Transition Metal Catalyst Free Synthesis of Olefins from Organoboron Derivatives**

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Dedicated to the memory of Prof. Dr. Carsten Schmuck
Abstract: Stereoselective preparation of highly substituted olefins is still a severe challenge that requires well defined elimination precursors. Organoboron chemistry is particularly suited for the preparation of molecules with adjacent stereocenters. As organo boron substrates with leaving groups in β-position can undergo stereospecific syn- or anti-elimination, this chemistry harbors great potential for the synthesis of complex olefins. In recent years three main strategies emerged, which differ in their approach to the β-functionalized organoboron elimination precursor. (i) Stereoselective preparation of such elimination precursor can be achieved by addition of a boron-stabilized anion (d) to an aldehyde or ketone (a) or diastereoselective 1,3-rearrangement of suitable boron-ate-complexes. Stereospecific methods rely either on (ii) diastereospecific 1,2-metalate rearrangement of boron-ate-complexes that involve opening of appropriate heterocycles or (iii) addition of chiral carbenoids (d*) to chiral boronates (a*) with a leaving group in α-position.

1. Introduction

The stereoselective synthesis of highly substituted olefins is still a challenging task in organic chemistry. To illustrate the underlying problems some classical strategies for olefin syntheses and their associated problems are depicted in Scheme 1. Disubstituted alkenes can be prepared with good E/Z-selectivity by classical methods such as the Wittig [2] or Julia-olefination [3] (Scheme 1A). However, in higher substituted olefins steric hindrance in the transition state, as well as the final product, hampers alkene formation. This low reactivity can be overcome with more reactive methods (e.g. HWE [4] or McMurry [5]). However, all carbonyl based connective olefinations encounter a fundamental problem of stereoselectivity when the synthesis of higher substitution patterns is attempted. At the end of the day, the selectivity of these reactions depends on the steric and/or electronic differences of the aldehyde's and/or the ylide's/sulfone's substituents. Thus, higher substitution patterns with similar substituents cannot be prepared stereoselectively with these methods. A common alternative is the utilization of organometallic chemistry for olefin synthesis. Carbometalation of alkynes, followed by alkylation or cross coupling of the addition products can lead to highly substituted alkenes (1, Scheme 1B). While the carbometalation step is indeed stereospecific, its regioselectivity depends on the nature of the substituents R1 and R2. As carbometalation of alkenes suffers from the same issue, similar limitations are met in Heck couplings as well. In both cases good results in the synthesis of highly substituted alkenes were achieved, with anion stabilizing groups at R2 steering carbometalation. However, the stereodefined synthesis of highly substituted alkenes with sterically and electronically similar substituents like 1a is not possible by either of these methods. Stereoselective elimination of well-defined precursors as shown in Scheme 1C is a potential solution for the problem. However, simple elimination of H–X suffers from classic problems of regioselectivity.
tivity (Hofmann vs. Sayezeff).\textsuperscript{[1]} The Peterson olefination\textsuperscript{[11]} avoids this issue by strictly defining the elimination partners (i.e. the hydroxyl- and the silyl group), as well as the elimination mechanism (syn vs. anti). Unfortunately, this requires either the stereoselective synthesis of the corresponding precursors of type 2, or at least their separation. Fortunately, $\beta$-elimination of boranes and boronic esters (R$_2$B-X) can be achieved in a manner similar to the elimination of R$_5$Si-X (Scheme 1D).\textsuperscript{[12]}

As boronic esters have been used extensively (e.g. in conjunction with carbenoids) for the stereoselective synthesis of adjacent stereocenters (3), a great potential for the synthesis of stereochemically well defined olefins arises.\textsuperscript{[13]} Suitable elimination precursors of type 3 can be synthesized in a stereoselective manner, before they are subjected to either stereospecific syn-, or anti-elimination.

For the purpose of this review, we will categorize these methods based on the synthesis of the pivotal elimination precursor 3. Therefore, three approaches are distinguished: (i) stereoselective methods, such as the addition of boron-stabilized anions to suitable $\alpha^1$-building blocks\textsuperscript{[14]} (i.e. aldehydes), (ii) stereospecific 1,2-metate rearrangement of boronate-complexes under opening of three membered heterocycles and (iii) a stereospecific umpolungs-strategy, that employs chiral carbanions and boronates with a leaving group in $\alpha$-position (i.e. a chiral $\alpha^1$-synthon).

In the following sections we discuss key examples for these approaches, as well as selected results from other publications on organoboron chemistry, that might help to overcome some of the current limitations.

