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Tandem allylboration-ring-closing metathesis reactions for the preparation of biologically active molecules*

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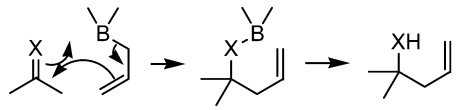
Abstract: The development of asymmetric synthesis during the past two decades aided organic chemists considerably in the synthesis of complex natural products. Organoborane chemistry continues to play an important role in asymmetric synthesis. One of the important reactions that has become very common in the arsenal of synthetic chemists is allylboration and related reactions. Another important reaction that has recently attained enormous importance in organic chemistry is the ring-closing metathesis (RCM) reaction. Indeed, a combination of allylboration and RCM reactions provides an excellent route to cyclic ethers, lactones, lactams, etc. Herein, we describe a sequential asymmetric allylboration and RCM reaction protocol that has been utilized for the synthesis of several α-pyrone-containing natural products, particularly biologically active molecules.

INTRODUCTION

Almost four decades ago, Mikhailov and Bubnov introduced the reaction of triallylborane with carbonyl groups producing homoallylic alcohols [1]. This stereospecific reaction occurs with allylic rearrangement, following an S_E2' pathway, and is capable of providing a wide range of homoallylic alcohols, amines, etc. with excellent stereoselectivity (eq. 1) [2]. Hoffmann and coworkers pioneered an asymmetric version of this reaction. Brown and others have subsequently developed several asymmetric allylborating agents during the last two decades, making it one of the commonly utilized reagents for the syntheses of complex molecules.



(1)

We have utilized a tandem allylboration-ring-closing metathesis (RCM) reaction sequence for the synthesis of several molecules, particularly those containing lactenones, lactones, and their derivatives (Scheme 1).

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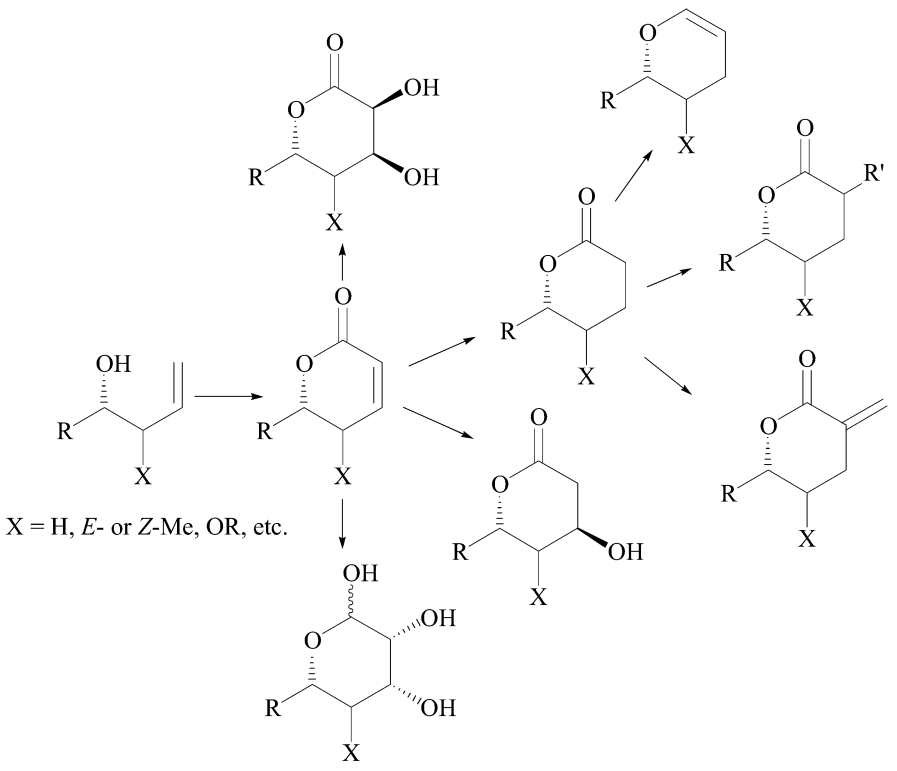
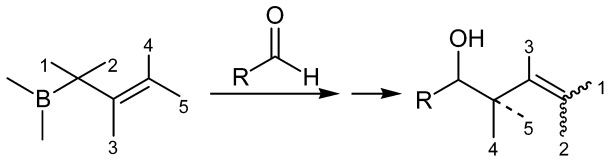


Scheme 1 Applications of lactenones and lactones in organic synthesis.

