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Allenylation and propargylation reactions of ketones, aldehydes, imines, and iminium ions using organoboronates and related derivatives

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Abstract

Allenyl- and propargylboronates have emerged as versatile reagents to effect regioselective propargylation or allenylation reactions of aldehydes, ketones, imines, and iminium ions. These boron-derived reagents have the ability to undergo transmetalation reactions with other metals (Ag, Cu, In, and Zn), often using only catalytic amounts of these metals, leading to more facile and highly regioselective reactions. Enantioselective organocatalyzed reactions have also been developed using, chiral diols, aminophenols, and phosphoric acids. This short review highlights recent developments in this area.

Keywords

iminium, ions, organoboronates, imines, aldehydes, related, ketones, derivatives, reactions, propargylation, allenylation

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Allenylation and Propargylation Reactions of Ketones, Aldehydes, Imines and Iminium Ions using Organoboronates and Related Derivatives

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Abstract Allenyl and propargyl boronates have emerged as versatile reagents to effect regioselective propargylation or allenylation reactions of aldehydes, ketones, imines and iminium ions. These boron derived reagents have the ability to undergo transmetalation reactions with other metals (Ag, Cu, In and Zn), often using only catalytic amounts of these metals, leading to more facile and highly regioselective reactions. Enantioselective organocatalyzed reactions have also been developed using, chiral diols, aminophenols and phosphoric acids. This Short Review highlights recent developments in this area.

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Key words homopropargylic alcohol, α -allenyl alcohol, homopropargylic amine, α -allenyl amine, allenylboronate, propargylboronate, enantioselective

1 Introduction

Homopropargylic and α -allenyl alcohols and amines are valuable precursors for the synthesis of bioactive molecules, especially heterocyclic compounds via metal-catalyzed cyclization processes.¹ These precursor compounds are generally prepared from the reactions of carbonyl compounds (aldehydes or ketones) or imines, respectively with metallated propargyl (**C**) or allenyl (**D**) reagents (Scheme 1). These organometallic reagents can react with the aforementioned electrophiles to give either allenyl (**E**) or propargyl (**F**) products (Scheme 1). The regioselectivities of these reactions for allenyl versus propargyl products is dependent upon the nature of the metal ([M] = Mg, Li, Ti, Zn, Al, Sn, Si or B),² the substituents on both reaction partners as well as the reaction temperature and solvent.¹⁻³ In recent years allenyl (**A**) and propargyl (**B**) boronates (and sometimes the related boronic acids or potassium trifluoroboronates) have emerged as versatile reagents to effect regioselective propargylation or allenylation reactions of aldehydes, ketones or imines (and sometimes iminium ions). These boron derived reagents have the advantage of higher stability to air and protic solvents than many other organometallic reagents and the ability to undergo transmetalation reactions with other metals (Ag, Cu, In and Zn), often using only catalytic amounts of these metals, leading to more facile, tunable and highly regioselective reactions. Such boron reagents can also be used for diastereoselective and enantioselective allenylation or propargylation reactions. This Short Review highlights recent developments in this area.^{4,5}

Scheme 1 Synthesis of homopropargylic (F) and α -allenyl (E) alcohols and amines from metal-catalyzed reactions of allenyl (A) and propargyl (B) boronates

2 Synthesis of Homopropargylic and α -Allenyl Alcohols

2.1 Direct synthesis of Racemic Homopropargylic and α -Allenyl Alcohols

The reactions between allenyl (A) and propargyl (B) boronates and aldehydes or ketones, in the absence of a catalyst, are normally sluggish and often require elevated temperatures to achieve respectable chemical yields of the alcohol products. For example, an early study by Blais *et al.* in 1974 reported a 70% yield of a 93:7 mixture of the homopropargylic and α -allenyl alcohol products, respectively from the reaction of the allenylboronate **1** with *n*-butanal at 150 °C (Scheme 2 (a)).⁶ A related study reported in the same year showed that dibutyl allenylboronate also provided homopropargyl alcohol products and that the regioselectivity was dependent upon the solvent and reaction temperature.⁷ The pinacol allenylboronate **3** was found to be essentially unreactive (0.5–1% conversion) towards 4-anisaldehyde **4** at 20 °C over 18 h in THF or toluene (Scheme 2 (b)),⁸ while the propargyl boronate **5** was found to be more reactive towards **4** under similar reaction conditions and gave a 1:2 mixture of the homopropargylic and α -allenyl alcohols **6** and **7**, respectively (Scheme 2 (c)).⁹ In a rare example, allenylboronic acid **8** was demonstrated to provide the homopropargylic alcohol **9** in 40% yield from its reaction with cyclohexanecarbaldehyde in toluene, (the reaction time and temperature were not disclosed) containing four molar equivalents (equiv) of pentanol and molecular sieves (Scheme 2 (d)).¹⁰ A more recent study clearly demonstrated that potassium allenyltrifluoroborate **10** was more reactive towards 3-nitrobenzaldehyde than pinacol allenylboronate **3**, however the % conversion using the more reactive **10** was poor (30%) even after 12 h at room temperature (Scheme 2 (e)).¹¹

Scheme 2 Direct propargylation and allenylation reactions of aldehydes with allenyl and propargyl boronates and related reagents

The regiochemistry of these reactions was consistent with the previously proposed cyclic transition states **11** and **12** involving coordination between the boron and carbonyl oxygen (Scheme 3).^{6,12} These simplified models can be used to conveniently explain why, in the absence of a metal catalyst, allenylboronate reagents favour homopropargylic alcohol products, and propargylboronates favour α -allenyl alcohol products.

Scheme 3 Proposed cyclic transition states **11** and **12** for propargylations and allenylations, respectively

In 2009 Fandrick *et al.* reported a new method for the regioselective propargylation of aromatic aldehydes.¹³ While the

reaction of diethanolamine boronate **13** with 4-anisaldehyde was relatively slow (2 days at 55 °C) and poorly regioselective (propargyl:allene = 1.3:1, Scheme 4) the reaction of this aldehyde with the propargyl boron reagent **14**, prepared *in situ* by deprotonation of **13** with lithium bis(trimethylsilyl)amide (LiHMDS), was more efficient (18 h at 55 °C) and highly regioselective for the propargyl alcohol product **6** (propargyl:allene > 30:1, Scheme 4). Reduced regioselectivity (propargyl:allene = 8:1) and chemical yield (20%) was observed when NaHMDS was used. This procedure worked equally well with other aromatic aldehydes (yields 53–62%). The regiochemical outcomes of these reactions was rationalized as proceeding via a six-membered closed transition state involving lithium chelation between the aldehyde carbonyl and an oxygen of **14**. The crystalline compound **13** is readily prepared from **5** in 90% yield upon treatment with diethanolamine (MTBE, 1 h, rt).

