines were not appropriate for the hydrogenolysis, whereas an electron-donating phosphine appeared to be appropriate. A wide range of

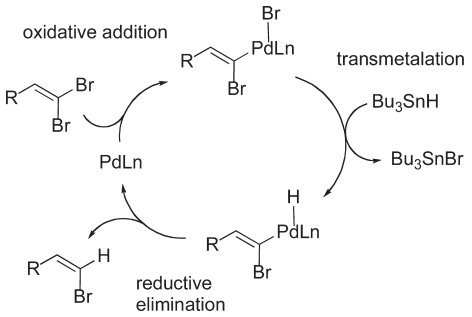
Scheme 224



Scheme 225



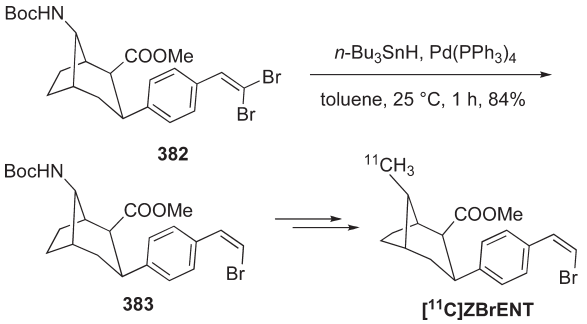
Scheme 226



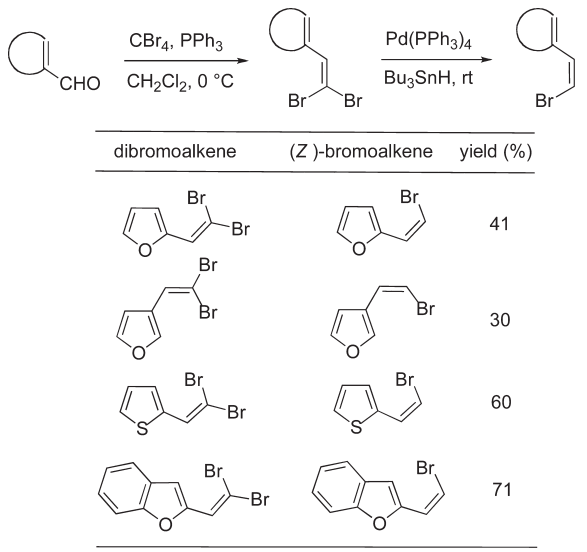
solvents, except EtOH, AcOH, and $CHCl_3$, were found compatible with the reaction, which however proceeded also in these solvents by addition of a cosolvent or radical scavenger. Among the sources of hydride (Et_3SiH, BH_3 complexes, Bu_3SnH, $NaBH_4$, $Na(CN)BH_3$, etc.), Bu_3SnH was found to be the best reagent because it allows the transfer of its hydride from tin to palladium very smoothly. The attempt to use of Bu_3SnX species [Bu_3SnCN, $(Bu_3Sn)_2$, etc.] in order to substitute the (*E*)-bromide by the X group, rather than H, failed.

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

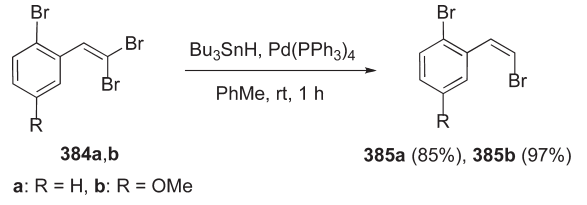
Scheme 227



Scheme 228



Scheme 229

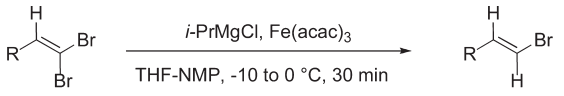


Under the optimized conditions [$Pd(PPh_3)_4$ or $Pd(OAc)_2$/$2PPh_3$ and Bu_3SnH in benzene or toluene at room temperature], a number of 2-(hetero)aryl- and 2-alkyl-1,1-dibromoalkenes were stereoselectively converted into (*Z*)-1-bromoalkenes in good to high yields (Table 2).

Hydrogenolysis of 1,1-dibromopolyenes and 1,1-dibromoenynes showed that their reactivity is greater than simple 1,1-dibromoalkenes (Table 3). It is noteworthy that no other stereoisomer was formed with these substrates.[266]

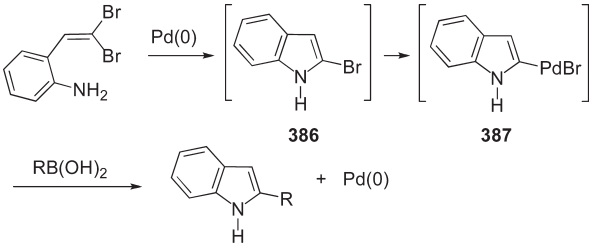
The hydrogenolysis of fully substituted 1,1-dibromoalkenes was also examined.[266] Due to the steric hindrance of the vicinal C−C bonds, these dibromides showed poor yield and selectivity (Scheme 224). Only in one case of 4-(dibromomethylene)-cyclohexylbenzene, the related bromoalkene, in which the

Scheme 230

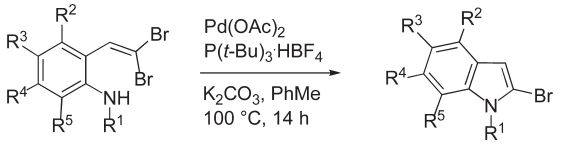


R	yield (%)
2-quinolinyl	84
3,4-$(MeO)_2C_6H_3$	70
2-naphthyl	79

Scheme 231



Scheme 232



R^1	R^2	R^3	R^4	R^5	yield (%)
H	H	H	H	H	81
H	OBn	OMe	H	H	73
H	H	OMe	H	H	64
H	H	*t*-Bu	H	*t*-Bu	81
H	H	I	H	H	68
H	H	Br	H	H	71
H	H	CO_2Me	H	H	75
H	H	H	OBn	H	84
H	H	H	CF_3	H	72
H	H	H	F	H	82
H	H	H	CO_2Me	H	84
H	H	H	H	OMe	80
Ph	H	H	H	H	72

C−Br bond is located *gauche* between the axial and equatorial C−H bond, was obtained as a single isomer in high yield (82%).

While the Pd-catalyzed hydrogenolysis of 1,1-dibromoalkenes with Bu_3SnH proceeded smoothly at room temperature, that of the dichloro counterpart, such as the 1,1-dichloro-3-phenyl-1-butene, did not occur even in refluxing benzene and by slow addition of the reducing reagent. On the other hand, 1,1-diiodo-1-alkenes reacted easily, giving however disappointing results.

The dibromoalkene formation and subsequent hydrogenolysis could be also carried out from the aldehyde in a sequential one-pot process, although the reaction required a considerable amount of Bu_3SnH.[266] Thus, 2-phenylpropanal and *p*-tolualdehyde were converted under Ramirez conditions to the related

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

dibromoalkenes, which were not isolated but treated with Bu_3SnH (5 equiv) and a catalytic amount of $Pd(PPh_3)_4$ (6 mol %) to give the related (*Z*)-bromoalkenes in 81% and 84% yields, respectively (Scheme 225).

The catalytic cycle for the Pd-mediated hydrogenolysis of 1,1-dibromoalkenes was proposed (Scheme 226).[266] The high selectivity of the process was ascribed to the oxidative addition as the key step, where Pd(0) inserts into the sterically less hindered C−Br bond. In fact, the rate of the oxidative addition of Pd(0) into 1,1-dibromoalkenes was estimated to be 5−20 times faster than that to (*Z*)-1-bromoalkenes. When an excess of Bu_3SnH was used, overhydrogenolysis occurred to give terminal alkenes.

The Uenishi procedure was utilized by Goodman and co-workers in a study aimed at the biological evaluation of carbon-11 labeled 2*β*-carbomethoxy-3*b*-[4-((*Z*)-2-haloethenyl)phenyl]tropanes ([^{11}C]ZBrENT), to prepare the key intermediate **382** in 84% yield by hydrogenolysis of the dibromide **383** (Scheme 227).[268]

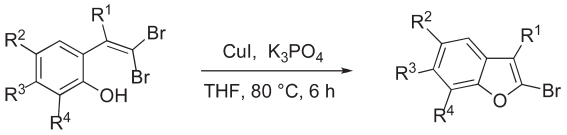
Hayford and co-workers, in a study aimed to obtain a practical route to (*Z*)-polyaromatic and heteroaromatic vinylacetylenes, examined two alternative strategies to obtain the key (*Z*)-vinylbromide intermediates, namely, the Wittig reaction [$Ph_3P(Br)CH_2Br$ and KO*t*-Bu] of aldehydes and the Pd-catalyzed hydrogenolysis of *gem*-dibromides by hydrogenolysis with Bu_3SnH.[269] Attempts to prepare both *π*-excessive and *π*-deficient substituted (*Z*)-vinylbromides via stereoselective Bu_3SnH reduction of heterocyclic *gem*-vinyldibromides gave disappointing results in terms of purity and isolated yields for *O*- and *N*-functionalized bromoolefins. For example, significant decomposition was observed with pyridine-containing precursors, while heteroarylaldehydes with sensitive functional groups, such as pyrrole-2-carboxaldehyde, failed to yield the expected products. Thus, for the conversion of *π*-deficient heteroaromatic vinylacetylenes to (*Z*)-bromoalkenes, the Wittig reaction was preferred, whereas the Bu_3SnH reduction was found to be more convenient to obtain *π*-excessive ones (Scheme 228).

An interesting example of regio- and stereoselective Pd-catalyzed hydrogenolysis with Bu_3SnH of 2-aryl-1,1-dibromoalkenes bearing another bromine on the aryl unity was reported (Scheme 229).[270] Thus, in the tribromides **384** only the (*E*)-vinyl bromide was selectively replaced by hydride in excellent yields (85−97%).

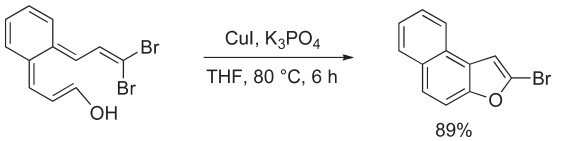
Figadère and co-workers found that 2-(hetero)aryl-1,1-dibromoalkenes were hydrodehalogenated by treatment with *i*-PrMgCl (1 equiv) and catalytic $Fe(acac)_3$ (5 mol %), under optimized reaction conditions, to give (*E*)-bromoalkenes (Scheme 230).[271] With aromatic alkenes, yields were good and the stereoselectivity was excellent (no *Z*-isomers were observed), whereas with aliphatic substrates either the corresponding alkyne was obtained or no reaction occurred. In the case of 1,1-dibromo-1,3-dienes, the expected reduced products were obtained, but in lower yields. Thus, this reaction seems to be limited to the conjugated alkenes.

3.1.6. Intramolecular Coupling. Lautens and co-workers have developed a method for the synthesis of 2-halogenated benzofurans, benzothiophenes, and indoles via intramolecular cross-couplings of 2-(2,2-dihalovinyl)-anilines, -phenols, and -benzothiols.[272,22] Initial attempts to isolate 2-haloheterocycles, supposed intermediates in the tandem intra- and intermolecular Pd-catalyzed cross-couplings of these compounds with an external nucleophile (e.g., a boronic acid) (Schemes 380−384), by carrying out the reaction in the absence of the coupling partner failed.[272] They suspected that the active Pd(0) catalyst was undergoing irreversible oxidative addition after the first turnover

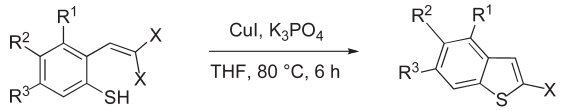
Scheme 233



R^1	R^2	R^3	R^4	yield (%)
H	H	H	H	93
H	Cl	H	H	99
H	Br	H	H	96
H	CO_2Me	H	H	93
H	H	OMe	H	89
H	OMe	H	OMe	95
Me	H	H	H	52

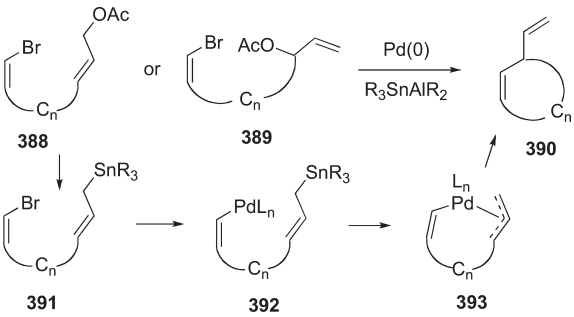


Scheme 234



X	R^1	R^2	R^3	yield (%)
Br	H	H	H	84
Br	Cl	H	H	91
Br	H	Me	H	99
Br	H	NO_2	H	82
Br	H	H	Br	88
Br	OMe	Br	H	96
Br	H	H	Br	91
Br	H	-OCH_2O-		74
Cl	H	H	H	62

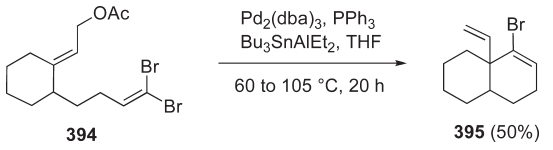
Scheme 235



to form catalytically inactive Pd(II) species such as **387** (Scheme 231). The presence of a boronic acid or similar coupling partner was necessary to liberate active Pd(0) and achieve catalyst turnover. However, the use of the bulky phosphine ligand $P(t\text{-}Bu)_3$ prevented inhibition of the catalyst by facilitating

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 236



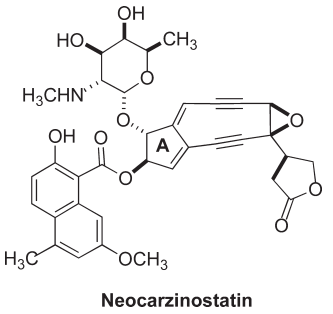
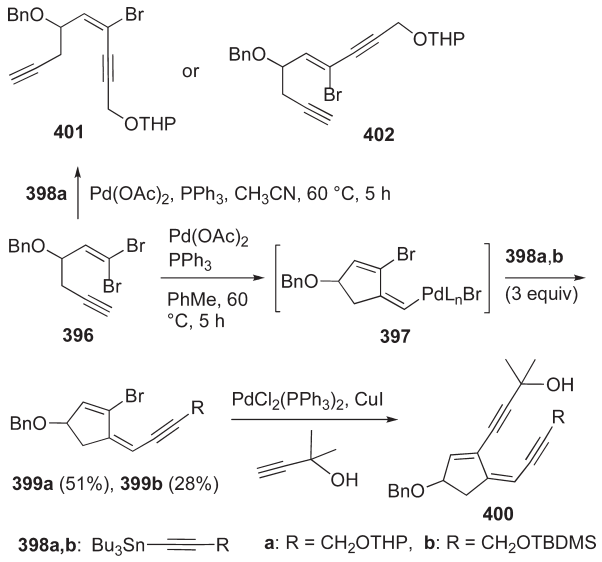


Figure 6

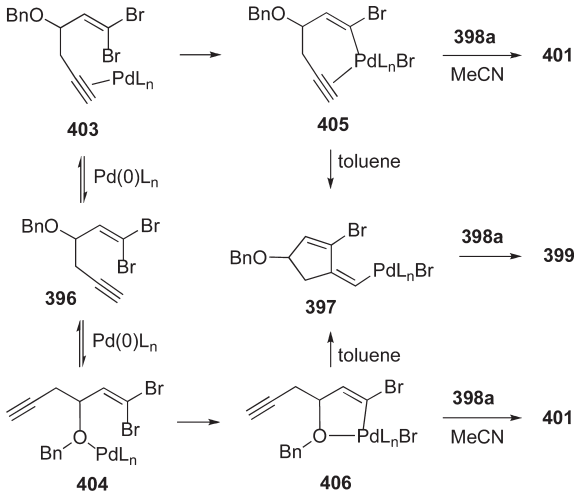
Scheme 237



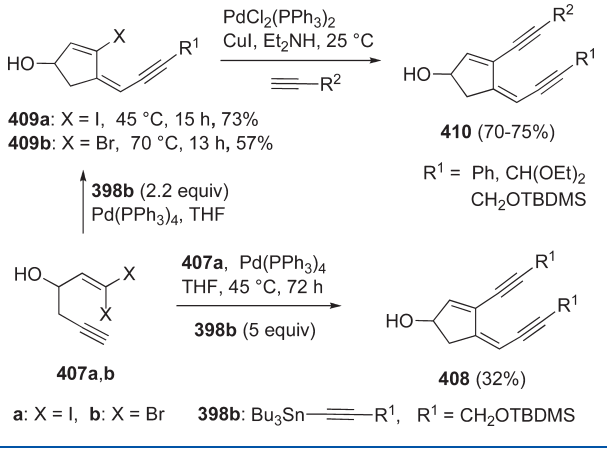
reversible oxidative addition into the product C−Br bond (**386** ⇌ **387**, Scheme 231). Thus, with use of $Pd(OAc)_2$ (5 mol %) and $P(t\text{-}Bu)_3 \cdot HBF_4$ (6 mol %) under optimized conditions, a broad range of electron-poor and electron-rich, sterically crowded *gem*-dibromoolefins underwent efficient C−N bond formation to form 2-bromoindoles (Scheme 232). Remarkably, the high levels of selectivity of the reaction allowed also obtaining indoles containing two reactive carbon−halide bonds. The mechanistic pathway of the reaction was investigated, demonstrating the involvement of aryl-palladium halides **387** in the catalytic cycle.

The same research group also reported that the use of a copper-based catalytic system [CuI (5 mol %) and K_3PO_4 (2 equiv)] allowed the synthesis in good to excellent yields of a wide range of 2-bromobenzofurans (Scheme 233) and 2-bromo(chloro)-benzothiophenes from 2-(2,2-dibromovinyl)phenols and 2-(2,2-dibromo(chloro)vinyl)benzenethiols, respectively (Scheme 234).[22] Electron-donating and electron-withdrawing groups, as well as

Scheme 238



Scheme 239



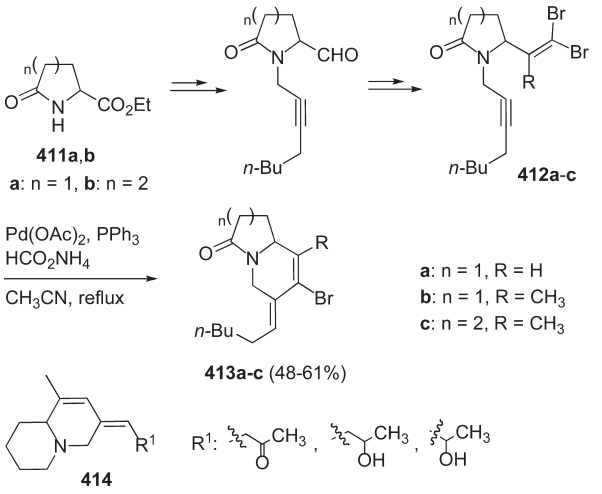
halo substituents, on the aryl ring of the starting material were well tolerated. On the other hand, the application of this methodology to 2-(2,2-dihalovinyl)anilines was unsuccessful.

3.1.7. Reductive Cyclization to Cyclic Compounds. Trost and Walchli reported a chemoselective reductive cyclization, catalyzed by palladium complexes, of a series of compounds **388** having both allylic acetate and aryl or vinyl bromide moieties to give the cyclic compounds **390** according to the general Scheme 235.[15] They described, among several substrates, an example in which the vinyl bromide moiety is part of a 1,1-dibromovinyl group (Scheme 236). Thus, treatment of **394** with (tri-*n*-butylstannyl)diethylalane and $Pd_2(dba)_3/PPh_3$ afforded the bicyclic compound **395** in 50% yield. The preferred mechanism (among others) for this coupling was envisioned to involve the formation of an allylstannane **392**, whose coupling with the vinyl bromide moiety was presumed to proceed through the π-complex **393** (Scheme 235). Final reductive elimination creates the new C−C bond in **390**.

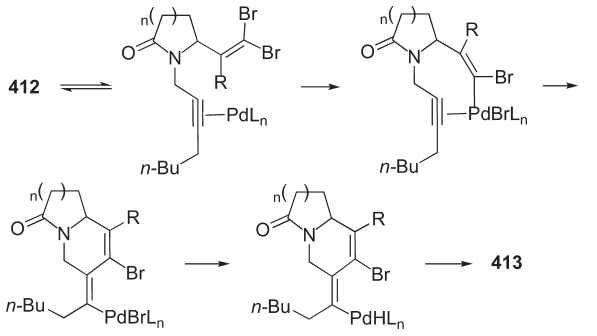
Two research groups developed an expeditious and versatile route for the construction of the biologically relevant core of the neocarzinostatin chromophore (Figure 6).[273,256] Both groups, to test the viability of their strategies, used readily available 1, 1-dibromohex-1-en-5-yn-3-ol derivatives as model substrates

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

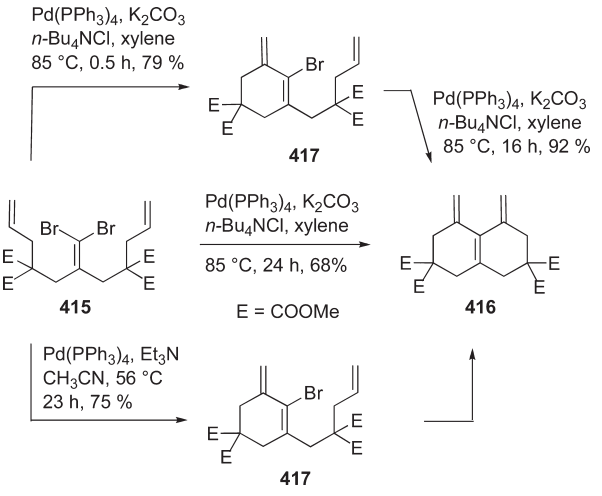
Scheme 240



Scheme 241

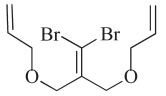
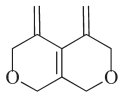
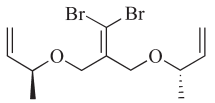
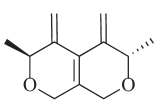
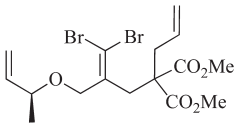
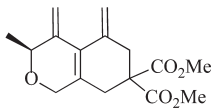
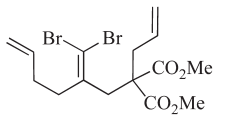
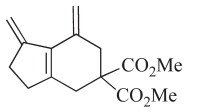
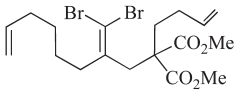
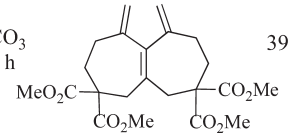


Scheme 242



(Schemes 237 and 238). Torii and co-workers described the Pd-catalyzed sequential formation of contiguous carbon−carbon bonds in a single operation to provide a straightforward and convergent synthesis path to an system with the desired olefin geometry (Scheme 237).[273] Thus, the treatment of the

Table 4. Synthesis of Bicyclics via Dicarbopalladation

Substrate	Conditions[a]	Product	Yield (%)
	**A**, 85 °C 16 h		83
	**A**, 85 °C 21 h		56
	**A**, 85 °C 15 h		67
	**A**, 85 °C 14 h		33
	**A**, Ag_2CO_3 80 °C, 5 h		39

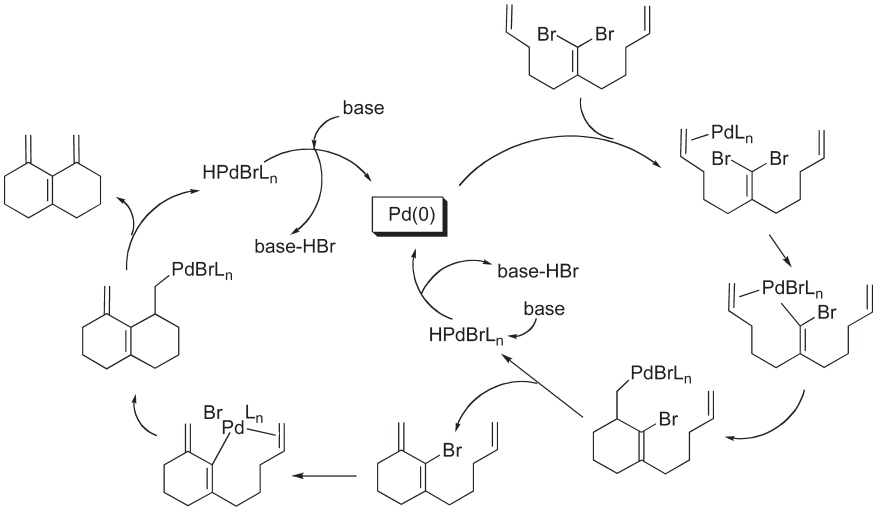
[a] (A) $Pd(PPh_3)_4$, K_2CO_3 and *n*-Bu_4NCl in xylene.

dibromide **396** with the alkynylstannane **398a** (3 equiv) in the presence of $Pd(OAc)_2$ and PPh_3 afforded in 51% yield the enyne system **399**, via formation of the intermediate Pd-complex **397**. On the other hand, when the reaction was carried out in acetonitrile the mono cross-coupling product **401** or **402** was obtained in good yield. Of these products the former was preferred since the formation of **402** appeared to indicate that the reaction proceeds through the oxidative addition of the (*Z*)-bromide. Such a predominant oxidative addition of the (*Z*)-bromide **396** would be explained by the initial coordination of Pd-catalyst to the triple bond or to the oxygen atom of the benzyloxy group to produce a transient π-complex **403** or **404**, which preferentially delivers the palladium to the (*Z*)-bromide to provide the critical Pd−C σ-bond species **405** or **406** (Scheme 238). These species then undergo carbometalation (migratory insertion) of the precoordinated alkyne to give the intermediate **397**, which by reaction with the allylstannnane **398a** affords **399**. Alternatively, transmetalation and coupling with **398a** leads to the coupled product **401**. In a related study, Nuss and co-workers developed their strategy starting from the diiodoenyne **407a**, which by treatment with 5 equiv of the allylstannane **398b** and in the presence of $Pd(PPh_3)_4$ (10 mol %) afforded the cyclic derivative **408** in 32% yield (Scheme 239).[256] On the other hand, when 2.2 equiv of **398b** was used, the cyclized product **409a**, possessing only the (*Z*)-C8−C9 olefin geometry, was obtained in high yield (73%). The use of the dibromide **407b** afforded an analogous cyclization to give **409b**, albeit in lower yield (57%) and at higher temperature (70 °C) and dilution. Moreover, in no case could the compound **407b** be converted directly into **408**. The compound **409a** was coupled in good yields (70−75%) with a series of alkynes to give enediynes **410**.

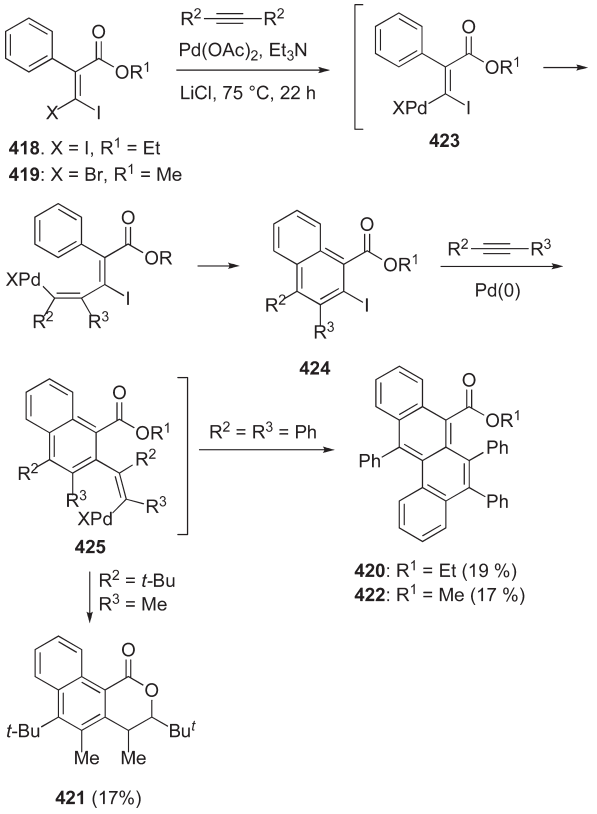
The mechanism proposed by Nuss was consistent with that of Torii (Scheme 238), except for the possibility of the chelation of

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

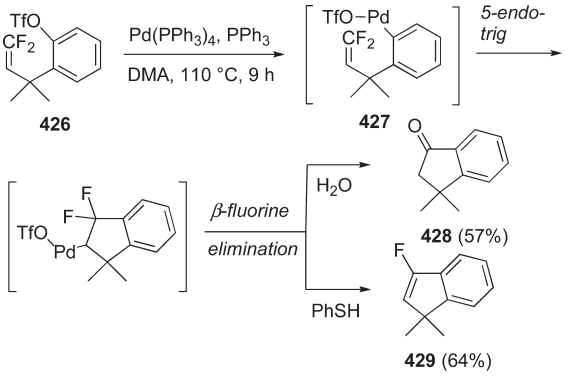
Scheme 243



Scheme 244



Scheme 245



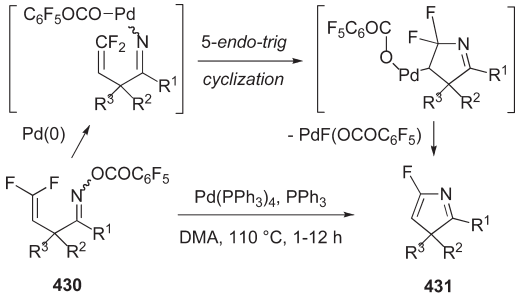
the Pd(0) to the oxygen atom. In fact, they observed similar reactivity between the free alcohol and the methoxymethyl (MOM)- and the *tert*-butyldimethylsilyl (TBDMS)-protected derivative of **407a** that would seem to preclude chelation of the oxygen as being critical in directing the oxidative addition.

An intramolecular Pd-catalyzed carbometalation−hydrogenolysis tandem process has been pursued for the stereoselective synthesis of the diene moiety in homopumiliotoxin alkaloids **414** (Scheme 240).[274] As model compounds for **414**, the pyrrolidinone derivatives **411a,b** were chosen and converted into the geminal dibromides **412a**−**c**. Treatment of **412a** with $Pd(OAc)_2$ (2 mol %), PPh_3 (4 mol %), and ammonium formate in boiling acetonitrile gave the quinolizidine skeleton of the homopumiliotoxin **413a** in 48% yield as single diastereomer. Under the same conditions, **412b** and **412c** gave the related cyclic products in 61% and 58% yield, respectively. The product always retained one bromine atom regardless of the excess of reducing agent. The preservation of the bromide allowed the further selective functionalization of the endocyclic double bond. One possible explanation for this result was that the more sterically hindered (*Z*)-vinyl bromide was activated to oxidative addition to palladium by prior coordination of the acetylene moiety and that the formed cyclic vinyl bromide was inert to further reduction under these reaction conditions (Scheme 241). However, since the yield of the cyclized product is moderate, the addition to the (*E*)-vinyl bromide also cannot be ruled out.

A Pd-catalyzed intramolecular carbometalation reaction for the efficient synthesis of bicyclic products from *gem*-dibromides has been described.[275] The 1,1-dibromoalkene **415** was used as a model substrate to test the bicyclic carbopalladation protocol under different reaction conditions. The best results were obtained with $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (10 equiv), and

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 246

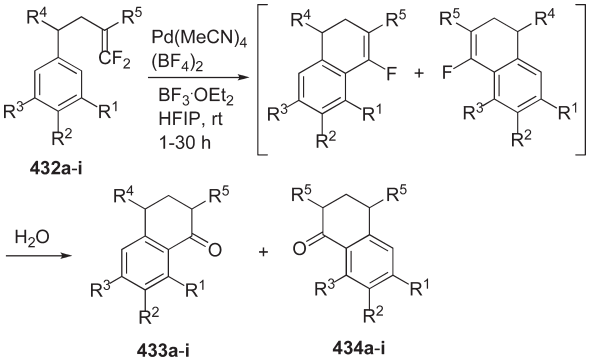


R^1	R^2	R^3	**431** yield (%)
Ph	Me	Me	71
Ph	-$(CH_2)_4$-		78
(*E*)-Me-CH=CH	Me	Me	6, 29
n-C_9H_{19}	Me	Me	14
CO_2t-Bu	Me	Me	47
-C_6H_3o-$(CH_2)_2$-			

n-Bu_4NCl (2 equiv) in xylene at 80−85 °C for 24 h, thus affording the fused 6,6-bicyclic product **416** in 68% yield (Scheme 242). Submission of the compound **415** to the same conditions for 0.5 h afforded in 79% yield the monocyclic compound **417** that was converted into **416** in 92% yield by further heating for 16 h. The compound **417** was also obtained in 75% yield under different conditions [$Pd(PPh_3)_4$ and Et_3N], demonstrating that the monocyclization and bicyclization can be controlled. By this protocol, a variety of bicyclic compounds with different ring sizes (5,6-, 6,6-, 6,7-, and 7,7-bicyclic compounds) as well attached functional groups were synthesized. Some representative examples are reported in Table 4. This study also demonstrated that the oxidative addition reaction of 1,1-dibromo-2,2-diphenylethene or 1,1-dibromo-2-phenylpropene with a stoichiometric amount of $Pd(PPh_3)_4$ afforded 1,2-diphenylacetylene and 1-phenylpropyne, respectively, indicating that an α-dehalopalladation reaction occurred to afford vinylic carbene intermediates. However, the α-dehalopalladation reaction was not observed in any precursors for bicyclization under the reaction conditions tested, probably due to the fast intramolecular carbopalladation reaction of the C═C bonds. The proposed stepwise cyclization catalytic cycle is illustrated in Scheme 243.

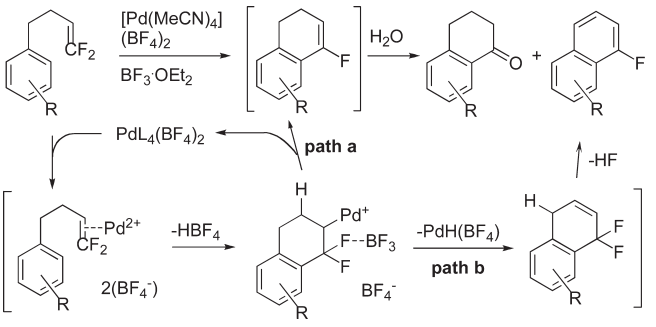
Larock and co-workers proposed the synthesis of isocoumarins and α-pyrones by treating halogen- or triflate-containing aromatics and α,β-unsaturated esters, respectively, with internal alkynes in the presence of a Pd catalyst.[184] This chemistry was also extended to a double annulation process, by employing geminal dihalo-substituted esters to synthesized polycyclic aromatic compounds (Scheme 244). Thus, when the dihalo-substituted esters **418** and **419** were reacted with diphenylacetylene or 4,4-dimethyl-2-pentyne in the presence of 10% of $Pd(OAc)_2$, 2 equiv of Et_3N, and 2 equiv of LiCl at 75 °C for 22−32 h, the double annulation products **420**−**422** were formed in 17−19% yields with the formation of four new carbon−carbon or carbon−oxygen bonds (Scheme 244). The reaction using the dihalides Br_2C═$CPhCO_2Et$, Br_2C═$C(CO_2Et)_2$, and I_2C═$C(CO_2Et)_2$ failed to give any double annulation products. The formation of the compounds **420** and **422** could be explained by oxidative addition of Pd(0) to the compound **418** or **419**, which

Scheme 247



R^1	R^2	R^3	R^4	R^5	**433**,**434** yield (%)	**433**/**434**
H	H	H	H	H	89	--
H	H	H	Me	H	83	--
H	Me	H	Me	H	79	--
H	OMe	H	Me	H	70	76:24
H	H	OMe	Me	H	66	79:21
H	OH	H	Me	H	78	65:35
H	CF_3	H	Me	H	15	--
H	H	H	H	*n*-C_5H_{11}	65	--
-CH=CH-CH=CH-		H	H	H	89	97:3

Scheme 248

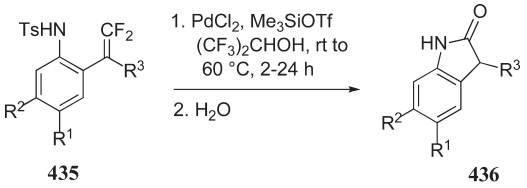


affords the vinylpalladium intermediate **423** in which the halogen *trans* to the carbonyl group undergoes preferential insertion. The vinylpalladium intermediate **423** undergoes insertion of a molecule of internal alkyne and subsequent substitution onto the adjacent phenyl ring to form the intermediate **424**. The vinylpalladium intermediate **425** is then formed by oxidative addition of Pd(0) to the compound **424** and subsequent insertion of a second molecule of internal alkyne. When diphenylacetylene was employed, the compound **420** or **422** was obtained, while with 4,4-dimethyl-2-pentyne, the compound **421** was produced. The formation of compounds **420** and **422** indicates that the production of aromatic rings is easier than that of α-pyrones.

3.1.8. Other Cyclizations. Ichikawa and co-workers developed the synthesis of ring-fluorinated indenes and 3*H*-pyrroles from 1,1-difluoroalkenes by a Heck-type 5-*endo-trig* cyclization with aryl- and aminopalladium species, respectively.[276] When the aryl triflate **426** was heated with a stoichiometric amount of $Pd(PPh_3)_4$ and PPh_3 in *N*,*N*-dimethylacetamide, the Heck-type

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

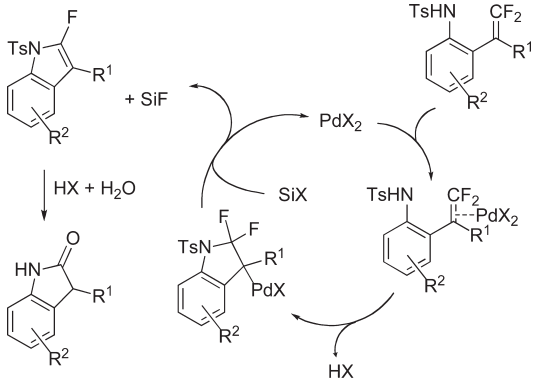
Scheme 249



435 436

R^1	R^2	R^3	**436** yield (%)
H	H	H	90
H	H	*n*-Bu	87
H	H	*s*-Bu	78
Cl	H	*n*-Bu	71
Me	H	*n*-Bu	91
H	Me	*n*-Bu	79
OMe	H	*n*-Bu	20

Scheme 250

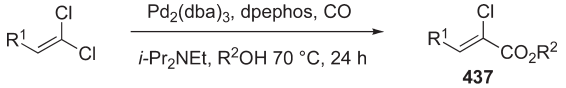


5-*endo-trig* cyclization proceeded to give the indanone **428** (57% yield) (Scheme 245).[276a] However, when the reaction mixture was treated with PhSH before quenching, the fluoroindene **429** was formed in 64% yield, confirming that 5-*endo-trig* cyclization was achieved by arylpalladium(II) species **427**, generated via oxidative addition of the aryl triflate **426** to Pd(0). An attempt to promote this cyclization with a catalytic amount of $Pd(PPh_3)_4$ and PPh_3 gave only 15% yield of **428**.

The synthesis of 5-fluoro-3*H*-pyrroles was developed starting from 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloximes (Scheme 246).[276b] The reaction, optimized by using 0.1 equiv of $Pd(PPh_3)_4$ and a stoichiometric amount of PPh_3, was successful for a variety of substrates but gave poor results in the case of substrates bearing a primary alkyl or an acyl group as R. The process was supposed to proceed via oxidative addition to Pd(0) to generate alkylideneaminopalladium species, followed by alkene insertion and subsequent β-fluorine elimination. The reaction takes advantage of the polarized double bond of 1,1-difluoroalkenes. In fact, when the related dichloro- or dibromoalkenes were subjected to the same reaction conditions, no cyclized product was observed; instead, the corresponding ketones generated via hydrolysis of the oxime moiety were obtained.

Ichikawa and co-workers developed also the first transition-metal catalyzed method for the electrophilic activation of electron-deficient 1,1-difluoroalkenes that successfully promotes their Wacker-type cyclization to afford 3,4-dihydronaphthalenones and oxindoles.[277] When *gem*-difluoroalkenes **432** were

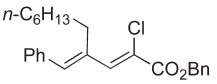
Scheme 251



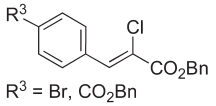
437

R^1	R^2	yield (%)	R^1	R^2	yield (%)
Ph	Me	68	4-FC_6H_4	Et	55
Ph	Et	87	4-FC_6H_4	Bn	82
Ph	*n*-Pr	65	4-ClC_6H_4	Bn	74
Ph	*n*-Bu	69	4-$MeOC_6H_4$	Et	48
Ph	Bn	87	4-$MeOC_6H_4$	Bn	80
Ph	MPM[a]	91	4-$MeO_2CC_6H_4$	Bn	78
n-C_5H_{11}	Bn	50	2-pyridyl	Bn	62
c-C_6H_{11}	Bn	63	(*E*)-PhCH=CH	Bn	71[b]

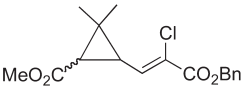
[a]MPM = 4-$MeOC_6H_4CH_2$
[b]*Z*/*E* : 65:35



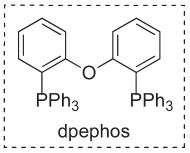
80% (*Z*/*E* : 95:5)



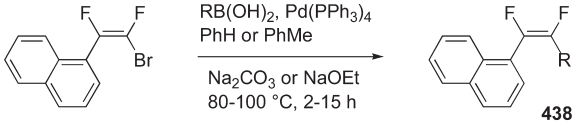
R^3 = Br, CO_2Bn
57%, Br/CO_2Bn = 35:65



62%



Scheme 252



438

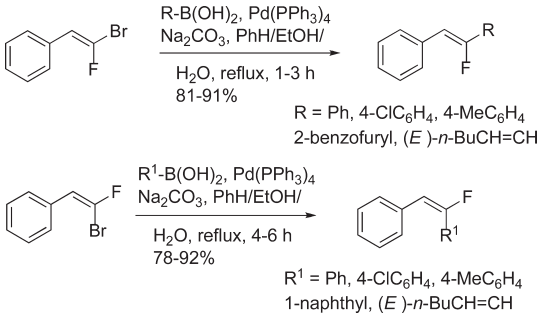
	R	**438** yield (%)
a	Ph	99
b	4-$MeOC_6H_4$	64
c	(*E*)-PhCH=CH	42

treated with 1 equiv of $BF_3 \cdot OEt_2$ and $[Pd(MeCN)_4](BF_4)_2$ in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a solvent with high ionizing power, the cyclization occurred to give, after hydrolysis, the cyclic ketones **433** along with their regioisomers **434** in good yields (Scheme 247).[277a] The treatment of dichloro- and dibromoalkene analogues of **432** with a catalytic amount of Pd(II) gave only a trace amount of cyclized products, and even 1 equiv of Pd(II) did not work well. The mechanism of the process was studied, and it was concluded that the Pd-catalyzed Friedel–Crafts-type cyclization proceeds presumably via β-fluorine rather than β-hydrogen elimination from the cyclized intermediate **A** (path a and b, respectively) (Scheme 248).

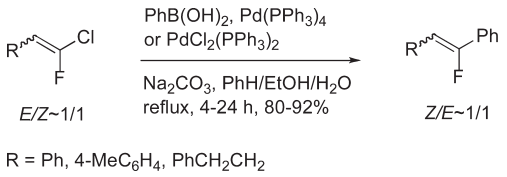
On the other hand, oxindoles **436** were obtained in high yield when β,β-difluorostyrenes **435** bearing a sulfonamido group at the *ortho* position were treated with trimethylsilyl trifluoromethanesulfonate in the presence of a catalytic amount of $PdCl_2$ (Scheme 249).[277b] The reactions proceeded via 5-*endo-trig* cyclization, hydrolysis, and desulfonylation. A plausible reaction mechanism for the oxindole synthesis was suggested (Scheme 250).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

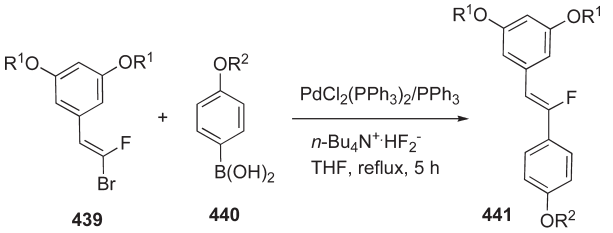
Scheme 253



Scheme 254



Scheme 255



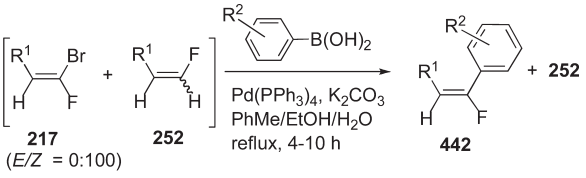
R^1	R^2	**441** yield (%)
Me	Me	86
Me	CH_3OCH_2O	83
CH_3OCH_2O	Me	71
CH_3OCH_2O	CH_3OCH_2O	84

3.1.9. Carboalkoxylation. Roulland and co-workers have recently disclosed a fully chemo- and stereoselective carboalkoxylation of 1,1-dichloroalkenes leading to (*Z*)-α-chloroacrylates **437** under atmospheric pressure of CO and in the presence of different alcohols by using $Pd_2(dba)_3$ (2.5 mol %) in combination with dpephos (5 mol %) as the catalytic system (Scheme 251).[278] For this reaction, the use of a large bite angle bisphosphine ligand such as dpephos appeared to be instrumental, as the use of less polar alcohol solvents, where CO is more soluble, led to higher yields.

3.2. Selective Monosubstitution of Mixed *gem*-Dihalovinyl Systems

3.2.1. Coupling with Organoboron Reagents. In 1-bromo-1-fluoroalkenes, the extremely large difference in reactivity between the two halogens allows coupling reactions to be carried out in a stereospecific way. Thus, Shimizu and co-workers performed the $Pd(PPh_3)_4$-catalyzed Suzuki cross-coupling of isomerically pure (*E*)-1-(2-bromo-1,2-difluorovinyl)naphthalene with arylboronic

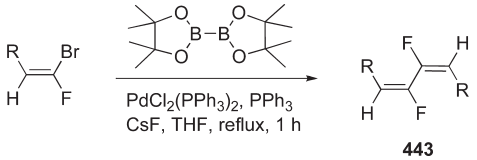
Scheme 256



R^1	R^2	**442** yield (%)[a]
Ph	3-MeC(O)	83
2-ClC_6H_4	H	82
2-ClC_6H_4	3-NO_2	90
2-ClC_6H_4	3-Cl	90
1-naphthyl	H	85
PhCH(Me)	2-Cl	92
PhCH(Me)	3-MeC(O)	93

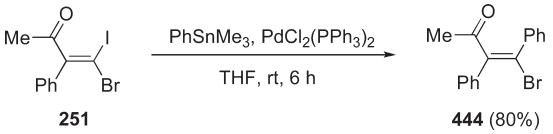
[a]Yield based on the amount of **442** in the starting mixture of **217** and **252**.

Scheme 257



R	**443** yield (%)	(*E*,*E*)/(*E*,*Z*)
Ph	73	98:2
4-ClC_6H_4	68	96:4
4-FC_6H_4	94	98:2
4-BrC_6H_4	65	93:7

Scheme 258

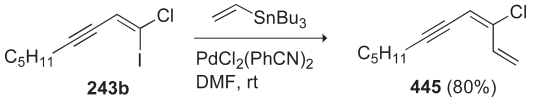


and (*E*)-styrylboronic acids to give 1,2-diarylalkenes **438a,b** and the diene **438c**, respectively, with complete retention of the olefin geometry in 42−64% yields (Scheme 252).[279]

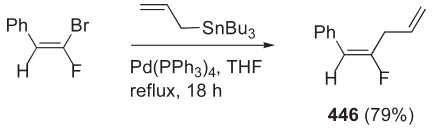
Analogously, McCarthy and co-workers reported that the cross-coupling of (*E*)- and (*Z*)-(2-bromo-2-fluorovinyl)benzene with a variety of boronic acids (1.2 equiv) proceeded in the presence of $Pd(PPh_3)_4$ (5 mol %) under Suzuki conditions to afford the related *Z* and *E* coupled products in high yields (Scheme 253).[211,280] On the other hand, the coupling reaction of aryl 1-fluorovinyl chlorides (about a 50/50 mixture of *E*/*Z* isomers) with phenylboronic acid proceeded smoothly, though a longer reaction time was required, to give the expected coupled products in high yields and with the same isomeric composition of the starting material (Scheme 254). In the case of (4-chloro-4-fluorobut-3-enyl)benzene the reaction with $PhB(OH)_2$ (3 equiv) was not complete after 48 h with $Pd(PPh_3)_4$ as the catalyst, but

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

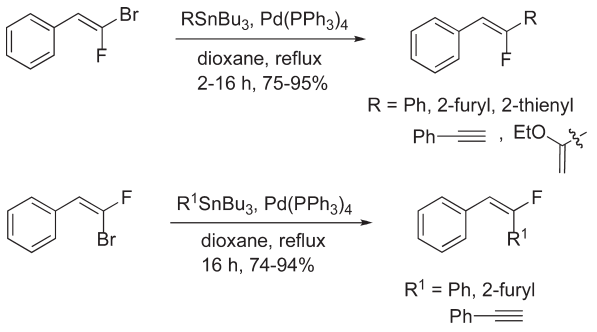
Scheme 259



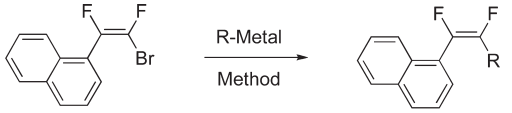
Scheme 260



Scheme 261



Scheme 262



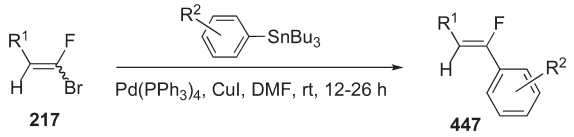
R = Ph; **method**: $RSiEtF_2$, $[PdCl(h^3\text{-}C_3H_5)]_2$
TBAF, DMF, 80 °C, 64 h; 50%
R = Ph; **method**: $RSnBu_3$, $PdCl_2(PPh_3)_2$
DMF, 90 °C, 2 h; 88%
R = (*E*)-PhCH=CH; **method**: $RSiMeF_2$, $[PdCl(\eta^3\text{-}C_3H_5)]$
TBAF, THF, 55 °C, 64 h; 55%

proceeded to completion in 24 h with $PdCl_2(PPh_3)_2$ in refluxing dioxane to afford the desired product in 83%.