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2. Diastereoselective Olefinations

2.1. Diastereoselectivity Based on Addition to $\alpha^1$-Reagents

This first section starts with a discussion of the addition of boron-stabilized anions (i.e. $\alpha^1$-reagents) to aldehydes and ketones (i.e. $\alpha^1$-building blocks). When followed by elimination, this reaction is referred to as the boron-Wittig reaction (Scheme 2).\textsuperscript{[15]} The diastereoselectivity of the initial addition is often critical for the overall $E/Z$-selectivity. Therefore, a short discussion of models that help to predict said selectivity is in order.

In principle three different types of transition state models for the addition of prochiral carbanions to prochiral carbonyl groups can be distinguished as shown in Figure 1: (i) chelation-based models, such as the classic Zimmerman-Traxler-model\textsuperscript{[16]} usually look at the cyclic transition states, from which the products arise. However, these models are usually not invoked for boron-Wittig reactions. (ii) After long disputes a (2+2)-cycloaddition mechanism has been widely accepted for Wittig reactions with destabilized ylides.\textsuperscript{[17]} In principle a similar transition state could play a role in some boron-Wittig reactions as well. However, as will be discussed in the following section, there is good evidence for the existence of open structures of type 3. While this does not exclude a (2+2)-cycloaddition mechanism, it would at least brand the resulting bora-oxetane as an unstable intermediate. (iii) A simple empirical model for the addition of prochiral anions to prochiral aldehydes has been suggested by Bassindale and Taylor.\textsuperscript{[17]} As shown in Figure 1, the model postulates that the anion will approach the carbonyl group in a way that places the smallest substituent ($R^2$) between the two carbonyl-substituents. Furthermore, the largest substituent ($R^1$) of the carbonyl is positioned on the same side as the smallest substituent of the carbonyl derivative ($R^3$). This automatically places the medium sized carbanion substituent ($R^4$) next to the largest substituent of the carbonyl...
compound (R'). It should be noted that this simple empirical model also correctly predicts the outcome of the Wittig-reaction with electron rich ylides. But although it might sometimes give the right result for the wrong reason, the Bassindale-Taylor model nevertheless is a great aid for understanding boron-Wittig reactions.

First varieties of the well-known Wittig reaction\textsuperscript{[18]} using boron\textsuperscript{[19]} or sulphur\textsuperscript{[20]} instead of phosphorus, were reported in the 1960s. In the 1980s Pelter and coworkers explored the “boron-Wittig” reaction and showed its mechanistic potential in analogy to the “silyl-Wittig” reaction (i.e. the Peterson olefination).\textsuperscript{[21]} As shown in Scheme 3A, reaction of lithiated dimesitylboranes (4) with aromatic aldehydes (5) led to alkenes of type 7. Depending on the substrates, this method is usable even at room temperature and preferably delivers E-alkenes such as 7a-E. Furthermore, reaction with non-enolisable and symmetrical ketones provided trisubstituted alkenes such as 7b in good yield. Reactions with enolisable ketones and aldehydes on the other hand proceed poorly at higher temperatures, but delivered up to 80% yield at -78°C. Initially the preference for E-alkenes of type 7-E led the researchers to the conclusion that the product must arise from oxaborotane 6-anti, by syn-elimination, just as in a classic Wittig-reaction. However, in later studies\textsuperscript{[21b]} they showed that alkaline oxidation of the addition product 6 primarily produced diol 8-syn. As the oxidation reaction proceeds under retention of configuration,\textsuperscript{[21]} 8-syn must have been formed from 6-syn. This means that alkene 7-E must have been formed by anti-elimination. The preferred formation of oxaborotanes 6-syn, thus mirrors the Wittig reaction (with electron rich substrates), in which syn-oxaphosphetanes are formed more swiftly. Due to the shorter length of the C-8-bond, bora-oxetanes of type 6, might well be better represented by the open structure 9, which can rotate freely and thus undergo different types of elimination. This was exploited by Pelter as shown in Scheme 3B.\textsuperscript{[21c]} On the one hand the preferred addition product 9-syn was trapped with trifluoroacetic anhydride (TFAA). Syn-elimination via a six membered transition state generated Z-alkenes (7c/d-Z). On the other hand, intermediates of type 9-zen could also be trapped with TMS-Cl at -78°C. Subsequent anti-elimination was triggered by the addition of aqueous HF-MeCN, thus delivering the corresponding E-alkenes (7c/d-E). Later investigations\textsuperscript{[21]} showed, that only benzylic aldehydes can undergo syn-elimination, when TFAA is used as a trapping agent. Aliphatic aldehydes can be turned into alkenes in the presence of protic acids (HX)\textsuperscript{[21d]} However, their elimination cannot be steered along the lines of the two stereospecific pathways that easily. Very sterically hindered aldehydes predominately formed Z-olefins, although the use of strong acids (e.g. HCl) increased the amount of E-alkenes distinctively. Although Pelter’s work on the boron-Wittig reaction did not lead to widespread adoption due to its limited substrate range, it nevertheless serves as an excellent example of the key concept (Scheme 1): a stereoselective synthesis of precursors of type 3, followed by a stereospecific elimination. A major discovery of Pelter was that oxaborotanes (6) are better described as β-alkoxy boranes (9), which can freely rotate around the newly formed C-C-bond. This fact is particularly relevant when bis(boryl)methane derivatives are employed, as discussed in the following section.