Scheme 4 Propargylation of aromatic aldehydes with propargyl diethanolamine boronate **13** and conjugate base **14**

Two recent reports by Oliveira highlight the use of potassium allenyltrifluoroborate **10** for the efficient propargylation of aldehydes at room temperature over relatively short reaction times (1.5–7 h). In the first study it was demonstrated that these reactions are promoted by Amberlyst A-31 resin to provide homopropargylic alcohols in yields ranging from 72–95% (Scheme 5).¹⁴ Electron rich and electron deficient benzaldehydes work equally well. Cinnamaldehyde and heptanal gave their respective homopropargylic alcohol products in 90 and 80% yields, respectively. Similar results were disclosed from a later study by the same research group using tonsil® (a modified bentonite clay in the acidic form) as a catalyst (150% m/m).¹¹

Scheme 5 Amberlyst A-31 resin promoted propargylation of aldehydes with potassium allenyltrifluoroborate **10**

2.2 Metal-catalyzed Synthesis of Racemic Homopropargylic and α -Allenyl Alcohols

In 2010 Fandrick *et al.* reported the zinc-catalyzed propargylation reactions of aldehydes and ketones using the pinacol propargylboronate **5**.⁹ These reactions required 2–5 mol% of diethylzinc (Et_2Zn) catalyst and were rapid at 20 °C (reaction times 30 min to 1 h), highly regioselective (propargyl:allene = 83:17 to 99:1), high yielding and worked equally well for aromatic and aliphatic aldehydes and ketones (Scheme 6). These reactions tolerated the presence of ester, halogen and acetamido substituents on the aromatic ring of the carbonyl components. The related diethanolamine boronate **13** was also effective, however these reactions were generally less regioselective (propargyl:allene >20:1 in most cases).

Scheme 6 Zinc-catalyzed propargylation reactions with propargylboronate **5**

The following year the same group reported the zinc-catalyzed allenylation reactions of aldehydes and ketones using the pinacol allenylboronate **3**.⁸ These reactions required 5 mol% of Et_2Zn catalyst and were performed at 0 °C over 18 h. These reactions were highly regioselective (allene:propargyl = 93:7 to 99:1), high yielding and worked equally well for aromatic and aliphatic aldehydes and ketones and tolerated ester, carbamate and primary bromide and chloride, all potentially reactive, functional groups (Scheme 7 (a)). The regioselectivity (allene versus propargyl) was found to be dependent upon the amount of Et_2Zn used and the solvent. The allene:propargyl ratio decreased with increasing Zn concentration. For example, using 4-anisaldehyde as the carbonyl component in toluene at 20 °C, 2 or 7 mol% Et_2Zn gave a 93:7 mixture of the allene and propargyl alcohol products, respectively. However, using 100 mol% Et_2Zn the ratio was 14:86, in favour of the propargyl product. The coordinating solvent THF also favoured formation of the propargyl product using 7 mol% of Et_2Zn (allene:propargyl = 30:70). In contrast, the isomeric propargylboronate **15** gave exclusively the corresponding propargyl product (Scheme 7 (b)).

The above zinc-catalyzed reactions (Scheme 7 (a)) of the allenyl reagent **3** using 5 mol% Et_2Zn give exclusively allenyl products. Based on earlier studies one can conclude that these reactions proceed via the propargylzinc intermediate **16** (Scheme 8) as these and related metallated propargyl intermediates have been shown to undergo reactions via a Se_2' -type mechanism with such electrophiles (Scheme 8).⁵ Likewise, we can conclude that the reaction of **15** shown in Scheme 7 (b) proceeds via the allenylzinc intermediate **17** shown in Scheme 8. The erosion of regioselectivity in the Et_2Zn catalyzed reactions of **3** and aldehydes when >10 mol% of Et_2Zn is employed is consistent with an enhanced rate of isomerization between the isomeric organozinc intermediates **16** and **17** under these conditions, favouring the more stable allenylzinc reagent **17**. Such equilibration reactions have been shown to be second order in $[\text{Zn}]$, consistent with a rate enhancement in isomerization while the competing reactions of these organozinc intermediates (**16** and **17**) for the electrophile are only first order in these organozinc reagents.⁸

The zinc-catalyzed regioselective allenylation and propargylation reactions of ketones was developed by Kobayashi using the allenylboronate **18** and catalytic $\text{Zn}[\text{N}(\text{TMS})_2]$ ($\text{Zn}(\text{HMDS})_2$) (Scheme 9).¹⁵ At $-40\text{ }^\circ\text{C}$ using 2 mol% of the zinc amide catalyst in toluene, allenyl products were favoured (allene:propargyl = 80:20 to 99:1). While at $15\text{ }^\circ\text{C}$ using 0.3 mol% of the zinc amide catalyst in THF, propargyl products were favoured (allene:propargyl = 40:60 to 4:96). The lower temperature results are consistent with those of Frandrick (Scheme 7) and a mechanism, similar to that shown in Scheme 8 has been proposed. At the higher temperature ($15\text{ }^\circ\text{C}$) the thermodynamically more stable allenylzinc reagent is favoured (analogous to **17**, Scheme 8, with ZnHMDS rather than ZnEt) which favours the propargyl products. The enantioselective versions of these reactions using chiral ligands are discussed in Section 2.5 (Scheme 29).

Fandrick reported the regioselective copper-catalyzed allenylation reactions of ketones and aldehydes using propargylboronate **5** in the presence of 2.5 mol% $\text{Cu}(\text{butyrate})_2$, 2.5 mol% LiO^tBu and 4 mol% of the chiral bidentate diphosphine, $(2R,2'R,5R,5'R)\text{-1,1'-(1,2-ethanediy)}\text{bis[2,5-diphenylphospholane]}$.¹⁶ These reactions worked well with substituted acetophenones (Scheme 10), tetralone and 4-phenylbutan-2-one. While the regioselectivities were good to excellent the ees of the resulting α -allenyl alcohol products were poor to modest (*ca* 5-64%). This method also worked well with aromatic aldehydes giving α -allenyl alcohol products in yields ranging from 71-93% and allene:propargyl product ratios ranging from 86:14-96:4.

In contrast the corresponding 1,1'-(1,2-ethanediyl)bis[2,5-dimethylphospholane] gave nearly exclusively the homopropargyl alcohol product (Scheme 11).¹⁶

The silver-catalyzed allenylation and propargylation reactions of methyl phenylglyoxylate using pinacol allenylboronate **3**, AgF (5-10 mol %), ^tBuONa (30 mol %) and ^tBuOH (1.1 equiv) in THF at RT was studied by Jarvo (Scheme 12).¹⁷ In the absence of an additional additive the allenyl product was favoured over the propargyl product (allene:propargyl = 5.8:1). Interestingly, the addition of 50 mol % *n*Bu₄I resulted in a switch in product selectivity favouring the propargyl product (allene:propargyl = 1:14.4). These results further imply the isomerization of allenyl and propargyl-metal (Ag) intermediates in these reactions. The enantioselective versions of these reactions using chiral ligands are discussed in Section 2.5 (Scheme 27).