Some of the recent developments in our laboratories are summarized below.

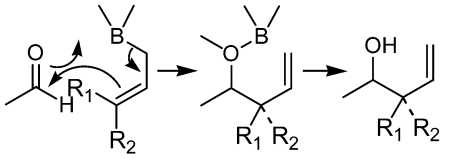
Allylboration and related reactions

Since the discovery of allylboration by Mikhailov and Bubnov, several substituted allylborating agents have been prepared during the ensuing decades to achieve the synthesis of several types of homoallylic alcohols (eq. 2) [3,4].



(2)

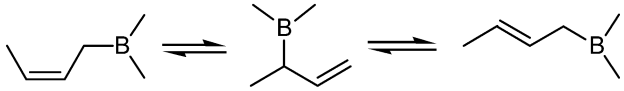
Of the several modified allylborations, crotylboration (eq. 3) is one of the most utilized reactions.



(3)

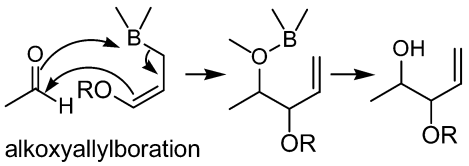
R_1 = Me, R_2 = H (*Z*-crotylboration)
R_1 = H, R_2 = Me (*E*-crotylboration)

However, a major problem with crotylboration is the scrambling of the reagent (eq. 4), resulting in poor diastereoselectivity of the products. It is crucial to control the allylic rearragements of crotylboranes to achieve maximum diastereoselectivity. Crotyldialkylboranes tend to rearrange more rapidly than crotylboronates. Conducting the reactions at low temperatures is essential to arrest the rearrangement and achieve high diastereoselectivity [5,6].



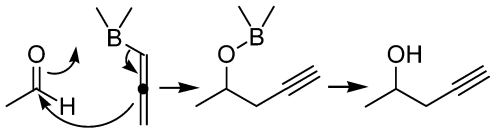
(4)

Alkoxyallylboration (eq. 5), allenylboration (eq. 6), and propargylboration (eq. 7) are variations of allylboration and undergo reaction via allylic rearrangement [3].



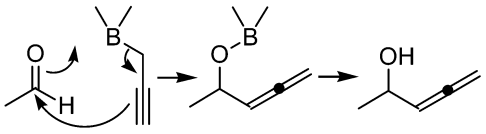
alkoxyallylboration

(5)



allenylboration

(6)



propargylboration

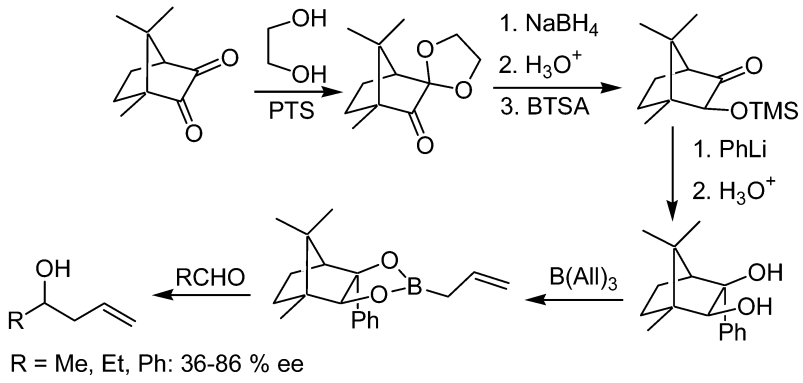
(7)

The product homoallylic alcohols and amines derived from all of these "allyl"boration reactions contain an alkene moiety, which could be further transformed into other functional groups. This aspect has been exploited well for the synthesis of several complex molecules, some of which are described below.

Asymmetric allylboration

Asymmetric "allyl"boration is an excellent route to prepare chiral homoallylic alcohols and amines in high diastereo- and enantioselectivity. Such molecules are important for the stereoselective synthesis of highly sophisticated conformationally nonrigid systems [7]. Accordingly, numerous searches for the most efficient reagent that can achieve both these selectivities in a single step have been made [7].

Hoffmann and coworkers reported the first asymmetric allylboration utilizing a chiral auxiliary derived from camphor (Scheme 2) [8]. Various allyl- and crotylboration reactions were also examined using this auxiliary for both single and double asymmetric synthesis [4a–d].