The synthesis of fluorinated analogues of resveratrol and pterostilbene was achieved by a lightly modified Suzuki reaction between *gem*-bromofluoroalkenes **439** with aryl boronic acids **440** (Scheme 255).[281] For these cross-couplings, the use of the $PdCl_2(PPh_3)_2/PPh_3$ system in the presence of the nonbasic reagent *n*-$Bu_4N^+ \cdot HF_2^-$ in THF afforded *O*-protected polyhydroxylated stilbenes **441**, monofluorinated on the central double bond, as sole (*Z*)-isomers (>95%) in high yields (71−86%).

Mixtures of (*Z*)-1-bromo-1-fluoroalkenes **217** and 1-fluoroalkenes **252**, which were kinetically prepared from 1-bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) (Scheme 155),[213,216] could be used in Suzuki coupling reactions to give in high yields mixtures of (*E*)-α-fluorostilbenes **442** and unreacted **252**, which were easily separated (Scheme 256).[282]

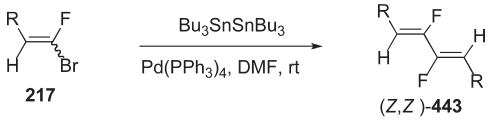
Scheme 263



217 *E*/*Z*	R^1	R^2	**447** yield (%)[a]	**447** *Z*/*E*
88:12	Ph	H	73	98:2
88:12	Ph	3-F	67	98:2
82:18	2-ClC_6H_4	H	71	94:6
82:18	2-ClC_6H_4	3-F	52	94:6
83:17	4-$MeOC_6H_4$	H	61	93:7
83:17	4-FC_6H_4	H	69	96:4
76:24	3-$O_2NC_6H_4$	H	53	87:13
88:12	3-ClC_6H_4	3-F	72	98:2
79:21	Ph(Me)CH	H	36	95:5

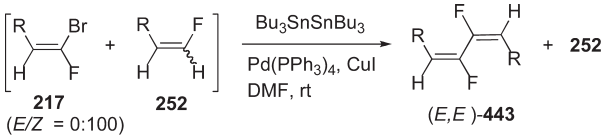
[a]Yield based on the amount of the (*Z*)-isomer in the starting *E*/*Z* mixture

Scheme 264



R	**217** *E*/*Z*	(*Z*,*Z*)-**443** yield (%)
Ph	85:15	64
2-ClC_6H_4	82:18	71
4-$MeOC_6H_4$	83:17	43
4-ClC_6H_4	88:12	72
4-FC_6H_4	87:13	72
3-$O_2NC_6H_4$	81:19	54
PhCH(CH_3)	83:17	67

Scheme 265

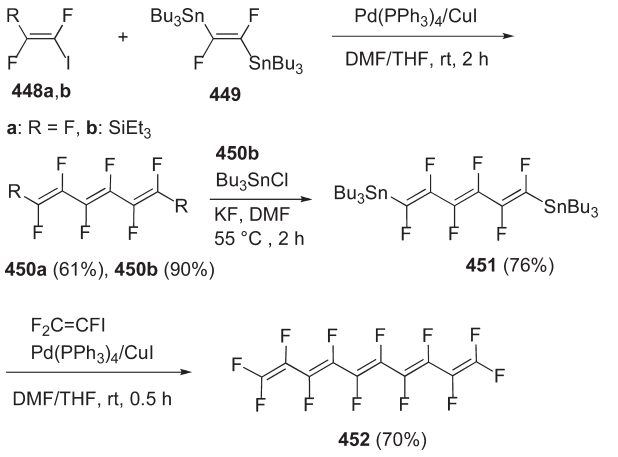


R	(*E*,*E*)-**443** yield (%)
Ph	93
2-ClC_6H_4	88
4-$MeOC_6H_4$	53

The cross-coupling reaction of (*Z*)-1-bromo-1-fluoroalkenes catalyzed by $PdCl_2(PPh_3)_2 \cdot 2PPh_3$ (3 mol %) and CsF in THF in the presence of bis(pinacolato)diboron led to 1,4-disubstituted (*E*,*E*)-2,3-difluorobuta-1,3-dienes **443** in high yields and stereoselectivities (Scheme 257).[283]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 266



3.2.2. Coupling with Organotin and Organosilicon Reagents. In 1-bromo(chloro)-1-iodo-1-alkenes, the higher reactivity of the iodo atom with respect to the other halogens permits stereospecific Stille-type reactions with the substitution of only the iodo atom independently from the alkene geometry. This difference of reactivity was evident in the Pd-catalyzed stereospecific hydrodehalogenation[207] of (*Z*)-3-bromo-3-iodo-2-phenylprop-2-enal by *n*-Bu_3SnH (Scheme 222) and cross-coupling[208] of the *β*,*β*-bromoiodoenone **251** with $PhSnMe_3$ giving **444** (Scheme 258). In these reactions, only the vinyl iodine atom was exchanged with a phenyl group or a hydrogen atom, respectively.

An example of stereospecific cross-coupling of 1-chloro-1-iodoalkenes is the Pd-mediated cross-coupling of (*Z*)-1-chloro-1-iodoenyne **243b** with tributyl(vinyl)tin to give the (*E*)-dienyne **445** in 80% yield (Scheme 259).[204]

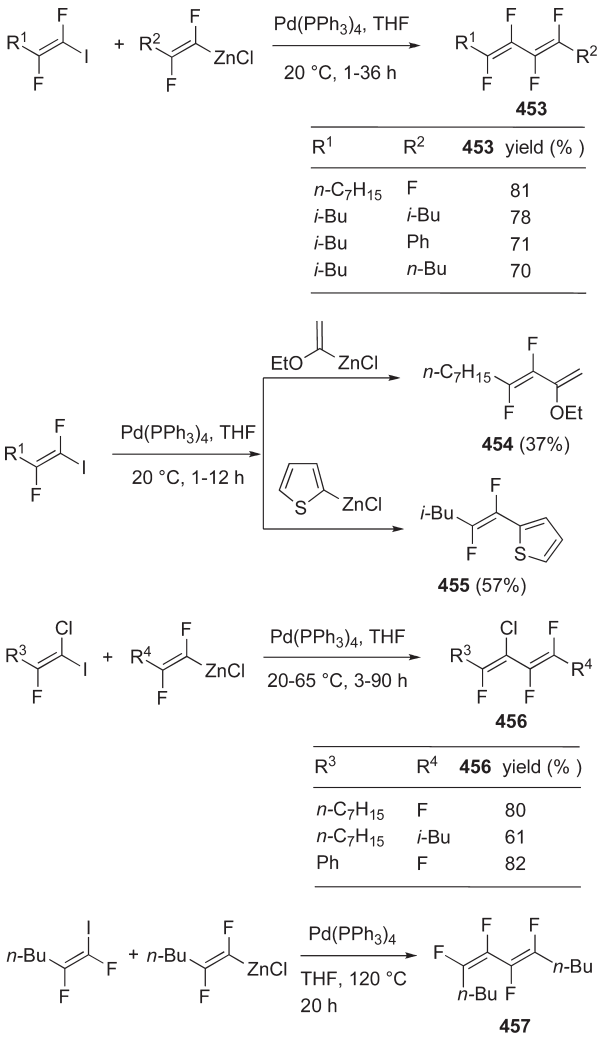
In the case of *gem*-bromofluoroalkenes, the enormous difference in reactivity between the two halogens permits stereospecific Stille reactions. Thus, the coupling of (*Z*)-(2-bromo-2-fluorovinyl)-benzene with allyltributyltin in the presence of $Pd(PPh_3)_4$ in refluxing THF afforded pure (*E*)-(2-fluoropenta-1,4-dienyl)benzene **446** in 79% yield (Scheme 260).[195]

The stereospecificity of the reaction was confirmed when both (*E*)- and (*Z*)-isomers of 1-fluoro-2-phenylvinyl bromide were coupled with a variety of organostannanes under Stille conditions (Scheme 261).[280] *β*-Fluorostilbenes were obtained with retention of configuration in good to excellent yields (74−95%).

An additional example is the coupling of (*E*)-1-(2-bromo-1,2-difluorovinyl)naphthalene with phenylmetal reagents (metal = Si or Sn) and (*E*)-difluoro(methyl)(3-phenylbut-2-en-2-yl)-silane, which in the presence of Pd catalysts ($[PdCl(\eta^3\text{-}C_3H_5)]_2$ or $Pd(PPh_3)_4$) gave in good yields a diarylethylene derivative and a diene with complete retention of the olefin geometry (Scheme 262).[279]

The observation that the (*E*)-isomer of 1-bromo-1-fluoroalkenes reacts faster than the corresponding (*Z*)-isomer at room temperature in Pd-catalyzed reactions allowed the Stille coupling of these compounds with high *E*/*Z* ratios and aryl stannanes to give (*Z*)-*α*-fluorostilbenes **447** with high stereoselectivity (Scheme 263).[282,284] It should be noted that in this transformation the Stille reaction was more stereoselective than the related Suzuki reaction.[284]

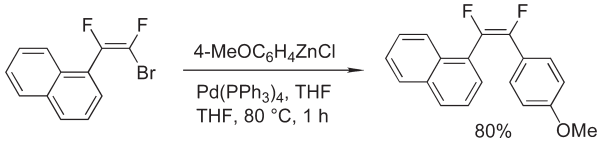
Scheme 267



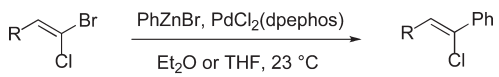
R^1	R^2	**453** yield (%)
n-C_7H_{15}	F	81
i-Bu	*i*-Bu	78
i-Bu	Ph	71
i-Bu	*n*-Bu	70

R^3	R^4	**456** yield (%)
n-C_7H_{15}	F	80
n-C_7H_{15}	*i*-Bu	61
Ph	F	82

Scheme 268



Scheme 269

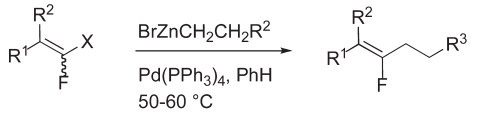


R	yield (%)	R	yield (%)
n-C_6H_{13}	84	Ph	82
(*S*)-Et(Me)CH	83	Me_3Si	90

A straightforward method to prepare symmetrical 1,4-disubstituted (*Z*,*Z*)- and (*E*,*E*)-2,3-difluorobuta-1,3-dienes **443** has been recently described (Schemes 264 and 265).[285] When high

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 270



225: X = I
226: X = Br
227: X = Cl

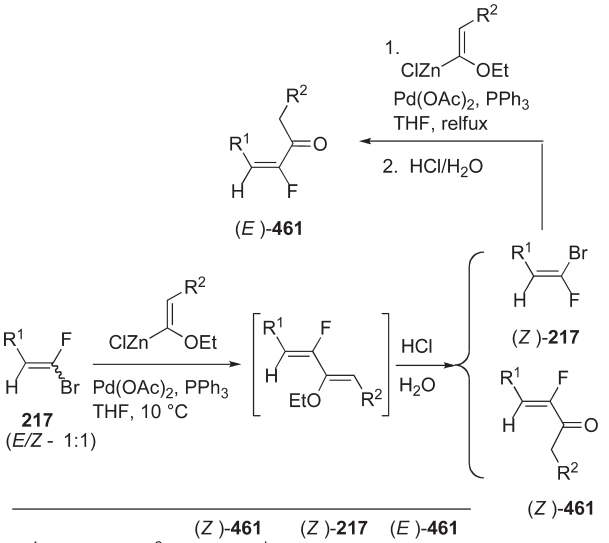
458: $R^3 = CH_2CO_2Et$
459: $R^3 = CH_2CH{=}CH_2$
460: $R^3 = CH(OCH_2)_2$

a: R^1 = Ph, R^2 = H; **b**: $R^1 = CH_2CH_2Ph$, R^2 = H
c: $R^1 = CH_2OCH_2Ph$, R^2 = H; **d**: R^1 = Ph, R^2 = Me

entry[a]	substrate(*E*/*Z*)	product (*Z*)	yield (%)
1	**225a** (95/5)	**458a**	70
2	**225a** (95/5)	**458a**[b]	93
3	**226a** (93/7)	**458a**	70
4	**227a** (93/7)	**458a**	80
5	**225a** (95/5)	**459a**	65
6	**225a** (95/5)	**460a**[b]	94
7	**225b** (84/16	**458b**[b]	82
8	**225b** (78/22)	**459b**	66
9	**225b** (15/85)	**460b**	14
10	**225c** (75/25)	**459c**[c]	56
11	**225c** (67/33)	**459c**[b]	86[d]
12	**225d** (49/51)	**458d**	45
13	**225d** (49/51)	**458d**[b]	60[e]
14	**225d** (49/51)	**459d**	45
15	**225d** (49/51)	**460d**	46

[a]Only representative results are reported. [b]$PdCl_2(dppb)_2$ is used. [c]$Pd_2(dba)_2$ is used [d]*E*/*Z* = 20/80. [e]*E*/*Z* =16/84.

Scheme 271



R^1	R^2	(*Z*)-**461** yield (%)[b]	(*Z*)-**217** yield (%)[c]	(*E*)-**461** yield (%)
4-$MeOC_6H_4$	H	85	86	72
2-naphthyl	H	86	85	81
4-$O_2NC_6H_4$	H	92	90	51
$PhCH_2CH_2$	H	79	79	70
4-$MeOC_6H_4$	Ph	93	99	98
4-$MeOC_6H_4$	Et	75	84	90

Only representative substrates are reported. [b]Based on starting (*E*)-**217** isomer. [c]Based on starting (*Z*)-**217** isomer

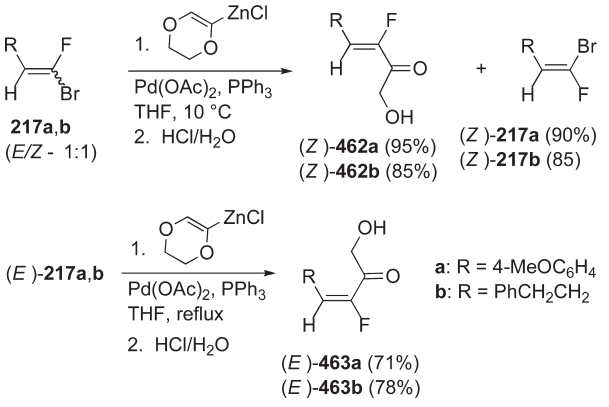
E/*Z* ratio 1-bromo-1-fluoroalkenes were reacted with $(Bu_3Sn)_2$ and catalytic $Pd(PPh_3)_4$, 1,3-dienes (*Z*,*Z*)-**443** were obtained in good yields (Scheme 264). On the other hand, mixtures of (*Z*)-1-bromo-1-fluoroalkenes **217** and 1-fluoroalkenes **252** (Scheme 155) underwent similar reactions with $(Bu_3Sn)_2$ in the presence of the couple $Pd(PPh_3)_4$ and CuI, to provide symmetrical 1,3-dienes (*E*,*E*)-**443** and unreacted **252** (Scheme 265).[285]

The catalytic system $Pd(PPh_3)_4$/CuI allowed also the cross-coupling between the distannane **449** and 1-fluoro-1-iodoethylenes **448** to give 1,3,5-hexatrienes **450** in high yields and isomeric purity (Scheme 266).[286] The triene **450b** was converted into the (3*E*,5*E*,7*E*)-pentaene **452** by treatment with the system Bu_3SnCl/KF, which exchanges of the trialkylsilyl group by a trialkylstannyl group to provide stereospecifically the triene **451** in good yield. Finally, $Pd(PPh_3)_4$/CuI catalyzed cross-coupling of **451** with 1,1,2-trifluoro-2-iodoethene **448a** gave the pentaene **452** in good yield (70%).

3.2.3. Coupling with Organozinc Reagents. Sauvêtre and co-workers reported the preparation of stereo-defined fluorinated dienes by Pd-catalyzed cross-coupling of organozinc reagents with *gem*-dihaloolefins.[287] Both 1-fluoro-1-iodo- and 1-chloro-1-iodoalkenes were effectively reacted with alkenyl organozinc reagents in the presence of $Pd(PPh_3)_4$ (5 mol %) to afford the expected cross-coupled products in high yields. The stereochemistry of these compounds reflects the geometry of the dihaloolefin because only the iodo atom undergoes selective substitution (Scheme 267).

An example of stereospecific Negishi arylation is the cross-coupling of pure (*E*)-1-(2-bromo-1,2-difluorovinyl)naphthalene

Scheme 272

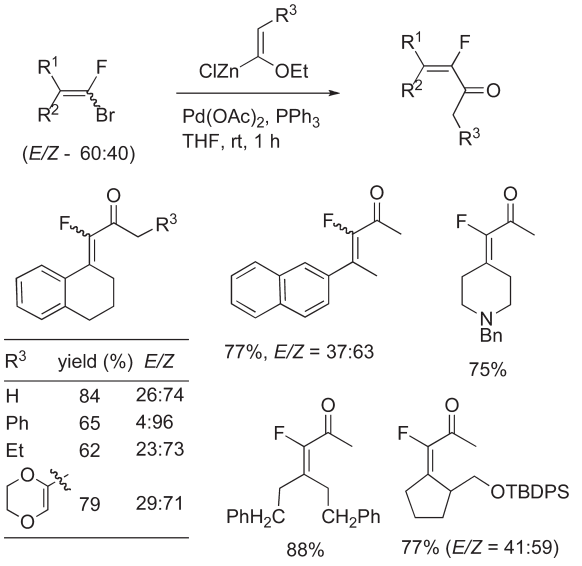


with (4-methoxyphenyl)zinc(II) chloride to give (*Z*)-1-[1,2-difluoro-2-(4-methoxyphenyl)vinyl]naphthalene in high yield (Scheme 268).[279]

Negishi and Shi, in a project aiming to obtain an effective procedure for the Pd-catalyzed selective tandem arylation−alkylation of 1,1-dihaloalkenes with organozinc reagents, initially optimized the *trans*-selective monoarylation process.[245] In the phenylation of a variety of 1-bromo-1-chloroalkenes with phenylzinc bromide, $PdCl_2$(dpephos) appeared to be superior to the other examined catalysts [$Pd(PPh_3)_4$, $PdCl_2$(dppb), $PdCl_2$(dppf), $Pd(Pt\text{-}Bu_3)_2$] (Scheme 269). Uniformly satisfactory

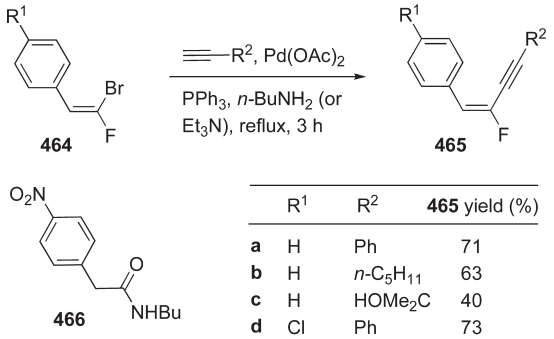
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 273



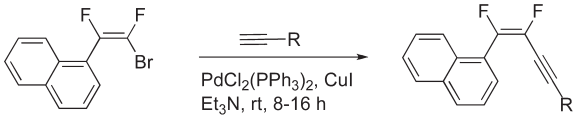
R^3	yield (%)	E/Z
H	84	26:74
Ph	65	4:96
Et	62	23:73
	79	29:71

Scheme 274



	R^1	R^2	**465** yield (%)
a	H	Ph	71
b	H	n-C_5H_{11}	63
c	H	$HOMe_2C$	40
d	Cl	Ph	73
e	NO_2	Ph	71

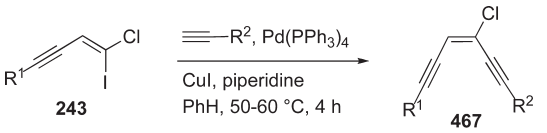
Scheme 275



results concerning both yields (82−90%) and stereoselectivities (>99% *trans*-isomer) were obtained.

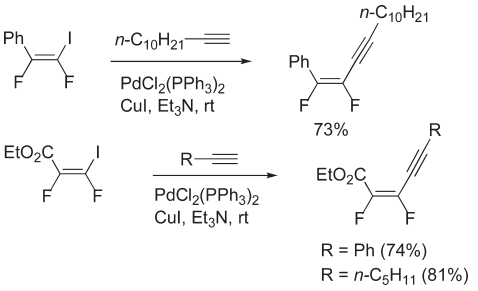
Also the Negishi cross-coupling of 1-fluoro-1-haloalkenes with alkylzinc reagents was reported to occur selectively to give fluoroalkenes.[196] With primary alkylzinc bromides, the highest yields were obtained with $Pd_2(dba)_3$ and $PdCl_2(dppb)$ as catalysts, but the best stereochemical outcome was achieved with the less reactive $Pd(PPh_3)_4$ (Scheme 270). The reaction was *trans*-selective giving pure (*Z*)-fluoroalkenes in most cases, and the formation of the corresponding (*E*)-isomers (for instance, entries 11 and 13 in Scheme 270) via *cis*-couplings was observed only in few instances. On the other hand, the coupling with

Scheme 276



R^1	R^2	**467** yield (%)
n-C_5H_{11}	$HOCH_2$	79
n-C_5H_{11}	$HO(CH_2)_2$	87
n-C_5H_{11}	Ph	90
n-C_5H_{11}	Me_3Si	72
n-C_5H_{11}	n-C_5H_{11}	85
Ph	Me_3Si	75
Ph	$HOCH_2$	71
Ph	$HO(CH_2)_2$	90
Ph	Ph	81

Scheme 277



branched alkylzincs gave contrasting results. Monoalkylation of **225a** with *t*-BuZnBr was effective, providing (*Z*)-(2-fluoro-3,3-dimethylbut-1-enyl)benzene in 80% yield by using $PdCl_2(dppb)$ as the catalyst, whereas couplings with secondary 2- or 3-pentylzinc bromides gave unsatisfactory results.

Pannecoucke and co-workers have recently described the synthesis of vinylic fluoride scaffolds via a Negishi cross-coupling of trisubstituted *gem*-bromofluoroolefins with alkoxyvinylzinc species mediated by $Pd(OAc)_2/PPh_3$ (Schemes 271 and 272).[219] At 10 °C, only the (*E*)-isomer of the *E*/*Z* mixture of the substrate reacted to give, after hydrolysis, stereospecifically (*Z*)-α-fluoro-α,β-unsaturated ketones in high yields. At the same time, the unreacted (*Z*)-isomer was recovered in high yields. Then, this (*Z*)-isomer was submitted to Negishi reaction in refluxing conditions to give stereospecifically (*E*)-α-fluoro-α,β-unsaturated ketones in good yields. This reaction was very efficient and the stereodifferentiation operating with the reaction temperature was possible whatever the nature of the R^1 (aliphatic and aromatic with functionality such as cyano, nitro, etc.) and R^2 groups. An example of application of this strategy to a chiral nonracemic compound was also successful.

More recently the same research group has extended this protocol to the synthesis of tetrasubstituted α-fluoroenones from tetrasubstituted *gem*-bromofluoroolefins (Scheme 273).[288] Reaction yields were good for all substrates (65−88%), that is, aliphatic (linear or cyclic) or aromatic molecules. Although no stereodifferentiation was obtained, an interesting feature was the possible separation of the *E*/*Z* products, starting from a

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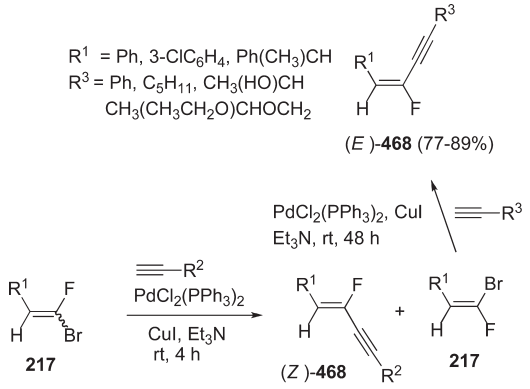
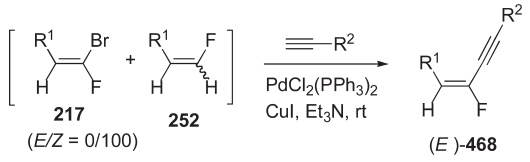
Scheme 278



217 *E/Z* [a]	R^1	R^2	468 yield (%)(*Z/E*)[b]
6:5	Ph	Ph	38 (100:0)
1:1	Ph	*n*-C_5H_{11}	46 (98:2)
1:1	3-ClC_6H_4	CH_3(OH)CH	48 (99:1)
7:3	Ph(CH_3)CH	CH_3(OH)CH	53 (98:2)
7:3	*n*-C_7H_{15}	Ph	64 (90:10)
6:5	Ph	$(CH_3)_3Si$	23 (99:1)

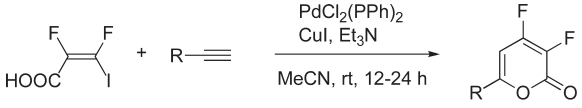
[a]Only representative results are reported.
[b]Yield based on the amount of the olefin consumed.

Scheme 279



R^1	R^2	(*E*)-468 yield (%)
2-ClC_6H_4	*n*-C_5H_{11}	92
2-ClC_6H_4	*n*-$C_{10}H_{21}$	72
4-$MeOC_6H_4$	*n*-C_5H_{11}	82
4-$MeOC_6H_4$	Ph	78
1-naphthyl	*n*-Bu	89
1-naphthyl	Ph	68

Scheme 280



R	yield (%)	R	yield (%)
Ph	62	4-$F_3CC_6H_4$	69
n-C_5H_{11}	59	4-$MeOC_6H_4$	71
Ph(CH_2)$_2$	64	2-py—	43

nonseparable *E*/*Z* mixture of tetrasubstituted *gem*-bromofluoroolefin. Depending on the substrate, partial isomerization occurred sometimes during the hydrolysis step, probably through a thermodynamic equilibrium of the tetrasubstituted α-fluoroenones in acidic medium.

3.2.4. Coupling with Alkynes. The coupling of (*Z*)-1-bromo-1-fluoro-1-arylethylenes **464** with 1-alkynes in the presence of $Pd(OAc)_2/PPh_3$ and *n*-$BuNH_2$ proceeded stereospecifically to give enynes (*E*)-**465** in moderate to good yields (40−71%) (Scheme 274).[194,204] However, in the case of the compound **464** with R = *p*-nitro, the use of Et_3N was necessary because of the formation of the amide **466** via Pd-catalyzed substitution of bromine with *n*-$BuNH_2$. The stereospecificity of the reaction was demonstrated because a 9:1 mixture of (*Z*,*E*)-**465a** was formed in 81% yield when a *E*/*Z* mixture in 9:1 ratio of the related starting material **464a** was used.

Complete retention of the olefin geometry was also observed in the Sonogashira coupling of (*E*)-1-(2-bromo-1,2-difluorovinyl)naphthalene with terminal alkynes to give s (Scheme 275).[279]

The higher reactivity of the iodo substituent with respect to the chloro one allows the Sonogashira coupling of 1-chloro-1-iodo-1-alkenes to occur stereospecifically. Thus, coupling of (*Z*)-l-chloro-1-iodoenynes **243** with terminal alkynes, in the presence of piperidine (2 equiv) and a catalytic amount of $Pd(PPh_3)_4$ and CuI provided (*E*)-chloroenediynes **467** in excellent yields (71−90%) (Scheme 276).[204]

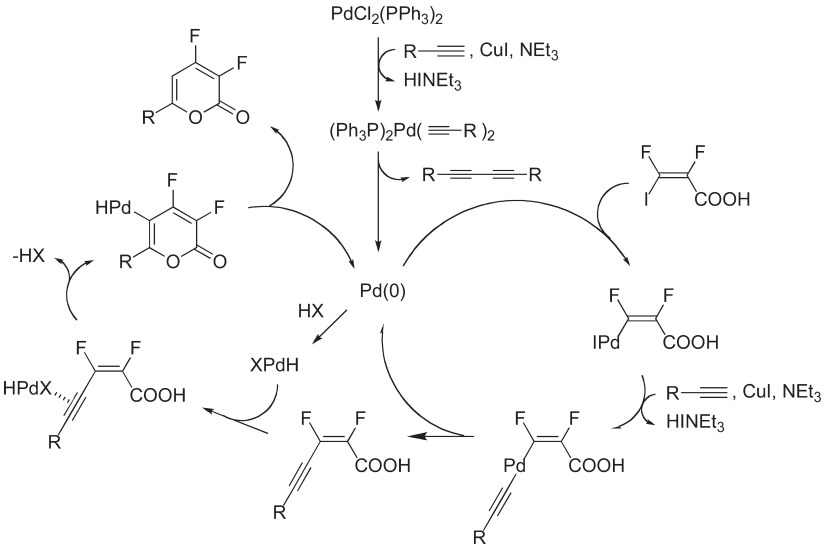
Isomerically pure 1-fluoro-1-iodoalkenes reacted similarly to 1-chloro-1-iodoalkenes with terminal alkynes at room temperature in the presence of catalytic $PdCl_2(PPh_3)_2$, CuI, and Et_3N to give stereospecifically the corresponding fluorinated enynes. Some examples of these enynes, which were later used for the synthesis of fluorinated naphthalenes,[208] 2-pyrones,[289] and 5-iodo-2-pyrones[289] are described in the Scheme 277. The high reactivity of 1-fluoro-1-iodo-1-alkenes under Sonogashira conditions makes the *Z*/*E* mixtures of these compounds give poor stereoselectivities.[217] Thus, for instance, when 1-fluoro-1-iodostyrenes with a *Z*/*E* ratio of 1:1 was reacted with phenylacetylene at room temperature, the *Z*/*E* ratio of the produced enyne improved to 7:3 after a short reaction time but became 1:1 after 16 h.[217]

On the other hand, the Sonogashira reaction of *E*/*Z* mixtures of 1-bromo-1-fluoro-1-alkenes allows a significantly better kinetic separation. Thus, under similar coupling conditions, the reaction of *E*/*Z* mixtures of 1-bromo-1-fluoroolefins **217** gave after 16−24 h predominately (*Z*)-monofluoroenynes (*Z*/*E* > 92/8) in good yields (Scheme 278).[217] Pure (*Z*)-**217** could be recovered and reacted with 1-alkynes under similar conditions, but it took longer reaction times (48 h) to give pure (*E*)-monofluoroenynes in excellent yields (78−89%). When the Sonogashira coupling of mixtures of (*E*)- and (*Z*)-**217** was carried out at room temperature for 48 h, monofluoroenynes were obtained as *E*/*Z* mixtures that were used without purification for the synthesis of fluorinated naphthalenes.[290]

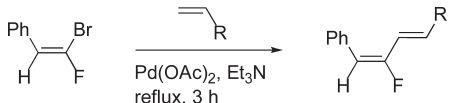
Alternatively, pure (*E*)-monofluoroenynes can be prepared via Sonogashira reaction of mixtures of 100% (*Z*)-1-bromo-1-fluoroalkenes **217** and their hydrodebrominated products **252**, obtained by kinetic reduction of *E*/*Z* ≈ 1:1 mixtures of 1-bromo-1-fluoroalkenes (Scheme 155).[290,291] Thus, when mixtures of **217** and **252**, terminal acetylenes, $PdCl_2(PPh_3)_2$ (4 mol %), and CuI (1 mol %) in Et_3N were reacted at room temperature, (*E*)-monofluoroenynes were successfully synthesized in high yields (Scheme 279).

Burton and Wang reported that the reaction of (*E*)-2,3-difluoro-3-iodoacrylic acid with a variety of terminal acetylenes

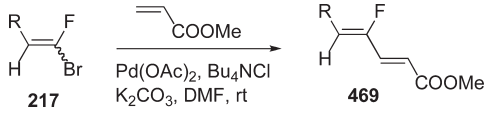
Scheme 281



Scheme 282



Scheme 283

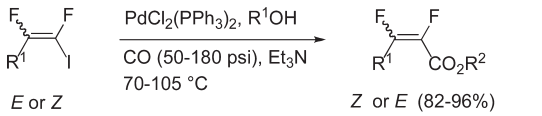


R	**217** *E*/*Z*	**469** yield (%)	(*E*,*Z*)/(*E*,*E*)[a]
Ph	85:15	70	95:5
2-ClC$_6$H$_4$	82:18	77	86:14
4-MeOC$_6$H$_4$	83:17	74	88:12
4-ClC$_6$H$_4$	88:12	82	96:4
4-FC$_6$H$_4$	87:13	78	91:9
3-O$_2$NC$_6$H$_4$	81:19	61	nd

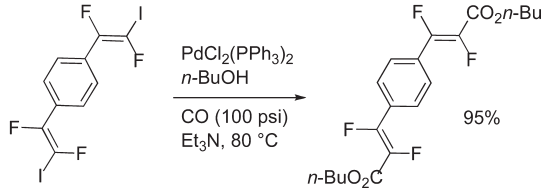
[a]Ratio of the crude reaction mixture

under cocatalysis of $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (5 mol %) gave difluorinated 2-pyrones as the sole products in satisfactory yields (Scheme 280).[289] The mechanism proposed to explain the formation of 2-pyrones is reported in Scheme 281. The Pd(0) is first formed in the presence of phenylacetylene. In the first catalytic cycle, the iodoacid reacts with the alkyne under Pd(0)-catalysis to produce the ynenoic acid. The Pd(0) species is regenerated after the first cycle and is readily converted into Pd(II) in the solution containing an acid moiety HX (X could be I^-, Cl^-, or (*E*)-CFI=CFCO$_2^-$). In the second catalytic cycle, the ynenoic acid is further transformed into the final

Scheme 284



R^1 = Ph, 4-MeOC$_6$H$_4$, 4-NCC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, *t*-Bu, *s*-Bu, *n*-Bu
R^2 = Et, *n*-Bu



product under the catalysis of Pd(II). Upon reductive elimination, the Pd(0) is regenerated to yield the difluorinated 2-pyrone.

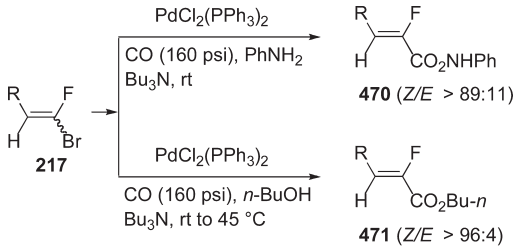
3.2.5. Coupling with Alkenes. Heck reaction of pure (*Z*)-(2-bromo-2-fluorovinyl)benzene with some ethylenic compounds afforded 1,3-dienes in high yields and stereoselectivity (Scheme 282).[195]

High stereoselectivity of the Heck reaction was also observed when 1-bromo-1-fluorostyrenes of high *E*/*Z* ratios (>81:19) were coupled with methyl acrylate to afford (*E*,*Z*)-dienes with higher diastereomeric ratio than the starting material (Scheme 283).[292] Heck reaction of (*Z*)-1-bromo-1-fluorostyrenes also occurred, but the (*Z*,*Z*)-diene products were difficult to separate in a pure form, because of their tendency to isomerize during the purification procedure.[292]

3.2.6. Carboalkoxylation and Carboamidation. Burton and co-workers reported that the carboalkoxylation of isomerically pure 1,2-difluoro-1-iodoalkenes gave the corresponding fluorinated esters with retention of configuration, in the presence of catalytic $PdCl_2(PPh_3)_2$, ethanol or butanol, Et_3N, and carbon monoxide (50−180 psi) under mild conditions in excellent yields (82−96%) (Scheme 284).[293] Under the same conditions, isomerically

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

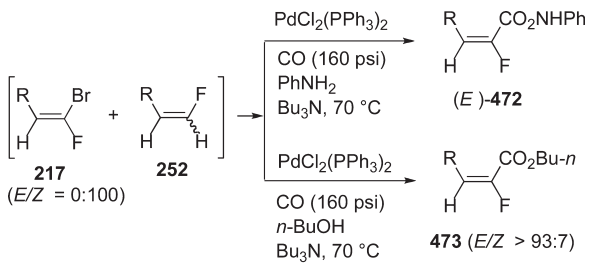
Scheme 285



R	**217** *E*/*Z*	**470** yield (%)[a]	**471** yield (%)[a]
Ph	85:15	72	46
2-ClC_6H_4	82:18	78	74
4-$MeOC_6H_4$	83:17	73	70
4-ClC_6H_4	88:12	78	44
4-FC_6H_4	87:13	75	77
3-$O_2NC_6H_4$	81:19	67	46
$PhCH(CH_3)$	83:17	56	55

[a]Yield based on the amount of the (*Z*)-isomer in the starting *E*/*Z* mixture

Scheme 286

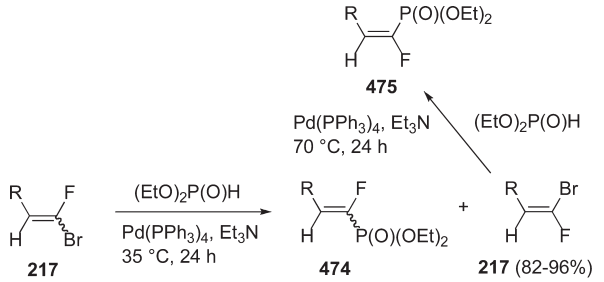


R	**472** yield (%)	**473** yield (%)
Ph	25	90
2-ClC_6H_4	27	94
4-$MeOC_6H_4$	inseparable	79
$PhCH(CH_3)$	74	92
1-naphthyl	42	81
n-C_7H_{15}	inseparable	inseparable

pure (*E*)-1,2-difluoro-1-iodoethene gave stereospecifically (*Z*)-ethyl 2,3-difluoroprop-2-enoate in good yield (63%).[294]

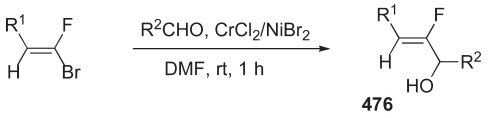
Burton and Xu described the highly stereoselective synthesis of (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated esters and amides.[213,216] The Pd-catalyzed carboalkoxylation of 1-bromo-1-fluoroalkenes with high *E*/*Z* (>81:19) ratio led to high *Z*/*E* (≥96:4) ratio of α-fluoro-α,β-unsaturated esters at room temperature (Scheme 285). On the other hand, a mixture of (*Z*)-1-bromo-1-fluoroalkenes and of their hydrodebrominated products (Scheme 155) underwent similar Pd-catalyzed carboalkoxylation reactions at 70 °C giving (*E*)-α-fluoro-α-unsaturated esters stereospecifically (Scheme 286). This methodology was also successfully applied for the stereospecific synthesis of (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated amides (Schemes 285 and 286): the Pd-catalyzed carboamidation reaction of high *E*/*Z*

Scheme 287



R	**217** *E*/*Z*	**474** yield (%)	**474** *E*/*Z*	**475** yield (%)
i-Pr	7:3	55	96:4	53
Ph	1:1	45	95:5	51
n-C_7H_{15}	1:1	45	95:5	60
2,3-$Me_2C_6H_3$	3:2	56	94:6	52
3-ClC_6H_4	3:2	44	96:4	55
$Ph(CH_3)CH$	3:2	49	92:8	56

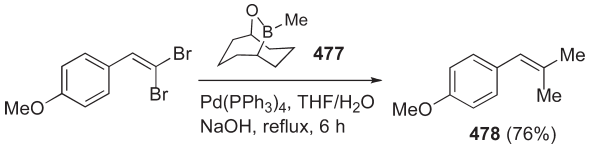
Scheme 288



R^1	R^2	**476** yield (%)
Ph	4-$MeOC_6H_4$	78
4-FC_6H_4	4-$MeOC_6H_4$	72
4-$O_2NC_6H_4$	4-$MeOC_6H_4$	0
Et	4-$MeOC_6H_4$	94
$PhCH_2$	4-$MeOC_6H_4$	60
Ph	4-FC_6H_4	34
Ph	4-$O_2NC_6H_4$	0
Ph	$PhCH_2CH_2$	45
4-$MeO_2CC_6H_4$	Ph	20

Only representative substrates are reported

Scheme 289

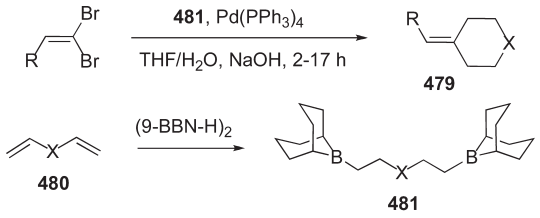


and (*Z*)-1-bromo-1-fluoroalkenes led to pure (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated amides, respectively.

3.2.7. Phosphorylation. Burton and co-workers provided a route to isomerically pure (*E*)- and (*Z*)-1-fluorovinylphosphonates from readily available *E*/*Z* mixtures of 1-bromo-1-fluoroolefins (Scheme 287).[215] Reaction of these mixtures with diethylphosphite and catalytic $Pd(PPh_3)_4$ in Et_3N at 30−40 °C gave mainly

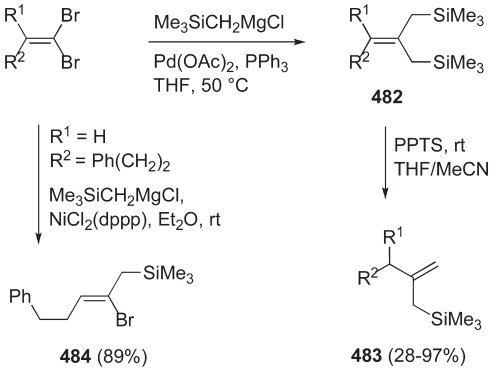
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 290



X	R	**479** yield (%)
CH_2	Ph	56
CH_2	4-biphenyl	42
CH_2	4-tolyl	34
CH_2	4-anisyl	76
CH_2	*n*-Bu	44
$SiMe_2$	Ph	45
$SiMe_2$	4-biphenyl	60
$SiMe_2$	2-furyl	36
$SiMe_2$	4-tolyl	25
$SiMe_2$	4-anisyl	41
$SiMe_2$	*n*-Bu	45
CHOTBDMS	Ph	38
CHOTBDMS	Me	64

Scheme 291

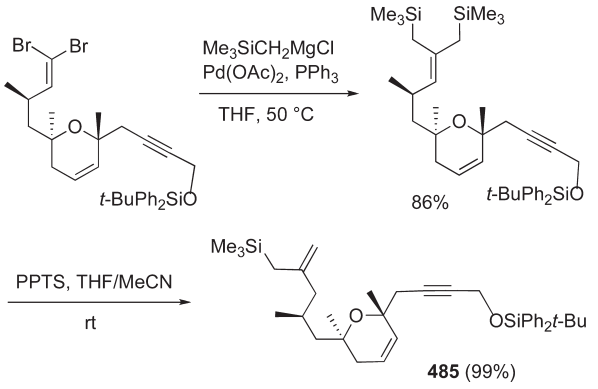


R^1	R^2	**482** yield (%)
$PhCH_2CH_2$	H	93
n-$C_{10}H_{21}$	H	94
c-C_6H_{11}	H	85
$PhCH(CH_3)$	H	79
Ph	H	43
-$(CH_2)_2CH(t\text{-}Bu)(CH_2)_2$-		21

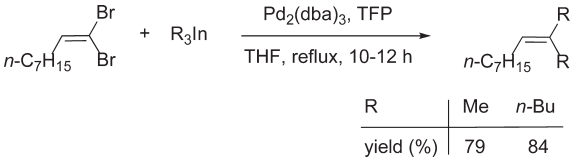
(*E*)-isomers of 1-fluorovinylphosphonates (*E*/*Z* ≥ 92:8) in good yields and unreacted (*Z*)-1-bromo-1-fluoroolefins. These isomers could be recovered and then phosphorylated at 70 °C to give pure (*Z*)-1-fluorovinylphosphonate in 51−60% yields. On the other hand, the phosphorylation reaction of *E*/*Z* mixtures of 1-fluoro-1-iodoalkenes such as PhCH=CFI gave unsatisfactory results concerning both yields and selectivities.

3.2.8. Hydroxyalkylation. Pannecoucke and co-workers[218] have recently developed a method to obtain (*Z*)-2-fluoroallylic alcohols **476** from the related (*Z*)-bromofluoroolefins via a Nozaki−Hiyama−Kishi-type reaction (Scheme 288). The yields were moderate to good, ranging from 34% to 94%, for substrates with both aromatic and aliphatic substituents. Functional groups on both the aldehyde and bromofluoroolefin were tolerated except the reducible ones, such as the nitro or ester groups, for which the yield of the Nozaki−Hiyama−Kishi coupling was zero or very poor. In contrast to trisubstituted bromofluoroolefins, the tetrasubstituted ones gave unsatisfactory results, in accordance with the fact that the intermediate chromium species in the Nozaki−Hiyama−Kishi reaction was more difficult to be formed and less stable when chromium was in the *cis*-position of a substituent, thus leading to rapid decomposition. An example of diastereoselective reaction was also reported (Scheme 157).

Scheme 292



Scheme 293



R	Me	*n*-Bu
yield (%)	79	84

3.3. Homodisubstitution

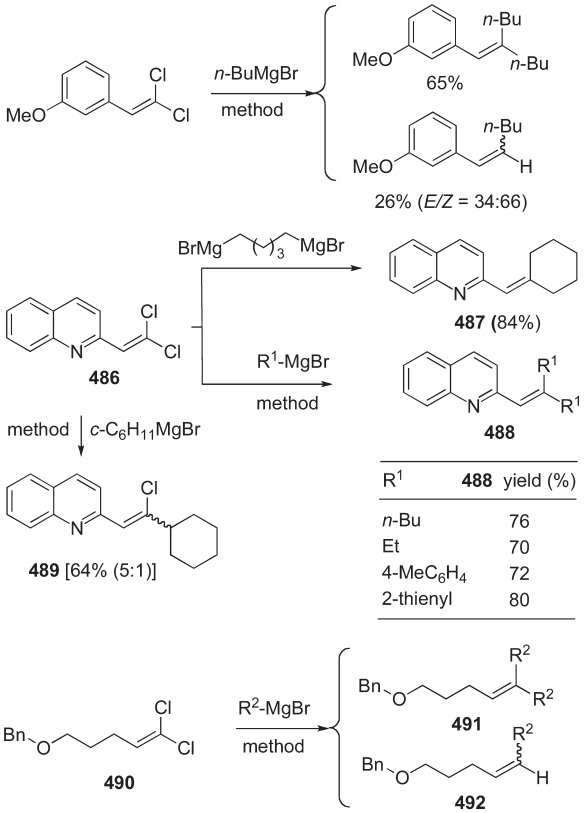
3.3.1. Coupling with Alkylmetal Reagents. Soderquist and Santiago reported that the Pd-catalyzed cross-coupling of vinyl, alkynyl, and aryl bromides with the air-stable 10-methyl-9-oxa-10-borabicyclo[3.3.2]decane **477** gave excellent yields of the related methylated products.[295] Among them, the coupling of 1-(2,2-dibromovinyl)-4-methoxybenzene to give the dimethylated alkene **478** in good yield (76%) was described (Scheme 289).

The same research group illustrated also that both carbo- and heterocyclic six-membered ring systems **479**, containing an exocyclic carbon−carbon double bond, were prepared from α,ω-dienes **481** through cross-coupling of their dihydroboration products **481** with either aromatic or aliphatic vinylidene dibromides in a one-pot Pd-catalyzed sequence (Scheme 290).[296] The intramolecular coupling process catalyzed by $Pd(PPh_3)_4$ (6 mol %) occurred smoothly at room temperature requiring generally less than 8 h to give the cyclic compounds **479** in 25−76% yields. Attempts to extend this methodology to five-membered ring systems were unsuccessful.

Uenishi and co-workers recently reported the synthesis of 1-trimethylsilyl-2-trimethylsilylmethyl-2-alkenes **482** by tandem Pd-catalyzed Kumada−Tamao−Corriu cross-coupling reaction of 1,1-dibromoalkenes with an excess of silylmethyl Grignard

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 294

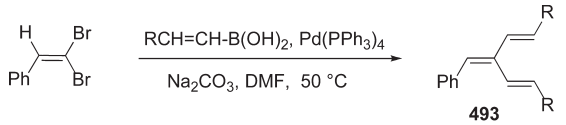


R^1	**488** yield (%)
n-Bu	76
Et	70
4-MeC_6H_4	72
2-thienyl	80

	R^2	**491** yield (%)	**492** yield (%)	*E*/*Z*
a	*n*-Bu	59	0	0
b	*n*-$C_{12}H_{25}$	59	0	0
c	$BrMgO(CH_2)_3$	21	30	0
d	*c*-C_6H_{11}	12	45	64:36
e	Ph	0	35	94:6

Method: Grignard reagent (3 equiv), $Fe(acac)_3$ (10 mol%), THF -30 °C, 1.5-18 h.

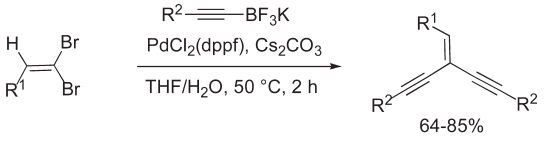
Scheme 295



R	yield (%)	R	**493** yield (%)
n-Bu	66	$HO(CH_2)_4$	40
t-Bu	58	Ph	54

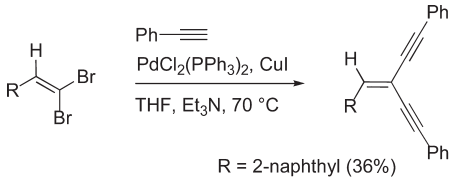
reagents in good to excellent yields, though undesired reactions occurred partially in some cases (Scheme 291).[297,298] On the other hand, nickel-catalyzed cross-coupling of (4,4-dibromobut-3-enyl)benzene with Me_3SiCH_2MgCl in ether at room temperature gave 2-bromo-5-phenyl-1-trimethylsilyl-2-pentene **484** in 89% yield (Scheme 291).[298] From **482**, 2-trimethylsilylmethyl-1-alkenes **483** were then prepared in excellent yields by selective

Scheme 296



R^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 1-naphthyl, *n*-C_8H_{17}
R^2 = *n*-Bu, 3-Cl-propyl, isopropenyl, Ph, 4-MeC_6H_4

Scheme 297



R = 2-naphthyl (36%)
R = pentafluorophenyl (55%)

monoprotodesilylation (Scheme 291).[298] This protocol was used for the synthesis of the compound **485**, a key fragment in the synthesis of the cancer-therapy agent (−)-laulimalide (Scheme 292).[299]

Perez Sestelo and co-workers, by reacting 1,1-dibromonon-1-ene with methyl- and *n*-butylindium organometallics under $Pd_2(dba)_3$/TFP (1:1, 2 mol %) catalysis, obtained the related doubly cross-coupled products dimethyl- and di-*n*-butylalkenes in 79% and 84% yields, respectively (Scheme 293).[236]

Satisfactory results were also obtained with the use of $Fe(acac)_3$ as the catalyst in the coupling of 1,1-dichloroalkenes with Grignard reagents derived from alkyl halides (Scheme 294).[51] Under optimal reaction conditions, 3 equiv of R-MgBr and 10 mol % $Fe(acac)_3$ reacted with (hetero)aryl-derived substrates to afford good yields of dicoupled products with dehydrochlorinated coupled compounds as the minor byproduct. Interestingly, the reaction of **486** with the 1,5-di-Grignard reagent derived from 1,5-dibromopentane gave the cyclized product **488** in excellent yield (84%), through an intramolecular coupling reaction. On the other hand, the cyclohexylmagnesium bromide led only to the monocoupled compound **489** in good yield (64%) as a 5:1 mixture of isomers. The aliphatic substrate **490** led to dicoupled products **491** in low to moderate yields, often with relevant amounts of the alkenes **492**. The reaction of **490** with phenylmagnesium bromide failed to give the expected dicoupled product, but afforded only the alkene **492e**.

