Stereocontrolled Synthesis of Tetrasubstituted Olefins

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1. Introduction

The efficient regio- and stereoselective synthesis of tetrasubstituted olefins bearing four different carbon-linked groups presents a particular challenge in organic synthesis. The congested nature of the double bond can make it difficult for reagents to approach, and the eclipsing interactions in the products destabilize both the products and the transition states leading to them. This eclipsing destabilization can be severe enough to force geometric distortions of the sp^2 centers. These issues are compounded by the modern expectation of forming single isomers on diverse scaffold. As a consequence of these formidable barriers, only recently has serious study been directed toward this synthetic challenge.

The significance of tetrasubstituted olefins is reflected in their presence in drugs such as Tamoxifen **1**[1] or Vioxx **2**,[2] natural products such as Nileprost analogues **3**[3] or *epi*-Illudol **4**,[4] and in derivatives of these and other biologically active substances (Figure 1).[5] Recently, compounds containing

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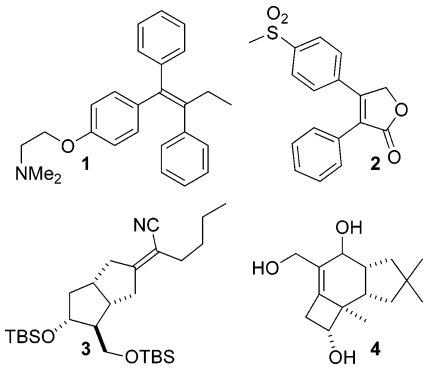


Figure 1. Biologically active compounds containing tetrasubstituted olefins.

tetrasubstituted alkenes have been examined for their potential as dipeptide mimetics[6] and as polymerization substrates or catalysts.[7] Stereodefined tetrasubstituted olefins are also key starting materials for various asymmetric transformations such as hydrogenations,[8] osmylations,[9] epoxidations,[10] and other processes that generate contiguous, stereogenic, sp^3-hybridized centers.[11]

Tetrasubstituted olefins are implicated in materials research because useful physical,[12] structural, and electronic properties may arise from the presence of the double bond.[13] A number of helicenes containing fully substituted alkenes have been prepared and are being studied as potential liquid crystals.[14] The hindered olefins are twisted in these compounds, imparting helical chirality to the structures. In other structures, the tetrasubstituted olefin may be conjugated in such a way so as to produce chromophores. The rotationally locked nature of the tetrasubstituted olefin can be exploited in molecular switches and other devices.[15] These compounds have been explored extensively for their potential use in optical data storage, among other applications.[16]

Classical double bond-forming methods such as the Wittig and Horner−Wadsworth−Emmons reactions encounter serious problems of generality and stereoselectivity when used to form tetrasubstituted double bonds. For this reason, indirect methods have been developed to synthesize tetrasubstituted olefins in geometrically defined ways. In this review, approaches to tetrasubstituted olefin formation are described that use a variety of strategies, with focus being on those olefins in which all four appendages are linked by carbon−carbon bonds. There are many examples of "tetrasubstituted olefins" possessing heteroatom linkages (enol ethers and enamines, for example) that have not been included here. Currently, the most frequently used routes to tetrasubstituted olefins employ different types of alkynyl carbometallation strategies, although another common technique is the transformation of existing olefins. Some representative papers using "traditional" olefin formation methods such as the Wittig and Horner−Wadsworth−Emmons reactions are discussed briefly, and for more details of these processes, the reader is directed toward comprehensive reviews of these reactions.[17] The descriptions of cycloaddition reactions to form tetrasubstituted olefins have been limited because the olefin moieties are often produced as an artifact of the method rather than as a targeted preparation, and because many of these processes have been previously reviewed.[18] Strategies such as olefin metathesis, radical sequences, and ynolate chemistry are just beginning to emerge as viable techniques for the formation of tetrasubstituted olefins, and we have highlighted the key contributions in this area. Reflective of the difficulty of the problem, most methods that were developed prior to 1995 produce mixtures of isomers. Only in the last 10 years or so has more attention been devoted to this selectivity problem, and technology is slowly emerging to form single isomer products.

1.1. Structures of Tetrasubstituted Olefins

The construction of tetrasubstituted olefins first requires a consideration of their shape and steric requirements. Fully substituted contiguous sp^2 centers experience eclipsing and steric interactions that can severely distort the double bonds. The degree of distortion is reflected in twisting along the olefin and depends on the steric demands of the substrates. Tetra-aryl-substituted product **5** was isolated and crystallized by Daik et al. in 1998.[19] The X-ray structure showed an 11−12° departure from planarity for the olefin system, as shown in Figure 2. The geminal substituents on each terminal carbon

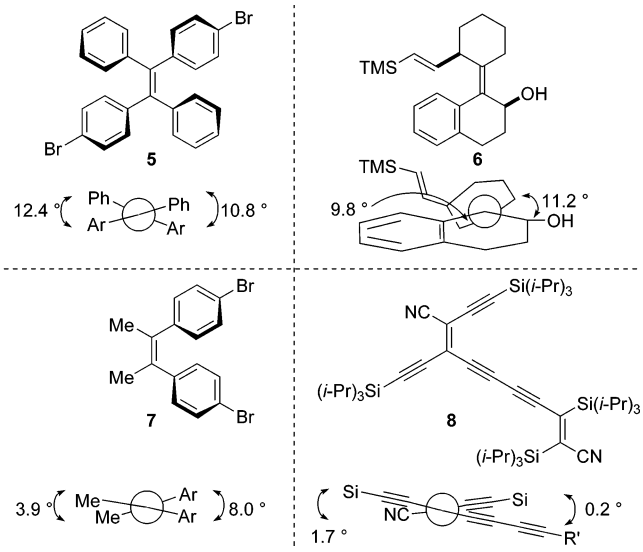


Figure 2. Selected examples of twisting about double bonds to minimize steric interactions.

(Ar and Ph) of the alkene remain almost 180° apart, and so the compounds are twisted along the axis of the double bond, as in the Newman projection of **5**. Similar twisting was found in cycloalkyl product **6**, prepared by Tietze et al., in which the improper torsion was found to be as much as 11°.[20] Smaller substituents on the olefin carbons reduce the steric compression and give flatter structures. The methyl groups in **7** experienced less eclipsing than the aryl rings, resulting in an olefin that was closer to planarity.[19] The aryl groups produced more steric strain, resulting in a slightly larger dihedral angle between these moieties than between the methyl groups. Olefin **8** was affected very little by the acetylene groups, a fact reflected in the very small dihedral angles along the olefin bond.[21] Twisted tetrasubstituted olefins have also been demonstrated in several other systems.[5b,d,22]

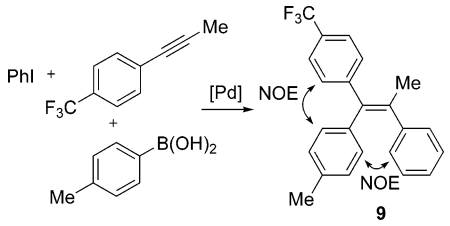
1.2. Structure Determination

It is generally straightforward to determine the relative ratios of isomeric products obtained from various synthetic strategies, using techniques such as NMR, GC, or HPLC. Challenges may be experienced when using LC or HPLC, however, because the low polarity of many of the products

can impair resolution. In a surprising number of reports, researchers have assigned the stereochemistry of their products based only on the syn or anti preferences of the chosen reaction processes, an assumption that has, in some cases, been shown to be false. Establishing the regiochemistry and stereochemistry of tetrasubstituted olefins in the absence of X-ray results requires particular attention to detail because no direct NMR couplings to olefinic protons are available. NOE measurements can be complicated with these compounds as each substituent can experience interactions with two of the other groups.

This method of structure determination has been used by the Larock group, in which the structures of tetrasubstituted olefins such as **9** were proven through NOESY experiments performed on each product of the study (Scheme 1).[23] The

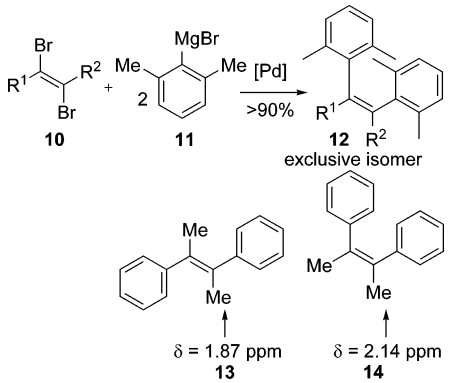
Scheme 1. Representative Use of an NOE Network To Determine Regio- and Stereochemistry



regiochemistry of addition was first elucidated, using an NOE interaction between the geminal aryl moieties. The second key observation showed that addition of the two components across the alkyne had proceeded in a syn fashion, made evident by the NOE enhancement found between the substituents as shown.

In much of the tetrasubstituted olefin literature, the structures of products are assumed rather than rigorously confirmed. For example, the bromination of alkynes is known to proceed in an anti fashion; therefore, it is often assumed that subsequent organometallic couplings, for example, will produce products that retain a trans relationship between the newly introduced substituents. The implications of this are that some methods may actually produce different products from those reported. A case in point is coupling reactions of (*Z*)-dihaloalkenes, which frequently result in stereochemical changes, and therefore product geometry issues. In a report by Rathore et al.,[24] (*E*)-dibromoolefins **10** underwent double Kumada coupling with congested Grignard reagent **11**, affording the (*Z*)-product **12** exclusively, a fact clearly established by X-ray (Scheme 2). This result could not have been anticipated by a simple assumption of the retention of

Scheme 2. A Surprising Result Requiring Careful Product Identification



configuration during coupling, especially given the size of the Grignard reagent transferred.

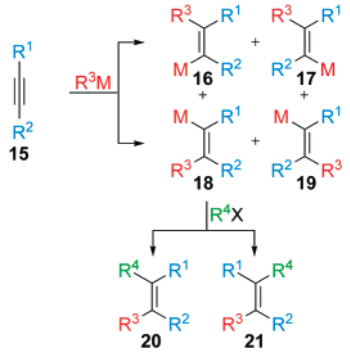
The analysis of chemical shift patterns has been employed to establish stereochemistry. For example, the methylene hydrogens of (*Z*)-stillbene-type hydrocarbons (**14**) are reported to resonate downfield of the signals of the corresponding protons of the (*E*)-isomer **13**.[25] This has been supported conclusively in at least one case by using X-ray crystallography to correlate the NMR assignments.[19]

In the following pages, the articles that have reported clear and thorough product identification have been highlighted as a reference point for those seeking to establish the regio- and stereochemistry of tetrasubstituted olefin products.

2. Carbometallation of Alkynes

The carbometallation of alkynes is the most widely used method for the formation of tetrasubstituted olefins.[26] In principle, a high degree of control is possible in these processes, and significant structural variation is attainable because of the convergent nature of the strategy. Regio- and stereocontrol are two key issues to be addressed in this technology, as multiple products are possible (Scheme 3).

Scheme 3. Regio- and Stereoisomeric Possibilities from Carbometallation Processes



The problem of regioselectivity has been addressed by the use of directing groups, or by employing symmetrical alkynes as substrates. The use of symmetrical alkynes greatly simplifies many of the synthetic issues; however, this results in a decrease in structural flexibility. With unsymmetrical alkyne substrates, directing groups of some sort are routinely employed to avoid the formation of isomeric mixtures. This directing influence may be steric, electronic, or chelating in nature.

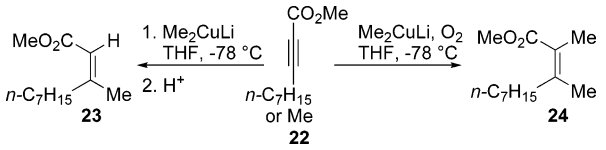
Depending on the nature of the metal or catalyst used, the carbometallation of the alkyne may proceed in a syn or anti fashion. Although the initial addition across the π bond may be stereoselective or stereospecific, in some cases there is configurational erosion or full inversion during the subsequent coupling reaction (i.e., **18** can produce **20** or **21** depending on reaction conditions). This is usually a consequence of the low reactivity of the intermediates; however, some researchers have identified electronic contributions to these occurrences, particularly when the intermediate organometallic species is of low nucleophilicity. Loss of configurational integrity typically occurs through enolization or elimination processes. This can be suppressed by manipulating the ionic character of the metal, by improving substrate design, by carefully selecting the catalyst, or by simply keeping the solution cold. In the following sections, the strategies have been organized according to the metal used

to affect the carbometalation. The strategies relating to the reactions of allenes, however, have been treated separately.

2.1. Copper

Some of the earliest attempted carbometalations involved the syn conjugate addition of copper species to α,β-acetylenic esters **22**. Regiochemical control was achieved by directing the addition of the organic substituent to the β-position (Scheme 4).[27] Quenching the reactions at −78 °C gave

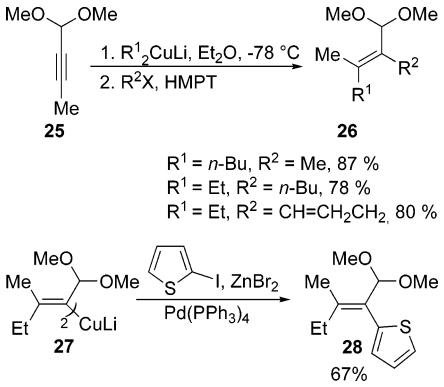
Scheme 4. Carbocupration of Alkynoates



trisubstituted olefins such as **23** in good yield and with excellent stereoselectivity (*E*:*Z* 99.5:0.5 to 99.8:0.2) provided that THF was used as the solvent. It was noted that equilibration of the cuprate intermediates occurred at higher temperatures and so quenching at −78 °C was imperative. Using a large excess of Gilman reagent in the presence of oxygen gave the tetrasubstituted product **24** in unspecified yield.[28]

Alexakis et al. approached the problem of enolization by using acetals as directing groups (Scheme 5).[29] The addition

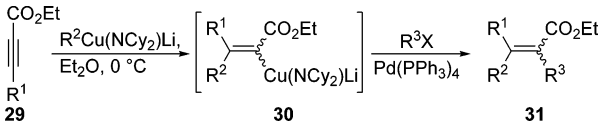
Scheme 5. Tetrasubstituted Olefins from Alkynyl Acetals



of Gilman reagents to alkynyl acetals proceeded with high selectivity and stereointegrity in THF at low temperatures. Significant effort was invested to elucidate the factors controlling regio- and stereoselectivity in the initial cuprate addition. Copper species derived from organolithiums were required, and the reactions had to be performed in THF to prevent the competing elimination pathway to form allenes. The intermediate vinylogous cuprates proved to have low reactivity, and tetrasubstituted olefins could only be obtained by using powerful electrophiles such as methyl iodide or allyl bromide. More diversity was achieved using electrophiles such as butyl iodide in the presence of 4 equiv of HMPT, and two examples were given of palladium-mediated cross-couplings after in-situ conversion of the cuprates to the corresponding zinc species.

The palladium-catalyzed cross-coupling of organocuprates was subsequently used to generate tetrasubstituted olefins from acetylenic esters (Table 1).[30] In this study, cuprates carrying a dicyclohexylamido dummy ligand were employed. The addition of $R^2Cu(NCy_2)Li$ to an acetylenic ester at 0 °C gave an intermediate organocuprate species that was

Table 1. Tetrasubstituted Olefins by Organocuprate Addition to Acetylenic Esters

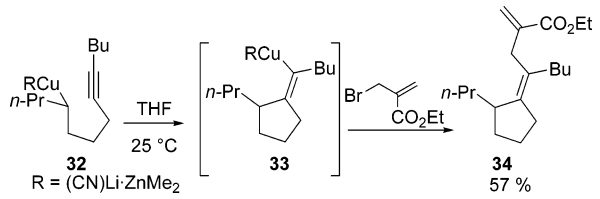


entry	R^1	R^2	R^3X	yield (*Z*:*E*)
1	Me	Me	PhI	89
2	Me	Me	PhBr	60
3	Me	Me	(*E*)-BuCH=CHI	62
4	Me	Me	(*E*)-PhCH=CHBr	59
5	Me	Me		70
6	Me	Me	$PhCH_2I$	53
7	Me	Bu	PhI	61 (40:60)
8	Me	Ph	PhI	77 (44:56)
9	Ph	Me	PhI	52 (38:62)

efficiently coupled to several vinylogous halides in the presence of $Pd(PPh_3)_4$. This method was useful for the formation of tetrasubstituted olefins that carried identical substituents on the β-carbon of the unsaturated ester **31** ($R^1 = R^2 =$ Me), because the low reactivity of the intermediate copper species (**30**) necessitated room-temperature treatment during the palladium-catalyzed cross-coupling reaction. This increased temperature resulted in ca. 1:1 mixtures of *E* and *Z* isomers through enolization of the intermediate copper anions when the preparation of differentially substituted products ($R^1 \neq$ Me) was attempted (entries 7−9). One example was reported of a tetrasubstituted double bond bearing four different groups with an *E* to *Z* ratio of 6:4 (entry 7).

The difficulties associated with achieving regiochemical control in the addition of alkyl copper onto simple alkynes were addressed by Rao and Knochel who used an intramolecular delivery of the organocopper species (Scheme 6).[31]

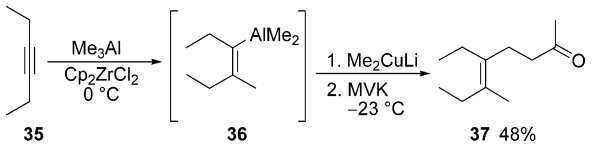
Scheme 6. Intramolecular Carbocupration



Thus, zinc−copper intermediates such as **32** generated from the corresponding alkylzinc halides and CuCN·LiCl underwent an intramolecular carbometallation to produce cyclic intermediates **33**. Because the structures of the intermediate vinyl cuprates precluded enolization, the condensations could be done at elevated temperatures without any loss of stereochemical integrity, thus increasing the reactivity of **33** toward electrophiles.

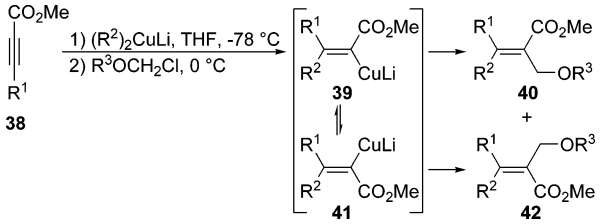
Regiochemical issues have been circumvented by using symmetrically substituted alkynes. Thus, the Wipf group[32] employed Schwartz chemistry[33] by exposing 3-hexyne to Me_3Al in the presence of Cp_2ZrCl_2 to generate vinylic alane **36** (Scheme 7). This intermediate could then be transmetalated to the corresponding copper reagent for subsequent condensations with methyl vinyl ketone (MVK). In this manner, derivative **37** was made in 48% overall yield.

Scheme 7. Approach to Tetrasubstituted Alkenes Using Symmetric Alkynes



Deslongchamps and co-workers exploited the reactivity of α-halo ethers to improve the scope of electrophilic additions with vinyl cuprates (Table 2).[34] The high reactivity

Table 2. Addition of Organocuprates and α-Halo Ethers to Acetylenic Esters



entry	R^1	R^2	R^3	yield (%) (**40**:**42**)
1	$TBDPSO(CH_2)_2$	Me	$BnOCH_2$	59 (24:1)
2	$TBDPSO(CH_2)_2$	Me	$4\text{-}MeOC_6H_4OCH_2$	66 (6:1)
3	$TBDPSO(CH_2)_2$	Me	$Me_3Si(CH_2)_2OCH_2$	68 (>25:1)
4	$TBDPSO(CH_2)_2$	Me	$MeOCH_2$	87 (25:1)
5	$TBDPSO(CH_2)_2$	Bu	$Me_3Si(CH_2)_2OCH_2$	61 (4.5:1)
6	$TBDPSO(CH_2)_3$	Me	$4\text{-}MeOC_6H_4OCH_2$	72 (6:1)
7[a]	Et	Me	$BnOCH_2$	70 (10:1)

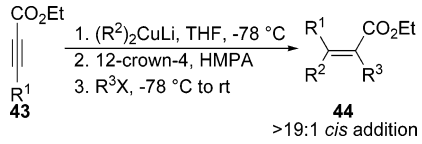
[a] Ethyl ester was used.

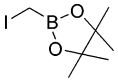
of the α-halo ethers allowed the temperature of the final alkylation to be lowered to 0 °C, thus improving selectivity. This method delivered more than 10 examples of tetrasubstituted products **40** and **42** in yields greater than 59%, with typical selectivities of greater than 5:1 (**40**:**42**). In four cases, the minor products (**42**) were not detected.

This technology was later expanded to improve the substrate scope (Table 3).[35] Excellent regio- and stereoselectivities were achieved by using additives such as HMPA and 12-crown-4 to control the extent of allenoate formation. 12-Crown-4 was added to chelate excess lithium, a species known to degrade stereochemical information in related substrates.[11a,36] The use of this additive alone gave unsatisfactory yields with the electrophiles attempted, and to overcome this several equivalents of HMPA were included. These conditions were applied to a number of active electrophiles giving excellent selectivity in all cases. This methodology has since been applied to acid-catalyzed allylboration reactions to generate stereogenic quaternary centers.[37]

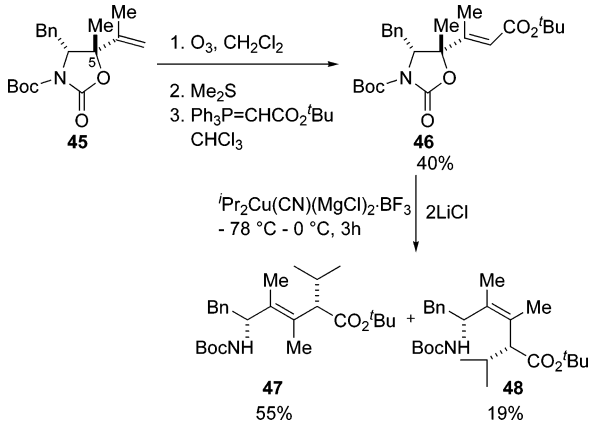
Oishi and co-workers have reported the preparation of di-, tri-, and tetrasubstituted olefins through the ring opening of chiral 1,3-oxazolidin-2-ones by organocopper reagents (Scheme 8).[38] Two examples showed the application of this methodology to the synthesis of tetrasubstituted olefins. The treatment of oxazolidinone **45** with ozone and dimethylsulfide followed by an *E*-selective Wittig reaction gave α,β-enoates **46** in 40%

Table 3. Addition of Organocuprates and α-Halo Ethers to Acetylenic Esters



entry	R^1	R^2	R^3X	yield (%)
1	Et	Me	ICH_2SnBu_3	80
2	Et	Me	ICH_2SiMe_3	30
3	Et	Me	$BrCH_2Ph$	40
4	Et	Me	$BrCH_2CH{=}CH_2$	76
5	Et	Me	$BrCH_2C(Br){=}CH_2$	57
6	Et	Me	$BrCH_2CH{=}CMe_2$	78
7	Et	*s*-Bu	$BrCH_2CH{=}CH_2$	72
8	$TBDPSOCH_2$	Me	$BrCH_2CH{=}CH_2$	85
9	Et	Me		66

Scheme 8. Ring Opening of Chiral 1,3-Oxazolidin-2-ones by Organocopper Reagents



yield for the isomer shown and in 71% yield for the isomer epimeric at C5. An organocopper-mediated alkylation of **46** gave a mixture of tetrasubstituted products **47** and **48** in 55% and 19% yields (HPLC), respectively. Treatment of the C5 epimer gave a mixture of the related products in 75% and 20% yields (*E*:*Z*). The authors gave a detailed analysis of two plausible mechanistic pathways, suggesting that the reaction could proceed either via a direct alkylation by the organocopper reagent or through a copper π-allyl complex. This methodology has since been used by the same workers in the synthesis of dipeptide mimetics that were subjected to conformational studies.[6] The tetrasubstituted olefin moieties were employed as amide isosteres in this study.

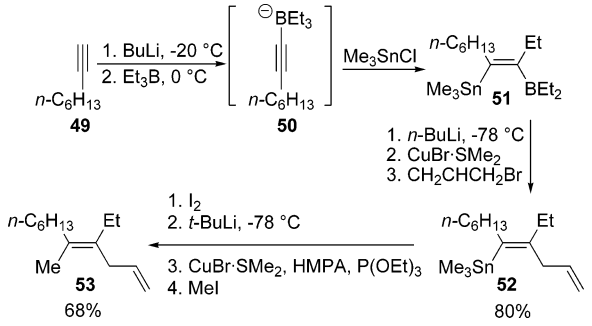
2.2. Boron

The use of boron instead of copper for the carbometallation of alkynes offers significant reactivity advantages because the intermediate vinyl boranes make excellent cross-coupling partners for subsequent palladium-mediated processes. Regiochemical issues can be addressed through the use of directing groups, or avoided by making symmetrically substituted products. The loss of stereochemical information occurs less frequently with these types of reactions than with organocuprates because unactivated alkynes can be used as substrates. The initial carbometallations occur with cis geometry, although a loss of stereopurity sometimes occurs during the subsequent cross-coupling reaction. Substrate

scope can be somewhat limited for these reactions as the couplings are normally done with simple aryl and alkenyl partners.

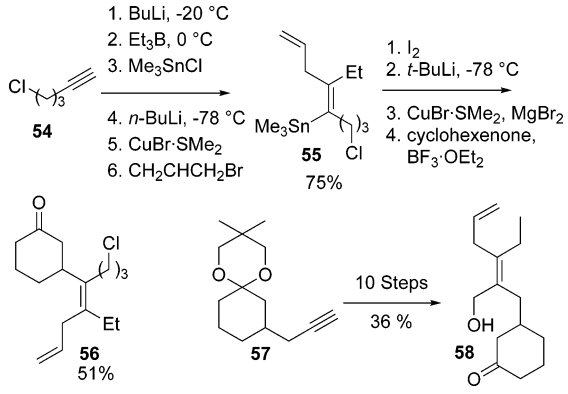
Early work illustrated a method for the generation of tetrasubstituted alkenes involving a tin-induced alkyl transfer from a boron-ate complex followed by functionalization (Scheme 9).[39] In this method, a lithium acetylide, generated

Scheme 9. Rearrangement of Boron Ate-Complexes To Give Tetrasubstituted Olefins



from acetylene **49**, was transmetalated with Et_3B to produce -ate complex **50**. This material then rearranged and was trapped in the presence of trimethyltin chloride to afford tin adduct **51** as a single isomer.[40] The intramolecular delivery of the ethyl group from boron ensured that the process was regiospecific. The crude intermediate **51** underwent transmetallation twice, once with *n*-BuLi and then with CuBr·SMe_2, a process that was necessary to avoid losing stereochemical information. The resulting organocuprate was quenched with allylbromide to give vinyl tin adduct **52**. The tin group proved to be remarkably resistant to lithium exchange, allowing for excellent regioselectivity in this process. The low reactivity of the tin moiety necessitated a halogen exchange before subsequent elaboration could be attempted, and a further three steps (lithium exchange, copper exchange, and quench with MeI) were required to produce adduct **53** as a single isomer in 54% overall yield from **49**. This 10-step sequence was applied in two other cases (Scheme 10), using cyclohexenone as the terminal electro-

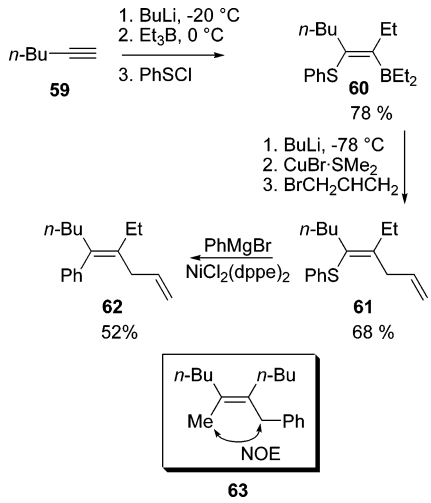
Scheme 10



phile. In each case, single isomers were obtained.

Using a similar method, Gerard et al. demonstrated the rearrangement of a boron-ate complex in the presence of PhSCl to give the intermediate species **60** in 78% overall yield from **59** (Scheme 11).[41] Direct coupling to produce **62** using the Suzuki−Miyaura protocol failed, giving *n*-Bu−C≡C−Et instead, and therefore an alternate route was required. The vinyl borane **60** was transmetalated with

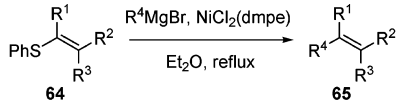
Scheme 11. Rearrangement of Boron Ate-Complexes To Give Tetrasubstituted Olefins

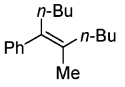
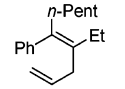
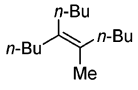
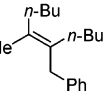


butyllithium, and the resulting lithio species transmetalated with copper to give a product that could then react with allylbromide to afford **61**. A final nickel-mediated cross-coupling reaction with **61** gave **62** as the endpoint of the seven-step sequence in 28% overall yield (based on recovered starting material) from **59**. One example was given of a tetrasubstituted olefin, which was obtained as a single isomer.

This method was subsequently elaborated, and the preparation of a series of tetraalkyl-substituted olefins disclosed (Table 4).[42] Commencing with intermediate boranes similar

Table 4. Transformation of β-Chalcogeno Alkenyllboranes



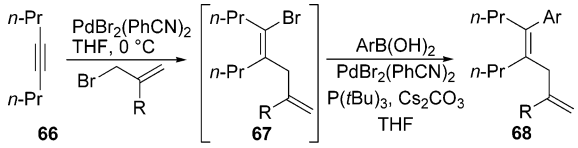
entry	R^1	R^2	R^3	R^4	product	*E/Z*	yield (%)
1	*n*-Bu	*n*-Bu	Me	Ph		>99:1	82
2	*n*-Pent	Et	allyl	Ph		<1:99	38
3	*n*-Bu	*n*-Bu	Me	*n*-Bu		-	70
4	*n*-Bu	*n*-Bu	CH_2Ph	Me		>99:1	24

to **60** in structure, a lithium−boron exchange was performed using MeLi in the presence of HMPA. The resulting lithio species could be converted to the corresponding cuprates by the addition of CuI, and then alkylation was accomplished as before using reactive electrophiles. Reactions that were performed in the presence of HMPA could be run at slightly elevated temperatures (−33 °C), thus increasing the reactivity of the metal species and delivering corresponding yield improvements. When less active alkylating agents were employed, the presence of $P(OEt)_3$ during the alkylation was necessary to realize significant amounts of intermediates (**64**) analogous to **61**. The scope of the final nickel-catalyzed

coupling was expanded in this account to include a variety of Grignard coupling partners. The structures of the final products were inferred on the basis of the preference of the boron-to-lithium exchange to occur with retention of stereochemistry,[11] and by the results of an NOE experiment that was conducted on one isomer (**63**).

A method was recently reported to prepare tetrasubstituted olefins as part of skipped diene systems.[43] A technique developed by Kaneda and co-workers[44] was modified to produce skipped dienes such as **68** (Scheme 12). In the

Scheme 12. Tetrasubstituted Olefins in a Skipped Diene System



R = H, Ar = 3-$NO_2C_6H_4$, 79 %
R = Me, Ar = *N*-tosyl-3-indoyl, 83 %

original work,[44] it was found that a large excess of allyl bromide was necessary to promote the initial alkyne addition, a constraint that limited the practicality of the process. Rawal's group demonstrated that slow addition of the alkyne reduced polymerizing side reactions and gave the desired bromides **67**. Regiochemical issues in these reactions were circumvented by using symmetrical alkynes.[45] The subsequent Suzuki reactions could then be done in the same flask simply by adding the appropriate reagents upon completion of the allyl additions. The stereochemical assignments of the final products were based on the initial syn addition across the alkyne.

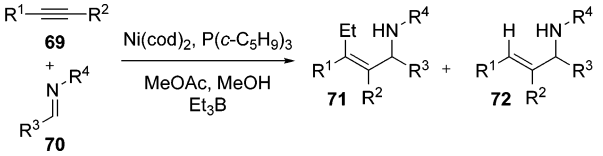
Patel and Jamison developed a multicomponent method of tetrasubstituted olefin formation involving a nickel-catalyzed addition of imines to alkynes, followed by an alkylative coupling with an ethyl group from the borane to give **71** (Table 5).[46] The reactions were regioselective (>9:1) with respect to imine addition and were accompanied by small amounts of reduction products **72** (4−10%). Nine different imines, bearing a variety of functional groups, were successfully coupled with two different alkynes (PhC≡CMe and *n*Pr−C≡C−*n*Pr). It was also found that aryl and vinylboronic acids, used in the place of triethylborane, were compatible with the process, resulting in yields of 68−72%.

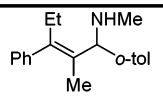
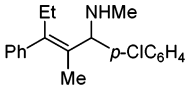
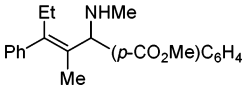
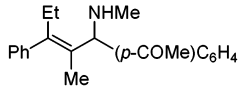
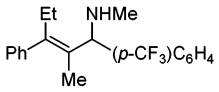
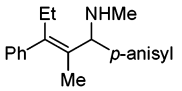
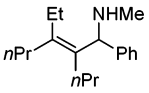
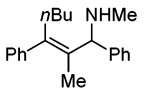
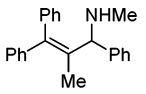
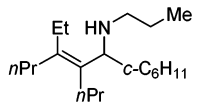
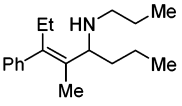
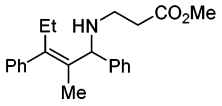
Suginome, Yamamoto, and Murakami used a directing group to control the cyanoboration of homopropargylic alcohols (Scheme 13).[47] Primary homopropargylic alcohols, such as **73**, were converted to initial cyanoboryl ethers **74** by a three-step procedure. Compound **74** smoothly underwent a cyclo-cyanoboration with the alkyne moiety, giving intermediate adduct **75** as a single stereoisomer in 94% isolated yield. In the examples provided, the products were obtained as single isomers, but slight *E*/*Z* isomerization was observed in one case (93:7). The intermediate boryl ether **75** was converted to tetrasubstituted alkene **76** using rhodium catalysis. Two other examples were given of tetrasubstituted olefins (**77** and **78**), each obtained by a Suzuki cross-coupling using the appropriate aryl iodide.

