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Functionalized 1-Alkoxy-1,3-dienes: Their Preparation and Applications in Synthetic Organic Chemistry

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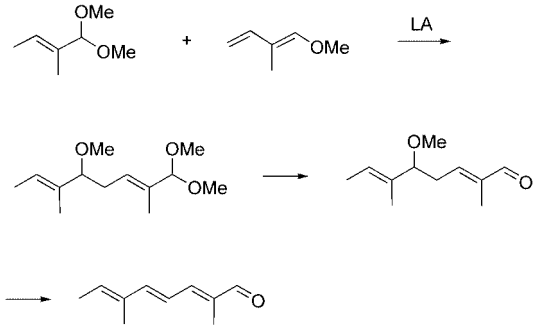
Keywords: Arylation / Conjugation / Cross-coupling / Dienes / Elimination

The reaction of various α,β-unsaturated acetals with two equivalents of the Schlosser reagent LIC-KOR [equimolar mixture of BuLi (LIC), and *t*BuOK (KOR)] gives 1-metalated (1*E*)-1-alkoxy-1,3-dienes. These products can be transformed into trienic derivatives that are apt to participate in intramolecular Diels–Alder (IMDA) cycloaddition reactions, and can also be transformed into bifunctional (γ-halo-α-carbonyl) reagents. Moreover, the metalated dienes can be readily functionalized with suitable electrophiles to afford products that have been found to be useful reagents for the Stille and Suzuki cross-coupling reactions or arylated according to the conditions of the Heck process. Other significant syntheses of dienic and polyenic structures are reported along with some of their applications in organic synthesis.

1. Introduction

The regio- and stereoselective synthesis of conjugated dienes is of great value in organic chemistry by itself as well as for utilization in other reactions such as, for example, the Diels–Alder cycloaddition[1] or the coupling of alkyl dienol ethers with α,β-unsaturated acetals to give δ-alkoxy-α,β-unsaturated aldehydes.[2] This reaction, promoted by Lewis acids (Scheme 1), has found widespread application as an alternative to the aldol condensation, and has been reported to be a powerful tool for carotenoid synthesis. The reaction is not restricted to enol ethers as building units, and 1-alkoxy dienes have also been used as coupling reagents for chain extension; an exhaustive report has been published by Rüttiman.[3]

Various new methods for the preparation of conjugated dienes have so far been developed, and it is known that substituted alkenes, dienes, and other unsaturated systems are useful intermediates for the preparation of dyes, UV screens, and drugs.[4] In connection with this increasing attention all methods that allow straightforward modification of these derivatives deserve to be reviewed, and among these the metalation and functionalization with suitable electrophiles hold a prominent role.



Scheme 1. Reaction of α,β-unsaturated acetals with dienol ethers.

2. Metalation of Conjugated Dienes

It has been reported by Schlosser and co-workers, and by Brandsma, Schleyer et al. that enol ethers without allylic hydrogen atoms undergo deprotonation at the α-vinylic position activated by the presence of a heteroatom.[5] (Scheme 2, A) When an alkyl substituent is present on the double bond, metalation may take place at both the allylic and vinylic sites to afford the corresponding nucleophilic intermediates which yield, upon reaction with electrophiles, different regioisomeric products, the ratio of which is controlled by the steric bulk of the R^2 substituent (Scheme 2, B).

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

As for the metalation of conjugate dienes with alkali metals, it has been reported that 1,3-dienes can undergo undesired reactions. Thus, while 2,3-dimethyl-1,3-butadiene can be metalated, as reported by Bates, Gordon et al., using Schlosser's superbases[6] to afford mono-and dimetalated derivatives (Scheme 2, C), isoprene undergoes addition to the double bond under the same experimental conditions (Scheme 2, D). Only the combination of LTMP and *t*BuOK has been reported by Brandsma and colleagues to be a reagent suitable for the preparation of the desired isoprenyl–metal intermediate.[7] On the other hand, it has been successively established that 1-alkoxy-1,3-dienes easily and selectively undergo hydrogen–metal exchange at the vinylic α-position when using Schlosser's mixed base LIC-KOR (Scheme 2, E).[8] Conjugated alkoxy dienes can, in turn, be obtained by treatment of α,β-unsaturated acetals with Schlosser's reagent.[9] Furthermore, when the reaction was carried out using two equivalents of base the α,β-unsaturated acetal afforded the metalated 1-alkoxy-1,3-diene directly in an elimination/metalation sequence in a one-pot procedure (Scheme 3).[10]