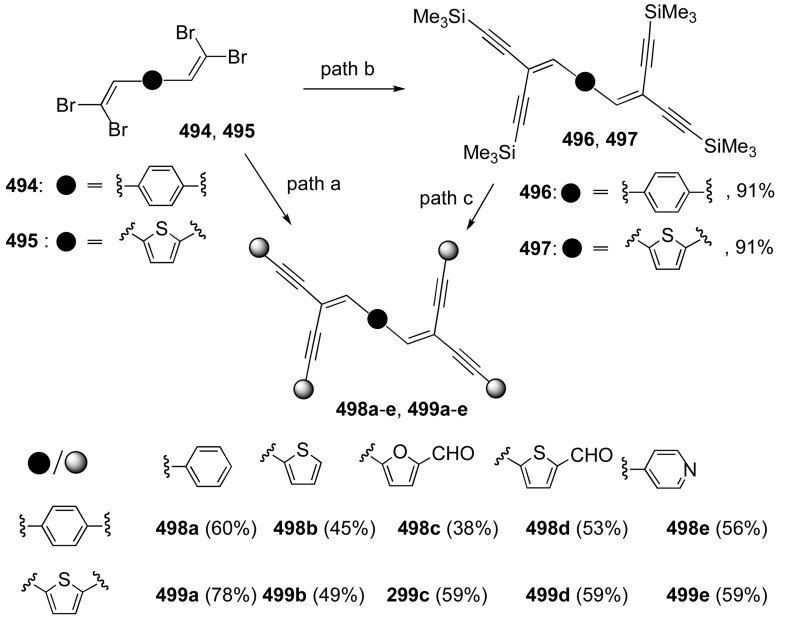
3.3.2. Coupling with Alkenynylmetal Reagents. Oh and Lim optimized the reaction conditions for the double Suzuki reactions of (2,2-dibromovinyl)benzene with alkenylboronic acids (4 equiv) for obtaining the cross-conjugated trienes **493** in 40−66% yields in the presence of 3 mol % $Pd(PPh_3)_4$ and 12 equiv of Na_2CO_3 (Scheme 295).[300]

3.3.3. Coupling with Alkynylmetal Reagents. Kabalka and co-workers developed an efficient synthesis of cross-conjugated enediynes by the cross-coupling of potassium alkynyltrifluoroborates with 1,1-dibromoalkynes (Scheme 296).[301] Optimal reaction conditions were found to be 10 mol % $PdCl_2(dppf)$ and 3 equiv of Cs_2CO_3 in THF/H_2O (20:1) at 50 °C for 2 h.

Neckers and co-workers described the synthesis of enediynes by coupling of the parent *gem*-alkenes with phenylacetylene in the presence of catalytic $PdCl_2(PPh_3)_2$ and CuI (Scheme 297).[302]

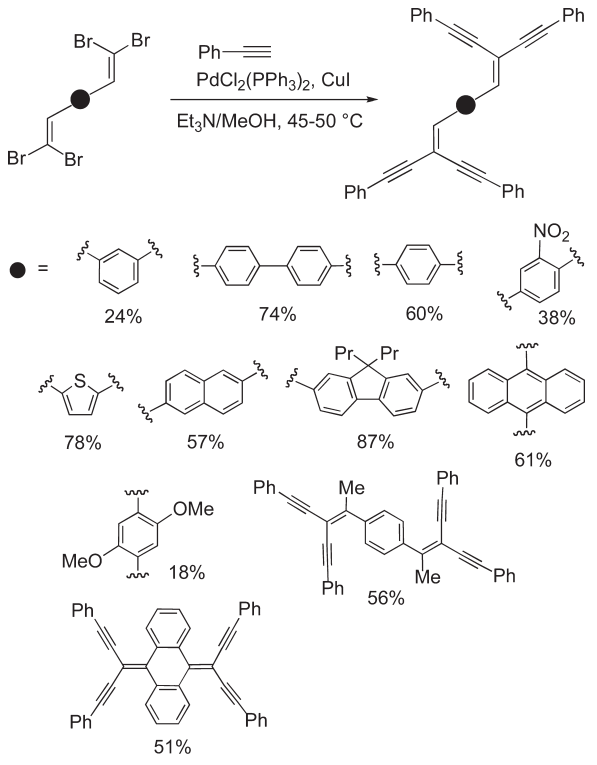
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 298



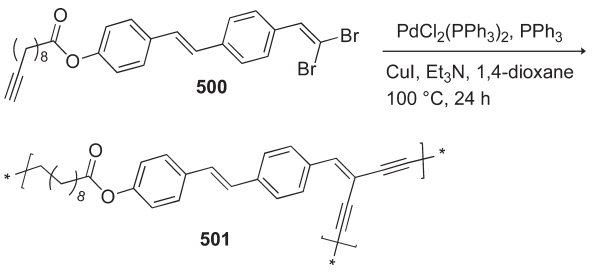
a: Phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N/MeOH, 45-50 °C; b: trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N/MeOH, 45-50 °C; c: ArBr, KF, $PdCl_2(PPh_3)_2$, CuI, Et_2NH/MeOH, 45-50 °C for **498b**, **499b** and $PdCl_2(PPh_3)_2$, CuI, Et_3N/MeOH, 45-50 °C for the others, as the CuX, CuI was used for all the fluorophores except **498c** and **499c**, which used CuI.

Scheme 299



Two complementary Pd/Cu-catalyzed Sonogashira cross-coupling methods were also followed to synthesize a family of bis-endiynes (Schemes 298 and 299).[303] One is a Sonogashira reaction between 1,4-bis(dibromovinyl)benzene **494** or 1,4-bis-(dibromovinyl)thiophene **495** and phenylacetylene (path a, Scheme 298). Fluorophores **498a** and **499a** were synthesized by this method. The other one is a modified Sonogashira reaction between the TMS-protected tetraalkyne **496** (or **497**) and aromatic bromides (path b, c). This procedure consists of the in situ liberation of the alkyne functionality in the presence of KF from the corresponding TMS-protected compounds and then coupling with aromatic bromides. A number of bis-enediynes bearing different core aryl groups were also synthesized by this protocol (Scheme 299).

Scheme 300

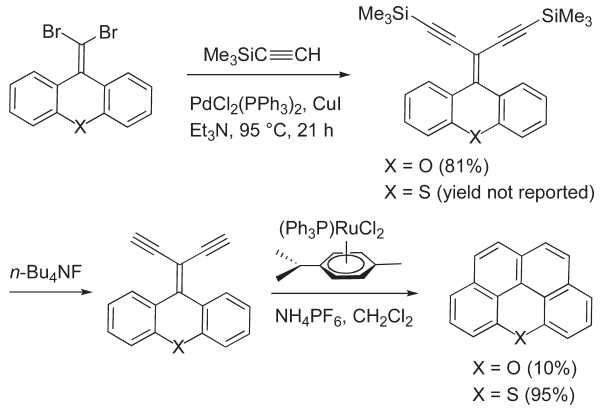


Kim and Kim prepared the dibromoolefin **500**, which they submitted to intramolecular Sonogashira coupling with $PdCl_2(PPh_3)_2$ (1.5 mol %), PPh_3 (1.5 mol %), and CuI (6.5 mol %) to produce the conjugated enediyne polymer **501** (Scheme 300).[304]

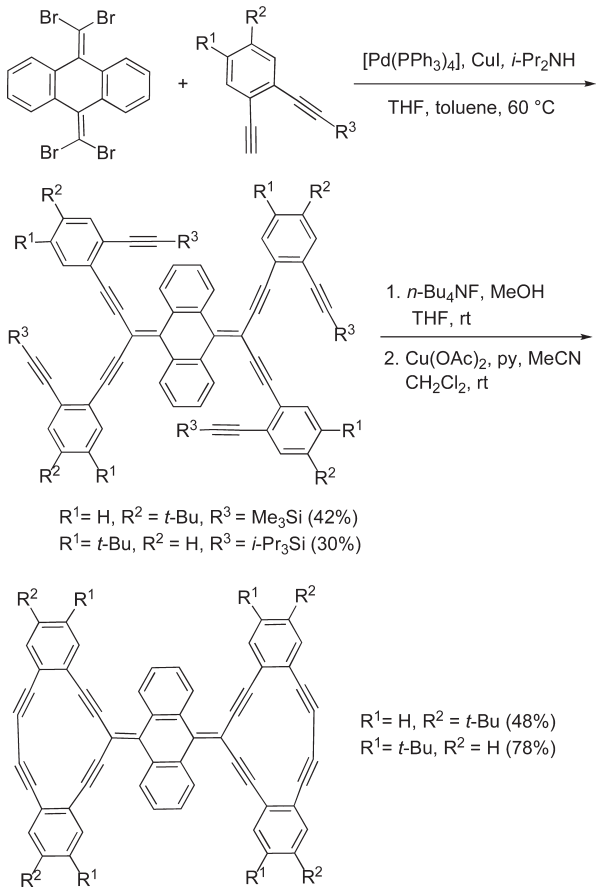
A double Sonogashira coupling of 1,1-dibromoalkenes with trimethylsilylacetylene, followed by desilylation, produced diynes that were key intermediates for the synthesis of polycyclic

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 301



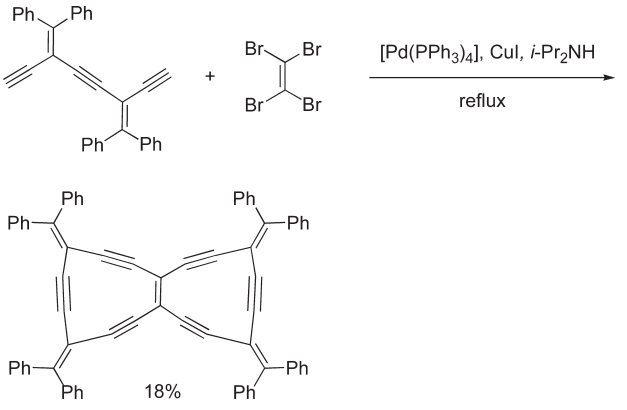
Scheme 302



aromatic hydrocarbons and heterocycles containing a newly formed naphthalene ring system embedded in a larger polycyclic network.[305] The synthesis of two representative examples is shown in Scheme 301.

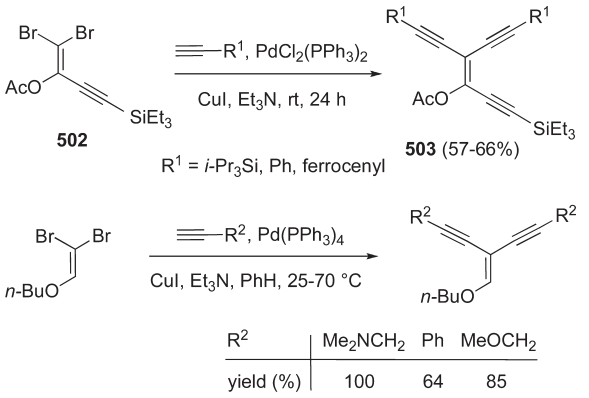
The synthesis of cross-conjugated bis-dehydroannulenes with different topologies of the π-electrons by Cu(II)-mediated oxidative coupling of the related precursors, which were in turn obtained by 4-fold Sonogashira couplings of the appropiate tetrabromide with terminal acetylenes, has been reported.[306] An example of this strategy for the synthesis of bis-dehydro[13]annulenes containing a 9,10-dehydroanthracene core is outlined in Scheme 302.

Scheme 303



Carbon-rich, highly conjugated bis-expanded radialene and radiaannulene compounds were prepared by Sonogashira cross-coupling of the corresponding enyne precursors with tetrabromoethene.[307] A representative example is shown in Scheme 303.

Scheme 304

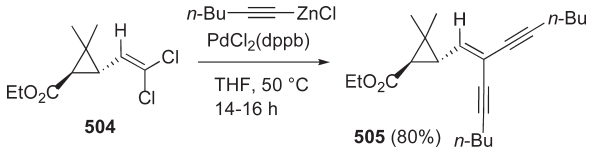


Two examples of Sonogashira reactions of 2,2-dibromoethenyl ethers with terminal alkynes have been described.[41b,308] Tykwinski and Rankin reported that the coupling of **502** with terminal alkynes, incorporating the triisopropylsilyl, phenyl, or ferrocenyl moiety, in the presence of $PdCl_2(PPh_3)_2$, CuI, and Et_3N generated triynes **503** in 57−66% yields after 24 h at room temperature (Scheme 302).[41b] On the other hand, the alkynylation of the corresponding vinyl triflate of **502** was unsuccessful. In the second example, the cross-coupling of 2,2-dibromoethenyl butyl ether with methoxypropyne and dimethylaminopropyne afforded the related enediynes in the presence of 2 mol % $Pd(PPh_3)_4$, CuI, and Et_3N in benzene at room temperature, whereas phenylacetylene required heating at 70 °C (Scheme 304).[308]

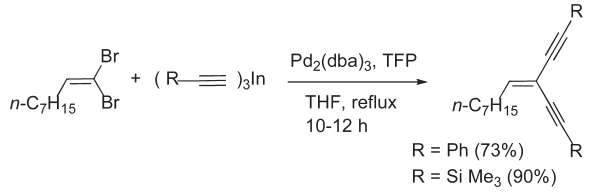
Minato, studying the monocoupling of (2,2-dihaloethenyl)cyclopropanecarboxylates with organozinc reagents (Scheme 188),[244] found that when the reaction of **504** was carried out with an excess amount of 1-hexenylzinc chloride (2.5 equiv) in the presence of $PdCl_2$(dppb) the cross-conjugated enediyne **505** was formed in 80% yield after 14−16 h at 50 °C (Scheme 305).[244]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

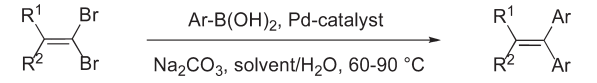
Scheme 305



Scheme 306



Scheme 307



Two examples of $Pd_2(dba)_3$/TFP catalyzed cross-coupling of ethynylindium organometallics with a 1,1-dibromoolefin have been reported to give excellent yields of the related doubly cross-coupled products (Scheme 306).[236] The use of a low loading of catalyst (2 mol %) with R_3In is remarkable.

3.3.4. Coupling with (Hetero)arylmetal Reagents. Miller and co-workers reported the Suzuki diarylation of 1,1-dibromoalkenes derived from ketones to give tetrasubstituted alkenes in 24−95% yields (Scheme 307 and Table 5).[309] In general, 1,1-dibromoalkenes derived from cyclic ketones underwent coupling more efficiently than acyclic derivatives with $PdCl_2(PPh_3)_2$ (10 mol %) as the catalyst. The use of higher temperature and $Pd(PPh_3)_4$ was needed to afford reasonable yields of coupled products arising from acyclic dibromoalkenes, the only exception being the ester methyl 4-(1,1-dibromoprop-1-en-2-yl)benzoate, which gave a high yield of dicoupled product. A variety of aryl boronic acids were also well tolerated.

The synthesis of fluorinated tetrasubstituted alkenes was also achieved via Pd-catalyzed bis-Suzuki coupling of 2-trifluoromethyl-1,1-dibromoalkenes with aryl and heteroaryl boronic acids in excellent yields (Scheme 308).[310]

Chen and co-workers have recently reported the use of the Pd complex **506** (0.02 mol %) in Suzuki−Miyaura cross-couplings of aryl 1,1-dibromoalkenes in neat water under air atmosphere (Scheme 309).[311] Trisubstituted arylalkenes were obtained in good yields (72−89%), whereas lower selectivity for the aliphatic 1,1-dibromodec-1-ene (53% yield) was achieved.

Mori and co-workers have very recently demonstrated that the preparation of multiple substituted thiophene derivatives could be pursued starting from the vinylidene bromide **507** by a Suzuki−Miyaura coupling and Pd-catalyzed CH-insertion strategy (Scheme 310).[312] Initial attempts at coupling **507** with arylmagnesium and arylstannane reagents failed to give the expected dicoupled products **508**, which were on the other hand obtained by coupling with arylboronic esters under Suzuki−Miyaura coupling conditions [$Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %)]. The use of a precise amount of boron reagent (3.0 equiv) and K_2CO_3 (6 equiv) was essential to obtain a variety of diaryl derivatives **508** in high yields. The thiophene derivatives **508** were then subjected to functionalization at the 5-position of the thiophene ring by a Pd-catalyzed CH-arylation reaction in the presence of $AgNO_3$/KF as an activator.

A double Suzuki−Miyaura reaction has been used to synthesize substituted diarylmethylidenefluorene derivatives (Scheme 311).[313] Thus, the coupling of the 9-(dibromomethylene)-9*H*-fluorene with differently substituted arylboronic acids under optimized reaction conditions [$PdCl_2(PPh_3)_2$ (7.5 mol %), $ArB(OH)_2$ (1.5 equiv)] led to the formation of symmetrically tetrasubstituted alkenes. In general, reactions of boronic acids with electron-withdrawing substituents on the aromatic ring were facile and good yields (79−88%) were obtained, whereas those of boronic acids with electron-donating groups were sluggish and resulted in lower yields (44−61%).

Tykwinski and Rankin studied the Suzuki and Stille reactions of the vinyl acetate **502** (Scheme 312).[41b] The Suzuki cross-coupling of **502** with various substituted phenylboronic acids by using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base, produced the diarylated vinyl acetates **511** in 50−85% yields in less than 24 h at 110 °C, as long as the reaction was kept strictly anhydrous. On the other hand, the conversion of **502** to heteroaryl-substituted vinyl acetates **512** (50−66% yields) was possible by the Stille cross-coupling method, requiring reaction times of 2−4 h by using $Pd(PPh_3)_4$ as the catalyst in DMF at 120 °C (Scheme 312).

Minato described the diheteroarylation of (2,2-dihaloethenyl)cyclopropanecarboxylates. In particular, the cross-coupling of **513** with an excess amount of 2-thienylzinc chloride (2.8 equiv) in the presence of $PdCl_2$(dppb) afforded the dicoupled product **514** in 57% yield (Scheme 313).[244]

Shen and Wang reported that when the Stille coupling of methyl 4-(2,2-dibromovinyl)benzoate was carried out with 2.2 equiv of trimethyl(phenyl)tin in the presence of $Pd_2(dba)_3$ (2.5 mol %) and TFP (15 mol %) for 48 h, the related dicoupled product was formed in quantitative yield (Scheme 314).[247]

Figadère, Alami, and co-workers described that under optimal reaction conditions, the reaction of 1,1-dichloro-2-(2-quinolyl)ethylene with 4-MeC_6H_4MgBr and 2-thienylMgBr (3 equiv) in the presence of $Fe(acac)_3$ (10 mol %) afforded high yields of the related dicoupled products (Scheme 315).[51]

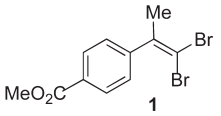
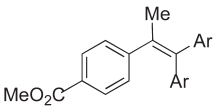
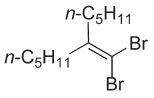
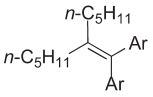
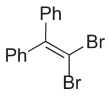
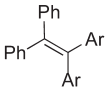
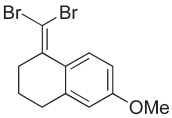
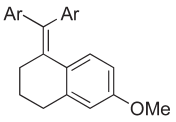
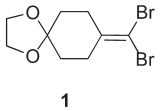
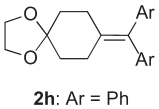
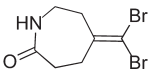
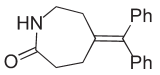
The $Pd_2(dba)_3$/TFP (1:1, 2 mol %) catalyzed cross-coupling of triphenylindium with 1,1-dibromonon-1-ene was reported to give good yield (72%) of the related diphenylated product (Scheme 316).[236]

3.4. Selective Disubstitution

3.4.1. Tandem C−C/C−C Coupling. *3.4.1.1. Alkenylation−Alkylation.* Molander and Yokoyama developed an effective one-pot synthesis of stereo-defined, trisubstituted, conjugated dienes by using alkenyl- and alkyltrifluoroborates through the sequential disubstitution of 1,1-dibromoalkenes (Schemes 317 and 318).[314] The process was optimized with 1,1-dibromo-2-cyclohexene **515** as the *gem*-dibromide, potassium (*E*)-1-hex-5-enoic acid trifluoroborate, methyl ester, and potassium 2-phenylethyl trifluoroborate as the coupling partners. Under optimal reaction conditions, compound **515** was smoothly coupled with a variety of functionalized alkenyl trifluoroborates followed by alkyltrifluoroborates in the presence of Pd-$(PPh_3)_4$ (7 mol %) as the catalyst (Scheme 317). However, when the potassium salts of methyl, ethyl, and 4-pentenyl trifluoroborate

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Table 5. Tetrasubstituted Alkenes from 1,1-Dibromoalkenes[a] (Scheme [307])

dibromoalkene	$ArB(OH)_2$	method	product	yield (%)
 **1**	Ar = 3-MeC_6H_4	A	 **2a**: Ar = 3-MeC_6H_4	97
	Ar = 4-$MeSC_6H_4$	A	**2b**: Ar = 4-$MeSC_6H_4$	95
 **1**	Ar = Ph	A	 **2c**: Ar = Ph	26
	Ar = 4-pyridyl	B	**2d**: Ar = 4-pyridyl	46
 **1**	Ar = 4-$MeOC_6H_4$	B	 **2e**: Ar = 4-MeOPh	87
	Ar = 3-$F_3CC_6H_4$	B	**2f**: Ar = 3-F_3CPh	75
	Ar = 3-thiophenyl	B	**2g**: Ar = 3-thiophenyl	40
 **1**	Ar = Ph	A	 **2h**: Ar = Ph	77
	Ar = 4-$MeOC_6H_4$	A	**2i**: Ar = 4-$MeOC_6H_4$	79
	Ar = 3-$F_3CC_6H_4$	A	**2j**: Ar = 3-$F_3CC_6H_4$	95
	Ar = 3-thiophenyl	A	**2k**: Ar = 3-thiophenyl	80
	Ar = 4-pyridyl	B	**2l**: Ar = 4-pyridyl	36
 **1**	Ar = Ph	A	 **2h**: Ar = Ph	89
	Ar = 4-$MeOC_6H_4$	A	**2i**: Ar = 4-$MeOC_6H_4$	97
	Ar = 3-MeC_6H_4	A	**2j**: Ar = 3-MeC_6H_4	82
	Ar = 4-FC_6H_4	A	**2k**: Ar = 4-FC_6H_4	87
	Ar = 4-NCC_6H_4	B	**2l**: Ar = 4-NCC_6H_4	75
 **1**	Ar = Ph	A	 **2m**	92

[a] Only representative examples are reported. Method A: $ArB(OH)_2$ (4−6 equiv), $PdCl_2(PPh)_2$, Na_2CO_3, THF/H_2O (4/1), 65 °C. Method B: $ArB(OH)_2$ (4−6 equiv), $Pd(PPh)_4$, Na_2CO_3, DME/H_2O (4/1), 90 °C.

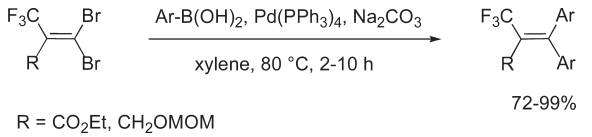
were used as substrates for the second coupling, the addition of $Pd(dppf)\cdot CH_2Cl_2$ (5 mol %) was necessary to obtain the desired products in excellent yields. Finally, this protocol was applied with success to a diverse group of 1,1-dibromoalkenes, including conjugated ones (Scheme 318). Stereoselectivities were generally quite high; thus while trisubstituted dienes **516** were obtained as single stereoisomers, in other cases the isomeric composition of the product depended upon the steric properties of the starting *gem*-dihalide. Curiously, in this study $Pd(PPh_3)_4$ proved to be the most effective catalyst, although this particular system is not normally used for alkyl cross-coupling due to its inability to suppress competitive β-hydride elimination.

Negishi and co-workers carried out a deep investigation aimed at the selective alkylation, especially methylation, of 2-bromo-1,3-dienes obtained stereoselectively by Pd-catalyzed cross-coupling reaction of 1,1-dibromoalkenes with alkenylzinc derivatives[233,234] (Scheme 174). The results of this study indicated that in the substitution of the bromide in the examined dienes, complete stereoinversion of the initially dibromo-bearing double bond (path a, Scheme 319) or no alkene stereoisomerization (path b, Scheme 319) could be obtained by using different Pd catalysts.

Initially, they found that the methyl−bromide exchange in a (*Z*,*E*)-2-bromo-1,3-diene occurred with clean stereoinversion (≥97%) of the Br-bearing C═C bond to produce the related methylated (*Z*,*E*)-diene instead of the expected (*E*,*E*)-diene when $PdCl_2(dpephos)_2$ or $PdCl_2(dppf)$ were utilized as catalysts, whereas the use of $PdCl_2(TFP)_2$ or $Pd(PPh_3)_4$ led to a slightly lower stereoselectivity level of about 95% (path a, Scheme 319).[233] To further probe this process, a number of stereoisomerically pure (≥98%) 2-bromo-1,3-dienes (obtained

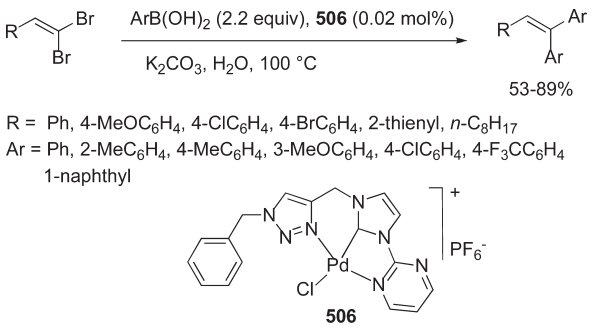
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 308



R = CO_2Et, CH_2OMOM
Ar = Ph, 2-MeC_6H_4, 4-EtC_6H_4, 4-ClC_6H_4, 3-$F_3CC_6H_4$, 3-$MeOC_6H_4$
4-$F_3CC_6H_4$, 3-$MeSC_6H_4$, 4-$MeSC_6H_4$, 2-thienyl

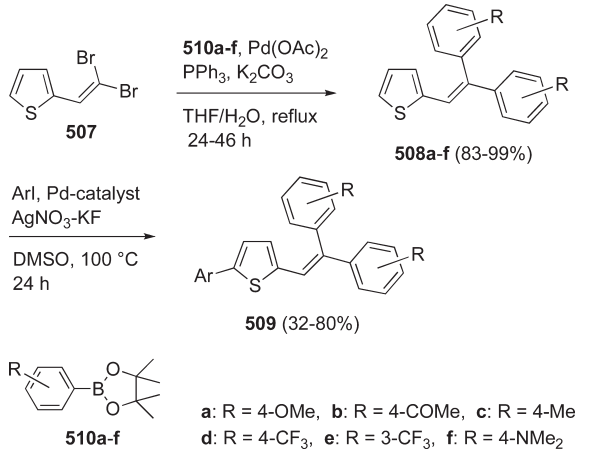
Scheme 309



R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-thienyl, *n*-C_8H_{17}
Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-$F_3CC_6H_4$
1-naphthyl

506

Scheme 310

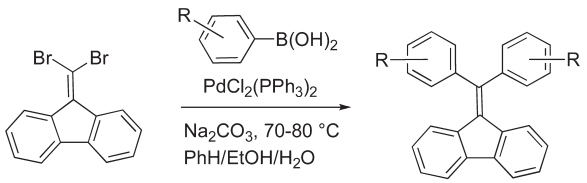


a: R = 4-OMe, **b**: R = 4-COMe, **c**: R = 4-Me
d: R = 4-CF_3, **e**: R = 3-CF_3, **f**: R = 4-NMe_2

according to Scheme 174) were submitted to coupling with a number of organozinc derivatives in the presence of 5 mol % $PdCl_2$-(dpephos)$_2$ (Scheme 320). Under these conditions, stereoinversion occurred with high stereoselectivity, except in the cases in which the R^1 group in the 2-bromo-1,3-diene was an alkenyl or alkynyl group (R^1 = $Me_3SiC{\equiv}C{-}CH{=}CH$ and R^1 = $Me_3SiC{\equiv}C$, respectively), which totally inhibited stereoisomerization, or when R^1 is a phenyl group, which led to partial stereoinversion. These results were attributed to chelation of Pd by a π-bond in the γ,δ-position that inhibited the stereoinversion process (Scheme 321). Although the mechanism of this stereoinversion was not completely elucidated, that proposed in Scheme 321 (stereoinversion via a $\pi{-}\sigma{-}\pi$ rearrangement) appeared to be compatible with the observed results. This strategy was exploited in the synthesis of (−)-callystatin A (Scheme 322).[235]

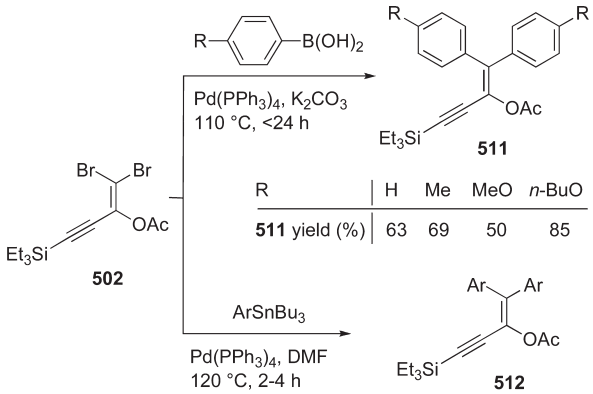
Next, it was found that the bromide in 2-bromo-1,3-dienes could substituted with methyl and higher alkyl groups with nearly

Scheme 311



R	yield (%)	R	yield (%)
H	61	3-NO_2	79
4-Me	67	3,4-$(OMe)_2$	44
4-Cl	81	4-COMe	88
4-NMe_2	69	3-COMe	81
3-OMe	73		

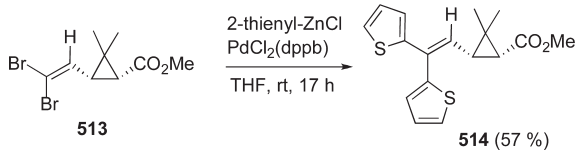
Scheme 312



R	H	Me	MeO	*n*-BuO
511 yield (%)	63	69	50	85

Ar	**512** yield (%)
2-thienyl	66
2,2'-dithienyl	50
2-furyl	57

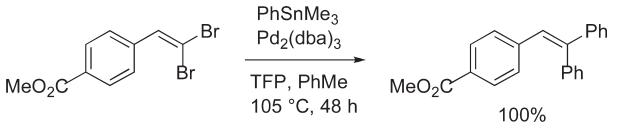
Scheme 313



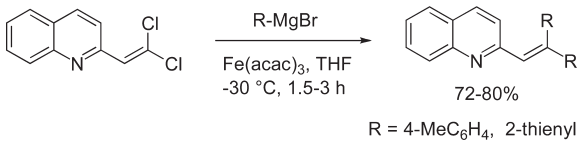
full retention of configuration by coupling with the corresponding organozinc reagents in the presence of Pd catalysts (2 mol %) containing P(*t*-Bu)$_3$ or NHC [*N*,*N*-bis(2,6-diisopropylphenyl)imidazolium chloride] (path b, Scheme 319).[234] A number of stereoisomerically pure (≥98%) 2-bromo-1,3-dienes (obtained according to Scheme 174) by using P(*t*-Bu)$_3$ in THF at room temperature afforded both high yield and stereoselectivity of alkylated dienes in the cases where R^4 in the starting diene was H, though in some instances significantly higher yields were obtained with NHC instead of P(*t*-Bu)$_3$ (Scheme 323). When R^4 in the starting diene was not H but a *n*-butyl group unpredictable

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

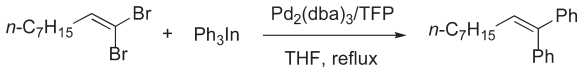
Scheme 314



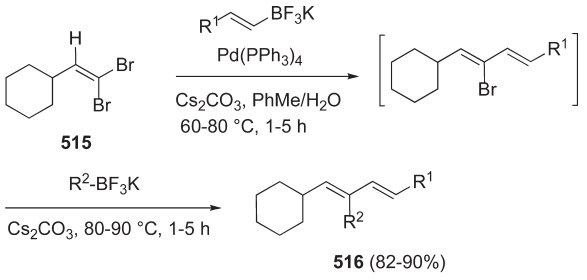
Scheme 315



Scheme 316



Scheme 317



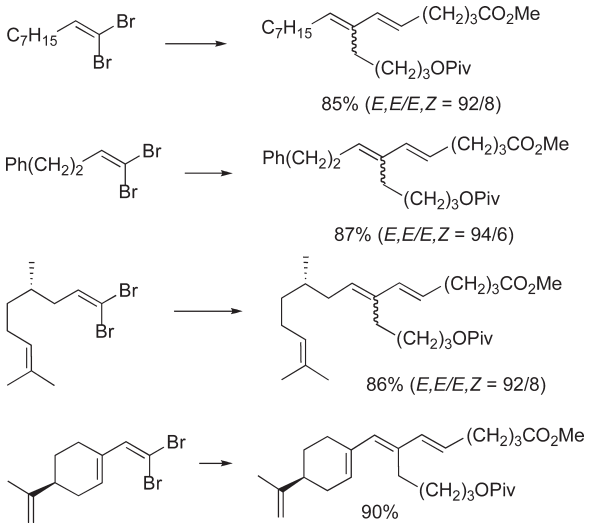
R^1 = $MeO_2C(CH_2)_2$, $NC(CH_2)_3$, $Cl(CH_2)_3$, $Ph(CH_2)_2$
R^2 = $Ph(CH_2)_2$, $PivO(CH_2)_4$, $BnO(CH_2)_4$, $NC(CH_2)_4$, $MeCO(CH_2)_4$ $PhS(CH_2)_3$, Me,[a] Et,[a] $H_2C{=}CH(CH_2)_3$[a]

[a]$Pd(dppf)\cdot CH_2Cl_2$ was added in the second step

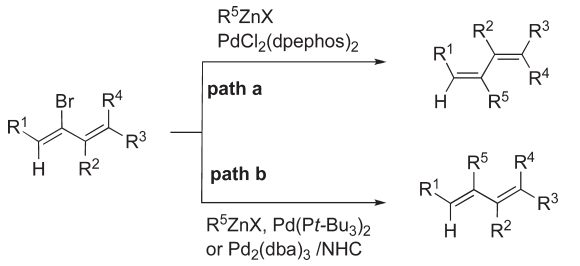
results were obtained and optimization of the reaction conditions were required. However, diethyl ether in conjunction with either $P(t\text{-}Bu)_3$ or NHC permitted a stereoselectivity range of 94−95%.

3.4.1.2. Alkenylation−Arylation, −Alkenylation, and −Ethynylation. Negishi and co-workers showed that not only the alkylation but also the arylation, alkenylation, and ethynylation of 2-bromo-1,3-dienes could be carried out stereoselectively by the proper choice of the Pd catalyst.[233,234] Thus, it was demonstrated that the substitution of the bromide in the diene **517**, used as a model substrate, by the organozinc reagents, phenyl-, vinyl- and ethynylzinc(II) bromide, afforded the related coupling products **518** in very high yields (92−96%) and with complete stereoinversion when $PdCl_2(dpephos)_2$ was used as the catalyst (Scheme 324).[233] On the other hand, the coupling of **517** with phenylzinc(II) bromide in the presence of $Pd(Pt\text{-}Bu_3)_2$ afforded the diene **519** with nearly full retention of configuration and high yield (96%) (Scheme 324).[234]

Scheme 318



Scheme 319



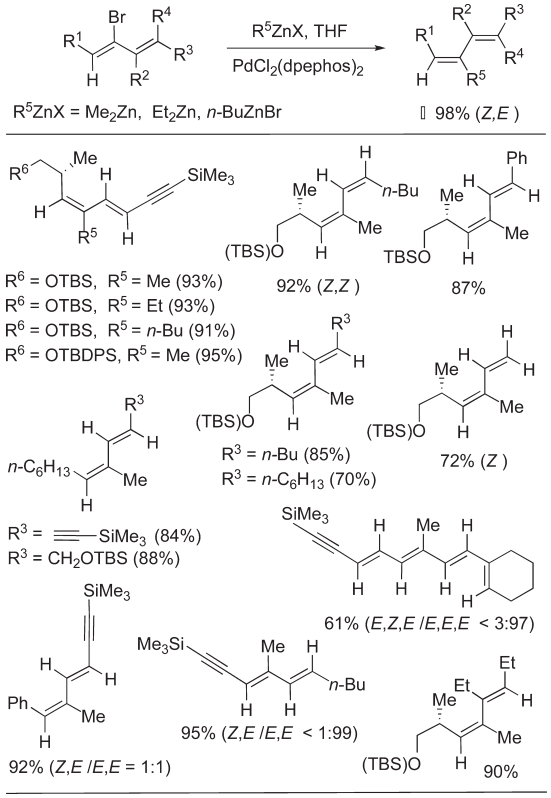
The bromobutenolide **293**, formed by the Stille coupling of the γ-(dibromomethylene)butenolide (Scheme 177), was submitted to further coupling in the presence of $Pd(dba)_2$ (6 mol %) and $AsPh_3$ (20 mol %) with an excess (1.41−1.52 equiv) of phenyltributylstannane to give in high yield (88%) the dicoupled product (*Z*,*E*)-**520** as single stereoisomer (Scheme 325).[237]

Shen and Wang in their study on the Stille reaction of 1, 1-dibromoalkenes with organostannanes also pursued with success a one-pot process of sequential couplings with two different stannanes by using $Pd_2(dba)_3$/TFP as the catalyst (Scheme 191).[247] Among the prepared dicoupled products an example of vinylation followed by phenylation was also reported (Scheme 326).

3.4.1.3. Alkenylation−Aminocarbonylation. Willis and co-workers have recently demonstrated that a Pd-catalyzed intermolecular aminocarbonylation/intramolecular amidation sequence could be used to convert a range of 2-(2-haloalkenyl)aryl halide substrates efficiently and selectively to the corresponding to 2-quinolone and isoquinolone systems.[229] In particular, in this study two of these substrates, obtained from 1-bromo-2-(2,2-dibromovinyl)benzene via selective cross-coupling reactions (Schemes 169 and 184), were treated with octylamine (2 equiv) in the presence $Pd_2(dba)_3$ (3 mol %) and $P(t\text{-}Bu)_3$ (6 mol %) under carbon monoxide atmosphere to give the related 2-quinolones in good yields (Scheme 327).

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 320

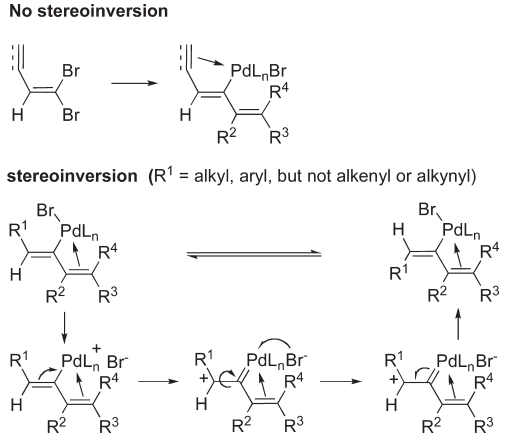


3.4.1.4. Arylation−Arylation and −Alkenylation. Cossy and co-workers, observing the relative ease with which the *gem*-dibromoenamide **295** underwent double Suzuki−Miyaura cross-coupling (Scheme 181), examined the possibility of carrying out consecutive cross-couplings with two different boronic acids.[17] Initially, the β-bromoenamide **521**, obtained in 74% yield by reaction of **295** with 1.05 equiv of 2-methoxyphenyl boronic acid in the presence of 5 mol % $Pd(PPh_3)_4$ and NaOH as the base, was effectively coupled with 4-fluorophenylboronic acid under the same conditions to give the dicoupled product **522** in 80% yield. Next, the same reaction conditions turned out to be satisfactory to achieve, with similar efficiency, the two consecutive Suzuki−Miyaura couplings in a one-pot transformation. Thus, the *gem*-dibromoenamide **295** was first coupled with 4-fluorophenylboronic acid (1 equiv) and upon completion of the reaction, 3,4-(methylenedioxy)phenylboronic acid was added to the reaction mixture as a partner for the second cross-coupling to afford the dicoupled product **524** in 70% yield (Scheme 328).

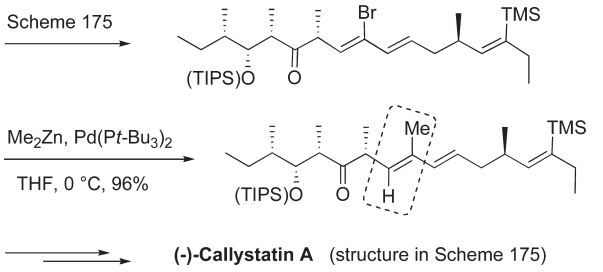
Mori and co-workers have very recently reported a single example of stereoselective diarylation of 1,1-dibromoalkenes by pursuing the Suzuki−Miyaura coupling (Scheme 329).[312] In this case, 2-(2,2-dibromovinyl)thiophene was first coupled with the arylboronic ester **527a** [$Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %)] to give in 80% yield the monosubstituted product **525**, which was then coupled under the same reaction conditions with the boronic ester **527b** to afford the dicoupled product **526** in 95% yield. The corrected amount of boron reagent (2.2 equiv) and K_2CO_3 (3 equiv) was essential to obtain high yield of both **525** and **526**.

Chelucci and co-workers have recently reported, in their approach to 5-aryl-1,10-phenanthrolines, a protocol for the

Scheme 321



Scheme 322

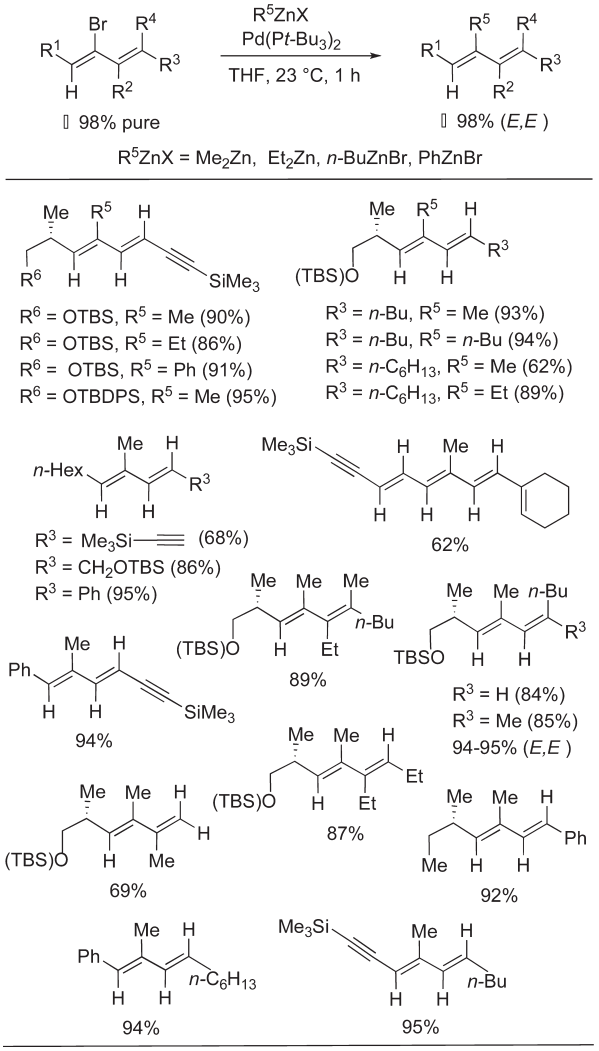


synthesis of stereo-defined 1-(hetero)aryl substituted 1,2-bis-(2-bromopyridin-3-yl)ethenes by tandem Suzuki−Miyaura cross-couplings (Scheme 330).[241] Starting their investigations and taking into account that substrate **298** contains not only two *gem*-dibromides with different reactivity but also the highly electrophilic Br−pyridine bond, **298** was coupled first with $PhB(OH)_2$ to obtain selectively the monocoupled alkene **299a** (Scheme 330). Then, on assessing the relative reactivity of the two remaining bromides, it was found that submitting **299a** to coupling with $PhB(OH)_2$ in the presence of $Pd_2(dba)_3$ (5 mol %) and TFP (30 mol %) could provide the trisubstituted alkene **528** in 74% yield. The greater reactivity of the two *gem*-dibromides with respect to the pyridine bromide being established, the stereoselectivity of the reaction was examined by reacting **299a** with 4-methoxy-3-methylphenylboronic acid and the pyridylboronate **532**. In both cases, the coupling occurred with retention of configuration, and the stereo-defined trisubstituted alkenes **529** and **530** were isolated in 85% and 70% yield, respectively. Finally, the target 1,2-bis(2-bromopyridin-3-yl)-1-phenylethene **531a** was obtained in good yield (77%) by cross-coupling of **299a** with the pyridylboronate **533**. On these findings, a variety of other dibromides **299** were successful coupled with **533** to give trisubstituted alkenes **531** in good yields (52−71%) (Scheme 331).

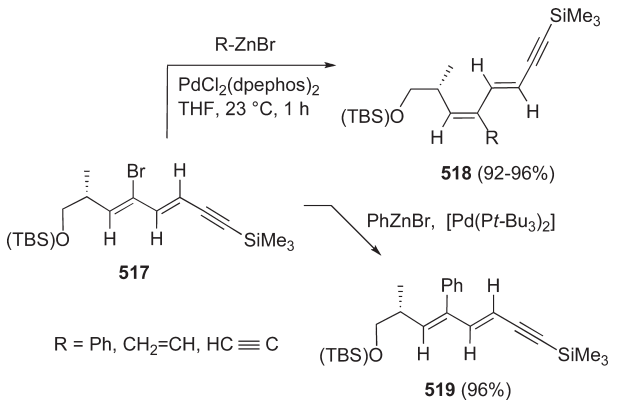
These results demonstrated clearly that in tribromide **298** the insertion of the Pd(0) complex onto the (*E*)-bromoalkene bond is faster than that onto the (*Z*)-bromoalkene bond, which is in turn faster than that onto the C−Br bond of the pyridine moiety (Figure 7). This should be of interest since it contrasts with the products obtained in the Pd(0)-catalyzed coupling reactions of (*Z*)-2-bromo-5-(2-bromovinyl)furan **534** in which the initial Pd

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 323

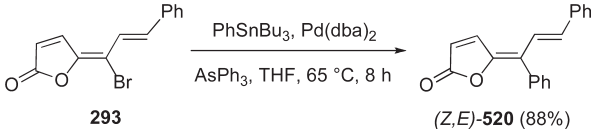


Scheme 324

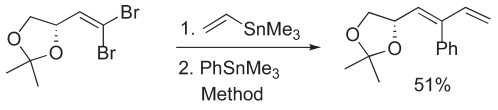


attack onto the C−Br bond of the furan is followed by that on the C−Br bond of the alkene[302] (Figure 7). In fact, since the C−Br bond of the pyridine is more electrophilic than that of the furan, it would be expected that in the coupling of **299a**, formed after the first coupling of **298** with phenylboronic acid, the C−Br bond of

Scheme 325

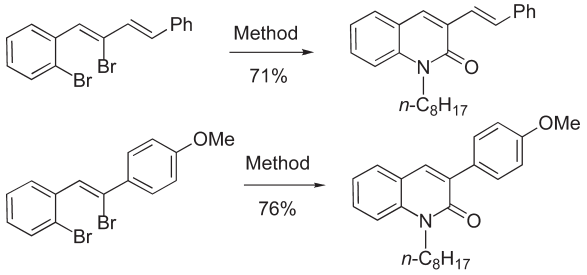


Scheme 326



Method: vinylSnMe$_3$ (1.0 mmol), Pd$_2$(dba)$_3$ (0.025 mmol) TFP (0.15 mmol), toluene, 100 °C, 4 h, then PhSnMe$_3$ (1.1 mmol), Pd$_2$(dba)$_3$, (0.025 mmol) , TFP (0.15 mmol) 100 °C, 36 h.

Scheme 327



Method: CO (1 atm), Pd$_2$(dba)$_3$ (3 mol%), P(*t*-Bu)$_3$ (6 mol%), *n*-C$_8$H$_{17}$NH$_2$ (2 equiv), Cs$_2$CO$_3$ (3 equiv), PhH, 100 °C, 3 h; then purged with N$_2$, 100 °C, 16 h.

the pyridine moiety should undertake the oxidative addition to Pd(0) faster than that of the (*Z*)-bromoalkene part.

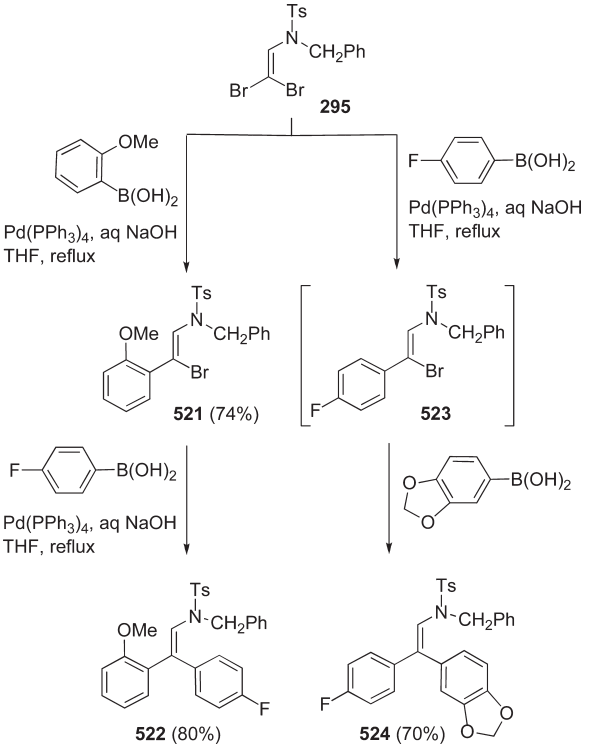
A one-pot process of sequential coupling of **298** with phenylboronic acid in the presence of Pd$_2$(dba)$_3$/TFP and then with pyridylboronate **533** also allowed the preparation of **299a** in 65% yield, which is very close to that obtained in the two-step protocol (67% overall) (Scheme 332).