Subsequently, it was shown that when chloroboryl ethers were treated with alkynyl stannanes in the presence of a nickel catalyst, trans addition across the alkyne occurred, to deliver cycloboranes such as **80** (Scheme 14).[48] The production of the trans product **80** was thought to arise from a cis/trans isomerization prior to insertion into the alkyne, brought about by unfavorable steric interactions between the nickel complex and the bulky amine group on the boron. One of the crude intermediates, **80** (R^2 = Et, R^3 = Ph, R^1 = Me), was cross-coupled with an aryl iodide or a vinyl bromide to afford products **81** and **82**, respectively.

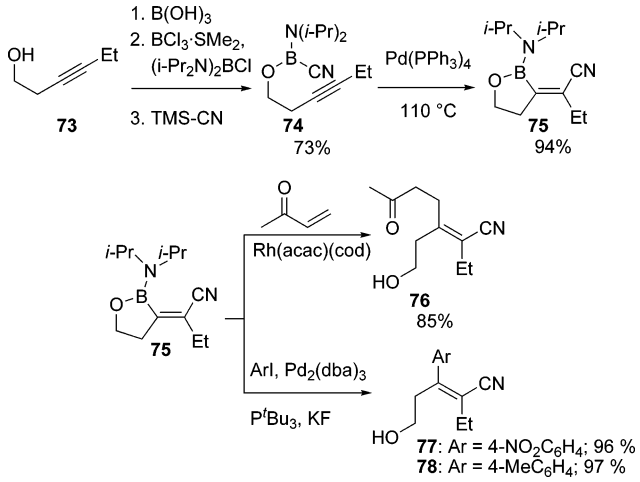
This methodology also worked in an intermolecular sense (Table 6), achieving excellent regioselectivity for differentially substituted alkynes, provided that a bulky cyanoborane was employed.[49]

Table 5. Multicomponent Assembly of Alkynes, Imines, and Organoboron Reagents



entry	product	yield (%)	ratio (**71**:**72**)	regio-selectivity
1		85	94:6	90:10
2		95	96:4	90:10
3		82	> 96:4	90:10
4		78	> 96:4	91:9
5		98	96:4	89:11
6		64	86:14	91:9
7		91	94:6	-
8		70	90:10	91:9
9		65	-	93:7
10		52	> 96:4	-
11		30	90:10	91:9
12		75	94:6	91:9

Scheme 13. Intramolecular Cyclocyanoboration of Alkynes



Scheme 14. Tetrasubstituted Esters from Cycloboration of Chloroboryl Alkynyl Ethers

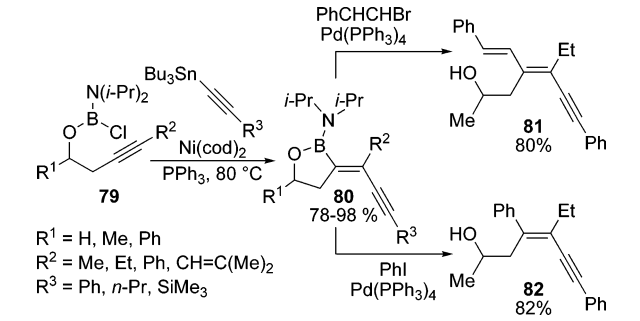
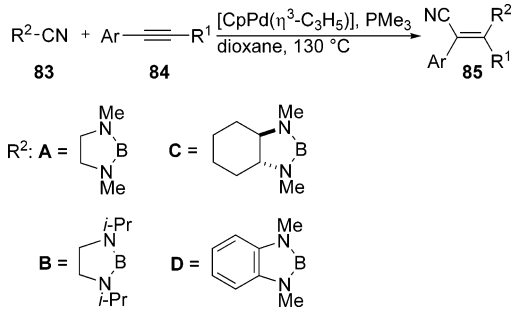


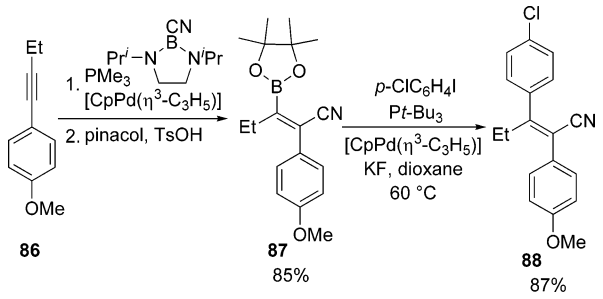
Table 6. Intermolecular Cyanoborane Addition to Alkynes



entry	Ar	R^1	R^2	regioisomeric ratio	yield (%)
1	Ph	Me	**A**	85:15	77
2	Ph	Me	**B**	95:5	94
3	Ph	Me	**C**	83:17	97
4	Ph	Me	**D**	83:17	96
5	Ph	Bu	**B**	95:5	89
6	4-$EtO_2CC_6H_4$	Bu	**B**	88:12	72
7	4-$CF_3C_6H_4$	Me	**B**	93:7	81
8	2-$CH_3C_6H_4$	Bu	**B**	98:2	59
9	2-$MOMOC_6H_4$	Bu	**B**	99:1	80
10	1-naphthyl	Me	**B**	99:1	72
11	2-naphthyl	Bu	**B**	91:9	61

One demonstration of the conversion of these borylated products into tetrasubstituted olefins using a Suzuki coupling reaction afforded **88**, the precursor to a squalene synthetase inhibitor, in 74% overall yield from the starting alkyne **86** (Scheme 15). For the Suzuki process to be successful, however, the boron moiety first had to be converted to the pinacol boronate ester.

Scheme 15. Generation of Tetrasubstituted Olefins from Intermolecular Cyanoboration

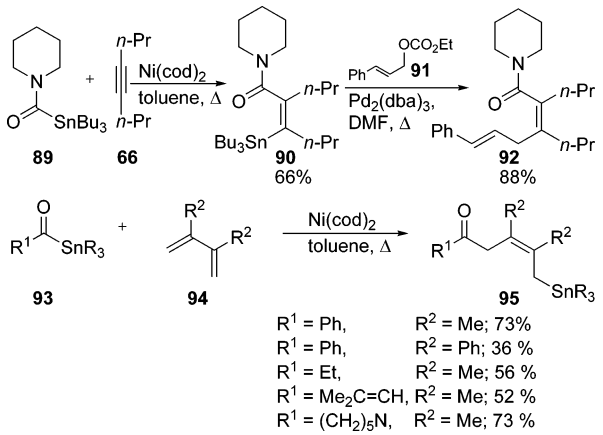


2.3. Tin

The use of tin coupling reactions in tetrasubstituted olefin preparation has received somewhat less attention than the use of boron or copper. As with all methods using tin, toxicity and purification problems are encountered, in addition to the wonderful smell. The tin-mediated methods tend to be highly stereoselective but moderately regioselective.

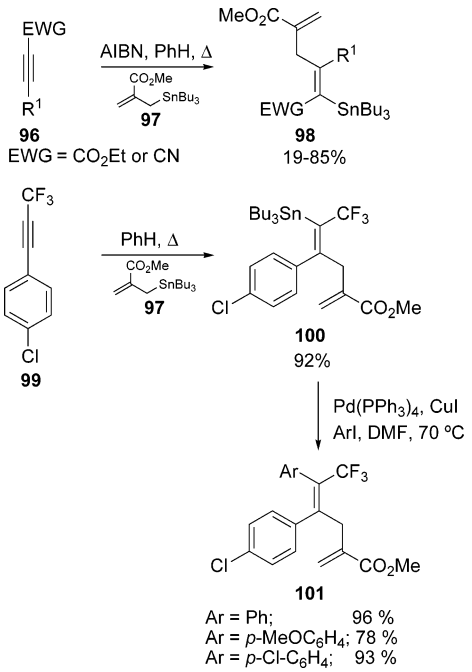
Shirakawa et al. found that $Ni(cod)_2$ catalyzed the addition of an allyl or acyl stannane such as **89** to an alkyne such as **66** to give an initial vinylic stannane **90** with excellent cis-selectivity (>99:1) (Scheme 16).[50] In the case of unsymmetrical alkynes, the major regioisomers resulted from addition of the tributyltin moiety to the more electron-deficient alkynyl carbon. Two examples of tetrasubstituted alkenes were given in which the substrate was then elaborated using palladium-mediated allylation and carbonylation reactions. While the acylstannylations gave mixtures of regioisomers in ratios as low as 2:1, the allylstannylations were highly regioselective with many reactions giving selectivities of more than 99:1. These authors later reported a variation in which acyl stannanes could be added across disubstituted dienes (**94**) to afford derivatives such as **95**.[51] Yields of 36−73% were realized, and single isomers were obtained when symmetrically substituted dienes were employed.

Scheme 16. Addition of Acyl Stannanes to Alkynes



When differentially substituted alkynes were used, a radical carbostannylation could be done regioselectively if electron-withdrawing groups were present. This principle was demonstrated by Miura et al., who used alkynoate esters such as **96** to direct the addition of tin radicals to the triple bond (Scheme 17).[52] Vinyl tin species such as **98** were obtained in 19−85% yields along with small amounts of stereo- and regioisomeric side products. The resulting vinyl tin com-

Scheme 17. Carbostannylation of Differentially Substituted Alkynes

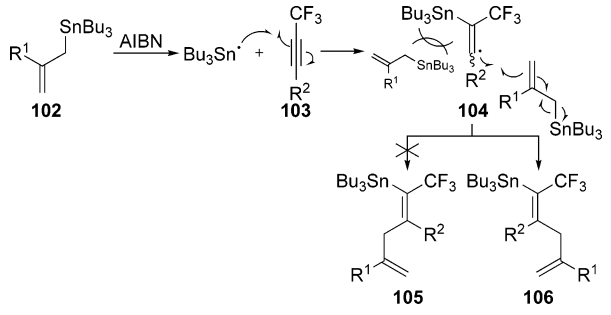


pounds (**98**) were not converted to tetrasubstituted olefins, but in principle the products could be so utilized.

In a similar strategy, CF_3 groups were used, instead of alkynoate esters, to direct the addition of tin radicals (Scheme 17). The CF_3 group exerted powerful regiocontrol, completely reversing the selectivity observed for aryl-alkyl-alkynes. Allyl tin reagent **97** was successfully added to a series of CF_3-substituted alkynes such as **99**, which gave the corresponding olefins **100**. Addition occurred in a trans fashion with complete control of regio- and stereochemistry.[53] Eight related alkynes were carbostannylated in 44−99% isolated yields. Further Stille couplings of stannane **100** with three different aryl iodides gave the corresponding tetrasubstituted olefins **101** in 78−96% yield.

The proposed mechanism for the carbostannylation reaction involved an initial addition of a Bu_3Sn radical to the alkyne **103**. This resulted in an intermediate radical **104**, which had indeterminate stereochemistry at the sp^2-hybridized center (Scheme 18).[53] Selective addition of the allyltin

Scheme 18. Proposed Mechanism of Radical Carbostannylation of Alkynes



moiety was thought to be a consequence of strong steric interactions between the Bu_3Sn group and the incoming allyl reagent, forcing these two groups to become anti to one another in the product (**106**).

The one-pot synthesis of tetrasubstituted alkenes was subsequently accomplished via the carbopalladation of fluorine-containing acetylene derivatives (Table 7).[54] In this account, the fluorinated substituents did not seem to provide sufficient electronic bias to govern the regioselectivity of the addition. Mixtures of regioisomers were obtained when iodides and boronic acids bearing different aryl substituents were employed (entries 11−15).

This method was complimentary to a technique reported by the Ramachandran group that involved the radical-mediated addition of fluoroalkyl iodides to alkynes.[55] Although most of the alkynes described were terminal, two internal alkynes were employed, giving vinylic iodide products. These could, in principle, serve as coupling partners to generate tetrasubstituted alkenes. Yields greater than 72% and *E*/*Z* ratios of more than 91:9 were obtained, although regioisomers resulted from the use of an unsymmetrical alkyne.

2.4. Magnesium

The addition of Grignard reagents to alkynes has proven to be highly successful, using directing groups to achieve reliable regioselectivity. The organomagnesium addition to the alkyne often proceeds in a trans fashion, resulting in predictable stereochemical outcomes. This anti addition is complementary to many transition metal-catalyzed processes, which often occur in a syn manner. All of the methods shown build on a previously developed carbomagnesiation process,[56] in which 2 equiv of a Grignard reagent was added to propargylic alcohols in a highly selective fashion (Scheme 19).

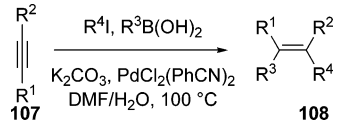
This process was exploited by the Negishi group, who showed that the magnesium species could be converted into iodides **111**, intermediates that could be cross-coupled using zinc reagents after protecting the hydroxyl group.[57] The anti addition of the Grignard reagent set the initial stereochemistry that was preserved in the subsequent coupling to give tetrasubstituted olefins such as **112**. The group later utilized this technology to synthesize a series of bisabolenes.

The Oshima group found that the carbomagnesiation could be catalyzed by manganese compounds.[58] Propargylic or homopropargylic alcohols (or ethers) **113** could be treated with organomanganese species and then trapped with electrophiles such as benzaldehyde or allyl bromide to directly afford tetrasubstituted alkene products such as **114** (Table 8). This process typically occurred in a syn fashion.

Another example of a tetrasubstituted olefin being produced by this type of Grignard addition was disclosed in 1990 (Scheme 20).[59] This method built on the carbomagnesiation process developed earlier[56] in which 2 equiv of Grignard reagent was added to propargylic alcohols, giving the cyclic intermediate **116**, in a highly selective manner. Quenching this intermediate with I_2 gave the corresponding iodo alcohol that could be protected with a TBS group to afford **117** in 51% yield from **115**. It was found that compound **117** could be rendered nucleophilic by lithium exchange followed by copper exchange and that the resulting intermediate could be exposed to a Michael acceptor to afford **118** as the sole product.

This methodology was extended and made practical by eliminating the halogenation/double-exchange sequence through direct electrophile displacement (Scheme 21).[60] The cyclomagnesium species were formed directly and could be treated with aldehydes to give tetrasubstituted olefins such as **121**. For successful reactions, the aldehyde addition required reflux temperatures in a mixture of THF and

Table 7. Carbopalladation of Fluorine-Containing Acetylene Derivatives



entry	R^1	R^2	R^3	R^4	yield (%)[a]	ratio
1	CF_3	4-ClC_6H_4	Ph	Ph	85	
2	CF_3	4-ClC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	(86)	
3	CF_3	4-ClC_6H_4	4-MeC_6H_4	4-MeC_6H_4	82	
4	CF_3	4-$MeOC_6H_4$	Ph	Ph	(88)	
5	CF_3	4-MeC_6H_4	Ph	Ph	81	
6	CF_3	3-$MeOC_6H_4$	Ph	Ph	71	
7	CF_3	2-$MeOC_6H_4$	Ph	Ph	(85)	
8	CF_3	$Ph(CH_2)_3$	Ph	Ph	(83)	
9	CHF_2	4-ClC_6H_4	Ph	Ph	80	
10	$(CF_2)_2CHF_2$	4-ClC_6H_4	Ph	Ph	73	
11	CF_3	4-ClC_6H_4	4-$MeOC_6H_4$	Ph	(76)	40:60
12	CF_3	4-ClC_6H_4	Ph	4-$MeOC_6H_4$	(80)	63:37
13	CF_3	4-ClC_6H_4	Ph	4-MeC_6H_4	(89)	39:61
14	CF_3	4-ClC_6H_4	Ph	3-$MeOC_6H_4$	(84)	57:43
15	CF_3	4-ClC_6H_4	Ph	2-$MeOC_6H_4$	(60)	62:38

[a] Values in parentheses were based on ^{19}F NMR spectra.

Scheme 19. Carbomagnesiation of Propargylic Alkynes

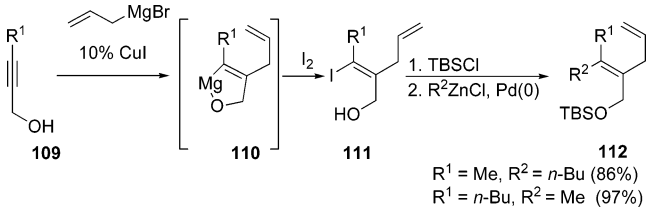
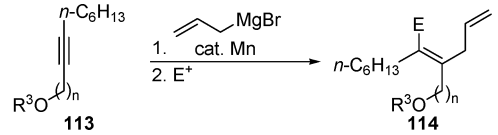
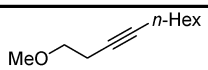
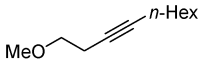
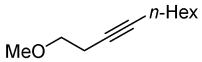
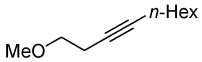
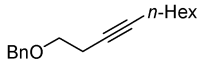
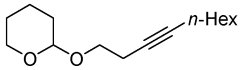


Table 8. Conversion of Propargylic and Homopropargylic Ethers to Tetrasubstituted Olefins



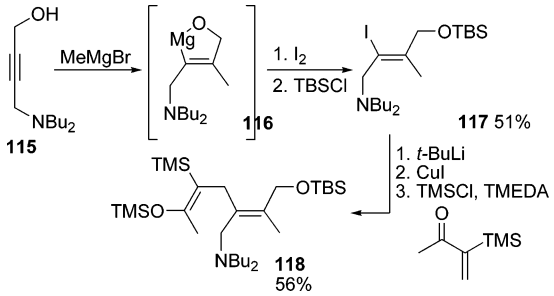
entry	substrate	electrophile	yield (%)
1		PhCHO	92
2		n-$C_6H_{13}CHO$	87
3		CH_2=$CHCH_2Br$	77
4		-	80[a]
5		-	78[a]
6		-	35[a]

[a] Excess Grignard reagent employed and reaction performed open to air.

cyclohexane. A variety of propargylic alcohols were converted to olefin products in yields varying from 68% to 86%.

Also reported was the condensation of the intermediate cyclomagnesium species such as **120** with CO_2 giving two furanones, including Vioxx.[60,61] This method was further adapted to include halide electrophiles[62] by using palladium catalysis to cross-couple the intermediate magnesium complexes with a variety of aryl and vinylic halides (Table 9).

Scheme 20. Carbomagnesiation−Iodination−Michael Sequence



Scheme 21. Carbomagnesiation−Carbonyl Trapping

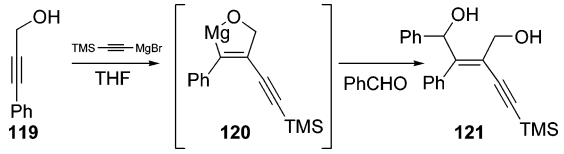
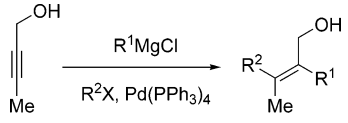


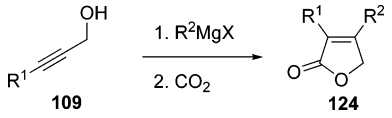
Table 9. Three-Component Coupling of Alkenes and Dienes



entry	R^1	R^2X	yield
1	Ph	PhI	73
2	Ph	p-$MeOC_6H_4I$	71
3	Ph	CH2=$CHCH_2I$	64
4[a]	CH_2=$CHCH_2$	PhI	60
5	Ph	Me_2C=CMeBr	71
6	CH_2=CH	PhI	41
7	Me	PhI	10

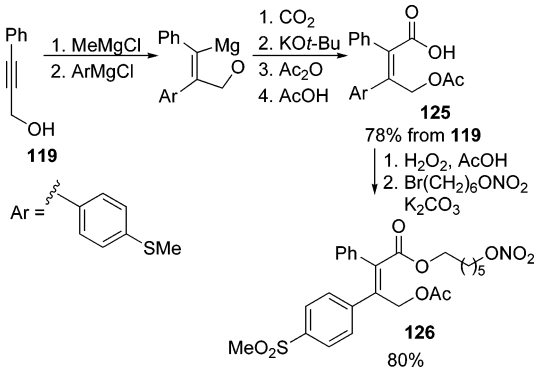
[a] CH_2CHCH_2MgBr was used.

Table 10. Preparation of Butenolides



entry	R^1	R^2	yield (%)
1	Me	Et	30
2	Ph	Me	51
3	Ph	Et	45
4	Ph	$CH_2CH{=}CH_2$	61
5	PhCC−	Et	38
6	$CH_2{=}(Me)C-$	Et	38

Scheme 22. Application of the Hydroxy-Directed Carbometallation



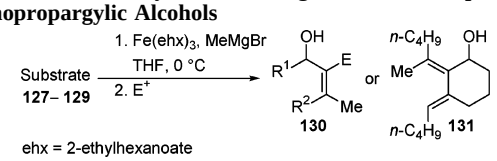
Duboudin and Jousseaume have also described the exposure of propargylic alcohols to Grignard reagents and subsequent trapping with carbon dioxide to give butenolides **124** (Table 10).[63]

This carbomagnesiation strategy has been used by Merck & Co. to synthesize a NO-releasing prodrug of Vioxx (Scheme 22).[64] Significant effort was devoted to modifying and optimizing the reaction to sucessfully acetylate the intermediate magnesium alkoxide and prevent facile cyclization to the corresponding furanone. All steps in the reaction were carefully examined, and a particularly important factor was the sequestering of excess CO_2 with potassium *tert*-butoxide prior to acetylation. Thus, tetrasubstituted alkene **125** was obtained after six steps from **119** in 78% overall yield. This was impressive because the first sequence attempted gave a 6% yield. As in the aforementioned methods, regio- and stereoselectivity were excellent.

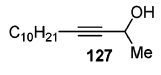
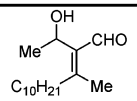
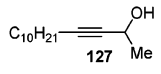
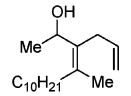
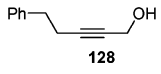
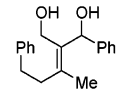
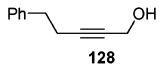
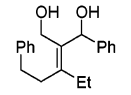
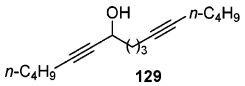
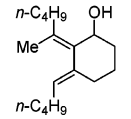
A complementary method was disclosed by Zhang and Ready in which iron-catalyzed carbomagnesiation of propargylic and homopropargylic alcohols generated tri- and tetrasubstituted olefins with the opposite regio- and stereoselectivity as had been previously observed (Table 11).[65] In this method, alcohols were treated with a Grignard reagent in the presence of $Fe(ehx)_3$ (ehx = 2-ethylhexanoate). Syn addition of the Grignard reagent across the triple bond followed by electrophilic trapping gave products **130**. Trapping of the vinyl iron or magnesium intermediate species generated from one substrate (**129**) with a pendant alkyne gave diene **131** in good yield.

The arylmagnesiation of alkynes using an iron/copper catalyst system was recently described (Scheme 23).[66] This process employed a syn addition across the alkyne to give an intermediate magnesium reagent that could be trapped with benzaldehyde or benzyl bromide to give tetrasubstituted olefins.

Table 11. Iron-Catalyzed Carbomagnesiation of Propargylic and Homopropargylic Alcohols

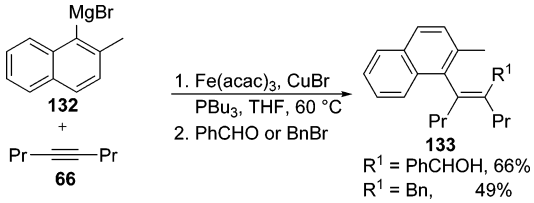


ehx = 2-ethylhexanoate

entry	substrate	E^+	product	yield (%)
1		DMF		50
2		$CuCN_2{\cdot}LiCl$, allyl bromide		61
3		PhCHO		51
4[a]		PhCHO		52
5[b]		-		70

[a] EtMgBr was used. [b] $Fe(acac)_3$, CuBr, and Bu_3P were used.

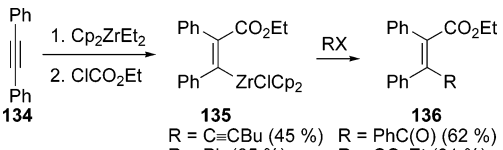
Scheme 23. Syn Arylmagnesiation of Alkynes



2.5. Other Metals

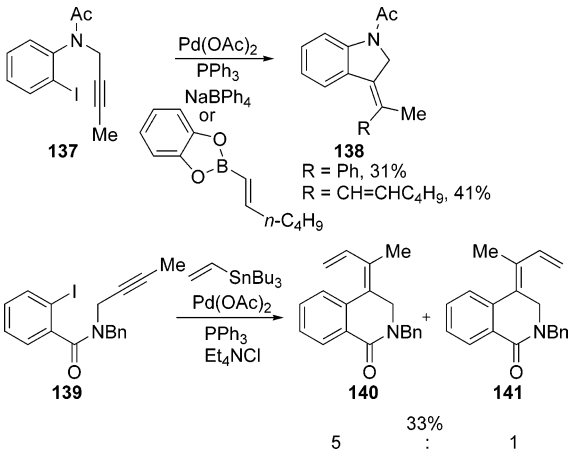
Carbozirconation is a highly reliable method to functionalize alkynes, proceeding with a high degree of stereoselectivity, and consistently providing syn isomers.[33] The regioselectivity of zirconium additions has been extensively studied, and these reagents have significant potential for preparing tetrasubstituted olefins. Takahashi et al. described a zirconium-based method to selectively construct functionalized α,β-unsaturated esters (Scheme 24).[67] Thus, diphenylacetylene was treated with Cp_2ZrEt_2 in the presence of ethyl chloroformate to produce an intermediate acyl zirconium species that could be cross-coupled with electrophiles in the presence of $Pd(PPh_3)_4$ to give tetrasubstituted olefins **136** in 31−65% yield. Four examples were illustrated, and in each case the addition was found to occur in the expected syn fashion.

Scheme 24. Carbozirconation Generates Tetrasubstituted Olefins



Grigg and co-workers showed that carbopalladations could be carried out intramolecularly to give products such as **138**. This compound was isolated as a single isomer in 31% yield after Suzuki-type coupling (Scheme 25).[68] A hexenyl group

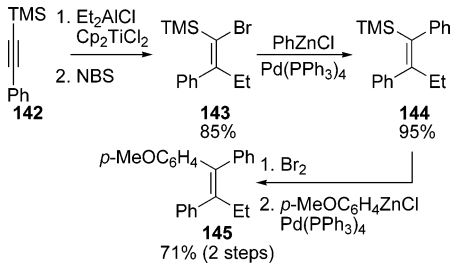
Scheme 25. Intramolecular Carbopalladation



was also transferred in slightly higher yield (41%). In this example, regiochemistry was controlled by the intramolecular reaction in which only the formal *exo*-dig pathway was productive. Indolylborate could be used in similar reactions as transfer reagents,[69] and tin coupling partners could be used in place of the boron reagents.[70] These reactions occurred successfully in both the 5-*exo*-dig and the 6-*exo*-dig modes in the four examples described. The 5-*exo*-dig processes gave single isomer products, whereas one of the 6-*exo*-dig cyclizations gave a 5:1 mixture of syn and anti isomers **140** and **141** in 33% combined yield.

Carboalumination has been used to prepare Tamoxifen through the addition of Tebbe-type reagents to alkynes (Scheme 26). In this case, TMS acetylene **142** was exposed

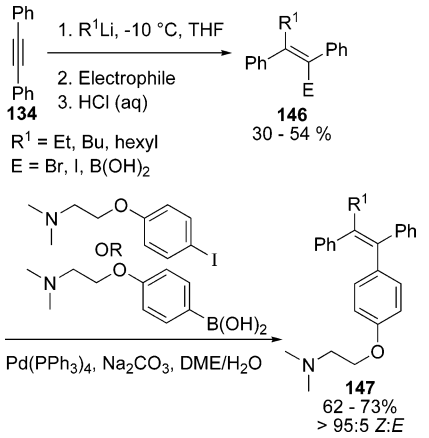
Scheme 26. Carboalumination Route to Tetrasubstituted Alkenes



to Et_2AlCl and Cp_2TiCl_2 to effect carboalumination, and the resulting intermediate was quenched at low temperature with NBS to afford silylbromide **143**.[71] This material was subjected to Negishi coupling conditions to introduce a second phenyl group with excellent yield and stereocontrol. After exchanging the silicon group with bromine, a second Negishi reaction supplied tetrasubstituted product **145** in 71% yield over the two steps. This material was then elaborated to Tamoxifen using a four-step sequence. In a subsequent communication, a modification of this route allowed the synthesis of Tamoxifen in 35% yield in a single operation from diphenyl acetylene.[1b]

Tamoxifen and related compounds have similarly been prepared by carbolithiation strategies.[1d] The carbolithiation of diphenylacetylene generated a series of (*E*)-1-lithio-1,2-diphenylalkyl-1-enes (Scheme 27). These alkenes were

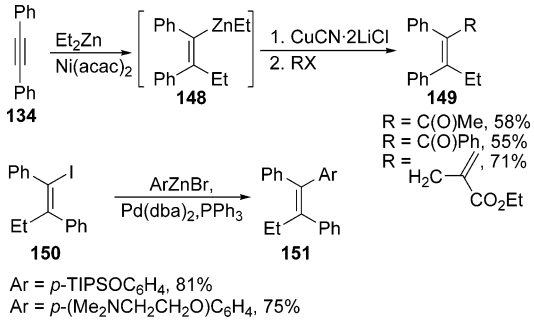
Scheme 27. Carbolithiation of Diphenylacetylene To Form Tamoxifen



reacted in situ with electrophiles such as 1,2-dibromoethane, 1,2-diiodoethane, or triisopropylborate to form tetrasubstituted precursors **146**. These materials were treated with either an aryl iodide or an arylboronic acid, as appropriate, in refluxing DME/H_2O using $Pd(PPh_3)_4$ as catalyst and Na_2CO_3 as a base to give tetrasubstituted olefins **147** in 62−73% yield and with >95:5 selectivity (*E*:*Z*).

Zinc has been used in several instances to prepare tetrasubstituted olefins, primarily through Negishi coupling reactions, but also in other contexts. For example, a carbozincation of alkynes was described in which nickel catalysis provided smooth syn addition to diphenylacetylene affording a vinyl zinc intermediate (**148**). This material could be captured with different electrophiles to give tetrasubstituted products (Scheme 28).[72] Although the intermediate zinc

Scheme 28. Carbozincation of Alkynes



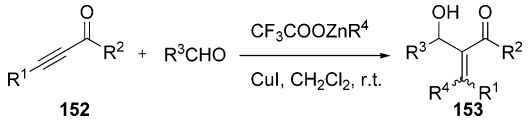
species could be directly coupled with electrophiles in the presence of CuCN and LiCl,[73] the authors reported that superior results were obtained when the intermediate zinc species were captured with I_2 and the resulting vinylic iodides cross-coupled with other organozincs under Negishi conditions. Similar results were described using cobalt catalysts to mediate initial allyl zinc couplings.[74]

Xue et al. found that organozinc species reacted with β-substituted α,β-acetylenic ketones, when CuI was used as a catalyst, to give tetrasubstituted olefin products as mixtures of stereoisomers (Table 12).[75]

A nickel-catalyzed five-component reaction utilizing dimethylzinc, symmetric alkynes, 1,3-butadiene, aldehydes, and amines furnished either **154** or **155** depending on the type of amines employed (Scheme 29).[76] Aromatic amines gave product **154**, while aliphatic amines gave product **155**.

A common limitation of the carbometallation of internal alkynes is the issue of regioselectivity. Nishikawa, Yorimitsu,

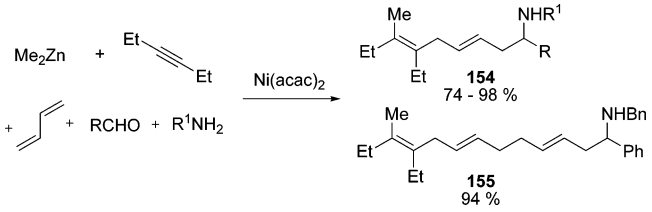
Table 12. Carbozincation of Alkynes Promoted by CuI



152 153

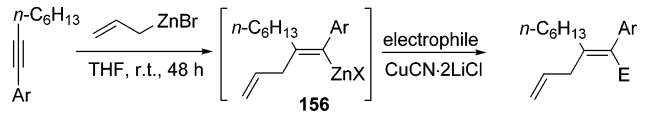
entry	R^1	R^2	R^3	R^4	yield (%)	*Z*:*E*
1	*n*-C_3H_7	Ph	Ph	Me	91	4:1
2	*n*-C_3H_7	Ph	4-MeC_6H_4	Me	88	3:1
3	*n*-C_3H_7	Ph	Ph	Et	85	1.2:1
4	*n*-C_3H_7	Ph	4-$MeOC_6H_4$	Et	90	1.3:1
5	Ph	Ph	Ph	Et	85	3:1
6	*n*-C_3H_7	Me	4-$MeOC_6H_4$	Et	82	1.2:1

Scheme 29. Nickel-Catalyzed Five-Component Coupling



and Oshima reported that the allyzincation of 1-aryl-1-alkynes took place with high regio- and syn stereoselectivity when the reaction was catalyzed by cobalt (Scheme 30).[77]

Scheme 30. Cobalt-Catalyzed Regio- and Stereoselective Allylzincation of 1-Aryl-1-alkynes

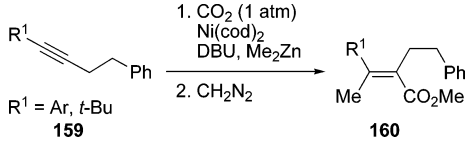


157: Ar = 4-ClC_6H_4, E = CH_3CO; 44 %
158: Ar = 3,5-$(CF_3)_2C_6H_3$, E = CH_2=$CHCH_2$; 70 %

Numerous examples were reported that gave trisubstituted products after quenching the intermediate alkenylzinc compound **156** with H_3O^+. In addition, two examples were shown in which the alkenylzinc compound was condensed with acetyl chloride or allyl bromide in the presence of CuCN·2LiCl to give tetrasubstituted olefins **157** and **158**, whose geometries were confirmed by NOE experiments.