Scheme 2 Original asymmetric allylboration.

α-*Pinene-derived "allyl"borane reagents*

α-Pinene has been proven to be an excellent chiral auxiliary for various types of asymmetric transformations [3e,f]. Accordingly, α-pinene was utilized for the preparation and reaction of several remarkably successful diisopinocampheyl"allyl"boranes (Fig. 1) [3a]. The preparation and applications of representative examples of reagents are discussed below.

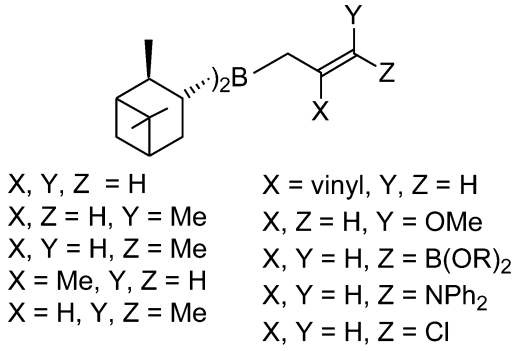
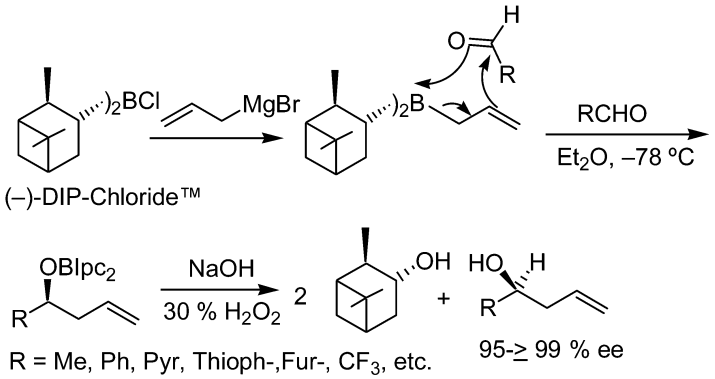


Fig. 1 α-Pinene based "allyl"borane reagents.

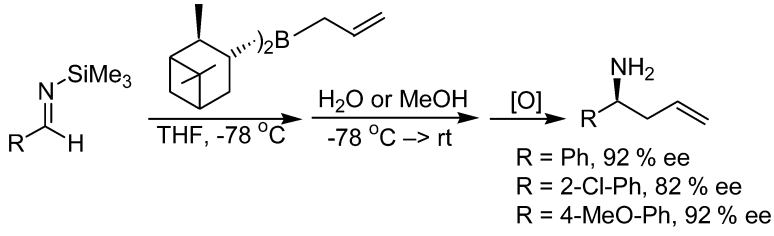
B–Allyldiisopinocampheylborane

We introduced *B*-allyldiisopinocampheylborane for allylboration and achieved an economical preparation of optically active homoallylic alcohols with predictable stereochemistry and high ee [9]. The reagent prepared from either *B*-chlorodiisopinocampheylborane (DIP-Chloride™) [10] or *B*-methoxydiisopinocampheylborane and allylmagnesium bromide provides high ee for most of the aldehydes tested, including heterocyclic [11] and fluorinated aldehydes [12] (Scheme 3). With chiral aldehydes, the reagent controls the diastereoselectivity and high de and ee are achieved [13]. High selectivities were also achieved for the allylboration of a series of dialdehydes [14].



Scheme 3 Preparation and reactions of *B*-allyldiisopinocampheylborane.

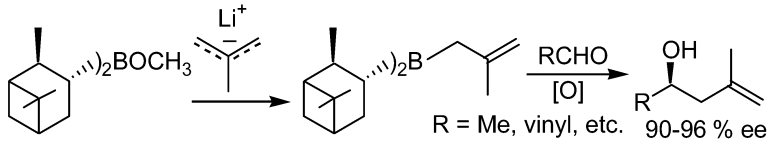
Recently, we have shown that this reagent provides high ee for homoallylic amines produced by the allylboration of imines generated from *N*-silyl imines (eq. 8) [15].



(8)

B-Methallyldiisopinocampheylborane

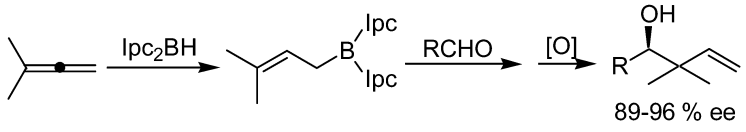
This reagent, readily prepared from Ipc_2BOMe and methallyllithium, upon treatment with aldehydes produces methallyl alcohols in very high ee [16] (eq. 9).