Shen and Wang reported the Stille reaction of 1,1-dibromoalkenes with organostannanes to afford, in the presence of Pd$_2$(dba)$_3$ (2.5 mol %) and TFP (15 mol %) under optimal reaction conditions, (*Z*)-1-substituted-1-bromo-1-alkenes in good yields (Scheme 191).[247] From the monocoupled product (*Z*)-methyl 4-(2-bromo-2-phenylvinyl)benzoate, two related trisubstituted alkenes were also synthesized in quantitative yields by coupling the remaining bromide with tributyl(2-furyl)tin or tetramethyltin, with either DMF or toluene as the reaction solvents, though the former afforded faster reaction rate (Scheme 333). On this basis, a one-pot process of sequential coupling of various 1,1-dibromoalkenes with two different stannanes was then pursued with success (Scheme 334).

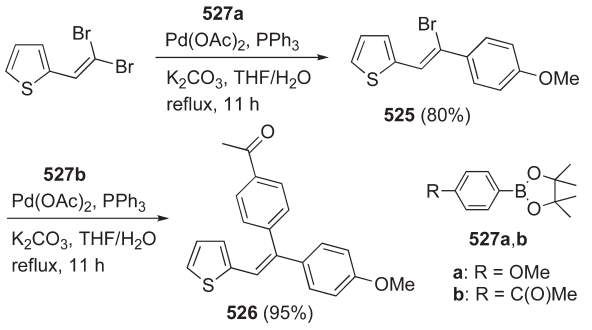
Minato and Tamao submitted (*Z*)-chloroalkenes, formed by Pd-catalyzed stereoselective monoarylation of 1,1-chloroalkenes with Grignard or organozinc reagents (Scheme 187), to a new reaction with Grignard reagents in the presence of PdCl$_2$(dppb) (1 mol %) as the catalyst to produce in excellent yields stereo-defined

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 328



Scheme 329

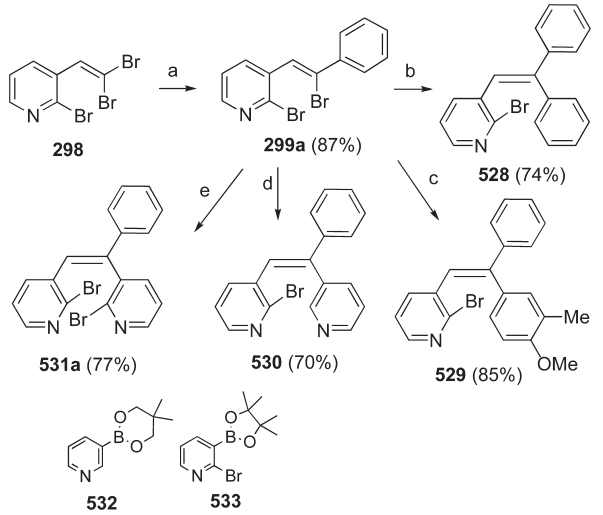


trisubstituted alkenes (Scheme 335).[13] Opposite stereoisomers **535d** and **535e** were merely obtained bychanging the order of the treatment of the starting material, 1-(2,2-dichlorovinyl)-4-methoxybenzene, with the two Grignard reagents, PhMgBr and 4-ClC_6H_4MgBr.

The bromobutenolide **298**, formed by the Stille coupling of the γ-(dibromomethylene)butenolide **292** (Scheme 192), was submitted to further coupling in the presence of $Pd(dba)_2$ (6 mol %) and $AsPh_3$ (20 mol %) with an excess (1.52 equiv) of styryltributylstannane to give in high yield (80%) of the dicoupled product (*E*,*E*)-**520** as a single stereoisomer (Scheme 336).[237]

Lautens and co-workers reported the synthesis of the *N*-fused heterocyclic systems **537** and **539** by Pd-catalyzed reaction of *gem*-dibromoolefins with boronic acids via tandem Suzuki–Miyaura coupling and direct arylation (Schemes 337 and 338).[315] A deep investigation to optimize the reaction of dibromovinyl system **536a** with $PhB(OH)_2$ to obtain the desired product **537a** showed that this could be obtained in 90% yield by reaction with

Scheme 330



a: $PhB(OH)_2$ (1.05 equiv), $Pd_2(dba)_3$ (2.5 mol%), TFP (15%), 1,4-dioxane, Cs_2CO_3 (2.0 equiv), H_2O, 65 °C, 14 h; b: $PhB(OH)_2$ (1.05 equiv), $Pd_2(dba)_3$ (5 mol%), TFP (30 mol%), 1,4-dioxane, Cs_2CO_3 (2.0 equiv), H_2O, 65 °C, 24 h; c: conditions in c, 3-Me-4-$MeOC_6H_3B(OH)_2$ (1.05 equiv), 14 h, 85 %; d: conditions in c, **532** (1.05 equiv), 24 h; e: conditions in c, **533** (1.05 equiv), 24 h.

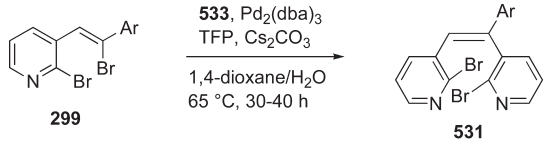
1.5 equiv of the boronic acid and $Pd(OAc)_2$ (4 mol %), sphos (8 mol %), Cs_2CO_3 (2 equiv), toluene (0.04 M), and water (5 equiv). The addition of water had a dramatic effect on both the reactivity of the substrate and the reduction of byproduct. The methodology also proved to be compatible with a variety of aryl, alkenyl, and alkyl boronic acids, as well as boronic esters, giving good to excellent yields. Also substituents on the aromatic ring and on the dibromo alkene partner were well tolerated. The protocol was extended to include other heteroaromatic ring systems. Thus, the indole derivative **538a** gave the desired product **539a** in good yield (Scheme 338), but attempts to incorporate other aromatic ring systems such as furans, thiophenes, pyrazoles, and tetrazoles failed. On the other hand, the pyridine derivative **538b** gave **539b** in good yield (63%) (Scheme 338).

The mechanistic pathway of the tandem coupling was studied with the substrate **536a** (Scheme 339). Initially, to test the possibility that an alkyne precursor could be a possible intermediate in the formation of the product **537a**, alkynes **540** were subjected to reaction with phenyl boronic acid in the presence of palladium, but the desired product was not observed. Then, compounds **541** and **542** were prepared in order to elucidate which reaction occurred first between the two remaining possible pathways, namely, the direct arylation (path a) or the Suzuki coupling (path b). Coupling of **541** quantitatively led to the production of **537a**, while the direct arylation of **542** in the presence of 0.5 equiv of $PhB(OH)_2$ gave a mixture of the desired product **537a** and bis-Suzuki coupling product **543**. Since **543** was observed as a side product when more than 1.5 equiv of boronic acid was used with **536a**, it was concluded that **542** is a possible intermediate under the reaction conditions, thus suggesting that the dominant process is the Suzuki coupling/direct arylation sequence (Scheme 340).

Lautens and Bryan have recently reported that the methylenindene scaffold can be synthesized from *gem*-dibromoolefins by

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 331



	Ar	531 yield (%)		Ar	531 yield (%)
a	Ph	77	d	2-Me-4-MeOC$_6$H$_3$	71
b	4-O$_2$NC$_6$H$_4$	53	e	3-pyridyl	63
c	3-ClC$_6$H$_4$	66	f	5-methylthien-2-yl	52

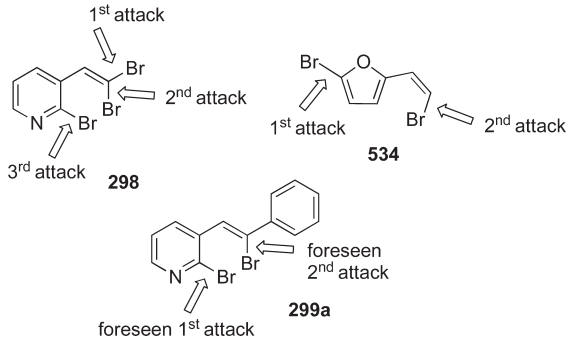
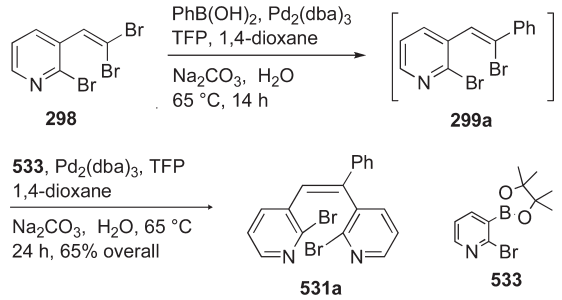
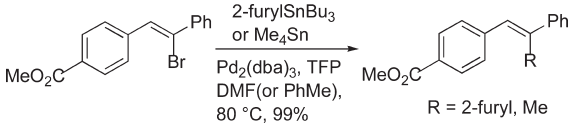


Figure 7

Scheme 332

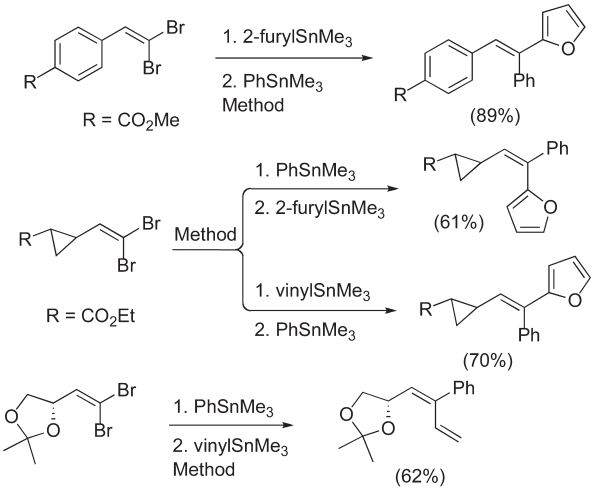


Scheme 333



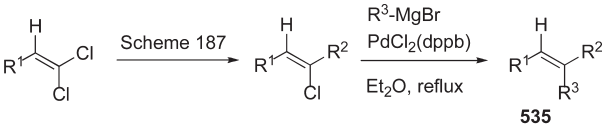
an efficient Pd-catalyzed tandem intermolecular Suzuki/intramolecular Heck reaction.[316] After screening various parameters, it was found that under optimized conditions a variety of 1-(2,2-dibromovinyl)-2-vinylbenzene derivatives reacted with different boronic acids (1.5 equiv) in the presence of $Pd_2(dba)_3$ (2.5 mol %) and TFP (10 mol %) to give methylenindene products in good yields (Scheme 341). The choice of the ligand was found to be crucial to control the selectivity of the reaction. Thus, when sphos or Bu_4NBr or P(*t*-Bu)$_3$ was used as the ligand, 2-bromo-1-methylene-1*H*-indene derivatives were obtained as the sole products. An overview of the proposed mechansim is displayed

Scheme 334



Method: stannane 1 (1.0 mmol), $Pd_2(dba)_3$ (0.025 mmol), TFP (0.15 mmol), PhH 100 °C, 48 h, then stannane 2 (1.1 mmol), $Pd_2(dba)_3$ (0.025 mmol) , TFP (0.15 mmol), 100 °C.

Scheme 335



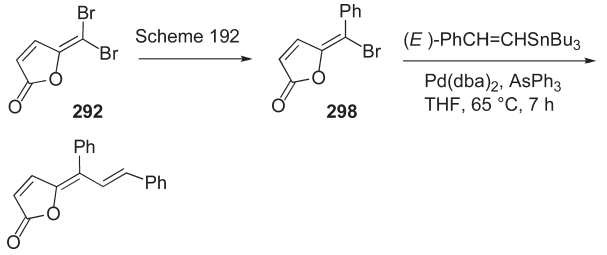
	R^1	R^2	R^3	535 yield (%)
a	Ph	Ph	4-MeOC$_6$H$_4$	75
b	Ph	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$	65
c	Ph	*n*-C$_4$H$_9$	*n*-C$_6$H$_{13}$	77[a]
d	4-MeOC$_6$H$_4$	Ph	4-ClC$_6$H$_4$	68
e	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	Ph	81

[a]$NiCl_2$(dppb) was used as the catalyst

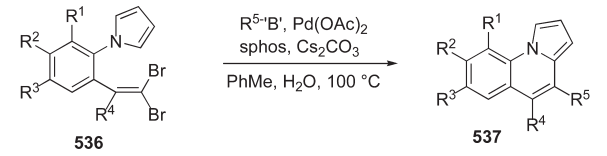
in Scheme 342. Path I is followed exclusively when small monodentate phosphines are used as ligands. In this pathway, oxidative addition of Pd(0) to the (*E*)-bromide occurs, followed by transmetalation with a boronate and reductive elimination of intermediate **547** to regenerate a Pd(0) species. This intermediate may then undergo an E2 elimination to give the alkyne byproduct **548** (an isolated product from the reaction mixture) or reenter the catalytic cycle through oxidative addition to the remaining alkenyl bromide. In the latter case, the alkenylpalladium undergoes carbopalladation, followed by bond rotation and *β*-hydride elimination to give the (*Z*)-methyleneindene **545**. When an electron-rich, sterically crowded ligand such as P(*t*-Bu)$_3$ or sphos is used, path II is followed. In this case, apparent oxidative addition to the (*Z*)-bromide occurs, and the Heck reaction proceeds as expected giving product **546**. Under the conditions conducive to path I, the product **546** does not undergo subsequent Suzuki coupling despite the presence of a boronic acid. Whether the (*Z*)-alkenylpalladium intermediate indeed arises from a selective oxidative addition, possibly directed by the olefin of the Heck acceptor, or is in fact obtained by an isomerization of the (*E*)-alkenylpalladium bromide is an issue that has yet to be determined.

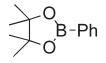
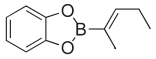
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 336



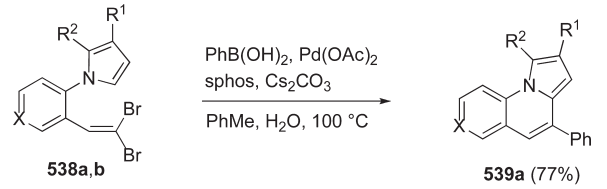
Scheme 337



	R^{5}-'B'	R^1	R^2	R^3	R^4	**537** yield (%)
a	$PhB(OH)_2$	H	H	H	H	90
b	4-$MeOC_6H_4B(OH)_2$	H	H	H	H	82
c	2,3-$(MeO)_2C_6H_3B(OH)_2$	H	H	H	H	67
d	3-$ClC_6H_4B(OH)_2$	H	H	H	H	62
e	2-$FC_6H_4B(OH)_2$	H	H	H	H	46
f	2,6-$F_2C_6H_3B(OH)_2$	H	H	H	H	0
g	3-thienylB$(OH)_2$	H	H	H	H	67
h	1-naphthylB$(OH)_2$	H	H	H	H	76
i	(*E*)-PhCH=CHB$(OH)_2$	H	H	H	H	62
j	$PhCH_2CH_2B(OH)_2$	H	H	H	H	87
k	$PhB(OH)_2$	MeO	H	H	H	93
l	$PhB(OH)_2$	H	BnO	H	H	52
m	$PhB(OH)_2$	H	Cl	H	H	83
n	$PhB(OH)_2$	H	H	MeO_2C	H	70
o	$PhB(OH)_2$	H	H	H	F_3C	85
p	BEt_3	H	H	H	H	61
q		H	H	H	H	50
r		H	H	H	H	30

Only representative examples are reported

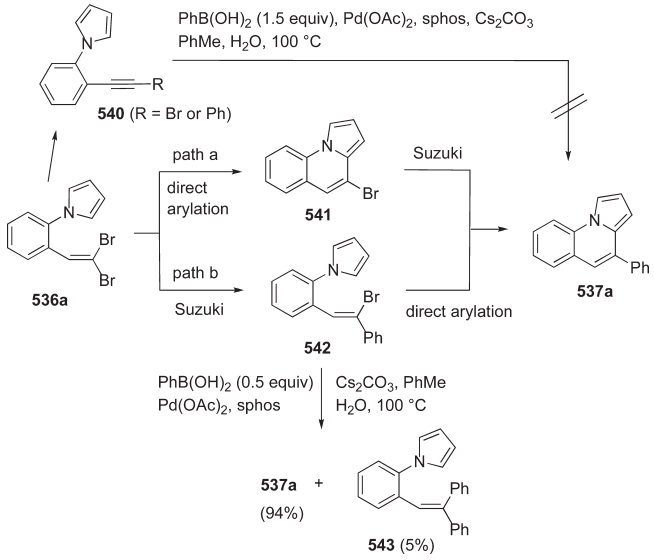
Scheme 338



a: X = CH, R^1-R^2 = CH=CH-CH=CH
b: X = N, R^1 = R^2 = H

Similar work for the methylenindene scaffold synthesis was also independly reporded by Wu and co-workers.[317] After optimization of the reaction conditions [$Pd(OAc)_2$ (2.5 mol %), PPh_3 (5 mol %), KOH (3.0 equiv), toluene, 100 °C], they examined the scope of this tandem reaction with a series of 1-(2,2-dibromovinyl)-2-alkenylbenzenes **544** and arylboronic acids (Scheme 343). All reactions gave rise to the desired products

Scheme 339



in good yields, the electron effect on the aromatic backbone of the substrates was not observed, and the cyano group on the alkene moiety was well tolerated.

An alternative route to 1-methyleneindenes from alkynyl *gem*-dibromides has been recently reported by Wu and co-workers.[318] By using $Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %), 1-(2,2-dibromovinyl)-2-alkynylbenzenes **549** were reacted with various arylboronic acids to generate a number of 1-methyleneindenes **550** in good to excellent yields (Scheme 344). The proposed route for the Pd-catalyzed tandem reactions implies that oxidative addition of Pd(0) to **549**, subsequent transmetalation of arylboronic acid and reductive elimination would occur to generate the intermediate **551**, with the release of Pd(0) (Scheme 345). Then, Pd(0) would react with the vinyl bromide in **551** by oxidative addition, leading to the intermediate **552**. Intramolecular insertion of Pd(II) to the alkynyl group gives rise to intermediate **553**, which then reacts with arylboronic acid via transmetalation. Subsequently reductive elimination occurs to form the desired product **550** and Pd(0), which would reenter the catalytic cycle.

3.4.1.5. Arylation−Alkylation. Negishi and Shi developed an effective procedure for the Pd-catalyzed selective tandem arylation−alkylation of 1,1-dihaloalkenes with organozinc reagents.[245] A number of (*Z*)-α-halostyrenes **554**, obtained by monoarylation of 1,1-dihaloalkenes (Scheme 189), was submitted to a second substitution with alkylzincs by using 2 mol % $Pd(tBu_3)_2$ as the catalyst (Scheme 346). This catalyst was employed to prevent undesirable stereoisomerization that occurs in Pd-catalyzed cross-coupling reactions of stereo-defined alkenyl halides under the influence of proximal π-bonds, such as alkenyl[259] or alkynyl.[234] In this way, trisubstituted alkenes were obtained in >90% yield and with ≥98−99% stereoselectivity.

However, despite these highly satisfactory results, some limitations were also noted. Unlike its bromo analogue, the reaction of (*Z*)-α-chlorohexylstyrene with either Me_2Zn or Et_2Zn in the presence of 5 mol % $Pd(Pt\text{-}Bu_3)_2$ in THF did not proceed to a detectable extent even at 50 °C. In sharp contrast, the corresponding reaction with MeMgBr at 50 °C gave the desired product in nearly quantitative yield. So, despite generally

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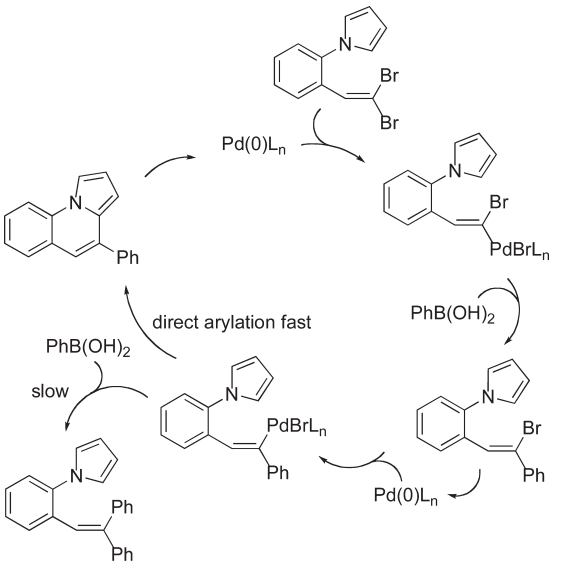
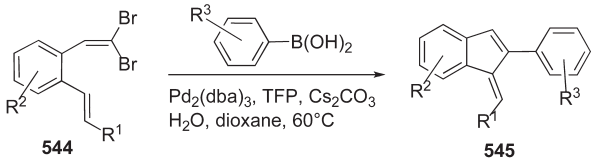
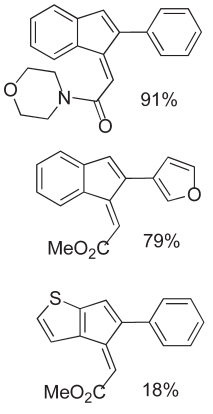
Scheme 340



Scheme 341

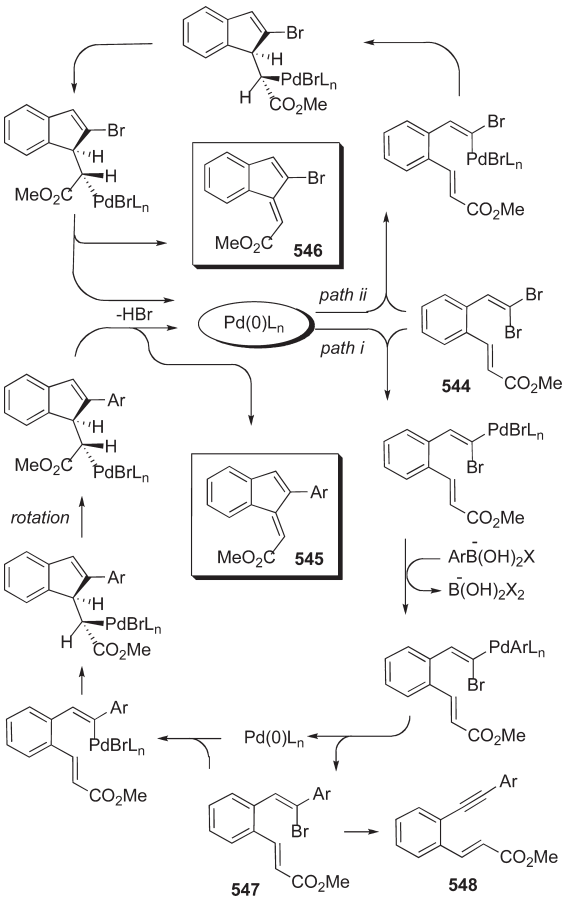


R^1	R^2	R^3	**545** yield (%)
CO_2Me	H	3,4-$(OMe)_2$	77
CO_2Me	H	Ph	83
CO_2Me	H	2-Me	80
CO_2Me	H	4-CO_2Me	87
CO_2Me	H	4-CHO	65
CO_2Me	H	4-NHBoc	79
CO_2Me	H	3-NO_2	70
CO_2Me	5-OMe	H	83
CO_2Me	5-F	H	64
CO_2Me	5-Cl	H	71
CO_2Me	5-CF_3	H	50
4-$MeOC_6H_4$	H	H	72
2,5-$Me_2C_6H_4$	H	H	92
4-pyridyl	H	H	71
Ph	H	H	85
CN	H	H	26
t-BuOC(O)	H	H	62



unfavorable chemoselectivity profiles that the Grignard reagents display, their distinctively higher reactivity observed in this case makes it worthwhile to consider Mg as a potentially useful metal countercation in certain cases of Pd-catalyzed cross-couplings. On the other hand, the reaction of (*Z*)-1-bromo-1-phenyl-1-octene with Me_4Sn gave, under optimized conditions (5 mol % $Pd(PtBu_3)_2$, DMF, 23 °C, and 24 h), (*E*)-non-2-en-2-ylbenzene in 84% GLC yield along with a 5% yield of its (*Z*)-isomer. The use of 5 mol % $Pd_2(dba)_2$ and 30 mol % TFP in conjunction with Me_4Sn and DMF, as reported for the only previously known case of Pd-catalyzed methylation of (*Z*)-α-bromostyrenes,[247] led to

Scheme 342



the formation of (*E*)-non-2-en-2-ylbenzene in 69% yield and with 95% stereoselectivity. Although only a very limited amount of experimental data is available for comparison, the Pd-catalyzed alkylation with alkylstannanes does appear to be slower than those with Zn or Mg. Moreover, both product yields and stereoselectivity appear to be comparatively lower.

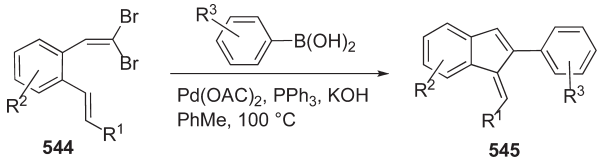
Next, the one-pot process was examined by treating 1,1-dibromooct-1-ene with PhZnBr and then with Me_2Zn in the presence of catalytic $PdCl_2$(dpephos) (Scheme 347). In this way, the desired product **556** was formed in 83% yield. While there was no indication for the formation of the (*Z*)-isomer of **556** in the alkylation of (*Z*)-1-(1-bromooct-1-enyl)benzene in the presence of $Pd(Pt\text{-}Bu_3)_2$, in this case the (*Z*)-isomer of **556** was also obtained in 3% yield. Therefore, when removal of the (*Z*)-isomer is facile and practical, this one reaction vessel might prove to be more desirable in an overall sense than the two-step procedure.

3.4.1.6. Arylation−Ethynylation. One example of synthesis of trisubstituted alkene by sequential arylation−ethynylation of a *gem*-dibromoalkene was reported by Minato.[244] In this case, cross-coupling of the bromoalkene **557**, obtained by stereoselective monoarylation of the related 1,1-dibromalkene (Scheme 188), with hexenylzinc chloride and by using $PdCl_2$(dppb) as the catalyst, afforded stereoselectively the enyne **558** in 96% yield (Scheme 348).

In a single case an alkynylindium reagent has been coupled with an internal monobromide obtained from the related dibromide (Scheme 197). Thus, tris((trimethylsilyl)ethynyl)indium by coupling with (*Z*)-(1-bromonon-1-enyl)benzene in the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

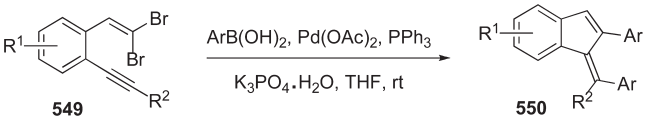
Scheme 343



R^1	R^2	R^3	**545** yield (%)
CO_2Et	H	4-Me	81
CO_2Et	H	4-OMe	71
CO_2Et	H	4-Me	70
CO_2n-Bu	H	4-Me	90
CO_2Et	4-F	4-Me	85
CO_2Et	5-F	4-Me	80
CO_2Et	5-Cl	4-F	85
CO_2Et	4,5-$(OMe)_2$	4-Me	70
CO_2Et	5-Me	4-Me	76
CN	H	4-Me	98
CN	H	4-F	93

Only representive examples are reported

Scheme 344



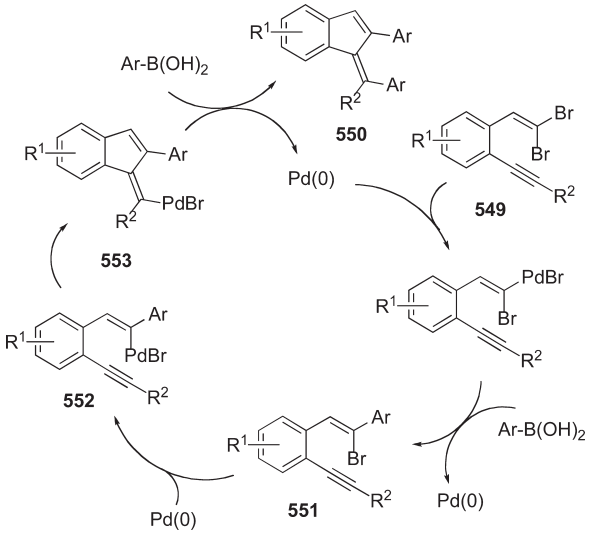
R^1	R^2	Ar	**550** yield (%)
H	Ph	4-MeC_6H_4	86
H	Ph	4-$MeOC_6H_4$	75
H	Ph	Ph	80
H	Ph	4-$F_3CC_6H_4$	70
H	Ph	4-NCC_6H_4	72
H	Ph	4-$MeO_2CC_6H_4$	74
H	Ph	4-$O_2NC_6H_4$	88
H	*n*-Bu	Ph	62
4-F	Ph	Ph	82
4-F	Ph	4-NCC_6H_4	74
4-F	Ph	4-$MeO_2CC_6H_4$	75
4,5-$(OMe)_2$	Ph	Ph	95
4,5-$(OMe)_2$	Ph	4-$MeO_2CC_6H_4$	72

presence of $Pd(Pt\text{-}Bu_3)_2$ at room temperature gave the related enyne in 50% yield (Scheme 349).[236]

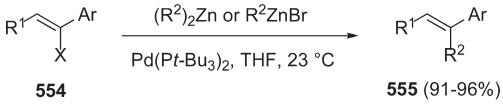
3.4.1.7. Ethynylation−Alkenylation, −Arylation, −Ethynylation, −Alkylation, and −Alkynylation. Linstrumelle and co-workers described for the first time the tandem cross-coupling of *gem*-dihaloalkenes with acetylenes to afford enediynes.[14] Thus, 2-chlorooct-1-en-3-yne obtained by Pd(0)/Cu(I)-mediated cross-coupling of 1,1-dichloroethylene with $n\text{-}C_3H_7C{\equiv}CH$ (Scheme 198) was submitted to a second Sonogashira coupling with $Cl(CH_2)_3C{\equiv}CH$ (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) and CuI (5 mol %) to give 1-chloro-6-methylenedodeca-4,7-diyne in 75% yield (Scheme 350).[14]

The same research group reported later that the cross-coupling of a number of chloroenediynes **467** (Scheme 276) with 1-alkynes in the presence of $PdCl_2(PhCN)_2$ (5 mol %), CuI (10 mol %), and piperidine took place to afford isomerically

Scheme 345



Scheme 346



X = Br, Cl
R^1 = $n\text{-}C_6H_{13}$, (*S*)-Et(Me)CH, Ph, Me_3Si
R^2 = Ph, 2-thienyl, 2-thiazolyl

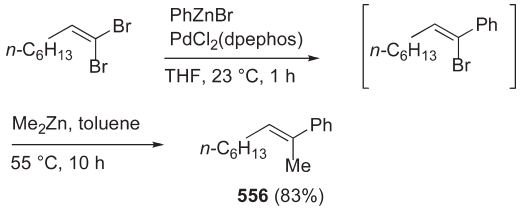
pure enetriynes **559** in moderate to good yields (44−78%) (Scheme 351).[204]

Uenishi and co-workers reported that from the bromoenyne **326a**, obtained by *trans*-selective monoalkynylation of (4,4-dibromobut-3-enyl)benzene (Scheme 199), a number of geometrically pure branched enynes were formed by Pd- or Ni-catalyzed cross-coupling reactions (Scheme 352).[252] Thus, the 1,1-dialkynyl-1-alkene **560** was obtained in 95% yield by Sonogashira coupling of **326a** with hexyne, while the Suzuki−Myamura coupling of **326a** with 1-hexenylboronic acid proved **561** in 82% yield. On the other hand, Kumada−Tamao−Coriu coupling of **326a** with ethyl- and trimethylsilylmagnesium bromide in the presence of $NiCl_2$(dppp) gave (*E*)-alkenes **562a** and **562b** in 71% and 53% yield, respectively. These three sp-, sp^2- and sp^3-carbon coupling reactions occurred to give a single stereoisomer with retention of configuration.

A study on the stereospecific methylation and ethylation of the monobromo alkenes **563** was carried out by Negishi and co-workers (Scheme 353).[259] The use of the Pd−phosphine complexes used for the *trans*-selective monoalkynylation of 1,1-dibromoalkenes proved to be unsatisfactory for the second-stage alkylation, as was $NiCl_2$(dppe). The use of the bulky trialkylphosphine-containing Pd complex, $Pd(PtBu_3)_2$, was found to be critically important. With this catalyst and alkylzincs, Me_2Zn, MeZnCl(Br), and Et_2Zn, as alkylating agents, the alkylation of **563** was achieved in >90% yields with ≥98% retention of configuration. The potentially of this alkynylation−methylation protocol for the synthesis of trisubstituted alkynes containing asymmetric carbon centers in the α- or β-position of the alkene moiety was also demonstrated with some examples.

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 347



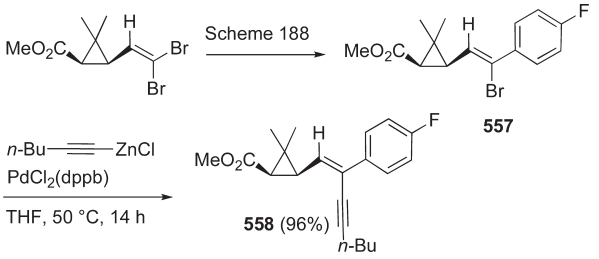
Perez Sestelo and co-workers found that organoindium reagents could be coupled with internal monobromides in the presence of $Pd(Pt\text{-}Bu_3)_2$ at room temperature without detectable isomerization (Scheme 354).[236] Thus, a variety of aryl-, alkyl-, and alkynylindium reagents gave, in the second step of a stepwise coupling sequence, trisubstituted alkenes in good yields (62−99%).

3.4.1.8. Alkylation−Alkylation, −Arylation, −Alkenylation, and −Alkynylation. Roulland and co-workers, who established efficient and selective Suzuki−Miyaura conditions affording monochlorinated olefins from 1,1-dichloroalkenes (Schemes 213 and 214), studied also the preparation of stereospecifically trisubstituted alkenes.[75] The 2-(dicyclohexylphosphino)biphenyl ligand (5 mol %), well-known to promote coupling with chlorinated electrophilic coupling partners,[319] in combination with $Pd_2(dba)_3$ (2.5 mol %) allowed cross-couplings of some (*Z*)-chloroalkenes with various boron (alkyl and aryl) nucleophiles in good yields (Scheme 355). Also $PdCl_2(dppp)$ (7 mol %) proved to be a suitable catalyst for this reaction.

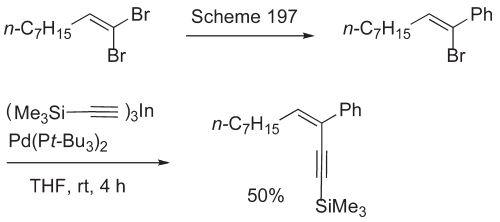
In the first reported case of stepwise dialkylation of 1,1-dihaloalkenes, the second substitution of the initially formed (*Z*)-(2-chlorohex-1-enyl)benzene (Scheme 217) was achieved by using *n*-hexylmagnesium bromide and $NiCl_2(dppb)$ (1 mol %) as the catalyst, to produce in good yield (77%) the stereodefined trisubstituted alkene (*Z*)-(2-butyloct-1-enyl)benzene (Scheme 356).[13]

This protocol proved to be very satisfactory for the methylation of (*Z*)-2-chloro-1-phenyl-1-decene, concerning both yield and stereoselectivity (Scheme 357).[264] Also in the case of (*Z*)-8-chloro-7-hexadecene, the yield was very high, but the product was essentially a 1:1 mixture of *E*/*Z* isomers. The use of some other chelating ligands containing the diphenylphosphino group, such as dppf and dpephos, improved the *E*/*Z* ratio, which however never exceeded 6:1 (Scheme 357). Next, it was found that by using $Pd(Pt\text{-}Bu_3)_2$ as the catalyst, the desired product (7*E*)-8-methyl-7-hexadecene was obtained in 90% yield and with high stereoselectivity (*E*/*Z* = 97:3). Even with the use of $Pd(Pt\text{-}Bu_3)_2$, however, (*Z*)-chloroalkenes could not be alkylated in useful yields with higher alkyl magnesium halides, such as *n*-$C_8H_{17}MgBr$. On the other hand, the use of Pd complexes with $P(c\text{-}C_6H_{11})_3$ or $P(c\text{-}C_5H_9)_3$, led to the formation of the desired alkylation products in high yields (Scheme 355). Interestingly, satisfactory results were also observed with the use of $Fe(acac)_3$ as the catalyst (Scheme 357).[264] Pd complexes with $P(c\text{-}C_6H_{11})_3$ or $P(c\text{-}C_5H_9)_3$ appeared to be generally satisfactory catalysts for the second substitution not only with Grignard reagents containing alkyl and allyl groups (Scheme 357) but also with those having aryl (Scheme 358) and alkenyl (Scheme 359) groups. Despite all these favorable results, the reaction of (*Z*)-(TBS)-OCH(Me)CH_2CH=C(Cl)Me with *n*-C_6H_{13}C≡CMgBr in the presence of 5 mol % $Pd(P(c\text{-}C_6H_{11})_3)_2$ failed to give the

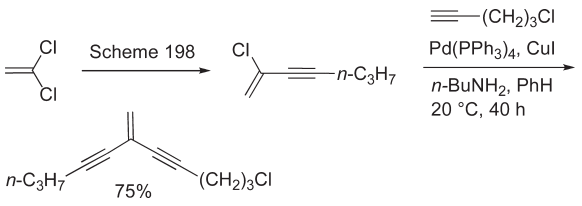
Scheme 348



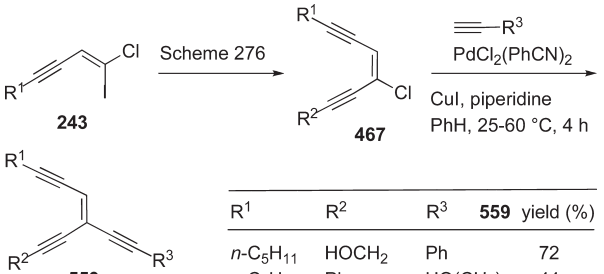
Scheme 349



Scheme 350



Scheme 351



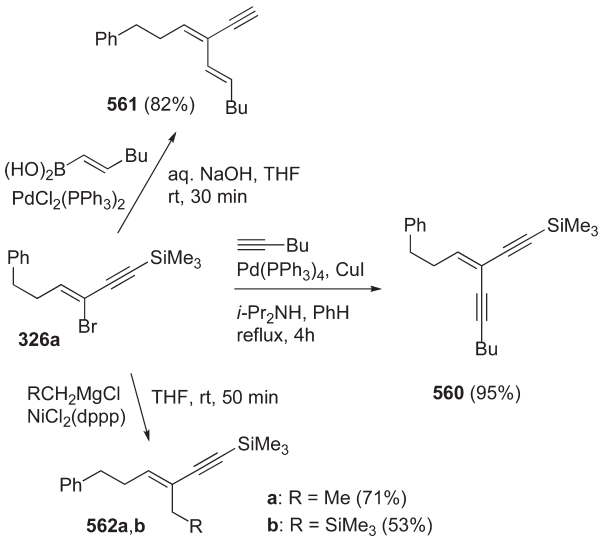
R^1	R^2	R^3	**559**	yield (%)
n-C_5H_{11}	$HOCH_2$	Ph		72
n-C_5H_{11}	Ph	$HO(CH_2)_2$		44
n-C_5H_{11}	Me_3Si	$HOCH_2$		45
n-C_5H_{11}	*n*-C_5H_{11}	Ph		64
Ph	Me_3Si	Me_3Si		75
Ph	$HO(CH_2)_2$	Ph		78
Ph	Ph	Ph		59

alkynylation product. However the use of $Et_3SiC{\equiv}CH$ or *i*-$Pr_3SiC{\equiv}CH$ in MeCN in the presence of 2-dicyclohexylphosphino-2′,4′,6′,-triisopropyl-1,1′-biphenyl proved to be reasonably satisfactory (Scheme 360).

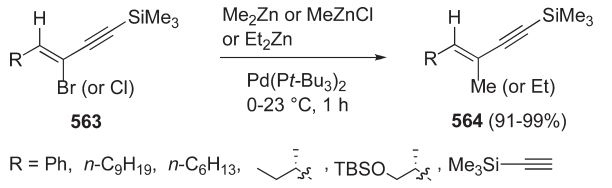
3.4.1.9. Carbonylation−Arylation and −Alkylation. Roulland and co-workers investigated the Pd-catalyzed cross-coupling of α-chlororacrylates, obtained by Pd-catalyzed carbonylation of

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

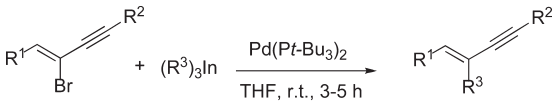
Scheme 352



Scheme 353



Scheme 354

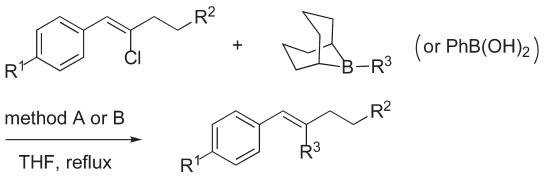


R^1	R^2	R^3	yield (%)
Ph	Me_3Si	Ph	99
n-C_7H_{15}	Ph	Ph	62
Ph	Me_3Si	n-Bu	69
n-C_7H_{15}	Me_3Si	Me	70
Ph	Me_3Si	Ph—≡	87
n-C_7H_{15}	Ph	Me_3Si—≡	80

1,1-dichloroalkenes (Scheme 251) with various boron nucleophilic coupling partners, by using $Pd_2(dba)_3$ (2.5 mol %) in combination with 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (Ruphos) (10 mol %) as the catalytic system (Scheme 361).[278] The reaction worked successfully with various types of organoboron reagents (boronic acid, boronic ester, potassium trifluoroborate, and trimethylboroxine), affording disubstituted acrylates with a similar efficiency in all cases.

3.4.2. Tandem C−C/C−O Coupling. 3-Substituted isocumarins were synthesized in good to excellent yields via Pd-catalyzed coupling of 2-(2,2-dibromovinyl)benzoates with organostannanes (Scheme 362).[320] The best reaction conditions were found by using $Pd_2(dba)_3$ in combination with TFP as

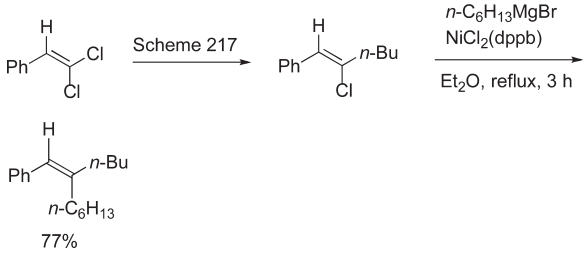
Scheme 355



R^1	R^2	R^3	method	yield (%)
OMe	n-C_5H_{11}	Ph	A	58
OMe	$BnOCH_2$	$Ph(CH_2)_3$	B	69
OMe	$PhCH_2$	Ph	A	66
CO_2Me	$PhCH_2$	n-C_7H_{15}	B	69
F	n-C_5H_{11}	$Ph(CH_2)_3$	A	74
F	$PhCH_2$	n-C_7H_{15}	A	74

Method A: $Pd_2(dba)_3$ (2.5 mol%) , 2-(dicyclohexylphosphino)biphenyl (5 mol%), KF, K_3PO_4 (3 equiv), THF, reflux.
Method B: $PdCl_2(dppp)$ (7 mol%) KF, K_3PO_4 (3 equiv), THF, reflux.

Scheme 356



the ligand, but with vinyltributyltin an improved yield was obtained when PPh_3 was used. Employing acids instead of the methyl esters gave lower yields.

The proposed mechanism of the reaction is shown in Scheme 363. This catalytic cycle was supported by the consideration that when the dibromide **565** was reacted with vinyltributyltin, the intermediate product **568** (R^1 = vinyl) was isolated and converted into the isocumarin **566** (R^1 = vinyl) in good yield (63%). When excess trimethylphenyltin was used, a mixture of both the corresponding isocumarin **566** (R^1 = phenyl) and disubstituted product **569** (R^1 = phenyl) was obtained. Because of the fast transmetalation rate of vinyltributyltin, only divinylation was instead observed when an excess of this reagent was used.

Bisseret and co-workers examined the reaction of 2-(2,2-dibromovinyl)phenol **570** with $PhSnMe_3$, 4-$MeOC_6H_4B(OH)_2$, and $(PhBO)_3$ under Pd catalysis (Scheme 364).[321] When the coupling partner was omitted, high yield (82%) was obtained of the dibenzofuran **572**, which also proved to be the only significant byproduct in all Stille and Suzuki coupling experiments. Benzofuran formation was increased when a higher amount of the coupling partner was used. A mechanism that accounts for the formation of the heteroaryl derivatives, based on that advocated for the related formation of isocoumarin derivatives (Scheme 363), was proposed.

Very recently, Lautens and co-workers have described the development of a new reactivity of β,β-dibromoenamides to generate 2-oxazolones (Scheme 365) and α-aminoketones

dx.doi.org/10.1021/cr200165q |Chem. Rev. 2012, 112, 1344–1462

(Scheme 461).[322] Conducting the coupling of the β,β-dibromoenamide **573a** with phenylboronic acid, they found, after varying several parameters, that the Buchwald's catalyst **Pd-1** (6 mol %) in dioxane at 100 °C with K_3PO_4/Et_3N as bases formed the 2-oxazolone **574a** in 80% yield in 12 h (Scheme 365). Under these optimized conditions, the reactions of a variety of β,β-dibromoenamides with a number of boronic acids were examined, and 2-oxazolones were obtained in moderate to good yields (Scheme 365). The results of the mechanistic studies for the 2-oxazolone synthesis showed two possible pathways, though the intermolecular Suzuki−Miyaura coupling/intramolecular C−O coupling sequence (path a) was preferred (Scheme 366).

3.4.3. Tandem C−H/C−C Coupling. To prepare alkenes with defined geometry, metal-catalyzed, particularly Pd-catalyzed, cross-couplings of stereo-defined alkenyl halides or alkenylmetals have been proven to be reliable, since these reactions occur with high stereoselectivity to give the resulting internal alkenes with retention of the configuration of the starting material.[323] Pd-catalyzed hydrogenolysis of 1,1-dibromoalkenes with Bu_3SnH offers a convenient entry to (*Z*)-1-bromoalkenes, which can be cross-coupled with a variety of reagents to give (*Z*)-alkenes.

In Schemes 367−369 are described some representative examples of Pd-catalyzed cross-coupling reactions of (*Z*)-1-bromo-1-alkenes obtained from 1,1-dibromoalkenes. The Suzuki coupling of the bromoalkene **576** with the alkenylboronic acid **577** in the presence of catalytic amount of $Pd(PPh_3)_4$ afforded the polyene **578** in 77% yield (Scheme 367).[324]

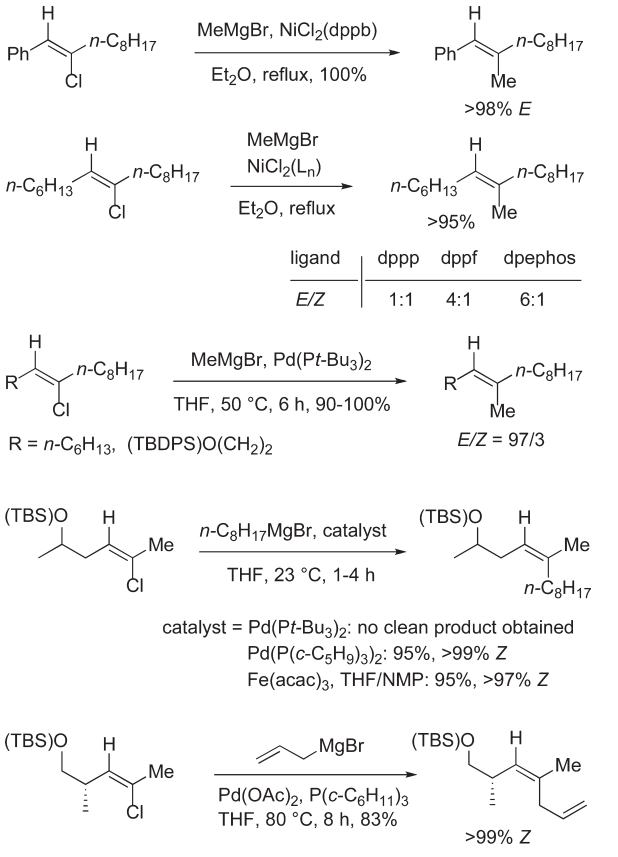
A practical synthesis of (*Z*)-polyaromatic and heteroaromatic vinylacetylenes has been recently reported. This approach was based on the Sonogashira reaction ($PdCl_2(PPh_3)_2$, CuI, Et_3N) of (*Z*)-vinylbromides with trimethylsilylacetylene (Scheme 368).[52]

In a catalytic approach to the synthesis of steroid derivatives, Tietze and co-workers reported that the Heck reaction catalyzed by $Pd(OAc)_2$ and PPh_3 of the cyclic alkene **581** with the double functionalized (*Z*)-1-bromo-2-(2-bromovinyl)-4-methoxybenzene **385b** (Scheme 229) afforded chemoselectively the compound **582** in 50% yield (Scheme 369).[270]

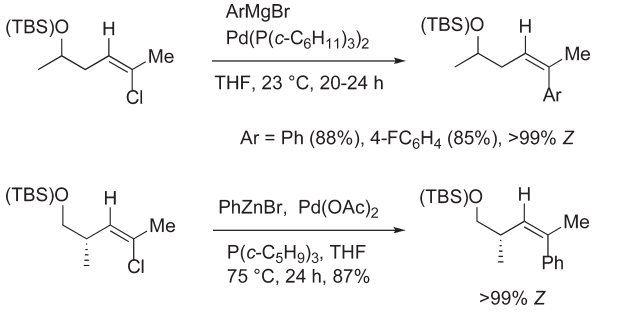
Uenishi and co-workers demonstrated that the stereoselective Pd-catalyzed hydrogenolysis of 1,1-dibromoalkenes could be followed by a successive cross-coupling reaction of the product (*Z*)-bromoalkene.[266,267a] In fact, the Pd(0) species are still alive in the final stage of the hydrogenolysis and the single byproduct Bu_3SnBr does not disturb the successive cross-coupling reactions. The two reactions could be carried out either in a stepwise manner or in one pot under the same Pd catalysts. Thus, immediately after the hydrogenolysis of the dibromide **583** was completed, the reaction mixture was subjected to a one-pot Suzuki reaction, affording stereoselectively the triene **584** in 54% yield (Scheme 370). In the same manner, the one-pot Sonogashira reaction of **583** gave the dienyne **585** in 61% yield. The success hydrogenolysis of dibromoenynes **586** allowed also the facile one-pot preparation of (*Z*)-3-hexene-1,5-diynes **587** (Scheme 371).