2.2. Selectivity based on Diastereoselective Elimination

As shown in Scheme 4A bis(boryl)methane derivatives of type 10 can be lithiated readily with sterically hindered LiTMP and then be employed for boron-Wittig chemistry. Matteson and coworkers\textsuperscript{[22]} generated the lithiated species 11a either by deprotonation of glycolester 10a\textsuperscript{[22a]} or anionic deborylation of tris(ethylenedioxyoxy)borymethane 12.\textsuperscript{[22c]} The group successfully explored both alkylation of 10a\textsuperscript{[22a]} and its boron-Wittig reaction with aldehydes (14) and ketones (15) yielding vinyl-boronates of type 13. The group also found that a complexing agent for lithium cations such as DABCO (diazabicyclooctane) and HMMP (hexamethylyphosphoramide) or TMEDA (tetramethyl-ethylendiamine) aids reactivity.\textsuperscript{[22d]}

Unfortunately, the glycolester 10a is hydrolytically sensitive and its preparation not trivial. In 2015 Marken and coworkers adapted the reaction to the commercially available pinacol ester 10b\textsuperscript{[23]} from which the synthesis of alkyl substituted derivatives of type 10c is straightforward (Scheme 4B).\textsuperscript{[23]} By
reacting these substrates with suitable aldehydes and LiTMP in THF substituted vinyl-boronic esters (16) were readily available with impressive stereoselectivity. When the substituents on the aldehyde (R1) and the bis-boronate (R2) were small, the (B)-trans isomers (16-(B)trans) were formed predominately (16 a-b). However, when both R1 and R2 were large, the selectivity was inverted and isomers of type 16-(B)cis predominated (16 c). The latter trend could be intensified by using dimethylpentadiolato (dmpd) boronic esters. In some cases, this even allowed for an inversion of stereoselectivity, as can be seen in 16-(B)cis and 16-(B)trans, in which the exchange of the boronic ester led to an inversion of diastereoselectivity. Products that would formally require the use of formaldehyde like 16 f, were prepared from CH2I2.

The stereoselectivity observed for 16 a-e can be rationalized with the help of the Bassindale-Taylor model. It predicts that 3c is formed in the conformation depicted in Scheme 4. As both boronic esters are in principle available for elimination the stereoselectivity of the reaction must arise in the elimination step (3c → 16). Syn-elimination of one of the two diastereotopic boronic esters (BL) requires rotation of 3c around the newly formed C–C bond. That also means that either R2, or one of the boronic esters (BL) must rotate into a syn-periplanar conformation relative to R1. This explains why the relative bulk of these two substituents is a key factor for the stereoselectivity observed in the formation of 16 a-e.