(9)

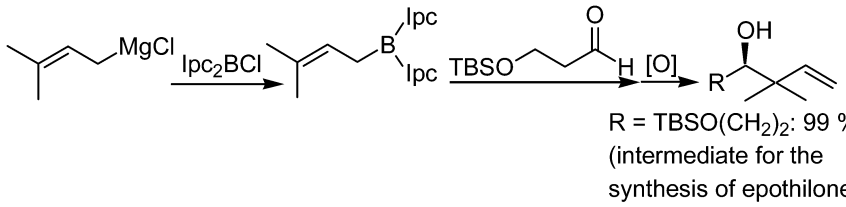
3,3-Dimethylallyldiisopinocampheylborane

The original synthesis of this reagent involves the hydroboration of 1,1-dimethylallene. Allylboration typically provides products in 89–96 % ee with predictable configuration (eq. 10) [17].



(10)

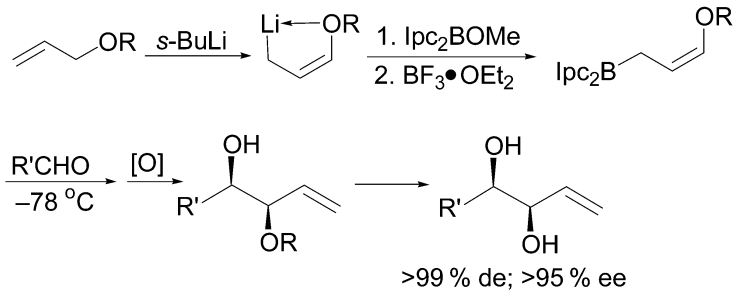
Subsequently, we have developed a more economical synthesis of this reagent from the corresponding dimethylallylmagnesium chloride and DIP-chloride (eq. 11) [18]. This reagent has been applied for the preparation of an intermediate during the synthesis of epothilone C [18].



(11)

[Z]-3-Alkoxyallyldiisopinocampheylborane

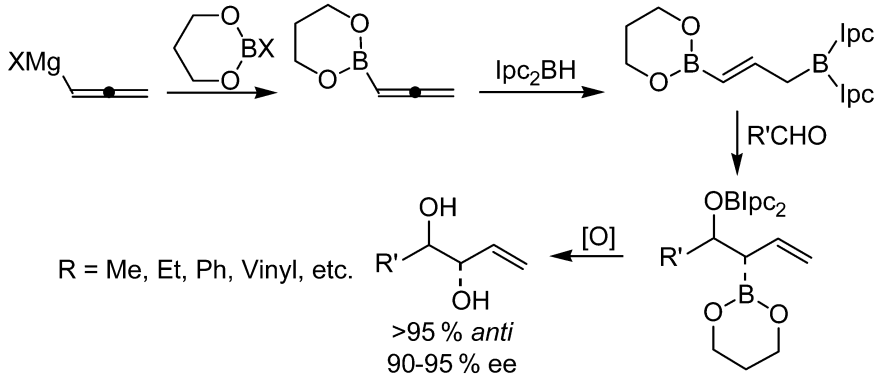
Stereoselective preparation of the diastereomers of vicinal diols is important in organic chemistry. This task can be accomplished via alkoxyallylboration reaction. Metal salts of allyl alkyl ethers remain in the *Z*-form due to chelation [19]. Transmetalation with boron retains the *Z*-stereochemistry [20]. Synthesis of [*Z*]-γ-alkoxyallyldiisopinocampheylborane was achieved by the reaction of the lithium salt of allyl alkyl ether with *B*-methoxydiisopinocampheylborane, followed by treatment with $BF_3{\cdot}Et_2O$ [21]. The reaction of this reagent with aldehyde at low temperatures exhibits high *syn*-selectivities. This reaction allows for the preparation of *syn*-1,2-diols in high ee by the removal of the alkyl protecting groups (Scheme 4). We have applied this reagent for the preparation of several styryllactones possessing medicinal properties (vide infra) [22].



Scheme 4 Preparation of *vic. syn*-diols.