While alkenes with *Z* stereochemistry can be obtained from 1,1-dibromoalkenes via hydrogenolysis with Bu_3SnH under Pd-catalysis, those with *E* stereochemistry can be obtained according the procedure developed by Figadère and co-workers, who found that (*E*)-bromoalkenes were formed from 2-(hetero)aryl-1,1-dibromoalkenes by treatment with *i*-PrMgCl and catalytic $Fe(acac)_3$ (Scheme 230).[271] According these findings, these researchers studied the possibility to perform the hydrodehalogenation and the cross-coupling reaction of 1,1-dibromo-2-aryl-1-ethenes in a

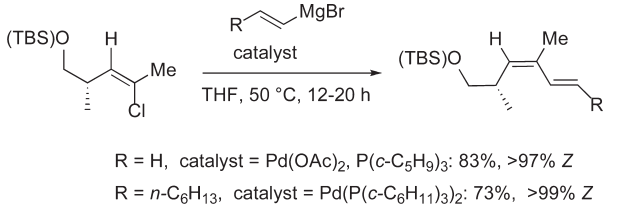
Scheme 357



Scheme 358



Scheme 359



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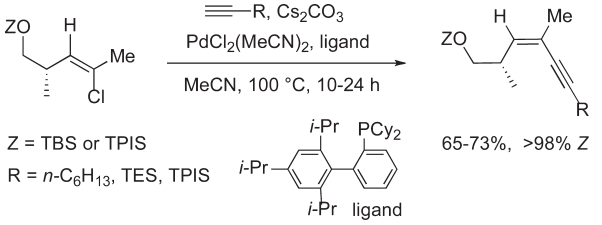
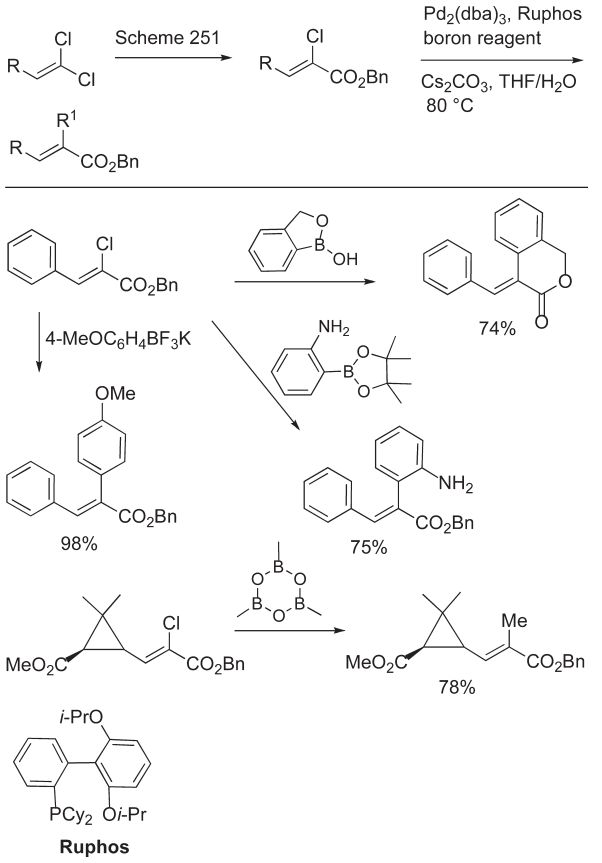
Scheme 360



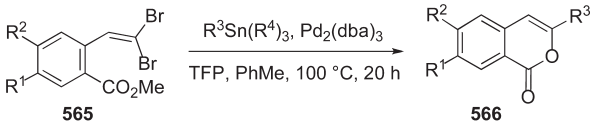
Scheme 361



one-pot sequence by treating these compounds either with 2 equiv of a Grignard reagent in the presence of $Fe(acac)_3$ (5 mol %) or with 1 equiv of *i*-PrMgCl followed by 1 equiv of a different Grignard reagent (Scheme 372).[271] When 1,1-dibromo-2-quinolyl-1-ethene was treated directly with 2 equiv of dodecylMgBr (method A), the related *E*-alkene **588a** was obtained in 45% yield. On the other hand, when the same dibromide was first reacted with 1 equiv of *i*-PrMgCl and then 1 equiv of *n*-dodecylMgBr (method B), **588a** was isolated in 63% yield. In contrast, 4-(2,2-dibromovinyl)-1,2-dimethoxybenzene afforded **588b** in 45% yield whatever method (A or B) was used. Finally when 1,1-dibromo-2-quinolyl-1-ethene was treated through method B, but with 1 equiv of PhMgBr instead of *n*-dodecylMgBr, the compound **588c** was obtained in 47% yield.

Okamoto and co-workers observed that by heating under reflux a THF solution of 2-alkyl-substituted 1,1-dihalo-2-phenyl-1-alkenes **589** with an excess of phenylmagnesium bromide

Scheme 362



$R^3Sn(R^4)_3$	R^1	R^2	R^3	**566** yield (%)
$PhSnMe_3$	H	H	Ph	92
2-furyl$SnBu_3$	H	H	2-furyl	85
3-furyl$SnBu_3$	H	H	3-furyl	81
2-thienyl$SnBu_3$	H	H	2-thienyl	80
vinyl$SnBu_3$	H	H	vinyl	30[a]
vinyl$SnBu_3$	H	H	vinyl	52[b]
$PhSnMe_3$	CO_2Me	H	Ph	71
$PhSnMe_3$	H	CO_2Me	Ph	78
$PhSnMe_3$	OMe	H	Ph	81
$PhSnMe_3$	H	OMe	Ph	81

[a]Reaction time: 48 h; [b]PPh_3 instead of TFP

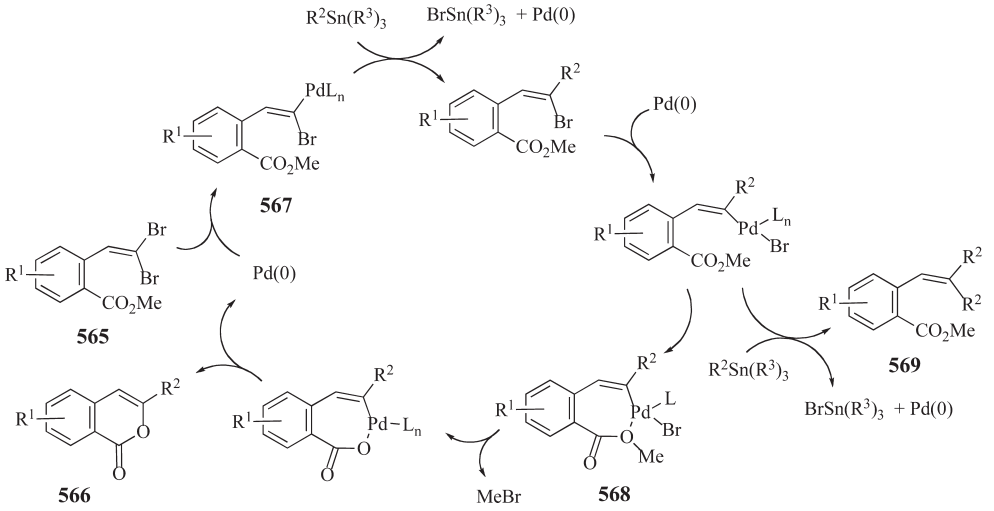
(12 equiv) in the presence of $NiCl_2$(dppp) (2 mol %), (*E*)- and (*Z*)-1,2-diphenyl-1-alkenes were obtained as the major products (Scheme 373).[325] A possible reaction mechanism was proposed.

Xu and Su have recently reported a one-pot procedure for the regioselective Pd-catalyzed synthesis of substituted (*Z*)-3-arylmethyleneisoindolin-1-ones **594** from *o-gem*-dihalovinylbenzamides **593** and organoboron reagents (Scheme 374).[326] The formation of **594** arises from a domino elimination/5-*exo*-cyclization/Suzuki coupling sequence, resulting in the formal tandem C−H/C−C coupling of the dihaloalkene moiety of **593** (Scheme 375). After extensive optimization, it was found that the combination of $PdCl_2(PPh_3)_2$ (5 mol %), $ArB(OH)_2$ (2 equiv), and NaOH (3 equiv) in THF under reflux afforded the best results for **594** (Scheme 374). The mechanism proposed to rationalize this Pd-catalyzed tandem reaction involves the dehydrobromination of **595** to furnish the alkynyl bromide intermediate **595**, which is then attacked by the nitrogen of the amide group providng (*Z*)-3-(bromomethylene)isoindolin-1-one **596** regioselectively via a 5-*exo*-cyclization process (Scheme 375). Finally, **596** leads to the 3-arylmethyleneisoindolin-1-one **594** through the classic Suzuki cross-coupling.

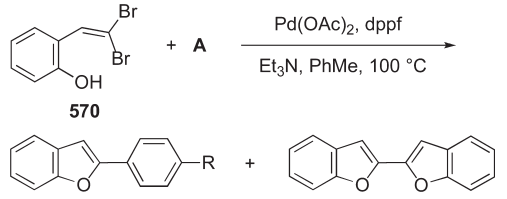
3.4.4. Tandem C−H/C−P Coupling. Evano and co-workers have recently described an efficient and stereoselective procedure for the preparation of (*E*)-1-alkenylphosphonates by copper-mediated cross-coupling between 1,1-dibromoalkenes and dialkyl phosphates (Scheme 376).[327] The reaction allows for the formal substitution of both bromine atoms by a hydrogen and a dialkoxyphosphoryl group, respectively. Copper(I) and an excess of dialkylphosphite in the presence of Cu(I) acts as both a selective reducing agent via Hirao reduction,[1d,g,i] and cross-coupling partner for the primary formed 1-bromoalkene. The reaction was best performed with K_3PO_4 as base, CuI (40 mol %) as a source of Cu(I), and *N*,*N*′-dimethylethylenediamine (80 mol %) as the ligand in toluene at 120 °C for one day (Scheme 376). By use of these conditions, a variety of 2-aryl- and 2-alkyl-1-alkenylphosphonates were obtained in moderate to good yields (45−84%) with useful levels of stereoselectivity (*E*/*Z* > 80/20) and with minor amounts of side products resulting from the dimerization of the starting dibromide. 1,1-Dibromoalkenes derived from benzophenone and acetophenone afforded efficiently the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 363

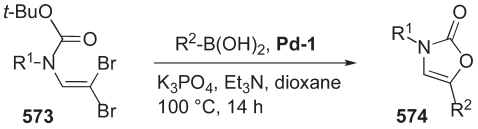


Scheme 364



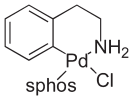
A	571/572	yield (%)
No reactant	0/1	82
$PhSnMe_3$ (1.2 equiv)	1/1	70
$PhSnMe_3$ (3 equiv)	4/1	75
$(PhBO)_3$ (1.2 equiv)	3/2	91
$(PhBO)_3$ (3 equiv)	1/0	80
$4\text{-}MeOC_6H_4B(OH)_2$ (1.2 equiv)	1/1	78
$4\text{-}MeOC_6H_4B(OH)_2$ (3 equiv)	1/0	82

Scheme 365



	R^1	R^2	**574** yield (%)
a	$PhCH_2$	Ph	80
b	$PhCH_2$	$2\text{-}MeC_6H_4$	50
c	$PhCH_2$	$4\text{-}MeC_6H_4$	65
d	$PhCH_2$	$4\text{-}FC_6H_4$	50
e	PhCH(Me)	Ph	91
f	PhCH(Me)	$2\text{-}MeC_6H_4$	84
g	PhCH(Me)	$4\text{-}MeC_6H_4$	80
h	PhCH(Me)	$4\text{-}FC_6H_4$	75
i	PhCH(Me)	3-thienyl	87

Only representative examples are reported



Pd-1

related phosphonates in 58% and 78% yields, respectively. Exclusive formation of 1-alkenylphosphonates was in sharp contrast with the results from the Hayes's group, who showed that alkynylphosphonates were predominantly formed upon reaction of alkenyl-dibromides and dialkyl phosphites with $Pd(OAc)_2$, dppf, and propylene oxide in DMF at 80 °C (Scheme 449).[328]

3.4.5. Tandem C−N/C−C Coupling. Bisseret and co-workers, examining the Suzuki reaction of *N*-(2-(2,2-dibromovinyl)-phenyl)ethanamide with *p*-methoxyphenylboronic acid, observed that when $Pd_2(dba)_3$ was used as the catalyst, the *N*-acetyl indole **597** was obtained in 52% yield (Scheme 377).[321]

Lautens and co-workers have recently published a series of papers on the use of *gem*-dihalovinylanilines for the synthesis of indole derivatives via C−N/Suzuki,[329] C−N/Heck,[330] or C−N/Sonogashira[331] reactions (Scheme 378). Moreover, the methodology was applied in the synthesis of azaindoles and thienylpyrroles,[332] as well as a family of KDR kinase inhibitors.[333]

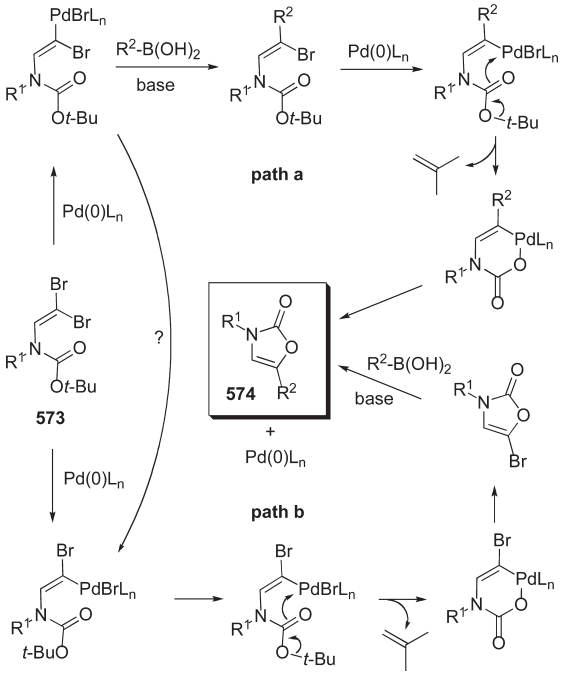
By tethering a *gem*-dihalovinyl group *ortho* to aniline, Lautens and Fang envisaged a modular synthesis of functionalized indole derivatives[329] via tandem Pd-catalyzed intramolecular C−N (Buchward−Hartwig amination) and intermolecular C−C bond (Suzuki−Miyaura coupling) formation (Scheme 379).

After initial studies focused on screening the best reaction conditions (activating groups to the nitrogen, inorganic bases, phosphine ligands, and Pd sources), it was found that with catalytic $Pd(OAc)_2$ and sphos, under optimized conditions, a broad scope of organoboron reagents successfully gave the expected 2-substitued indoles in good yields (73−86%) (Scheme 380).[329]

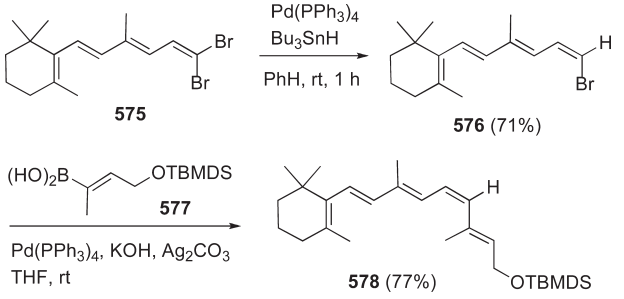
Various substituted *ortho-gem*-dibromovinylanilines were also evaluated with phenylboronic acid (Scheme 381). A broad spectrum of electron-withdrawing and electron-donating functionalities were compatible on the aniline substrates. Also 2,3-disubstituted indoles were obtained in good yields under the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

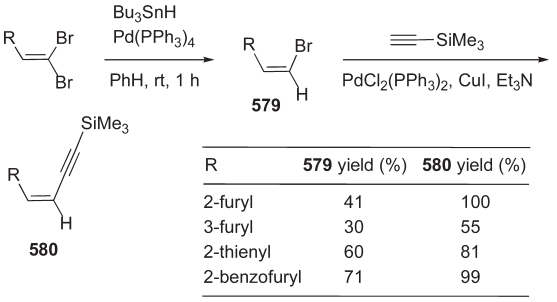
Scheme 366



Scheme 367

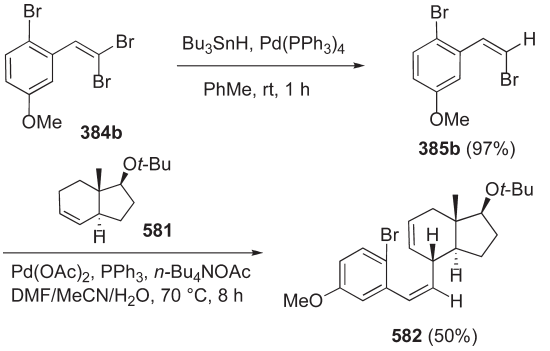


Scheme 368

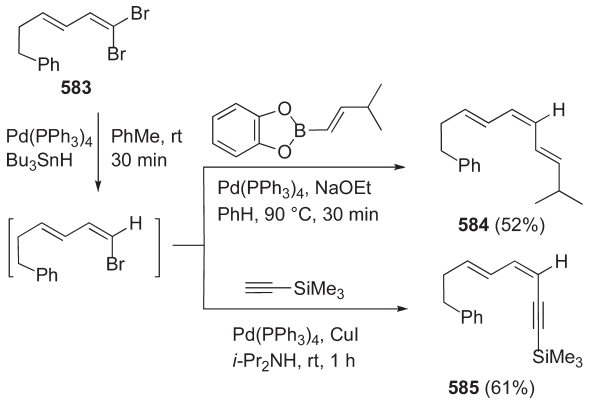


R	**579** yield (%)	**580** yield (%)
2-furyl	41	100
3-furyl	30	55
2-thienyl	60	81
2-benzofuryl	71	99

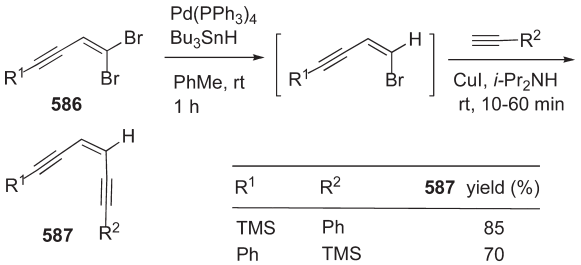
Scheme 369

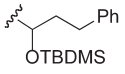
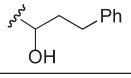


Scheme 370



Scheme 371



R^1	R^2	**587** yield (%)
TMS	Ph	85
Ph	TMS	70
Ph		64
Ph		54

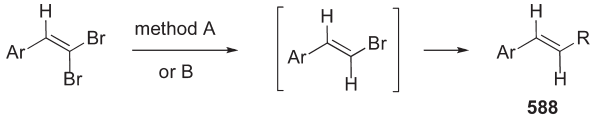
standard conditions. Interestingly, *ortho-gem*-dichlorovinylanilines gave better yields than the related bromides suggesting that the Pd(0) oxidative addition into the C−Cl bond is more selective than that into the corresponding C−Br bond.

The scope of the tandem coupling reaction with substituents on the aniline nitrogen was also explored.[329] Thus, *N*-benzyl, *N*-alkyl, and *N*-aryl *gem*-dibromoanilines were subjected to tandem coupling reaction to give in all cases very good yields of 1,2-disubstitued indoles (eight examples). *N*-Arylated *gem*-dichloro substrates were similarly subjected to tandem coupling affording 1,2,3-trisubstituted indoles (six examples) in high yields (Scheme 382).

Lautens and Fang studied the mechanistic pathway of the tandem coupling in order to determine whether the Suzuki (path a) or the Buchwald−Hartwig coupling (path b) is faster or they

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

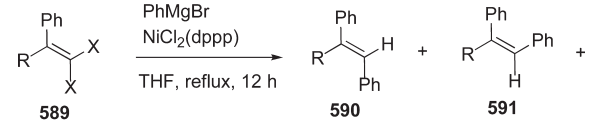
Scheme 372



Ar	R	method	588 yield (%)
2-quinolinyl	n-$C_{12}H_{25}$	A	**a** 45
2-quinolinyl	n-$C_{12}H_{25}$	B	**a** 65
3,4-$(MeO)_2C_6H_3$	n-$C_{12}H_{25}$	A	**b** 45
3,4-$(MeO)_2C_6H_3$	n-$C_{12}H_{25}$	B	**b** 44
2-quinolinyl	Ph	B	**c** 47

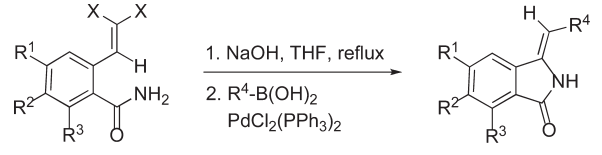
Method A: $C_{12}H_{25}MgBr$ (2 equiv), $Fe(acac)_3$ (5 mol%), THF-NMP, -10 to 0 °C, 3 h.
Method B: *i*-PrMgCl (1 equiv), $Fe(acac)_3$ (5 mol%), THF-NMP, -10 to 0 °C, 30 min, then n-$C_{12}H_{25}MgBr$ or PhMgBr (1 equiv), 3 h

Scheme 373



		yield (%)		
X	R	**590**	**591**	**592**
Cl	Me	59	12	3
Br	Me	53	20	2
Cl	Et	50	16	2
Cl	*i*-Pr	20	8	0

Scheme 374

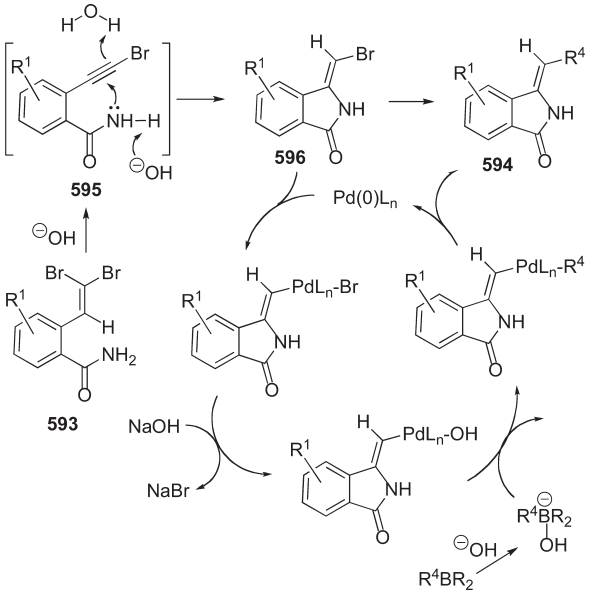


X	R^1	R^2	R^3	R^4	**594** yield (%)
Br	H	H	H	Ph	84
Br	H	H	H	2-MeC_6H_4	86
Br	H	H	H	3-$O_2NC_6H_4$	63
Br	H	H	H	3-FC_6H_4	85
Br	H	H	H	4-$TsOC_6H_4$	77
Br	H	H	H	2-naphthyl	78
Br	H	H	H	2-thienyl	76
Br	H	F	H	4-MeC_6H_4	87
Br	H	H	Cl	4-MeC_6H_4	70
Br	Br	H	H	4-MeC_6H_4	0, (67)[a]
Cl	H	H	H	4-MeC_6H_4	92

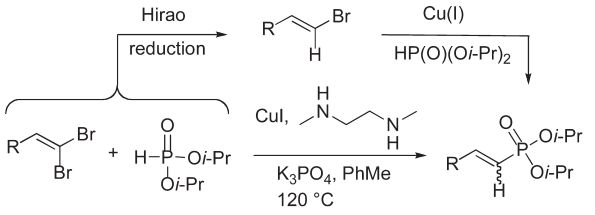
Only representative examples are reported
[a]The yield refers to the double Suzuki reaction

have similar rates (Scheme 383).[329a] Initially, compounds **599** and **600**, which could be intermediate in the reaction pathway

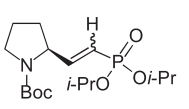
Scheme 375

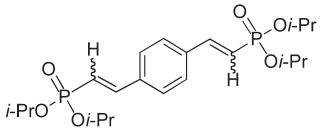


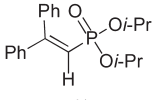
Scheme 376

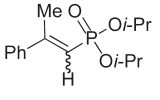


R	yield (%)	*E*/*Z*	R	yield (%)	*E*/*Z*
Ph	60	90:10	2-naphthyl	60	92:08
4-*i*-PrC_6H_4	58	92:8	9-anthracenyl	8	95:05
2-$MeOC_6H_4$	67	89:11	(*E*)-PhCH=CH	71	88:12
4-ClC_6H_4	56	89:11	Et	45	81:19
4-FC_6H_4	52	87:13	n-C_8H_{17}	59	92:08
3-$O_2NC_6H_4$	84	88:12	*t*-Bu	48	95:05
2-$MeO_2CC_6H_4$	52	83:17	c-C_6H_{11}	54	93:07
4-$F_3CC_6H_4$	67	80:20	$PhCH_2$	62	95:05


55% (*E*/*Z* = 86:14)


83% (E,/E/E,Z/Z,Z: 88/12/0)

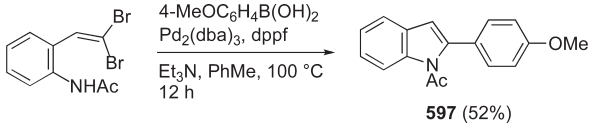

58%


78% (*E*/*Z* = 90:10)

based on the two mechanisms were prepared. By subjection of **599** to the usual coupling conditions with $PhB(OH)_2$, a mixture of the intramolecular C−N coupling product **601** and an intermolecular Suzuki product **602** was obtained. Since the formation of **602** was never observed as a byproduct of the tandem coupling reaction, the compound **599** was not considered a likely intermediate under the reaction conditions. On the

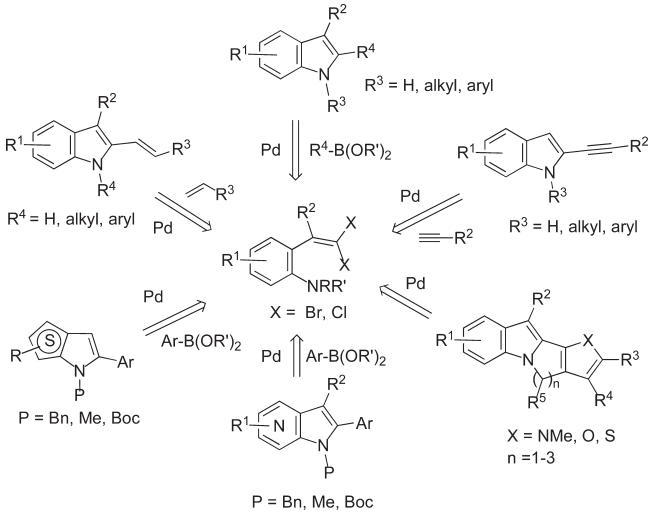
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 377

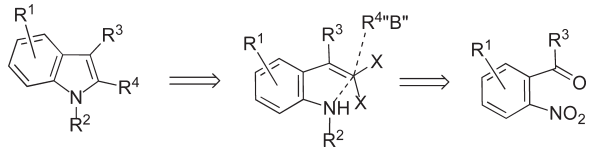


597 (52%)

Scheme 378



Scheme 379

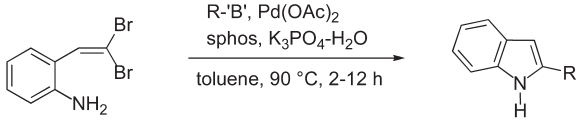


other hand, the Suzuki reaction of **600** with $PhB(OH)_2$ gave **601** quantitatively in accord with path b. These studies suggested that the C−N bond formation could be the first coupling step.

Mechanistic studies were also carried out. To this purpose, the deuterium labeled *ortho-gem*-dibromovinylaniline **603** was prepared, which, by coupling under the standard conditions, gave the expected indole **605** with 16% deuterium leaching at C-3 (Scheme 384). Moreover, the *N*-deuterated dibromoalkene **606** gave the indole **605** with some deuterium incorporation at the C3 carbon (19%) in the presence of $K_3PO_4 \cdot D_2O$. These phenomena were not explicable by invoking a direct Buchwald−Hartwig amination and imply that a second process may complete with C−N coupling. They proposed that the dominant process is the direct C−N coupling (path a, Scheme 384) accompanied by a minor pathway involving the alkyne intermediate **608** formed by β-hydride elimination from the complex **607** (path b). A Pd(II)-mediated 5-*endo-dig* cyclization then gives the 2-bromoindole **604**, which subsequently undergoes Suzuki coupling with $PhB(OH)_2$. Proton exchange of DPd(II)Br with a proton source such as the boronic acid or the amine may be responsible for the observed deuterium leaking.

Lautens and co-workers have extended the methodology of the tandem C−N/Suzuki coupling toward the synthesis of

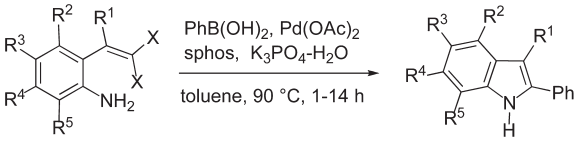
Scheme 380



R-'B'	yield (%)	R-'B'	yield (%)
$PhB(OH)_2$	84	1-hexenylB$(OH)_2$	80
4-$MeOC_6H_4B(OH)_2$	83	(3-hexenen-3-yl)catechol borane	73
2-$MeC_6H_4B(OH)_2$	82	Et_3B	77
4-$F_3CC_6H_4B(OH)_2$	75	*n*-hexylBBN	79
3-thienylB$(OH)_2$	86	BnO$(CH_2)_4$BBN	78

Only representive examples are reported

Scheme 381



R^1	R^2	R^3	R^4	R^5	X	yield (%)
H	Me	H	H	H	Br	77%
F	H	H	H	H	Br	88%
OMe	OBn	OMe	H	H	Br	72%
H	F	H	H	H	Br	87%
H	H	H	CO_2Me	H	Br	90%
H	H	H	CF_3	H	Br	90%
H	H	OBn	OBn	H	Br	72%
H	H	H	H	Me	Br	89%
H	H	H	-CH=CH-CH=CH-		Br	77%
CF_3	H	H	H	H	Br	9%
Ph−≡	H	H	H	H	Br	77%
4-FC_6H_4	H	H	H	H	Br	90%
H	H	H	H	H	Cl	95%
Me	H	H	H	H	Cl	96%

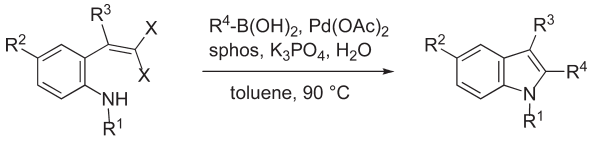
Only representive examples are reported

azaindoles and thienylpyrroles with *gem*-dichlorovinyl pyridine or thiophene substrates.[332]

3.4.5.1. Synthesis of 7-Azaindoles. Initial experiments showed that the conditions developed for indole synthesis (Schemes 380−382) via tandem C−N/Suzuki coupling of the *gem*-dibromovinylpyridine **609a** with $PhB(OH)_2$ [$Pd(OAc)_2$ and sphos][329] failed to give the desired 7-azaindole product **610a**, due presumably to the formation of the complex **612**, which causes catalyst poisoning (Scheme 385). However, when the *N*-benzyl substrate **609b** was used under these conditions, the desired *N*-benzyl-7-azaindole **610b** was obtained in 74% yield. Further investigation revealed that the corresponding *gem*-dichlorovinylpyridine **611** gave **610b** with a significantly improved yield (90%), and therefore, the scope of this reaction in the synthesis of azaindole isomers was next explored employing only *gem*-dichlorovinyl substrates. Thus, a range of 7-azaindoles were prepared as shown in Scheme 386.[332] Substrates with a benzyl, methyl, or *tert*-butoxycarbonyl (Boc) group on the nitrogen produced successful reactions giving 7-azaindole derivatives in 62−97% yields. Interestingly, a 2,3-disubstituted

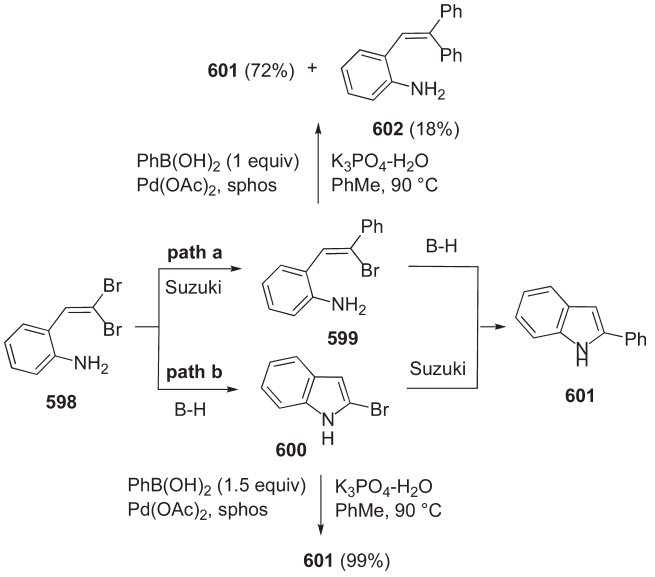
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 382



R^1	R^2	R^3	R^4	X	yield (%)
Ph	H	H	Ph	Br	92
Bn	H	H	Ph	Br	82
i-Pr	H	H	Ph	Br	71
$3,4(MeO)_2C_6H_3$	H	H	$4\text{-}F_3CC_6H_4$	Br	81
Ph	H	Me	$4\text{-}FC_6H_4$	Cl	96
Me	NO_2	Me	Ph	Cl	90

Scheme 383



7-azaindole was also obtained in excellent yield from the related tetrasubstituted olefin, although prolonged heating was required that caused partial loss of the Boc group.

3.4.5.2. Synthesis of 6-Azaindoles. The efficiency of the 6-azaindole formation with the Boc-protected chloro substrate **613** and various boronic acids was examined (Scheme 387). Under usual conditions ($Pd(OAc)_2$ and sphos), aryl boronic acids with electron-donating or electron-withdrawing groups or *ortho*-substituents were tolerated. A 2-pentenyl azaindole, which could be further functionalized, was prepared in good yield (79%) using an alkenyl boronic acid. Heteroaryl boronic acids such as 3-thienyl boronic and quinolinyl boronic acid were also successfully applied to the synthesis of 6-azaindole. The Boc-protected azaindole could be deprotected under acidic conditions.

3.4.5.3. Synthesis of 5-Azaindoles. Initial attempts to form the 5-azaindole **616a** from the parent substrate **615** by using 1.5 equiv of $PhB(OH)_2$ were disappointing, but when 1.2 equiv of the organoboron reagent was employed, the expected 5-azaindole was obtained in high yield (Scheme 388). The evaluation of a number of electron-poor, electron-rich, hindered, and heterocyclic arylboronic acids showed that this strategy was effective for a wide range of boronic acids. After the survey of biphenyl phosphine ligands, XPhos was found to be the best in this circumstance.

3.4.5.4. Synthesis of 4-Azaindoles. Attempts to synthesize the 4-azaindole **620** from the substrate **617** failed probably due to formation of the palladium species, which by coordination to the pyridyl nitrogen retards the C−N bond formation (Scheme 389). In fact, when the pyridyl nitrogen was protected as *N*-oxide, **618**, the tandem coupling successfully occurred to afford the desired *N*-oxy-4-azaindole **619a** and **619b** in good to excellent yields (Scheme 389). In addition, the carbobenzyloxy (Cbz) group was completely deprotected under the reaction conditions. Deoxygenation of the *N*-oxy-4-azaindole **620a** to give the 2-phenyl 4-azaindole **620b** was performed in good yield using PCl_3.

3.4.5.5. Synthesis of Thienopyrroles. Subjecting the Boc-protected aminothiophene **621** to the usual reaction conditions afforded the Boc-protected thienopyrroles **622** in good yields, though depending on the boronic acid some fine-tuning by Buchwald's biphenyl family of phosphine ligands was required to obtain good yields (Scheme 390). Thiophene substrates with either a free NH_2 or *N*-alkyl failed to give the desired thienopyrroles due to the instability of these substrates, whereas the reaction with hindered boronic acids such as *o*-tolyl boronic acid resulted in very low yield.

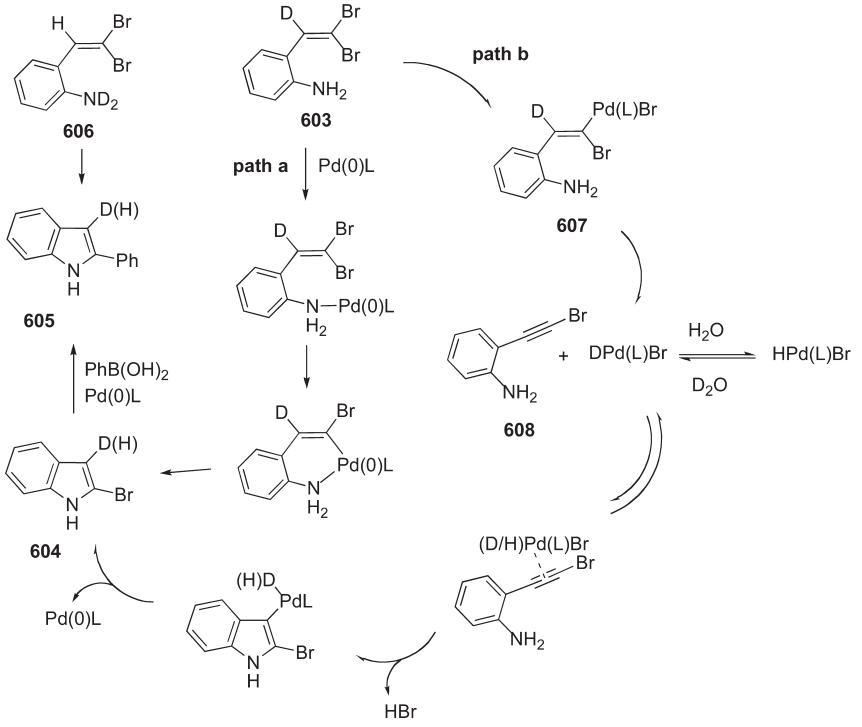
Very recently, Lautens and co-workers have successfully demonstrated their methodology for the synthesis of indoles in the preparation of a family of KDR kinase inhibitors **623** containing an indol-2-yl quinolin-2-one structure (Scheme 391).[334]

Lautens and co-workers reported that novel tetracyclic and pentacyclic indole derivatives can be prepared from readily available *gem*-dibromovinyl substrates in a single step by means of an efficient Pd-catalyzed domino Buchwald−Hartwig amination/direct arylation reaction.[334] After optimization of the reaction conditions, $Pd_2(dba)_3$ (3 mol %), $P(2\text{-}MeOC_6H_4)_3$ (12 mol %), and Ag_2CO_3 (0.5 equiv), as a scavenger of the liberated halide, which may act as a catalyst poison, the scope of the domino process was investigated with 11 substrates (Scheme 392). It was found that tetracycles bearing a wide variety of functional groups could be synthesized in good yields (73−92%). Only when the vinyl hydrogen in the substrate was replaced by an aryl group, was the reactivity completely shut down. Next, the variation of the heterocycle (Scheme 393) and the modification of the linker between the nitrogen atom and the thiophene were examined (Scheme 394). Concerning the first point, the reaction proceeded smoothly with benzothiophene (78% yield), but with nitro-substituted thiophene it led to a sluggish reaction and the expected product could be obtained in 50% yield. The retarded reactivity of this substrate suggested that the reaction proceeded via an arylation pathway, possibly an electrophilic aromatic substitution, rather than a Heck-type pathway. Furan and pyrrole derivatives were also successful, albeit in lower yields. From the two examined cases on the effect of ring size, the reaction proceeded smoothly with a six-membered ring, while it proved to be more difficult with the phenyl-fused seven-membered ring, giving 71% yield but only by raising the catalyst loading to 10 mol % (Scheme 394).

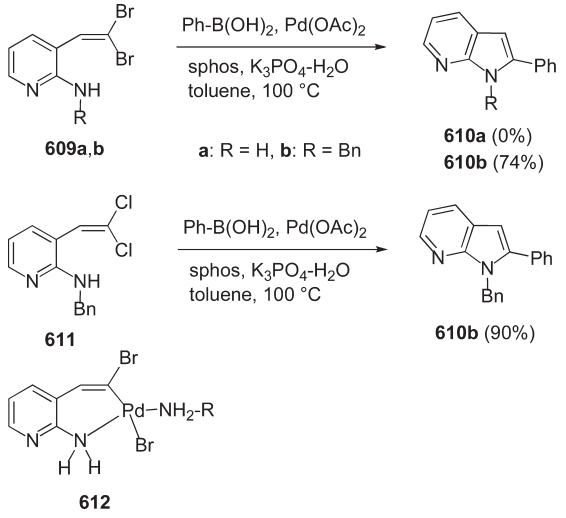
Bao and co-workers have recently developed a one-pot protocol to synthesize pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives **627** from *ortho-gem* dibromovinyl isocyanates **624** and *N*-alkylanilines, through a nucleophilic addition/Cu-catalyzed N-arylation/Pd-catalyzed C−H activation sequential process (Scheme 395).[335]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

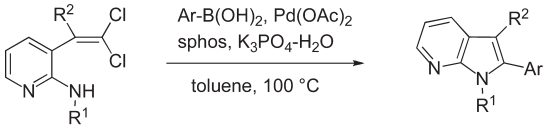
Scheme 384



Scheme 385



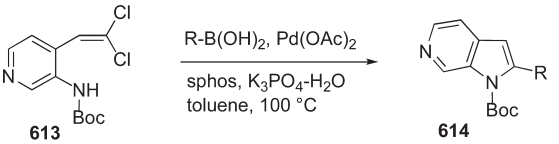
Scheme 386



R^1	R^2	Ar	yield (%)
Bn	H	Ph	90
Me	H	Ph	84
Me	H	4-$F_3CC_6H_4$	87
Me	H	4-$MeOC_6H_4$	83
Boc	H	Ph	62
Boc	Me	Ph	97[a]

[a]R = Boc/H = 40/57

Scheme 387

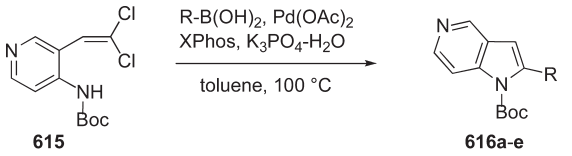


R	**614** yield (%)	R	**614** yield (%)
Ph	87	2-naphthyl	70
2-MeC_6H_4	73	2-thienyl	50
4-$F_3CC_6H_4$	72	penten-1-yl	79
4-$MeOC_6H_4$	81	2-methoxyquinolin-3-yl	91

Obtaining nearly quantitatively the intermediate urea derivatives **625**, they initially addressed their efforts to the Cu-catalyzed N-arylation to bromoindoles **626**. After extensive optimizations, it was found that the use of CuI (10 mol %) as the copper source, *N*,*N*′-dimethylethylenediamine (20 mol %) as the ligand, and K_2CO_3 as the base in toluene at 120 °C allowed conversion of **625** into **626** in high yields. Finally, the conversion of **626** to **627** was examined by a Pd-catalyzed C−H activation process. Conditions employing $PdCl_2$(dppf) (10 mol %) and KOAc (1.5 equiv) in toluene at 120 °C were selected as optimal. The one-pot protocol was then pursued, and the obtained results using a variety of isocyanates and *N*-alkyl-anilines are reported in Scheme 396. Moderate to good yields were generally attained, but as a limitation of this method, *N*-methylaniline, bearing a

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

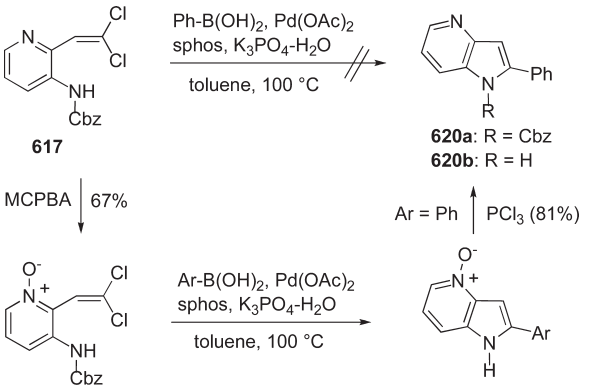
Scheme 388



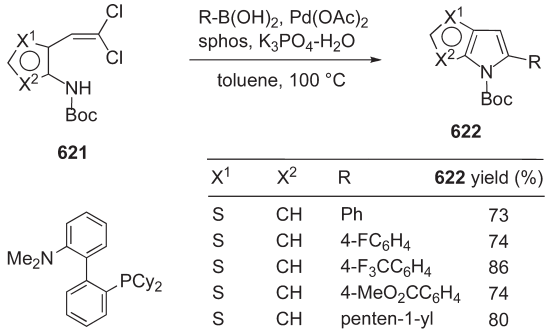
R	616 yield (%)	R	616 yield (%)
a Ph	87	**d** 2-MeC_6H_4	75
b 2-FC_6H_4	88	**e** 2-thienyl	80[a]
c 4-$MeOC_6H_4$	68		

[a]sphos was used instead of XPhos

Scheme 389



Scheme 390



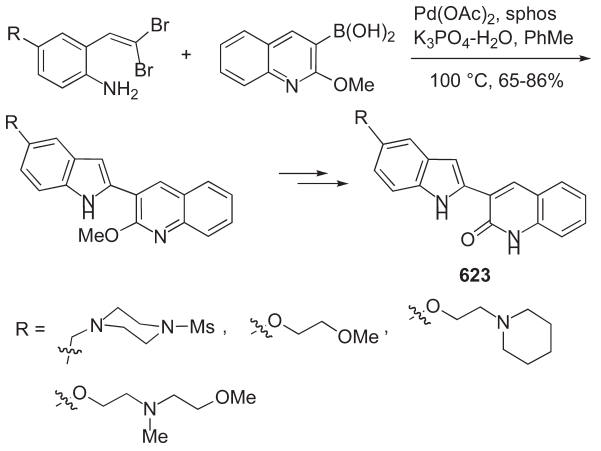
X^1	X^2	R	622 yield (%)
S	CH	Ph	73
S	CH	4-FC_6H_4	74
S	CH	4-$F_3CC_6H_4$	86
S	CH	4-$MeO_2CC_6H_4$	74
S	CH	penten-1-yl	80
CH	S	3-thienyl	73
CH	S	Ph	76[a]
CH	S	PhCH=CH	71[a]

[a]DavePhos was used instead of sphos

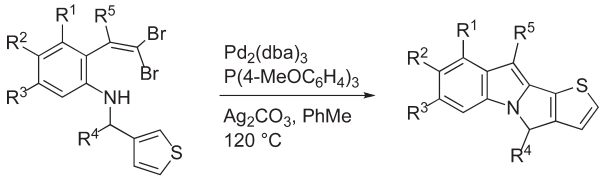
strongly electron-withdrawing group on the phenyl ring, such as 4-NO_2 and 4-Ac, which had a detrimental effect on the nucleophilicity, failed to react with the isocyanate **624** to afford the addition product. Moreover, the use of diphenylamine was also unsuccessful, due to its high steric hindrance.

The same group have more recently reported an extension of their method to obtain a variety of unsymmetrical 1,1′-carbonyl-2,2′-biindolyl derivatives **631** (Scheme 397).[336] In this circumstance,

Scheme 391



Scheme 392



R^1	R^2	R^3	R^4	R^5	yield (%)
F	H	H	H	H	87
OSO_2Ph	OMe	H	H	H	91
H	OBn	H	H	H	80
H	H	Cl	H	H	92
H	H	H	H	Ph	traces
H	H	H	Me	H	83

Only representative examples are reported

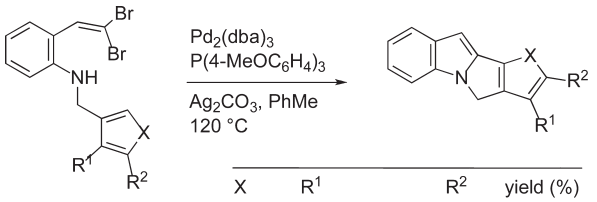
the starting materials, *N*-(2-(2,2-dibromovinyl)phenyl)-1-*H*-indole-1-carboxamides **630**, were prepared by reaction of *o-gem*-dibromovinylanilines **628** with 1*H*-indole-1-carbonyl chloride derivatives **629**.

After a deep investigation, the same conditions used for obtaining **627** (Scheme 396) were also found to be the best ones for the one-pot conversion of **630** into the final products **631**. The protocol proved to be general, and moderate to good yields of 2,2′-biindolyl derivatives **631** were obtained. However, the access to unsymmetrical products bearing electron-deficient groups on both indole rings was unsuccessful. When indole was replaced with pyrrole, the reactions occurred smoothly to afford the products **632** in moderate yields (Scheme 397).

Next, Lautens and co-workers described a tandem Pd-catalyzed C−N/Heck reaction that provides a highly efficient and modular synthesis of 2-vinyl indoles and their tricyclic derivatives from *ortho-gem*-dibromovinylanilines.[330] Under the optimized reaction conditions, various alkenes with different electronic character were converted into the related 2-vinyl indoles by using *N*-benzyl-2-(2,2-dibromovinyl)aniline in good yields (40−82%) (Scheme 398). The effect of the substitution with electron-rich and electron-deficient groups and different steric hindrance on the aniline nitrogen had a little effect on the yield.

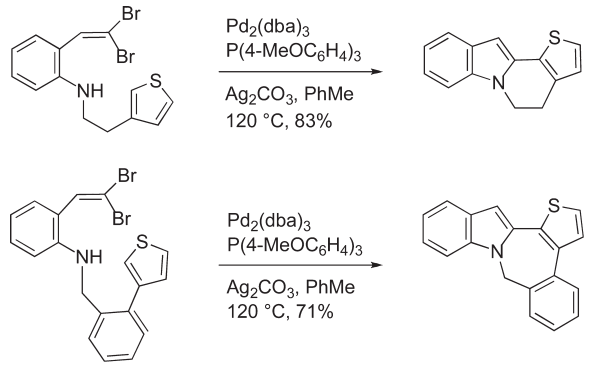
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 393

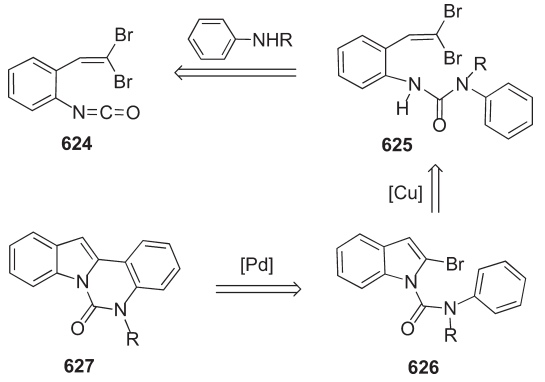


X	R^1	R^2	yield (%)
S	-CH=CH-CH=CH-		78
S	H	NO_2	50
O	H	H	72
NMe	H	H	55

Scheme 394



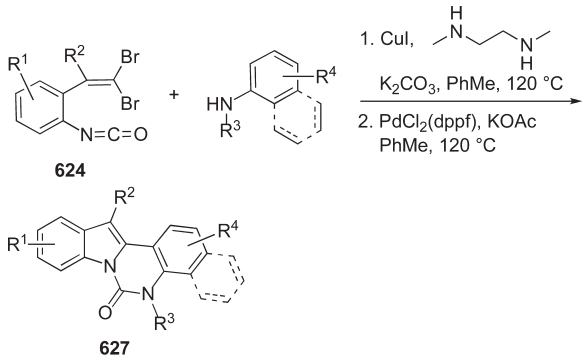
Scheme 395



The methodology was validated through evaluation of various dibromovinylanilines substituted on the phenyl ring (Scheme 399). Finally, an intramolecular version of this methodology was developed to provide the formation of pyrido- and azepinoindole derivatives in good yields (58−72%) (Scheme 400).