Moreover, because the metalation reaction affords a localized vinylic nucleophile, regioselective addition of the electrophile is always observed. Complete diastereoselectivity is also achieved and pure (*E*)-functionalized dienes are isolated (Scheme 4).[11,12]

As shown in Scheme 4, various functional groups can be bonded to the α site of α-alkoxy dienes in an addition or substitution reaction. The nature of the products varies from carbonyl derivatives, which are obtained by addition of the metalated dienes to carbon dioxide,[11b] esters,[11b] and carbonates,[11b] to allylic and homoallylic alcohols, which are achieved by reaction with aldehydes[11b,11c] and oxiranes,[11a,11d] respectively. Finally, reaction with alkyl halides[11a,11b] and chlorosilanes[11a,11b] gives the expected substitution derivatives.

The functionalized dienes, like all enol ethers, undergo acidic hydrolysis to afford enones. According to this ap-

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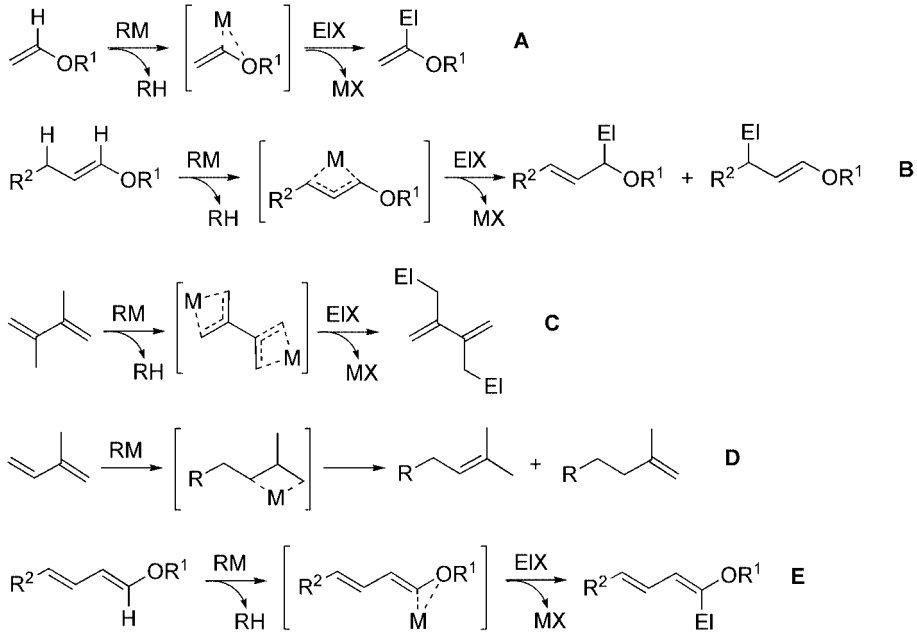
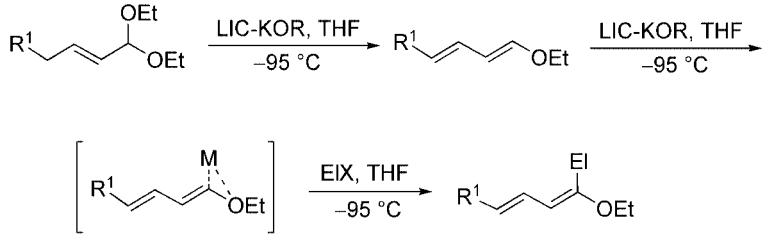
Cristina Prandi was born in Novara (Italy), and she attended the University of Torino where graduated in Biology in 1988. She enrolled in the doctoral program of Biology and Biotechnology of Fungi, conducted graduate work under the supervision of Prof. Iacopo Degani, and received her PhD in June 1993. In July 1993 she was appointed Assistant Professor of Organic Chemistry at the University of Piemonte Orientale and started working under the direction of Prof. P. Venturello. In 2005 she moved to the University of Torino. Her research interests include organometallic chemistry, transition-metal-catalyzed cross-coupling reactions, and natural products' synthesis.