methyl phenylglyoxylate using pinacol allenylboronate **3**

2.3 Enantioselective Synthesis of Homopropargylic Alcohols using Chiral Allenylboronates

In the early 1980's Yamamoto reported a practical and efficient method for the synthesis of enantiomerically enriched homopropargyl alcohols from the reactions of aldehydes and chiral allenylboronate esters prepared from the reactions of allenylboronic acid **8** and L- or D-dialkyl tartrates (2 equiv).^{10,18} The allenylboronic acid **8** and the dialkyl tartrates were first reacted over 24 h in the presence of 5 Å sieves to form the corresponding chiral allenylboronate esters. These were then treated with the aldehydes at -78 °C for 20 h. The resulting homopropargyl alcohol products were obtained in enantiomeric purities (ees) ranging from 60-99% depending upon the nature of the ester alkyl group. The more hindered D- and L-bis(2,4-dimethyl-3-pentyl) tartrate performed the best (ee 92->99%), while the more common ethyl and isopropyl diesters worked equally well but were less enantioselective (Scheme 13 (a)). To rationalize the configurational outcome of the products a transition state intermediate was proposed that was similar to **11** in Scheme 3, where steric interactions between the R group of the aldehyde and alkyl group (R') of the chiral ester were minimized (Scheme 13 (b)).

In 1993 Hayashi reported the asymmetric synthesis of axially chiral (3-substituted-1,2-butadienyl)-1,3,2-benzodioxaboroles from the palladium-catalyzed hydroborations of but-1-en-3-ynes.¹⁹ The hydroboration of but-1-en-3-yne gave the corresponding (*R*)-allenylborane which reacted with benzaldehyde at -78 °C with warming to room temperature in chloroform solution to give a 3:1 mixture of *syn*- and *anti*-homopropargyl products, respectively (Scheme 14). The enantiomeric purities of the products were modest reflecting the low enantiomeric purity of the allenylborane (Scheme 14). A solution to this problem is presented in Scheme 20.

2.4 Enantioselective Synthesis of Homopropargylic and α -Allenyl Alcohols Using Chiral Organocatalysts

Schaus demonstrated the asymmetric propargylation of ketones using the allenylboronate **19** and chiral biphenols (Scheme 15 (a)). (*S*)-3,3'-dibromoBINOL ((*S*)-Br₂-BINOL) proved the most enantioselective of the biphenols trialed.²⁰ Best results were obtained using aryl alkyl ketones and α,β -unsaturated ketones (up to 98% ee), while the reaction using 2-phenylethyl methyl ketone was the least enantioselective (58% ee). The reactions of acetophenone with 2.5 equiv of racemic allenylboronates **20** afforded *syn*-homopropargyl alcohol products as the major diastereomers which were obtained in high enantiomeric purities (Scheme 15 (b)). The authors proposed that these reactions involve a BINOL/boronate exchange reaction at the boron in **20** leading to a new, and more reactive, chiral boron intermediate. Two diastereomeric boron intermediates are formed that react with acetophenone at different rates (allowing for kinetic resolution) and, under the reaction conditions, *syn* products are obtained with good levels of diastereoselectivity and high levels of enantioselectivity. The reactive intermediate is thought to involve coordination of the boron to one oxygen atom of the chiral BINOL and one oxygen atom of ethylene glycol.

Hoveyda reported the catalytic enantioselective allenylation reactions of *N*-protected isatins using pinacol allenylboronate **3** and the readily prepared aminophenol catalyst **21** (0.5 mol%) and *t*BuONa (0.5 mol%) (Scheme 16).²¹ These reactions were highly regioselective for the allenyl products (<2% propargyl products detected) and proceeded in high yields, providing allenyl products in high enantiomeric purities (92-96% ee). The analogous reaction on *N*-TBS-isatin gave the corresponding allene product after *N*-TBS deprotection in 90% yield (>98% ee) on a gram scale using 0.25 mol% catalyst.

Scheme 16 Catalytic enantioselective allenylation reactions of *N*-protected isatins using pinacol allenylboronate **3**

More recently, Hoveyda reported the catalytic enantioselective allenylation reactions of trifluoromethyl aryl ketones, trifluoromethyl alkyl ketones or pentafluoroethyl phenyl ketone using pinacol allenylboronate **3** and the triphenylsilyl substituted aminophenol catalyst **22** (Scheme 17).²² The reactions, shown in Schemes 16 and 17, are thought to involve a propargyl boron intermediate in which the boron is coordinated

to the phenol oxygen and the benzylamino group of the catalyst (Figure 1). The amino group remains protonated and is internally H-bonded to the carbonyl group of the *N,N*-dimethylamido group. This protonated N enhances the Lewis acidity of the B enhancing substrate binding and C-C bond formation. Further, the internal H-bonding results in high enantioselectivities by making the catalyst-substrate complex more rigid. This is illustrated for the reactions with trifluoromethyl ketones which have been suggested to involve C-F...H-N interactions (Figure 1).

A chiral Brønsted acid catalyzed asymmetric propargylation of aldehydes using pinacol allenylboronate **3** was developed by Antilla and Houk.²³ This method involved treating a toluene solution of the aldehyde and **3** (1.5 equiv) with 20 mol% of the 3,3'-bis(2,4,6-*i*Pr)-(*R*)-BINOL derived phosphoric acid **23** in the presence of 4 Å molecular sieves at -20 °C for 96 h (Scheme 18). The resulting homopropargyl alcohol products were obtained in excellent yields (89-96%). Aromatic aldehydes gave products in the highest enantiomeric purities (91-96% ee) while aliphatic aldehydes gave products in 77-82% ee. Computational studies indicated a strong H-bond between the Brønsted acid and the pseudo-equatorial oxygen of the allenyl boronate and that steric interactions between the substrates and the bulky 3,3' substituents in **23** are important in controlling enantioselectivity.

The chiral phosphoric acid **23** has also been successfully used by Reddy for the catalytic asymmetric synthesis of α -allenyl alcohols from aldehydes and the propargyl boronate **5** (Scheme 19).²⁴ Cyclohexane was found to be the best solvent at 0 °C for 12 h. Molecular sieves provided no enhancement of enantioselectivity. The TMS group of the resulting allene product was removed by treatment with tetrabutylammonium fluoride. Product yields (89-94%) and ees were high (82-99%). Cinnamaldehyde gave the lowest ee (82%) while dihydrocinnamaldehyde (ee 96%) and cyclohexanecarboxaldehyde (ee 99%) gave the highest. A boat-like transition state structure, involving H-bonding between the phosphonic acid and the pseudo-axial oxygen of the propargylboronate was proposed.