The synthesis of 2-alkynyl indoles from *gem*-dibromovinylanilines and terminal alkynes via tandem Ullmann/Sonogashira couplings has been also reported by Lautens and co-workers (Scheme 401).[331] After screening a range of Pd catalysts, bases, and phosphine ligands, the best conditions were found to be Pd/C, $P(4\text{-}MeOC_6H_4)_3$, and *i*-Pr_2NH in toluene/H_2O at 100 °C. The optimized conditions were then applied to various aromatic

Scheme 396



R^1	R^2	R^3	R^4	yield(%)
H	H	Me	H	78
4,5-$(OMe)_2$	H	Me	H	65
5-Br	H	Me	H	57
4-Cl	H	Me	H	63
4-Br	H	Me	H	61
H	CF_3	Me	H	67
H	H	Me	4-Me	80
H	H	Me	4-OMe	67
H	H	Me	2-Me	62
H	H	Me	3,5-Me_2	64
H	H	Me	3-Me	68
H	H	Me	4-Cl	77
H	H	Me	4-Br	71
H	H	Me	4-OCF_3	69
H	H	Bn	H	87
H	H	Me	1-naphthyl	69

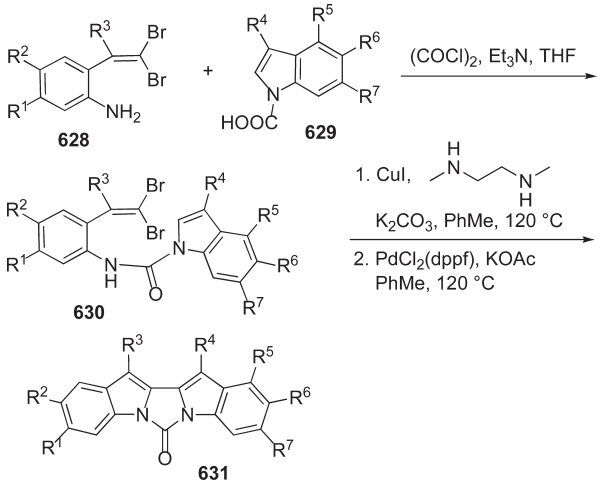
and aliphatic terminal alkynes with different electronic properties using 2-(2,2-dibromovinyl)aniline as the substrate. In all cases, the expected 2-alkynyl indoles **631** were isolated in moderate to good yields (40−85%) (Scheme 401). Altering the electron-donating and electron-withdrawing groups did not affect the efficacy of the tandem reaction, giving the products in 55−84% yields (Scheme 402). The presence of alkyl or aryl substituents on the aniline nitrogen of the *gem*-dibromovinylanilines in general lowered the yield, although longer reaction times and higher catalyst loadings could be used to force the reaction completion. A mechanism that accounts for the formation of 2-alkynyl indoles from the dibromovinyl precursors was proposed (Scheme 410).

Very recently, a very efficient method for the synthesis of substituted 2-carboxyindoles from 2-(2,2-dibromovinyl)anilines by a tandem Pd-catalyzed C−N/C-carbonylation sequence under 10 atm of carbon monoxide (Schemes 403 and 404) has been reported.[337] After a series of optimization experiments, $PdCl_2(PPh_3)_2$ (5 mol %) and PPh_3 (10 mol %) were shown to catalyze the formation of 1*H*-indole-2-carboxylate in 70% yield. This protocol was next extended to other substrates substituted with different groups in the aromatic ring and at the nitrogen, and the target indoles were isolated in good yields (60−78%) (Scheme 403). Interestingly, when the tribromide **632** was subjected to the catalytic system, the indole **634** was isolated in 65% yield, providing that three steps (C−N-coupling and two consecutive carbonylations) can take place in the same autoclave (Scheme 404).

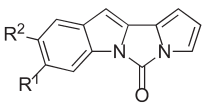
Pontikis and Florent have recently reported an effective domino N−C coupling/carbonylation/C−C coupling sequence

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 397



R^1	R^2	R^3	R^4	R^5	R^6	R^7	**631** yield(%)
H	H	H	H	H	H	H	74
OMe	OMe	H	H	H	H	H	77
H	Cl	H	H	H	H	H	65
H	Br	H	H	H	H	H	62
Br	H	H	H	H	H	H	67
H	H	CF_3	H	H	H	H	70
H	H	H	Me	H	H	H	80
H	H	H	H	Me	H	H	63
H	H	H	H	H	Me	H	68
H	H	H	H	H	H	Me	72
H	H	H	H	H	OMe	H	71
OMe	OMe	H	H	H	OMe	H	75
H	Br	H	H	H	H	H	57

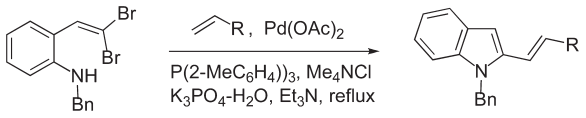

632

R^1	R^2	**632** yield (%)
H	H	67
OMe	OMe	68
H	Br	62

as a route to 2-(hetero)aroylindoles.[338] The one-pot protocol involved the reaction of 2-*gem*-dibromovinylanilines with boronic acids (1.1 equiv) and the use of $Pd(PPh_3)_4$ (5 mol %) as the catalyst under carbon monoxide atmosphere (12 bar) (Scheme 405). Under optimized reaction conditions, an array of 2-aroylindoles **634** bearing different functional groups were obtained in fairly good yields. The application of the domino reaction to heteroarylboronic acids was explored and proved to be compatible with various substrates such as thiophen-3-, benzofuran-2-, or dibenzofuran-4-boronic acids providing 2-heteroaroylindoles in fair to good yields (Scheme 406). The domino process implies that 2-bromoindoles, formed in the first intramolecular N−C coupling, could generate, by the migratory insertion of carbon monoxide, an acylpalladium species, which could undergo transmetalation with a boronic acid to afford the product.

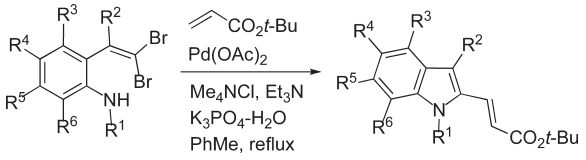
Taylor and co-workers have recently developed tandem hydrazine condensation/Suzuki−Miyaura cross-coupling reactions that afford 1,3,5-trisubstituted functionalized pyrazoles **635** in good yields, by a one-pot treatment of a variety of *β*,*β*-dibromoenones with 1,1-dimethylhydrazine and functionalized arylboronic acids in the presence of catalytic $Pd(PPh_3)_4$

Scheme 398



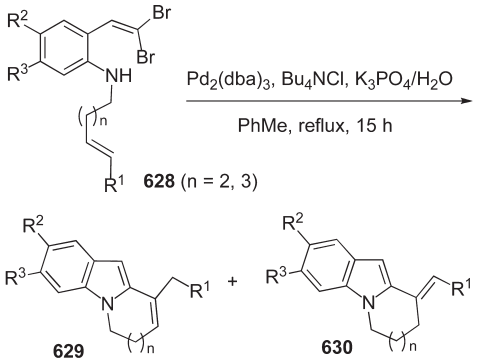
R	yield (%)	R	yield (%)
CO_2t-Bu	79	SO_2Ph	40
Ph	65	CN	70
4-ClC_6H_4	65	$H_{15}C_7CH(OH)$	82
4-$MeOC_6H_4$	73	O N−C(O)	63

Scheme 399



R^1	R^2	R^3	R^4	R^5	R^6	yield (%)
H	H	Me	H	OMe	OMe	53
Bn	H	F	H	F	H	70
Bn	H	H	F	CO_2Me	H	71
Bn	H	H	OBn	H	H	64
Bn	H	H	H	OBn	OBn	39
Bn	H	H	H	-CH=CH-CH=CH-		43

Scheme 400



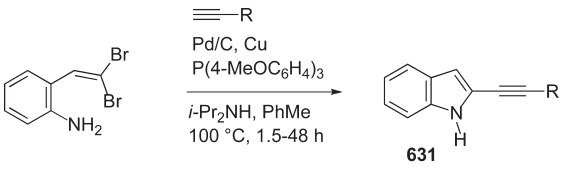
n	R^1	R^2	R^3	**629**,**630** yield (%)	**629**/**630**
1	CO_2t-Bu	H	H	76	3:1
1	CO_2t-Bu	OBn	H	58	3:1
1	CO_2t-Bu	H	CO_2Me	67	7:1
1	Me	H	H	72	1:0
2	CO_2t-Bu	H	H	70	2:3

(Scheme 407).[34] This tandem process provides yields that are superior to the sequential two-step process, namely, initial formation of 5-bromopyrazoles from *gem*-dibromoenones and 1,1-dimethylhydrazine, followed by Suzuki coupling.

3.4.6. Tandem C−O/C−C Coupling. Lautens and co-workers developed a procedure for the synthesis of 2-alkynyl indoles

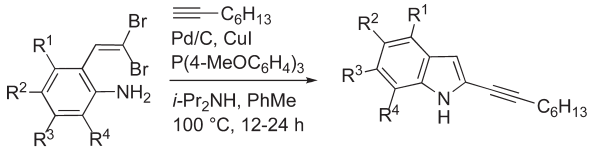
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 401



R	**631** yield (%)	R	**631** yield (%)
C_6H_{13}	83	$NC(CH_2)_3$	50
TMS	57	Ph	85
$HOCH_2$	40	3-pyridyl	81
$NC(CH_2)_3$	71	$Cl(CH_2)_4$	70
$(THP)OCH_2$	65		

Scheme 402

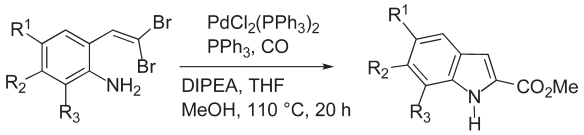


R^1	R^2	R^3	R^4	yield (%)
H	CO_2Me	H	H	84
OBn	OMe	H	H	81
F	H	H	H	72
H	H	-CH=CH-CH=CH-		55

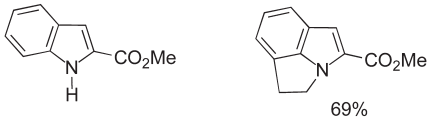
from *gem*-dibromovinylanilines and terminal alkynes via tandem cross-couplings (Schemes 401 and 402) and then extended this methodology to the synthesis of 2-alkynylbenzofurans from *gem*-dibromovinylphenols.[331] By use of a catalytic amount of Pd/C and P(*p*-$MeOC_6H_4)_3$, under optimized conditions, a variety of 2-alkynylbenzofurans **636** were synthesized from 2-(2,2-dibromovinyl)phenol **572** in 49−80% yields (Scheme 408). Similarly, various substituents on the benzene ring were well tolerated (Scheme 409). A plausible mechanism that accounts for the formation of 2-alkynyl benzofurans and indoles and from the dibromovinyl precursors was proposed (Scheme 410).

3.4.7. Tandem C−N/C−C and C−N/C−H Coupling. Lautens and co-workers, developing their studies on the selective tandem C−N/C−C coupling of *gem*-dihalovinyl systems to generate indoles (Scheme 378), have shown recently that these systems can undergo CuI-catalyzed tandem intramolecular C−N/C−N coupling (Scheme 378).[339] In particular, the *gem*-dibromovinyl moiety of **637** performed an intramolecular amidation, followed by a sequential C−N coupling with the tethered carbamate generating imidazoindolones **638** (Scheme 411). Initial attempts to convert **637a** by using Pd/phosphine-based systems was unsuccessful in generating the desired product **638a**, giving only the corresponding 2-bromoindole intermediate in moderate yield. However, Buchwald combination of CuI and *N*,*N*-dimethylethane-1,2-diamine successfully gave **638a** in moderate yield and 34% enantiomeric excess. Next, by screening a range of diamines, bases, and solvents and the amount of copper salt, it was found that 2.5 mol % CuI and 5 mol % racemic *trans*-cyclohexane-1,2-diamine under optimized conditions converted

Scheme 403



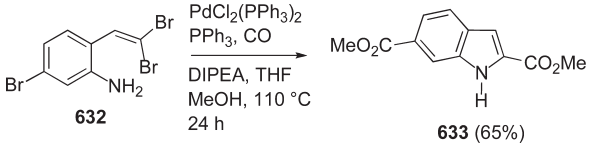
R^1	R^2	R^3	yield (%)
H	H	H	70%
OBn	H	H	2%
F	H	H	78%
OMe	OMe	H	62%
H	CO_2Me	H	73%
Cl	H	H	68%
-OCH_2O-		H	67%
OMe	H	OMe	75%
H	-CH=CH-CH=CH-		60%



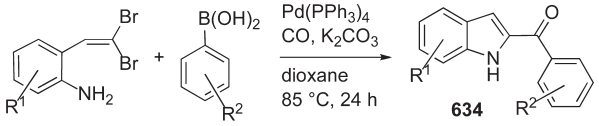
R = *n*-Bu (67%), Bn (70%), Ph (72%), Ts (50%)

69%

Scheme 404



Scheme 405

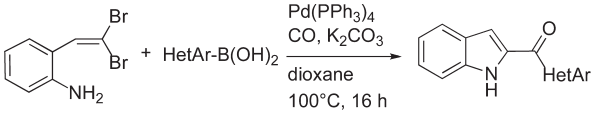


R^1	R^2	yield (%)	R^1	R^2	**634** yield (%)
3-Cl	H	68	H	2-OMe	40
4-CO_2Me	H	50	H	2,6-Me_2	0
4,5-OCH_2O-	H	56	H	4-Cl	70
4,5-$(OMe)_2$	H	55	H	4-CF_3	73
4-OBn	H	73	H	4-OMe	61
3,4,5-$(OMe)_3$	H	65	H	4-CONHMe	29
				3,4,5-$(OMe)_3$	63

directly a number of *gem*-dibromoalkenes **637** into the imidazoindolones **638** in good yields (Scheme 411). Also the presence of electron-donating and electron-withdrawing groups on the aromatic ring did not seem to affect the efficiency of the cyclization reaction (Scheme 412). An example of 3-substituted imidazoindolones was also reported, but in this event a higher catalyst loading (10 mol %) was required to obtain the desired product in good yield (52%) since the usual conditions gave mainly monocyclized product (40%) and the desired product (28%) (Scheme 413). In some cases, the preservation of the

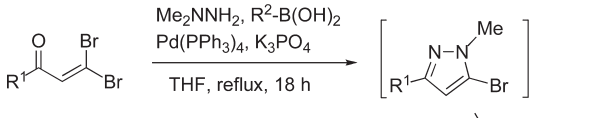
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

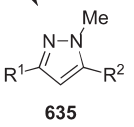
Scheme 406



HetAr	yield (%)	HetAr	yield (%)
2-thienyl	67	4-dibenzofuranyl	71
2-benzofuranyl	58	2-naphthyl	70
4-isoquinolinyl	71		

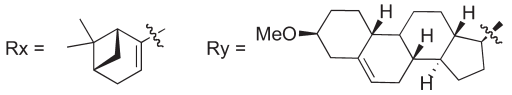
Scheme 407



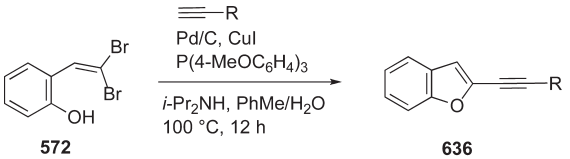


635

R^1	R^2	**635** yield (%)
Ph	Ph	76
Ph	Me	73
Ph	4-$MeOC_6H_4$	69
Ph	4-ClC_6H_4	49
Ph	4-MeC_6H_4	40
4-$MeOC_6H_4$	Ph	66
4-$O_2NC_6H_4$	Ph	68
2-naphthyl	Ph	63
2-thienyl	Ph	76
Me	Ph	73
Ph	(*E*)-MeCH=CH	57
Rx	Ph	59
Ry	Ph	76



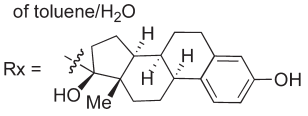
Scheme 408



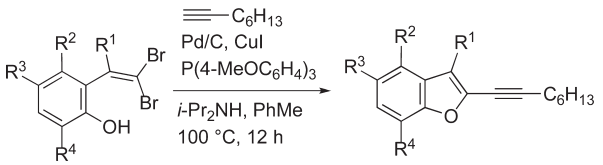
572 636

R	yield (%)	R	yield (%)
n-C_6H_{13}	80	$(CH_2)_2CH_2CN$	76
$SiMe_3$	47[a]	Ph	71[a]
CH_2OH	49	3-pyridyl	61[a]
CH_2OTDPS	80	Rx	69
CH_2CH_2OH	63		

[a]Toluene was used as solvent instead of a mixure of toluene/H_2O



Scheme 409



R^1	R^2	R^3	R^4	yield (%)
H	H	CO_2Me	H	93
H	-CH=CH-CH=CH-		H	98
H	H	H	OMe	80
Me	H	H	H	82

chiral center originating from the amino acid remained very high, while for the remaining cases, the enantiomeric excess of the imidazoindolones was highly variable. The extent of racemization was related to the lifetime of the 2-bromoindole intermediate, which is dependent on the rate of the second amidation step, and to the fact that the proton at the stereocenter of the intermediate is much more acidic than that in the starting material due to its ketone character.

Evano and co-workers have found that while the copper-catalyzed reaction between lactams and 1,1-dibromoalkenes gave ynamides when cesium carbonate in dioxane was used (Schemes 453 and 454),[340] ketene *N,N*-acetals were obtained by switching to potassium phosphate in toluene at 80 °C (Scheme 414).[341] Under these conditions, a variety of ketene *N,N*-acetals could be obtained in moderate to good yields, with the exception of alkyl-substituted dibromoalkenes. The double amidation was also examined. Thus, carbamate-protected diamines were reacted with (2,2-dibromovinyl)benzene under standard conditions, but instead of the expected cyclic ketene aminals, protected tetrahydropyrazine derivatives were isolated in moderate yields (37−43%) (Scheme 415). The mechanism of the reaction was also investigated, and experimental results appeared to indicate that the reaction proceeds through a cross-coupling/dehydrobromination/hydroamidation sequence (Scheme 416).

Urabe and co-workers have recently reported a concise preparation of 1,4-diaza (or partially oxa)-2-cycloalkenes based on a copper-catalyzed double amination of haloacetylenes.[342] Moreover, it was found that by a convenient modification of the above transformation, *gem*-dibromoolefins worked equally well to produce tetrahydropyrazines in good yields (Scheme 417). The proposed reaction course most likely involved the in situ formation of bromoacetylenes via the dehydrobromination of dibromoolefins under the basic reaction conditions, followed by *N*-alkynylation (Scheme 417). The second amination of the acetylenic bond proceeded in a 6-*endo*-*dig* manner under copper catalysis to produce the final products. Thus, the global process results in a formal C−N/C−H coupling sequnce of the dihaloalkene moiety of the substrate.

3.4.8. Tandem C−S/C−C Coupling. Lautens and co-workers have disclosed a tandem catalytic reaction of a *gem*-dihalovinyl thiophenol system in which an intramolecular S-vinylation is paired with an intermolecular C−C bond-forming reaction (Suzuki−Miyaura, Heck, or Sonogashira reaction) to yield 2-substituted benzothiophenes.[343] After extensive optimization, it was found that by treatment in a sealed tube of 2-(2,2-dibromovinyl)benzenethiol with 1.7 equiv of organoboronic

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

acids (10 examples) or other organoboron reagents (4 examples) in the presence of $PdCl_2$ (3 mol %) and sphos (3 mol %), 2-substituted benzothiophenes were obtained in high yields (Scheme 418).

The utility of the methodology was verified by examining substituent effects in the thiophenol substrate (Scheme 419). Thus, thiophenols **639** were reacted with 2,3-dimethoxyboronic acid under standard conditions. In contrast to the boronic acid, the electronic nature of the thiophenol fragment had a significant effect on the outcome of the reaction. Thus, for instance, the nitro substituent did not give the tandem coupling product but instead produced the 2-bromobenzothiophene derivative in moderate yield (46%). Moreover, starting materials with halogen substituents in the benzene ring were found to react unselectively at all bromine-substituted positions, and the corresponding diarylated products were obtained. The reactivity of dichlorovinyl substrates was similar to that of the dibromo counterparts.

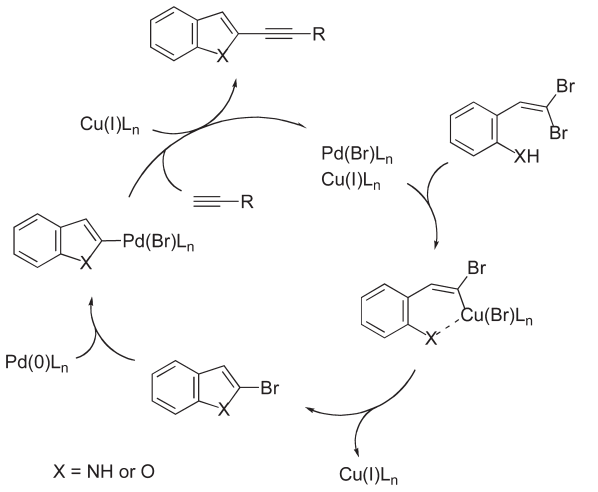
The method was also extended from Suzuki−Miyaura coupling reactions to other Pd-catalyzed cross-coupling processes.[343] The tandem C−S coupling/Heck reaction of 2-(2,2-dibromovinyl)benzenethiol with *N*-acryloylmorpholine or 1-decen-3-ol proceeded under Jeffrey-type conditions[344] to give the corresponding product in 75% and 69% yield, respectively (Scheme 420). The substrate was also amenable to a tandem C−S coupling/Sonogashira reaction. The treatment of **639** with a terminal alkyne under Pd-catalyzed conditions in the presence of CuI gave the product of the tandem reaction in moderate yields (Scheme 420). Notably, this reaction could be catalyzed by Pd/C, which is a vastly preferable precatalyst to more expensive and air-sensitive Pd(0) or Pd(II) complexes. Some results provided evidence of the mechanism that the present transformation proceeds through reductive elimination from a thiopalladium species, rather than through addition of the thiol to an intermediate alkyne formed by elimination of HBr.[345]

Very recently, Alper and Zeng have developed a strategy for the synthesis of 2-carbonylbenzo[*b*]thiophene derivatives **641** based on a one-pot Pd-catalyzed intramolecular C−S coupling/intermolecular carbonylation reaction sequence from 2-*gem*-dibromovinylthiophenols **639** (Scheme 421).[346] After optimizing reaction conditions that implied the use of both the bulky electron-rich Ruphos (other bulky electron-rich phosphine such as XPhos and DavePhos were effective as well, albeit giving lower yields) and inorganic bases, such as K_2CO_3 instead of oganic bases such as Et_3N, under 150 psi of CO, they obtained a variety of benzo[*b*]thiophene-2-carboxylates and benzo[*b*]thiophene-2-carboxamides in moderate to good yields varying both nucleophiles and the thiophenol backbone (Scheme 421).

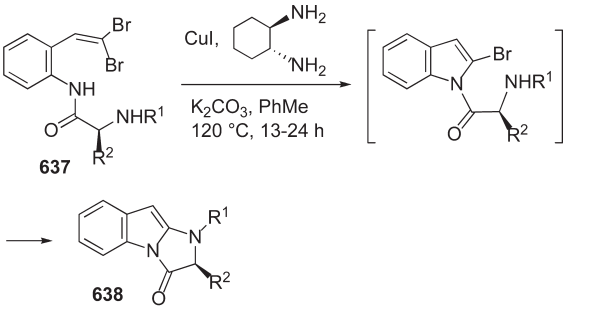
The proposed mechanism for the formation **641** is depicted in Scheme 422. The key point that provided insight into the mechanism of this process was that the six-membered thiolactone **643**, potentially formed from the intermediate **642** via CO insertion into the C−Pd bond, was not detected in all cases, probably because the seven-membered transition state was unfavorable relative to the formation of the five-membered 2-halobenzo[*b*]thiophene **644**. Moreover, the conversion of **639** into the product **641** was not quantitative, and **644** was detected as a byproduct.

3.4.9. Tandem C−S/C−N Coupling. Chen and co-workers have recently reported a concise and practical preparation of imidazol[2,1-*b*]thiazole and related N-fused heterocyles based on a copper-catalyzed 1,2-aminothiolation of 1,1-dihaloalkenes (Schemes 423 and 424).[347] Under the optimized conditions (10 mol % CuI, 15 mol % DMEDA, and 2−5 equiv of Bu_4NF),

Scheme 410



Scheme 411



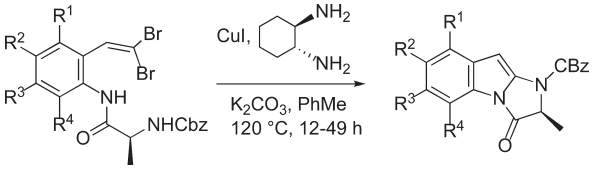
	R^1	R^2	**638** yield (%)	ee (%)
a	CBz	Me	84	86
b	Boc	H	74	
c	CBz	$PhCH_2$	73	76
d	CBz	*i*-Pr	63	4[a]
e	CBz	*i*-Bu	68	89
f	CBz	$BnO_2C(CH_2)_2$	71	6
g	CBz	$BocHN(CH_2)_4$	69	93

[a]The ee of the starting material was 4%

the aminothiolation of 1,1-dihaloalkenes with 2-mercaptobenzoimidazole was found to be quite general with respect to the substituents, giving the products in 67−90% yields (Scheme 423). However, while (hetero)aryl and alkenyl 1,1-dibromoalkenes underwent aminothiolation to give exclusively isomers **645**, linear aliphatic olefins furnished isomers **646** as the major products, except in the case of the *t*-Bu substituent. The methodology was also applied with success to the aminothiolation of unsubstituted and substituted 2-mercaptoimidazole, perimidine, and pyrimidine derivatives with aromatic and aliphatic dibromoalkenes (Scheme 424). Most probably the reaction involved 1-bromoalkyne intermediates, generated in situ from dehydrohalogenation of 1,1-dibromoalkenes. 1-Bromoalkynes derived from aromatic substrates underwent copper-catalyzed C−S coupling to give alkynyl thioethers, while a C−S coupling took place with 1-bromoalkynes from aliphatic substrates to

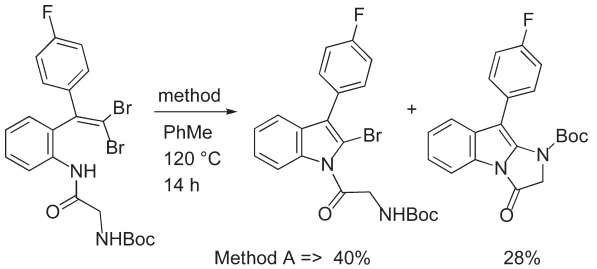
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 412



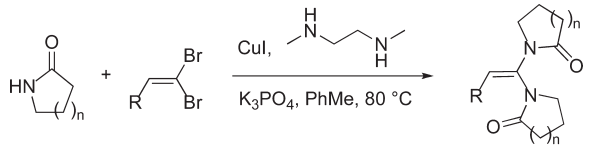
R^1	R^2	R^3	R^4	yield (%)	ee (%)
Me	H	H	H	78	73
H	OBn	OBn	H	69	89
H	H	CF_3	H	67	64
OBn	OMe	H	H	67	81
H	H	F	H	65	89
H	H	H	OMe	56	28

Scheme 413



Method A: CuI (2.5 mol%), *trans*-cyclohexane-1,2-diamine (5 mol%) K_2CO_3 (2 equiv)
Method B: CuI (10 mol%), *trans*-cyclohexane-1,2-diamine (20 mol%) K_2CO_3 (2 equiv)

Scheme 414

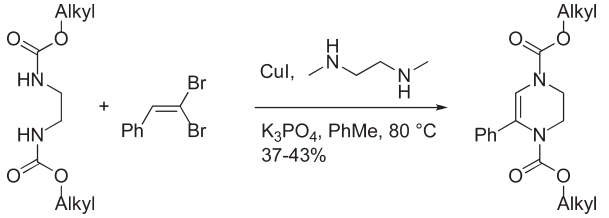


n	R	yield (%)	*n*	R	yield (%)
1	Ph	94	1	(*Z*)-PhCH=CH	85
1	4-$MeOC_6H_4$	56	1	$(TBPOS)OCH_2$	51
1	3-$O_2NC_6H_4$	60	1	*n*-C_8H_{17}	0
1	2-naphthyl	58	0	Ph	84
1	2-thienyl	73			

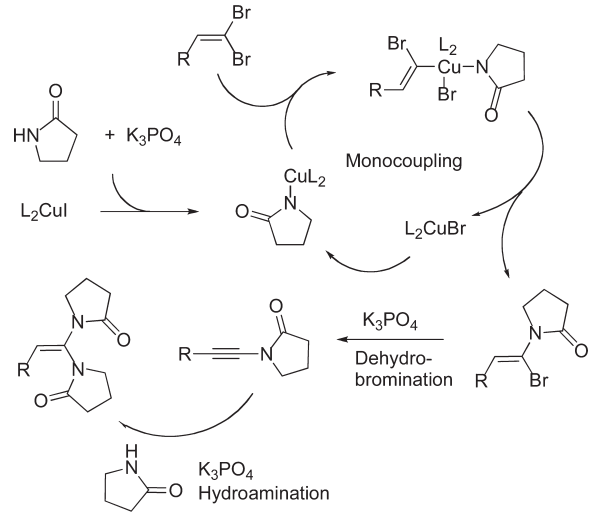
afford ynamides (Scheme 425). In both cases, formation of the products was achieved via a 5-*endo-dig* cyclization.

3.4.10. Tandem C−P/C−N and C−P/C−O Coupling. Bisseret and co-workers examined the reaction of 2-(2,2-dibromovinyl)aniline **598** and of its *N*-Boc derivative **647** with diethylphosphite in the presence $Pd(OAc)_2$, dppf, and Et_3N. Thus, under these conditions, **647** yielded only a complex mixture, whereas the free aniline **598** gave the phosphorylated-2-indolyl derivative **648a** in 63% yield (Scheme 426).[321]

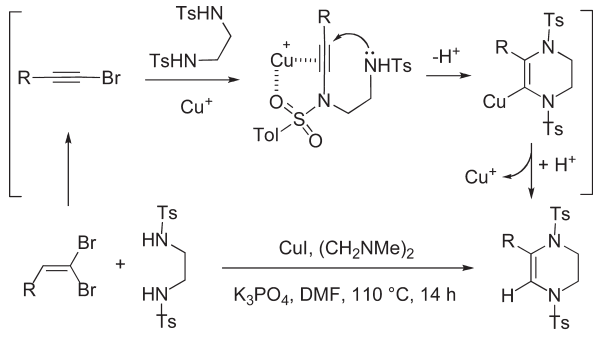
Scheme 415



Scheme 416



Scheme 417

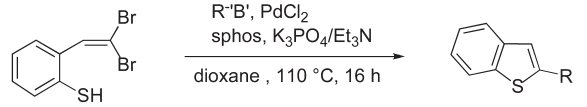


R	yield (%)
n-C_8H_{17}	70
CH_2=$CH(CH_2)_2$	67
$CH_3(CH_2)_4CH(Et)$	71
t-Bu	51

The same research group also examined the Pd-catalyzed reaction ($Pd(OAc)_2$ and dppf or TFP) of vinylphenol derivatives **572** with diethylphosphite under different conditions than those used by Lera and Hayes (Scheme 449) in order to maximize the benzofuran formation (Scheme 427).[321] The reaction afforded in every case a mixture of the alkyne **650** and the phosphorylated benzofuran **651**. The best yield of **651** was obtained starting from the 2-(2,2-dibromovinyl)phenol

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

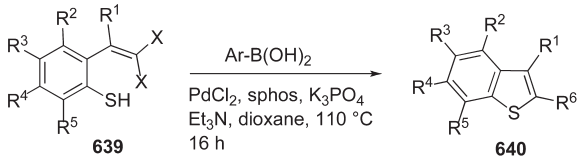
Scheme 418



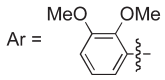
R-'B'	yield (%)	R-'B'	yield (%)
4-FC_6H_4-$B(OH)_2$	91	3-thienyl-$B(OH)_2$	99
3-ClC_6H_4-$B(OH)_2$	83	3-furyl-$B(OH)_2$	96
4-AcC_6H_4-$B(OH)_2$	84	2-MeO-3-quinolinyl-$B(OH)_2$	83
3-$O_2NC_6H_4$-$B(OH)_2$	76	(*E*)-PhCH=CH-$B(OH)_2$	87
2-MeC_6H_4-$B(OH)_2$	82	Ph-BF_3K	84
Ph-B(O)O	80	CH_2=CH-BF_3K	85
		Et_3B	80

Only representative examples are reported

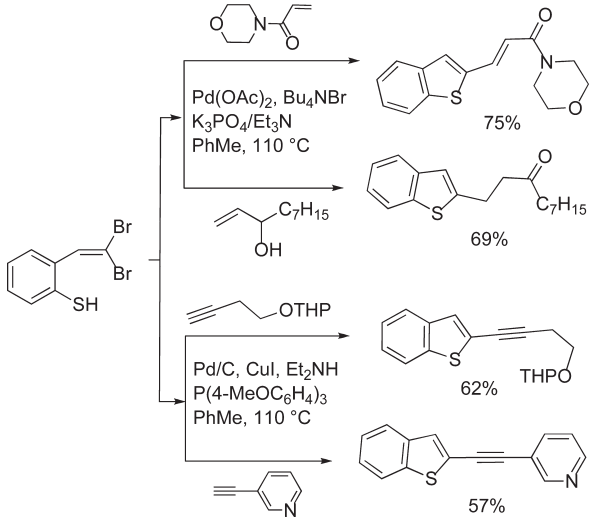
Scheme 419



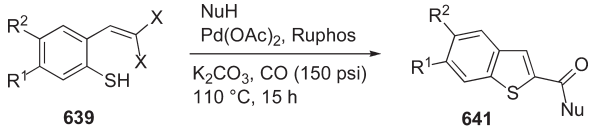
R^1	R^2	R^3	R^4	R^5	R^6	**640** yield (%)	from **639**
H	Ar	H	H	H	Ar	76%	X = Br, R^2 = Cl
H	H	F	H	H	Ar	78%	X = Br
H	H	Ar	H	H	Ar	84%	X = Br
H	H	Me	H	H	Ar	84%	X = Br
H	H	NO_2	H	H	Br	46%	X = Br
H	H	H	Ar	H	Ar	90%	X = Br, R^4 = Br
H	H	-OCH_2O-		H	Ar	64%	X = Br
H	H	H	H	CF_3	Ar	45%	X = Br
H	H	H	H	H	Ar	77%	X = Cl
Me	H	H	H	H	Ar	81%	X = Cl



Scheme 420



Scheme 421



X	R^1	R^2	NuH	**641** yield (%)
Br	H	H	MeOH	73
Br	H	H	PhOH	24
Br	H	H	*n*-$C_6H_{13}NH_2$	54
Br	H	H	*t*-$BuNH_2$	58
Br	Cl	H	CH_2=$CHCH_2NH_2$	64
Br	H	F	MeOH	44
Br	H	OMe	MeOH	57
Br	-OCH_2O-		MeOH	70
Cl	H	H	MeOH	52

Only representative examples are reported

572 and running the reaction in toluene in the presence of Et_3N as the base and dppf as the ligand.

3.5. Conversion to Alkynes

3.5.1. Disubstitued Alkynes and Poliynes. 1,1-Dibromoalkenes have been used as equivalents of 1-bromo-1-alkynes in Pd-catalyzed reactions. Zapata and Ruiz described for the first time that the Stille coupling of 1-(2,2-dibromovinyl)benzene with 1-propenyltributyltin in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ and CuI afforded an *E*/*Z* mixture in a 26:74 ratio of the enyne **652** in 39% yield (Scheme 428).[348] To explain the unexpected formation of this product, a possible pathway was proposed, where initial dehydrobromination of the *gem*-dibromide gives a ω-bromophenylacetylene, which in turn reacts with 1-propenyltributyltin to produce enyne **652**.

Shen and Wang reported the Stille reaction of 1,1-dibromoalkenes with aryl- and vinyl-stannanes.[247] Depending on the reaction conditions, (*Z*)-1-aryl(alkenyl)-1-bromoalkenes or internal alkynes were formed (Scheme 191). After a systematic investigation to determine the optimal reaction conditions, it was found that when the coupling reactions of a variety of dibromides with $PhSnMe_3$ were performed with catalytic $Pd_2(dba)_3$, TFP, and diisopropylethylamine (used to neutralize the HBr generated from the reaction) in DMF and *i*-PrNEt, alkynes **653** were obtained in good to excellent yields (Scheme 429). Alkyne formation was unaffected by the electronic character or position of the substituents on the 1,1-dibromoalkene. Poorly reactive phenylstannane favored the formation of the alkynes **653**, regardless of which ligand was used, whereas more reactive organostannanes (vinyl, furyl) required, for the formation of the alkynes **653**, the very electron-rich ligand $P(4\text{-}MeOC_6H_4)_3$.

The proposed mechanism for the formation of alkynes **659** or monobromides **660** is shown in Scheme 430. In highly dipolar, coordinating solvents such as DMF, the complex **654**, formed by initial oxidative insertion of the *gem*-dibromide into Pd(0), may undergo ligand/solvent exchange to form complex **655**. The Pd−C bond in **654**, and especially in **655**, is polarized by the solvent, which may lead to the formation of the Pd-carbenoid **656** (path a). The highly dipolar solvent also stabilizes the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

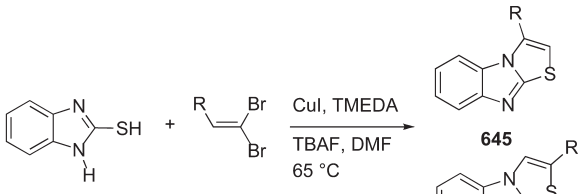
complex **656**, which favors its formation. Rearrangement of **656** results in the formation of the complex **657**, which loses HBr to form the alkynyl Pd-species **658**. Alternatively, elimination of HBr from either the complex **654** or **655** could also occur to give the complex **658** (path b). Coupling of **658** with a stannane affords the alkyne **659**. The rate of transmetalation determines the formation of either the monobromide **660** or terminal alkyne **659**. When $PhSnMe_3$, a slow transmetalating stannane, is used in the Stille reaction in a highly dipolar solvent, alkynes **659** are the products regardless of which ligand is used. When fast transmetalating organostannanes, such as 2-(tributylstannyl)furan and tributyl(vinyl)tin, are used in the reaction, monobromides **660** are formed even in DMF with the TFP ligand (path c). On the other hand, a very electron-rich ligand, $P(4\text{-}MeOC_6H_4)_3$, promotes much slower transmetalation than TFP and leads to the exclusive formation of alkynes **659** regardless of which stannane is used.

This method was also followed to construct the *trans*-chlorocyclopropane dienyne fragment of the antitumor agent callipeltoside (Scheme 431).[349] Thus, when diene stannanes were employed in the coupling with (1*R*,2*S*)-1-chloro-2-(2,2-dibromovinyl)cyclopropane under Shen conditions,[247] the related dienynes were obtained in 80−95% yields.

Next, Shen and Thomas developed an extension of their methodology to the synthesis of both symmetric and unsymmetric 1,3-diynes.[350] Under optimized reaction conditions [$Pd_2(dba)_3$ (2.5 mol %), TFP (15 mol %), CuI (20 mol %), and *i*-Pr_2NEt (2.5 equiv)] the homocoupling of 1,1-dibromoalkenes to give the symmetric 1,3-diynes **661** proceeded in moderate to good yields (Scheme 432). The homocoupling was catalyzed by a weak ligand, TFP, and the addition of a catalytic amount of CuI accelerated the reaction. When this protocol was applied to the Sonogashira reaction, a mixture of products was obtained, with the major product being the 1,1-diynyl-1-alkene **665** (Scheme 433). However, when the very electron-rich phosphine $P(4\text{-}MeOC_6H_4)_3$ was used as the ligand, good yields of the desired unsymmetric diynes **664** were obtained without CuI. When the optimal reaction conditions [$Pd_2(dba)_3$ (1 mol %), $P(4\text{-}OMeC_6H_4)_3$ (4 mol %) and Et_3N (3 equiv)] were determined, a wide variety of unsymmetric 1,3-diynes **664** were produced (Scheme 433).

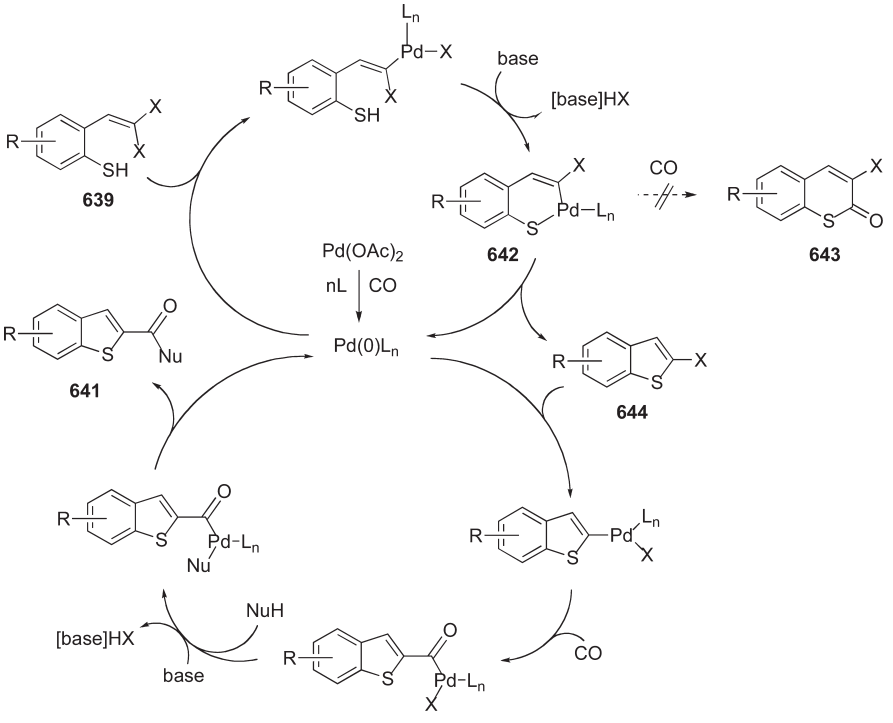
A plausible mechanism for the reaction was proposed (Scheme 434). The 1,1-dibromoalkene undergoes normal Pd insertion to give the intermediate **654**. In a highly dipolar solvent such as DMF and in the presence of a base, **654** transforms into the alkynylpalladium **658** (Scheme 430). In the absence of both CuI and a terminal alkyne, **658** would yield the homocoupling **661**, with a mechanism similar to the homocoupling of aryl

Scheme 423



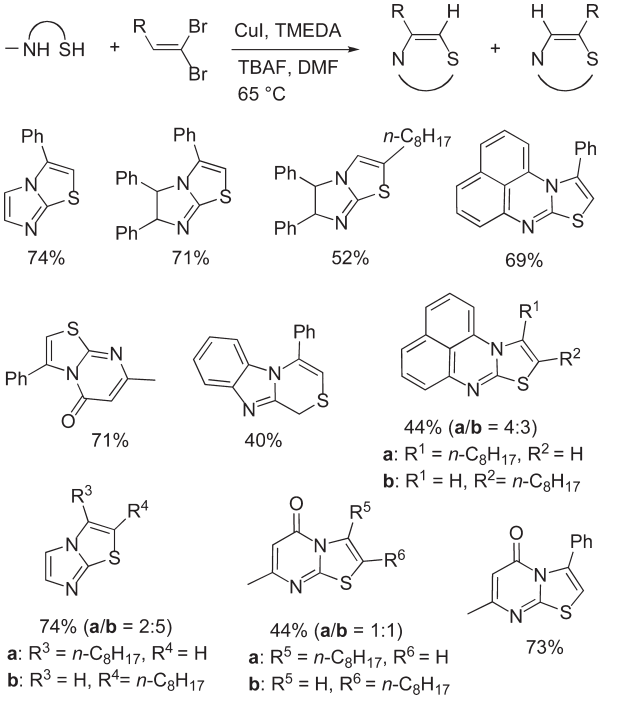
R	645,646 yield (%)	645/646	R	645,646 yield (%)	645/646
Ph	75	100:0	2-furyl	76	100:0
4-$MeOC_6H_4$	74	100:0	(*E*)-PhCH=CH_2	80	100:0
4-$O_2NC_6H_4$	90	100:0	*n*-C_8H_{17}	81	13:87
4-ClC_6H_4	81	100:0	*n*-C_6H_{13}	72	14:86
4-MeC_6H_4	86	100:0	*i*-Bu	79	14:86
2-naphthyl	67	100:0	*c*-C_6H_{11}	70	20:80
2-pyridyl	82	100:0	*t*-Bu	70	75:25
2-thienyl	86	100:0			

Scheme 422

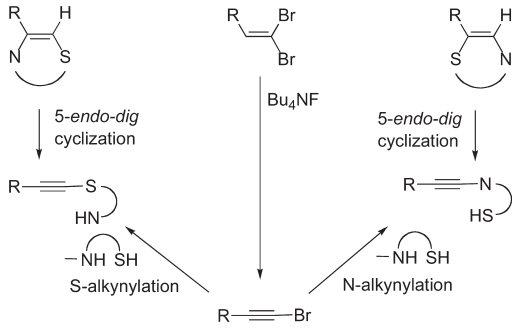


dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

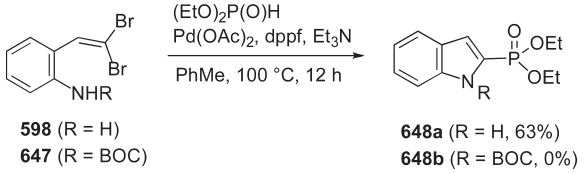
Scheme 424



Scheme 425

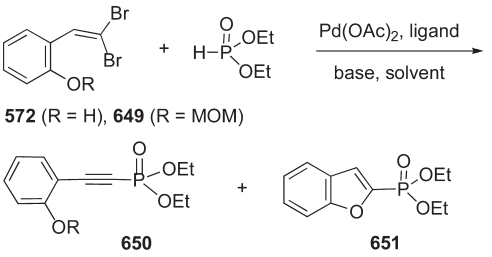


Scheme 426



halides. In the presence of CuI, the palladium in **658** may interchange with Cu(I) to give alkynylcopper **666**, which couples with **658** at much faster rate to give product **661**. This may explain the catalytic role of CuI. Because the alkynylcopper **666** couples fast with organopalladium species, formation of the monobromide **667** from the coupling of **654** and **658** becomes competitive with the transformation of **654** to **658**. Further coupling of **667** with **666** results in the product **662**. The homocoupling also produces Pd(II) species, which are reduced

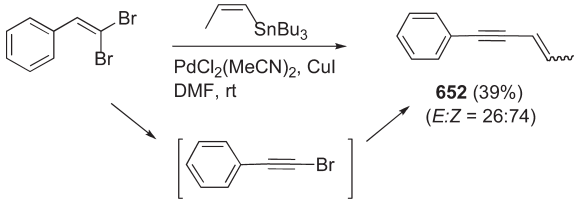
Scheme 427



R	base	solvent	T (°C)	ligand	650/651	yield (%)
H	Et_3N	PhMe	100	dppf	1/1	91
H	Et_3N	DMF	80	dppf	1/1	60
MOM	None	DMF	80	dppf	degradation	--
MOM	PO[a]	DMF	80	dppf	2/1	65
MOM	PO	PhMe	100	dppf	1/1	75
MOM	PO	PhMe	100	TFP	no react	--

[a]PO: propylene oxide

Scheme 428



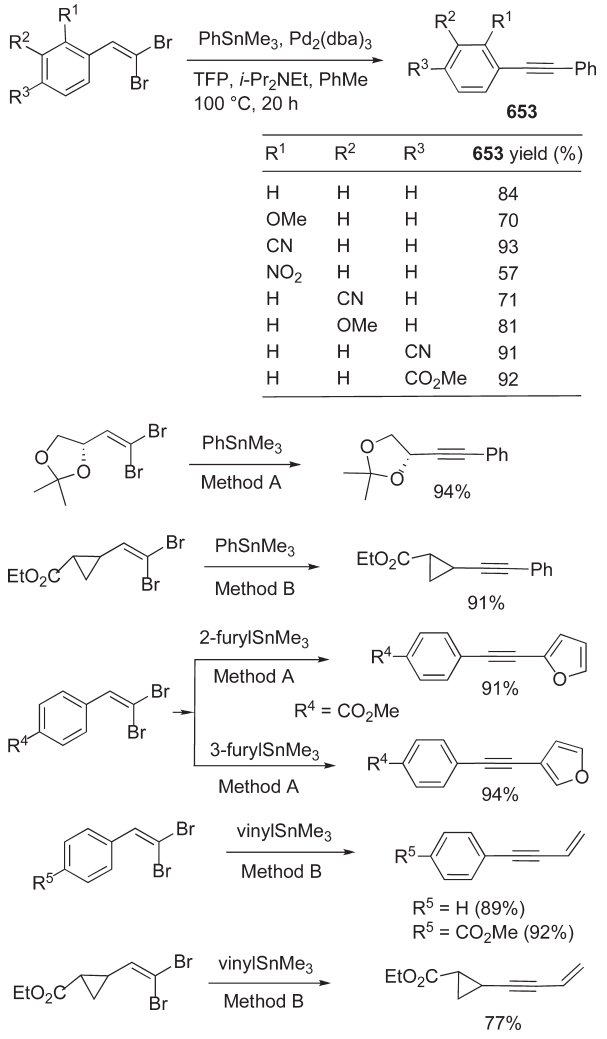
by Et_3N to Pd(0) species to complete the palladium cycle. A parallel mechanism could be derived from the formation of unsymmetric 1,3-diynes **664** and byproduct **665**, as also shown in Scheme 432. The palladium cycle in these reactions ends with Pd(0) species, so that no reduction of Pd(II) species is necessary.