Chiara Zavattaro was born in Bra (Italy) in 1979 and graduated in chemistry at the University of Torino in 2003. In 2003 she obtained a scholarship to attend PhD courses at the University of Torino. Prof. P. Venturello, and Dr. V. Farina (Boehringer-Ingelheim) are the supervisors of her PhD thesis. Presently she is spending nine months at Stanford University in the research group of Professor Barry M. Trost.

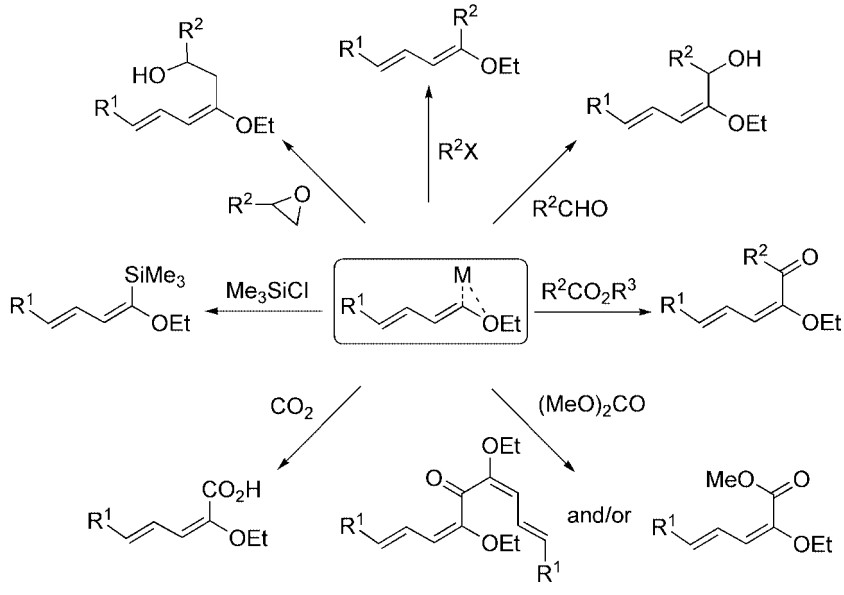
Paolo Venturello was born in 1948 in Torino, Italy. After his degree in Chemistry in 1973 at the University of Torino he spent two years at the University of Padova, where he joined the group of Professors Giorgio Modena and Gianfranco Scorrano, working on acidity functions. In 1985 he was appointed Associate Professor of Organic Chemistry at the Faculty of Science of the University of Torino. In subsequent years he participated in research on phase-transfer catalysis and insoluble reagents and catalysts. His current research interest focuses on the reactivity of α,β-unsaturated acetals in the presence of Schlosser's lithium-potassium reagents. In 2001 he was appointed Full Professor of Organic Chemistry at the Faculty of Science of the University of Torino. His studies have revealed the significance of acetals as building blocks for the synthesis of conjugate structures useful for Diels–Alder cycloaddition, for the synthesis of allyl and vinyl halides, and for the preparation of organotin and organoboron reagents.



Scheme 2. Different reactivity of unsaturated derivatives with organometallic reagents.

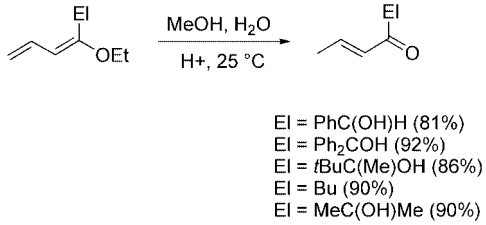


Scheme 3. Synthesis and functionalization of 1-alkoxy-1,3-dienes.



Scheme 4. Functionalization reactions of metalated 1-alkoxy-1,3-dienes.

proach a masked a[1] reagent (the 1-metalated 1-alkoxy diene) is bonded to an electrophile (Scheme 5).[5a,13] The acid-catalyzed conversion of substituted alkoxy dienes into α,β-unsaturated carbonyl compounds has been carried out following two different methods − in a protic (H_2O/MeOH) or aprotic ($CHCl_3$) medium − and different products have been isolated depending on the reaction conditions.



Scheme 5. Acid-catalyzed conversion of alkoxy dienes into carbonyl derivatives.