In 2019 the Morken group extended this concept to the stereoselective boron-Wittig reaction of lithiated bis[pinacolatoboryl]methane (11 b) with ketones (15) that carry substituents with a distinguished steric bias (Scheme 5).23 As already recognized by Matteson,22 the presence of amine ligands can be beneficial in boron-Wittig reactions. To a certain extent, in situ preparation of 11 b with LiTMP already provides a decent amino ligand (TMP ), but Morken and coworkers tested several other tri- and tetradeionate amines, in order to optimize the E/Z ratio of this challenging reaction. The best results were obtained when 11 b was prepared in a ligand free manner and PMDTA (1.5 equiv., method A) or TMTAN (0.5 equiv., method B) were added subsequently. Products like 18 a and 18 b were mainly obtained as E-alkenes, independently of the method. For other substrates the choice of the amine additive was much more important and could even invert diastereoselectivity (18 c and 18 d). In order to explain this intriguing observation, Morken and co-workers invoked the Bassindale-Taylor model.
which initially predicts the formation of 3d-1. According to Reich and coworkers both PMDTA (17a) and TMTAN (17b) divide dimeric Li-enolates into monomeric moieties, with the latter being the more efficient ligand.\[^{[24]}\] Greater dissociation of the O–Li bond in the addition product leads to faster syn-elimination, via conformation 3d-2, which is formed directly from 3d-1 by rotating one of the boronates towards the smaller substituent \(R^3\). With a less efficient ligand, like PMDTA, dissociation of the O–Li bond takes place to a lesser extent, which slows down syn-elimination and stabilizes the addition products 3d. Therefore, complete bond rotation has enough time to occur. From this Curtin-Hammet situation Morken suggests that elimination preferably occurs from conformation 3d-3. Here, the bulky amine ligand is positioned on the side of the smaller substituent (\(R^3\)), which results in the positioning of the remaining B(pin) group on the other side, i.e. next to the larger substituent \(R^1\).

Thus, Morken established reliable routes to both mono- and disubstituted vinyl boronic esters, which are excellent precursors for the synthesis of di- and trisubstituted alkenes, as will be discussed in the next chapter. The synthesis of trisubstituted vinylboronates through boron-Wittig reaction and their conversion into tetrasubstituted alkenes was described by Cuenca, Fernández and co-workers (Scheme 6).\[^{[25]}\] Therefore, TMS-methylidiboronate 11d, was prepared by insertion of a TMS-diazomethane-derived carbene into B(pin) \(\rightarrow\) (19). The reaction agent 11d was then deprotonated with Li-TMP and added to different cyclic and non-cyclic ketones (15). This resulted in silanes of type 20. Good diastereoselectivity was obtained for ketones with a distinguished steric bias, while more remote differences led to diastereomeric mixtures (cf. 20a and 20b).

In general, the TMS group was preferably located on the side with a bulkier substituent (20a–d). Furthermore, a coordinating effect of the 2-pyridyl substituent in 20e was confirmed by \(^1\)H NMR. In the corresponding 2-thiophenyl derivative 20f no such effect was detected, so a difference in size between the phenyl- and the thiophene substituent might be best envoked to explain the moderate selectivity observed for 20f (30% de). The Bassindale-Taylor model predicts the outcome of the reaction of a ketone with sterically different substituents and 11d correctly, if one assumes a smaller effective size for the TMS group compared to the boronic esters. Given the greater length of the C–Si bond over the C–B bond\[^{[27]}\] this is a reasonable assumption.

Furthermore, Fernández and coworkers showed that silylboronates of type 20 can be functionalized directly in one-pot Suzuki-Miyaura couplings to substitute the boronate selectively. The silyl group on the other hand can also be selectively converted into the corresponding iodide using \(\text{I}/\text{AgNO}_3\). Both reactions can be conducted consecutively as showcased by the authors in their synthesis of \(Z\)-Tamoxifen: conversion of 20g into the iodide was followed by a Suzuki-Miyaura coupling, which proceeded in the presence of the pinacol ester.\[^{[28]}\] A second Suzuki-Miyaura coupling led to \(Z\)-Tamoxifen under retention of configuration. Fernández and coworkers recently also published an excellent review on boron-Wittig reactions, which contains numerous examples beyond the scope of this article.\[^{[15]}\]

### 2.3. Selectivity from Diastereoselective 1,3-Rearrangement

Another approach to trisubstituted vinylboronates, was published by Liu and coworkers\[^{[29]}\] and is shown in Scheme 7. Lithiumenolates derived from ketones of type 21, can be converted into vinyl-pinacol boronic esters by reaction with bis-pinacolatoborane and magnesiumoxide. The enolate initially forms ate-complexes of type 23 with B(pin). The carbon bound ate-complex 23b can undergo a Mg(OMe)\(_2\) promoted 1,3-metallate rearrangement. In order for this rearrangement to occur, the migrating B(pin)\(^{-}\) group needs to interact with the \(\pi^*\)-orbital of the carbonyl moiety and must thus be transferred from either above (23b-1) or below (23b-2) the \(\pi\)-O-plane. As 23b-1 positions \(R^1\) and \(R^2\) \(antiparallel\) from each other, the 1,3-migration preferably occurs from this conformation and forms 3f diastereoselectively. In order to affect syn-elimination 3f needs to rotate again, which leads to 24, from which the alkene is formed, as in a boron-Wittig reaction.