Highly diastereo- and enantiospecific synthesis of *anti*- and *syn*-homopropargyl alcohols has been developed by Roush via chiral Brønsted acid catalyzed propargylation reactions of aldehydes using the axially chiral pinacol allenylboronate (*M*)-**24**.²⁵ The uncatalyzed reaction of enantiomerically pure (*M*)-**24** with benzaldehyde results in a 1:1.2 mixture of diastereomers (*syn*-**26** and *anti*-**25**, respectively, Scheme 20) differing only at the configuration at the carbinol carbon. The configuration at the Me bearing stereocentre being induced by the axial chirality of the allenylboronate. When this and related reactions were performed using different aldehydes in the presence of the (*S*)-Brønsted acid **23** (Scheme 20 (a)) then product diastereoselectivities were excellent (*anti*:*syn* > 50:1) for both aromatic and aliphatic aldehydes. In each case *anti*-homopropargyl products **25** were obtained in > 98% ee and in high yields. In contrast related reaction using the enantiomeric

phosphoric acid catalyst, the (*R*)-Brønsted acid **23**, were less diastereoselective for the *syn*-homopropargyl products **26**, however synthetically useful diastereoselectivities could be obtained for aromatic aldehydes (*dr* ≥ 9:1) (Scheme 20 (b)). The reactions of cinnamaldehyde (*syn:anti* = 2:1), hydrocinnamaldehyde (*syn:anti* = 1:2) and cyclohexancarboxaldehyde (*syn:anti* = 1:4.5) were poorly diastereoselective, with the latter two aldehydes favouring the *anti*-product **25**. It was proposed that reactions involving (*M*)-**24** and the (*S*)-Brønsted acid **23** were the stereochemically matched combination and proceeded through a boat-like transition state **27** (Scheme 20(c)). While reactions favouring the *syn*-diastereomers using the (*R*)-Brønsted acid **23** (the mismatched situation) were proposed to proceed through transition state **28** in which the aldehyde R group and the terminal Me group of the allene reagent are eclipsed (Scheme 20 (c)). When R is less sterically demanding (i.e., a flat aromatic ring) then the role of the chiral catalyst is more dominant resulting in ≥ 9:1 *syn*-diastereoselectivity. However, when R is more bulky (e.g. cyclohexyl) steric factors override the influence of the chiral catalyst and *anti*-products are favoured.

This study was extended to chiral α -methyl substituted aldehydes **29** with some having further stereogenic centres at the β (*R* or *S* configurations) and γ positions (Scheme 21 (a)). Their reactions with (*M*)-**24** and the (*S*)-Brønsted acid **23** were all highly diastereoselective for the *anti*, *anti*-stereotriads **30**. While the reactions of the aldehydes **31** with (*P*)-**24** and the (*R*)-Brønsted acid **23** were highly diastereoselective for the *anti*, *anti*-stereotriads **32**, having the opposite configuration at the three stereocentres nearest the alkyne moiety to those in **30** (Scheme 21 (b)). *Anti*, *syn*-stereotriads (for example **34**) were

efficiently obtained from chiral aldehydes (for example **33**) using (*P*)-**24** and the (*R*)-Brønsted acid **23** (Scheme 21 (c)).

Roush *et al.*²⁶ further developed an enantioselective synthesis of *anti*-homopropargyl products employing the chiral Brønsted acids (*R*)- or (*S*)-**23** to affect efficient kinetic resolution/allenylboration reactions of achiral and chiral aldehydes using 2.8 equivalents of racemic **24**. The diastereoselectivities and enantioselectivities were generally high. For example, the reaction of racemic **24** (2.8 equiv) and **33** in the presence of the (*S*)-Brønsted acid **23** gave the *anti*, *anti*-stereotriad diastereomer of **34** in 85% yield (*dr* = 8:1).

2.5 Metal-catalyzed Enantioselective Synthesis of Homopropargylic and α -Allenyl Alcohols

In 2010 Fandrick *et al.*²⁷ reported the copper-catalyzed asymmetric propargylation reactions of aldehydes using the pinacol propargylboronate **5**, 7 mol% Cu(II) isobutyrate, 7 mol% *t*BuOLi and the chiral (2*R*,2'*R*,3*R*,3'*R*) bisdihydrobenzoxaphosphole ligand **35** (MeO-BIBOP) (Scheme 22). Aromatic aldehydes and α -methyl cinnamaldehyde all worked efficiently (yields 77–99%) and provided homopropargyl alcohol products in high enantiomeric purities (97–99% ee). A single aliphatic aldehyde example

(CbzNHCH₂CH₂CHO) provided the corresponding propargyl product in 95% yield and 90% ee.

Scheme 22 Copper-catalyzed asymmetric propargylation reactions of aldehydes using the chiral ligand MeO-BIBOP **35**

In 2010 Kanai and Shibasaki²⁸ reported the first asymmetric propargylation of ketones using pinacol allenylboronate **3**, 2 mol % CuOAc, LiOtPr (0.5 equiv) and the chiral, conformationally constrained 13-membered macrocyclic diphosphine ligand **36** (2.4 mol%) (Scheme 23). Substituted acetophenones worked well (90-95% ee) while the reaction of ethyl phenyl ketone was poorly enantioselective (42% ee). Alkyl or vinyl methyl ketones gave homopropargylic alcohols in yields of 65-90% and in 72-86% ee.

Scheme 23 Asymmetric propargylation of ketones using pinacol allenylboronate **3** and chiral ligand **36**

The following year Frandrick²⁹ reported a Cu-BINAP catalyzed propargylation of ketones with the pinacol propargylboronate **5** (Scheme 24) in the presence of LiOtBu (8 mol%). Jarvo⁵ has suggested that the copper-catalyzed reactions shown in Scheme 23 may proceed through a Lewis acid-catalyzed process via direct γ -addition of allenylborolane while those shown in Scheme 22 and 24 by the mechanism proposed by Fandrick involving a reactive allenyl-copper intermediate which reacts with the ketone via a S_E2' process (Scheme 25, compare with Scheme 8)).

Scheme 24 Copper-BINAP catalyzed propargylation of ketones with the pinacol propargylboronate **5**

Scheme 25 Proposed mechanism of propargylation involving a reactive allenyl-copper intermediate which reacts with the ketone via a S_E2' process

Shimizu and Kanai³⁰ reported that the diastereoselective propargylation reactions of unprotected aldoses can be achieved using the pinacol allenylboronate **3**, mesitylcopper (MesCu) or CuClO₄(MeCN)₄ (2.5 mol%) and the chiral spiroketal-bisphosphine **37** (2.5mol%). The later Cu salt requires CF₃COOK (5 mol%) to generate CF₃COOCu *in situ*. B(OMe)₃ (2 equiv) was included in these reactions to facilitate ring-opening of the aldose to the reactive aldehyde form. The configuration of the newly formed stereocentre could be controlled by the configuration of the chiral ligand giving ready access to either *syn* or *anti* products (Scheme 26). It is likely the reactions shown in Schemes 23 and 26 are proceeding via Lewis-acid activation and γ -attack by the allenyl reagent **3**.