In particular, (2-hydroxyethyl)-substituted alkoxy dienes have been reported to be convenient intermediates for the synthesis of both (*E*)-1-hydroxyhex-4-en-3-ones and tetrahydropyran-4-ones[11a,11d] (Scheme 6).

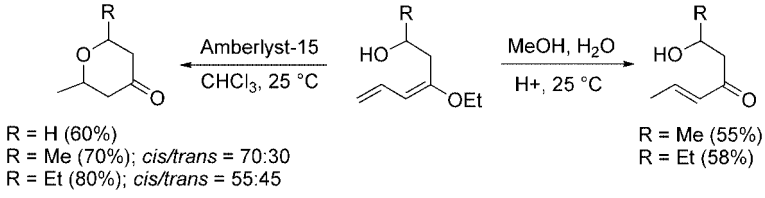
According to the above procedure, substituted 2,2-di-*tert*-butyl-3-ethoxy-5-methyl-2,5-dihydrofuran has also been prepared[11c] (Scheme 7).

The cyclization reactions proceed through an intramolecular acid-catalyzed addition reaction to the carbon–carbon double bond, which can be promoted either by the aprotic non-nucleophilic medium (Scheme 6, Amberlyst-15/$CHCl_3$), or by the steric bulk of the *t*Bu groups (Scheme 7).

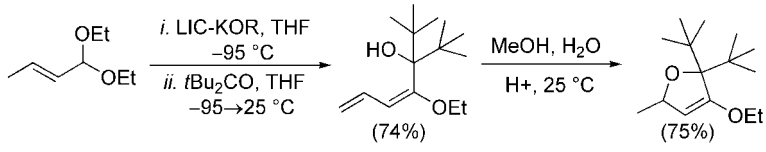
3. Conjugated Dienes and the Diels–Alder Cycloaddition

Cyclic α,β-unsaturated acetals derived from various diols (Figure 1) undergo eliminative ring fission to afford hydroxy-functionalized (*E*)-butadienes, which are readily transformed into trienes useful for intramolecular Diels–Alder cycloaddition (IMDA) by esterification with α,β-unsaturated acyl chlorides,[13b,14a] or by oxidation with TPAP, followed by Wittig–Horner olefination (Scheme 8).[13c]

Interestingly, esterification of hydroxy-functionalized dienes gives trienes that selectively yield fused macrocyclic structures (Scheme 8) due to the activation of both diene and dienophile moieties.[15] According to FMO analysis, the fused cycloadduct is favoured as the COOR group increases the size of the C(1) LUMO coefficient and the OR group increases, through conjugation, that of the HOMO coefficient at C(12), relative to C(2) and C(9), respectively. These medium-ring lactones ([4.6.0] or [3.6.1]) show interesting features since they have been recognized as substructures in various products of natural origin.[16] Moreover, the hexahydrobenzofuran nucleus obtained by IMDA reaction of



Scheme 6. Synthesis of tetrahydropyranones.



Scheme 7. Synthesis of dihydrofurans.

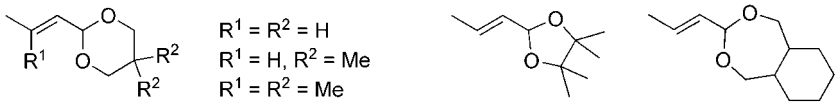
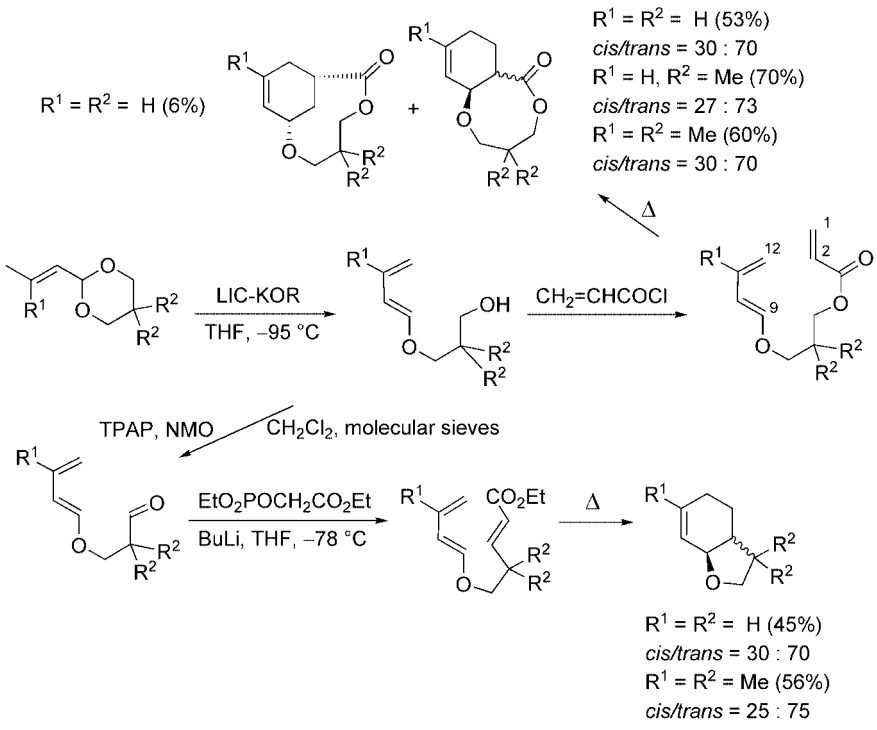