Tykwinski and co-workers have recently reported that by a one-pot protocol, triynes and tetraynes were formed from the reaction of a dibromovinyl triflate with a terminal alkyne under Pd-catalyzed cross-coupling conditions (Schemes 435 and 436).[41a] While initial attempts toward Sonogashira coupling of the vinyl triflate **668** with alkynes led only to a mixture of products resulting from an indiscriminate cross-coupling of the alkyne with both the triflate and dibromoolefin groups, it was next found that the reaction could bring triynes. After several attempts, a reasonably optimized set of conditions, consisting in the use of $Pd(OAc)_2$ (10 mol %) in combination with $P(t\text{-}Bu)_3$ (20 mol %), CuI (20 mol %), and $i\text{-}Pr_2NH$ (4 equiv), allowed the vinyl triflate **668** to be cross-coupled with several terminal alkynes and diynes to give triynes in moderate yields (0−68%). The potential usefulness of this procedure was next extended toward longer polyynes **671** by reaction of **668** with substrates **670** bearing the 1,1-dibromovinyl moiety, leading also in this case to triynes and tetraynes in 31−50% yields (Scheme 436).

The domino coupling reactions of 1,1-dibromoalkenes with triarylbismuth nucleophiles has been very recently demonstrated to furnish disubstituted alkynes directly under catalytic palladium conditions.[351] The coupling of triarylbismuths as multicoupling nucleophiles with 3 equiv of 1,1-dibromoalkenes afforded high yields of alkynes in a short reaction time. Some representative results, among the 33 alkynes described, are reported in

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

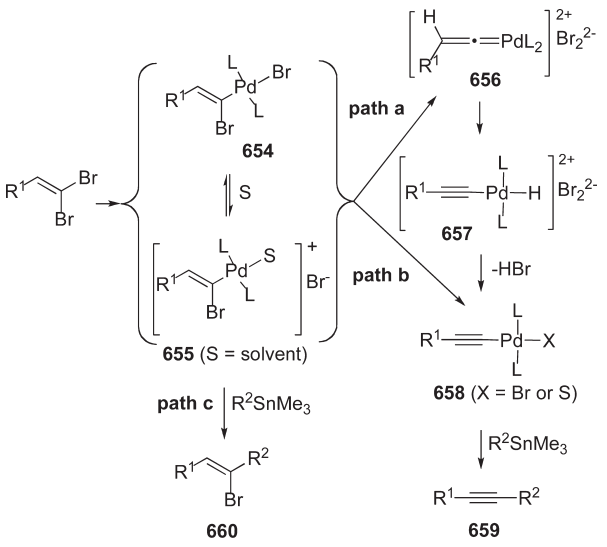
Scheme 429



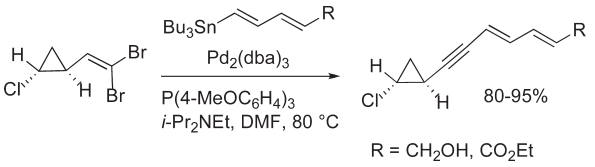
R^1	R^2	R^3	**653** yield (%)
H	H	H	84
OMe	H	H	70
CN	H	H	93
NO_2	H	H	57
H	CN	H	71
H	OMe	H	81
H	H	CN	91
H	H	CO_2Me	92

Method A: $Pd_2(dba)_3$, TFP, *i*-Pr_2NEt, DMF, 80 °C, 10 h
Method B: $Pd_2(dba)_3$, $P(4\text{-}MeOC_6H_4)_3$, *i*-Pr_2NEt, DMF, 80 °C, 10 h

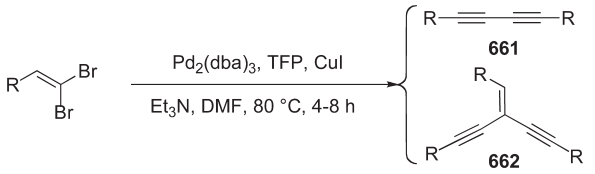
Scheme 430



Scheme 431

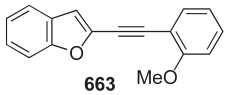


Scheme 432



R	**661**,**662** yield (%)	**661**/**662**
$4\text{-}MeO_2CC_6H_4$	89	93:7
Ph	71	100:0
$4\text{-}MeOC_6H_4$	98	88:12
$3\text{-}MeOC_6H_4$	86	100:0
$2\text{-}MeOC_6H_4$	61	64:36[a]
3-pyridyl	77	100:0
$c\text{-}C_6H_{11}$	82	100:0
t-Bu	91	80:20
EtO_2C	50	100:0

[a]In this case the ratio refers to **661**/**663**.



663

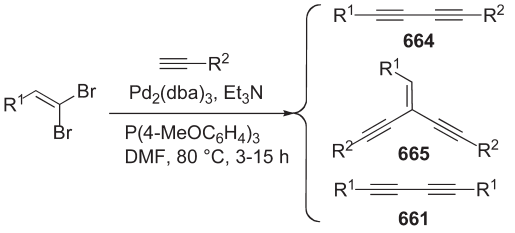
Scheme 437. The versatility of this reaction has been additionally demonstrated in di- and tricouplings, and an interesting example is illustrated in Scheme 438. The proposed mechanistic cycles for the formation of an internal alkyne in a domino process is depicted in Scheme 439. Since a control reaction involving a two-step protocol demonstrated the facile formation of 1-bromoalkyne from 1,1-dibromoalkene via dehydrobromination and its effective coupling with $BiPh_3$, furnishing an internal alkyne in high yield, the reaction path A was supposed to be favored, although neither path B nor other possibilities could be excluded.

Oh and Lim were able to perform the double alkenylation of 1,1-dibromoalkenes under Suzuki−Miyaura conditions at 50 °C but found that when the same coupling was performed at a higher temperature, alkynes could be obtained. Thus when (2,2-dibromovinyl)benzene was heated at 120 °C with various organoboronic acids (1.2 equiv) in the presence of $Pd(PPh_3)_4$ (3 mol %) and Na_2CO_3 (6 equiv), the related alkynes were isolated in 46−85% yields (Scheme 440).[300]

Two protocols for the one-pot synthesis of internal alkynes in good to excellent yields from 1,1-dibromoalkenes have been recently reported. These methods hinge upon the Suzuki−Miyaura coupling followed by dehydrobromination of the intermediate coupled products (Scheme 441).[352,353] In the former the couplings were carried out by using the Shen protocol ($Pd_2(dba)_3$/TFP), followed by addition to the converted dibromides of $Bu_4N(OH)\cdot 30H_2O$ (5 equiv) and heating at 65 °C for 1 h

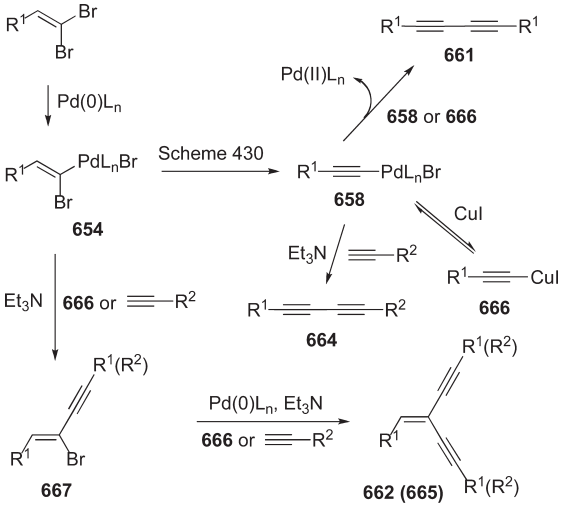
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 433



R^1	R^2	**664**,**665**,**661** yield (%)	**664**/**665**/**661**
4-$MeO_2CC_6H_4$	SPIT	82	96:0:4
4-$MeO_2CC_6H_4$	n-C_5H_{11}	97	91:0:9
4-$MeO_2CC_6H_4$	4-$MeOC_6H_4$	98	65:23:12
4-$MeO_2CC_6H_4$	$HO(CH_3)_2C$	77	92:0:8
4-$MeO_2CC_6H_4$	2-pyridyl	62	74:0:26
4-$MeO_2CC_6H_4$	EtO_2C	16	0:0:100
2-$MeOC_6H_4$	Ph	95	77:0:23
2-$MeOC_6H_4$	SPIT	94	72:0:28
	Ph	75	63:9:28
	TIPS	91	75:0:25
	Ph	62	100:0:0
	TIPS	78	87:0:13

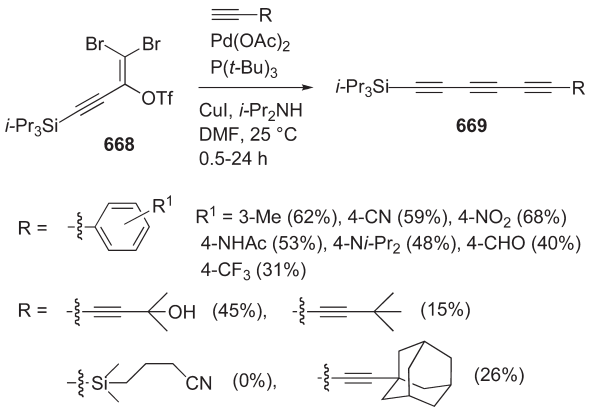
Scheme 434



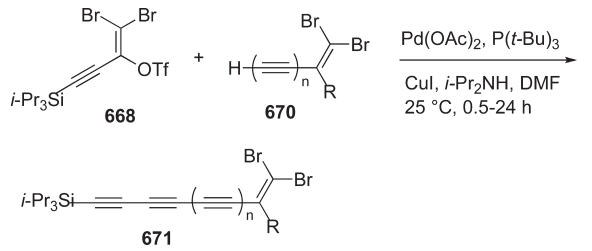
(method A, Scheme 191).[352] In the latter, the alkynes were obtained in a one-pot, one-step process in the presence of the cyclobutene-1,2-bis(imidazolium) salt **672** (3 mol %), $Pd(OAc)_2$ (3 mol %), and KO*t*-Bu (3 mol %) in the temperature range of 65−90 °C (method B, Scheme 441).[353]

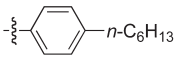
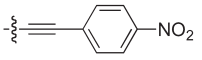
Piguel and co-workers have recently disclosed that 1,1-dibromoalkenes can be employed as alkynyl equivalents in the copper-catalyzed direct alkynylation of azoles (Schemes 442 and 443).[354] Initially, 5-phenyloxazole was reacted with various (hetero)aryl and alkenyl 1,1-dibromoalkenes in the presence of

Scheme 435

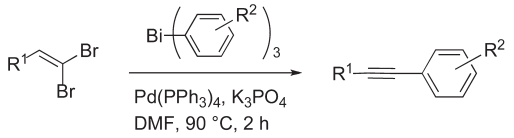


Scheme 436



n	R	**671** yield (%)	n	R	**671** yield (%)
1	Sii-Pr_3	50	2		49
1	n-Bu	31	2		49

Scheme 437

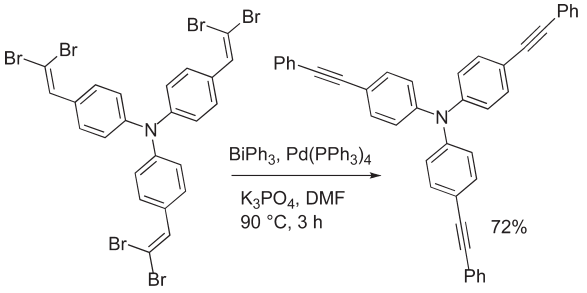


R^1	R^2	yield (%)	R^1	R^2	yield (%)
Ph	4-OMe	84	2-naphthyl	H	80
4-$MeOC_6H_4$	H	83	2-pyridyl	H	81
4-NCC_6H_4	4-Me	81	2-thienyl	3-OMe	81
4-$O_2NC_6H_4$	H	60	c-C_6H_{11}	4-COMe	60
4-ClC_6H_4	H	64	2-furyl	4-OMe	73
4-$(Me_2N)C_6H_4$	4-OMe	63	Ph$(CH_2)_3$	4-OMe	70
3,4-$(MeO)_2C_6H_3$	H	79			

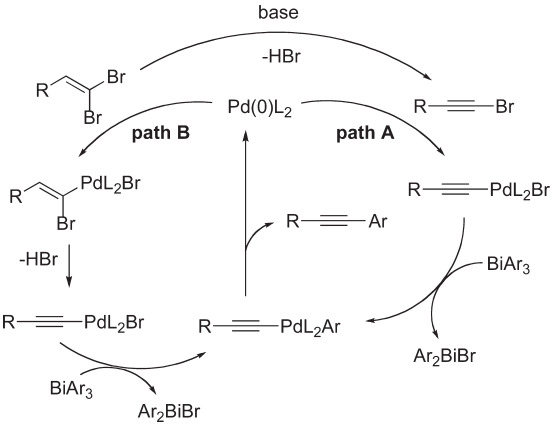
CuBr·SMe_2 (5 mol %), dpephos (10 mol %), and LiO*t*-Bu (6 equiv), to give the related 2-alkynyl-5-phenyloxazols in moderate to good yields (Scheme 442). However, these conditions were not found to be applicable to 1,1-dibromoalkenes bearing a simple alkyl substituent but were effective with other substituted phenyloxazols and additional heterocycles, such as benzoxazole, benzothiazole, 1,2,4-triazole, and *N*-benzyl-6-chloropurine (Scheme 443). A mechanism for the reaction was also proposed

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

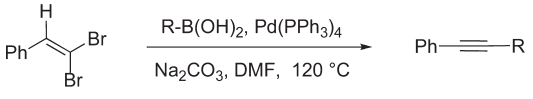
Scheme 438



Scheme 439

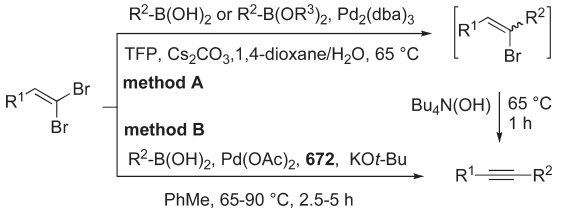


Scheme 440



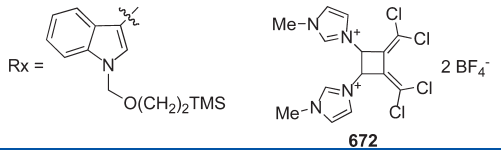
R	yield (%)	R	yield (%)
n-BuCH=CH	77	PhCH=CH	70
t-BuCH=CH	82	Ph	85
$HO(CH_2)_4CH=CH$	46		

Scheme 441



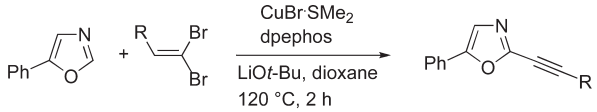
R^1	R^2	method	yield (%)
$4\text{-}MeOC_6H_4$	Ph	A	56
$4\text{-}O_2NC_6H_4$	Ph	A	82
3-pyridyl	Ph	A	67
3-pyridyl	Ph	B	83
2-furyl	Ph	A	79
$3\text{-}MeC_6H_4$	3-pyridyl	A	48
3-pyridyl	3-pyridyl	A	82
3-pyridyl	5-Me-thien-2-yl	A	67
c-C_5H_9	Ph	B	73
PhCH=CH	Ph	B	74
9-anthranyl	$2\text{-}MeC_6H_4$	B	79
Rx	Ph	B	69

Only representative examples are reported



672

Scheme 442



R	yield (%)	R	yield (%)
Ph	70	$3\text{-}BrC_6H_4$	63
$4\text{-}PhC_6H_4$	60	$4\text{-}FC_6H_4$	65
$4\text{-}F_3CC_6H_4$	59	$3\text{-}O_2NC_6H_4$	44
$4\text{-}NCC_6H_4$	48	$3,4\text{-}(MeO)_2C_6H_3$	67
2-thienyl	73	(*E*)-PhCH=CH	67
2-furyl	61	$4\text{-}((EtO)_2CH)C_6H_4$	55
1-naphthyl	81		

taking into account two possible pathways (Scheme 444). On the basis of some experimental evidence, they supposed that the direct alkynylation with 1,1-dibromoalkenes proceeds through path b.

Evano and co-workers have very recently found that after reaction optimization, 1,1-dibromoalkenes dimerize readily in the presence of copper iodide (0.5 equiv), *N*,*N*-dimethylethane-1,2-diamine (1 equiv), and Cs_2CO_3 (3 equiv) in DMF to give symmetrical 1,3-diynes (Scheme 445).[355] The reaction was found to be selective and rather general, furnishing the corresponding diynes in moderate to good yields, even with complex and sensitive dibromides, the only exception being the cinnamaldehyde-derived dibromide, which failed to give the corresponding dienediyne, most probably because of the polymerization of the latter during the reaction. A possible mechanism for the reaction was proposed (Scheme 446).[355] The 1,1-dibromoalkene would first undergo copper insertion into the more reactive *trans* C−Br bond to give intermediate **673**, and next in a highly dipolar solvent such as DMF and in the presence of Cs_2CO_3, the alkynylcopper **674** would be formed. Ligand exchange between two alkynylcoppers would then give the dialkynylcopper **675** together with the formation of copper trihalide as one of the final products, which accounts for the stoichiometry (0.5 equiv of copper salt/dibromide) of the reaction. Finally, reductive elimination from **675** would give the 1,3-diyne **661**.

In 1983, Alper and co-workers described the Pd(0)- and phase-transfer-catalyzed carbonylation of vinylic dibromides.[356] When vinylic dibromides derived from aromatic aldehydes were reacted with carbon monoxide, a catalytic amount of Pd(diphos)$_2$, benzyltriethylammonium chloride as a phase-transfer agent, and 5 N NaOH in benzene, diynes **675** were formed in reasonable yields (Scheme 447). The coupling was also applied to the dibromide **676** derived from α-methylcinnamaldehyde, which gave the polyunsaturated hydrocarbon **677** in 41% yield

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

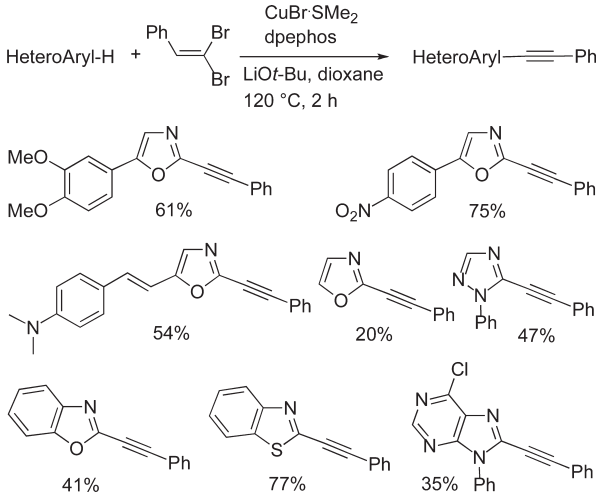
(Scheme 447). On the other hand, when the same process was carried out under different conditions, carboxylic acids **688**−**690** and **691** were obtained in high yields (Schemes 456−458).[357]

An isolated example of direct conversion of a 1,1-dibromoalkene into the related alkyne by Fe catalysis was reported.[271] Thus, when 1,1-dibromonon-1-ene was treated with *i*-PrMgCl in a THF−NMP solution at −10 °C in the presence of $Fe(acac)_3$ (3 mol %) for 30 min, 1-nonyne was obtained in 80% yield (Scheme 448). The mechanism of this reaction was not elucidated but was supposed to probably take place through a Frietsch−Buttenberg−Wiechell rearrangement.[358]

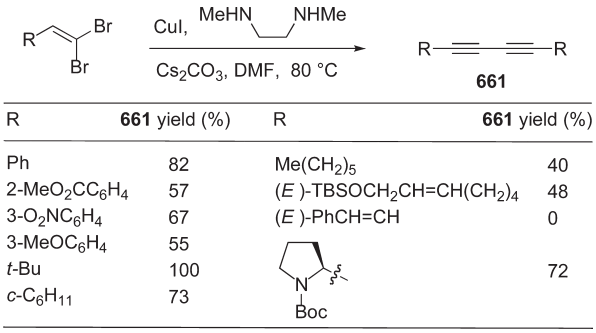
3.5.2. Functionalized Alkynes. A method for the Pd-catalyzed synthesis of alkynylphosphonates from 1,1-dibromoalkenes and dimethyl phosphite has been developed (Scheme 449).[328] In general, the best catalytic system for this transformation was found to be $Pd(OAc)_2$, dppf, and propylene oxide. The use of TFP as the ligand in the coupling reaction was examined, but this led to a reduction in yield in most cases, except with 2-(2,2-dibromovinyl)furan for which the yield of the related alkyne **678** could be improved dramatically from 16% to 60% when the ligand was changed from dppf to TFP. A valuable application of this methodology was the preparation in 52% yield of the nucleotide dimer **681** by coupling of the dibromide **679** with the highly functionalized H-phosphonate **680** (Scheme 450).

A series of ribonucleoside 1-alkynylphosphonates have been recently synthesized following this protocol (Scheme 451).[359] When DMF was used as the solvent, the expected alkynylphosphonates were obtained in 44−76% yields depending on the substituents in the tetrahydrofuran ring, whereas with toluene, a new and unique product corresponding to the bromo-alkenylpho-

Scheme 443

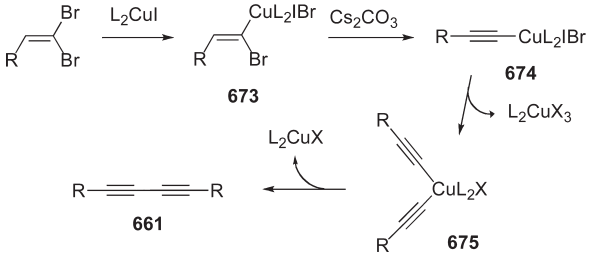


Scheme 445

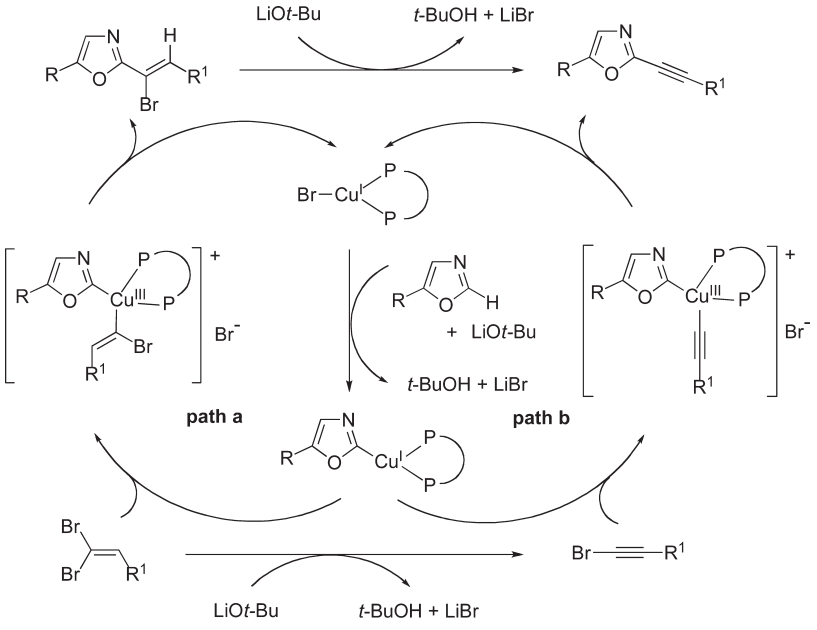


R	**661** yield (%)	R	**661** yield (%)
Ph	82	$Me(CH_2)_5$	40
2-$MeO_2CC_6H_4$	57	(*E*)-$TBSOCH_2CH{=}CH(CH_2)_4$	48
3-$O_2NC_6H_4$	67	(*E*)-PhCH=CH	0
3-$MeOC_6H_4$	55		
t-Bu	100		72
c-C_6H_{11}	73		

Scheme 446

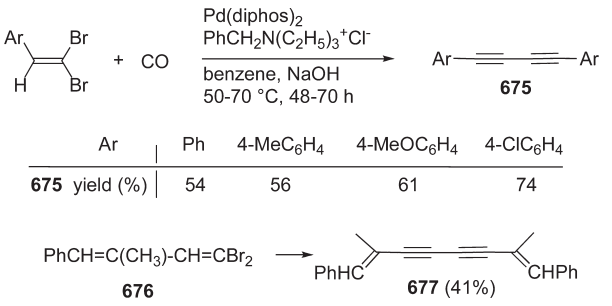


Scheme 444



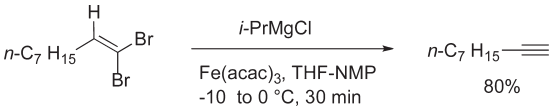
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 447

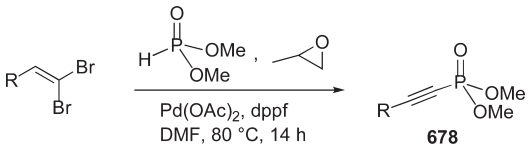


Ar	Ph	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$
675 yield (%)	54	56	61	74

Scheme 448



Scheme 449

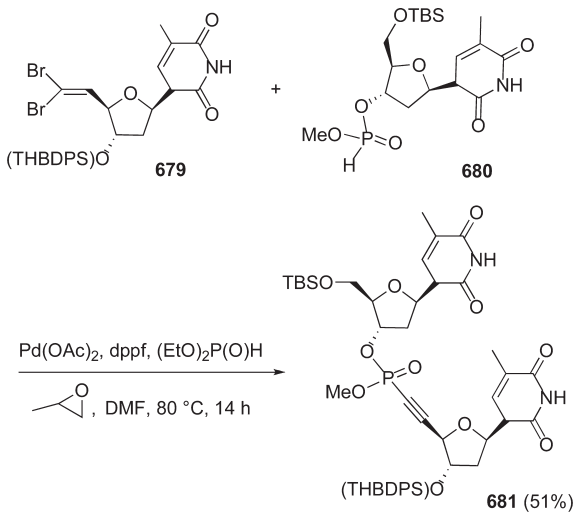


R	yield (%)[a]	R	yield (%)[a]
Ph	76 (35)	2-furyl	16 (60)
4-AcOC$_6$H$_4$	68	*c*-C$_6$H$_{11}$	76 (35)
4-MeOC$_6$H$_4$	73	*n*-C$_7$H$_{15}$	56 (27)
4-O$_2$NC$_6$H$_4$	27 (31)		

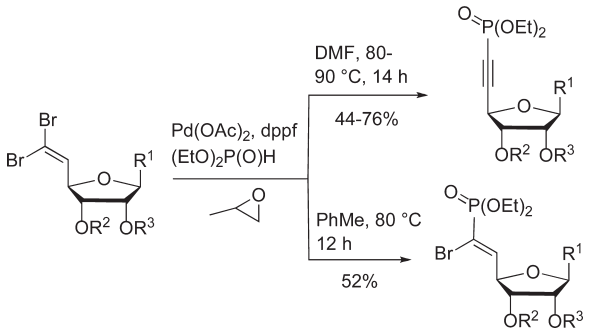
[a]The yields in parenthesis were obtained when dppf was replaced with TFP as the ligand

sphonate was isolated in good yield (52%). A possible mechanism, which accounts for the formation of both alkynyl- and bromo-alkenylphosphonate derivatives, was proposed (Scheme 452). The nature of the solvent appeared as a key parameter of the reaction course as previously observed by Shen co-workers, who reported a ligand effect on the product distribution (i.e., alkyne formation vs monocoupling) (Schemes 191 vs 429).[247] Thus, formation of the alkynylphosphonate **685** could result from two consecutive oxidative Pd(0) insertions. During the first catalytic cycle, the formation of alkynyl bromide derivative **683** (path a) is due to *cis*-β-hydrogen elimination from the bromoalkene Pd complex **682**. Then, a second Pd(0) insertion leads to alkynyl Pd complex **684**, which undergoes coupling with diethylphosphite to afford the desired alkynylphosphonate derivative **685**. A working hypothesis was that in highly dipolar and coordinating solvents such as DMF, the intermediate **685** is efficiently formed (path a), or alternatively an elimination of HBr from complex **682** is favored and leads directly to the formation of the bromo-alkenylphosphonate **686**. Additional experiments carried out in toluene, with a postponed addition of diethylphosphite (47% yield) or increasing amount of Pd catalyst (48% yield), had no effect on the yield of the reaction and did not show the formation of other derivatives than **686**.

Scheme 450



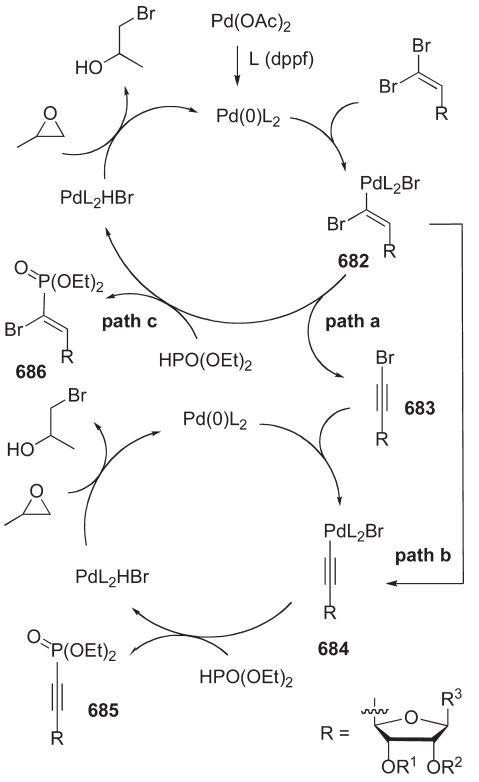
Scheme 451



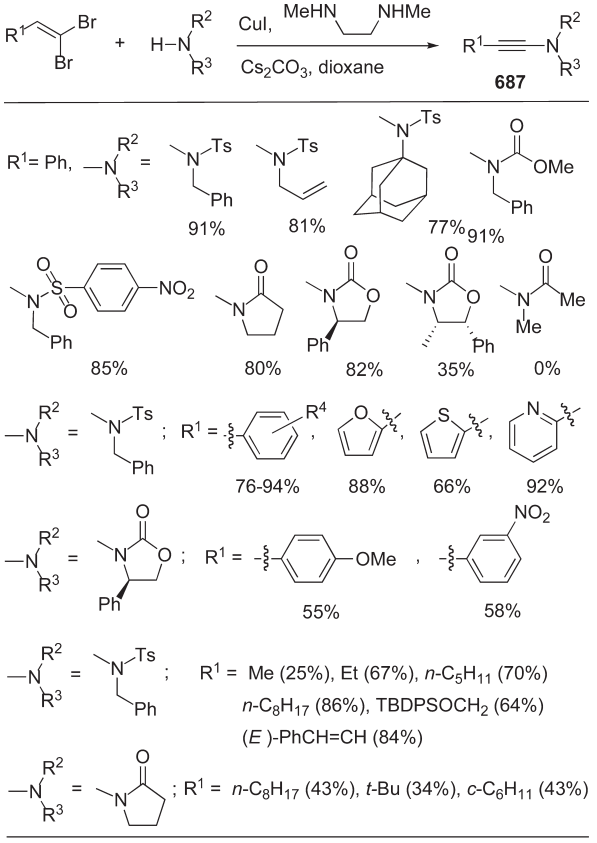
Based on these precedents, Evano and co-workers have very recently reported an attractive preparation of ynamides based on the generation of sp^2 carbenoid intermediates starting from readily available 1,1-dibromoalkenes and their further reaction with nitrogen nucleophiles (Scheme 453).[340] The reaction of various nitrogen nucleophiles with (2,2-dibromovinyl)benzene (1.5 equiv) in the presence of catalytic amounts of CuI (12 mol %), *N*,*N*-dimethylethylenediamine (18 mol %), and Cs_2CO_3 (4 equiv), afforded the related ynamides **687** in good to excellent yields (Scheme 453). In all cases, no formation of products resulting from monocoupling or from dehydrobromination of the starting material was detected. Tosylamines, oxazolidinones, carbamates, and amides were all viable substrates, whereas acyclic secondary amides were not suitable substrates, most likely because of their increased steric hindrance compared with their cyclic homologues and their lower acidity. The reaction was also found to be compatible with a variety of aromatic and heteroaromatic groups present on the 1,1-dibromoalkene moiety (Scheme 453). The scope of the reaction was also investigated with respect to 2-alkyl or 2-alkenyl-substituted 1,1-dibromoalkene coupling partners (Figure 8). As expected, the reaction was found to be more difficult, but good yields of ynamide derivatives were obtained in most cases, even in the presence of bulky substitutents; in the cases of the less reactive pyrrolodin-2-one and acetaldehyde-derived dibromide, the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 452



Scheme 453



Only representive examples are reported

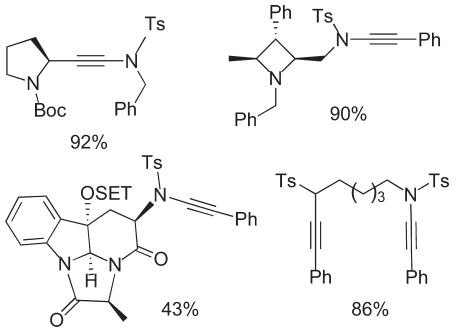
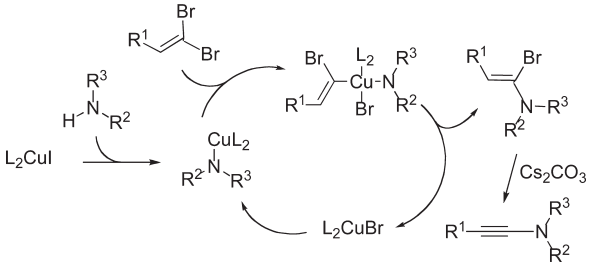
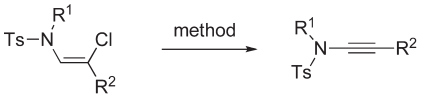


Figure 8

Scheme 454

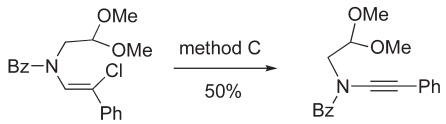


Scheme 455



R^1	R^2	method	yield (%)
3-butenyl	Ph	A	56
3-butenyl	2-$MeOC_6H_4$	B	84
3-butenyl	4-FC_6H_4	B	89
$PhCH_2$	Ph	B	81
$PhCH_2$	2-$MeOC_6H_4$	B	65
$PhCH_2$	3-butenyl	B	65
4-$MeOC_6H_4$	Ph	C	54

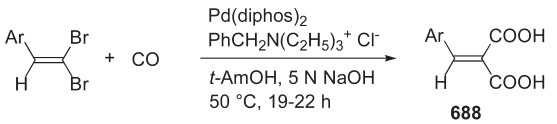
method:
A = LiHMDS, THF, 0 to rt
B = NaOH (50% aq), *n*-$BuNHSO_4$ (10-20%), PhH, rt
C = as method B, but at 50 °C



ynamides were isolated in moderate yields. This protocol was however found to be general since a wide range of aliphatic and vinylic 1,1-dibromoalkenes reacted successfully. Finally, the formation of ynamides from complex substrates was evaluated with success (Scheme 453). A possible simplified mechanism, which accounts for the formation of ynamides from 1,1-dibromoalkenes, was also proposed (Scheme 454).[340] This mechanism is based on the known higher reactivity of the *trans* C−Br bond of dibromides toward oxidative insertion and would involve a

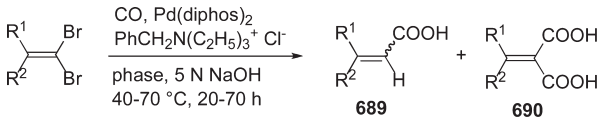
dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

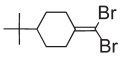
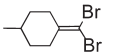
Scheme 456



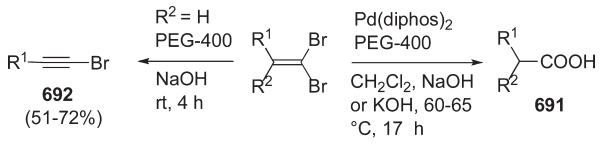
Ar	Ph	4-MeOC$_6$H$_4$
688 yield (%)	93	87

Scheme 457



R^1	R^2	phase	**689**,**690** yield (%)	**689**/**690**
n-C_6H_{13}	H	benzene	55	1:0
c-C_6H_{11}	H	benzene	6	1:0
c-C_6H_{11}	H	*t*-AmOH	32	0:1
$C_2H_5CH(Me)$	H	benzene	64	1:0
$C_2H_5CH(Me)$	H	*t*-AmOH	82	0:1
Ph	Ph	*t*-AmOH	59	1:6
		benzene	84	1:0
		t-AmOH	80	0:1
		benzene	33	1:6
		t-AmOH	28	0:1

Scheme 458

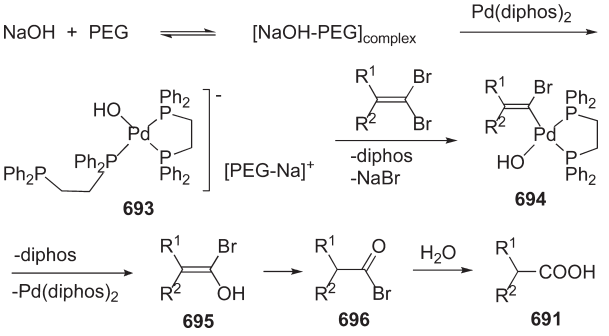


R^1	R^2	**691** yield (%)
Ph	H	95
2-MeC$_6$H$_4$	H	52
4-MeC$_6$H$_4$	H	68
4-ClC$_6$H$_4$	H	35
4-MeOC$_6$H$_4$	H	85
PhCH=CH	H	58
Ph	CH_3	18
-$(CH_2)_2$CH(CH_3)-		23
-$(CH_2)_2$-		42

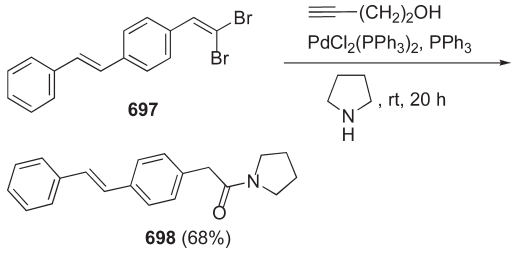
regioselective coupling to yield 1-bromo-1-amino-1-alkenes, whose subsequent dehydrobromination would then give the ynamides. This mechanism was supported by the isolation or not of some key intermediates.

Cossy and co-workers in a study aimed at the synthesis of disubstituted ynamides converted in good yields β-chloroenamides, prepared from β,β-dichloroenamides (Scheme 181), into the related ynamides by an E_2 elimination by treatment with an appropriate base (LiHMDS or NaOH/*n*-BuNHSO$_4$) under different conditions (Scheme 455).[17]

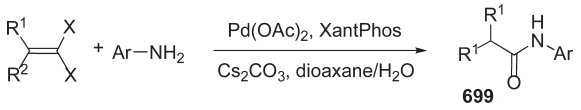
Scheme 459



Scheme 460



Scheme 461



	X	R^1	R^2	Ar	**699** yield (%)
a	Br	Me	Ph	4-MeC$_6$H$_4$	91
b	Br	Me	Ph	4-ClC$_6$H$_4$	70
c	Br	Me	4-MeC$_6$H$_4$	Ph	71
d	Br	Me	4-MeC$_6$H$_4$	Ph	80
e	Br	Me	4-O$_2$NC$_6$H$_4$	Ph	64
f	Br	Me	3-BrC$_6$H$_4$	Ph	54
g	Br	-$(CH_2)_4$-		Ph	82
h	Br	-$(CH_2)_5$-		Ph	92
i	Br	Me	2-furyl	Ph	51
j	Br	Me	PhCH=CH	Ph	74
k	Br	Me	Ph	1-naphthyl	72
l	Br	Me	Ph	5-pyrimidinyl	52
m	Cl	Me	Ph	4-MeC$_6$H$_4$	55
n	Cl	Me	Ph	4-MeC$_6$H$_4$	52

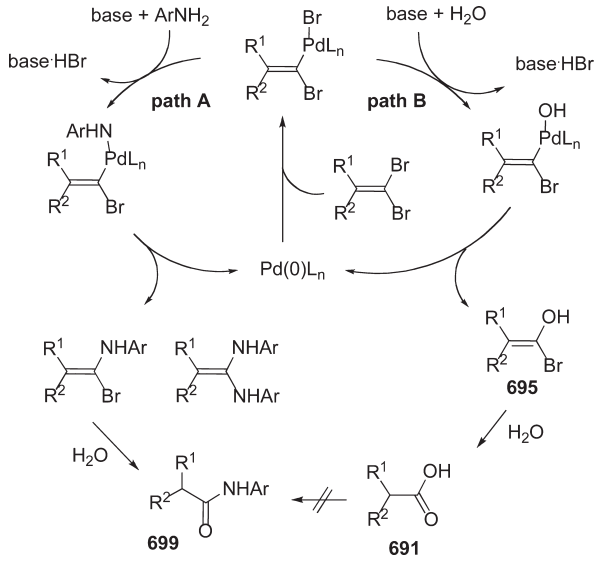
Only representative examples are reported

3.6. Conversion to Carboxylic Acids, Amides, and Ketones

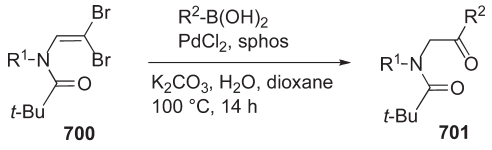
Alper and co-workers, carrying out the Pd(0)- and phase-transfer-catalyzed carbonylation of vinyl dibromides derived from aromatic aldehydes, found that when these substrates were treated with carbon monoxide, catalytic Pd(diphos)$_2$, benzyltriethylammonium chloride as a phase-transfer agent, and 5 N NaOH in benzene, diynes **675** were formed in reasonable yields (Scheme 447).[356] On the other hand, when the same process was carried out in *tert*-amyl alcohol as the organic phase, diacids **688** were obtained in high yields (Scheme 456).[356]

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 462



Scheme 463



	R^1	R^2	**701** yield (%)
a	$PhCH_2$	Ph	72
b	$PhCH_2$	4-MeC_6H_4	74
c	$PhCH_2$	2-ClC_6H_4	36
d	$PhCH_2$	4-$MeOC_6H_4$	75
e	$PhCH_2$	3-thienyl	57
f	Me	Ph	57
g	2-$FC_6H_4CH_2$	Ph	83
h	$EtO_2CCH_2CH_2$	Ph	85

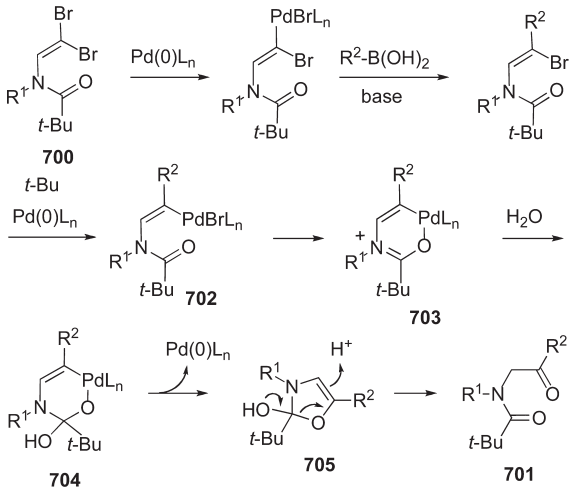
Only representative examples are reported

α,β-Unsaturated monoacids were the major or only products formed by using dibromides derived from aliphatic aldehydes or ketones carrying out the reaction in benzene solution, whereas dicarbonylation of all classes of vinylic dibromides to diacids occurred by using *tert*-amyl alcohol as the organic phase (Scheme 457). Mechanisms were proposed for these selective transformations.

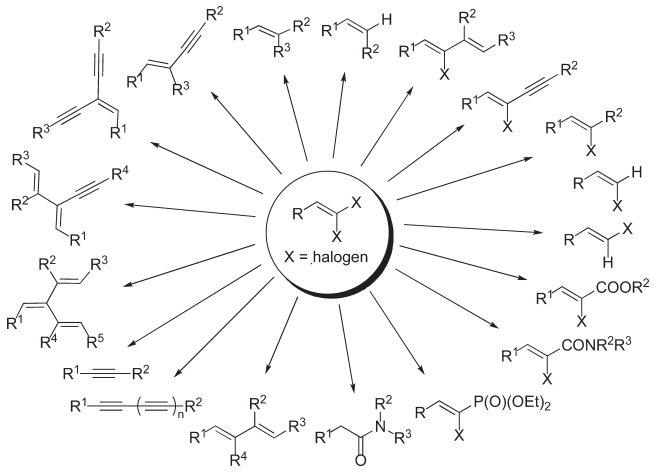
A few years later, Alper and co-workers, examining the dehydrohalogenation of vinylic dibromides under basic conditions in the presence of poly(ethylene glycol) (PEG-400) and NaOH, found that vinilyc dibromides derived from aldehydes afforded bromoacetylenes in 51−72% yields (Scheme 458).[357] However, when the reaction was repeated in the presence of a catalytic amount of $Pd(diphos)_2$, carboxylic acids **691** were formed in 18−95% yields (Scheme 458).[357]

The hypothesized mechanism requires the initial interaction of PEG with NaOH, which would give a complex that could then add to the Pd catalyst affording **693** (Scheme 459). The latter is

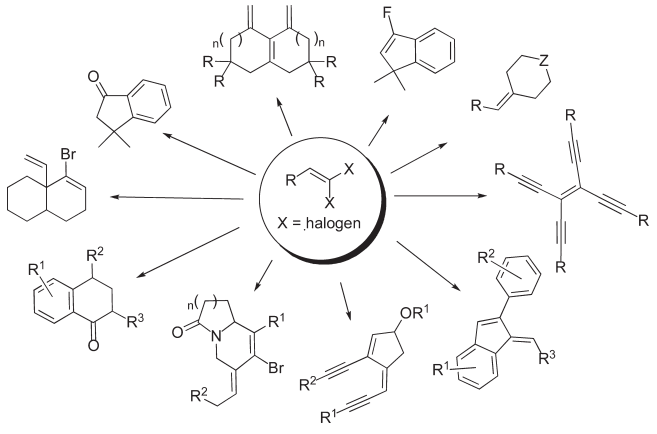
Scheme 464



Scheme 465



Scheme 466



then converted into **694** by reaction with the organic substrate, either by electron-transfer or by ionic pathway. Reductive elimination would then give the enol **695** [the Pd catalyst would

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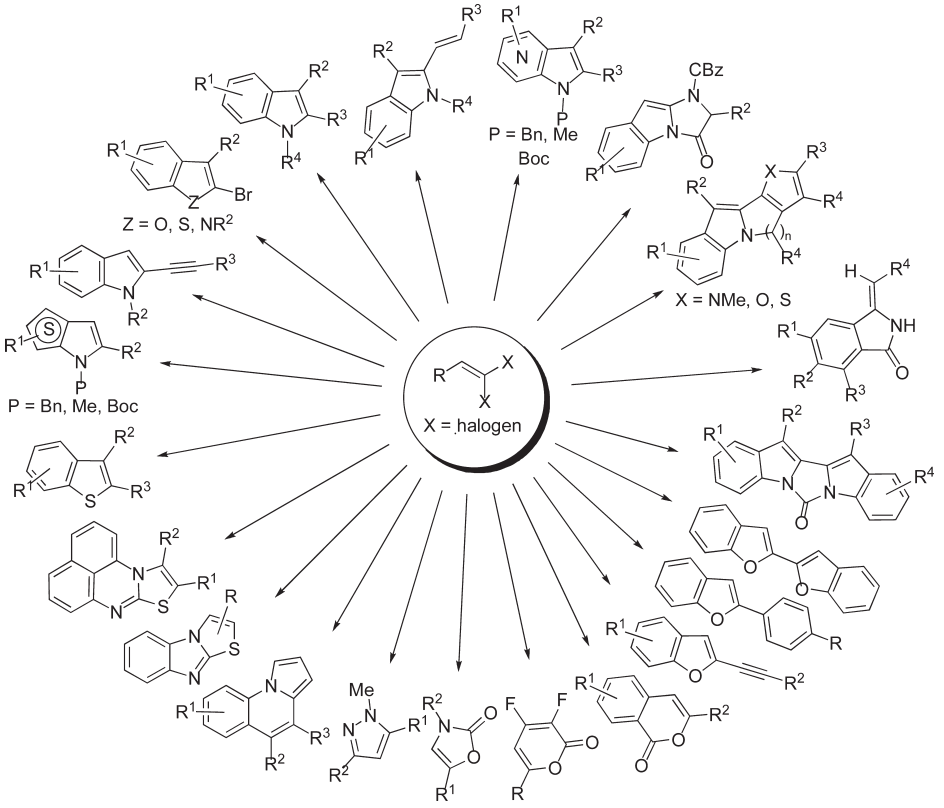
Scheme 467



be regenerated in this step]. Tautomerism of **695** to acid bromide **696** and subsequent hydrolysis would afford the product **691**. Bromoacetylenes were not intermediates in the conversion of vinylic dibromides to acids because the related carboxylic acid was not detected when 1-(2-bromoethynyl)-4-methylbenzene was exposed to the same reaction conditions.

Kim and co-workers found that when the dibromomide **697** was submitted to the Sonogashira reaction with but-3-yn-1-ol by using pyrrolidine as the reaction solvent in the presence of catalytic $PdCl_2(PPh_3)_2$, PPh_3, and CuI, the related 1-aryl-1,3-diyne (Scheme 199) was obtained in only 10% yield with the amide **698** as a byproduct. However, when the reaction was carried out without CuI, the yield of **698** could be increased up to 68% (Scheme 460).[251] Further studies on the formation of **698** revealed that the reaction is very facile in the presence of sufficient water, even without a Pd catalyst.[6] Similar results were also obtained by Shen and Kunzer.[7]

Wu and co-workers have recently reported a route to prepare homologated *N*-aryl monosubstituted carboxamides from ketones via *gem*-dihaloolefin intermediates.[360] After extensive optimization, the combination of $Pd(OAc)_2$ (5 mol %), XantPhos (10 mol %), and Cs_2CO_3 in dioxane/H_2O was found to be the best system to convert both a variety of *gem*-dihaloolefins and aryl amines into *N*-aryl monosubstituted carboxamides **699** in moderate to good yields (Scheme 461). The proposed mechanism for the conversion of *gem*-dihaloolefins to carboxamides **699** is shown in Scheme 462. When the acid **691a** (R^1 = Me, R^2 = Ph) was heated with *p*-methylaniline, under the usual conditions, only a trace amount of the related carboxamide **699a** could be observed, indicating that these compounds might not be achieved through carboxylic acids, which could be generated through path B (Scheme 462). From these results, the formation of a C−N bond appeared to be faster than that of a C−O bond in the presence of arylamine under palladium catalysis (path A, Scheme 462).