Scheme 26 Copper-catalyzed diastereoselective propargylation reactions of unprotected aldoses using the pinacol allenylboronate **3** and chiral ligand **37**

Scheme 27 Silver-catalyzed enantioselective propargylation reactions of ketones using pinacol allenylboronate **3** and (R,R)-Walphos-8

The silver-catalyzed enantioselective propargylation reactions of ketones using pinacol allenylboronate **3**, (R,R)-Walphos-8 (6 mol%), AgF (5-10 mol %), *t*BuONa (15 mol%) and *t*BuOH (1.1 equiv) in MeOH then *t*BuOMe at -20 °C was developed by Jarvo (Scheme 27(a)).¹⁷ α -Ketoesters gave mixtures of propargyl and allenyl products (propargyl:allene = 2:1 to 4:1) with good enantioselectivities for the propargyl products (86-91% ee). However, much better regioselectivities (>30:1) were obtained using acetophenones providing homopropargyl alcohol products in enantiomeric purities ranging from 81-90%. One aliphatic ketone example was provided (2-phenylethyl methyl ketone) which proceeded with lower regioselectivity (propargyl:allene = 8:1) and enantiomeric purity (71% ee). In contrast *ortho*-substituted benzophenones gave homopropargyl products with high regioselectivity (propargyl:allene > 30:1) with ees ranging from 81-97% (Scheme 27(b)).

Fandrick³¹ also reported the zinc-catalyzed asymmetric propargylation reactions of trifluoromethyl ketones using the pinacol propargylboronate **5** and Et₂Zn (25 mol%), *N*-isopropyl-L-proline (27 mol%) as a chiral ligand and 2 mol% water in THF at -40 °C for 2 d (Scheme 28). Chemical yields were high and enantiomeric purities ranged from 60-84% ee.

Scheme 28 Zinc-catalyzed asymmetric propargylation reactions of trifluoromethyl ketones using the pinacol propargylboronate **5**, Et₂Zn and *N*-isopropyl-L-proline as a chiral ligand

Kobayashi¹⁵ reported a zinc-catalyzed asymmetric allenylation reaction of methyl phenylglyoxylate and the asymmetric propargylation reaction of 4-bromoacetophenone using the allenylboronate **18**, catalytic Zn[N(TMS)₂]₂ (5 mol%) and the chiral diamine **38** and the Inda-box ligand **39**, respectively, at -40 °C (Scheme 29). These were the only examples reported and thus the generality of these reactions was not fully explored. The absolute configuration of these products was not elucidated.

Scheme 29 Zinc-catalyzed asymmetric allylation and propargylation reactions with allenylboronate **18**, Zn(HMDS)₂ and chiral ligands **38** or **39**

3 Synthesis of Homopropargylic and α -Allenyl Amines

3.1 Direct Synthesis of Homopropargylic and α -Allenyl Amines from Imines and Iminium Ions

Similar to the reactions of allenylboronates with aldehydes (Scheme 2) the reactions of imines with allenylboronates are generally not fruitful apart from the reactions of imines derived from salicylaldehydes or cyclic imines. In the examples shown in Scheme 30 salicylaldehyde benzylimine **40** reacts efficiently with pinacol allenylboronate **3** at room temperature in MeOH to give exclusively the racemic homopropargylamine product **42** in 87% yield.³² In contrast, 2-methoxybenzaldehyde benzylimine **41** was completely unreactive under the same reaction conditions. This significant difference in reactivity can be explained by the enhanced electrophilicity of the imine **40** due to internal H-bonding with the *ortho*-hydroxy substituent as shown in intermediate **44** with γ -attack by the boronate. While formation of the zwitterionic intermediate **45** is possible through B-N coordination and then intramolecular γ -attack by the allenylboronate, such an intermediate however does not explain the rate enhancing role of the *ortho*-hydroxy group.

Scheme 30 Reactions of pinacol allenylboronate **3** with benzyl imines of alicyclaldehyde and 2-methoxybenzaldehyde

Fandrick³³ reported that the uncatalyzed reaction of the pinacol propargylboronate **5** with dihydroisoquinoline **46** proceeded at room temperature to yield the allene **47** in 97% yield (Scheme 31). This reaction was highly regioselective (propargyl:allene > 20:1). A reactive intermediate involving B-N coordination, related to intermediate **12** in Scheme 3, is possible. When MeO-BIBOP **35** was used as the catalyst propargyl products were favoured (Scheme 50).

Scheme 31 The uncatalyzed reaction of pinacol propargylboronate **5** with dihydroisoquinoline **46**

Thiama and Pyne³² have shown that the three component, one-pot reactions (the boronic acid Mannich reaction or borono-Mannich reaction or the Petasis reaction) involving salicylaldehyde, a primary or secondary amine and pinacol allenylboronate **3** regioselectively provide racemic homopropargylic or α -allenyl amines, respectively. Reactions involving secondary amines give α -allenyl amine products **48** exclusively while primary amines provide homopropargylic amines **49** (Scheme 32). These regiochemical outcomes were rationalized as proceeding via the reactive intermediates, **44** (Scheme 30, for primary amines) and the zwitterionic intermediate **50** (Scheme 33, for secondary amines).

The borono-Mannich reactions of α -hydroxy aldehydes **51** (as their cyclic acetal dimers) with primary or secondary amines and pinacol allenylboronate **3** regioselectively provided *anti* α -allenyl amines **52** (Scheme 33). Enantiomerically enriched α -hydroxy aldehydes give *anti* α -allenyl amines **52** in high enantiomeric purities. The *anti*-diastereoselectivity and product regioselectivity was explained as a result of the intermediate **53** in which $A_{1,3}$ -strain is minimized.³² A related study by Petasis³⁴ using glycoaldehyde **51** ($R^1 = H$) and allenylboronic acid **8**, rather than the boronate **3**, observed the same regiochemical outcomes with benzylamine and dibenzylamine, however the reaction with 4-methoxyaniline gave a 1:1 mixture of allene and propargyl products while and the chiral amines, (*S*)-2-amino-2-phenylethanol and L-phenyllysine, gave exclusively the propargyl products. The potentially chelating groups (OH and COO^-) on these amines may be responsible for these particular regiochemical outcomes. Reactions of secondary amines with glyceraldehyde (**51**, $R^1 = HOCH_2$) gave *anti* α -allenyl amines **52** while benzylamine gave the propargyl product with low diastereoselectivity (de = 23%).³⁴

Using glyoxylic acid (monohydrate) as the aldehyde component, it was found that primary amines gave α -propargyl amino acids **55** while secondary amines gave α -allenyl amino acids **54** (Scheme 35).³⁴ These differences in regiochemical outcomes between primary or secondary amines were the same as those found in the related reactions of salicylaldehyde with pinacol allenylboronate **3** (Scheme 32). Reactive intermediates related to **44** and **50** (involving B-coordination to the COO^- of the glyoxylic acid) may be also be involved. In a shorter study Chambers and Pyne³⁵ found that the reaction of glyoxylic acid (monohydrate), pinacol allenylboronate **3** and dibenzylamine gave the corresponding α -allenylglycine of **54** ($R^1 = R^2 = Bn$) while the reaction using diphenylmethylamine, rather than dibenzylamine, gave a 27:73 mixture of propargyl and allenyl products, respectively.