Figure 1. Cyclic α,β-unsaturated acetals.



Scheme 8. Synthesis of trienes and IMDA.

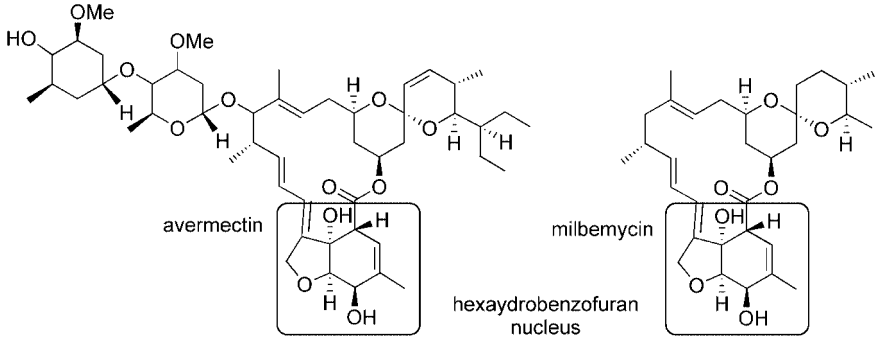


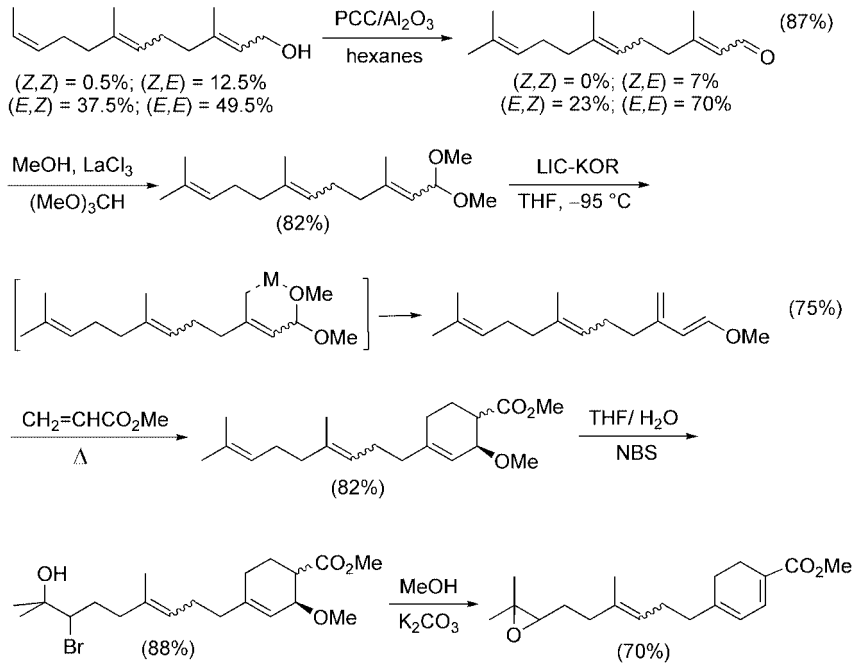
Figure 2. Structures of macrolides containing the hexahydrobenzofuran nucleus.

functionalized trienes has been recognized as a useful building block[17] for the synthesis of avermectin and for the α-series of milbemycin,[18] both of which are macrolides that exhibit a potent broad spectrum of antiparasitic activity in both humans and animals (Figure 2).