[E]-3-(2,6-dioxaborolyl)allyldiisopinocampheylborane

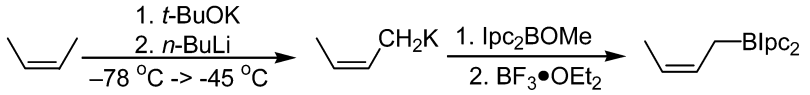
We achieved the synthesis of vicinal *anti*-diols in excellent enantio- and diastereomeric purities via the γ-borolylallylborane reagent prepared via the hydroboration of allenylboranes, which was in turn prepared by the treatment of allenylmagnesium bromide with the corresponding chloroborane (Scheme 5) [23].



Scheme 5 Preparation of *vic. anti*-diols.

B-*[E]- and [Z]-Crotyldiisopinocampheylborane*

Hoffmann synthesized *E*- and *Z*-crotylboronates and reported that the stereochemistry is transferred during the crotylboration of aldehydes [4]. The preparation of isomerically pure *E*- and *Z*-crotylboronates involving the use of isomerically pure crotylpotassium, was reported by Schlosser [24]. We utilized a similar procedure for the synthesis of isomerically pure *B*-[*E*]- and [*Z*]-crotyldiisopinocampheylboranes (eqs. 12, 13) [6].



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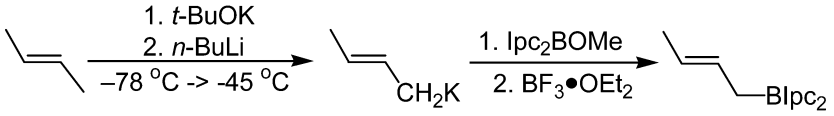
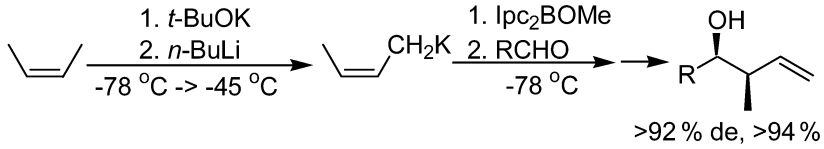


(13)

The original preparation involved the liberation of pure crotylborane reagent from the "ate" complex using BF_3–Et_2O [6]. However, we have recently found that the addition of BF_3–Et_2O is unnecessary. Accordingly, our new reaction protocol involves the addition of the aldehydes to the "ate" complex as shown in eq. 14 [25].



(14)

The reaction of these complexes with aldehydes achieved the synthesis of the four possible isomers of β-methylhomoallylic alcohols with remarkable optical and geometric efficiencies. It is important to maintain the reaction temperatures below –45 °C to avoid the scrambling of the crotylboranes. The reagent controls the diastereoselectivity in reactions with chiral aldehydes. Thus, it is possible to prepare all of the eight diastereomers at will by the appropriate choice of the reagent and the chiral aldehyde [25,26].

Applications of allyl- and crotylboration

Asymmetric "allyl"boration is one of the very useful reactions for the synthesis of complex natural products and biologically active molecules. Both tartrate- and pinane-derived reagents have been widely exploited for syntheses. The applications of pinane-based "allyl"boranes have been reviewed before [3a,e,f].

Allylboration and ring-closing metathesis reaction: A powerful combination

Recent developments in RCM have revolutionized the synthesis of carbocyclic compounds. Several novel ruthenium catalysts have been developed by Grubbs and coworkers (Fig. 2) [27].

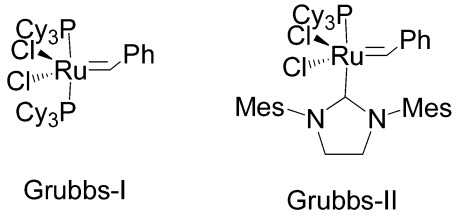


Fig. 2 Grubbs's RCM catalysts.

The appropriate utilization of one of the ruthenium catalysts handles even difficult cyclizations. The reaction occurs via a mechanism shown in Fig. 3.