The Mori group has developed a nickel-catalyzed alkylative carboxylation of alkynes that was used to make four tetrasubstituted olefins with complete stereoselectivity (in one case, a 3:1 mixture was obtained).[78] Regioselectivity was apparently controlled by steric interactions as the initial carbonylation occurred at the less hindered side of the triple bond. The intermediate oxanickel species that resulted from CO_2 insertion underwent coupling with Me_2Zn to afford **160** after esterification with diazomethane (Scheme 31). This

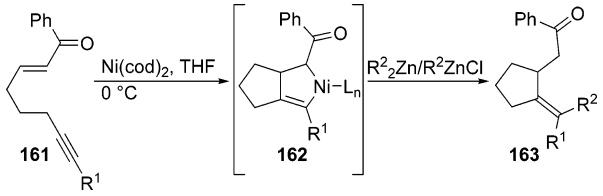
Scheme 31. Alkylative Carboxylation of Alkynes



methodology was applied to the synthesis of Tamoxifen, affording the drug in eight steps in 36% overall yield.[1e]

Montgomery's research group has extensively used organozinc reagents, together with nickel-catalyzed reactions, to construct tetrasubstituted olefins by intramolecular alkyne additions. It was initially shown that enones could serve as effective electrophiles for a multicomponent process involving alkynes and alkyl zinc reagents.[79] Earlier work by Ikeda and Sato had demonstrated that, in the presence of TMSCl under nickel catalysis, enones would serve as electrophilic π-allyl partners for alkyne insertions[80] and that tetrasubstituted olefins could be realized from this process (only one example was shown). It was found that $Ni(cod)_2$ would catalyze multicomponent additions of alkynes, enones, and alkyl zincs, without the need for TMSCl, if the reaction was run intramolecularly. The reaction was presumed to operate via the formation of a nickel(0) π-complex that underwent oxidative cyclization to form metallocycle **162** (Scheme 32).[81] This complex could then undergo transmetallation with

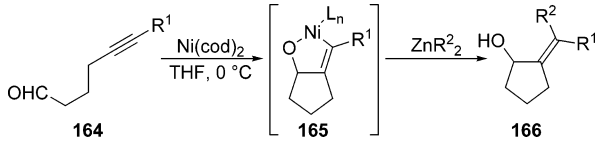
Scheme 32. Intramolecular Carbozincation



the organozinc, followed by reductive elimination to produce the tetrasubstituted olefins **163**. These compounds were obtained as single isomers, with the regioselectivity of the addition being dictated by the steric constraints of the substrate. A dramatic effect was observed if phosphine ligands were used together with alkyl zincs containing β-hydrogens.[79] Under these conditions, a trisubstituted product was obtained, resulting from a β-hydride elimination that was likely a consequence of the increased electron density imparted by the phosphine ligands. These ligands presumably displaced the electron-poor alkene spectator ligands that are known to promote reductive elimination. Two examples were given of tetrasubstituted olefins that were produced stereoselectively. The intermolecular variant was also successful using aldehydes and terminal alkynes, giving trisubstituted olefins.

Other electrophilic partners could participate in this process. Aldehydes gave allylic alcohols through a multicomponent ynal cyclization (Scheme 33).[81c] Treatment of

Scheme 33. Carbozincation−Aldehyde Trapping

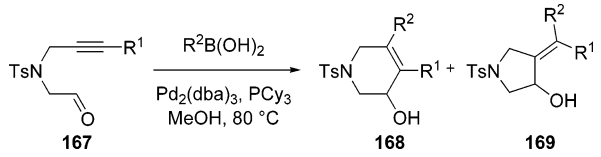


substrates **164** with $Ni(cod)_2$ and a suitable alkyl zinc resulted in smooth conversion to the tetrasubstituted products with complete stereocontrol. This method was extremely flexible because a common intermediate was used. The desired substituted alkynals **164** were prepared simply by a Sonogashira extension or acetylide alkylation to give the corresponding alkyne. Four examples were given, with yields ranging from 64% to 76%. The reaction was thought to proceed through oxametallacycle **165**, which would be produced by the oxidative cyclization of the nickel species, alkyne, and aldehyde, or by the carbometallation of the alkyne followed by cyclization with the aldehyde. Once **165** was formed, transmetallation and reductive elimination provided the observed products **166**. Reductive cyclization

was only efficient if PBu_3 was added as a ligand in conjunction with alkyl zinc reagents.

A trans-selective variant of the above reaction could be accomplished through the use of a palladium catalyst (Table 13) to give tetrasubstituted alkenes.[82] Employing terminal

Table 13. Trans-Selective Addition of Organoboron Reagents

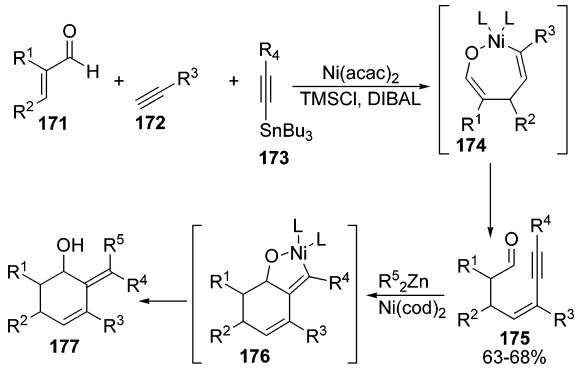


entry	R^1	R^2	yield (%)	**168**:**169**
1	Me	Ph	90	61:39
2	Bu	Ph	66	83:17
3	4-MeC_6H_4	4-$MeOC_6H_4$	97	93:7

alkynes as substrates gave products of type **168** almost exclusively, while mixtures of **168** and **169** were observed when an internal alkyne was used.

A four-component extension of the Ikeda group's three-component method[80] was subsequently developed (Scheme 34).[83] By including an alkynylstannane, and performing the

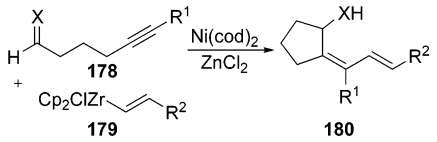
Scheme 34. Four-Component Nickel-Catalyzed Cyclization



reaction intermolecularly, substituted carbocycles bearing exocyclic tetrasubstituted double bonds were obtained. Several tetrasubstituted examples were given that were isolated as single alkene isomers (Table 14). This process involved a sequence of two nickel-mediated oxidative cyclizations, both of which occurred with complete syn selectivity. Thus, an initial cyclization between components **171**, **172**, and **173** gave aldehydes **175**, which were then exposed to alkyl zincs in the presence of $Ni(cod)_2$ affording the products **177**.

Recently, it has been shown that zirconium can participate in analogous processes (Scheme 35).[84] A catalytic amount of zinc was required for the successful vinylzirconation of alkynes. These reactions were followed by intramolecular additions to a variety of electrophiles. Thus, alkynyl enones were cyclized in the presence of vinyl zirconium reagents using $Ni(cod)_2$ and $ZnCl_2$ as catalysts. The cyclic products

Scheme 35. Nickel-Catalyzed Cyclizations and Couplings with Vinyl Zirconium Reagents



X = O or HC-C(O)R^3

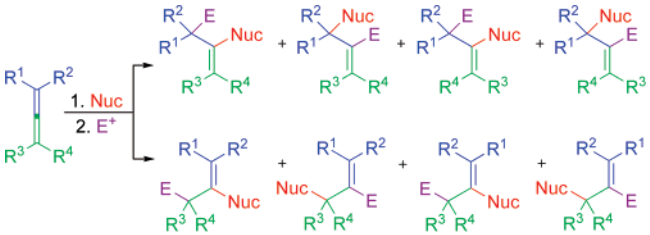
R^1 = Me, Ph; R^2 = C_6H_{13}, Ph

contained highly substituted 1,3-dienes, which are potentially valuable synthetic intermediates. Using ynals as precursors, the reaction was found to be capable of producing both five- and six-membered rings, and worked well in the presence of amines. When enones were used as electrophiles, the reaction would not function intermolecularly, in contrast to the tin process described above;[83] however, an intermolecular version of the alkynal process producing trisubstituted olefins was provided.

2.6. Additions to Allenes

Allenes provide an interesting case of tetrasubstituted olefin formation.[85] These functional groups are known to insert rapidly into carbon metal bonds, readily forming π-allyl complexes.[86] Carrying out a carbometallation across one of the π bonds of the allene system creates new sp^2 and sp^3 centers and leaves behind an olefin product. Issues of regioselectivity become more complex here as the reagents must not only select the correct double bond, but must add in the correct direction to that bond (Scheme 36). This raises

Scheme 36. Possible Regioisomers from the Addition to Allenes



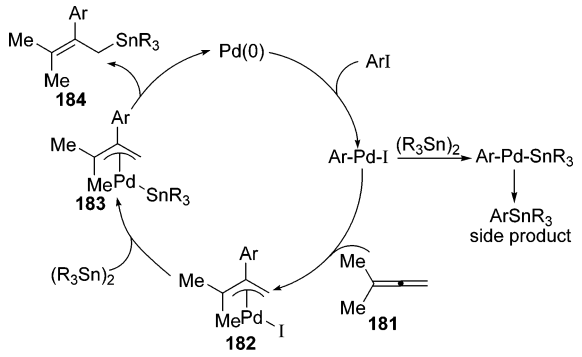
the possibility of forming four distinct regioisomers from the allene, in addition to the issue of stereocontrol during the process.

The problem of regioselectivity in the allene insertion process has been extensively studied by the Cheng group. In an early report, it was shown that symmetrically substituted allene **181** could be carbostannylated using palladium catalysis to give allylstannanes such as **184** (Scheme 37).[87] This reaction proceeded in a typical manner, in which carbopalladation of the allene afforded the π-allyl intermediate **182**. Transmetallation of **182** gave **183**, and reductive elimination subsequently occurred, during which the tin added to the less-substituted carbon, thus delivering the major product **184**. Aryl, vinyl, or heterocyclic iodides could be

Table 14. Multicomponent Coupling To Give 177

entry	R^1	R^2	R^3	R^4	R^5 (reagent)	yield of **175** (%)	yield of **177** (%) (dr)
1	H	H	H	Ph	Et (Et_2Zn)	68	81
2	Me	H	H	Ph	Me (MeLi/$ZnCl_2$)	63	74 (2.7:1)
3	H	H	H	Ph	Me (MeLi/$ZnCl_2$)	68	71
4	H	Me	H	Ph	Me (MeLi/$ZnCl_2$)	67	80 (5.3:1)

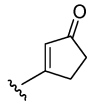
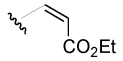
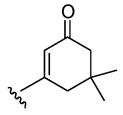
Scheme 37. Aryl Stannylation of Allenes



used as coupling partners, and the reactions were highly regioselective, producing a single isomer in each case. Yields varied between 26% and 93%.[87a] For an effective reaction, syringe pump addition of the tin component was required. Surprisingly, the less reactive reagent $Bu_3SnSnBu_3$ produced a more effective reaction than $Me_3SnSnMe_3$. This was postulated to be a consequence of a competing two-component coupling between the dialkyl tin reagent and the aryl iodide. As $Me_3SnSnMe_3$ was more reactive, this competing process was more significant when this reagent was used, and lower yields of the desired three-component coupling product **184** were observed.

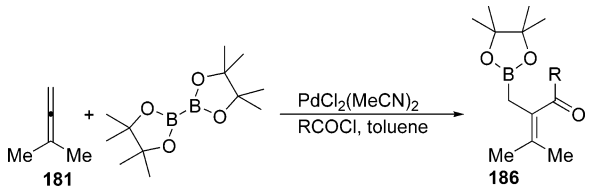
The analogous silicon variation has also been reported.[87b] Symmetrically substituted allene **181** was coupled with the same iodides as in the above study, but this time $Bu_3SnSiMe_3$ was used as the coupling partner. Efficient overall carbosilylation was realized in yields over 80% giving numerous examples of single isomer allylsilane products bearing tetrasubstituted olefins (Table 15).

Table 15. Three-Component Coupling Incorporating Allenes

entry	R	yield (%)
1	Ph	85
2	4-$NO_2C_6H_4$	88
3	4-$MeOC_6H_4$	86
4	2-$MeOC_6H_4$	83
5	3-$EtO_2CC_6H_4$	82
6	2-thienyl	85
7		82
8		78
9		61
10		83

The use of boron was subsequently explored in an acylboration sequence (Scheme 38).[87c,88] Symmetrically

Scheme 38. Allylic Boranes from Allenes

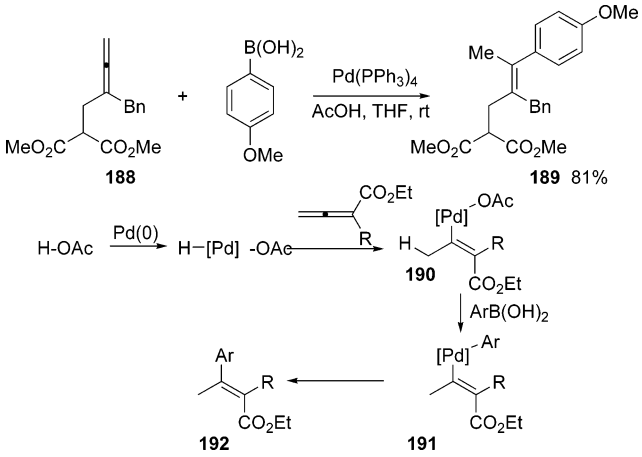


substituted allene **181** was coupled with a series of acyl chlorides using pinacolborane to give the corresponding allylboranes **186**. Fifteen examples of single isomer allylborane products bearing tetrasubstituted olefins were produced, in yields ranging from 57% to 92%.

In the above reaction, the production of an allylboron species represents a valuable synthetic intermediate. The utility of this was demonstrated in a multicomponent variation that introduced further diversity.[89] By employing substituted phenylboronic acids and adding CsF, further coupling took place to furnish tetrasubstituted olefin products. The halide partner could be aryl, vinyl, heterocyclic, or even an α-haloester. Iodides and bromides readily underwent the process, and a variety of substituents were tolerated on the arylboronic acid moiety.

Ma and co-workers exploited the electronic and steric biases inherent in the allene system to carry out hydropalladations (Scheme 39).[90] They found that aryl substituents

Scheme 39. Hydropalladation−Transmetallation of Allenes

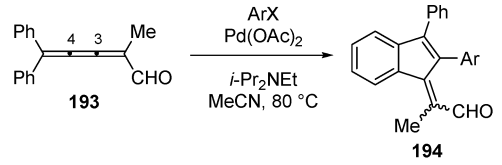


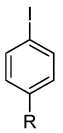
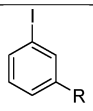
could be added across one double bond of the allene, in the presence of acetic acid, using boronic acids together with $Pd(PPh_3)_4$ as a catalyst. Allene **188** was converted into tetrasubstituted olefin **189** in 81% yield, as a 91:9 mixture of *E*/*Z* isomers. Four other examples were illustrated, giving similar yields and ratios of products. Selectivity was significantly improved when the starting allene bore an ester substituent. Compound **190** was converted to **192** in 86% yield as a single regioisomer and with excellent control of stereoselectivity (R = *n*-C_3H_7, Ar = 4-$MeOC_6H_4$, 97:3). Four other examples proceeded equally successfully, in most cases providing only one isomer of the product. While hydropalladation processes typically add first to the central carbon of the allene to generate a π-allyl intermediate,[85] in this case a less commonly observed regioselection was operative. The initial hydropalladation gave **190**, in which the palladium was situated on the central carbon, precluding formation of

a π-allyl intermediate, as is typically implicated in allene chemistry. Subsequent transmetallation and elimination gave the major regioisomer **192**.

Furuta and co-workers explored domino Heck reactions of unsymmetrically substituted [3]cumulenes (Table 16).[91]

Table 16. Domino Heck-C−H Activation Reaction of Unsymmetrically Substituted [3]Cumulenes



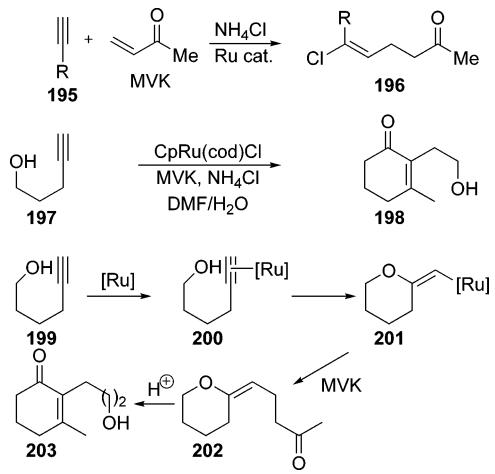
entry	ArX		yield (%)	ratio ($Z:E$)
1	PhI		61	3.4 : 1
2		R = OMe	46	3.6 : 1
3		R = OMs	39	2.4 : 1
4		R = NO_2	66	4.3 : 1
5		R = Br	55	2.7 : 1
6		R = OMe	47	2.3 : 1
7		R = OMs	62	2.3 : 1
8		R = NO_2	47	2.5 : 1

The aryl palladium species, generated from the oxidative addition of the palladium catalyst with the aryl halide, inserted selectively into the C3−C4 double bond of cumulene **193**. A C−H insertion reaction at the ortho position of the neighboring phenyl moiety, followed by reductive elimination, gave the tetrasubstituted alkene products **194** as mixtures of *E*/*Z* isomers in yields of 39−66% (combined yields of the mixtures of isomers obtained).

2.7. Direct Alkyne Functionalization

While developing a method for the stereoselective formation of vinyl chlorides (**196**) from terminal alkynes (**195**), Trost and Pinkerton found that several substrates did not form the expected vinyl chloride but instead were converted to tetrasubstituted olefins such as **198** (Scheme 40).[92] In this study, ruthenium catalysts were developed to form vinyl

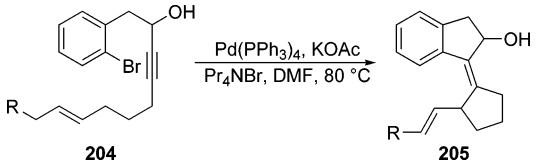
Scheme 40. Ruthenium-Catalyzed Generation of Cycloalkenes



halides such as **196** in a multicomponent process involving alkynes, methyl vinylketone, and a halide source (tetraalkylammonium salts). While exploring the substrate scope of the reaction, these researchers found that two alkynes, **197** and **199**, unexpectedly formed carbocycles bearing a tetrasubstituted double bond. This result was rationalized by an intramolecular nucleophilic attack of the hydroxyl group onto an activated alkyne as shown. This process would only occur if the hydroxyl were situated at a suitable distance from the alkyne, such that the rate of this intramolecular process was competitive with intermolecular capture by the halide.

A cascading cyclization process that delivered tetrasubstituted olefins in a specialized ring system was developed in which two successive palladium-mediated cyclizations across unsaturated bonds produced central tetrasubstituted alkenes (Scheme 41).[20] Aryl bromides such as **204**, when

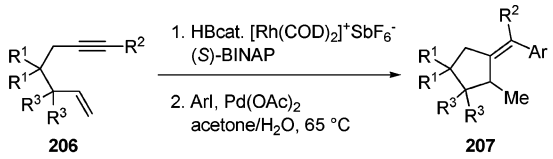
Scheme 41. Allylsilane-Terminated Domino−Heck Double Cyclization

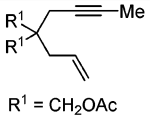
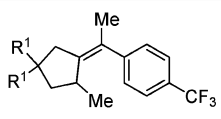
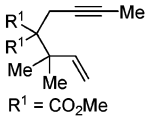
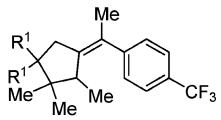
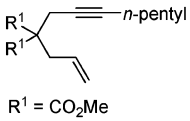
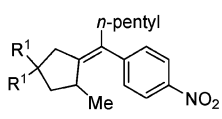
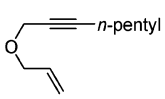
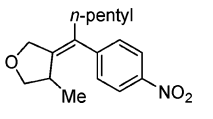


exposed to the appropriate palladium catalyst, underwent an initial ring closure involving the triple bond, followed by a Heck process with elimination to give the products shown. The process worked well to give five- to seven-membered rings from the initial ring closure, and five- to six-membered rings from the second ring-forming process.

A rhodium-catalyzed cyclization/hydroboration of 1,6-enynes (**206**) permitted the simultaneous generation of a chiral center and a tetrasubstituted olefin moiety (Table 17).[93] A ligand screen was performed and (*S*)-BINAP proved to

Table 17. Rhodium-Catalyzed Asymmetric Cyclization/Hydroboration of 1,6-Enynes



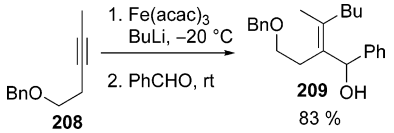
entry	enyne	product	yield (%)	ee (%)
1	 $R^1 = CH_2OAc$		61[a]	87
2	 $R^1 = CO_2Me$		70	45
3	 $R^1 = CO_2Me$		68	82
4			40	98

[a] 20:2:1 mixture of isomers.

be the best. In this report, four tetrasubstituted olefin examples were reported in addition to other cyclization products.

An iron-catalyzed carbolithiation process was shown to generate tetrasubstituted olefins when the product of the alkynyl carbolithiation was quenched with aldehydes or ketones (Scheme 42).[94] Three examples were provided of

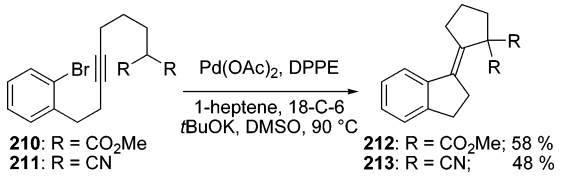
Scheme 42. Carbolithiation−Carbonyl Trapping



reactions with benzaldehyde, propionaldehyde, and 1-phenylpropanone. Single isomers were obtained in all reported cases.

This type of reaction could also be done with the nucleophilic capture of an intermediate palladium π-complex in a Wacker-type process (Scheme 43).[95] Thus, bromides

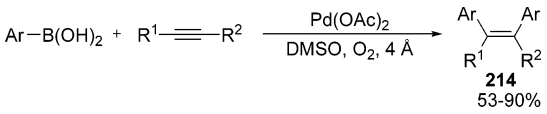
Scheme 43. Wacker-Type Cyclization of Palladium π-Complexes



210 or **211**, in the presence of $Pd(OAc)_2$ and DPPE, underwent cyclization to the corresponding products **212** and **213** as single isomers in 58% and 48% yields, respectively.[96]

An interesting multicomponent reaction has been developed by the Larock group involving the direct addition of aryl boronic acids to alkynes (Scheme 44).[97] This process

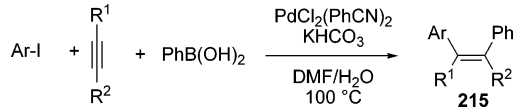
Scheme 44. Pd-Catalyzed Addition of Arylboronic Acids to Alkynes



featured an unusual twist in which the regiochemical issue was circumvented by adding the same aromatic group to both ends of the alkyne. Stereochemical control was complete, and the reaction tolerated a wide variety of functional groups on the substrate (OH, CHO, ketone, ester, TMS, aryl). Unfortunately, the reaction failed for dialkyl-substituted alkynes, but a wide variety of tetrasubstituted olefins bearing three or four aryl groups were prepared. Several key experimental modifications made this process possible. Improved yields were observed when molecular sieves were used, either by providing a surface upon which the reactions could take place or by simply acting as water scavengers.[98] The reaction proceeded much faster if performed under an O_2 atmosphere rather than being simply left open to air, and the $Pd(OAc)_2$/DMSO system was found to be superior to others tested.[99] Two possible mechanistic pathways were presented, although investigations to support one over the other are still in progress.[97b]

Another multicomponent process saw the palladium-catalyzed coupling of iodides and boronic acids with alkynes (Table 18).[23,100] The reactions required tight control of

Table 18. One-Pot Route to Tetrasubstituted Alkenes from Alkynes



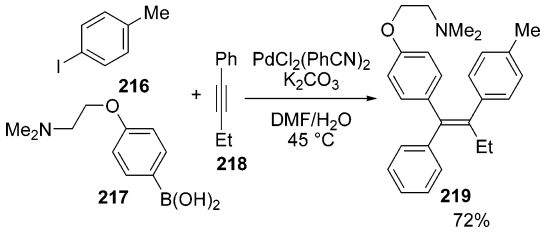
entry	Ar	R^1	R^2	yield
1	Ph	Me	Ph	90
2	Ph	n-C_4H_9	Ph	86
3	Ph	Ph	Ph	92
4	4-MeC_6H_4	COMe	Ph	80 (1:2)[a]
5	4-MeC_6H_4	CO_2Et	Ph	78 (1:2)[a]
6	Ph	CH_2OH	Ph	77
7	Ph	Me	CO_2Et	82
8	Ph	$CH(OEt)_2$	Ph	85
9	Ph	CO_2Et	CO_2Et	78
10	Ph	n-C_3H_7	n-C_3H_7	32
11	Ph	Ph	4-$NO_2C_6H_4$	88

[a] Mixture of regioisomers.

stoichiometry, solvent, and base. The presence of water was necessary for efficient conversion to products, with optimal results being obtained in 4:1 DMF:H_2O. Using $KHCO_3$ as the base gave significant advantages over other bases such as KF or K_2CO_3, and a 2:1:3 ratio of iodide:alkyne:boronic acid gave the cleanest reactions. Other stoichiometries resulted in oligomer formation after multiple alkyne insertions.

Regioselectivity was reasonable for this process (mixtures of 2:1 to 15:1 were obtained), and the geometry of the major products was found to be a consequence of steric effects in which the aryl iodide tended to add to the less-hindered carbon. Electronic influences were also seen, as the arylboronic acid was connected to the electron-deficient side of the alkyne. These compounds were well-characterized, and NOE data were presented to support the assignments. The reaction was stereospecific, and no evidence of trans-addition was reported. In all, more than 16 tetrasubstituted olefins were prepared, each bearing at least three aryl groups. This method was employed to construct Tamoxifen (**1**) and derivatives such as **219** in a highly convergent synthesis in which the product was obtained as a mixture of regioisomers that was obtained in a ratio of more than 20:1 (Scheme 45).

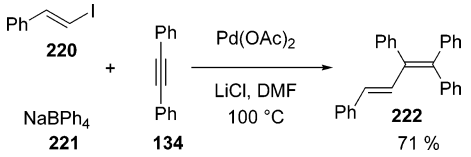
Scheme 45. Three-Component Coupling of Aryl Iodides, Internal Alkynes, and Arylboronic Acids



Notably, olefin (**219**) was obtained in 72% yield using the multicomponent, single-step process.[100]

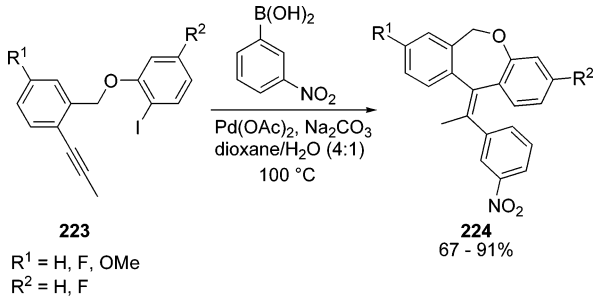
An extension of this work described the coupling of vinyl iodides and aryl boronic acids across alkynes to give tetrasubstituted olefins bearing 1,3-diene and 1,3,5-triene units (Scheme 46).[101] The additions were completely stereoselective, but regioselectivity was limited in this method. Unsymmetrical alkynes gave low ratios of products (1.5:1 ratio of regioisomers) unless a strong electron-withdrawing group was present as one substituent of the alkyne.

Scheme 46. A Representative Three-Component Coupling To Give 1,3-Dienes



Researchers at Eli Lilly & Co. have prepared dibenzoxapines containing tetrasubstituted exocyclic alkenes as single stereoisomers through the cyclocarbopalladation of alkynes (Scheme 47).[102] The cyclization precursors (**223**) were

Scheme 47. Cyclocarbopalladation of Alkynes



prepared through Sonogashira couplings of aryl halides followed by either Mitsunobu reactions or a two-step alkylation procedure. Alkynyl halides **223** were then exposed to a variety of boronic acids, in the presence of $Pd(OAc)_2$ and Na_2CO_3 in dioxane/water at 100 °C. The use of water as a co-solvent and ligand-free conditions proved to be critical to give the seven-membered rings **224**.

Carbometallation is the most widely used strategy for the generation of tetrasubstituted alkenes as evidenced by the number of methods that have been developed to address the various challenges in the formation of these substrates. The regioselectivity in most of these has been controlled by electronic differentiation on the alkyne. Steric differentiation of the alkynyl termini can also be effective, but requires a significant size difference between the substituents.

The stereochemistry of the initial attack usually proceeds reliably, with most reagents showing a strong preference for syn addition. Anti carbometallation is sometimes observed and dominates the carbomagnesiation of propargyl alcohols. Low temperatures during the carbometallation step normally must be maintained to preserve stereochemical information, particularly when lithium and copper serve as the counterion. This often requires reactive electrophiles to be used, although additives can prevent stereochemical degradation. Metals such as boron and tin can resist stereochemical degradation, and a wide variety of organometallic coupling techniques are available to further elaborate these intermediates.

Developing technologies in this field include radical processes, in which the stereochemistry is typically controlled by sterics, as well as allene reactions, which offer somewhat more regiochemical control as the initial addition usually occurs on the central carbon. Highly efficient multicomponent processes offer significant advantages by delivering complex products in a single chemical transformation. Geometric control remains a significant obstacle to overcome in many cases.

3. Manipulation of Existing Olefins

Tetrasubstituted double bonds of distinct geometry can be prepared by manipulating a pre-existing olefin template. The stereocontrolled generation of the template is often the most difficult aspect of this chemistry as mixtures of regio- and stereoisomers are often obtained. The types of templates that can be synthesized are currently somewhat limited, thus diminishing the scope of attainable olefins. Some examples of common motifs are shown in Figure 3. Cyclic templates

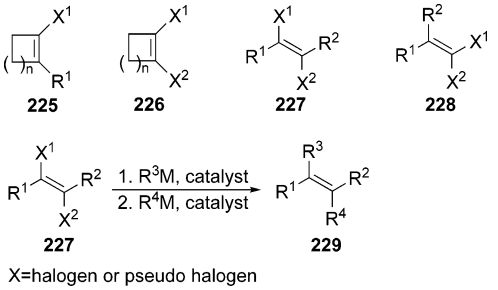


Figure 3. Common olefin template motifs and general template strategy.

such as **225** and **226** are generally formed from the halogenation or metalation of an existing olefin, although Dieckmann condensations have also been used. Acyclic templates such as **227** and **228** are often synthesized by the halogenation or metalation of alkynes, or occasionally by a Claisen condensation. Templates such as **228** present the possibility of carbene generation during halogen−metal exchange, and so the metal partner must be chosen with care. A few examples exist in which unsubstituted alkenes are sequentially coupled, thereby directly accessing tetrasubstituted olefins without the need for intermediate template generation.

The next challenge is faced once the desired template has been created, as suitable conditions must be found to transform the material into a tetrasubstituted olefin. The desired olefins **229** are typically synthesized either via halogen substitution of a template such as **227**, followed by coupling with an organometallic complex, or by halogen−metal exchange followed by coupling with an organohalide.

Regioselectivity is the first issue faced here because identical halogens ($X^1 = X^2$) are often employed at both template locations, and the system therefore requires some type of influence that distinguishes the two. The simplest way to avoid regioisomers is to use symmetric substrates, a tactic that limits the types of products that can be synthesized. Other alternatives expand the scope of products by exploiting steric or electronic biases in the substrate, or by the use of directing groups. Over-reaction during the couplings can be problematic, resulting in consecutive substitution at both of the halo-substituted carbons, producing symmetric products.

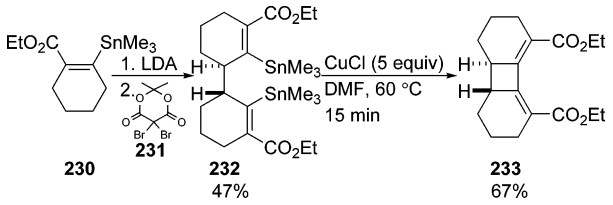
Stereoselectivity is the largest hurdle to overcome in any tetrasubstituted olefin synthesis. Cyclic templates circumvent this problem, but generating acyclic molecules in this manner requires built-in functionality such that the ring can be opened once the desired olefin has been installed. The use of an acyclic olefin template will usually give products of defined stereochemistry provided that the original template was created or isolated as a single isomer. It is always necessary to verify the structure of the products, rather than rely on literature precedent, as occasionally stereochemical information is lost, particularly when highly ionic conditions are used, or when enolization provides a mechanism for olefin isomerization.

3.1. Cyclic, Monosubstituted Olefin Templates

When employing cyclic templates, stereocontrol is not an issue and so researchers using cyclic substrates focus on the challenge of regioselectivity. Several of the following studies describe the coupling of cyclic α-halo (or OTf) ketones to form tri- and tetrasubstituted olefins. While the focus of these studies was not the production of tetrasubstituted alkenes, these papers have been included as they describe useful methodology, which may lead to further developments for the formation of tetrasubstituted olefins.

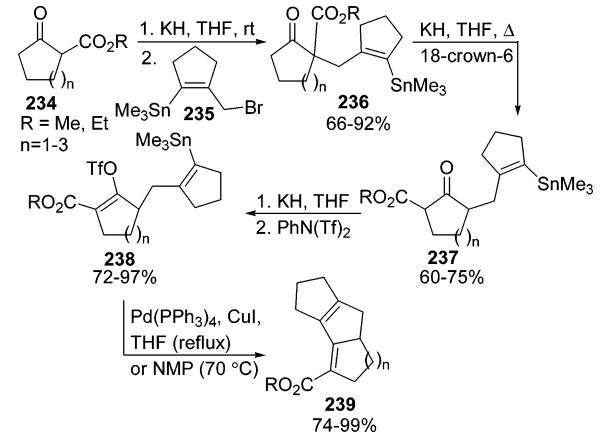
Piers and Romero generated carbocyclic systems bearing polysubstituted conjugated diene units such as **233**, via an intramolecular CuCl-mediated stannane coupling of **232** (Scheme 48). The required β-trimethylstannyl-α,β-unsaturated ester **230**, prepared from 2-ethoxycarbonylcyclohexanone, was deprotonated with LDA, and the resulting enolate was exposed to the brominating agent shown (**231**) to provide the dimeric stannane **232** in 47% yield. A final ring closure using 5 equiv of CuCl in DMF at 60 °C gave tetrasubstituted diene **233** in 67% yield. This methodology was used in the construction of four- to eight-membered rings and tolerated remote substituents such as esters and haloalkyl groups.