Chambers and Pyne³⁵ demonstrated that the borono-Mannich reactions of ethyl glyoxylate, primary or secondary amines and pinacol allenylboronate **3** or potassium allenyltrifluoroborate **10** were highly regioselective and gave ethyl α -propargylglycinates **56** (Scheme 36). These results are different to those found using glyoxylic acid and allenylboronic acid **8**, supporting the mechanism schemes shown in Scheme 37. For reaction of glyoxylic acid with secondary amines the regiochemical outcome can be explained by the intermediate **57** involving B-O coordination via the carboxylate group followed by intramolecular transfer by α -attack of the allenyl reagent (Scheme 37). While the ion-pair intermediate **58** can be invoked to explain the formation of the propargyl products arising from the reaction of ethyl glyoxylate.

Scheme 36 Borono-Mannich reactions of ethyl glyoxylate, amines and pinacol allenylboronate **3** or potassium allenyltrifluoroborate **10**

Scheme 37 Possible intermediates for borono-Mannich reactions of glyoxylic acid and ethyl glyoxylate

3.2 Metal-catalyzed Synthesis of Racemic Homopropargylic and α -Allenyl Amines

Kobayashi³⁶ reported the regioselective synthesis of racemic homopropargylic and α -allenyl amines from the copper(II) or bismuth(III)-catalyzed reactions of the hydrazone ester of ethyl glyoxylate **59** with pinacol allenylboronate **3** (Scheme 38) in aqueous DMF. The Cu(OH)₂-catalyzed reaction favoured the propargyl product **60** (allene:propargyl: = 9:91) while the Bi(OH)₃-catalyzed reaction favoured the allenyl product **61** (allene:propargyl: = 94:6). The yields for both reactions were quantitative.

Scheme 38 The regioselective synthesis of racemic homopropargylic and α -allenyl amines

A mechanistic study using α -deuterated **3** (97% D incorporated) indicated the terminal position of the propargyl product **60** from the Cu-catalyzed reaction was 97% deuterated while the internal position of the allenyl product **61** was 97% deuterated

(Scheme 39). These studies indicated that Cu(OH)₂ had acted as a Lewis acid catalyst to activate the hydrazone and **3** reacted via γ -addition to afford the propargyl product **60**. The Bi-catalyzed reaction was consistent with formation of a bismuth-propargyl intermediate. This could be formed from **3** via transmetalation from B to Bi followed by addition to the hydrazone via a S_E2' type mechanism.

Scheme 39 A mechanistic study using deuterated **3**

3.3 Enantioselective Synthesis of α -Allenyl Amines Using Catalytic Amounts of a Chiral Aminophenol

Hoveyda³⁷ developed a catalytic enantioselective synthesis of *N*-Boc- α -allenyl amines from *N*-Boc protected imines **62** using pinacol allenylboronate **3**, aminophenol catalyst **21** (0.1 mol%), *t*BuONa (5.0 mol%) and isopropanol (2.3 equiv) in toluene at 22 °C for 14 h. (Scheme 40). These reactions were highly regioselective for the allenyl products **63** (<2% propargyl products detected in most cases) and proceed in high yields and provided allenyl products in high enantiomeric purities (>98% ee in most cases). One of the few exceptions was the pyridyl *N*-Boc imine derived from nicotinaldehyde which provided the allenyl product with relatively poor regioselectivity (allene:propargyl = 90:10) and enantioselectivity (68% ee). The H-bonded transition state structure **64**, similar to that proposed in Figure 1, was postulated (Scheme 40).

Scheme 40 Chiral aminophenol catalytic enantioselective synthesis of *N*-

Boc- α -allenyl amines3.4 Metal-catalyzed Diastereoselective Synthesis of Chiral Homopropargylic and α -Allenyl Amines from Chiral *N*-*tert*-Butylsulfinyl Imines

Fandrick³⁸ described the zinc-catalyzed (20 mol% Et₂Zn) reactions of (*R*)-*N*-*tert*-butylsulfinyl imines **65** derived from aromatic and aliphatic aldehydes and pinacol propargylboronate **5** in THF at room temperature. Propargyl derivatives **66** were generally obtained in good yields and with high diastereoselectivities (Scheme 41). A mechanism, involving an allenyl-zinc intermediate related to that shown in Scheme 8 was proposed. The chelated 6-membered transition state structure **67** was proposed to account for the stereochemical outcome of these reactions.

Scheme 41 Zinc-catalyzed reactions of (*R*)-*N*-*tert*-butylsulfinyl imines **65** and pinacol propargylboronate **5**

Chaipukdee and Pyne³⁵ demonstrated that the (*S*)-*N*-*tert*-butylsulfinyl imine of ethyl glyoxylate **68** underwent an indium chloride catalyzed addition reaction with allenyl potassium trifluoroborate **10** in DMF in a highly regioselective and diastereoselective manner to give, after *N*-deprotection, (*S*) ethyl α -propargylglycinate, in 97% ee. The stereochemical outcome was rationalized by invoking the chelated In-allenyl intermediate **71** (Scheme 42).

Scheme 42 Indium-catalyzed reactions of (*R*)-*N*-*tert*-butylsulfinyl imine **68** and allenyl potassium trifluoroborate **10**

The method developed by Fandrick (Scheme 40) was used by Fustero and Barrio *et al.*³⁹ to study the zinc-catalyzed reaction of the chiral *N*-*tert*-butylsulfinylimine **72** with pinacol allenylboronate **3** (Scheme 43). The propargyl product **73** was obtained in 60% yield with high chemoselectivity and diastereoselectivity (dr >20:1). This reaction was much higher yielding and much more diastereoselective than that involving addition of stoichiometric propargylzinc bromide (33% yield, dr = 5:1).

Scheme 43 Zinc-catalyzed reaction of the chiral *N*-*tert*-butylsulfinylimine **72** with pinacol allenylboronate **3**

3.5 Metal-catalyzed Enantioselective Synthesis of Chiral Homopropargylic and α -Allenyl Amines

The silver-catalyzed enantioselective propargylation reactions of *N*-tosyl imines **74** using pinacol allenylboronate **3**, (*R,R*)-Walphos-1 (12 mol%), AgF (10 mol%), ^tBuOK (20 mol%) and ^tBuOH (1.1 equiv) in MeOH then THF at -20 °C has been developed by Jarvo (Scheme 44).⁴⁰ Aromatic derived *N*-tosyl imines gave high yields of propargyl products **75** in high enantiomeric purities (90-98% ee), while aldimines derived from α -methyl cinnamaldehyde and 2,2-dimethyl-4-pentenal provided propargyl products in reduced yields (47 and 40%, respectively) and enantioselectivities (89 and 74% ee, respectively).

Scheme 44 The silver-catalyzed enantioselective propargylation reactions of *N*-tosyl imines **74** using pinacol allenylboronate **3** and (*R,R*)-Walphos-1

Javo's group extended these studies to reactions of cyclic *N*-sulfonyl ketimines **76** and **78** (Scheme 45).⁴¹ Under similar conditions to those used in Scheme 43 propargylated products **77** and **79** were obtained, respectively, often in high yields and in high enantiomeric purities (90-98% ee).