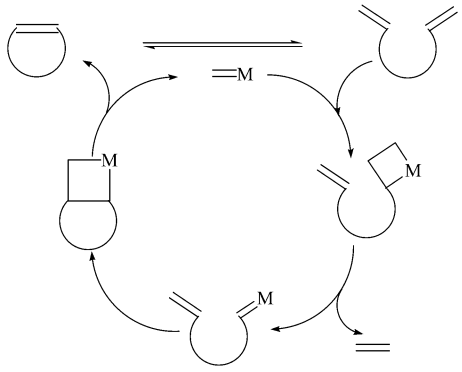
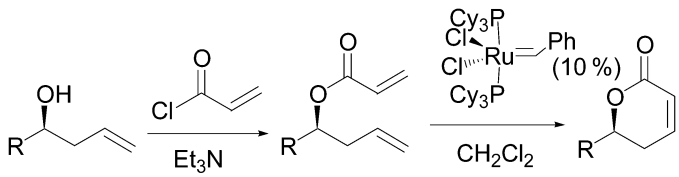


Fig. 3 Catalytic cycle for RCM reactions.

We have recently applied a tandem allylboration-RCM reaction sequence for the synthesis of cyclic ethers and esters. For example, sequential asymmetric allylboration and RCM reaction provides a simple route for the synthesis of several lactone-containing molecules. Representative examples of our syntheses are shown below. Our protocol for α-pyrone synthesis involves the esterification of homoallylic alcohols derived from allylboration with acryloyl chloride, followed by RCM using Grubbs' ruthenium catalyst (eq. 15) [27].



(15)

Utilizing this strategy, we have synthesized several α-pyrone containing natural products, such as masoia lactone [27], goniothalamin [27], and argentilactone (Fig. 4) [28].

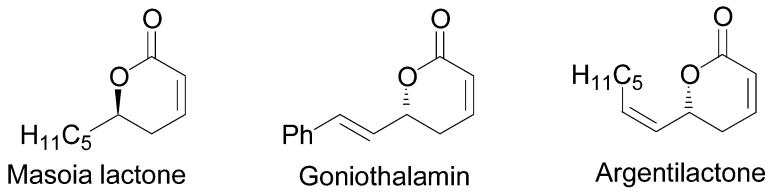
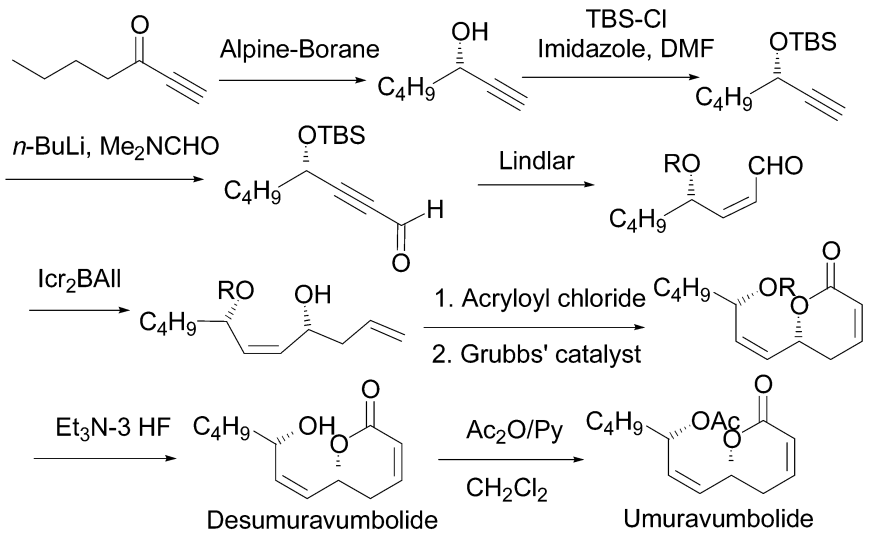


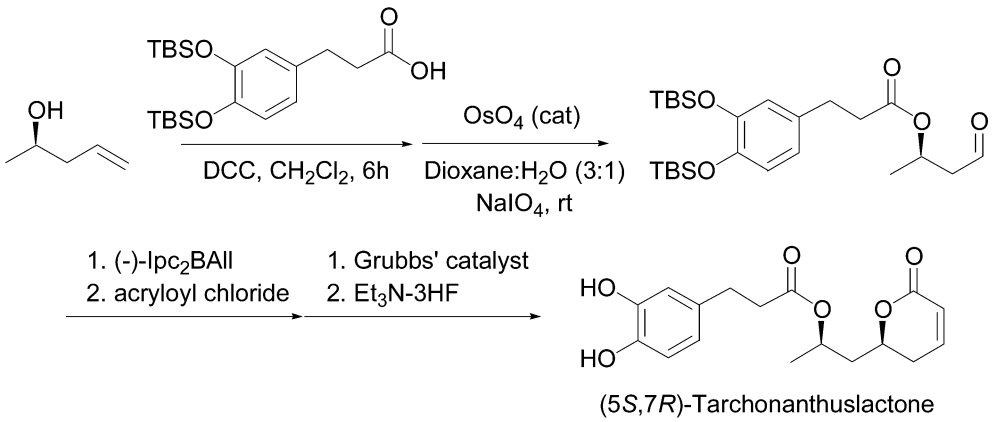
Fig. 4 α-Pyrone-containing natural products.