Scheme 48. Polysubstituted Conjugated Dienes



The formation of tricyclic compounds such as **239** (Scheme 49) has also been explored by the Piers group.[103]

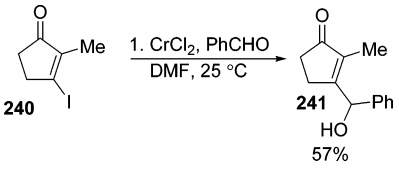
Scheme 49. Polycycles via Sequential 1,3-Ester Shift and Stille Reaction



The required olefin templates (**235**) were generated from the reduction of esters of type **230**, followed by treatment of the resulting alcohols with Ph_3PBr_2 in the presence of imidazole. These reagents were used to alkylate 2-ethoxycarbonylcyclopentanone or 2-ethoxycarbonylcyclohexanone, thus providing access to the derivatives **236**. A subsequent 1,3-ester shift of **236** and functional group manipulations gave the required coupling partners **238**. Intramolecular Stille coupling reactions led to tricyclic dienes **239**. It was shown using related substrates that many functional groups were tolerated in the Stille process, including ketones, acetals, and esters. The intramolecular couplings were fast and regiospecific, giving the desired products in excellent yields.

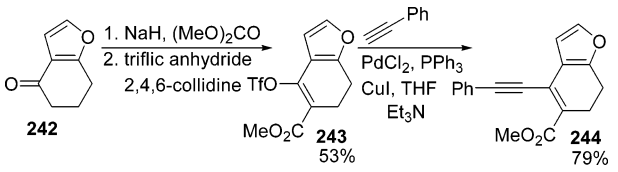
Metal insertion into the carbon−halogen bond of β-halogenated enones results in the generation of umpolung reagents, because the typical reactivity of the β-position of an α,β-unsaturated carbonyl is reversed. Knochel and coworkers have used this technique and have described the preparation and reactivity of several types of organozinc, organochromium, and organocopper derivatives (Scheme 50).[104] A wide variety of cyclic, heterocyclic, and acyclic iodo-enones have been coupled with vinyl, aryl, stannyl, and acyl electrophiles, forming trisubstituted olefins. One tetrasubstituted olefin was formed through the insertion of $CrCl_2$ into β-iodoenone **240**, followed by condensation with benzaldehyde, to give **241** in 57% yield.

Scheme 50. Generation of Nucleophilic β-Enone



Hesse and Kirsch recently used a β-vinyl triflate (**243**) in a Sonogashira coupling to generate the corresponding tetrasubstituted olefin **244** in 42% overall yield (Scheme 51).[105]

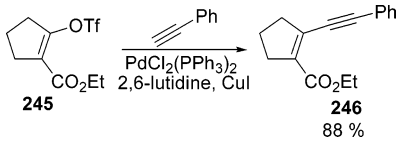
Scheme 51. Sonogashira Coupling with a Vinyl Triflate



This method enabled the generation of a β-substituted enone **243** by carbonylation of a cyclic ketone (**242**), provided the starting ketone was symmetrical or bore a single enolizable proton.

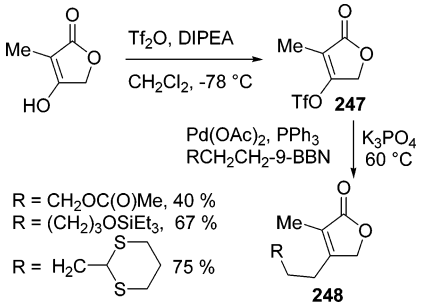
Substrates of type **243** could also be generated by a Dieckmann condensation, followed by enolate trapping to give β-triflate esters such as **245** (Scheme 52). Nakatani et al. showed that a subsequent Sonogashira coupling reaction with phenylacetylene gave tetrasubstituted alkene **246** in 88% yield.[106] The presence of the highly activated triflate in both of these substrates could potentially allow many alternatives to the Sonogashira coupling reaction to proceed under mild conditions.

Scheme 52. Sonogashira Coupling with Vinyl Triflate Template Generated from a Dieckmann Condensation



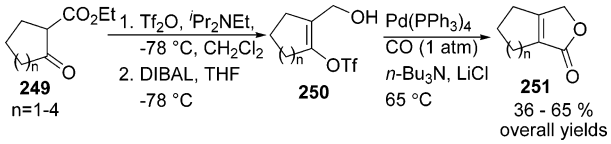
Butenolides have been functionalized at the 3-position to provide an insertion point for palladium-catalyzed cross-coupling with 9-alkyl-9-borobicyclo[3.3.1]nonanes (Scheme 53).[107] In this method, β-ketolactones were converted to the corresponding enol triflates **247**, and these compounds underwent alkyl Suzuki coupling to deliver tetrasubstituted olefins **248**. Three examples were provided of fully substituted alkenes that were prepared in 40−75% yield.

Scheme 53. Suzuki Coupling of an Enol Triflate



Bicyclic rings could be generated by analogous reactions, using carbon monoxide as the coupling partner, in a process developed by Crisp and Meyer (Scheme 54).[108] Treatment

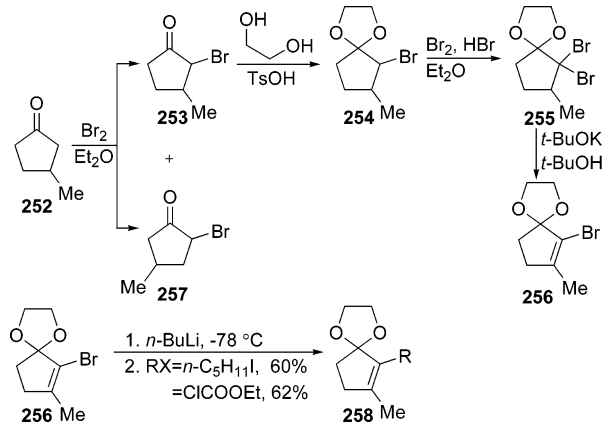
Scheme 54. Olefin Templates Applied to the Synthesis of Bicyclic Molecules



of β-ketoester **249** with triflic anhydride, followed by exposure to DIBAL, generated the olefin template **250**. The vinyl triflate **250** was then extended with carbon monoxide in the presence of a palladium catalyst, base, and lithium chloride to afford a variety of tetrasubstituted bicyclic rings **251** ($n = 1-4$) in 36−65% overall yields.

In most cases, the coupling of α-halo enones requires more forcing conditions than the corresponding β-halo counterparts due to the reduced reactivity of the α-position. Transformations of α-bromoketone derivatives such as **253**, to tetrasubstituted olefins such as **258**, were initially achieved in the late 1970s (Scheme 55).[109] The α-bromovinyl acetals **256**

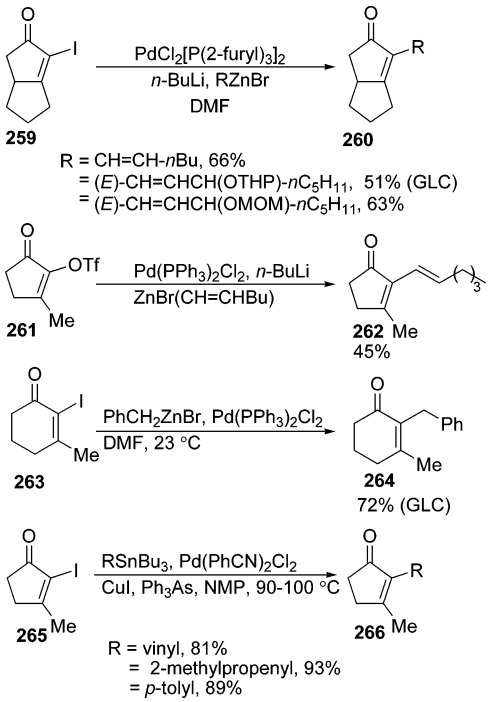
Scheme 55. Coupling of α-Bromoacetals



required for this transformation were prepared from the corresponding ketones (**252**) using a four-step sequence as shown.[110] Decomposition of the bromoenone was observed under the coupling conditions unless the carbonyl was first protected, and only highly activated electrophiles could be employed in this process.

The palladium-catalyzed cross-coupling of alkenyl zincs with cyclic α-iodoenones[111] has been described by Negishi and co-workers (Scheme 56).[112] The increased reactivity of iodide over bromide allowed the cross-coupling reactions to proceed without carbonyl protection. Four examples were

Scheme 56. Negishi and Stille Coupling of α-Iodides and Triflates



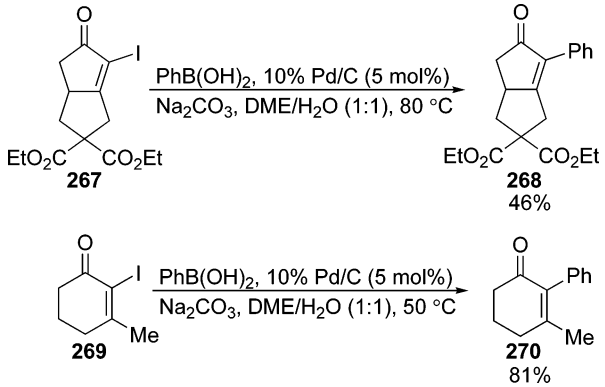
shown, in which the α-iodide or triflate (**259** or **261**) was coupled to an alkenyl zinc partner under palladium catalysis.

Later studies expanded the scope of these reactions, which had initially been limited to α-alkenylation and α-arylation. In 2000, the palladium-catalyzed α-alkynylation of cyclic iodoenones to give trisubstituted alkenes was reported and, impressively, the α-alkylation of cyclic iodoenones such as **263** with organozincs to give tri- and tetrasubstituted alkenes.[113] Although stringent reaction conditions were required for this process, the use of organozinc reagents expanded the scope of the reaction significantly.

Stille reaction conditions were also employed to generate tetrasubstituted olefins from similar templates. Thus, α-iodo enones **265** were coupled with a variety of alkenyl, alkynyl, and aryl stannanes to give tetrasubstituted alkenes **266** (Scheme 56).[114] Higher temperatures were required to effect the sterically hindered couplings; however, the reactions were complete in under 7 h.

Recently, a Suzuki−Miyaura coupling of α-iodocycloenones with arylboronic acids was disclosed (Scheme 57).[115] The catalyst used was simply 10% Pd/C and could be recycled after minimal workup. This represented the first

Scheme 57. Suzuki Coupling Using Pd/C as Catalyst



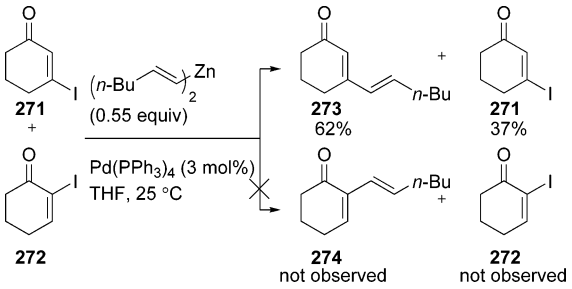
time that metallic palladium had been used for α-halo-cycloenone coupling reactions with arylboronic acids. The reactions typically proceeded in air and at room temperature, in a mixture of DME and H_2O. Most of the reported substrates gave trisubstituted olefin products in isolated yields of over 80%. Two examples, **267** and **269**, gave tetrasubstituted olefin products, although higher temperatures were required. This method was extremely practical, cost-effective, and highly amenable to extension.

3.2. Cyclic Di-halosubstituted Enones and Lactones

Cyclic dichloro-, dibromo-, or diiodosubstituted enones and lactones can undergo controlled, sequential organometallic coupling reactions to give fully substituted products with more structural diversity. Regioselectivity is the only issue to address as the cyclic structures preclude the formation of stereoisomers. This regiocontrol normally arises from the presence of a carbonyl group that provides electronic differentiation between the reaction sites. The more activated, electron-poor β-site reacts significantly faster than the α-positions, although over-addition at the α-site is a common side reaction in these processes.

The elevated reactivity of β-haloenones over the α-halo variants was illustrated by the Negishi group in a competition experiment.[112] An equimolar mixture of β- and α-iodoenones (**271** and **272**) was subjected to an organozinc reagent using conditions under which coupling was known to occur on both substrates (Scheme 58). The results showed that coupling

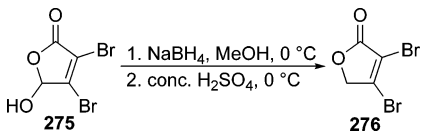
Scheme 58. Competition Experiment between α- and β-Iodo Enones



occurred exclusively at the β-position of enone **271** to give alkene **273**. An instability of the α-haloenone **272** was also demonstrated, as neither the coupled α-product **274** nor the starting material **272** were detected after the reaction. This instability mandated that conditions be controlled such that cross-coupling reactions of **272** occurred faster than the competing decomposition pathway.

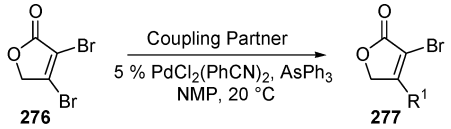
Bellina and co-workers have explored the Sonogashira, Stille, and Suzuki coupling reactions of 3,4-dibromo and 3,4-dichloro furanones such as **276** (Scheme 59),[116] which were

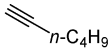
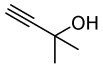
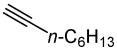
Scheme 59. Preparation of Dibromo Olefin Template 276



readily prepared from the reduction of mucobromic or mucochloric acids such as **275**.[117] Aryl substituents were selectively coupled to the β-position of dibromofuranone **276** via the Stille reaction (Table 19, entries 1−4).[116b] A number

Table 19. Coupling of Dibromofuranone 276 with a Variety of Coupling Partners



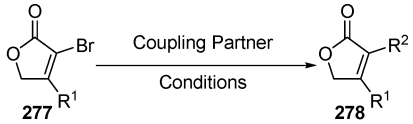
entry	coupling partner	yield (%)
1	$PhSnBu_3$	76
2	$4\text{-}MeOC_6H_4SnBu_3$	68
3	$3\text{-}FC_6H_4SnBu_3$	58
4	$4\text{-}MeC_6H_4SnBu_3$	73
5		78
6[a]	$n\text{-}C_8H_{17}B(OH)_2$	71
7[a]	$t\text{-}C_4H_9O(CH_2)_6B(OH)_2$	70
8[a]	$n\text{-}C_4H_9B(OH)_2$	79
9[b]		85
10[b]		84
11[c]		91
12[c]		40
13[c]		30
14[c]		75

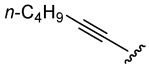
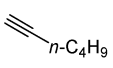
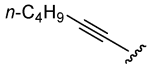
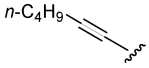
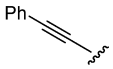
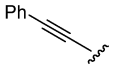
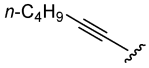
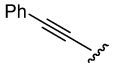
[a] 3 equiv of Ag_2O was added, THF was used instead of NMP, reflux, 24 h. [b] $P(2\text{-furyl})_3$ was used in place of $AsPh_3$ and 10% CuI was added, toluene:water (1:1) was used in place of NMP, 40 °C. [c] $P(2\text{-furyl})_3$ was used in place of $AsPh_3$ and 10% CuI was added, toluene was used in place of NMP, 60 °C.

of side-products were observed, however, including addition of the undesired alkyl tin substituents (i.e., CH_3 when $ArSn(CH_3)_3$ was employed as the coupling partner) rather than the targeted aryl moiety. Attempts to couple alkyl substituents with substrates **276** using the Stille process gave poor results, although unbranched alkyl groups could be introduced using alkyl boronic acids (entries 6−8). It was not possible to couple hindered alkyl substituents using either Suzuki (iPrB(OH)$_2$) or Kumada protocols (iPrMgBr). To circumvent this, an indirect route was employed to access the β-isopropyl derivative of **277**. Thus, a Stille coupling reaction was carried out using (2-methylvinyl)tributyltin, and the resulting terminal olefin was reduced by hydrogenation with Wilkinson's catalyst to furnish the corresponding β-isopropyl furanone in 78% yield (entry 5).[116d] Alkynyl substituents could be coupled to **276** using tin derivatives. Sonogashira reactions of furanone **276** with a variety of acetylenes proceeded using electron-donating acetylenes (entries 9−14).[116a]

The compounds of type **277** were converted to tetrasubstituted structures using various coupling reactions (Table 20). Using the Stille reaction, α-aryl substituents were introduced onto the enone carrying a phenyl substituent at position three (entries 1 and 2). Simple methyl transfers could

Table 20. Coupling of α-Bromoenone 277 with Various Coupling Partners To Form Tetrasubstituted Olefins



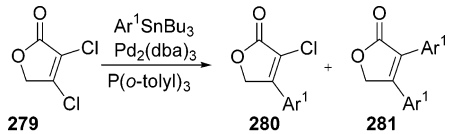
entry	R^1	coupling partner	R^2	conditions[a]	yield (%)
1	Ph	3,5-$Cl_2C_6H_3SnBu_3$	3,5-$Cl_2C_6H_3$	A	26
2	Ph	4-$MeSC_6H_4SnMe_3$	4-$MeSC_6H_4$	A	23
3	Ph	$SnMe_4$	Me	B	58
4	*n*-C_8H_{17}	$SnMe_4$	Me	C	90
5	*t*-$C_4H_9O(CH_2)_6$	$SnMe_4$	Me	C	88
6	*i*-Pr	$PhCH_2ZnBr$	$PhCH_2$	D	36
7		$PhCH_2SnBu_3$	$PhCH_2$	E	22
8				F	31
9		4-$MeOC_6H_4SnBu_3$	4-$MeOC_6H_4$	C	50
10		2-$MOMOC_6H_4SnBu_3$	2-$MOMOC_6H_4$	C	36
11		(2-furyl)$SnBu_3$		C	15
12		4-$MeOC_6H_4B(OH)_2$	4-$MeOC_6H_4$	G	59
13		3,4,5-$(MeO)_3C_6H_2B(OH)_2$	3,4,5-$(MeO)_3C_6H_2$	G	69

[a] Conditions: A, 5% $PdCl_2(PhCN)_2$, 10% $AsPh_3$, 10% CuI, NMP, 80 °C, 3 d. B, 5% $Pd_2(dba)_3$, 10% $AsPh_3$, 10% CuI, NMP, 80 °C, 3 d. C, 5% $PdCl_2([(o\text{-tolyl})_3P]_2$, 10% CuI, NMP, 85 °C, 3 d. D, 5% $PdCl_2([(o\text{-tolyl})_3P]_2$, DMF/THF (1:1), 60 °C. E, 2.5% $Pd_2(dba)_3$, 10% P(2-furyl)$_3$, 10% CuI, NMP, 80 °C. F, 5% $PdCl_2(MeCN)_2$, 10% $AsPh_3$, 10% CuI, 4 equiv of KF, toluene, 90 °C. G, 5% $PdCl_2(PPh_3)_2$, toluene/water (1:1), 3 equiv of CsF, 5 mol % $BnEt_3NCl$, 60 °C.

also be done using Me_4Sn.[116c] Other products were obtained through Stille couplings using tetramethyltin in the presence of both phenyl and long-chain alkyl groups at the β-carbon (entries 3, 4). A more complex side chain at carbon 3 of the enone was also tolerated (entry 5). The introduction of a benzyl moiety in the presence of an isopropyl or isopropenyl substituent was possible, using either Negishi or Stille conditions (entries 6, 7).[116d] A Sonogashira reaction was demonstrated in one case at the α-position, giving the desired product in 31% yield.[116a] In this account, the authors also described a series of Stille-type couplings with enones bearing alkynyl groups at the β-position (entries 9−11). The Suzuki reaction proved to be the most successful when alkynyl groups were present in the β-position, and two electron-donating arylboronic acids were employed, to give products in 59% and 69% yields, respectively (entries 12, 13). Single regioisomers were obtained in all cases, as coupling occurred selectively at the β-position of the dibromides, followed by coupling at the α-position.

The analogous dichlorofuranones were of interest not only for their utility in tetrasubstituted olefin formation, but also for their anti-cancer properties.[118] Initially the coupling of dichloroenones had suffered from poor yields, but optimization quickly improved the results.[119] Suzuki coupling reactions of **279** with aryl boronic acids, bearing electron-donating or electron-withdrawing groups, gave 53−78% isolated yields of the mono-coupled products **280** (Scheme 60). When phenylboronic acid was employed, double

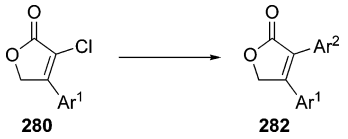
Scheme 60. Coupling of Dichloro Enones



Ar^1 = Ph, 53%
= 4-$MeOC_6H_4$, 78 %
= 3,4-$(MeO)_2C_6H_3$, 75 %
= 2-naphthyl, 67 %

coupling to give product **281** was a significant side reaction. The analogous Stille process produced slightly improved yields, but mixtures of mono- and double-coupled products **280** and **281** were realized. Efforts toward the deliberate generation of **281** from **279** using large excesses of arylboronic acids were successful, giving yields of 60−67%. Attempts to generate **282** from **280** via the Stille or Suzuki

Table 21. Preparation of Tetrasubstituted Lactones



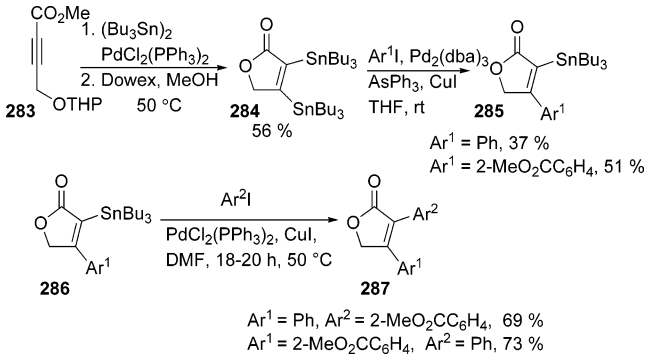
entry	Ar^1	Ar^2	conditions[a]	yield (%)
1	Ph	3,4,5-$(MeO)_3C_6H_2$	A	42
2	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	A	58
3	3,4-$(MeO)_2C_6H_3$	3,4,5-$(MeO)_3C_6H_2$	A	58
4	2-naphthyl	3,4,5-$(MeO)_3C_6H_2$	A	39
5	4-$MeOC_6H_4$	3,4-$(MeO)_2C_6H_3$	B	46
6	4-$MeSC_6H_4$	Ph	B	26

[a] A: $Ar^2B(OH)_2$, $Pd_2(dba)_3$, *t*-Bu_3P, KF, toluene. B: Ar^2SnBu_3, $Pd(OAc)_2$, Cy_3P, KF, toluene.

processes resulted in lower yields of 26−58% (Table 21). The best results were achieved using Suzuki-type conditions with *t*-Bu_3P as the ligand. With these conditions, yields ranged from 39% to 58% (Table 21, entries 1−4). The use of tin reagents as coupling partners resulted in slightly lower recoveries. The reason for this observation, when using the differential-substitution sequence, in light of the facile conversions of **279** to **281**, was not clear.

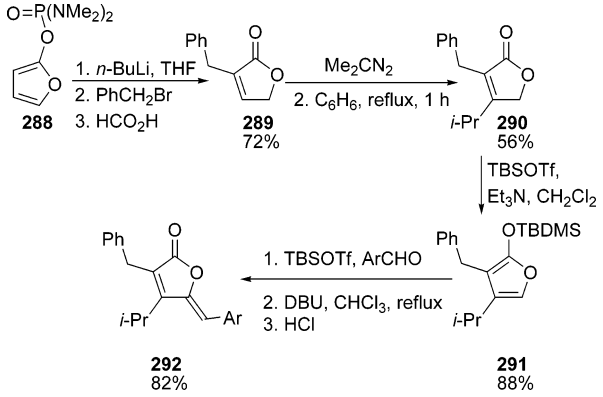
Olefin templates can also serve as the nucleophilic component in cross-coupling reactions to obtain tetrasubstituted alkenes. Mabon, Richecoeur, and Sweeney[120] generated cyclic olefin templates **284** by bis-stannylation of alkyne **283**[121] followed by an acid-catalyzed cyclization (Scheme 61). Subsequent Stille coupling reactions provided trisubstituted furanones as single regioisomers in yields of 22−51%. It is likely that steric hindrance from the remaining tributyltin substituent was a major factor that inhibited the initial coupling. Two examples illustrated the viability of a second Stille process to form tetrasubstituted olefins. Two aryl iodides were introduced onto α-stannyl enones **286** to produce the corresponding tetrasubstituted olefin products **287**. Higher temperatures were required to force these reactions at the less activated α-position, but conversions were significantly better than for the initial coupling reactions.

Scheme 61. Stannyl−Olefin Templates



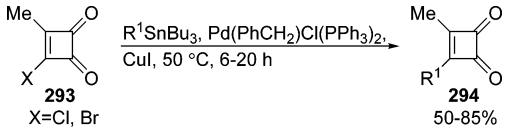
A previous approach to substituted furanones, Nostoclides I and II, employed furanolate chemistry.[122] Using straightforward reactions, the desired product was obtained in 30% overall yield (Scheme 62). Tetramethyldiamidophosphate **288** was ortho-lithiated, and the resulting anion trapped with benzyl bromide to provide butenolide **289** in 72% yield. The isopropyl group was introduced regioselectively in 56% yield via a 1,3-dipolar cycloaddition, followed by thermolysis to release gaseous nitrogen. Aromatization was accomplished by treatment of the tetrasubstituted butenolide with triethylamine and *tert*-butyldimethylsilyl triflate, providing furan **291** in 88% yield. The desired target **292** was obtained as a mixture of diastereomers (4.3:1) after *tert*-butyldimethylsilyl triflate-induced aldolization and dehydration.

Scheme 62. Nostoclides via Furanoate Chemistry



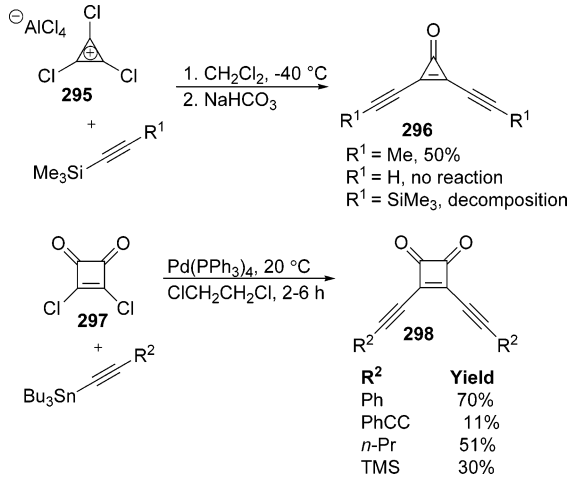
Substituted cyclobutenediones are important in the synthesis of quinine and alkylidenecyclopentenones, and the use of alkene templates to prepare these cyclobutenediones has emerged as a complementary method to the classic squaric acid ester sequences.[123] Liebeskind and Wang employed the Stille reaction to generate differentially substituted cyclobutenedione products (Scheme 63).[124] The coupling reactions proceeded smoothly with both chlorides and bromides (**293**), using aryl, alkynyl, and vinyl stannanes bearing electron-donating and electron-withdrawing groups, to give fully substituted butenediones **294**.

Scheme 63. Synthesis of Fully Substituted Cyclobutenediones



Rubin and co-workers described the generation of 2,3-dialkynyl-2-cyclopropenones **296** and 3,4-dialkynyl-3-cyclobutene-1,2-diones **298** from precursors **295** and **297**, respectively (Scheme 64).[125] The reactions of trichlorocyclopropenylium tetrachloroaluminate **295** with alkynylsilanes

Scheme 64. Synthetic Design of Strained Ring Systems Containing Tetrasubstituted Olefins



were first studied. The reaction was quite successful when 1-(trimethylsilyl)-1-propyne (R^1 = Me) was employed as a coupling partner at −40 °C followed by quenching with water, giving the desired cyclic olefin **296** in 50% yield. Unfortunately, it was not possible to obtain the unsubstituted or silyl-substituted products by this method, as the acetylenic substrates were either unreactive (R^1 = H) or decomposed under the reaction conditions (R^1 = $SiMe_3$).

The investigators then turned to the reaction of dichlorocyclobutenone **297**. Stille coupling reactions with this substrate proved to be successful with the four stannanes tested; however, purification of the products was very difficult due to tributyltin chloride contamination. The key product (R^2 = TMS) decomposed extensively during chromatographic purification on silica. Seeking alternatives, zinc acetylides were tested. These worked well only in the case of phenyl acetylide, as other substrates either did not react or decomposed rapidly. The use of copper acetylides, rather than tin reagents, proved ideal, and of the number of silyl acetylides that were used, *tert*-butyldimethylsilyl and triisopropylsilyl-substituted derivatives gave the highest yields (57% and 59%, respectively). Having achieved the synthesis of their starting materials, the formation of cyclobutenodehydroannulenes and analogues was examined.[125]

Barluenga et al. accessed cyclic olefin templates via the electrophilic iodoarylation of alkynes.[126] A wide variety of trisubstituted vinyl iodides were produced using this method, and while these were not transformed to tetrasubstituted alkenes, in principle they could have been. Three examples were shown in which the cyclic bromo-iodo intermediates **301** were converted to tetrasubstituted olefins **302** (Scheme 65 and Table 22). In all cases, the first coupling occurred

Scheme 65. Cyclic Olefin Templates

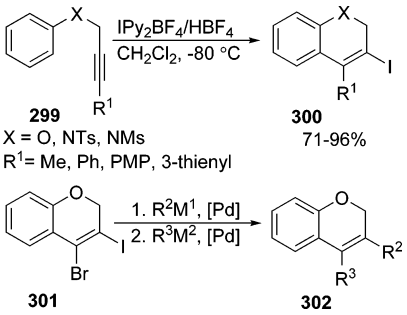


Table 22. Conversion of Bromoiodo Derivatives 301 into Tetrasubstituted Olefins 302

entry	R^2	R^3	yield (%)
1	4-MeC_6H_4CHCH	4-$MeOC_6H_4$	72
2	Ph	4-$MeOC_6H_4$	54
3	3-thienyl	4-MeC_6H_4CC	67

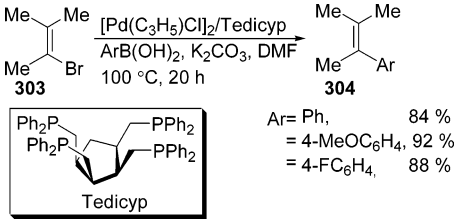
selectively at the iodide position, and the subsequent coupling occurred at the bromide position. High temperatures were required to effect the coupling reactions, and in many cases heating in sealed tubes was necessary.

3.3. Geminally Symmetric Olefin Templates

There are significantly fewer methods available for the formation of acyclic, tetrasubstituted double bonds than for the formation of cyclic olefins. Yields can erode dramatically when mixtures of isomers are formed in the process, and so methods often employ geminally symmetric double bonds as templates. This facilitates the discovery of new methodology to access molecules of intriguing architecture before the issue of asymmetrically substituting the double bonds must be addressed. Some of the successful techniques for the generation of acyclic, tetrasubstituted double bonds are described below.

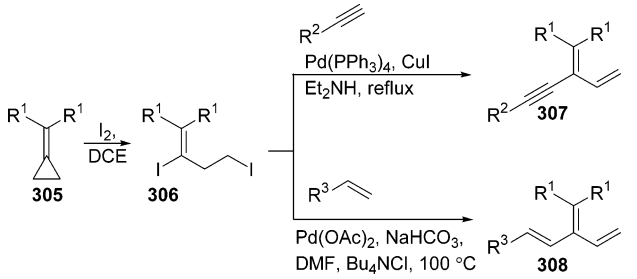
In 2003, a new tetraphosphane ligand was disclosed by Berthiol et al., and the utility of this ligand was demonstrated in the Heck and Suzuki reactions (Scheme 66).[127] Tetrasubstituted olefins were successfully generated via Suzuki reactions using extremely low catalyst loading (<0.1% palladium).

Scheme 66. Generation of Tetrasubstituted Olefins Using Tedicyp



Shao and Shi reported methodology for the formation of acyclic 2-alkynylbuta-1,3-dienes **307** from diiodide precursors **306** (Table 23) that were prepared from an electrophilic

Table 23. Tetrasubstituted Alkenes via Iodide Templates



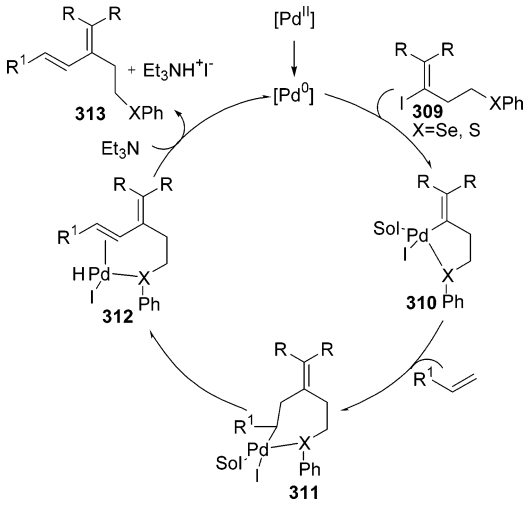
entry	R^1	R^2	yield (%) (**307**)
1	4-$MeOC_6H_4$	Ph	91
2	4-MeC_6H_4	Ph	87
3	4-ClC_6H_4	Ph	97
4	Ph	4-$MeOC_6H_4$	99
5	4-ClC_6H_4	4-$MeOC_6H_4$	99
6	4-$MeOC_6H_4$	CH_2OH	30
7	4-MeC_6H_4	CH_2OH	49
8	Ph	CH_2OH	28
9	4-$MeOC_6H_4$	CH_2OBn	92
10	4-MeC_6H_4	CH_2OBn	78
11	4-$MeOC_6H_4$	*n*-C_4H_9	51
12	4-MeC_6H_4	*n*-C_4H_9	47

ring opening of methylene cyclopropanes.[128] The reaction worked with a wide variety of aryl alkynes, although significantly lower yields were observed when coupling reactions were attempted with alkyl alkynes. In each case, elimination of the alkyl iodide was observed, giving an extended conjugated system. This was perhaps unfortunate, as the alkyl iodides would have provided a handle for further elaboration. The effectiveness of the method could only be demonstrated with symmetric cyclopropanes because mixtures of isomers were obtained when the geminal substituents (R^1) were different.[129] The analogous Heck reactions were then examined, which produced conjugated trienes, such as **308**, in yields of 30−99%.[129b] Again, elimination of the alkyl

iodide occurred under the reaction conditions, producing triene products.