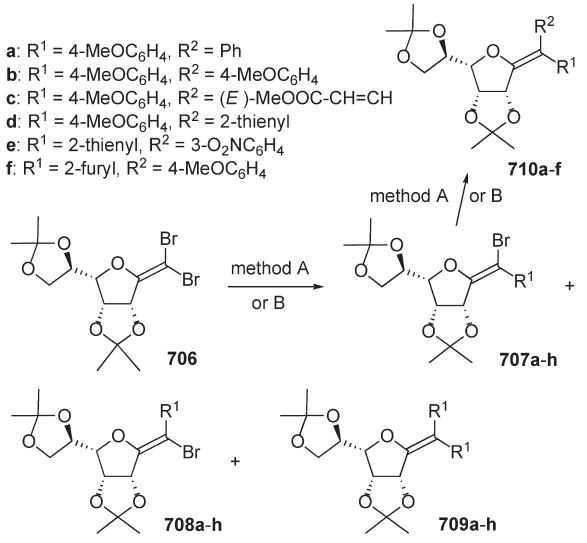
Very recently, Lautens and co-workers have described the development of a new reactivity of β,β-dibromoenamides to generate 2-oxazolones (Scheme 365) and α-aminoketones (Scheme 463).[322] They found than when the coupling of β,β-dibromoenamide **700a** with phenylboronic acid was carried out under a combination of $PdCl_2$ and sphos (6 and 12 mol %, respectively), an efficient synthesis of the α-amino ketone **701b** with K_2CO_3 as base was obtained (Scheme 463). Under these optimized conditions, the reactions of a variety of β,β-dibromoenamides with a number of boronic acids were examined, and 2-oxazolones were formed in moderate to good yields. The proposed mechanism, supported by experimental data, for the α-amino ketone synthesis is illustrated in the Scheme 464. In the key step, the complex **702** transforms into the cationic oxo-palladium species **703**, which provides the intermediate **704** via nucleophilic attack of water. Finally, reductive elimination of **704** gives the compound **701** by decomposition of the amide hemiacetal **705**, followed by protonation.

4. CONCLUSION

This review provides a systematic summary of methods for the synthesis of 1,1-dihalo-1-alkenes and a deep overview of metal-catalyzed processes, which lead to the formation of new C−C,

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

Scheme 468



a: R^1 = Ph, **b**: R^1 = 4-$MeOC_6H_4$, **c**: R^1 = 2-thienyl, **d**: R^1 = 3-$O_2NC_6H_4$
e: R^1= 2-furyl, **f**: R^1= (*E*)-MeOOC-CH=CH, **g**: R^1= (*E*)-Me_3Si-CH=CH
h: R^1 = (*E*)-Ph-CH=CH

$R^1B(OH)_2$ or R^1SnBu_3	method	**707**/**708**/**709** ratio	**707** yield (%)
$PhB(OH)_2$	A	1/0/1	**a**-60
$PhSnBu_3$	B	2/1/0	**a**-33
4-$MeOC_6H_4B(OH)_2$	A	5/1/1	**b**-62
2-thienyl$B(OH)_2$	A	4/1/0	**c**-60
2-thienyl$SnBu_3$	B	2/1/1	**c**-60
3-$O_2NC_6H_4B(OH)_2$	A	6/1/2	**d**-61
2-furyl$B(OH)_2$	A	9/0/1	**e**-60
(*E*)-MeOOC-CH=CH$SnBu_3$	B	7/1/1	**f**-60
(*E*)-Me_3Si-CH=CH$SnBu_3$	B	10/1/3	**g**-0[a]
(*E*)-Ph-CH=CH$SnBu_3$	B	10/1/3	**h**-0[a]

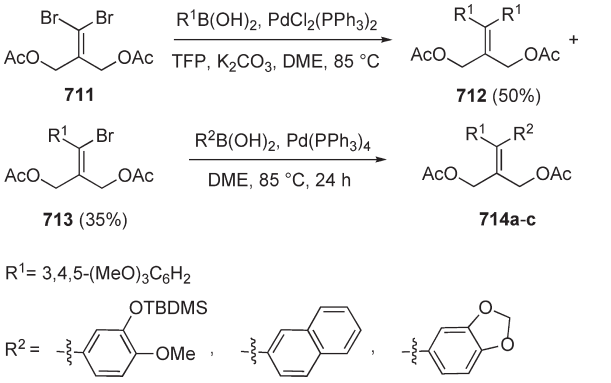
[a]Decomposed on column chromatography

starting glycal	$R^2B(OH)_2$ or R^2SnBu_3	method	**710** yield (%)
707d	$PhB(OH)_2$	A	**a**-85
707d	4-$MeOC_6H_4B(OH)_2$	A	**b**-95
707d	(*E*)-MeOOC-CH=CH$SnBu_3$	B	**c**-66
707d	2-thienyl$B(OH)_2$	A	**d**-60
707c	3-$O_2NC_6H_4B(OH)_2$	A	**e**-85
707e	4-$MeOC_6H_4B(OH)_2$	A	**f**-85

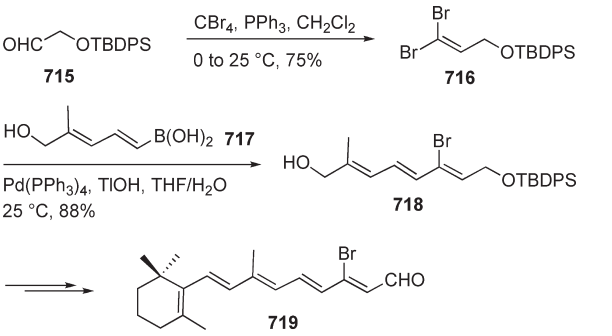
Method A: $R^1B(OH)_2$ or $R^2B(OH)_2$, $PdCl_2(PPh_3)_2$ (5 mol %), TFP (30 mol%), K_2CO_3, DME, 85 °C, 24 h.
Method B: R^1SnBu_3 or R^2SnBu_3, $Pd_2(dba)_3$ (5 mol%), TFP (30 mol%), MePh, 140 °C, microwave irradiation, 45 min.

C−H, C−N, etc. bonds by an effective replacement of one or both halogen atoms with other elements. In this way, *gem*-dihaloalkenes by selective monosubstitution and stepwise cross-coupling reactions with a wide array of reagents as coupling partners provide a variety of important products such as stereodefined substituted alkenes, polyenes, alkynes, polyynes, carboxylic acids, etc. (Scheme 465). The *gem*-dihalovinyl moiety represents also a very attractive key unit for metal-mediated syntheses of carbocycles (Scheme 466) and heterocycles such as indoles, benzofurans, azoles, etc. (Scheme 467) by a judicious selection of the coupling partners and well-designed starting materials. Mechanistic aspects related to these transformations are also illustrated. Without question, each of these elegant

Scheme 469



Scheme 470



transformations sets an impressively high standard for future synthetic efforts targeting members of a growing class of important natural products, medicines, and organic intelligent materials.

Appendix 1

Chapleur and co-workers have developed efficient methods for the preparation of disubstituted *exo*-glycals as single stereoisomers by Suzuki and Stille cross-couplings of 1,1-dibromo-D-gulo-hept-1-enitol **706** readily available from the corresponding protected D-gulono-γ-lactone[31] (Scheme 468).[361] After optimization, the combination of $PdCl_2(PPh_3)_2$ (5 mol %) and TFP (30 mol %) resulted to be the best catalytic system for the coupling of **706** with a number of (hetero)aryl boronic acids, affording satisfactory yields and good to excellent selectivity for the *Z*-isomers **707** (Scheme 468). On the other hand, $Pd_2(dba)_3$ (5 mol %) and TFP (30 mol %) showed to be the best combination for the coupling with tin reagents, although in this case the reactions under microwave irradiations led to higher stereoselectivity and to better yields of pure compounds **707**, as compared to thermal activation (Scheme 468). Next, the remaining bromine atom in the *Z*-isomers **707a**−**f** was subtituted with (hetero)aryl groups by Pd-catalyzed cross-couplings under similar reaction conditions used for the coupling reactions of **706**. In this way, stereodefined disubstituted compounds **710** were obtained in excellent yields (Scheme 468). This approach was highly versatile, since the desired stereoisomer could be synthesized in a stereochemically pure form by simply modifying the

dx.doi.org/10.1021/cr200165q |*Chem. Rev.* 2012, 112, 1344–1462

order of the reagents. More recently, the same group has prepared other disubstituted *exo*-glycals related to **710** from **706**, and their simplified analogues **714a-c** from the 1,1-dibromoalkene **711** (Scheme 469) by selective sequential Suzuki cross-coupling reactions.[362] It should be noted that in the coupling of **711** the disubstitued compound **712** was formed in 50% yield while the monosubstituted **713** was isolated in 35% yield, likely because of a faster coupling reaction on **713** as compared to **711**. All these new compounds were evaluated for antiproliferative activity against a panel of human tumor cell lines. In a study aimed to the stereocontrolled synthesis of retinoids functionalized at the 13-carbon, de Lera and co-workers reported the preparation of the retinal analogue (13Z)-13-bromo-13-desmethylretinal **719** (Scheme 470). The key step of this synthesis was the stereoselective Pd-catalyzed cross-coupling of the 1,1-dibromoalkene **716** with the boronic acid **717** that afforded the bromoalkene **718** in 88% yield.[363]

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BIOGRAPHY

Giorgio Chelucci was born in Cagliari (Sardegna, Italy) and studied Chemistry at the University of Sassari (Sardegna), where he received his laurea degree in 1978. After 5 years of postlaurea work, he became a Researcher in the Department of Chemistry at the University of Sassari. His research activity is documented by about 140 scientific peer-reviewed papers, 4 book chapters, and 3 patents. His research centers on the design, synthesis, and application in asymmetric catalysis of chiral ligands with particular interest toward those based on the pyridine framework and on metal-catalyzed catalytic reactions.

ACKNOWLEDGMENT

Financial support from the University of Sassari is gratefully acknowledged.

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AIBN	azobis(isobutyronitrile)
aq	aqueous
Ar	aromatic
BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
Bu	butyl
Cat	catalytic
Cbz	carbobenzyloxy
cod	cyclooctadiene
d	days
DABCO	1,4-diazabicyclo[2,2,2]octane
DavePhos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DIBAL	diisobutylaluminium hydride
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
diphos	1,2-bis(diphenylphosphino)ethane
dpephos	bis(2-diphenylphosphinophenyl)ether
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1′-bis(diphenylphosphino)ferrocene
equiv	equivalent
Et	ethyl
FVP	vacuum pyrolysis
h	hour
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HTIB	[hydroxy(tosyloxy)iodo)]benzene
KHDMS	potassium hexamethyldisilazide
L	ligand
LDA	lithium diisopropylamide
LiHDMS	lithium hexamethyldisilazide
LTMP	lithium tetramethylpiperidide
JohnPhos	biphenyl-2-yldi-*tert*-butylphosphine
Me	methyl
MCPBA	3-chloroperbenzoic acid
min	minutes
MTBD	1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*,*N*-bis(2,6-diisopropylphenyl)imidazolium chloride
NMP	*N*-methylpyrrolidone
NIS	*N*-iodosuccinimide
M	metal
p	*para*
PEG	poly(ethylene glycol)
Piv	pivaloyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py	pyridine
rt	room temperature
Ruphos	2-dicyclohexylphosphino-2′,6′-di-iso-propoxy-1,1′-biphenyl
s	*sec*
t	*tert*
sphos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBDPS	*tert*-butyldiphenylsilyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TDAE	tetrakis(dimethylamino)ethylene

TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylene-1,2-diamine
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
XantPhos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

REFERENCES

(1) For 1-halo-1-alkenes, see:(a) Horibe, H.; Kondo, K.; Okuno, H.; Aoyama, T. *Synthesis* **2004**, 986. (b) Feroci, M.; Orsini, M.; Palombi, L.; Sotgiu, G.; Inesi, A. *Electrochim. Acta* **2004**, *49*, 635. (c) Kadota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 8645. (d) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491. (e) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 4102. (f) Lin, S. T.; Lee, C. C.; Liang, D. W. *Tetrahedron* **2000**, *56*, 9619. (g) Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215. (h) Harada, T.; Katauhira, T.; Oku, A. *J. Org. Chem.* **1992**, *57*, 5805. (i) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745.

(2) For 1-halo-1-alkynes, see:(a) Okutami, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442. (b) Söederberg, B. C. G.; Gorugantula, S. P.; Howerton, C. R.; Petersen, J. L.; Dantale, S. W. *Tetrahedron* **2009**, *65*, 7357.

(3) For terminal alkynes, see:Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(4) For conjugated dienes, see:Shono, T.; Hayata, Y.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2006**, *47*, 1257.

(5) For aryl methyl ketones, see:Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* **2003**, *44*, 4685.

(6) For acetic acids, see:Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925.

(7) For amides, see:Shen, W.; Kunzer, A. *Org. Lett.* **2002**, *4*, 1315.

(8) For amidines, see:Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857.

(9) For 1,1,1-trifluoroderivatives, see:Cantet, A. C.; Gesson, J.-G.; Renoux, R.; Jouannetaud, M. P. *Tetrahedron Lett.* **2007**, *48*, 5255.

(10) Synthesis of heterocycles. For isoquinolines and quinolines, see:(a) Ichikawa, J. *Chim. Oggi* **2007**, *25*, 54. (b) Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth.* **2006**, *83*, 111. (c) Ichikawa, J.; Sokoda, K.; Moriyama, H.; Wada, Y. *Synthesis* **2006**, 1590. (d) Zhang, A.; Zheng, X.; Fan, J; Shen, W. *Tetrahedron Lett.* **2010**, *51*, 828. For benzimidazoles, see:(e) Shen, W.; Kohn, T.; Fu, Z.; Jiao, X.-Y.; Lai, S.; Schmitt, M. *Tetrahedron Lett.* **2008**, *49*, 7284. For 2-arylmethylimidazolines, see:(f) Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857. For 4,5-dihydro-1*H*-imidazoles, see:(g) Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Synlett* **2004**, 819.

(11) After the completation of this review, an account summarizing cross-coupling reactions of vinyl dibromides appeared in the literature: Legrand, F.; Jouvin, K.; Evano, G. *Isr. J. Chem.* **2010**, *50*, 1. Moreover a recent review has described in part the catalytic reactions of 1,1-dihalo-1-alkenes:Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405. For older accounts on 1,1-dihalo-1-alkenes, see:(a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 650. (b) Xu, B.; Ma, S. *Chin. J. Org. Chem.* **2001**, *21*, 252.

(12) The rates of palladium-catalyzed cross-coupling reactions of (*E*)- and (*Z*)-1-halo-1-alkenes are substantially different:Rossi, R.; Carpita, A. *Tetrahedron Lett.* **1986**, *27*, 2529.

(13) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257.

(14) Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649.

(15) Trost, B. M.; Walchli, R. *J. Am. Chem. Soc.* **1987**, *109*, 3487.

(16) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

(17) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905.

(18) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(19) (a) Posner, G. H.; Loomis, G. L.; Sawaya, H. S. *Tetrahedron Lett.* **1975**, *16*, 1373. (b) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4823. (c) Olah, G. A.; Wu, A. *Synthesis* **1990**, 885. (d) Hassig, R.; Seebach, D.; Siegel, H. *Chem. Ber.* **1984**, *117*, 1877.

(20) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *16*, 1373.

(21) (a) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *48*, 4823. (b) Jiang, B.; Ma, P. *Synth. Commun.* **1995**, *25*, 3641.

(22) Newman, S. G.; Aureggi, A.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236.

(23) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.

(24) Langille, N. F.; Panek, J .S. *Org. Lett.* **2004**, *6*, 3203.

(25) Fang, Y.-Q.; Lifchits, O.; Lautens, M. *Synlett* **2008**, 413.

(26) Combret, J. C.; Villiéras, J.; Lavielle, G. *Tetrahedron Lett.* **1971**, *15*, 1035.

(27) Speziale, A. J.; Ratts, K. W. *J. Am. Chem. Soc.* **1962**, *84*, 854.

(28) Maercker, A. *Org. React.* **1965**, *14*, 270.

(29) (a) Savignac, P.; Coutrot, P. *Synthesis* **1976**, 197. (b) Sato, H.; Isono, N.; Miyoshi, I.; Mori, A. *Tetrahedron* **1996**, *50*, 8143.

(30) Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8575.

(31) Lakhrissi, Y.; Taillefumier, C.; Chrétien, F.; Chaplerur, Y. *Tetrahedron Lett.* **2001**, *42*, 7265.

(32) Dolhem, F.; Lièvre, C.; Demailly, G. *Tetrahedron Lett.* **2002**, *43*, 1847.

(33) Quesada, E.; Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Tetrahedron* **2006**, *62*, 6673.

(34) Beltrán-Rodil, S.; Edwards, M. G.; Pigh, D. S.; Reid, M.; Taylor, R. J. K. *Synlett* **2010**, 602.

(35) Rezaei, H.; Normant, J. F. *Synthesis* **2000**, 109.

(36) Ranu, B. C.; Samanta, S.; Das, A. *Tetrahedron Lett.* **2002**, *43*, 5993.

(37) Fisher, R. P; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis* **1982**, 127.

(38) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.

(39) Sahu, B.; Gururaja, G. N.; Mobin, S. M.; Namboothiri, I. N. N. *J. Org. Chem.* **2009**, *74*, 2601.

(40) Galzunova, E. Y.; Lutsenko, S. V.; Efimova, I. V.; Trostyanskaya, I. G.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1988**, *34*, 1104.

(41) (a) Azyat, K.; Jahnke, E.; Rankin, T.; Tykwinski, R. R. *Chem. Commun.* **2009**, 433. (b) Rankin, T.; Tykwinski, R. R. *Org. Lett.* **2003**, *5*, 213.

(42) Barluenga, J.; Liavona, L.; Concellon, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 297.

(43) Atkins, P. J.; Gold, V.; Wassef, W. N. *J. Chem Soc., Chem. Commun.* **1983**, 283.

(44) Gajewski, R. P.; Jackson, J. L.; Jones, J. L.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1989**, *54*, 3311.

(45) Suryawanshi, S. N.; Nayak, U. R. *Indian J. Chem.* **1979**, *18B*, 500.

(46) Pawluc, P.; Hreczycho, G.; Walkowiak, J.; Marciniec, B. *Synlett* **2007**, *13*, 2061.

(47) Dabdoub, M. J.; Dabdoub, V. B.; Baroni, A. C. M. *J. Am. Chem. Soc.* **2001**, *123*, 9694.

(48) (a) Korotchenko, V. N.; Shastin, A. V.; Nenajdenko, V. G.; Balenkova, E. S. *Org. Biomol. Chem.* **2003**, *1*, 1906. (b) Korotchenko, V. N.; Shastin, A. V.; Nenajdenko, V. G.; Balenkova, E. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 883.

(49) Bozhenkov, G. V.; Flov, Y. L.; Toryashinova, D. S.-D.; Levkovskaya, G. G.; Mirskova, A. N. *Russ. J. Org. Chem.* **2003**, *39*, 807.

(50) Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* **1962**, *84*, 132.

(51) Dos Santos, M.; Frank, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. *Synlett* **2004**, *15*, 2697.

(52) (a) Okamoto, Y.; Yoshikawa; Hayashi, T. *J. Organomet. Chem.* **1989**, *359*, 143. (b) Isaacs, N. S.; Kirrkpatrick, D. *J. Chem. Soc., Chem. Commun.* **1972**, 443.
(53) Raulet, C.; Levas, E. *C. R. Acad. Sci., Ser. C.* **1970**, *270*, 1467.
(54) Soulen, R. L.; Carlson, S. C.; Lang, F. *J. Org. Chem.* **1973**, *38*, 479.
(55) Vinczer, P.; Struhar, S.; Novak, L.; Szantay, C. *Tetrahedron Lett.* **1992**, *33*, 683.
(56) (a) Chapleur, Y. *J. Chem. Soc., Chem. Commun* **1984**, 449. (b) Bandzouzi, A.; Chapleur, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 661. (c) Bandzouzi, A.; Chapleur, Y. *Carbohydr. Res.* **1987**, *171*, 13.
(57) Lakhrissi, M.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752.
(58) Takeda, T.; Endo, Y.; Sheker Reddy, A. C.; Sasaki, R.; Fujiwara, T. *Tetrahedron* **1999**, *55*, 2475.
(59) Burton, G.; Elder, J. S.; Fell, S. C. M.; Stachulski, A. V. *Tetrahedron Lett.* **1988**, *29*, 3003.
(60) Salmond, W. G. *Tetrahedron Lett.* **1977**, *14*, 1239.
(61) Olah, G. A.; Yamada, Y. *J. Org. Chem.* **1975**, *40*, 1007.
(62) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.
(63) Waschbüsch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Synthesis* **1997**, 727.
(64) Seyferth, D.; Marmor, R. S. *J. Organomet. Chem.* **1973**, *59*, 237.
(65) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, 458.
(66) Savignac, P.; Petrova, J.; Dreux, M.; Coutrot, P. *Synthesis* **1975**, 535.
(67) Pflieger, D.; Muckenstrurm, B. *Tetrahedron* **1989**, *45*, 2031.
(68) Lee, K.; Shin, W. S.; Oh, D. Y. *Synth. Commun.* **1991**, *21*, 1657.
(69) (a) Carran, J.; Waschbüsch, R.; Marinetti, A.; Savignac, P. *Synthesis* **1996**, 1494. (b) Mourièr, V.; Waschbüsch, R.; Carran, J.; Savignac, P. *Synthesis* **1998**, 271.
(70) (a) Bal'on, Y. G.; Paranyuk, V. E.; Shul'man, M. D. *Zh. Obshch. Chim.* **1974**, *44*, 2633. (b) Viehe, H. G.; Franchimont, E.; Valange, P. *Chem. Ber.* **1963**, *96*, 426. (c) Bergmann, E. D.; Ginsburg, D.; Lavie, D. *J. Am. Chem. Soc.* **1950**, *72*, 5012. (d) Merz, A.; Tomahogh, R. *Chem. Ber.* **1977**, *110*, 96.
(71) Wyvratt, J. M.; Hazen, G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52*, 944.
(72) Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211.
(73) (a) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435. (b) Wang, Z.; Campagna, S.; Xu, G.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 4007. (c) Wang, Z.; Campagna, S.; Yang, K.; Xu, G.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *J. Org. Chem.* **2000**, *65*, 1889.
(74) Tanaka, H.; Yamashirta, S.; Yamanoue, M.; Torii, S. *J. Org. Chem.* **1989**, *54*, 444.
(75) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220.
(76) Li, J.; Xu, X.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 9349.
(77) Roulland, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3762.
(78) Reeve, W.; Brown, R.; Steckel, T. F. *J. Am. Chem. Soc.* **1971**, *93*, 4607.
(79) Villieras, J.; Bacquet, C.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1974**, 1731.
(80) Takai, K.; Kokumai, R.; Nobunaka, T. *Chem. Commun.* **2001**, 1128.
(81) Hosomi, A.; Inaba, M.; Sakurai, H. *Tetrahedron Lett.* **1983**, *24*, 4727.
(82) Krabbenhoft, H. O. *J. Org. Chem.* **1978**, *43*, 1305.
(83) Blinn, R. C.; Gunther, F. A. *J. Am. Chem. Soc.* **1950**, *72*, 1399.
(84) Shastin, A. V.; Korotchenko, V. N.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 6557.
(85) Ratavelomanana, V.; Linstrumelle, G.; Normant, J.-F. *Tetrahedron Lett.* **1985**, *21*, 2575.
(86) (a) Dixon, S. *J. Org. Chem.* **1956**, *21*, 400. (b) U.S. Patent 3,712,929 1973; *Chem. Abstr.* **1973**, *78*, No. 1242469q. (c) Okuhara, K. *J. Org. Chem.* **1976**, *41*, 1487.
(87) (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619. (b) Burton, D. J.; Yang, Z.-Y.; Qui, W. *Chem. Rev.* **1996**, *96*, 1641.
(88) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, U.K., 2006.
(89) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.
(90) Lim, M. H.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 529.
(91) (a) Serafinowski, P. J.; Brown, C. A. *Tetrahedron* **2000**, *56*, 333. (b) Serafinowski, P. J.; Barnes, C. L. *Tetrahedron* **1996**, *52*, 7929.
(92) Zhao, Y.; Liu, H. *J. Org. Chem.* **2001**, *66*, 6810.
(93) Nowak, I.; Robins, J. M. *Org. Lett.* **2005**, *7*, 721.
(94) Ocampo, R.; Dolbier, W. R., Jr.; Paredes, R. *J. Fluorine Chem.* **1998**, *88*, 41. (a) Ocampo, R.; Dolbier, W. R., Jr.; Bartberger, M. D.; Paredes, R. *J. Org. Chem.* **1997**, *62*, 109.
(95) Kitazume, T.; Ohnogi, T. *Synthesis* **1988**, 614.
(96) Fuchikami, T.; Shibata, Y.; Suzuki, Y. *Tetrahedron Lett.* **1986**, *27*, 3173.
(97) Kitazume, T.; Ohnogi, T.; Miyauchi, H.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 5630.
(98) (a) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1409. (b) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *Synlett* **1995**, 659. (c) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *Tetrahedron Lett.* **1995**, *36*, 5003.
(99) Kendrick, D. A.; Kolb, M. *J. Fluorine Chem.* **1989**, *45*, 265.
(100) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135.
(101) Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4870.
(102) (a) Yamazaki, T.; Ishikawa, N. *Chem. Lett.* **1984**, 521. (b) Yamazaki, T.; Takita, K.; Ishikawa, N. *Nippon Kagaku Kaishi* **1985**, *11*, 2131.
(103) Tellier, F.; Baudry, M.; Sauvêtre, R. *Tetrahedron Lett.* **1997**, *38*, 5989.
(104) Ichikawa, J.; Miyazaki, H.; Sakoda, K.; Wada, Y. *J. Fluorine Chem.* **2004**, *125*, 585.
(105) Mori, T.; Iwai, Y.; Ichikawa, J. *Chem. Lett.* **2005**, *34*, 778.
(106) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425.
(107) Cunico, R. F.; Motta, A. R. *Org. Lett.* **2005**, *7*, 771.
(108) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006.
(109) (a) Ichikawa, J.; Fukui, H.; Ishibashi, Y. *J. Org. Chem.* **2003**, *68*, 7800. (b) Ichikawa, J.; Ishibashi, Y.; Fukui, H. *Tetrahedron Lett.* **2003**, *44*, 770.
(110) Ichikawa, J.; Wada, Y.; Fujisawa, M.; Sakoda, K. *Synthesis* **2002**, 1917.
(111) Watanabe, S.; Sugahara, K.; Fujita, T.; Sakamoto, M.; Kitazume, T. *J. Fuorine Chem.* **1993**, *62*, 201.
(112) (a) Park, H. M.; Uegaki, T.; Konno, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron Lett.* **1999**, *40*, 2985. (b) Yamanaka, H.; Uegaki, T.; Ishihara, T.; Kubota, T.; Gupton, J. T. *J. Fluorine Chem.* **1999**, *97*, 101.
(113) Funabiki, K.; Sawa, K.; Shibata, K.; Matsui, M. *Synlett* **2002**, 1134.
(114) Uneyama, K.; Yang, F.-Y.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*, 2045.
(115) Portella, C.; Shermolovich, Y. *Tetrahedron Lett.* **1997**, *38*, 4063.
(116) Uneyama, K.; Maeda, K.; Kato, T.; Katagiri, T. *Tetrahedron Lett.* **1998**, *39*, 3741.
(117) Uneyama, K.; Mizutani, G.; Maeda, K.; Kato, T. *J. Org. Chem.* **1999**, *64*, 6717.
(118) Uneyama, K.; Mizutani, G. *Chem. Commun.* **1999**, 613.
(119) Uneyama, K.; Kato, T. *Tetrahedron Lett.* **1998**, *39*, 587.
(120) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323.
(121) For a short account, see:Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, *114*, 127.
(122) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103.
(123) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893.
(124) Kobayashi, T.; Nakagawa, T.; Amii, H.; Uneyama, K. *Org. Lett.* **2003**, *5*, 4297.

(125) Jiang, B.; Zhang, X.; Shi, G.-Q. *Tetrahedron Lett.* **2002**, *43*, 6819.
(126) Shi, G.-Q.; Cai, W.-L. *J. Org. Chem.* **1995**, *60*, 6289.
(127) Tius, M. A.; Busch-Petersen, J.; Marris, A. R. *Chem. Commun.* **1997**, 1867.
(128) Cohen, S. G.; Wolosinski, H. T.; Scheuer, P. J. *J. Am. Chem. Soc.* **1949**, *71*, 3439.
(129) Hagooly, A.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2002**, *67*, 8430.
(130) Nguyen, T.; Wakselman, C. *J. Fluorine Chem.* **1995**, *74*, 273.
(131) Torii, S.; Tanaka, H.; Yamashita, S. *Jpn. Kokai Tokkyo Koho* **1996**No. JP-08225487.
(132) Okano, T.; Shimizu, T.; Sumida, K.; Eguchi, S. *J. Org. Chem.* **1993**, *58*, 5163.
(133) Yamada, S.; Noma, M.; Konno, T.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2006**, *8*, 843.
(134) Morken, P. A.; Lu, H.; Nakamura, A.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 4271.
(135) Tamura, M.; Sekiya, A. *J. Fluorine Chem.* **1995**, *71*, 119.
(136) For a recent review, see:Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130.
(137) Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1992**, *33*, 3101.
(138) Boger, D. L.; Jenkins, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 8860.
(139) (a) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Eur. J. Org. Chem.* **2005**, 2218. (b) Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53. (c) Dunkel, M.; Reither, V.; Ebel-Will, S.; Ludwig, J. *Nucleosides, Nucleotides Nucleic Acids* **1995**, *14*, 799.
(140) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273.
(141) Prakash, G. K. S.; Wang, Y.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 1361.
(142) Zhang, L.; Li, Y.; Hu, J. *J. Fluorine Chem.* **2007**, *128*, 755.
(143) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203.
(144) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444.
(145) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 786.
(146) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006**, *62*, 5973.
(147) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913.
(148) Kim, K.-I.; McCarthy, J. R. *Tetrahedron Lett.* **1996**, *37*, 3223.
(149) Jeong, I. H.; Min, Y. K.; Kim, Y. S.; Kim, B. T.; Cho, K. Y. *Tetrahedron Lett.* **1994**, *35*, 7783.
(150) Saito, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Hiroaki, H.; Taguchi, T. *J. Fluorine Chem.* **2003**, *123*, 75.
(151) Shi, G.-Q.; Huang, X.-H. *Tetrahedron Lett.* **1996**, *37*, 5401.
(152) Van Der Puy, M. *J. Fluorine Chem.* **1997**, *81*, 187.
(153) Bégué, J. P.; Bonnet-Delpon, D.; Percy, J. M.; Rock, M. H.; Wilkes, R. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1857.
(154) Bégué, J. P.; Bonnet-Delpon, D.; Rock, M. H. *Tetrahedron Lett.* **1994**, *35*, 6097.
(155) Burton, D. J.; Yang, Z.-Y.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993.
(156) (a) Tellier, F.; Sauvêtre, R. *Tetrahedron Lett.* **1995**, *36*, 4223. (b) Sauvêtre, R.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 957.
(157) Gillet, J. P.; Sauvetre, R.; Normant, J. F. *Synthesis* **1986**, 538.
(158) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758.
(159) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1998**, *63*, 1714.
(160) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257.
(161) Purrington, S. T; Thomas, H. N. *J. Fluorine Chem.* **1998**, *90*, 47.
(162) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799.
(163) For trifluoromethylated carbanion synthons, see: Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817.
(164) Garayt, M. R.; Percy, J. M. *Tetrahedron Lett.* **2001**, *42*, 6377.
(165) (a) Percy, J. M.; Prime, M. E. *J. Org. Chem.* **1998**, *63*, 8049. (b) Broadhurst, M. J; Percy, J. M.; Prime, M. E. *Tetrahedron Lett.* **1997**, *38*, 5903. (c) Blades, K.; Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron Lett.* **1996**, *37*, 6403.
(166) (a) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* **1995**, *51*, 10289. (b) Crowley, P. J.; Howarth, J. A.; Owton, W. M.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 5975.
(167) Ichikawa, J.; Jyono, H.; Yonemaru, S.; Okauchi, T.; Minami, T. *J. Fluorine Chem.* **1999**, *97*, 109.
(168) (a) Brown, S. J.; Corr, S.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 5269. (b) Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 2453. (c) Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluorine Chem.* **1999**, *99*, 127. (d) Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *Chem. Commun.* **1996**, 49. (e) Banger, K. K.; Brisdon, A. K.; Gupta, A. *Chem. Commun.* **1997**, 139.
(169) Filler, R.; Lin, S.; Zhang, Z. *J. Fluorine Chem.* **1995**, *74*, 69.
(170) Crowley, P. J.; Howarth, J. A.; Owton, W. M.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 5975.
(171) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 1641.
(172) For references concerning these transformations, see ref 160.
(173) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.
(174) (a) Jin, E.; Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 1221. (b) Jin, E.; Xu, Y.; Huang, W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 795.
(175) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1215.
(176) Brigaud, T.; Doussot, P.; Portella, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2117.
(177) Lefebvre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 1941.
(178) (a) Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1999**, *55*, 7233. (b) Lefebvre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 4348.
(179) (a) Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.* **1996**, *37*, 6115. (b) Berber, H.; Brigaud, T.; Lefebvre, O.; Plantier-Royon, R.; Portella, C. *Chem.—Eur. J.* **2001**, *7*, 903.
(180) Gavina, F.; Luis, S. V.; Ferrer., P.; Costero, A. M.; Marco, J. A. *J. Chem. Res., Synop.* **1986**, 330.
(181) Kadota, I.; Ueno, H.; Ohno, H.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 8645.
(182) Michael, P.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8579.
(183) Bonnet, B.; Le Gallic, Y.; Plé, G.; Duhamel, L. *Synthesis* **1993**, 1071.
(184) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
(185) Cloarek, J.-M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 4731.
(186) Cohen, M. J.; McNeilis, E. *J. Org. Chem.* **1984**, *49*, 515.
(187) Barluenga, J.; Rodriguez, M. A.; Gonzilez, J. M.; Campos, P. J.; Asensio, G. *Tetrahedron Lett.* **1986**, *27*, 3303.
(188) Barluenga, J.; Rodriguez, M. A.; Campos, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 5567.
(189) Janas, J. J.; Asirvathan, K. V.; McNelis, E. *Tetrahedron Lett.* **1985**, *26*, 1967.
(190) Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* **1988**, 236.
(191) Mendoza, A.; Matterson, D. S. *J. Organomet. Chem.* **1978**, *152*, 1.
(192) Lei, X.; Dutheuil, D.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* **2004**, *6*, 2101.
(193) Kuroboshi, M.; Yamada, N.; Takebe, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 6271.
(194) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1990**, *31*, 4449.
(195) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 741.
(196) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405.
(197) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45.

(198) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1994**, *37*, 3579.
(199) Shastin, A. V.; Muzalevsky, V. M.; Balenkova, E. S.; Nenajdenko, V. G. *Mendeleev Commun.* **2006**, *16*, 178.
(200) Zweifel, G.; Lewis, W.; On, H. P. *J. Am. Chem. Soc.* **1979**, *101*, 5101.
(201) Fisher, R. P.; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis* **1982**, 127.
(202) Barluenga, J.; Rodriguez, M. A.; Campos, P. J. *Tetrahedron Lett.* **1990**, 2751.
(203) (a) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315. (b) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1994**, *50*, 5335.
(204) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687.
(205) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4823.
(206) Barluenga, J.; Rodriguez, M. A.; Campos, P. J. *Synthesis* **1992**, 270.
(207) Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1992**, *50*, 7705.
(208) Angara, G. J.; Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1992**, *50*, 2285.
(209) Wang, Y.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 10743.
(210) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109.
(211) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 827.
(212) Galli, C.; Guarnieri, A.; Kock, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* **1997**, *62*, 4072.
(213) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346.
(214) Xu, J.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 3743.
(215) Zhang, X.; Burton, D. J. *J. Fluorine Chem.* **2001**, *112*, 47.
(216) Xu, J.; Burton, D. J. *Org. Lett.* **2002**, *4*, 831.
(217) Zhang, X.; Burton, D. J. *J. Fluorine Chem.* **2001**, *112*, 317.
(218) Dutheuil, G.; Lei, X.; Pannecoucke, X.; Quirion, J.-C. *J. Org. Chem.* **2005**, *70*, 1911.
(219) Dutheuil, G.; Paturel, C.; Lei, X.; Couve-Bonnaire, S.; Pannecoucke, X. *J. Org. Chem.* **2006**, *71*, 4316.
(220) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710.
(221) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541.
(222) (a) For typical procedures, see:Smith, K. In *Organometallics in Synthesis, A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: New York, 2002; pp 512−514. (b) Review:Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(223) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.
(224) (a) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2162. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (c) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708. (d) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157.
(225) (a) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russel, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. (b) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. (c) Wong, L. S. M.; Sharp, L. A.; Xavier, N. M. C.; Turner, P.; Sherburn, M. S. *Org. Lett.* **2002**, *4*, 1995.
(226) Hanisch, I.; Brückner, R. *Synlett* **2000**, 374.
(227) Shen, W. *Synlett* **2000**, *64*, 737.
(228) Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2006**, *348*, 347.
(229) Tadd, A. C.; Matsumo, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583.
(230) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *64*, 4912.
(231) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431.
(232) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042.
(233) Zeng, X.; Hu, Q.; Quian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636.
(234) Zeng, X.; Quian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259.
(235) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203.
(236) Riveiros, R.; Saya, L.; Perez Sestelo, J.; Sarandeses, L.-A. *Eur. J. Org. Chem.* **2008**, 1959.
(237) Sorg, A.; Siegel, K.; Brückner, R. *Synlett* **2004**, 321.
(238) For methods without sonication, see:(a) Villa, M. J.; Lete, E.; Badia, D.; Dominguez, E. *J. Chem. Res., Synop.* **1987**, 418. (b) Farmer, E. H.; Healey, A. T. *J. Chem. Soc.* **1927**, 1060.
(239) Yamada, S.; Noma, Y.; Honda, K.; Konno, T.; Ishihara, T. *J. Org. Chem.* **2008**, *73*, 522.
(240) Electron-poor arylboronic acids are known to give poor results in Suzuki reactions due to homocoupling and decomposition via deprotoborination processes. In fact, in most of the Suzuki−Miyaura reactions, a considerable excess of the boronic acid is used to allow for complete conversion of the coupling reaction. For a recent study on homocoupling reactions of boronic acids, see:Wong, M. S.; Zang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087.
(241) Chelucci, G.; Baldino, S. *Tetrahedron Lett.* **2008**, *49*, 2738.
(242) Takeda, Y.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8659.
(243) Bartolome, C.; Espinet, P.; Villafane, F.; Giesa, S.; Martin, A.; Orpen, A. G. *Organometallics* **1996**, *15*, 2019.
(244) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052.
(245) Shi, J.; Negishi, E. *J. Organomet. Chem.* **2003**, *687*, 518.
(246) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771.
(247) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.
(248) Knebelkamp, A.; Heitz, W. *Makromol. Rapid Commun.* **1991**, *12*, 69.
(249) (a) Gharat, L. A.; Martin, A. R. *Heterocycles* **1996**, *43*, 185. (b) Gharat, L. A.; Martin, A. R. *J. Heterocycl. Chem.* **1996**, *33*, 197.
(250) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203−229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
(251) Lee, H. B.; Huh, D. H.; Oh, J. S.; Min, G.-H.; Kim, B. H.; Lee, D. H.; Hwang, J. K.; Kim, Y. G. *Tetrahedron* **2001**, *57*, 8283.
(252) Uenishi, J.; Matsui, K. *Tetrahedron Lett.* **2001**, *42*, 4353.
(253) Uenishi, J.; Matsui, K.; Ohmiya, H. *J. Organomet. Chem.* **2002**, *653*, 141.
(254) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732.
(255) Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1062.
(256) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.
(257) Ogasawara, M.; Ikeda, H.; Ohtsuki, K.; Hayashi, T. *Chem. Lett.* **2000**, 776.
(258) Negishi, E.; Shi, J.; Zeng, X. *Tetrahedron* **2005**, *61*, 9886.
(259) Shi, J.; Zeng, X.; Negishi, E. *Org. Lett.* **2003**, *5*, 1825.
(260) Metay, E.; Negishi, E. *Org. Lett.* **2006**, *8*, 5773.
(261) Bryant-Friedrich, A.; Neidlein, R. *Synthesis* **1995**, 1506.
(262) Braun, M.; Rahematpura, J.; Bühne, C.; Paulitz, T. *Synlett* **2000**, *7*, 1070.
(263) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220.
(264) Tan, Z.; Negishi, E.-I. *Angew. Chem., Int. Ed.* **2006**, *45*, 762.
(265) Roulland, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3762.
(266) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965.
(267) (a) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 6759. (b) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1996**, *61*, 5716.
(268) Plisson, C.; McConathy, J.; Martarello, L.; Malveaux, E. J.; Camp, V. M.; Williams, L.; Votaw, J. R.; Goodman, M. M. *J. Med. Chem.* **2004**, *47*, 1122.
(269) Hayford, A.; Kaloko, J., Jr.; El-Kazaz, S.; Bass, G.; Harrison, C.; Corprew, T. *Org. Lett.* **2005**, *7*, 2671.
(270) Tietze, L. F.; Nobel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.

(271) Fakhfakl, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131.
(272) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.
(273) Torii, S.; Okumoto, H.; Tadokoro, T.; Nishimura, A.; Rashid, Md. A. *Tetrahedron Lett.* **1993**, *34*, 2139.
(274) McAlonan, H.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1996**, *39*, 7151.
(275) (a) Ma, S.; Xu, B. *J. Org. Chem.* **1998**, *63*, 9156. (b) Ma, S.; Xu, B.; Ni, B. *J. Org. Chem.* **2000**, *55*, 8532.
(276) (a) Ichikawa, J.; Sokoda, K.; Mohara, J.; Ito, N. *J. Fluorine Chem.* **2007**, *127*, 489. (b) Sokoda, K.; Mohara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684.
(277) (a) Yokata, M.; Fujita, D.; Ichikawa, J. *Org. Lett.* **2007**, *9*, 4639. (b) Tanabe, H.; Ichikawa, J. *Chem. Lett.* **2010**, *39*, 248.
(278) Arthius, M.; Lecup, A.; Roulland, E. *Chem. Commun.* **2010**, *46*, 7810.
(279) Shimizu, M.; Yamada, N.; Takebe, Y.; Hata, T.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2903.
(280) Chen, C.; Wilcoxen, K.; Huang, C. Q.; Strck, N.; McCarthy, J. R. *J. Fluorine Chem.* **2000**, *101*, 285.
(281) Eddarir, S.; Abdelhadi, Z.; Rolando, C. *Tetrahedron Lett.* **2001**, *42*, 9127.
(282) Xu, J.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 3743.
(283) Eddarir, S.; Rolando, D. J. *J. Fluorine Chem.* **2004**, *125*, 377.
(284) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2877.
(285) Xu, J.; Burton, D. J. *J. Fluorine Chem.* **2007**, *128*, 71.
(286) Liu, Q.; Burton, D. J. *J. Fluorine Chem.* **2009**, *130*, 922.
(287) (a) Tellier, F.; Sauvêtre, R.; Normant, J. F. *J. Organomet. Chem.* **1986**, *303*, 309. (b) Tellier, F.; Sauvêtre, R.; Normant, J. F. *J. Organomet. Chem.* **1985**, *292*, 19. (c) Tellier, F.; Sauvêtre, R.; Normant, J. F. *J. Organomet. Chem.* **1989**, *364*, 17. (d) Martinet, R; Sauvêtre, R.; Normant, J. F. *J. Organomet. Chem.* **1989**, *367*, 1.
(288) Dutheuil, G.; Lei, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron* **2009**, *65*, 6034.
(289) Wang, Y.; Burton, D. J. *J. Org. Chem.* **2006**, *70*, 3859.
(290) Wang, Y.; Xu, J.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 7780.
(291) Xu, J.; Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 2555.
(292) Xu, J.; Burton, D. J. *J. Fluorine Chem.* **2004**, *125*, 725.
(293) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **1999**, *40*, 2243.
(294) Wang, Y.; Lu, L.; Burton, D. J. *J. Org. Chem.* **2006**, *70*, 10743.
(295) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *39*, 5541.
(296) Soderquist, J. A.; Leon, G.; Colbert, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, *36*, 3119.
(297) Uenishi, J.; Ohmi, M. *Heterocycles* **2003**, *61*, 365.
(298) Uenishi, J.; Iwamoto, T.; Ohmi, M. *Tetrahedron Lett.* **2007**, *48*, 1237.
(299) Uenischi, J.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2756.
(300) Oh, C. H.; Lim, Y. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 663.
(301) Kabalka, G. W.; Dong, G.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 763.
(302) (a) Kaafarani, B. R.; Neckers, D. C. *Tetrahedron Lett.* **2001**, *42*, 4099. (b) Kaafarani, B. R.; Pinkerton, A. A.; Neckers, D. C. *Tetrahedron Lett.* **2001**, *42*, 8137.
(303) (a) Hwang, H. T.; Son, H. S.; Ku, J. K.; Kim, B. H. *Org. Lett.* **2001**, *3*, 2469. (b) Hwang, H. T.; Son, H. S.; Ku, J. K.; Kim, B. H. *J. Am. Chem. Soc.* **2003**, *125*, 11241.
(304) Kim, Y. M.; Kim, Y. G. *J. Ind. Eng. Chem.* **1999**, *5*, 74.
(305) Donovan, P. M.; Scott, L. T. *J. Am. Chem. Soc.* **2004**, *126*, 3108.
(306) Bandyopadhyay, A.; Varghese, B.; Hopf, H.; Sankararaman, S. *Chem.—Eur. J.* **2007**, *13*, 3813.
(307) Gholami, M.; Melin, F.; McDonald, R.; Ferguson, M. J.; Echegoyen, L.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 9081.
(308) Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Efimova, I. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1989**, *35*, 1273.
(309) Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, *2*, 254.
(310) Li, Y.-H.; Zhao, X.-M.; Lu, L. *J. Fluorine Chem.* **2004**, *125*, 1821.
(311) Gu, S.; Xu, H.; Zhang, N.; Chen, W. *Chem.—Asian J.* **2010**, *5*, 1677.
(312) Arai, N.; Miyaoku, T.; Teruya, S.; Mori, A. *Tetrahedron Lett.* **2008**, *49*, 1000.
(313) Ramana, C. V.; Redy, B. K. K.; Reddy, C. N.; Gonnade, R. G.; Gurjar, M. K. *Synlett* **2007**, 127.
(314) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493.
(315) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054.
(316) Bryan, C. S.; Lautens, M. *Org. Lett.* **2010**, *12*, 3704.
(317) Ye, S.; Ren, H.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 670.
(318) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950.
(319) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
(320) Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625.
(321) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907.
(322) Chai, D. I.; Hoffmeister, L.; Lautens, M. *Org. Lett.* **2011**, *13*, 106.
(323) *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.
(324) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Wada, A.; Ito, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 320.
(325) Okamoto, Y.; Yoshikawa, Y.; Hayaschi, T. *J. Organomet. Chem.* **1989**, *359*, 143.
(326) Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361.
(327) Evano, G.; Tadiparthi, K.; Couty, F. *Chem. Commun.* **2011**, *47*, 179.
(328) Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873.
(329) (a) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (b) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (c) Lautens, M.; Fang, Y.-Q. PCT Int. Appl. WO 06047888, 2006; *Chem. Abstr.* **2006**, *144*, No. 468020.
(330) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203.
(331) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.
(332) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.
(333) Fang, Y.-Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341.
(334) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633.
(335) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034.
(336) Wang, Z.-J.; Yang, F.; Xin, L.; Bao, W. *J. Org. Chem.* **2011**, *76*, 976.
(337) Vieira, T. O; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899.
(338) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Org. Lett.* **2009**, *11*, 4608.
(339) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.
(340) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.
(341) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454.
(342) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, U. *J. Am. Chem. Soc.* **2008**, *130*, 1820.
(343) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064.
(344) Jeffrey, T. *Tetrahedron* **1996**, *52*, 10113.
(345) For heterocycle synthesis through the Pd-catalyzed intramolecular addition of a nitrogen nucleophile to an alkyne, see:(a) Kaspar, L.; Ackermann, L. *Tetrahedron Lett.* **2005**, *61*, 11311. (b) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289. (c) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.
(346) Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868.
(347) Xu, H.; Zhang, Y.; Huang, J.; Chen, W. *Org. Lett.* **2010**, *12*, 3704.
(348) Zapata, A. J.; Ruiz, J. *J. Organomet. Chem.* **1994**, *479*, C6–C8.
(349) Olivo, H. F.; Velazquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055.
(350) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.
(351) Rao, M. L. M.; Jadhav, D. N.; Dasgupta, P. *Org. Lett.* **2010**, *12*, 2048.

(352) Chelucci, G.; Capitta, F.; Baldino, S; Pinna., G. A. *Tetrahedron Lett.* **2007**, *37*, 6514.
(353) Rahimi, A.; Schmidt, A. *Synthesis* **2010**, 2621.
(354) Berciano, B. P.; Lebrequier, S.; Besselièvre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038.
(355) Coste, A.; Couty, F.; Evano, G. *Synthesis* **2010**, 1500.
(356) Galam, V.; Gopal, M.; Alper, H. *Organometallics* **1983**, *2*, 801.
(357) Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354.
(358) (a) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795. (b) Stang, P. J. *Chem. Rev* **1978**, *78*, 383. For selected recent examples of polyynes formation by using the FBW rearrangement, see:(c) Spantulescu, A.; Luu, T.; Zhao, Y.; McDonald, R.; Tykwinski, R. R. *Org. Lett.* **2008**, *10*, 609. (d) Kendall, J.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *Org. Lett.* **2008**, *10*, 2163. (e) Luu, T.; Morisaki, Y.; Cunningam, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622. (f) Tobe, R.; Umeda, R.; Iwasa, N.; Sonoda, M. *Chem.—Eur. J.* **2003**, *9*, 5549.
(359) Meurillon, M.; Gallier, F.; Peyrottes, S.; Périgaud, C. *Tetrahedron* **2009**, *65*, 6039.
(360) Ye, W.; Mo, J.; Zhao, T.; Xu, B. *Chem. Commun.* **2009**, 3246.
(361) Novoa, A.; Pellegrini-Moïse, N.; Lamandé-Langle, S.; Chapleur, Y. *Tetrahedron Lett.* **2009**, *50*, 6484.
(362) Novoa, A.; Pellegrini-Moïse, N.; Bourg, S.; Thoret, S.; Dubois, J.; Aubert, G.; Cresteil, T.; Chapleur, Y. *Eur. J. Med. Chem.* **2011**, *46*, 3570.
(363) Alvarez, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 13779.

NOTE ADDED AFTER ASAP PUBLICATION

In the version published on November 15, 2011, there were errors in references 31−34, the author changed his address, and he added Appendix 1 and three new references. This was all taken care of in the version published on December 22, 2011.