We have described the first enantioselective synthesis of Umuravumbolide (Scheme 6), via Alpine-Borane® reduction of an acetylenic ketone and allylboration with *B*-allyldiisocaranylborane as key steps to induce asymmetry [29].



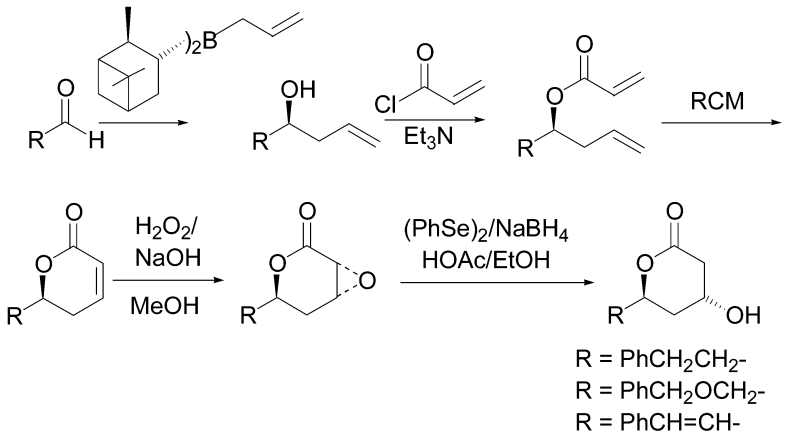
Scheme 6 Asymmetric synthesis of umuravumbolide.

A reagent-controlled synthesis of tarchonanthuslactone, described below, was also achieved using this strategy (Scheme 7) [30].



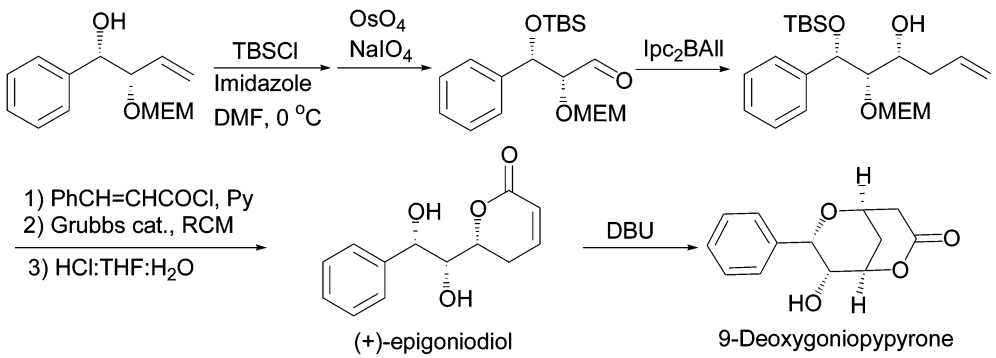
Scheme 7 Asymmetric synthesis of tarchonanthuslactone.

Starting with optically pure α-pyrones synthesized by the tandem allylboration-RCM strategy, we have prepared several analogs of hypercholesterolemic agents via diastereoselective *trans*-epoxidation and regioselective 1,3-reduction (Scheme 8) [31].



Scheme 8 Asymmetric synthesis of β-hydroxy-δ-lactones.

A convenient synthesis of styryllactone derivatives (+)-goniodiol, (–)-epigoniodiol, and (+)-deoxygoniopypyrone was also developed utilizing asymmetric alkoxyallylboration and RCM pathways as key steps (Scheme 9) [22].



Scheme 9 Asymmetric synthesis of styryllactone derivatives.

We extended the tandem "allyl"boration-RCM reactions to include crotylborated products during the synthesis of potent anticancer agent discodermolide (Fig. 5) and its analogs.