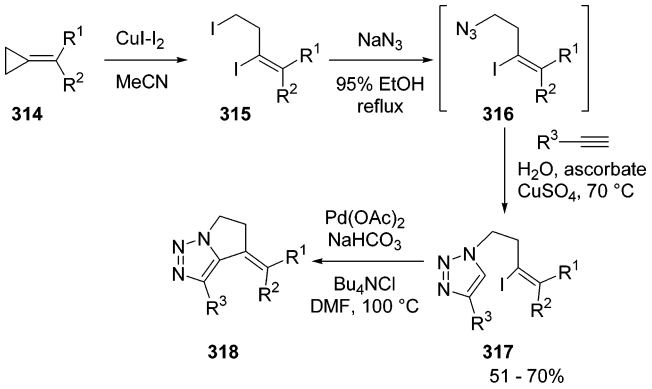
This method was later improved and expanded by replacing the iodine on the side chain of **306** with a selenium or sulfur substituent.[130] This avoided the elimination process during the coupling reaction and allowed for subsequent alkyl transformations at the selenium or sulfur position. Heck reactions were achieved with a wide variety of substrates, in yields of 82−94%. Kumada couplings were also successful, although lower yields were reported for substrates bearing electron-withdrawing aryl moieties. Suzuki and Negishi couplings were effective, and, notably, the Negishi reaction made possible the introduction of an alkyl substituent to the tetrasubstituted alkene. Most reactions proceeded at room temperature and in many cases without using ligands or additives. This was explained by a mechanism that involved the participation of the selenium or sulfur atom as a ligand to the palladium, thus activating and directing the catalyst to the desired site (Scheme 67). These reactions did not proceed with substrates lacking the selenium or sulfur atom (i.e., Se replaced with CH_3).

Scheme 67. Catalytic Cycle Describing the Role of the S or Se Substituent



This methodology was recently exploited by Chen and coworkers in their synthesis of pyrrolotriazoles (Scheme 68).[131]

Scheme 68. Synthesis of Pyrrolotriazoles



The olefin templates were prepared as before through the CuI-mediated dihalogenation of methylene cyclopropanes **314**, to give olefin templates **315**. These were treated with sodium azide in refluxing ethanol, and a variety of acetylenes were subsequently introduced to give 1,3-dipolar cycloaddition products **317** in yields of 51−70%. Intramolecular Heck reactions were then carried out to provide the final products **318**, which each contained a tetrasubstituted olefin moiety (Table 24). In one case, two different R groups on the methylene cyclopropane (**314**) were employed (entry 8).

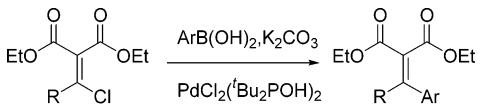
Table 24. Conversion of Template 317 to 318

entry	R^1	R^2	R^3	yield (%)[a]
1	Ph	Ph	n-C_4H_9	82
2	Ph	Ph	n-C_5H_{11}	85
3	Ph	Ph	$MeOCH_2$	52
4	4-ClC_6H_4	4-ClC_6H_4	n-C_4H_9	82
5	4-ClC_6H_4	4-ClC_6H_4	n-C_5H_{11}	58
6	4-FC_6H_4	4-FC6H4	n-C_4H_9	68
7	4-FC_6H_4	4-FC_6H_4	n-C_5H_{11}	70
8	Me	Ph	n-C_5H_{11}	71

[a] Yields are based on recovered **317**.

While a Knoevenagel condensation with a ketone will generate a tetrasubstituted olefin directly, this process generally only proceeds well with cyclohexanone or methyl ketone derivatives.[132] An indirect method of generating olefin templates from the Knoevenagel condensation has been reported by the Turner research group that provided additional product scope (Table 25). Treatment of diethyl malonate with an acyl chloride in the presence of $MgCl_2$, followed by chlorination with $POCl_3$/Bu_3N, gave vinyl chlorides **319**. Subsequent coupling reactions with arylboronic acids delivered the corresponding tetrasubstituted olefins **320**. Microwave irradiation was found to greatly increase the rate of the reaction, and it was shown that a wide variety of aryl substituents were tolerated, including those possessing unprotected amino and hydroxyl substituents.

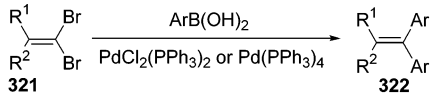
Table 25. Vinyl Chlorides from Modified Knoevenagel Condensation Sequence



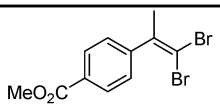
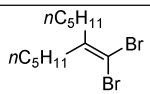
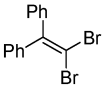
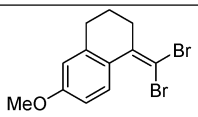
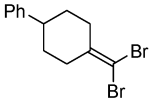
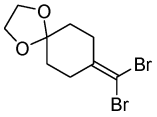
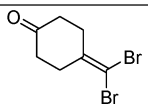
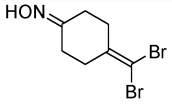
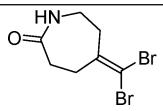
entry	R	Ar	yield (%)
1	Me	3-ClC_6H_4	70
2	Me	3,5-$F_2C_6H_3$	59
3	Me	3,5-$Me_2C_6H_3$	60
4	Me	4-$MeOC_6H_4$	65
5	Me	2-MeO-5-FC_6H_3	66
6	Me	3-$NO_2C_6H_4$	72
7	i-Pr	C_6H_5	71
8	i-Pr	3-ClC_6H_4	57
9	i-Pr	3-FC_6H_4	55
10	i-Pr	2-MeO-5-FC_6H_3	52
11	Ph	3-ClC_6H_4	55
12	Ph	2-MeO-5-FC_6H_3	50
13	Ph	3-$CF_3C_6H_4$	68
14	Ph	3-$NH_2C_6H_4$	60
15	Ph	3-HOC_6H_4	58

Geminal halide substitution provides more opportunities for elaboration,[133] but the control of stereoselectively poses a serious challenge. Methodology was disclosed forming geminally symmetric tetrasubstituted olefins (Table 26) using Corey−Fuchs[134] templates (**321**) that were generated from various ketones.[135] Suzuki coupling reactions with 4−6 equiv of various arylboronic acids furnished the olefins **322** in

Table 26. Coupling of Geminal Dibromo Olefins



321 322

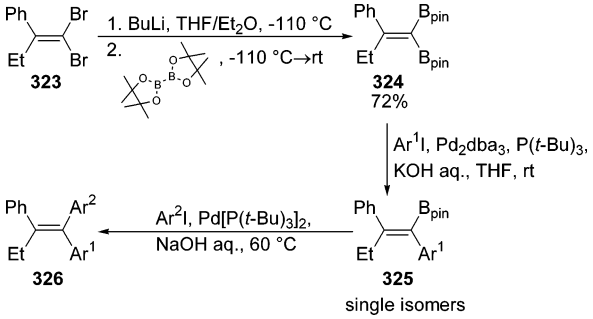
entry	alkene **321**	Ar	yield (%)
1		3-$MeOC_6H_4$	97
2		4-$MeSC_6H_4$	95
3		Ph	26
4[a]		4-pyridyl	46
5[a]		4-$MeOC_6H_4$	87
6[a]		3-$CF_3C_6H_4$	75
7		Ph	77
8		4-$MeOC_6H_4$	79
9		Ph	69
10		2-$CF_3C_6H_4$	24
11		Ph	89
12		4-$MeOC_6H_4$	97
13		4-MeC_6H_4	85
14		4-$MeOC_6H_4$	81
15		Ph	92

[a] $Pd(PPh_3)_4$ and DME/H_2O (4:1) were employed at 90 °C.

yields of 24−97%. A wide variety of functionalities were tolerated, including esters, acetals, ketones, oximes, and amides, but yields decreased when ortho-substituted aryls were employed, presumably due to the steric crowding in these already congested centers. Higher reaction temperatures were necessary to couple acyclic olefins, and it was found that large excesses of the boronic acids were required to force the reactions to completion. Interestingly, the mono-arylated products were never isolated, likely indicating that these substrates were more activated toward coupling than the dibromo starting materials. It was not possible to couple two different arylboronic acids using this method.

To achieve differentiation at the geminally substituted carbon, an extra step was added by Shimizu and colleagues to the sequence described above, giving the *gem*-diboryl alkenes **324** shown in Scheme 69.[136] Treatment of the 1,1-dibromoalkene **323** with butyllithium at −110 °C, followed by slow addition of the solution at −110 °C to bis-(pinacolato)diboron in THF, gave the 1,1-diborylalkenes **324**.

Scheme 69. Differentiation of Dibromo Substituents



323 324 72% 325 326 single isomers

These materials were then cross-coupled, and, impressively, single isomers (**325**) were formed, a fact that was confirmed by both NOE and X-ray analysis. Yields ranged from 39% to 87% for a wide variety of alkyl groups, including sterically crowded *i*-Pr and *t*-Bu moieties, although small drops in yields were observed when *tert*-butyl groups were present (39−54%). A wide range of functionality was tolerated on the aryl moiety, including a free aniline. Yields of 59−89% were achieved for the second, more difficult, coupling reaction to give final product **326** (Table 27). Often steric

Table 27. Conversion of 325 to Tetrasubstituted Olefins 326

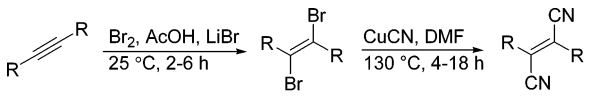
entry	Ar^1	Ar^2	yield (%) (**326**)
1	Ph	4-$Me_2N(CH_2)_2OC_6H_4$	59
2	4-FC_6H_4	4-$MeOC_6H_4$	75
3	4-$MeOC_6H_4$	4-$CF_3C_6H_4$	78
4	4-$MeOC_6H_4$	4-MeC_6H_4	89
5	4-$Me_2N(CH_2)_2OC_6H_4$	Ph	75
6	4-MeC_6H_4	Ph	89

hindrance is the factor that determines the regioselectivity in such couplings. However, it appeared that this was not the case in these substrates, as the Ar^1 moiety was delivered cis to the alkyl group in every example, even when the alkyl moiety was a *tert*-butyl group. Naturally, this incurred limitations, requiring at least one aryl and one alkyl group to be on the distal carbon, and only aryl couplings were described. The exceptional regioselectivity observed provided a distinct advantage over many other methods and makes an impressive contribution to the formation of tetrasubstituted olefins.

3.4. Acyclic, Vicinally Symmetric Olefin Templates

Methodology outside the domain of geminally substituted olefins requires controlling elements, either at the coupling stage or, more often, during the construction of the template. An early example by Fitzgerald and colleagues utilized symmetrical, 1,2-dibromo olefins for the generation of tetraazaporphyrins (Scheme 70).[137] Bromination of 3-hexyne

Scheme 70. 1,2-Dibromo Olefin Precursors to Tetraazaporphoryns



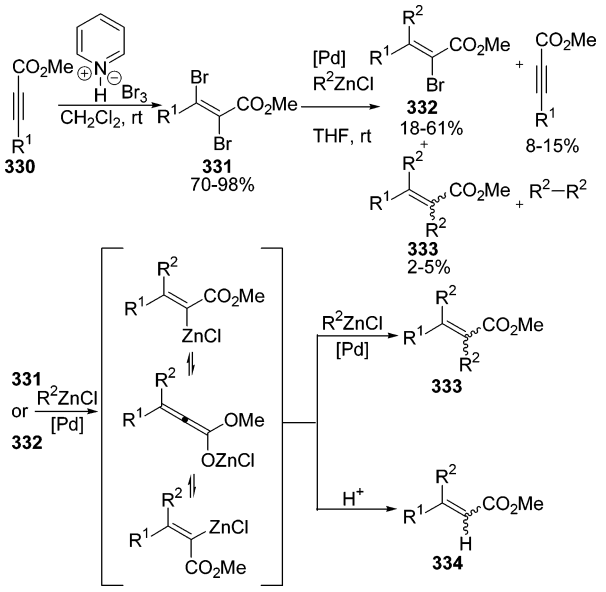
327 328 75-97% 329 R = Et, 78 % = Ph, 81 %

or diphenylacetylene **327** gave the dibromo alkenes **328**. These alkenes were converted, via the Rosenmund−von

Braun reaction, to dinitriles **329** that were further transformed to tetraazaporphoryns.

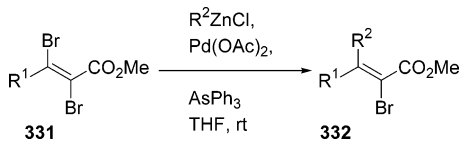
It has been shown that *E*-dibromo olefin templates **331** could be generated, in greater than 98% stereochemical purity, by the exposure of 2-alkynyl esters **330** to pyridinium bromide perbromide (Scheme 71).[138] Mixtures of *E* and *Z*

Scheme 71. Generation of *E*-Dibromo Alkenes for the Production of Tetrasubstituted Olefins



isomers were obtained if Br_2 was used alone at temperatures above −78 °C, or if the reaction was contaminated with traces of HBr.[139] Various palladium-catalyzed reactions of the 1,2-dibromo olefins gave the corresponding trisubstituted olefins in 18−61% yields (Table 28). Several side products

Table 28. Generation of Trisubstituted Alkenes from 2,3-Dibromoalkenoates



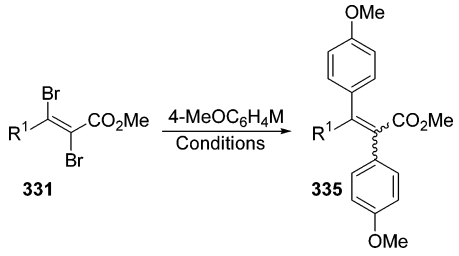
entry	R^1	R^2	yield (%)
1	C_5H_{11}	4-$MeOC_6H_4$	61
2	C_5H_{11}	2-$MOMOC_6H_4$	43[a]
3	C_5H_{11}	4-FC_6H_4	56
4[b]	Me	2-$MOMOC_6H_4$	24
5	C_5H_{11}	$C_6H_{13}C{\equiv}C$	57
6[b]	Me	4-$MeOC_6H_4$	49
7[b]	Ph	4-FC_6H_4	27
8[b]	Ph	4-$MeOC_6H_4$	18
9[b]	Ph	2-$MOMOC_6H_4$	38
10[b]	CO_2Et	4-$MeOC_6H_4$	43

[a] 5% $Pd(PPh_3)_4$ was used as catalyst. [b] The ethyl ester was employed.

were obtained in these reactions, including double-coupled products (2−5%), alkynes resulting from eliminations of the dibromide substrates (8−15%), and significant amounts of homocoupled biaryl materials. Mixtures of stereoisomers were observed when phenyl or ester substituents were present at R^1 (entries 7−10).

Tetrasubstituted olefins were subsequently obtained from these products, as mixtures of isomers, by Negishi or Stille coupling reactions (Table 29). The loss of stereochemical

Table 29. Generation of Tetrasubstituted Alkenes



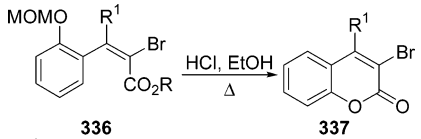
entry	R^1	M	conditions[a]	yield (*E*:*Z*)
1	C_5H_{11}	ZnCl	A	13% (1:1)
2[b]	C_5H_{11}	ZnCl	B	13% (12:88)
3	C_5H_{11}	$SnBu_3$	C	27% (*E*)
4	CO_2Et	ZnCl	B	*c*
5	CO_2Et	$SnBu_3$	C	60% (55:45)[d]

[a] Catalyst A: $Pd(PPh_3)_4$, THF, rt, 48 h. Catalyst B: $Pd(OAc)_2$, $AsPh_3$, THF, rt, ∼50 h. Catalyst C: $PdCl_2(PhCN)_2$, CuI, $AsPh_3$, NMP, rt. [b] Starting material was (*E*)-**332**; R^2 = 4-$MeOC_6H_4$. [c] An *E*/*Z* mixture was obtained but the ratio was not determined. The *E*-isomer was isolated in 39% yield. The ethyl ester was employed. [d] Yield and *E*/*Z* ratio were determined indirectly. The ethyl ester was employed.

integrity in these transformations was likely due to the formation of allenoate intermediates. A single isomer was achieved in only one example by using the Stille reaction, in 27% yield (entry 3). Trisubstituted side products (**334**) were obtained in the Negishi couplings as mixtures of isomers, which were probably derived from halogen−zinc exchange and isomerization through the zinc allenoates, followed by protonation in the workup stage.

Stereochemical assignments were made on the basis of chemical shifts. The authors noted that the methylene moieties of the R^1 substituents in products such as (*E*)-**335** resonated downfield of the corresponding signals of the corresponding *Z* isomer. In a few cases, a chemical transformation was used to establish olefin stereochemistry (Scheme 72). Alkenyl esters **336** were refluxed with HCl in EtOH to provide the corresponding lactones **337**.

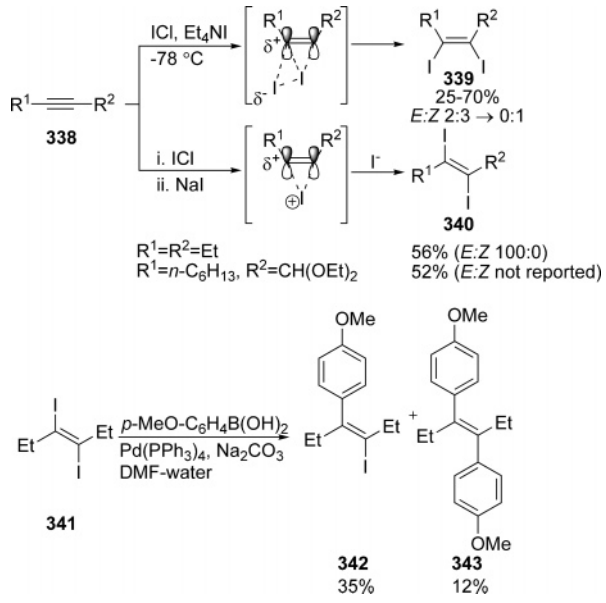
Scheme 72. Structural Proof via Derivatization



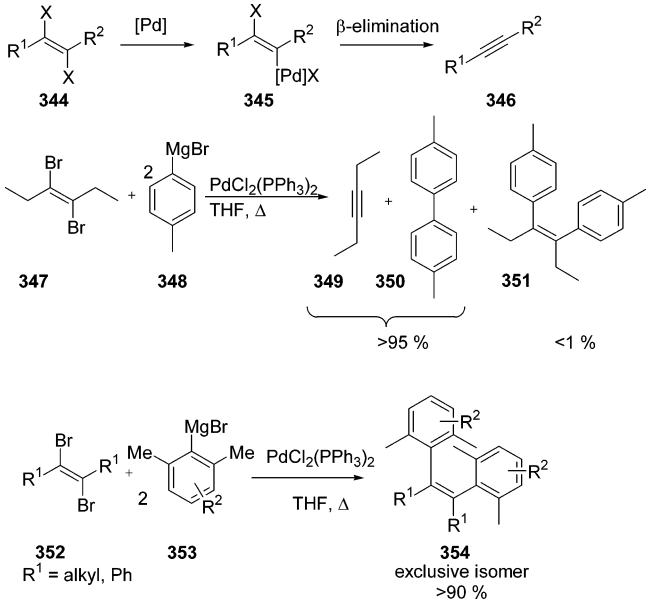
Hénaff and Whiting described a method for the selective formation of either *E*- or *Z*-diiodo templates.[140] By carefully controlling the reaction conditions, they could access either the *E*- or the *Z*-isomers (Scheme 73). Isomeric mixtures were obtained during the generation of most *Z*-iodo alkenes (**339**), and it was only possible to obtain pure *E* tetrasubstituted precursors in two cases. Suzuki or Stille coupling reactions of the *E*-diiodo templates **341** were described to give trisubstituted alkenes **342**, and one tetrasubstituted olefin (**343**) was reported, a result of over-addition to the *E*-diiodo substrate **341**, in a 12% yield. The attempted generation of *Z*-tetrasubstituted products from the corresponding *Z*-iodides (**339**) was not described.

A potential explanation for the extremely low yield of tetrasubstituted olefin **343** was the competitive palladium-catalyzed elimination of the vicinal dihalogens (Scheme 74).[138,141] Oxidative addition of palladium into the first

Scheme 73. Attempted Generation of Tetrasubstituted Olefins via Dihalo Olefin Templates



Scheme 74. Palladium-Catalyzed Elimination of Vicinal Dihalogens and Formation of Sterically Congested Tetrasubstituted Alkenes

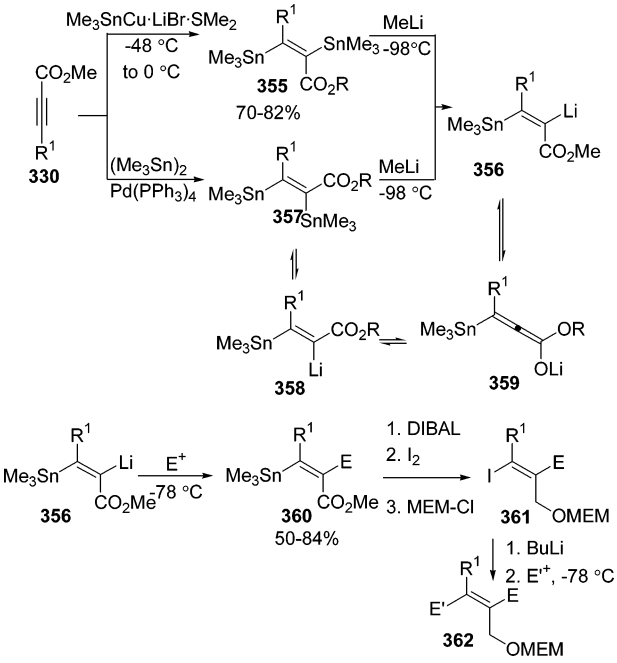


carbon−halogen bond of template **344** would form the organopalladium intermediate **345** that could then undergo subsequent β-halogen elimination to produce alkyne **346**. A reaction performed using *p*-tolyl-magnesium bromide **348** and dibromo alkene **347**[24] produced less than 1% of the desired tetrasubstituted isomer **351**, and instead gave the eliminated alkyne product **349** and biaryl **350**, consistent with the above hypothesis.

An interesting effect was demonstrated by the Rathore research group (Scheme 74).[24] Six different *trans*-dibromoalkenes (**352**) were coupled with ortho-substituted aryl magnesium bromides (**353**) in yields greater than 90%. Complete inversion of stereochemistry was noted in all cases to give exclusively the *Z*-alkene products (**354**). The stereochemistry was confirmed in one case by X-ray crystallographic analysis, and the remaining structures were assigned through the correlation of NMR chemical shifts. This method allowed access to highly hindered *Z*-tetrasubstituted alkenes (**354**) that are typically very difficult to prepare, but was only effective for di-ortho-substituted aryl Grignard reagents.

The elimination product was not observed when stannanes were used instead of halides, as illustrated by the Piers research group (Scheme 75).[142] Double stannylation of

Scheme 75. Stannylated Olefin Templates



alkynylesters **330** gave *E*- and *Z*-stannanes **355** or **357**. Tin−lithium exchange on *trans*-distannane **355** (R^1 = Me) provided the α-lithiated alkene **356** that captured strong electrophiles regioselectively (MeI, 84%; CH_2=$CHCH_2Br$, 79%; BnBr, 76%; C_4H_9I, 50%; cyclohexanone, 71%). Exposure of the *cis*-stannane **357** to methyllithium caused a rapid isomerization, after lithium exchange, to give **356** exclusively, presumably through allenoate **359**. Direct tin−lithium exchange was not possible at the β-position of **360**. Instead, the β-stannane **360** was reduced with DIBAl, treated with iodine, and protected to give vinyl iodides **361**. These compounds were then subjected to lithium−iodide exchange using butyllithium. Finally, an electrophile was introduced giving the tetrasubstituted products **362** (MeI, 93%; *n*-BuI, 65%; ICH_2CH=CMe_2, 67%; $I(CH_2)_5Cl$, 72%). Multiple steps were required, under strictly controlled conditions, and only highly activated electrophiles could be employed. Single isomers were produced, as shown by careful NOE analysis.

Efficient product isolation is desirable in any process. A way to achieve this goal was investigated by Brown and Armstrong through the use of solid support (Scheme 76).[143] Symmetrically substituted alkynes (**363**) were borylated[144] using palladium catalysis, and the crude products **364** were then coupled in solution with an organohalide. This process produced the trisubstituted olefin products **365**, together with some double-coupled products **366**. Subsequent resin-capture with a polymer-supported aryl iodide gave the resin-bound tetrasubstituted olefins **367** in good yields. Impurities and side products such as **366** remained in solution, and the desired alkenes **367** could be recovered from the resin by treatment with TFA (Table 30). Mixtures of regioisomers were obtained when differentially substituted alkynes were

Scheme 76. Synthesis of Pure Tetrasubstituted Olefins via Synthesis on Solid Support

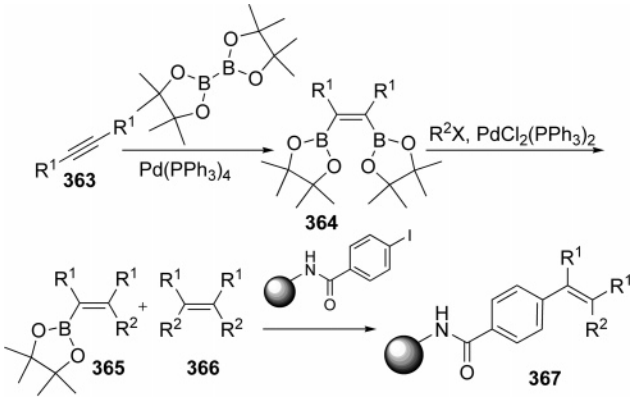


Table 30. Synthesis of Tetrasubstituted Olefins on Solid Support

entry	R^1	R^2	yield[a] (%)
1	Ph	Me	>95
2	Ph	2-Me-1-propenyl	78
3	Ph	2-propenyl	>95
4	Ph	Bn	>95
5	Ph	4-MeC_6H_4	83
6	Et	Me	>95
7	Et	2-Me-1-propenyl	75
8	Et	2-propenyl	>95
9	Et	Bn	83
10	Et	4-MeC_6H_4	85

[a] After removal of the solid support.

used, and the products had to be stable to the strong acidic media required to remove the polymer. Alkene isomerization was an additional complication as one of the conjugated alkene products was obtained as a mixture of *E* and *Z* isomers during the resin-removal phase.

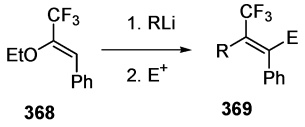
3.5. Differentially Substituted Olefin Templates

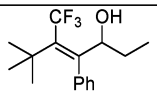
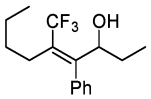
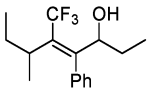
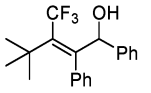
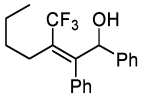
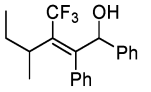
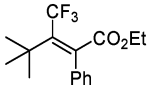
Additional control must be introduced when utilizing fully asymmetric templates. Reactivity is controlled primarily by electronic effects in these compounds, and additional control elements such as directing groups must therefore be present. The distinct advantage of these templates lies in their potential use to generate tetrasubstituted olefins bearing four different carbon substituents.

The Bonnet−Delpon group demonstrated that carbolithiation of alkenes such as **368** using various alkyl lithium reagents (*t*-BuLi, *n*-BuLi, *s*-BuLi), followed by trapping with electrophiles, generated tetrasubstituted alkenes stereoselectively in yields of 75−95% (Table 31).[145]

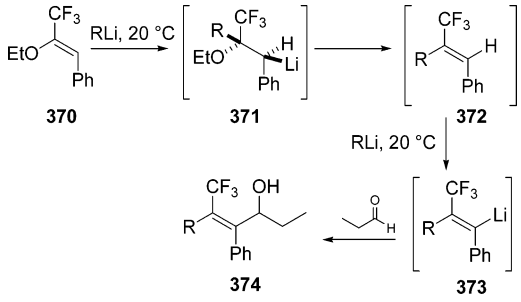
The mechanism of this transformation apparently involved an unusual pseudosubstitution of the ethoxy group. In the present case, the reaction was thought to involve a cis addition of alkyllithium across the double bond, a process encouraged by the electron-poor nature of the initial olefin (Scheme 77). Regioselectivity was controlled by the stabilizing influence of the β-aryl ring that was responsible for the reaction following a pseudosubstitution pathway. Because the reactions were performed at room temperature, anti-elimination of the intermediate species (**371**) occurred rapidly to produce trisubstituted olefins **372**. These compounds were deprotonaned in situ by a second equivalent of the alkyllithium affording the reactive species **373**, which reacted with an electrophile to give the final product.

Table 31. Carbolithiation of Trifluoromethyl Enolethers To Generate Tetrasubstituted Alkenes



entry	RLi	electrophile (E^+)	product	yield (%)
1	*t*-BuLi	C_2H_5CHO		75
2	*n*-BuLi	C_2H_5CHO		83
3	*s*-BuLi	C_2H_5CHO		82
4	*t*-BuLi	PhCHO		95
5	*n*-BuLi	PhCHO		85
6	*s*-BuLi	PhCHO		88
7	*t*-BuLi	$ClCO_2Et$		79

Scheme 77. Carbolithiation To Generate Alkenes



The efficient production of single isomer tetrasubstituted olefins bearing all different carbon substituents was described in a recent report (Scheme 78).[146] *E*-β-Chloro-α-iodo-α,β-unsaturated ester templates **376** were generated as single isomers by exposure of 2-alkynyl esters **375** to Bu_4NI in refluxing dichloroethane.[147] This method provided access to a variety of *E*-β-chloro-α-iodo-α,β-unsaturated esters, **376**, bearing aryl, alkyl, and hindered alkyl substituents at the R^1 position. Regioselective Sonogashira reactions occurred exclusively at the α-position to provide trisubstituted vinylic chlorides **377** (Table 32). This was in stark contrast to the results obtained with unsaturated esters bearing identical halogens at both positions, as those substrates reacted selectively at the β-position. The reactivity of vinyl iodides toward oxidative insertion overrode the higher reactivity typically observed at the β-position of α,β-unsaturated esters.

Scheme 78. *E*-β-Chloro-α-iodo-α,β-Unsaturated Ester Templates as Precursors to Tetrasubstituted Olefins

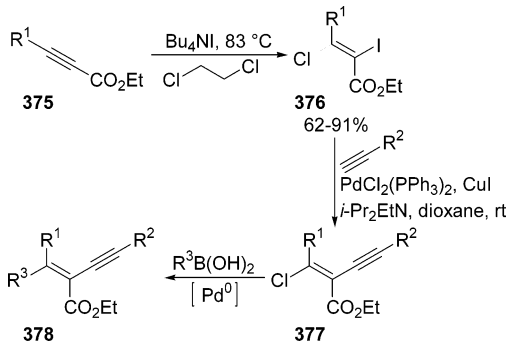
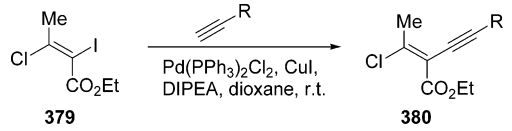


Table 32. Preparation of Trisubstituted Alkenes from β-Chloro-α-iodo-α,β-Unsaturated Esters

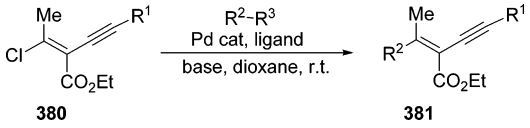


entry	R	yield (%)[a]
1[b]	Ph	78
2	4-FC_6H_4	77
3	TMS	68
4	C_6H_{13}	74
5	CH_2OTBS	76
6	$(CH_2)_2OTBS$	72

[a] Isolated yield. [b] 0 °C.

Subsequent coupling reactions, employing either the Sonogashira or the Suzuki process, provided the tetrasubstituted olefins **381** as single isomers (Table 33). Photoisomerization of the esters provided access to the opposite stereochemical isomers, and after reducing the esters with DIBAL, NOE analysis was used to unequivocally establish the structures of the products obtained.

Table 33. Preparation of Tetrasubstituted Alkenes from β-Chloro-α,β-Unsaturated Esters

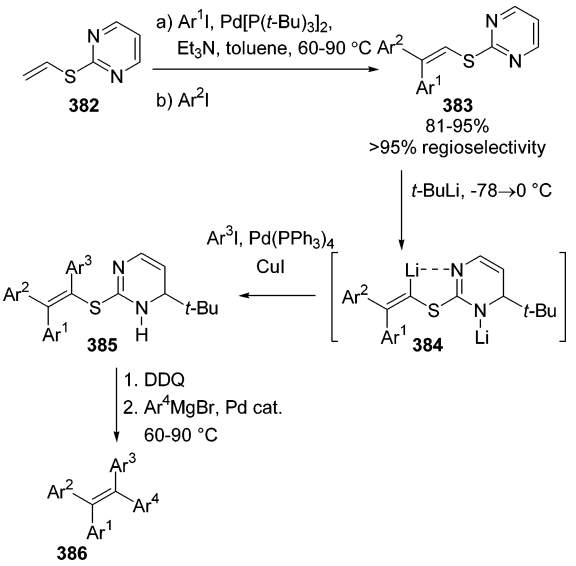


entry	R^1	R^2	R^3	yield (%)[a]
1[b]	Ph	PhCC−	H	55
2[b]	TMS	PhCC−	H	42
3[c]	TMS	Ph	$B(OH)_2$	77
4[c]	TMS	4-MeC_6H_4	$B(OH)_2$	75
5[c]	TMS	4-FC_6H_4	$B(OH)_2$	71
6[d]	TMS	PhCH=CH−	$B(OH)_2$	67
7[d]	TMS	$CH_3(CH_2)_5CH$=CH−	$B(OH)_2$	64

[a] Isolated yield. [b] Reaction conditions: phenylacetylene (6 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (15 mol %), DIPEA (3 equiv), dioxane (0.1 M), rt, 18 h. [c] Reaction conditions: $R^2B(OH)_2$ (2 equiv), $Pd_2(dba)_3$ (5 mol %), P^tBu_3·HBF_4 (20 mol %), Cs_2CO_3 (2 equiv), dioxane (0.1 M), rt, 2 h. [d] Reaction conditions: $R^2B(OH)_2$ (2 equiv), $Pd_2(dba)_3$ (5 mol %), S-Phos (20 mol %), K_3PO_4 (2 equiv), THF (0.1 M), rt, 2 h.