To help understand the mechanism of these processes the reaction of the phenyl substituted sulfonyl ketimine **80** with the isomeric pinacol propargylboronate **15** was studied under identical reaction conditions to this substrate with pinacol allenylboronate **3** (Scheme 46). The same propargyl product **81** was obtained from either of these reactions in similar yields (68% from **3** and 64% from **15**) and enantioselectivities (96% from **3** and 86% from **15**). In both cases <2% of the regioisomeric allene product was formed. It was also demonstrated that **3** and **15** are not in equilibrium under the reaction conditions. These results were consistent with equilibrating allenyl and propargyl silver intermediates with addition of the thermodynamically more stable allenyl-silver intermediate to **80** via a S_E2' process to give the observed propargyl product **81**.

Kobayashi⁴² developed a catalytic and enantioselective synthesis of α -allenyl amines from the indium(I) chloride catalyzed reactions between the racemic *N,O*-aminals **82** and pinacol allenylboronate **3** using the Ag-(*R*)-BINOL phosphonate **85** as the chiral catalyst (Scheme 47). These reactions involve the corresponding iminium ion intermediates, formed from the Lewis acid catalyst, with the (*R*)-BINOL phosphonate acting as the chiral counteranion. While only two examples were presented, these reactions favoured the allenyl products **83** over the propargyl products **84**. The former regioisomers could

be readily separated from the minor regioisomers by column chromatography and were obtained in good yields and 86-88% ee. The regiochemical outcomes of these reactions are opposite to those found by Jarvo using the unrelated substrates **74**, **76** and **78** (Schemes 44 and 45).

Hoveyda *et al.*⁴³ disclosed a highly enantioselective method for preparing homopropargyl amines from chiral *N*-heterocyclic carbene (NHC)-copper catalyzed enantioselective propargylation reactions of *N*-phosphinoyl imines **86** using pinacol allenylboronate **3**, the chiral C1-symmetric imidazolium salt **88** (1 mol%), CuCl or CuCl₂·2H₂O (1 mol %), ^tBuONa (5 mol%) and MeOH (2.0 equiv) in THF at -50 °C for 6 h (CuCl) or -78 °C then 15 °C for 30 min (CuCl₂·2H₂O) (Scheme 48). These reactions worked well with aryl, heteroaryl, alkyl and α,β -unsaturated *N*-phosphinoyl imines giving propargyl products in good to excellent yields, with <2% of the allene regioisomer formed and with excellent enantioselectivities (84-95% ee). It was proposed that the reactive intermediate is a NHC-copper-allenyl complex in which the copper activates the *N*-phosphinoyl imine by coordination to both the N and O of the imine.

Hoveyda⁴⁴ reported an analogous study using pinacol propargylboronate **5** (Scheme 49) and the chiral NHC precursor,

the imidazolium ion **90**. These NHC-copper catalyzed reactions gave the corresponding α -trimethylsilylallenyl amines **89** in good yields and enantioselectivities (82-96% ee). The corresponding propargyl products were formed in <4%. The exception was the *N*-phosphinoyl imine of 4-pyridinecarboxaldehyde which gave 16% of the propargyl product. Computational studies indicated that the trimethylsilyl substituent favours the NHC-copper-propargyl complex [(NHC)Cu-CH₂C≡CTMS] over the isomeric NHC-copper-allenyl complex [(NHC)Cu-C(TMS)=C=CH₂] by about 10 kcal/mol and that the Cu-propargyl species is the more reactive complex leading to allene products in high regioselectivities.

Fandrick³³ reported the enantioselective copper-catalyzed reactions of the pinacol propargylboronate **5** with cyclic aldimines **91**, including dihydroisoquinolines and 3,4-dihydro- β -carboline, gives propargylated products **92**, including **93** and **94**, respectively (Scheme 50). MeO-BIBOP **35** was used as the catalyst. The regiochemical outcomes of reactions were reverse of that found in the uncatalyzed reaction (Scheme 31).

Sieber *et al.*⁴⁵ reported that the rhodium-catalyzed enantioselective allenylation reactions of *N*-tosyl imines **74** with the pinacol propargylboronate **5** provided the *N*-tosyl- α -allenyl

amines **95** in usually good yields and in good to excellent enantioselectivities (78-98% ee) (Scheme 51). The imine from 4-chlorobenzaldehyde only gave a 35% yield (92% ee). The regioselectivities of these reactions were concentration dependent with higher substrate concentrations favoring propargyl products. The authors postulated that a [Rh-C(TMS)=C=CH₂] complex is formed initially which undergoes a metallotropic rearrangement to the more stable [Rh-CH₂C≡CTMS] complex to avoid steric interactions with the TMS group. The Rh-propargyl intermediate then leads to the allenyl products **95** via an S_E2' process. Higher imine concentrations allows binding of imine to the initially formed Rh-allene intermediate to compete with the metallotropic rearrangement reaction resulting in reduced regioselectivities.

4 Applications to synthesis

The alkyne and allene moieties of the aforementioned homopropargyl and α -allenyl alcohol and amine products can be transformed into a number of useful functional groups. For example, simple hydrogenation of homopropargyl products gives the corresponding alkene (e.g. using Lindlar's catalyst)⁴¹ or the alkane (e.g. using Pd/C).⁴¹ The homopropargyl alcohol **97** was regioselectively converted to the 2-bromoalkene **98** upon treatment with B-Br-9-BBN followed by an oxidative work up (Scheme 52 (a)).¹⁰ while the *Z*-1-iodoalkene **100** was prepared from its propargyl precursor **99** via 1-iodoalkyne formation (AgNO₃, *N*-iodosuccinamide (NIS)) and then selective reduction with *o*-nitrobenzenesulfonylhydrazide (*o*-NBSH) (Scheme 52 (b)).⁴³ The gold-catalyzed hydration of the homopropargyl alcohol **101** gave the β -hydroxy methyl ketone **102** (Scheme 52 (c)) while the benzoate ester derivative of **103** underwent ruthenium oxide catalyzed oxidative cleavage to the carboxylic acid **104** (Scheme 52 (d)). Ruthenium chloride (1 mol%) and oxone have also been used for this type of transformation.⁴³ Crabbé homologation of the homopropargyl alcohol **105** gave the allene **106** (Scheme 52 (e)).²³ The 3-allenyl isatin derivative **107** was efficiently converted to the diol **108** upon treatment with ozone followed by a reductive work up (Scheme 52 (f)).²¹

A number of heterocyclic compounds have been prepared via metal-catalyzed cyclization reactions of the hydroxyl or amino group onto the unsaturated moiety (Scheme 53). A gold-catalyzed oxidative cyclization of propargyl alcohol **105** gave the dihydrofuran-3-one **109** (Scheme 53 (a))²³ while the lactone **111** was prepared upon treatment of **110** with catalytic palladium and 2 equiv of CuCl_2 (Scheme 53 (b))²⁹ Silver-catalyzed cyclization reactions of **112**⁴⁰ and **114**⁴² gave the corresponding dihydropyrroles, **113** and **115** (Scheme 53 (c) and (d)) while titanium-catalyzed cyclization reactions of piperidines **116** gave access to the indolizidines **117–118** (Scheme 53 (e)).³³