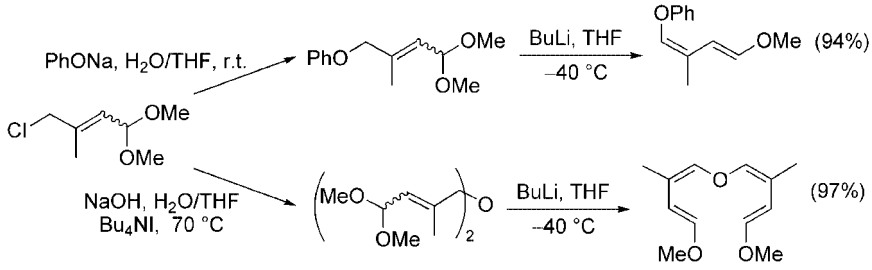
The versatility of the procedure that has been set up for preparing conjugated dienes starting from α,β-unsaturated acetals has also been exploited for the transformation of some derivatives of natural origin. In particular, a variety of structural modifications and functionalizations have been carried out on a commercially available mixture of farnesol isomers, leading to potentially useful synthetic mimics of naturally occurring juvenile hormones (Scheme 9).[19]

A stereocontrolled access to 1,4-dialkoxy-1,3-dienes and bis-dienes has been achieved by Duhamel, Maddaluno and colleagues starting from γ-functionalized α,β-unsaturated dimethyl acetals, which undergo a 1,4-elimination of methanol upon treatment with organolithium and organopotassium reagents (Scheme 10).[20] The obtained dienes and bis-dienes were then applied in [4+2] cycloaddition reactions, where they demonstrated a good thermal reactivity toward activated dienophiles.[21]

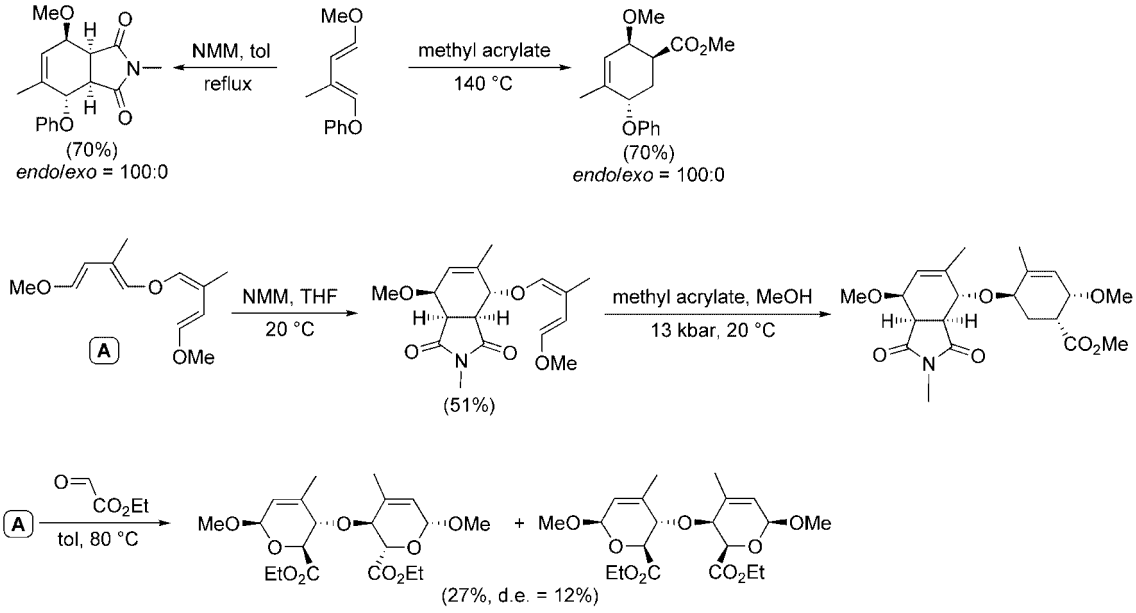
The reactions were totally regio- and *endo*-selective. Bis-dienes can also give mixed adducts by adding two different dienophiles successively, and double hetero-Diels–Alder reactions have been also performed to yield bicyclic skeletons of 4 ↔ 4′ disaccharidic structures (Scheme 11).[22]