An innovative approach developed by Itami and colleagues efficiently elaborated very simple alkene templates to tetrasubstituted olefins by using vinyl-2-pyrimidylsulfide precursors **382** (Scheme 79).[148] Beginning with the vinyl sulfide

Scheme 79. Pyrimidyl Sulfide-Templated Alkenes



382, two successive Heck reactions gave product **383** with defined stereochemistry. Exposure of **383** to 2 equiv of *t*-BuLi introduced a *t*-butyl substituent onto the pyrimidine ring, and the resulting lithio species underwent directed metalation at the α-position[149] of the alkene to generate intermediate **384**. This material suffered a cross-coupling reaction in the presence of an aryl iodide to afford the corresponding trisubstituted derivative **385**. Subsequent rearomatization of the pyrimidine gave the vinyl pyrimidyl sulfide that was subjected to a final palladium-catalyzed cross-coupling reaction with aryl Grignard reagents (Table 34). Low yields were obtained when Ar^3 was particularly bulky (2-naphthyl for example), although the palladium-catalyzed coupling reaction tolerated Grignard reagents bearing electron-withdrawing and electron-donating substituents.

Itami and co-workers also developed a copper-catalyzed carbomagnesation across alkynyl(2-pyridyl)silanes **387** to give products such as **388** (Scheme 80).[150] Borodesilylation occurred stereoselectively at low temperature, and subsequent treatment of the reaction intermediates with pinacol in the presence of triethylamine gave products **389** with retention of stereochemistry. Interestingly, it was found that the isomeric purities of **389** were greater than those of the starting alkenylsilanes. The authors felt this may have been due to reactivity differences between the isomeric alkenylsilanes during the borodesilylation. A final palladium-catalyzed cross-coupling reaction, with a wide variety of aryl iodides, gave tetrasubstituted olefins **390**.

Overall, olefin templates are emerging as a reliable method of forming tetrasubstituted alkenes; however, there is still significant room to improve the generality and practicality of the methods. The selective production of the template is a limiting factor for much of this chemistry, and, for reasons of convenience, symmetrical templates have often been used. Symmetrical carbon substitution often limits diversity, whereas symmetry in the construction handles (halogens) presents obstacles of regio- and stereocontrol. The most successful templates utilize electronic differences and/or directing groups to generate stereodefined products.

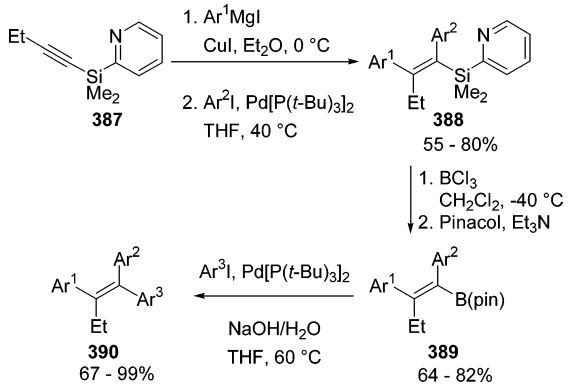
4. Carbonyl Olefination

A wide variety of structures can be made using carbonyl olefination processes, but serious limitations to this type of

Table 34. Generation of Tetrasubstituted Olefin 386 from 385

entry	Ar^1	Ar^2	Ar^3	Ar^4	yield (%)
1	Ph	Ph	4-$MeOC_6H_4$	Ph	72
2	Ph	Ph	4-$MeOC_6H_4$	2-naphthyl	46
3	Ph	4-$MeOC_6H_4$	4-MeC_6H_4	4-MeC_6H_4	40
4	4-MeC_6H_4	4-$MeOC_6H_4$	Ph	4-FC_6H_4	52
5	4-$MeOC_6H_4$	4-MeC_6H_4	Ph	4-FC_6H_4	42
6	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	Ph	22
7	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	2-naphthyl	14
8	4-$MeOC_6H_4$	4-MeC_6H_4	1-naphthyl	2-thienyl	21
9	1-naphthyl	1-naphthyl	4-MeC_6H_4	Ph	31

Scheme 80. Regio- and Stereoselectivity Achieved in the Pyridylsilane-Directed Carbometallation of Alkynes



reaction are evident during the formation of tetrasubstituted alkenes. Most of these methodologies are strongly affected by steric hindrance, and therefore the yields of tetrasubstituted olefins are generally low. Mixtures of stereoisomers are almost always obtained, due to the difficulty in generating stereochemical bias in the reactive intermediates. Nevertheless, most of the standard carbonyl olefination reactions have been employed in the synthesis of tetrasubstituted olefins. The successes and limitations of the classic Wittig, Horner−Wadsworth−Emmons, Julia, McMurry, metal carbene, and Peterson reactions in the formation of all-carbon tetrasubstituted alkenes are described below.[17]

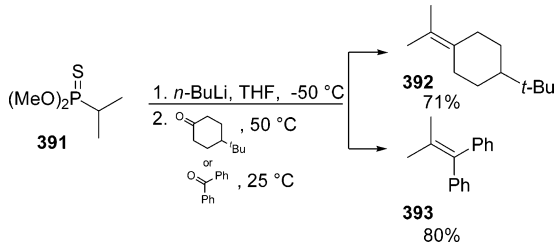
4.1. Wittig and Horner−Wadsworth−Emmons

Phosphorus-based olefination reactions are generally not amenable to the formation of tetrasubstituted olefins, as the ylides do not react well in sterically demanding environments. When tetrasubstituted olefins are formed, mixtures of stereoisomers are obtained unless the starting materials are symmetrically substituted.

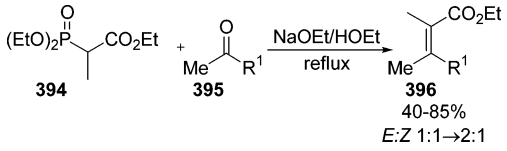
The standard Wittig reaction was employed by Scherer and Lunt, who synthesized a symmetrically substituted alkylidene cyclobutane.[151] The analogous reaction was employed by Utimoto, Tamura, and Sisido in the preparation of one symmetrically substituted alkylidene cyclopropane.[152] Corey and Kwiatkowski showed in 1966 that the Horner−Wadsworth−Emmons reaction could be used to form geminally symmetric tetrasubstituted olefins (**392** and **393**) if an α-lithiophosphonothioate was employed (Scheme 81).[153] They described the condensation of thiophosphonate **391** with two symmetric ketones to give olefins **392** and **393**. Reports in recent years still illustrate the difficulty of preparing tetrasubstituted olefins by the Wittig reaction.[154]

An early report by Gallagher and Webb illustrated the problem of forming tetrasubstituted olefins with differential substitution (Scheme 82).[155] They synthesized a variety of

Scheme 81. Thiophosphonate Approach



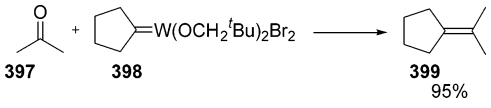
Scheme 82. Phosphonate Approach to Tetrasubstituted Olefins



tetrasubstituted olefins **396** by the reaction of triethyl phosphonoacetates **394** with ketones **395**. While asymmetrically substituted ketones reacted, the best *E*/*Z* selectivity obtained was 2:1. This selectivity problem has since been investigated, but has not been resolved for this method.[156]

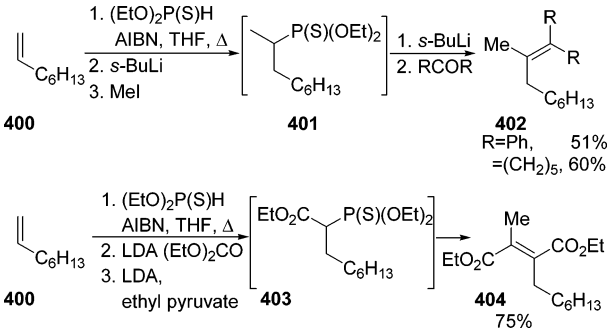
Tungsten-based reagents have been employed to synthesize tri- and tetrasubstituted olefins.[157] While the focus of this study was on the expansion of the Wittig reaction to less reactive functional groups such as esters, lactones, or amides, one example of a symmetrical, all-carbon substituted, tetrasubstituted olefin was given (Scheme 83).

Scheme 83. Application of Tungsten-Based Olefination Reagents



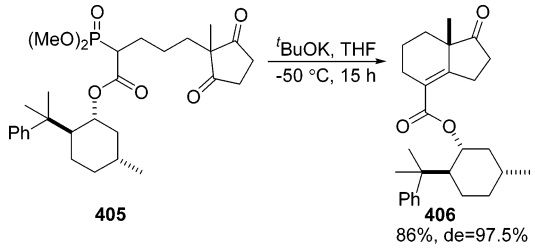
Very recently, carbonyl olefination was employed in an approach that combined a radical addition of phosphorus hydrides with the Horner−Wadsworth−Emmons reaction (Scheme 84).[158] Exposure of terminal alkene **400** to diethylthiophosphite, in the presence of AIBN, produced the corresponding phosphonothioate. This was immediately deprotonated, and the resulting anion was quenched with MeI. A second deprotonation with *s*-BuLi, followed by condensation with a ketone, produced the tetrasubstituted olefin **402**. While this method efficiently accomplished three operations in a single pot, the desired materials were inseparable from side products when symmetric ketones were employed (in two of the three examples given). A third example produced tetrasubstituted olefin **404**, bearing additional functionality, as a single isomer.

Scheme 84. Tandem HWE/Radical Approach



Stereoselectivity has been achieved using intramolecular approaches that restrict the freedom of the coupling partners, thus enabling the stereocontrolled formation of alkenes (Scheme 85). This strategy was used by Mandai and co-

Scheme 85. Intramolecular Diastereoselective Horner−Wadsworth−Emmons Reaction

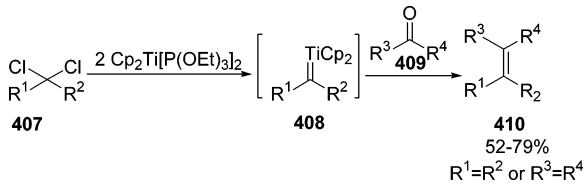


workers in their diastereoselective synthesis of the CD ring component of vitamin D_3.[159] Exposure of phophonate **405**, bearing a chiral auxiliary, to *t*-BuOK gave tetrasubstituted α,β-unsaturated ester **406** in 86% yield and 97.5% diastereomeric excess.

4.2. Olefination with Metal Carbenes

The reaction of metal carbenes with carbonyls is significantly affected by sterics, and this process generally fails to form tetrasubstituted olefins. This problem can be partially circumvented by the use of *gem*-dihalides as illustrated by the Takeda group (Scheme 86).[160] The reaction of *gem*-

Scheme 86. *gem*-Dichloroalkanes as Precursors



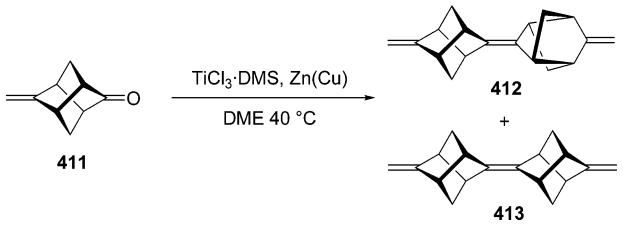
dichloro alkanes **407** with titanium complexes in the presence of various ketones gave the corresponding tetrasubstituted olefins **410** in 58−73% yields.

Either the *gem*-dichloro alkane **407** or the ketone **409** was symmetrical in all of the reported cases ($R^1 = R^2$ or $R^3 = R^4$), resulting in only one possible isomer being formed.

The McMurry reaction provides one of the most successful methods for the formation of tetrasubstituted olefins and has been extensively reviewed.[17,161] Titanium trichloride or titanium tetrachloride are typically used in conjunction with a reducing agent such as $LiAlH_4$ or Zn, in a refluxing solvent to effect the condensation of two ketones. The reaction is driven by the formation of a strong Ti−O bond, which overcomes the typical steric resistance to tetrasubstituted olefin formation, and has therefore frequently been used to prepare highly strained and sterically hindered molecules.[13,14,19,22,162] Similar to other carbonyl olefination reactions, mixtures of *E*/*Z* isomers are generally obtained.

A series of distellenes was prepared using the McMurry process to ligate the hindered-olefin termini together (Scheme 87). Ketone **411**, when treated with $TiCl_3$·DMS in the

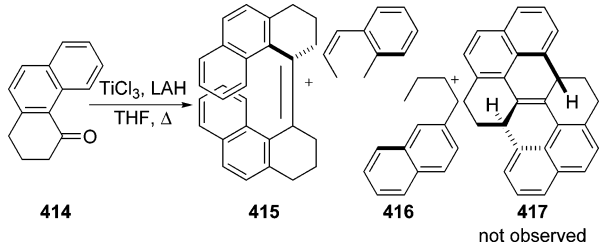
Scheme 87. Distellenes Prepared Using McMurry Coupling



presence of Zn/Cu couple, afforded a mixture of derivative **412** and **413** in 12% yield.[163]

The McMurry coupling has been used to generate optically active olefins, in which bulky substituents cause permanent, out-of-plane distortions in the double bond (Scheme 88).[164]

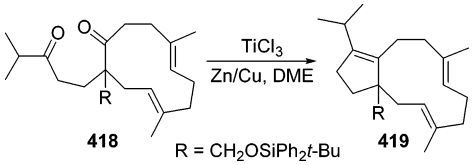
Scheme 88. Optically Active Alkenes



The difficult isolation and resolution of isomers was achieved by Feringa and Wynberg using chiral HPLC techniques (trans isomers could be completely resolved, cis isomers only partially).

The intermolecular coupling of two distinct carbonyl moieties generally provides a statistical mixture of products, although yields can be improved through the use of a large excess of one reagent, or by modifying the electronic properties of one or both compounds (particularly when one of the coupling partners is a diaryl ketone). The intramolecular variant is particularly valuable as the stereochemistry of the final product is dictated by the conformational restraints inherent in the molecule. The intramolecular McMurry reaction has been used to generate a number of terpenes,[17] such as δ-araneosene that was achieved by Jenny and Borschberg (Scheme 89).[165]

Scheme 89. δ-Araneosene via McMurry Reaction

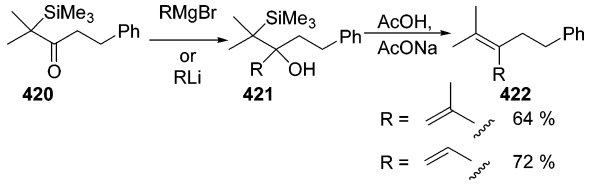


4.3. Peterson and Julia–Lythgoe Olefination

Elimination processes, such as the Peterson and Julia−Lythgoe olefinations, offer perhaps the most challenges for the generation of tetrasubstituted olefins, as they require the generation of two contiguous quaternary centers before an elimination can take place. Even if the two quaternary centers

can successfully be formed, the molecule must be able to adopt the required conformation for the elimination to succeed. The Peterson olefination, which occurs via the elimination of β-silyl alcohols, is quite limited for the formation of tetrasubstituted olefins. A rare example from the Jenkins group showed the preparation of two geminally symmetric tetrasubstituted olefins (Scheme 90).[166] Thus,

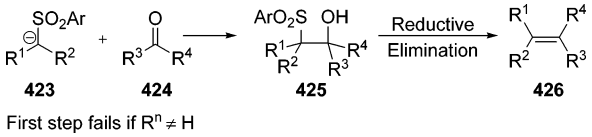
Scheme 90. Peterson Olefination



α-silyl ketone **420** was treated with two different alkylating reagents to give the β-silyl alcohols **421**. Subsequent exposure to sodium acetate in acetic acid provided the tetrasubstituted alkenes **422** in 64% and 72% overall yields, respectively.

The generation of intermediates bearing two contiguous quaternary centers is even more difficult in the Julia−Lythgoe olefination, in which β-hydroxy sulfones **423** are eliminated in the presence of a base (Scheme 91). The

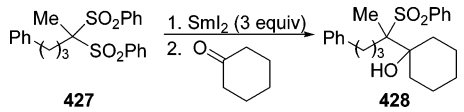
Scheme 91. Julia Sequence



synthesis of the β-hydroxysulfones that are required for tetrasubstituted olefin formation necessitates some modifications to the typical reaction conditions because it is extremely difficult to force secondary α-sulfonyl carbanions to react with ketones.

The synthesis of sterically congested β-hydroxy sulfones has been achieved by the Falck and Mioskowski groups by using a geminally substituted disulfone (Scheme 92).[167]

Scheme 92. SmI_2 Modification

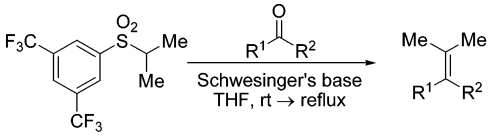


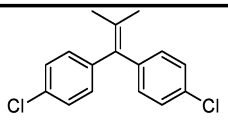
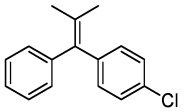
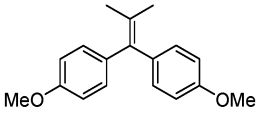
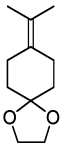
Treatment of disulfone **427** with samarium iodide followed by addition of cyclohexanone afforded β-hydroxysulfone **428** in 85% yield. The researchers did not proceed to the reductive elimination step to generate the tetrasubstituted olefins, so it is unclear whether the elimination would be possible.

Alonso and co-workers have employed electron-deficient sulfones such as **429** to facilitate the β-elimination step.[168] This method was highly successful when the sulfones were exposed to Schwesinger's base[169] and a variety of aldehydes, giving trisubstituted olefins as mixtures of isomers. Tetrasubstituted alkenes such as **430** were generated under similar reaction conditions, but heating at reflux was required to deliver the desired products (Table 35).

Sterically congested Julia−Lythgoe intermediates can be formed by using sulfoxides, as the resulting anions are far less stabilized, thus assisting the formation of the intermediate β-hydroxysulfoxides.[170] The equilibrium can be further shifted toward the products by trapping the hydroxide

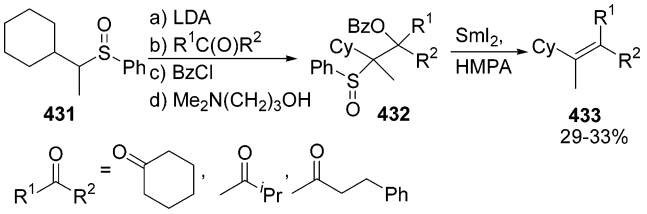
Table 35. Julia−Kocienski Olefination of Electron-Deficient Sulfones with Ketones



entry	olefin **430**	yield (%)
1		71
2		70
3		10
4		35

intermediate with an electrophile such as benzyl chloride. This approach was used to prepare three tetrasubstituted olefins (**433**) in 29−33% overall yields. Two of the products were obtained in greater than 9:1 selectivity in favor of the *E* isomer (Scheme 93).[171] The product distribution was

Scheme 93. Sulfoxide Modification



thought to be controlled by sterics as the larger substituents occupied positions trans to each other in the major products. This was one of the few cases in which the generation of differentially substituted tetrasubstituted olefins has been successfully accomplished using the Julia method.

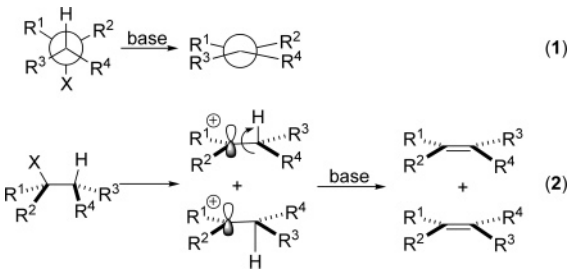
While carbonyl olefination techniques are widely used for the convergent formation of mono- and disubstituted olefins, their usefulness remains limited for the formation of tetrasubstituted double bonds. A uniquely effective method for the widespread formation of tetrasubstituted double bonds is the McMurry reaction, in which the formation of a strong titanium−oxygen bond provides an overwhelming driving force for the reaction. Essentially every method gives stereoisomers, unless intramolecular steric constraints limit the formation of the other isomers.

5. Elimination Reactions

The production of tetrasubstituted olefins via elimination reactions is often complicated by the synthesis of the precursors. The E2 reaction is the best way to ensure single

isomer products, but to achieve this, the relative stereochemistry of the two contiguous sp^3 centers in the substrate must be precisely controlled (Scheme 94).[18b,172] An additional

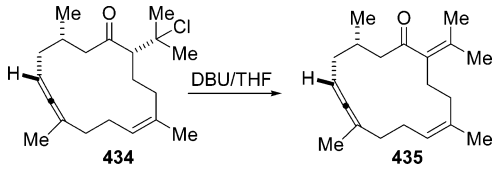
Scheme 94. E2 and E1 Elimination Reactions



complication exists because the hydrogen and leaving group in this material must adopt an antiperiplanar arrangement, a potentially problematic requirement because rotation between the tertiary and quaternary carbon centers may be difficult. This can force the substrate to follow the E1 pathway, resulting in a loss of stereochemical information. For E1 reactions, one must design the elimination such that the desired product is also the kinetic one (Scheme 94).

Exocyclic tetrasubstituted olefins have been generated by the elimination of β-chloroketones (Scheme 95).[173] Treatment

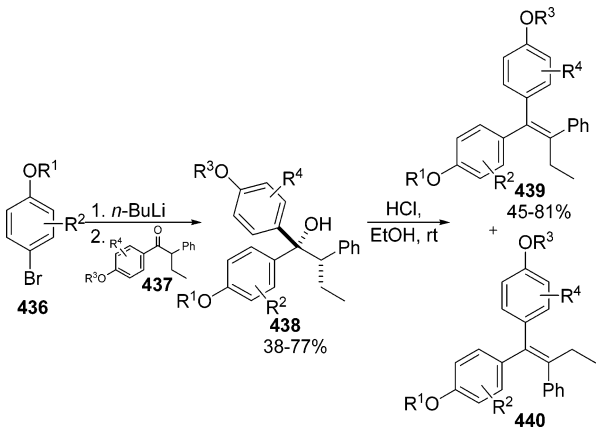
Scheme 95. Elimination of β-Chloroketone



of macrocycle **434** with DBU−THF (1:3) at reflux gave olefin **435** in 82% yield.

Approaches to Tamoxifen and analogues have employed tertiary alcohols that were subjected to acidic conditions to promote elimination (Scheme 96).[174] Selectivity for the

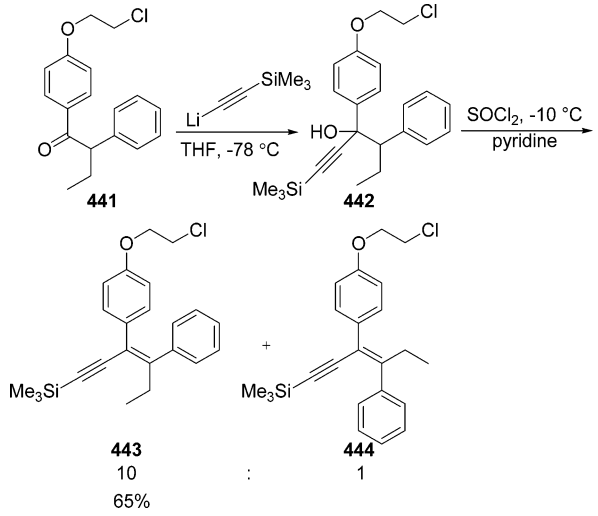
Scheme 96. Tamoxifen Analogues via Acid-Catalyzed Dehydration



diastereomer shown came from the preferred formation of the hydroxy intermediate **438**, which was separated from the undesired isomer by recrystallization. Alcohol **438** was dehydrated under strongly acidic conditions to afford **439**, together with the undesired isomer **440**, in approximately an 8:1 ratio.

Valliant et al. used a base-promoted approach to Tamoxifen analogues (Scheme 97).[175] Ketone **441** was treated with

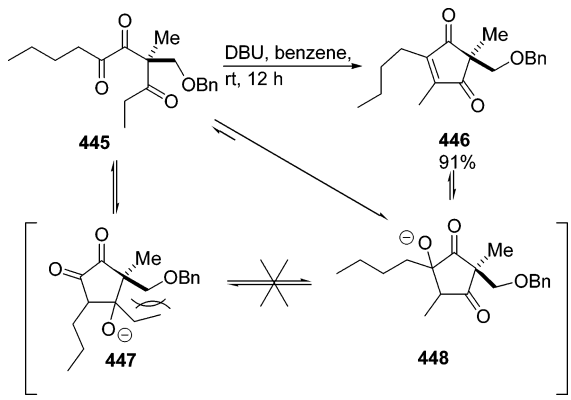
Scheme 97. Tamoxifen Analogue via Elimination



lithium (trimethylsilyl)acetylide at −78 °C to give tertiary alcohol **442** with undefined stereochemistry. The crude alcohol was dehydrated using thionyl chloride in pyridine to give a mixture of *E* and *Z* alkenes **443** and **444** in a 10:1 ratio, with the major isomer **443** being obtained in 65% yield after purification.

The application of the well-known and successful aldol reaction/dehydration sequence has been used in the synthesis of madindolines.[176] The Kobayashi group used this method to illustrate a novel stereoselective construction of a quaternary carbon. Intermediate **445** was subjected to DBU at room temperature, generating the desired tetrasubstituted alkene **446** in 91% yield (Scheme 98). While there were two

Scheme 98. Aldol/Dehydration Sequence

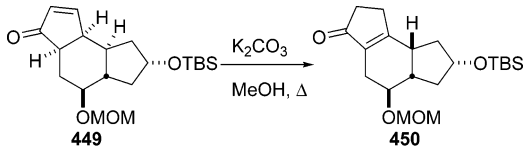


possible aldol products, **447** and **448**, destabilization of **447** would likely occur due to the presence of $A_{1,2}$ strain as shown. Thus, the more stable aldol product **448** would be formed preferentially, leading to tetrasubstituted alkene **446**. A final deprotection−oxidation sequence afforded the ultimate, enantiopure product.

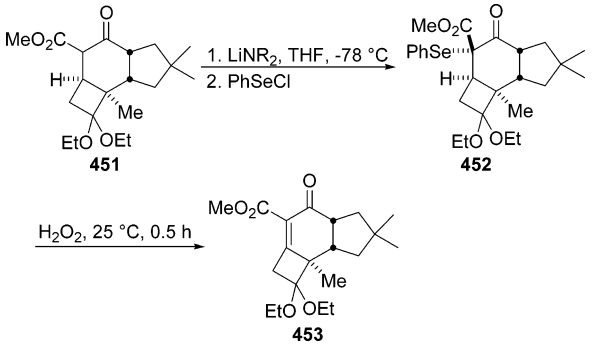
Isomerization of existing alkenes can also generate tetrasubstituted alkenes (Scheme 99).[177] Olefin **449** was isomerized in refluxing methanol in the presence of potassium carbonate to give the thermodynamic product: tetrasubstituted olefin **450**. Notably, the isomerization proceeded with total configurational inversion at the tertiary allylic site. The authors used this technology to synthesize Spinosyn A.

A few approaches to Illudol and analogues have employed selenium-based syn eliminations to achieve the tetrasubstituted olefin as the final product (Scheme 100).[178] Keto ester

Scheme 99. Base-Promoted Internalization of the Cyclopentenone Double Bond



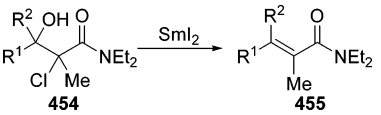
Scheme 100. Illudol via Se Syn Elimination



451 was treated with a strong base followed by the addition of phenyl selenium chloride to give intermediate selenide **452**. Oxidation with hydrogen peroxide promoted the syn elimination to give the advanced intermediate **453** bearing an internal tetrasubstituted olefin. Selenium-based syn eliminations were also used by Ott and Little in their synthesis of substrates used for the generation of the ABC-ring system common to Taxol and analogues,[179] and by Bella and coworkers in their synthesis of highly substituted butyrolactones.[180] Similar reactions, using selenoxides[181] or xanthates,[182] have been used to effect similar transformations in the context of natural product synthesis.

A samarium diiodide-promoted preparation of tetrasubstituted α,*β*-unsaturated amides **455**, from 2-chloro-3-hydroxyamides **454**, was described by Concellón et al. (Table 36).[183] Selectivity in the generation of di- and trisubstituted

Table 36. Samarium Diiodide-Promoted Synthesis of (*E*)-α,*β*-Unsaturated Amides

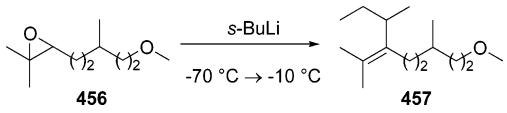


entry	R^1	R^2	% yield (% de)
1	Et	Et	70
2	$-(CH_2)_5-$		80
3	Et	Me	70 (42)
4	*n*-C_3H_7	Me	73 (40)
5	*n*-C_5H_{11}	Me	70 (44)
6	Ph	Me	71 (78)
7	Ph	Et	75 (91)
8	Bn	Me	96 (94)

amide products was excellent, and the diasteriomeric excesses ranged from 40% to 94%, in the generation of tetrasubstituted olefin products. A mechanism to explain the high stereoselectivity was proposed on the basis of chelation of the Sm^{III} center with both oxygen atoms.

The elimination of lithiated epoxides can also generate tetrasubstituted olefins.[184] Strong organometallic bases such as *n*-BuLi can deprotonate at the α-position of an epoxide such as **456** (Scheme 101).[185] The incorporation of the alkyl

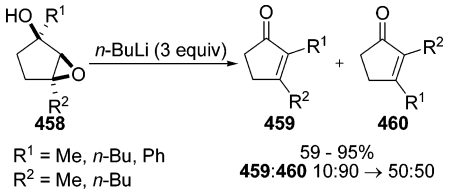
Scheme 101. Tetrasubstituted Olefins from Lithiated Epoxides



group and the elimination of lithium−oxide generated products such as **457**. Numerous examples of olefin products were reported, one of which was an acyclic tetrasubstituted olefin (**457**).

The elimination of α-hydroxy epoxides can also lead to tetrasubstituted olefin products (Scheme 102).[186] Treatment

Scheme 102. Reaction of α-Hydroxy Epoxides with a Strong Base



of α-hydroxy epoxides **458** with 3 equiv of *n*-butyllithium generated tetrasubstituted alkenones **459** and **460** in 59−95% combined yields.

In a related method, it was shown that LDA could be added to a mixture of an epoxide and a zirconacycle in THF at low temperature to produce olefin products as shown (Table 37).[187]

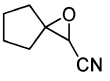
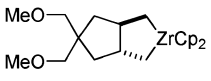
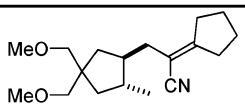
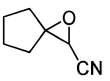
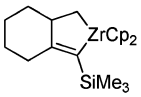
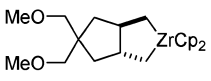
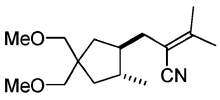
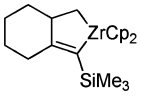
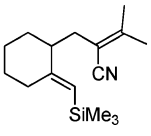
Elimination reactions are commonly employed for their simplicity. These reactions are most successful when applied to ring systems to ensure selectivity. Mixtures of isomers are generally obtained in acyclic systems, unless the geometry of the starting material has been tightly controlled and the substrate designed to avoid the E1 mechanism. Because of the difficulty in generating these starting substrates, eliminations are not commonly the reaction of choice for the selective formation of tetrasubstituted olefins.

6. Olefin Metathesis

Olefin metathesis is a powerful method for the formation of more substituted double bonds from those that are less substituted. It is commonly used in ring-closing and ring-opening reactions and has achieved broad applications in the synthesis of complex organic molecules.[188] Since the discovery of the cross metathesis reaction almost 50 years ago, extensive research has been devoted to the development of metathesis pre-catalysts, which show high activity, stability, and functional group tolerance (common metathesis pre-catalysts are shown in Figure 4). Schrock and Grubbs made the reaction practical by developing convenient and effective pre-catalysts that have been further improved by subsequent research. As many reviews have been published on the subject of olefin metathesis, herein we will focus only on applications to tetrasubstituted olefins.[189]

The first active metathesis pre-catalyst was introduced by Schrock in 1990.[190] This pre-catalyst (**461**) has very high activity and succeeds in the formation of sterically congested centers[191] such as tetrasubstituted alkenes (Table 38, entries 1−3). The electrophilic molybdenum center and the oxidation state of the metal result in high air and moisture sensitivity, and these factors, coupled with a low tolerance for polar and/or protic functional groups, can limit its applicability. The first generation Grubbs pre-catalyst **462** provided a metathesis

Table 37. Insertion of Lithiated Epoxides into Zirconacycles

entry	epoxide	zirconacycle	product	yield (%)
1				70
2				70
3				66
4				64

reagent that was very convenient to use, but proved to be incapable of generating tetrasubstituted olefins unless a relay group was employed. The second generation Grubbs pre-catalyst **463** has activity that approaches that of the Schrock pre-catalyst, while maintaining stability to air and moisture (entries 1−5).[192] Some of the limitations and successes of the second generation Grubbs pre-catalyst in the synthesis of heterocycles possessing tetrasubstituted alkenes have been previously described.[193,194]

The Hoveyda−Grubbs pre-catalyst (**464**) and derivatives have shown enhanced reactivity for disubstituted alkenes, particularly with electron-deficient substrates, but tends to be less efficient for the formation of tetrasubstituted olefins than the Schrock (**461**) or second generation Grubbs (**463**) pre-catalysts.[195] One type of tetrasubstituted olefin (entry 1) can be formed with this compound, however, in yields of 38−65%.[195a]

A number of useful applications have been demonstrated using ring-closing metathesis. Yoshida and Imamoto have developed a new approach to phenol derivatives (Scheme 103).[196] This method allowed the formation of specific phenols **467** that could not be selectively achieved using typical Friedel−Crafts conditions.