This way excellent \(Z\)-selectivity was achieved for ketones, which are not branched in the \(\alpha\)-position (22a–d). Symmetrically branched (i.e. \(R^2 = R^3\)) aldehydes (22e) and ketones (22f–g) also delivered good yields and avoided issues of diastereoselectivity. Classically enolate generation does not only suffer

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**Tetrasubstituted Olefins by bora-Wittig (Fernández 2016)**

![Scheme 6](image-url)
from issues of stereo- but also regioselectivity. Therefore, Liu’s method is compatible with many types of enolate formation, the diastereomeric bias of which is of minor concern, as the overall stereoselectivity originates from the 1,3-migration. The enolate for 22e was generated from the corresponding silylenol ether, while 22h was prepared from a diazoketone. For the synthesis of 22i, a boron-enolate was generated from benzoic acid (a) and a d1 building block of type 10c. Thus, Liu’s method does not only provide a highly stereoselective entry into vinyl boronic esters of type 22 (with R3 = H or R), but also a nice segue into the next paragraph. There, the formation of key elimination precursors of type 3 by 1,2-metalate rearrangement of boron-ate-complexes from three membered heterocycles is discussed.

3. Opening Small Heterocycles by 1,2-Rearrangement

3.1. The Zweifel-Olefination

In the previous section the conversion of a vinyl-boronic ester into a highly substituted olefin by Suzuki-Miyara coupling was shown in Scheme 6. While this famous cross-coupling is very useful, it suffers from the usual drawbacks of palladium chemistry (e.g. reduced substrate scope due to competing β-H-elimination). Another type of C–C coupling for olefins that proceeds via vinyl-boron-ate-complexes was first reported in 1967 by Zweifel and coworkers. E-Vinylboranes of type 25, which were derived from alkynes by hydroboration, can be converted into Z-alkenes (26a/b), by addition of iodide and sodium hydroxide in THF (Scheme 8, Method A). When the reaction is conducted in DCM with a halogen cyanide E-alkenes like 26c and 26d were obtained (Method B).

In both cases the reaction proceeds via a cyclic halonium ion of type 27, in which the borane has formed an ate-complex. Subsequent 1,2-metalate rearrangement leads to elimination precursors 3g/h. The key difference between the two methods lies in the type and amount of base employed. In mechanism A 3g can react with excess hydroxide to a new ate-complex, which undergoes anti-elimination to 26-Z. In mechanism B on the other hand no strong base is present and thus, the cyanide anion remains bound to the boron atom. The resulting electro-
ndeficient borane 3h then undergoes syn-elimination. The pivotal ate-complexes of type 27 do not necessarily have to be formed from vinyl-boron derivatives.

As shown in Scheme 9 the vinyl-group can also be introduced as a lithium species, which is reacted with a saturated borane and then converted into the key rearrangement precursor 27c by addition of iodine.[31]

Thus, pivotal features of the Zweifel-olefination have been demonstrated quite early, but an inherent problem of boranes as substrates lies in the transfer of only one of the borane’s alkyl groups. To some degree this limitation can be mitigated by the use of borinic esters.[32] However, modern Zweifel-reactions mostly employ the more stable boronic esters as shown in Scheme 10, in which the key strategies of the last 45 years are summarized. Vinylboronic esters (28) can be reacted with different alkyl or aryl metal species to vinyl-ate-complexes of type 30 (Route A). However, the same complexes can also be prepared by addition of a vinyl metal species (29) to an alkyl boronic ester (Route B). In both cases subsequent syn-addition of an electrophile followed by base induced anti-elimination leads to olefins of type 31 under overall inversion of configuration. Both approaches have been realized with alkyl lithium reagents in 1976 by Matteson[32] (31a) and Evans[33] (31b). In 1988 Brown and coworkers reported the synthesis of tertiary alkenes (31c) and the use of alkyl Grignards (31d).[32]

However, the use of Grignard reagents can be tricky for the introduction of vinyl groups. In 2011 Aggarwal and coworkers reported optimized conditions for Zweifel-olefinations with vinyl metal species (31e).[34] As magnesium forms a stable chelate complex with pinnacol, the reaction with vinyl magnesium bromide can lead to a trivinyl-borate species (Scheme 11A). Although this intermediate can also react to the desired olefination product, it requires three equivalents of vinyl magnesium bromide to do so. In practical terms this results in low yields when only one equivalent of the reagent is used. In the case of primary and secondary substrates this can be remedied by the addition of DMSO, while tertiary substrates require the use of an excess of vinyl Grignard (31e). Sterically extremely hindered substrates are best vinylated with the harder vinyl lithium, which can be conveniently prepared from the corresponding stannane. In 2017 the Aggarwal group also reported the use of heteroatom substituted vinyl lithium species (31f, Scheme 10) and a variation of the Zweifel-olefination using phenylselenyl chloride as an electrophile.[35]

The 1,2-metalate rearrangement produces selenylethers of type 3 (X=SePh), which can undergo base induced anti-elimination in the usual manner. Like in standard Zweifel-conditions (I2, NaOR) this leads to overall inversion (31g, Scheme 10).