Fandrick reported the diastereoselective synthesis of hexahydroisobenzofurans **121** (racemic) from the racemic α -allenyl alcohols **120** through rhodium-catalyzed [4+2] cycloaddition reactions (Scheme 54).⁸

Scheme 54 Diastereoselective synthesis of hexahydroisobenzofurans **121** from α -allenyl alcohols **120** through rhodium-catalyzed [4+2] cycloaddition reactions

The synthesis of *epi*-cytoxazone was achieved in three synthetic steps from the α -allenyl amine **122** as shown in Scheme 55. Iodination of **122** gave the diiodide **123** (*E:Z* = 1:1) which upon treatment with AgPF₆ (1.1 equiv) gave the oxazolidinone **124** via an intramolecular S_N2'-like process. Finally, lithium-iodine exchange of **124** and a MeOH quench followed by ozonolysis and borohydride reduction gave *epi*-cytoxazone.³⁷

Scheme 55 Synthesis of *epi*-cytoxazone

The ruthenium catalyzed alkene-alkyne ring-closing metathesis reaction of enyne **125** gave the spirocycle **126** in 76% yield having a useful diene moiety for additional functionalization (Scheme 56).⁴¹

Scheme 56 Synthesis of the spirocycle **126** by a ruthenium catalyzed alkene-alkyne ring-closing metathesis reaction.

Base promoted cyclization of the sulfonamide **73** diastereoselectively gives 1,3-disubstituted isoindolines **127** (Scheme 57). The thermodynamically more stable *cis*-isomer, *cis*-**127**, is obtained when tetrabutylammonium fluoride (TBAF) is used as base while DBU gives the kinetic product, the *trans*-isomer, *trans*-**127**. Treatment of related *trans*-products with TBAF produces the corresponding *cis*-isomers, however DBU had no effect.³⁹

Scheme 57 Synthesis of 1,3-disubstituted isoindolines **127** by base promoted cyclizations of the sulfonamide **73**

The enyne **130**, prepared from the α -allenyl amine **128** underwent a Ru-catalyzed cycloisomerization reaction to give the hexahydrocyclohepta[*c*]pyrrole **131** in 85% yield (Scheme 58).⁴⁵

Scheme 58 Synthesis of the hexahydrocyclohepta[*c*]pyrrole **131** by a Ru-

catalyzed cycloisomerization reaction

The homopropargyl alcohol **132** was converted to the chiral dihydropyranone **135** as shown in Scheme 59. A hydroxyl directed hydrosilylation of **132** gave a siloxane intermediate which upon a copper-catalyzed allylation procedure gave the *Z*-vinyl silane **133**. This was then transformed to the corresponding vinyl iodide **134** which upon *O*-deprotection and then a palladium-catalyzed carbonylation and olefin isomerization gave the chiral dihydropyranone **135** with little or any racemization.²⁷

Scheme 59 Synthesis of the chiral dihydropyranone **135**

The natural product, 2-keto-3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN) **138** has been prepared from the propargyl hexanol **136** (Scheme 60). Treatment of **136** with 5 equiv of bromine gave the dibrominated pyranose derivative **137**, which underwent a base promoted hydrolysis to the corresponding aldehyde. Upon oxidation with this with NaClO_2 KDN **138** was realized in 76% overall yield.³⁰

Scheme 60 Synthesis of the natural product, 2-keto-3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN) **138**

5 Conclusions

It is clear from this review that the reactions of allenyl or propargyl boronates, and related derivatives, with aldehydes, ketones, imines or iminium ions are often highly regioselective, giving usefully functionalized homopropargyl or α -allenyl alcohols or amines. Enantioselective versions have been achieved using chiral allenylboronates (having chiral esters or axial chirality, Schemes 13, 14, 20 and 21), chiral organocatalysts (diols or aminophenols or Brønsted acids, Schemes 15-17, 18-21) or chiral metal catalysts (Schemes 22-29 and 44-50). (*R*)-*N*-*tert*-butylsulfinylimines have also been employed as substrates allowing for diastereoselective reactions (Schemes 41-43).

The regiochemical outcomes of these reactions often depends upon the nature of either the metal catalyst or the organocatalyst. Substituents on the allenyl or propargyl boronate, the reaction temperature and solvent, and, in the case of metal catalyzed reactions, the ligand also influences the regiochemical outcomes.

For reactions involving allenylboronates **3** or **18** and aldehydes or ketones with catalysis by Et_2Zn (0 °C to -40 °C) or $\text{Zn}(\text{HMDS})_2$ at -40 °C, respectively, then α -allenyl alcohol products are favoured (Schemes 7 (a) and 9). Higher temperatures and more coordinating solvents (e.g. THF) produce more of the homopropargyl alcohol products. Under similar reaction conditions the propargyl boronates **5** and **15** give homopropargyl alcohol products (Schemes 7(b) and 28). The zinc-catalyzed reactions of the propargyl boronate **5** or the allenylboronate **3** with (*R*)-*N*-*tert*-butylsulfinylimines in THF at RT gives propargyl products (Schemes 41 and 43)). These results are consistent with the mechanistic scheme shown in Scheme 8, involving equilibrating propargyl- and allenylorganozinc species. Higher temperatures and THF favouring the allenylzinc species **17** which reacts with the electrophilic component via a $\text{S}_{\text{E}}2'$ process giving propargyl products.

The regiochemical outcomes of the copper(II)-catalyzed reactions of propargyl boronate **5** with aldehydes and ketones are dependent upon the nature of the ligand and the substrate (Scheme 10, 11 and 22). Aldehydes often favour propargyl products (Scheme 22), while methyl ketones favour allenyl products (Scheme 10) or propargyl products (Scheme 24) depending upon the ligand. In contrast, Cu(I) or Cu(II)-catalyzed reactions of allenylboronate **3** with imines gives propargyl

products (Schemes 38, and 48) while propargyl boronate **5** gives allenyl products (Scheme 49). The exception being cyclic imines which react with **5** under Cu(II)-catalysis to give propargyl products (Scheme 50).

Silver-catalyzed reactions of allenylboronate **3** with carbonyl compounds or imines generally favour propargyl products (Schemes 12, 27, 44, and 45). The unsubstituted propargyl boronate **15** also favoured the propargyl product (Scheme 46). The results of these silver-catalyzed reactions indicated that the reactive intermediate was an allenylsilver complex which was reacting with the electrophilic component via a S_E2' process.

The only reported rhodium-catalyzed reactions of propargyl boronate **5** gave allenyl products (Scheme 51), while the two reported indium-catalyzed examples gave opposite regiochemical outcomes (Scheme 42 and 47).

Future developments in the enantioselective area are expected, especially for the allenylation of ketones, and their imine derivatives, and the use of substituted allenyl and propargyl boronates.

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Biosketches

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