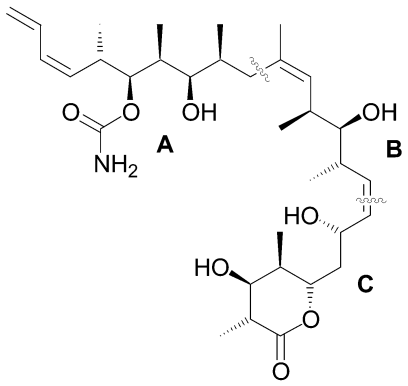
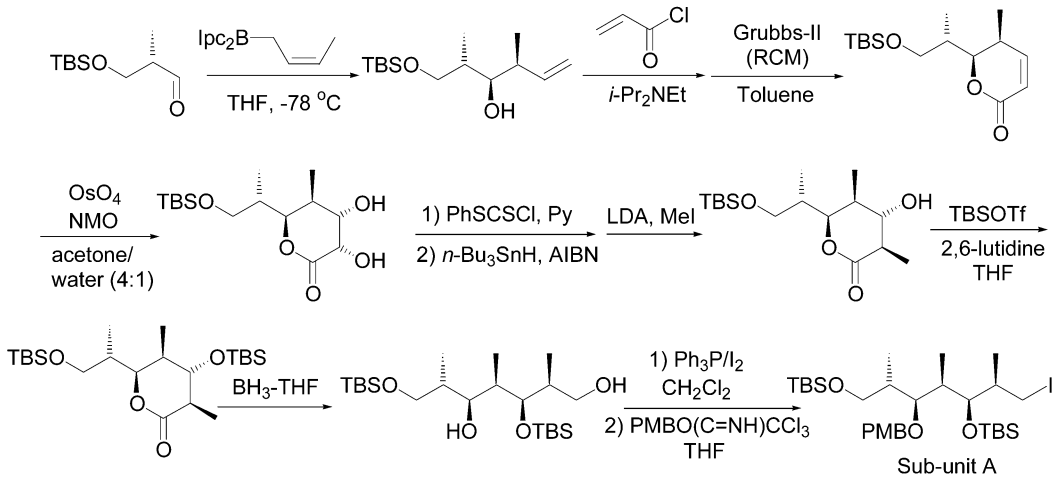
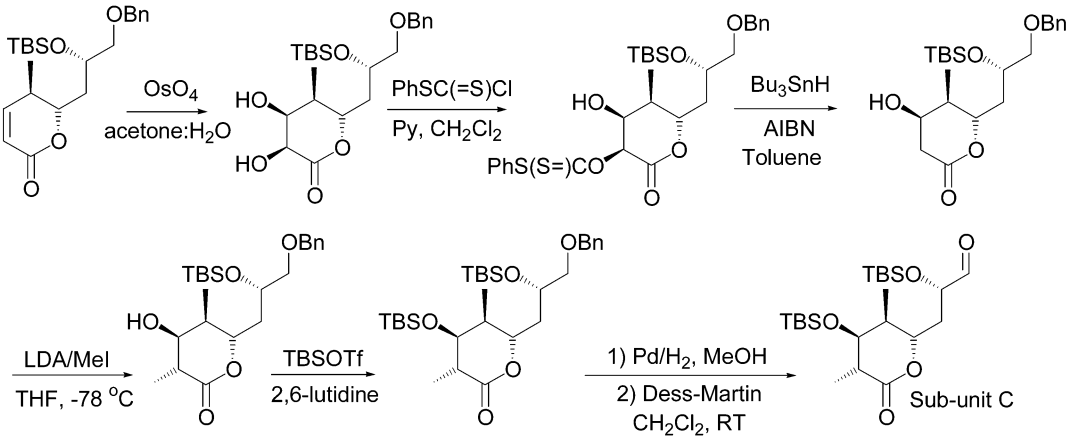


Fig. 5 Discodermolide, a potent anticancer agent.

The preparation of the subunits A, B, and C of discodermolide was achieved via "allyl"boration chemistry. As can be seen from the following schemes, sub-units A and C were prepared via crotylboration-RCM methodology (Schemes 10, 11) [32].



Scheme 10 Synthesis of subunit A of discodermolide.



Scheme 11 Synthesis of subunit C of discodermolide.

CONCLUSION

We have discussed the beginnings and modern developments in asymmetric "allyl"boration chemistry. We have also discussed more recent application of the product homoallyl alcohols derived from such "allyl"boration reactions. The combination of allylboration and RCM has been highly successful for the syntheses of several natural products, particularly complex natural products possessing important medicinal properties.

ACKNOWLEDGMENTS

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