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**Scheme 9.** Conversion of vinyl-metalates into alkenes by Zweifel-olefination.

**Scheme 10.** Conversion of boronic esters into alkenes by Zweifel-olefination.
However, oxidation of the selenylether 3j (Scheme 11B) to the selenoxide with mCPBA fostered syn-elimination. Thus, the overall reaction proceeded under retention (32a). This procedure provides a significant extension for Zweifel-olefinations of boronic esters, as they are more electron rich and thus do not undergo syn-elimination with halocyanides.

Thus, Aggarwal’s 2017 protocol completes the set of Zweifel-olefinations for boronic esters (top part of Scheme 10). Now both, vinyl-boronic esters and vinyl metal species, can be converted into substituted olefins under inversion or retention with high stereochemical fidelity. A more detailed discussion of the Zweifel-reaction can be found in an excellent review published by Armstrong and Aggarwal in 2017.[35]

Since then the Didier group has used Zweifel-olefinations for a variety of four membered (hetero)-cycles[36] and significantly extended the method by employing arylation as well as vinyl cerium species (Route A and B (Scheme 10), respectively).[37] These milder reagents allowed for an impressive substrate scope and tolerance of functional groups including heterocycles (31h, Scheme 10), esters, amides and nitriles. In the same year the group also reported an electrochemical variant of the Zweifel-olefination. Here the addition of an electrophile is replaced by oxidation at a glassy carbon electrode (GCE).[38] The resulting radical cation can also undergo 1,2-metalate rearrangement, after which oxidation by air delivers alkenes such as 31i. Due to the cation radical intermediate the reaction loses its stereofidelity, but preferably produces the thermodynamically more stable alkene.

3.2. Epoxide Olefination

For Zweifel-olefinations rearrangement precursors of type 27 are generated by addition of electrophiles to vinyl-ate-complexes[39] and an alternative route was realized by us in 2019 through the reaction of lithiated epoxides with boronic esters (Scheme 13).[41] Shimizu,[42] Blakemore[43] and Aggarwal[44] had described the insertion of lithiated epoxides into boronic esters, which proceeds through ate-complexes 27d and leads to alkenes 3k. To foster olefin formation, we initially attempted to mimic Pelter’s approach and react 3k with different acid chlorides. This led to unsatisfactory mixtures of E- and Z-
Iterative Epoxide Olefination (Hirschhäuser 2019)

Selected Examples

| Example | Yield (%) | Conditions |
|---------|-----------|------------|
| 36b     | 77%       | 2.0 equiv. LiTMP (THF, 0 °C, 2 h), to rt, elimination (60 °C, 2 h). |
| 36c     | 54%       | 2.0 equiv. LiTMP (THF, 0 °C, overnight). |
| 36d     | 96%       | 1.3 equiv. LiTMP (THF, 0 °C, overnight). |

Examples of Iterative Application

Scheme 13. Epoxide olefination and iterative application. (a) LiTMP (THF, 0 °C, 2 h), to rt, elimination (60 °C, 2 h). (b) LiTMP (THF, 0 °C, overnight), to rt, elimination (60 °C, 2 h). (c) mCPBA/NaHCO₃ (DCM, overnight). (d) BuLi/TMEDA (Et₂O, –78 °C, 0.25 h), R²B(pin) (38 °C, overnight). (e) t-BuLi/TMEDA (Et₂O, –78 °C, 0.25 h), R²B(pin) (38 °C, overnight).

O-Si- vs. O-B-Elimination (Aggarwal/Grayson 2019)

Selected Examples

Scheme 14. Synthesis of vinyl boronic esters/vinyl silyl compounds.
slanes of type 42 are thermodynamically more stable than the corresponding vinyl boronic esters 43, if R is sp2- or sp3-hybridized. Calculations of the relevant transition states revealed that O–Si-elimination is favored by 9.2 kcal/mol for R = Me. This concurs with chemical intuition, as the empty p-orbital of the boron-atom is better able to stabilize the developing negative charge in 44, than the highlighted α*-orbital of the TMS group in 45. However, as more electron deficient substituents (R) also provide stabilization for the newly forming carbanion, the higher lewis acidity of the boron atom favors O–B-elimination via transition state 45.