Neipp and Martin applied RCM to the formation of bridged azabicyclic structures, including one containing a tetrasubstituted olefin (Scheme 104).[197] While the desired tetrasubstituted olefin **469** was formed in good yield from diene **468**, high temperatures and multiple additions of the pre-catalyst were necessary.

The ability to recover and reuse pre-catalysts is highly valuable. Yao and Zhang have investigated a polymer-bound, fluorous pre-catalyst based on the Hoveyda−Grubbs design to investigate the beneficial effects of fluorine in metathesis

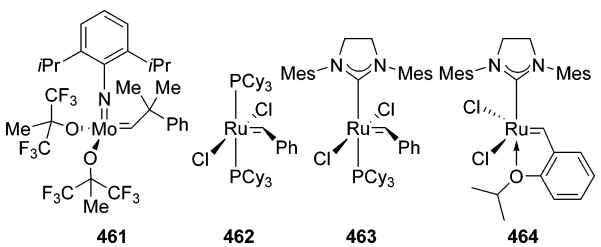
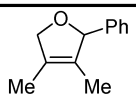
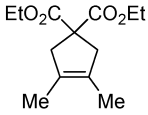
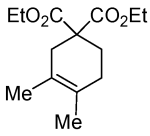
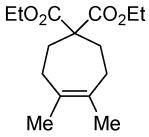
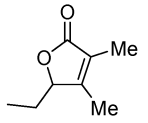
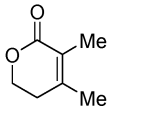


Figure 4. Common metathesis pre-catalysts.

Table 38. Pre-catalyst Comparison for the Generation of Tetrasubstituted Olefins

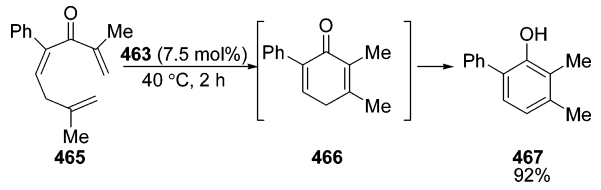
entry	product	pre-catalyst		
		Schrock **461**	Grubbs 1st **462**	Grubbs 2nd **463**
1		93%	N/A	N/A
2		93%	NR[a]	31%
3		52%	NR	90%
4		N/A	NR	71%
5		N/A	N/A	63%
6		N/A	N/A	42%

[a] NR = no reaction.

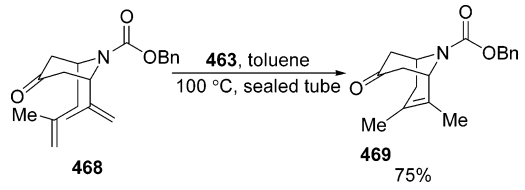
reactions.[198] The RCM activity of this polymer-bound pre-catalyst was tested with a wide variety of alkenes, and two tetrasubstituted olefins, **471** and **473**, were successfully formed (Scheme 105). Fluorous solvent was required to form the tetrasubstituted products with the fluorous polymer.

In an attempt to form acyclic, tetrasubstituted olefins, Denmark and Yang explored the RCM of alkenes using a

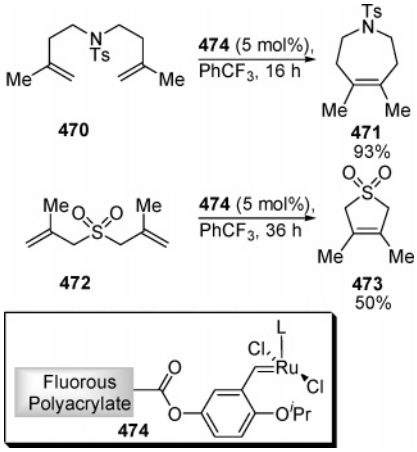
Scheme 103. Phenol Derivatives via RCM



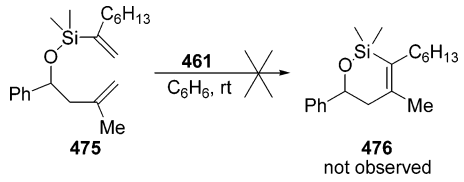
Scheme 104. Azabicyclic Structures via RCM



Scheme 105. Tetrasubstituted Olefins Using a Polymeric Fluorous Pre-catalyst



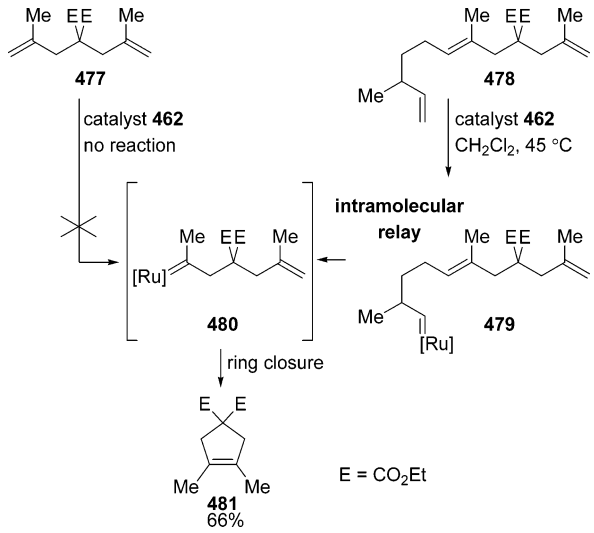
Scheme 106. Failure of Silicon Tethers in the RCM of Hindered Olefins



siloxy tether (Scheme 106). The ruthenium pre-catalysts failed for this application, and while it was possible to generate di- and trisubstituted alkenes using the Schrock pre-catalyst **461**,[199] even this reagent failed for substrate **475** in the formation of tetrasubstituted olefins.

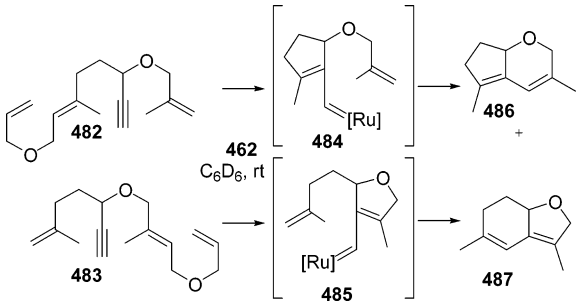
Relay ring-closing metathesis is a successful method used to form compounds that are difficult to access by typical RCM.[200] Hoye and co-workers have shown the efficiency of the relay ring-closing metathesis strategy (Scheme 107).[201] The Grubbs first generation pre-catalyst **462** failed to form tetrasubstituted alkenes directly, as it was not sufficiently active to form the required ruthenium intermediate **480** from the hindered, disubstituted precursor **477**. Incorporating a metathesis relay into substrate **478** enabled the favorable formation of the ruthenium intermediate **479**. Olefin **479** then metathesized with the nearest double bond, generating the desired intermediate **480**, which underwent ring-closing metathesis to give **481** in 66% yield. The beneficial application of the less active, but more selective, Grubbs pre-catalyst **462** was also described in this report (Scheme 107).

Scheme 107. Comparisons of Grubbs First Generation Pre-catalysts in RCM and RRCM



A tandem enyne metathesis process employed a relay tether that could be used to bias the reaction toward the desired product **486** or **487**, depending on the starting material chosen (Scheme 108). In this strategy, a discriminat-

Scheme 108. Selectivity of Grubbs First Generation Pre-catalyst in Enyne Metathesis

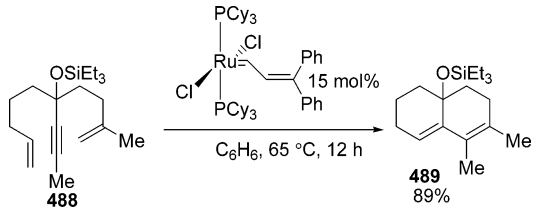


ing catalyst would be expected to undergo metathesis at the terminal double bond first. A subsequent ring closure with extrusion of dihydrofuran would then give intermediates such as **484** and **485**. These species would give rise to either of the tetrasubstituted olefin products **486** or **487**. The authors found that the less reactive Grubbs first generation pre-catalyst (**462**) gave the best discrimination for the terminal alkene. When compound **482** was exposed to pre-catalyst **462**, the initial reaction indeed occurred at the least-substituted alkene, and compound **486** was obtained almost exclusively (45:1, **486**:**487**). Similarly, when the tether directed the initial reaction to the right-hand side of the molecule (as in **483**), the reaction proceeded through species **485**, giving **487** as the major product (1:26, **486**:**487**).

A significant limitation when using metathesis technology to form tetrasubstituted olefins appears in the application of cross metathesis. The increasing activity and selectivity of metathesis pre-catalysts have allowed the preparation of olefins by cross metathesis with a high degree of functional group tolerance.[202] However, it has not yet been possible to synthesize tetrasubstituted olefins by cross metathesis.

Enyne metathesis constitutes an alternative method of forming olefins.[203] Dienynes were employed in ring-closing metathesis by Grubbs and co-workers for the generation of fused, bicyclic ring systems (Scheme 109).[204] One tetrasubstituted alkene example was shown, obtained using a

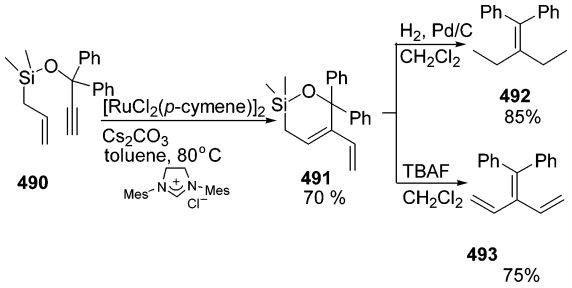
Scheme 109. Enyne Metathesis



derivative of the Grubbs first generation pre-catalyst, and, although successful, both a high pre-catalyst loading and an elevated temperature were required.

The Dixneuf group has shown the utility of silicon tethers in the generation of tetrasubstituted olefins by enyne metathesis (Scheme 110).[205] Temporary silicon tethers, useful

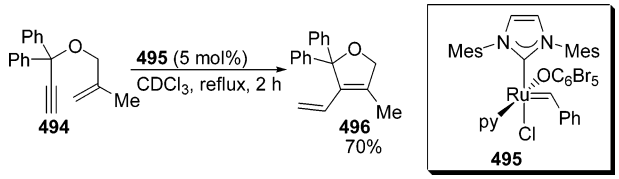
Scheme 110. Silicon Tether Enables Formation of Tetrasubstituted Olefins via Enyne Metathesis



for a variety of applications in organic chemistry, were employed to direct a favorable RCM giving alkene **491**, avoiding the difficulties associated with cross metathesis.[206] The tether was cleaved with simultaneous rearrangement of the double bonds, to afford products such as **492** and **493**.

The efficient generation of tetrasubstituted olefins has been demonstrated with ruthenium pseudohalide pre-catalysts designed by the Fogg research group (Scheme 111).[207]

Scheme 111. Tetrasubstituted Olefins via Enyne Metathesis

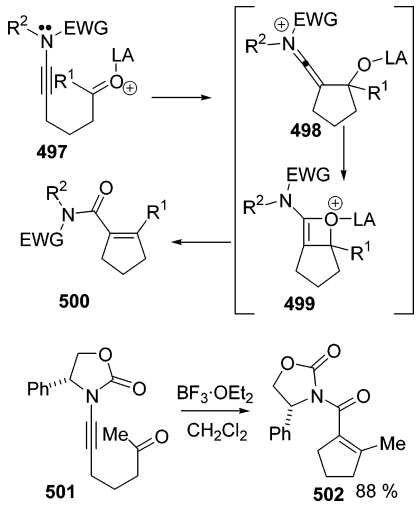


Substrate **494** was exposed to **495** (5 mol %) in refluxing chloroform for 2 h to provide metathesis product **496** in 70% yield, a result superior to those achieved using the second generation Grubbs (**463**), Hoveyda−Grubbs (**464**), or Grela pre-catalysts.[195b]

Ring-closing yne−carbonyl metathesis of ynamides has very recently been disclosed by the Hsung group (Scheme 112).[208] This Lewis-acid promoted reaction was accomplished in the absence of a traditional metathesis pre-catalyst and gave moderate to excellent yields. In this process, exposure of an ynamide to Lewis acid induces a cyclization to give a keteniminium ion **498** that rearranges via oxetene **499** to give **500**. Surprisingly, one of the best yields was achieved when forming a tetrasubstituted olefin (**502**). The lowest yields were obtained when non-amide starting materials were used or when the closure of seven-membered rings was attempted.

The success of metathesis in tetrasubstituted olefin synthesis depends largely on the pre-catalyst chosen. The

Scheme 112. Yne−Carbonyl Metathesis of Ynamides

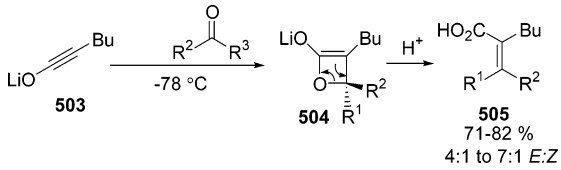


hindered substrates and products generally preclude the use of the Grubbs first generation pre-catalyst unless a relay strategy is used. The Schrock, Grubbs second generation, and Hoveyda pre-catalysts are the most commonly employed for direct ring-closing metathesis and enyne metathesis processes, and the Fogg pre-catalyst also shows potential in these reactions. Cross metathesis has not yet been realized in tetrasubstituted olefin production.

7. Ynolates

A convergent olefination reaction has recently emerged featuring the reaction of ynolates with aldehydes or ketones. An initial report by the Shindo research group described the formation of three tetrasubstituted olefins using this strategy (71−82%, R^1 = phenyl, R^2 = alkyl, Scheme 113).[209]

Scheme 113. Ynolate Precursors in Selective Formation of Tetrasubstituted Olefins



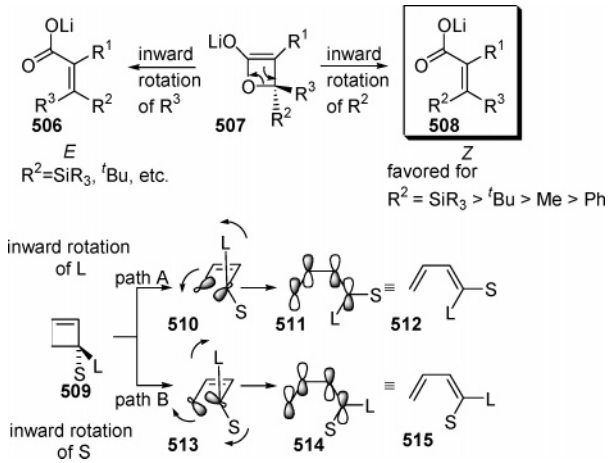
Exposure of alkynoate **503** to various ketones generated the corresponding β-lactone enolates **504** that opened to produce the corresponding α,β-unsaturated acids **505**.

This method provided access to sterically hindered tetrasubstituted olefins that could not be generated using the Wittig or Horner−Wadsworth−Emmons reactions. The products were obtained as mixtures of *E* and *Z* isomers in ratios as high as 7 to 1. An enormous increase in selectivity was achieved when acylsilanes were used, producing a wide variety of olefins in 74−98% yields.[210] These reactions proceeded at room temperature, were complete within an hour, and, impressively, >99:1 *Z*:*E* selectivity was achieved in every reported example. The drawback to this method was the need for additional transformations to generate all-carbon linked tetrasubstituted olefins, of which three examples were shown. This was addressed in a more recent study that explored the formation of all-carbon tetrasubstituted olefins directly.[211] The scope of the process was impressive, as even *t*-Bu groups were tolerated on the ynolate. In the absence of

the directing silyl group, the *Z*:*E* selectivities decreased to the range of 4:1 to 6:1.

Surprisingly, this process was not susceptible to steric factors, as was the case with most carbonyl olefination reactions. Similar to the silyl moiety, a bulky *t*-Bu group at R^2 finished cis to the carbonyl group in the major product (Scheme 114). Steric repulsion in the cyclobutane (**509**)

Scheme 114. Preferred Ring Opening of Oxetanes

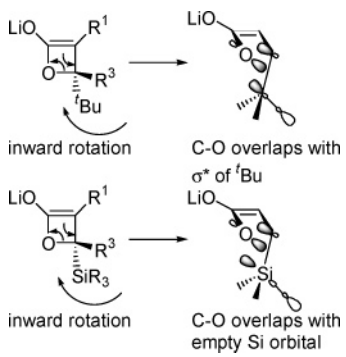


during the conrotatory ring-opening process might be expected to favor outward rotation of the large *tert*-butyl group (Scheme 114, path B). This clearly required an investigation, and the Shindo group has reported a mechanistic analysis.[211] Experimental results clearly showed that as the *β*-lactone enolate intermediate collapsed, inward rotation of the R^2 group was preferred over the inward rotation of R^3 in the order of silyl > *t*-Bu > Me > phenyl.

These observations were additionally supported by an analysis of stereoelectronic effects, in which Hammett plots indicated that the reaction was indeed dependent on the electron density of the system.[212] Electron-rich aryl groups were directed trans to the ester in the major products and electron-poor substituents were directed cis to the ester, presumably by influencing the stability of the C−O bond.

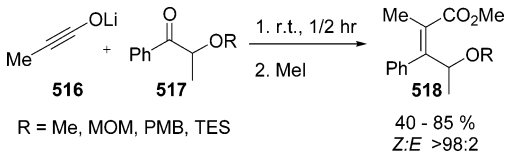
An analogy can be found in Houk's description of torquoselectivity in the ring-opening of 3,3-dialkylcyclobutenes, in which the best electron-accepting substituents rotate inward.[213] Mori and Shindo used theoretical calculations to elucidate the various secondary orbital effects present in the ring-opening reaction that supported the hypothesis that C−O overlap with an empty R^2 orbital was the dominant stereoelectronic interaction controlling selectivity (Scheme 115).[211,214]

Scheme 115. Orbital Explanation for Preferred Direction of Ring Opening



The heteroatom-guided, torquoselective olefination of α-oxy and α-amino ketones via ynolates is also able to produce tetrasubstituted olefins (Scheme 116).[215] A large

Scheme 116. Olefination of α-Oxy and α-Amino Ketones via Ynolates



variety of tetrasubstituted olefins were described, prepared with high *Z* selectivity (provided that there was a heteroatom in the α-position of the ketone). A theoretical discussion was given that explained the high ratios induced, invoking orbital and steric interactions rather than chelation.

An analogous method employing ynamines as substrates was successful in generating tetrasubstituted olefins (Scheme 117).[216] Exposure of CF_3-substituted ynamines to ketones

Scheme 117. Reaction of Ynamines and Carbonyl Compounds

in the presence of $BF_3{\cdot}OEt_2$ gave the corresponding enamides **519**. In one example, a differentially substituted ketone was employed, giving product **519** in a 71:29 *Z*:*E* ratio.

This method allowed access to products that could not be formed by traditional olefination methods such as Wittig or Horner−Wadsworth−Emmons reactions. The reaction tolerated aryl, alkyl, bulky alkyl, and acetal substituents; however, the full functional group tolerance has not yet been established. This chemistry provides a creative addition to commonly employed olefination techniques, and it will be interesting to see how this reaction will be developed in the future.

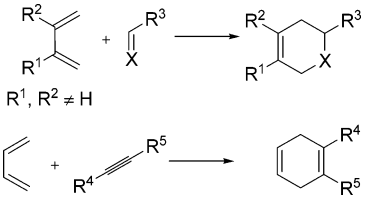
8. Cycloaddition and Sigmatropic Reactions

Cycloaddition reactions can be powerful methods of controlling stereochemistry and have occasionally been used to make tetrasubstituted olefins. Substrate scope may be limited by the requirements of the reaction, and not all isomers of a given target may be accessible. While regioselectivity is an issue for intermolecular processes, dictated by sterics and/or electronics in many cases, it is less of a concern in the intramolecular versions. When rings are formed, control of stereochemistry is typically straightforward. The advantage of cycloadditions is the ability to form single isomers through the virtue of predictable, cyclic transitions states. As these reactions have been previously reviewed, herein only key methods have been examined that have served to form tetrasubstituted olefins.

8.1. The Diels–Alder Reaction

There are two main ways by which the Diels−Alder reaction can be used to generate tetrasubstituted olefins

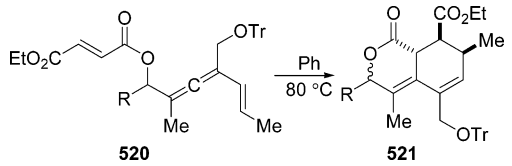
Scheme 118. Tetrasubstituted Olefins from Diels−Alder Reactions



(Scheme 118).[18] Either the diene can be substituted at the C2 and C3 positions,[22b,217] or a disubstituted alkyne can be used as the dienophile.[218]

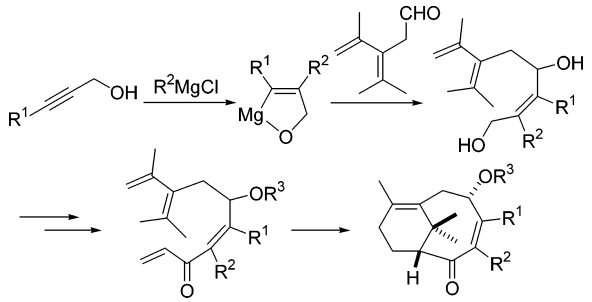
In efforts directed toward the synthesis of Quassinoids, the Spino group has highlighted the difficulty of preparing exocyclic tetrasubstituted double bonds.[219] Many approaches were attempted for the generation of this stubborn linkage, including displacements, 3,3-sigmatropic rearrangements, eliminations, and even the McMurry reaction, a process that is often successful for the preparation of hindered double bonds. Finally, the successful [4 + 2] cycloaddition of vinylallenes with tethered dienophiles such as **520** was employed (Scheme 119).

Scheme 119. Diene-Transmissive Diels−Alder Reaction Applied to Quassinoids



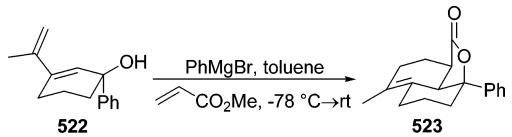
Diels−Alder cyclization strategies have been investigated by the Fallis research group. One of their strategies for the construction of the AB taxane ring system is described in Scheme 120.[220]

Scheme 120. Carbometallation-Diels−Alder Strategy for the Construction of the AB Taxane Ring System



The use of highly substituted dienes to generate complex organic molecules has been demonstrated by the Barriault research group in their investigations into the hydroxy-directed Diels−Alder reaction (Scheme 121).[22b] In this report,

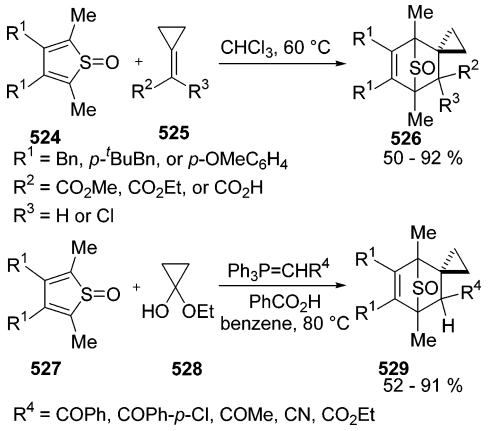
Scheme 121. Hydroxy-Directed Diels−Alder Reaction



they described the use of a temporary metal tether with tertiary allylic alcohols such as **522** to control the diastereoselectivity of the reaction. Selectivity and yields were excellent in this process.

While many thiophenes do not undergo cycloaddition reactions, thiophene *S*-oxides **524** underwent [4 + 2] cycloaddition reactions with methylenecyclopropane **525** to form single diastereomer products **526** (Scheme 122).[221]

Scheme 122. [4 + 2] Cycloaddition of Thiophene *S*-Monoxides to Activated Methylenecyclopropanes



Tetrasubstituted olefin products **529** could be obtained more efficiently by the Wittig olefination of cyclopropanes **528** and cycloaddition reaction with substrates **527** in one pot.

The *N*-heterocyclic carbene rhodium complex, [Rh(NHC)-Cl(cod)]/$AgSbF_6$, has been developed to catalyze intra- and intermolecular [4 + 2] and [5 + 2] cycloaddition reactions (Table 39).[222] The reactions proceeded very quickly, most in less than 10 min, and a variety of products were produced.

8.2. [2 + 2 + 2] Cycloaddition Reactions

Internal tetrasubstituted olefins have been generated under mild reaction conditions via the [2 + 2 + 2] cycloaddition of diynes with CO_2 (Scheme 123).[223] The reaction tolerated alkyl substituents at R^3 such as methyl, ethyl, and isopropyl, but did not allow very bulky substituents such as *tert*-butyl. The isolated yields were generally greater than 85%, except if R^1 or R^2 was a hydrogen, suggesting that the Thorpe−Ingold effect was operative in promoting the cyclization.

8.3. [4 + 3] Cycloaddition Reactions

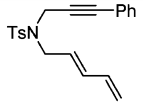
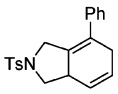
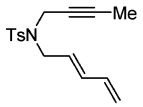
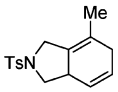
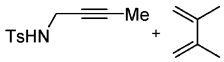
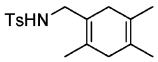
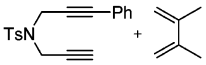
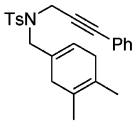
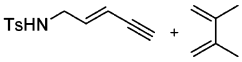
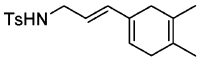
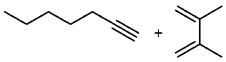
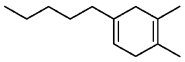
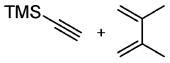
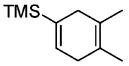
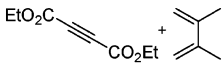
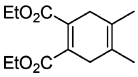
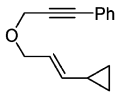
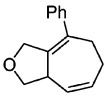
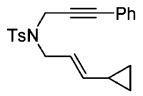
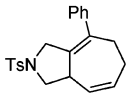
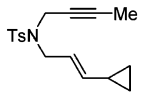
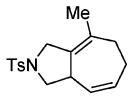
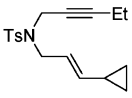
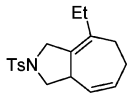
The synthesis of octahydroazulenes was reported by Trost and MacPherson.[224] In their report, enynes were exposed to $Pd(OAc)_2$, using *N*,*N*′-dibenzilideneethylenediamine as a ligand, to give cycloaddition products (Table 40). Seven-membered ring formation, and therefore tetrasubstituted olefin formation, was favored when larger substituents were present at R^1 and R^3/R^4 (entries 3, 5, 6), and the authors described the mechanistic factors that favored the formation of the seven-membered rings.

8.4. Sigmatropic Reactions

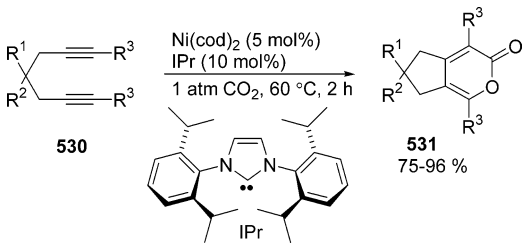
Tetrasubstituted olefins can be prepared by sigmatropic reactions, although a quaternary center must be present in the allylic position of the substrate. Tong and Kallmerten demonstrated the generation of tetrasubstituted double bonds using a [2,3] Wittig rearrangement (Scheme 124).[225] Construction of the quaternary center was achieved by chelation-controlled Grignard addition to various ketones such as **532**. Transmetallation of **533** with methyl lithium promoted the

Table 39. Rh−NHC-Catalyzed [4 + 2] and [5 + 2] Cycloaddition Reactions

Reactant(s) —[Rh(NHC)Cl(cod)]/$AgSbF_6$, CH_2Cl_2, 15 - 20 °C, < 10 min→ Product

entry	reactant(s)	product	yield (%)
1			99
2			97
3			80
4			97
5			72
6			50
7			61
8			99
9			96
10			95
11			93
12			94

Scheme 123. [2 + 2 + 2] Cycloaddition Reaction



[2,3] rearrangement through cyclic intermediates such as **534**, and the intermediate alkoxides were subsequently trapped with benzoyl chloride to afford the tetrasubstituted olefins **536**. The rearrangements of the syn substrates proceeded with similar yields and selectivities, and it was also shown that the reaction worked with a cyclic substrate.

The stereoselectivity in this method was later improved by Mulzer and List (Scheme 125).[226] This was achieved by the incorporation of an additional substituent on the starting alkene **538** that disfavored the transition states leading to minor products. The *E*:*Z* selectivities for product **541** were greater than 95:5 for the eight examples shown (except when R^2 was Ph), and yields ranged from 87% to 99%.

The control of alkene geometry has recently been achieved by using the Claisen rearrangement. McIntosh and co-workers have described the generation of exocyclic all-carbon, tetrasubstituted alkenes using the Ireland−Claisen reaction (Scheme 126, R^1 = H or Me, R^2 = Me or Br).[227] Treatment of the starting ester **542** with base triggered the Claisen rearrangement to produce tetrasubstituted olefins. Of the bases examined, LDA was found to work best, giving exclusively alkene **546** in two of the three substrates reported. In the third case presented, a 5:1 selectivity for **546** over **545** was realized. The origin of selectivity in this process was interesting. Presumably, the transition state **543** experienced a strong steric interaction involving the R^2 substituent and the metal alkoxide moiety that disfavored this transition state. A stereoelectronic component could also be operative in **544**. Orbital overlap of the C−O σ^* bond could occur with the π-system of the cyclohexene, facilitating C−O bond cleavage and accelerating the formation of **546**.

Endocyclic tetrasubstituted olefins have been obtained through the oxy-Cope reaction.[228] The addition of vinyl lithium at −78 °C resulted in attack on the concave face of the substrate **547** to give allyl alkoxide **548** (Scheme 127). The sigmatropic rearrangement of **548** was therefore set up to proceed as the reaction was warmed to room temperature. Quenching with sodium bicarbonate afforded the tetrasubstituted alkenes such as **550** in 56−65% yields. Sixteen examples were shown with a variety of substitution patterns, illustrating the generality of the system.

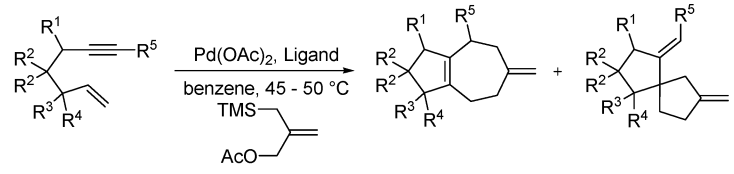
Cycloaddition strategies such as the Diels−Alder reaction proceed with good control of alkene geometry but require the formation of the appropriate substrate. Because sigmatropic rearrangements tend to proceed via defined, chairlike transition states, they are well-suited to the stereocontrolled formation of double bonds. There have been few examples to date explicitly targeting tetrasubstituted alkenes, but developments are underway.

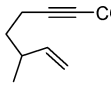
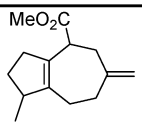
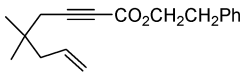
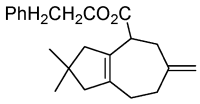
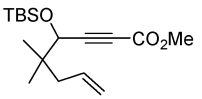
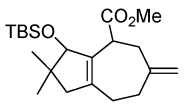
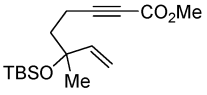
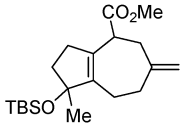
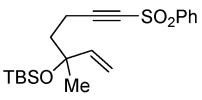
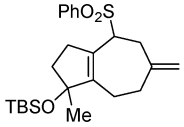
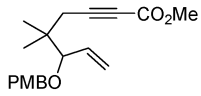
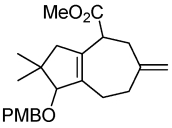
9. Radical Cyclizations

Radical reactions can give efficient access to cyclic and polycyclic molecules. The major advantages of radical reactions include mild conditions and high selectivity, although reagent toxicity and cost can be issues. Radical cyclizations can be used to form polycycles bearing tetrasubstituted olefins by incorporating an alkyne in the starting material.[229] An early example by Stork and co-workers illustrated this strategy with Bu_3SnH (Scheme 128).[230] The reactions proceeded in good yields and achieved the regioselective placement of the double bond, although mixtures of stereoisomers were obtained.

Since then, substantial research has been devoted to this methodology and, in particular, to the generation of single regio- and stereoisomers. An interesting example of cyclopropanation under free-radical conditions was observed by the Malacria group (Scheme 129).[231] While attempting the formation of a triquinane, the authors observed preferential 3-*exo*-trig cyclization instead of the anticipated 5-*exo*-trig pathway. It was postulated that the chemoselectivity was

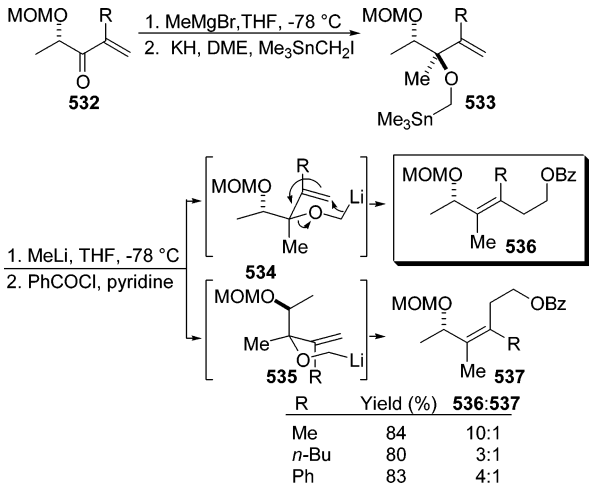
Table 40. Synthesis of Octahydroazulenes



entry	enyne	product	yield (%)	7:5-membered ring ratio
1[a]			76	2.4:1
2[a]			88	5.7:1
3[b]			87	7 only
4[a]			65	8.2:1
5[c]			73	36:1
6[a]			80	19:1

[a] *N*,*N*′-Dibenzylideneethylenediamine was employed as ligand. [b] No ligand was used. [c] Tetrakis(methoxycarbonyl)palladiumcyclopentadiene was used.