Looking back at the methods discussed so far numerous synergies immediately become apparent that could be exploited for the stereoselective synthesis of highly substituted olefins. Boron-Wittig reactions have been developed to a point, where they give convenient access to highly substituted vinylboronic esters. The selectivity of these reactions can be predicted by the Bassindale-Taylor model. Such vinyl-boronic esters could be subjected to Zweifel-olefinations, which allow for substituting the boronate with an alkyl metal species. More importantly the overall configuration of the final product can be chosen freely at this stage by promoting either syn- or anti-elimination. Finally, an epoxidation/olefination sequence could be employed for further substitution. However, at some point of every process, that employs achiral starting materials to synthesize olefins, a stereo- or regioselective step must occur, which is dependent on significantly different substrates. Thus, the seemingly simple example 1a (ethyl-propyl-butyl-pentyl-ethylene) shown in Scheme 1 would still be difficult to make this way. In the next section we will thus look at a somewhat different strategy, which relies on the synthesis of enantiomerically pure precursors of type 3 and their stereospecific elimination.

4. Boron compounds as α-synthons

Lately, an umpolungs strategy has emerged, that employs chiral carbanions that are combined with boronic esters carrying a leaving group in the α-position. As shown in Scheme 15A substitution of a chiral α-reagent, i.e. an α-chloro boronate and a chiral d-reagent, i.e. a MOM stabilized carbanion, had already been reported by Matteson in 1989.486

We currently attempt to extend this chemistry to alkyl lithium species, derived from carbanates and sterically hindered esters. Such chiral carbanions can be generated much more easily in scalenic form by Hoppe-lithiation with spartein or other chiral diamine ligands.496 However, the resulting coupling products of type 3o are quite prone to elimination (Scheme 15B). Interestingly, even racemic combinations of carbanions and α-halo boronates preferably deliver E-Alkenes such as 46 upon elimination.481 The reaction proceeds via a mixture of diastereomers of type 3o (and their enantiomers). The syn-periplanar transition state for the syn-elimination of 3o-threeo is sterically hindered less than the one for 3o-erythro. Thus, the E-alkene 46 is preferably formed. Through addition of fluoride anti-elimination of remaining 3o-erythro could be initiated and thus 46 was formed in 63% yield with 62% de. Our experiments in this particular area were rather of mechanistic than of preparative interest. Especially as Blakemore and coworkers490 had already realized a highly predictable synthesis of teriary alkenes by employing enantiomerically pure starting materials.

Their reaction of lithiated benzylic carbamates 47 with a neopentylglycol (npg) or pinacol boronic ester of type 48 is shown in Scheme 16 and proceeds in three stereospecific steps: The formation of a boron-ate-complex 49 (Step 1) is followed by a 1,2-metalate rearrangement under elimination of one of the two carbamates (3p, Step 2). In this anionotropic rearrangement both carbamates could theoretically serve as leaving groups. In this case, the non-benzylic anion (red) migrates preferably, so that 3p is formed instead of 3q. Most elimination precursors of type 3p are sufficiently stable, so that in step 3 the operator can choose whether to conduct an anti-elimination by adding NaOMe (yielding 50-E), or a syn-elimination by heating without additional base (yielding 50-Z).

Thus, there are two pivotal points in the sequence, at which the overall configuration of the alkene 50 can be choosen. Firstly, by selecting an appropriate combination of enantiomers of 47 and 48, a “like” combination of S-47 and S-48 or R-47, R-48 produces 3p or its enantiomer ent-3p, respectively. Both enantiomers can form the same alkenes of type 50 under the same conditions. An “unlike” pairing (S-47 and R-48 or R-47 and S-48) leads to one of two epimers of 3p, which have complementary reactivity. Now 50-Z would form upon anti-elimination with NaOMe and 50-E would form upon thermal syn-elimination. Both enantiomers of carbamates 48 are readily available via Hoppe-lithiation with the appropriate diamine. This is already sufficient for selecting the desired olefin configuration.496 Secondary carbamates such as S-47 can be prepared by a variety of methods.531 As examples 50a–50f
demonstrate, a wide range of styrene derivatives can be prepared in this manner. Given the sterically hindered nature of ate-complexes of type 49 the sterically less hindered neo-pentylglycol esters often deliver better results than their pinacol analogues. In the case of the sterically highly crowded 1-naphtyl derivative 49g competing O-migration to borinate 51g was observed. By adding MgBr₂, this transformation was achieved with high stereochemical fidelity and heating of 51g finally lead to the desired C-migration (3pg) and subsequent syn-elimination to 50g-E. While this side reaction does not allow for choosing the desired configuration at the elimination stage anymore, both 50g-E and 50g-Z were obtained by appropriate like or unlike combination of starting materials. In the meantime, this method has been applied by Blakemore and co-workers to the synthesis of a p-glycoprotein inhibitor and its isomere.

The overall concept of coupling carbenoids in order to make alkenes was discussed by Hoffmann and Blakemore in an interesting review article.\[53\]

5. Conclusions and Outlook

Olefinations based on the stereoselective generation of elimination precursors of type 3 have seen tremendous development in the last decade. In order to conclude this review, we have comprised the most recent methods discussed in Scheme 17, from which some interesting opportunities for combinations become apparent. As discussed in section 1, a wide variety of disubstituted vinylboronic esters have become available by the diastereoselective methods developed by Morken, Liu and Fernandez (section 1).

In section 2 we saw that such vinylboronic esters are excellent substrates for Zweifel-olefinations, which now allows for choosing, whether the boronate is substituted under retention or under inversion. Therefore, it does not matter, which diastereomere (e.g. of type 16) is preferably formed by diastereoselective olefination, as long as it is formed with a decent de. Finally, the trisubstituted olefins prepared this way could be converted into epoxides, which after lithiation can be converted into tetrasubstituted olefins. Unfortunately, lithiation of such highly substituted epoxides has a somewhat limited substrate scope.

In section 3 we encountered boronic esters as means to fuse chiral carbenoids into highly substituted olefins. Such carbenoids can be prepared from primary or secondary alcohols, which are protected as carbamates or triisopropylbenzoates.\[54\] While it might seem excessive to synthesize two chiral compounds in order to prepare an achiral olefin, this approach bears the potential to serve as an unified...
strategy for synthesizing even the most challenging olefins (such as 1a).

One potential route is depicted in the outlook-Scheme 18A. Secondary alcohols are easily prepared by Matteson-homologation of boronic esters,\(^{[3,5]}\) or by subsequent substitution and oxidation of 51\(^{[6,37]}\). Protection with a suitable directing group (DG) would deliver carbenoid precursors of type 52. If two carbenoids derived from 52 could be coupled, it might be possible to arrange at will four organometallic reagents around a stereochemically pure, tetrasubstituted olefin.

However, in order to achieve this lofty goal, some challenges still have to be overcome (Scheme 18B). Blakemore used benzylid, disubstituted carbenoids derived from carboxylates (47), which are comparably easy to generate. However, Aggarwal has shown that non-benzylid, disubstituted carbenoids are available from trisopropylbenzoates of type 52 (R'/R = Alkyl, DG = TIB).\(^{[46]}\) Another problem for the application of Blakemore’s method to tetrasubstituted alkenes lies in the high steric hindrance ate-complexes of type 53 would suffer. However, similarly crowded ate-complexes are formed as intermediates, when two adjacent quaternary stereocenters are generated by a boronate homologation. Aggarwal and co-workers were able to overcome the steric hindrance in this type of reaction by converting the boronic ester into a dimethylborane (Scheme 18C).\(^{[54]}\) Competing 1,2-migration of the methylgroups were of some concern, however, a clear preference for the tertiary (red) carbon atom was observed. In the proposed ate-complex 53 it does not matter which of the former carbenoids (red vs. blue) undergoes 1,2-migration, as long as no competing migration of R' takes place. Both carbenoid rearrangement products (54 and 55) should deliver the same alkene upon syn-elimination. So, could conversion into a borane work for Blakemore’s olefination as well?

All in all, recent advances in boron-based olefinations have focused heavily on controlling the elimination of boronic esters of type 3. At the same time strong advances are being made in the preparation of such motives by boronate homologation chemistry.\(^{[13]}\) Currently we do not yet live in a world, in which every tetrasubstituted olefin can be prepared in an isomerically pure fashion, for example by assembling four Grignard reagents around two carbenoids. However, it can at least be said that such a world is not inconceivable anymore.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Keywords:** boronic ester · boron Wittig · carbenoid · highly substituted alkene · olefination

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(A) Perspective: Dial an Alkene?

(B) Challenge: Hindered ate-Complexes

(C) Hindered ate-Complexes in Homolagation Reactions

Scheme 18. Outlook and challenges.

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