Scheme 124. Tetrasubstituted Olefins via [2,3] Wittig Rearrangement

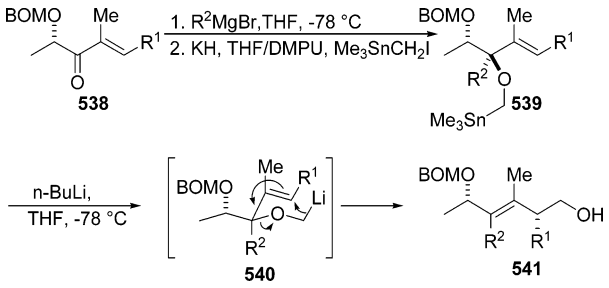


R	Yield (%)	536:537
Me	84	10:1
n-Bu	80	3:1
Ph	83	4:1

achieved due to the formation of a more thermodynamically stable double bond.

Vinyl radicals can initiate radical cyclization cascades as illustrated by Malacria et al. in 2000, in which a 5-*exo*-dig cyclization preceded other closures of silyl enol ethers

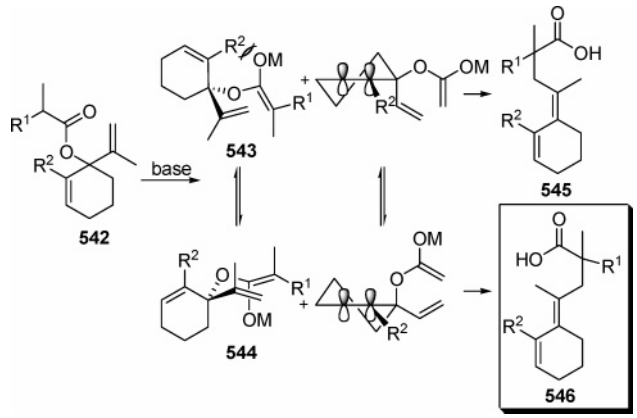
Scheme 125. Improvement in Selectivity of [2,3] Rearrangement by Incorporation of R[1]



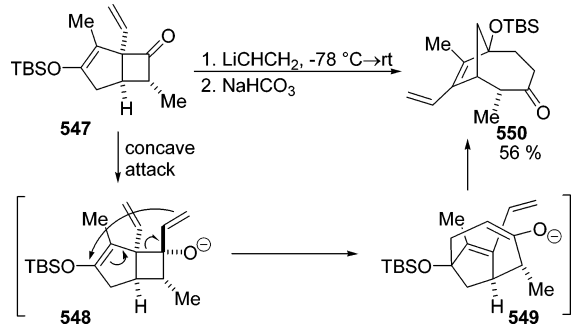
(Scheme 130).[232] In the case of aldehydes, a [1,5]-proton transfer first occurred to give a resonance-stabilized radical intermediate, which underwent 5-*exo*-trig cyclizations to give bicyclic and tricyclic structures. Vinyl radicals could also be generated from bromomethyldimethylsilyl propargy ethers to initiate radical cascade cyclizations.[233]

Radical closure to form tetrasubstituted alkene products was accomplished enantioselectively by employing sulfoxides as temporary auxiliaries (Scheme 131).[234] Vinyl sulfoxides such as **563**, when exposed to Bu_3SnH at low temperature, gave products **564** containing a tetrasubstituted alkene and new asymmetric center. These materials were

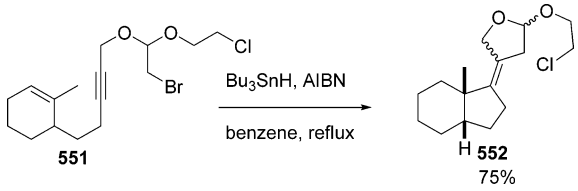
Scheme 126. Ireland−Claisen Reaction



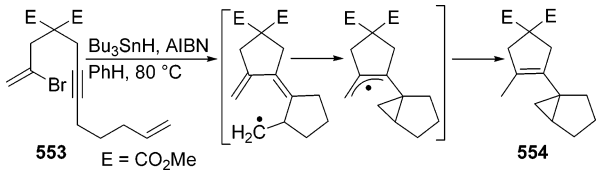
Scheme 127. Oxy-Cope Rearrangement



Scheme 128. Radical Cyclization To Generate Polycycles



Scheme 129. Tetrasubstituted Alkene Formation and Concurrent Cyclopropanation under Free Radical Conditions

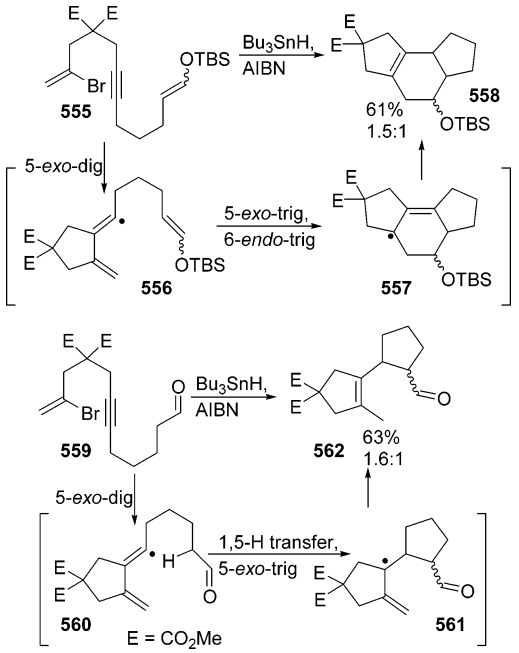


generated by an enantioselective 5-*exo*-trig cyclization followed by β-elimination. The process was efficient, giving two tetrasubstituted olefin products in 77% and 93% yield. By adding the bulky Lewis acid MAD, the authors were able to reverse the facial selectivity.

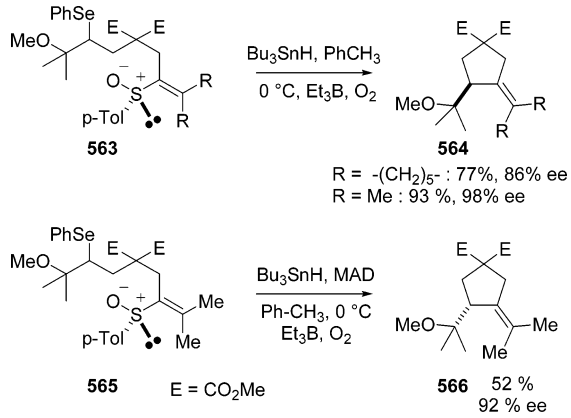
The exposure of alkynylcycloalkenones to UV light in the presence of various alkenes converted the substrates to systems bearing internal tetrasubstituted olefins (Scheme 132).[235] In many cases, however, mixtures of products were obtained.

Exocyclic, tetrasubstituted olefins have been generated diastereoselectively by Gansäuer and co-workers (Scheme 133).[236] The initial radical was generated from the reduction of Cp_2TiCl_2 with zinc. The resulting radical intermediate reacted with the exocyclic epoxide to suffer a 5-*exo*-dig cyclization that was followed by trapping of the resulting electrophile with an electron-deficient olefin. This reaction

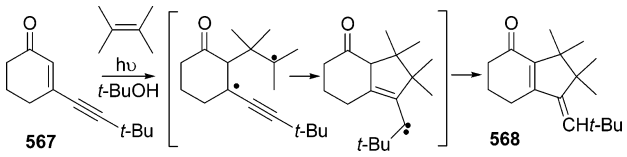
Scheme 130. Radical Cascadereactions To Form Polycycles



Scheme 131. Intramolecular Radical Vinylation Using Temporary Chiral Auxiliaries



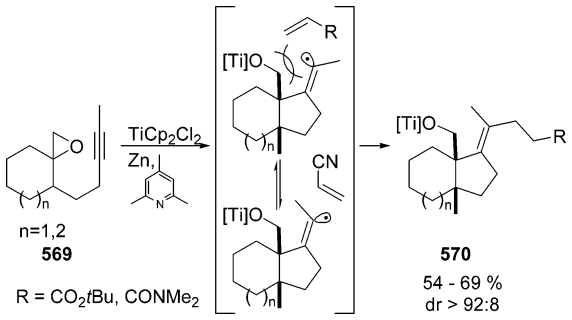
Scheme 132. Tetrasubstituted Olefins via Alkynylcycloalkenones



sequence furnished various bicyclic products bearing exocyclic tetrasubstituted olefins in yields of 54−69%, and with diastereoselectivities of greater than 92:8 as determined by NMR (assignment by NOE). An explanation of selectivity postulated that the approach of the olefin was hindered by the O[Ti] complex, forcing olefin isomerization prior to the reaction.[236,237]

Radical reactions can be used to generate many types of hindered carbon centers, including tetrasubstituted olefins. To date, however, the number of applications has been limited, and examples are generally only found as intermediate steps in total syntheses. There is significant potential here for future development, especially in reactions that involve alkynes.

Scheme 133. Exocyclic Tetrasubstituted Olefins Generated by a Radical Process



10. Conclusion

The stereoselective synthesis of tetrasubstituted olefins has become the subject of investigation in research groups around the world. Preparing these products as single isomers with four different carbon-linked groups was traditionally so difficult that the majority of the literature on this topic has been published in the past decade. Many of the methods that have been developed involve multiple steps and can involve challenging manipulations. The most successful methods employ short, indirect routes to the targets and use robust transformations.

The majority of the explored routes have used alkynyl carbometallation strategies, methods that have a great deal of potential in terms of generating product diversity. The main difficulties associated with these transformations are the regioselectivity of the initial carbometallation and the reactivity of the penultimate organometallic coupling partner. The latter issue often limits the final coupling to the use of strong electrophiles or results in a loss of stereochemical integrity. This area has seen the greatest evolution of reactivity, from the first applications of organocuprate technology to the development of complex, multicomponent reactions.

The transformation of existing olefins has also been widely used, and while this area has enjoyed the development of many of the more practical and general methods, there is still room to improve the substrate scope and to control the issue of isomerism. Olefin formation methods such as the Wittig and Horner−Wadsworth−Emmons reactions are less useful for the production of single isomer tetrasubstituted olefins because these processes are inefficient in sterically demanding environments. The McMurry coupling has been extremely successful in producing highly congested products, although stereochemistry can only be controlled in cyclic cases. Strategies such as olefin metathesis, radical processes, and ynolate chemistry are just beginning to emerge as viable techniques for the formation of tetrasubstituted olefins and offer potential in this area. This rapidly growing area of research will undoubtedly provide a wealth of new synthetic tools in the near future.

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12. References

(1) (a) Robertson, D. W.; Katzenellenbogen, J. A.; Hayes, J. R.; Katzenellenbogen, B. S. *J. Med. Chem.* **1982**, *25*, 167 and references therein. (b) Al-Hassan, M. I. *Synthesis* **1987**, 816. (c) Levenson, A. S.; Jordan, V. C. *Eur. J. Cancer* **1999**, *35*, 1628. (d) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2006**, *71*, 9552. (e) Shimizu, K.; Takimoto, M.; Mori, M.; Sato, Y. *Synlett* **2006**, 3182.

(2) (a) Caturla, F.; Amat, M.; Reinoso, R. F.; Cordoba, M.; Warrellow, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3209. (b) Wadman, M. *Nature* **2006**, *440*, 277. (c) Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.

(3) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643 and references therein.

(4) (a) Elliott, M. R.; Dhimane, A.-L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427 and references therein. (b) Arnone, A.; Brambilla, U.; Nasini, G.; Vajna de Pava, O. *Tetrahedron* **1995**, *51*, 13357.

(5) (a) Molander, G. A.; St. Jean, D. J., Jr. *J. Org. Chem.* **2002**, *67*, 3861. (b) Williams, R. B.; Norris, A.; Slebodnick, C.; Merola, J.; Miller, J. S.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2005**, *68*, 1371. (c) Di Fabio, R.; Alvaro, G.; Bertani, B.; Donati, D.; Giacobbe, S.; Marchioro, C.; Palma, C.; Lynn, S. M. *J. Org. Chem.* **2002**, *67*, 7319. (d) Cerda-García-Rojas, C. M.; Coronel, A. d. C.; de Lampasona, M. E. P.; Catalán, C. A. N.; Joseph-Nathan, P. *J. Nat. Prod.* **2005**, *68*, 659. (e) Clark, B.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H.; Bulheller, B.; Bringmann, G. *J. Nat. Prod.* **2005**, *68*, 1226. (f) Janini, T. E.; Sampson, P. *J. Org. Chem.* **1997**, *62*, 5069. (g) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337. (h) Forgione, P.; Wilson, P. D.; Yap, G. P. A.; Fallis, A. G. *Synthesis* **2000**, 921.

(6) Oishi, S.; Miyamoto, K.; Niida, A.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Kuroda, Y.; Asai, A.; Fujii, N. *Tetrahedron* **2006**, *62*, 1416.

(7) (a) Misumi, Y.; Masuda, T. *Macromolecules* **1998**, *31*, 7572 and references cited therein. (b) Hall, H. K. J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 440.

(8) (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (b) Cabeza, J. A.; Cativiela, C.; Villegas, M. D. D. D.; Oro, L. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1881. (c) Bernardinelli, G. H.; Kündig, E. P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta* **2001**, *84*, 3233. (d) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442.

(9) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289 and references cited therein.

(10) (a) Katsuki, T.; Martin, V. *Org. React.* **1996**, *48*, 1. (b) Shen, Y.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (c) Rozen, S.; Golan, E. *Eur. J. Org. Chem.* **2003**, *2003*, 1915. (d) Adam, W.; Blancafort, L. *J. Am. Chem. Soc.* **1996**, *118*, 4778. (e) Thede, K.; Diedrichs, N.; Ragot, J. P. *Org. Lett.* **2004**, *6*, 4595.

(11) (a) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 224. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (e) Varela, J. A.; Peña, D.; Goldfuss, B.; Denisenko, D.; Kulhanek, J.; Polborn, K.; Knochel, P. *Chem.-Eur. J.* **2004**, *10*, 4252. (f) Bauld, N. L.; Stufflebeme, G. W.; Lorenz, K. T. *J. Phys. Org. Chem.* **1989**, *2*, 585. (g) Meijere, A. D.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, *2000*, 3809. (h) Lhermitte, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2459. (i) De Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, *2000*, 3809. (j) Bräse, S.; Meijere, A. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545. (k) Gotoh, T.; Padias, A. B.; Hall, H. K. *J. Am. Chem. Soc.* **1986**, *108*, 4920. (l) Varela, J. A.; Peña, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001**, *3*, 2395.

(12) (a) Chiappe, C.; Detert, H.; Lenoir, D.; Pomelli, C. S.; Ruasse, M. F. *J. Am. Chem. Soc.* **2003**, *125*, 2864. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89.

(13) (a) Ayres, F. D.; Khan, S. I.; Chapman, O. L. *Tetrahedron Lett.* **1994**, *35*, 8561. (b) Gleiter, R.; Fritzsche, G.; Borzyk, O.; Oeser, T.; Rominger, F.; Irngartinger, H. *J. Org. Chem.* **1998**, *63*, 2878. (c) Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 5482. (d) Columbus, I.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 3402. (e) Khoury, R. G.; Jaquinod, L.; Smith, K. M. *Chem. Commun.* **1997**, 1057. (f) Cage-functionalized alkenes: Marchand, A. P.; Zope, A.; Zaragoza, F.; Bott, S. G.; Ammon, H. L.; Du, Z. *Tetrahedron* **1994**, *50*, 1687. (g) Lykakis, I. N.; Vougioukalakis, G. C.; Orfanopoulos, M. *J. Org. Chem.* **2006**, *71*, 8740. (h) Stratakis, M.; Nencka, R.; Rabalakos, C.; Adam, W.; Krebs, O. *J. Org. Chem.* **2002**, *67*, 8758. (i) Blanchard, P.; Brisset, H.; Riou, A.; Hierle, R.; Roncali, J. *J. Org. Chem.* **1998**, *63*, 8310. (j) Blanchard, P.; Brisset, H.; Illien, B.; Riou, A.; Roncali, J. *J. Org. Chem.* **1997**, *62*, 2401.

(14) (a) Harada, N.; Saito, A.; Koumura, N.; Uda, H.; de Lange, B.; Jager, W. F.; Wynberg, H.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7241. (b) Harada, N.; Saito, A.; Koumura, N.; Roe, D. C.; Jager, W. F.; Zijlstra, R. W. J.; de Lange, B.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7249. (c) Harada, N.; Koumura, N.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7256. (d) Treitel, N.; Eshdat, L.; Sheradsky, T.; Donovan, P. M.; Tykwinski, R. R.; Scott, L. T.; Hopf, H.; Rabinovitz, M. *J. Am. Chem. Soc.* **2006**, *128*, 4703. (e) Eelkema, R.; Pollard, M. M.; Katsonis, N.; Vicario, J.; Broer, D. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14397.

(15) (a) Browne, W. R.; Pollard, M. M.; de Lange, B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 12412. (b) Schreivogel, A.; Maurer, J.; Winter, R.; Baro, A.; Laschat, S. *Eur. J. Org. Chem.* **2006**, 3395.

(16) (a) Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron* **1993**, *49*, 8267. (b) Jager, W. F.; de Jong, J. C.; de Lange, B.; Huck, N. P. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 348. (c) Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127.

(17) For details on these processes and lead references, see: *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(18) (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(19) Daik, R.; Feast, W. J.; Batsanov, A. S.; Howard, J. A. K. *New J. Chem.* **1998**, 1047.

(20) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem.-Eur. J.* **2002**, *8*, 401.

(21) Moonen, N. N. P.; Boudon, C.; Gisselbrecht, J.-P.; Seiler, P.; Gross, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3044.

(22) (a) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608. (b) Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317.

(23) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

(24) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832.

(25) Leimner, H.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 3697.

(26) (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 387−420.

(27) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

(28) Whitesides, G. M.; San Filippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.

(29) Alexakis, A.; Commerçon, A.; Coulentianos, C.; Normant, J. F. *Tetrahedron* **1984**, *40*, 715.

(30) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 607.

(31) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735.

(32) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178.

(33) (a) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65. (b) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375. (c) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. (d) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.

(34) Hall, D. G.; Chapdelaine, D.; Préville, P.; Deslongchamps, P. *Synlett* **1994**, 660.

(35) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898. (b) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *68*, 6066.

(36) (a) Klein, J.; Levene, R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1971. (b) Nilsson, K.; Anderson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem.-Eur. J.* **1998**, *4*, 2051. (c) Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219.

(37) (a) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412. (b) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.

(38) Oishi, S.; Niida, A.; Kamano, T.; Miwa, Y.; Taga, T.; Odagaki, T.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1786.

(39) (a) Chu, K.-H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 767. (b) Wang, K. K.; Chu, K.-H.; Lin, Y.; Chen, J.-H. *Tetrahedron* **1989**, *45*, 1105.

(40) Hooz, J.; Mortimer, R. *Tetrahedron Lett.* **1976**, *17*, 805.

(41) Gerard, J.; Bietlot, E.; Hevesi, L. *Tetrahedron Lett.* **1998**, 8735.

(42) Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367.

(43) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317.

(44) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55.

(45) One TBSO-substituted propargylic alcohol gave a single isomer in 81% yield.

(46) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364.

(47) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358.

(48) Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2005**, *127*, 15706.

(49) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380.

(50) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221.

(51) Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 9030.

(52) (a) Miura, K.; Itoh, D.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 8539. (b) Miura, K.; Matsuda, T.; Hondo, T.; Ito, H.; Hosomi, A. *Synlett* **1996**, 555.

(53) Konno, T.; Takehana, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 2188.

(54) Konno, T.; Taku, K.-I.; Ishihara, T. *J. Fluorine Chem.* **2006**, *127*, 966.

(55) Jennings, M. P.; Cork, E. A.; Ramachandran, P. V. *J. Org. Chem.* **2000**, *65*, 8763.

(56) Mornet, R.; Gouin, L. *Tetrahedron Lett.* **1977**, *18*, 167.

(57) (a) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (b) Anastasia, L.; Dumond, Y. R.; Negishi, E. *Eur. J. Org. Chem.* **2001**, 3039.

(58) (a) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076. (b) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061.

(59) Germanas, J.; Vollhardt, K. P. C. *Synlett* **1990**, 505.

(60) (a) Forgione, P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11. (b) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793.

(61) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17.

(62) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

(63) (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 233. (b) Duboudin, J. G.; Jousseaume, B.; Saux, A. *J. Organomet. Chem.* **1979**, *168*, 1.

(64) Engelhardt, F. C.; Shi, Y.-J.; Cowden, C. J.; Conlon, D. A.; Pipik, B.; Zhou, G.; McNamara, J. M.; Dolling, U.-H. *J. Org. Chem.* **2006**, *71*, 480.

(65) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050.

(66) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164.

(67) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228.

(68) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803.

(69) Ishikura, M.; Takahashi, N.; Yamada, K.; Yanada, R. *Tetrahedron* **2006**, *62*, 11580.

(70) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525.

(71) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121.

(72) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299.

(73) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(74) Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* **2004**, 1573.

(75) Xue, S.; He, L.; Liu, Y.-K.; Han, K.-Z.; Guo, Q.-X. *Synthesis* **2006**, 666.

(76) Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 6332.

(77) Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* **2004**, 1573.

(78) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *Org. Lett.* **2005**, *7*, 195.

(79) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.

(80) (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248.

(81) (a) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467 and references therein. (c) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

(82) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406.

(83) Lazanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106.

(84) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743.

(85) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons Ltd.: Chichester, England, 2004.

(86) (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. (c) Vicart, N.; Cazes, B.; Gore, J. *Tetrahedron* **1996**, *52*,

9101. (d) Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154. (e) Larock, R. C.; Tu, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859.
(87) (a) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *Tetrahedron Lett.* **1999**, *40*, 6055. (b) Wu, M.-Y.; Yang, F.-Y.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 2471. (c) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576.
(88) (a) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (b) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761.
(89) Huang, T.-H.; Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 99.
(90) Ma, S.; Jiao, N.; Ye, L. *Chem.-Eur. J.* **2003**, *9*, 6049.
(91) Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun.* **2006**, 3648.
(92) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376.
(93) Kinder, R. E.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 1967.
(94) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621.
(95) Bruyère, C.; Monteiro, N.; Bouyssi, D.; Balme, G. *J. Organomet. Chem.* **2003**, *687*, 466.
(96) Bruyère, C.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007.
(97) (a) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, 3184.
(98) De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615.
(99) DMSO is known to facilitate the reoxidation of Pd(0) to Pd(II) by O_2: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766.
(100) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.
(101) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993.
(102) Yu, H.; Richey, R. N.; Carson, M. W.; Coghlan, M. J. *Org. Lett.* **2006**, *8*, 1685.
(103) Piers, E.; Romero, M. A.; Walker, S. D. *Synlett* **1999**, 1082 and references cited therein.
(104) Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, *49*, 29.
(105) Hesse, S.; Kirsch, G. *Tetrahedron Lett.* **2003**, *44*, 97.
(106) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.
(107) Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489.
(108) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972.
(109) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III. *Tetrahedron Lett.* **1978**, *19*, 4661.
(110) House, H. O.; McDaniel, W. C. *J. Org. Chem.* **1977**, *42*, 2155.
(111) (a) Preparation of cyclic α-iodoenones: McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045. (b) Preparation of bicyclic α-iodoenones: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, Takahashi, D. R., T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
(112) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453.
(113) Negishi, E.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.
(114) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.
(115) Felpin, F.-X. *J. Org. Chem.* **2005**, *70*, 8575.
(116) (a) Bellina, F.; Falchi, E.; Rossi, R. *Tetrahedron* **2003**, *59*, 9091. (b) Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749. (c) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 3851. (d) Bellina, F.; Rossi, R. *Synthesis* **2002**, 2729. (e) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017.
(117) Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997.
(118) Ortega, M. J.; Zubía, E.; Ocaña, J. M.; Naranjo, S.; Salvá, J. *Tetrahedron* **2000**, *56*, 3963.
(119) Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290.
(120) Mabon, R.; Richecoeur, A. M. E.; Sweeney, J. B. *J. Org. Chem.* **1999**, *64*, 328.
(121) This initial stannylation used a procedure developed by the Piers research group: (a) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1602. (b) Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421. (c) Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1986**, 626.
(122) Boukouvalas, J.; Maltais, F.; Lachance, N. *Tetrahedron Lett.* **1994**, *35*, 7897.
(123) (a) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (b) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.
(124) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.
(125) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607.
(126) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; González, J. M. *Chem. Commun.* **2005**, 2008.
(127) Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2003**, 1091.
(128) Shao, L.-X.; Shi, M. *J. Org. Chem.* **2005**, *70*, 8635.
(129) (a) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415. (b) Shi, M.; Shao, L.-X. *Synlett* **2004**, 807.
(130) (a) Shi, M.; Liu, L.-P.; Tang, J. *J. Org. Chem.* **2005**, *70*, 10420. (b) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2005**, *7*, 3085.
(131) Chen, W. L.; Su, C. L.; Huang, X. *Synlett* **2006**, 1446.
(132) Poondra, R. R.; Fischer, P. M.; Turner, N. J. *J. Org. Chem.* **2004**, *69*, 6920.
(133) (a) Neidlein, R.; Winter, M. *Synthesis* **1998**, 1362. (b) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2.
(134) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(135) Bauer, A.; Miller, M. W.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, 254.
(136) (a) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (b) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 790.
(137) Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686.
(138) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095.
(139) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.
(140) Hénaff, N.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 395.
(141) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453.
(142) (a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263. (b) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1602. (c) Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265. (d) Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421.
(143) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331.
(144) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018.
(145) (a) Bégué, J.-P.; Bonnet-Delpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111. (b) Bouvet, D.; Sdassi, H.; Ourévitch, M.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 2104.
(146) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615.
(147) Ho, M. N.; Lemay, A. B.; Ogilvie, W. W. *J. Org, Chem.* **2007**, *72*, 977.
(148) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778.
(149) Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.
(150) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670.
(151) Scherer, K. V., Jr.; Lunt, R. S., III. *J. Org. Chem.* **1965**, *30*, 3215.
(152) Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169.
(153) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
(154) Ramazani, A.; Azizian, A.; Bandpey, M.; Noshiranzadeh, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, 2731.
(155) Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122.
(156) Bestmann, H. J.; Ermann, P.; Ruppel, H.; Sperling, W. *Liebigs Ann.* **1986**, 479.
(157) Aguero, A.; Kress, J.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 531.
(158) Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T. *Org. Lett.* **2005**, *7*, 1597.
(159) Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847.
(160) Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.
(161) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) Lenoir, D. *Synthesis* **1989**, 883. (c) Dang, Y.; Geise, H. J. *J. Organomet. Chem.* **1991**, *405*, 1. (d) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 563. (e) Dushin, R. G. In *Comprehensive Organic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 1071. (f) Leckta, T. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; p 85. (g) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442. (h) Ephritikhine, M. *Chem. Commun.* **1998**, 2549.
(162) Khotina, I. A.; Izumrudov, V. A.; Tchebotareva, N. V.; Rusanov, A. L. *Macromol. Chem. Phys.* **2001**, *202*, 2360.
(163) Gleiter, R.; Fritzsche, G.; Boryzk, O.; Oeser, T.; Rominger, F.; Irngartinger, H. *J. Org. Chem.* **1998**, *63*, 2878.
(164) Feringa, B.; Wynberg, H. *J. Am. Chem. Soc.* **1977**, *99*, 602 and references cited therein.
(165) Jenny, L.; Borschberg, H.-J. *Helv. Chim. Acta* **1995**, *78*, 715.
(166) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Selim, M. R. *Tetrahedron Lett.* **1987**, *28*, 693.

(167) Chandrasekhar, S.; Yu, J.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 5441.
(168) Alonso, D. A.; Fuensanta, M.; Nájera, C. *Eur. J. Org. Chem.* **2006**, 4747.
(169) Schwesinger, R. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995; Vol. 6, p 4110.
(170) Satoh, T.; Hanaki, H.; Yamada, N.; Asano, T. *Tetrahedron* **2000**, *56*, 6223.
(171) Pospíšil, J.; Pospíšil, T.; Markó, I. E. *Org. Lett.* **2005**, *7*, 2373.
(172) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 3rd ed.; Plenum Press: New York, 1990.
(173) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057.
(174) McCague, R.; Leung, O.-T.; Jarman, M.; Kuroda, R.; Neidle, S.; Webster, G. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1201.
(175) Valliant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383.
(176) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429.
(177) (a) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *Tetrahedron Lett.* **1997**, *38*, 1271. (b) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543.
(178) (a) Semmelhack, M. F.; Tomoda, S.; Hurst, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 7567. (b) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747. (c) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381.
(179) Ott, M. M.; Little, R. D. *J. Org. Chem.* **1997**, *62*, 1610.
(180) Bella, M.; Piancatelli, G.; Pigro, M. C. *Tetrahedron* **1999**, *55*, 12387.
(181) (a) Shimizu, Y.; Shen, Z.; Ito, S.; Uno, H.; Daub, J.; Ono, N. *Tetrahedron Lett.* **2002**, *43*, 8485. (b) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1998**, *53*, 860. (c) Bella, M.; Piancatelli, G.; Pigro, M. C. *Tetrahedron* **1999**, *55*, 12387. (d) Amano, S.; Takemura, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Tetrahedron* **1999**, *55*, 3855. (e) Carda, M.; Marco, J. A. *Tetrahedron Lett.* **1991**, *32*, 5191. (f) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2613. (g) Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron* **1993**, *49*, 6429. (h) Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5117. (i) Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435. (j) Jacobs, R. T.; Feutrill, G. I.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 4051. (k) Al-Abed, Y.; Al-Tel, T. H.; Voelter, W. *Tetrahedron* **1993**, *49*, 9295. (l) Kido, F.; Noda, Y.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 5467. (m) Díaz, M.; Ibarzo, J.; Jiménez, J. M.; Ortuño, R. N. *Tetrahedron: Asymmetry* **1994**, *5*, 129.
(182) Kumamoto, T.; Tabe, N.; Yamaguchi, K.; Yagishita, H.; Iwasa, H.; Ishikawa, T. *Tetrahedron* **2001**, *57*, 2717.
(183) Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem.-Eur. J.* **2001**, *7*, 3062.
(184) (a) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337.
(185) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943.
(186) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700.
(187) (a) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 5275. (b) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201.
(188) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
(189) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. 1, 2, 3. (c) Schmidt, B.; Hermanns, J. *Top. Organomet. Chem.* **2004**, *7*, 223. (d) Connon, S. J.; Blechert, S. *Top. Organomet. Chem.* **2004**, *7*, 93. (e) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
(190) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
(191) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.
(192) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (e) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.
(193) (a) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517 and references cited therein. (b) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787 and references cited therein.
(194) Metathesis reactions of sulfur-containing compounds: Spagnol, G.; Heck, M.-P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767.
(195) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.
(196) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470.
(197) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.
(198) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74 and references therein.
(199) Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695.
(200) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.
(201) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.
(202) General model for selectivity in olefin cross metathesis: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(203) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
(204) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073.
(205) Sémeril, D.; Cléran, M.; Perez, A. J.; Bruneau, C.; Dixneuf, P. H. *J. Mol. Catal. A: Chem.* **2002**, *190*, 9.
(206) Use of silicon tethers in organic synthesis: Bols, M.; Skrydsrup, T. *Chem. Rev.* **1995**, *95*, 1253.
(207) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882.
(208) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231.
(209) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857.
(210) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840.
(211) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912.
(212) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443.
(213) (a) Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759. (b) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471.
(214) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945 and references therein.
(215) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.-Eur. J.* **2006**, *12*, 524.
(216) Mantani, T.; Shiomi, K.; Konno, T.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2001**, *66*, 3442.
(217) (a) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596. (b) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464. (c) Alward, S. J.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 121.
(218) (a) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11. (b) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* **2003**, *68*, 9809. (c) Werner, S.; Curran, D. P. *Org. Lett.* **2003**, *5*, 3293. (d) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H.; Ohashi, S.; Inagaki, S. *J. Org. Chem.* **1997**, *62*, 3026. (e) Fernàndez de la Pradilla, R.; Montero, C.; Tortosa, M.; Viso, A. *Chem.-Eur. J.* **2005**, *11*, 5136.
(219) (a) Spino, C. *Synlett* **2006**, 23 and references cited therein. (b) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283. (c) Spino, C.; Hill, B.; Dubé, P.; Gingras, S. *Can. J. Chem.* **2003**, *81*, 81.
(220) (a) Laurent, A.; Villalva-Servín, N. P.; Forgione, P.; Wilson, P. D.; Smil, D. V.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 215. (b) Villalva-Servín, N. P.; Laurent, A.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 227. (c) Villalva-Servín, N.; Laurent, A.; Yap, G.; Fallis, A. *Synlett* **2003**, 1263. (d) Smil, D. V.; Laurent, A.; Spassova, N. S.; Fallis, A. G. *Tetrahedron Lett.* **2003**, *44*, 5129.
(221) Thiemann, T.; Ohira, D.; Li, Y.; Sawada, T.; Mataka, S.; Rauch, K.; Noltemeyer, M.; Meijere, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2968.
(222) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71*, 91.
(223) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188.
(224) Trost, B. M.; Macpherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483.
(225) Tong, X.; Kallmerten, J. *Synlett* **1992**, 845.
(226) Mulzer, J.; List, B. *Tetrahedron Lett.* **1994**, *35*, 9021.
(227) McFarland, C.; Hutchison, J.; McIntosh, M. C. *Org. Lett.* **2005**, *7*, 3641.
(228) Verma, S. K.; Nguyen, Q. H.; MacDougall, J. M.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, *65*, 3379.
(229) Malacria, M. *Chem. Rev.* **1996**, *96*, 289 and references cited therein.
(230) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720 and references cited therein.
(231) (a) Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 718 and references cited therein. (b) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.
(232) Fensterbank, L.; Mainetti, E.; Devin, P.; Malacria, M. *Synlett* **2000**, 1342.
(233) Fensterbank, L.; Dhimane, A.-L.; Wu, S.; Lacote, E.; Bogen, S.; Malacria, M. *Tetrahedron* **1996**, *52*, 11405.

(234) Delouvrié, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc*. **1999**, *121*, 11395.
(235) (a) Rathjen, H.-J.; Margaretha, P.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 3904 and references cited therein. (b) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Org. Chem.* **1994**, *59*, 5393.
(236) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206.
(237) An alternative mechanism has been proposed: Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

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