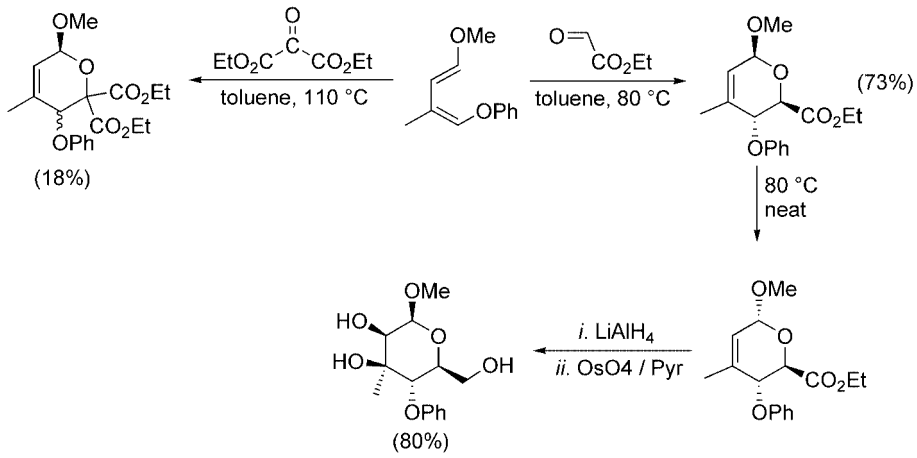
Scheme 9. Synthesis of a mimic of juvenile hormones.



Scheme 10. Conjugated elimination on α,β-unsaturated acetals: a route to functionalized 1,3-dienes.



Scheme 11. Cycloaddition reactions of 1,4-dialkoxy-1,3-dienes.

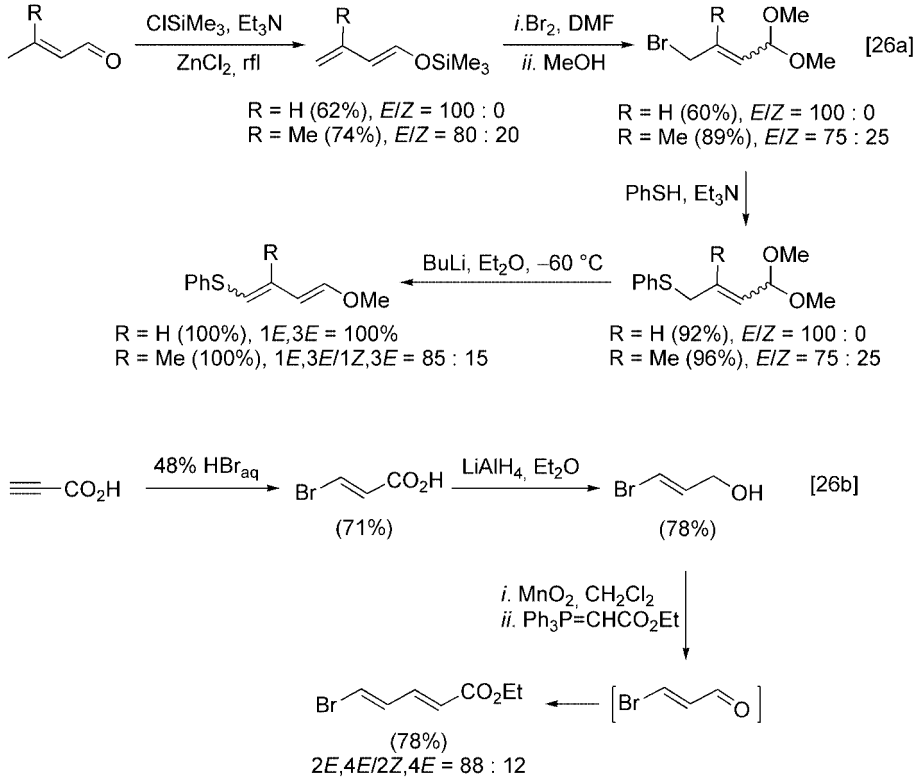


Scheme 12. Heterocycloaddition of 1,4-difunctionalized-1,3-dienes.

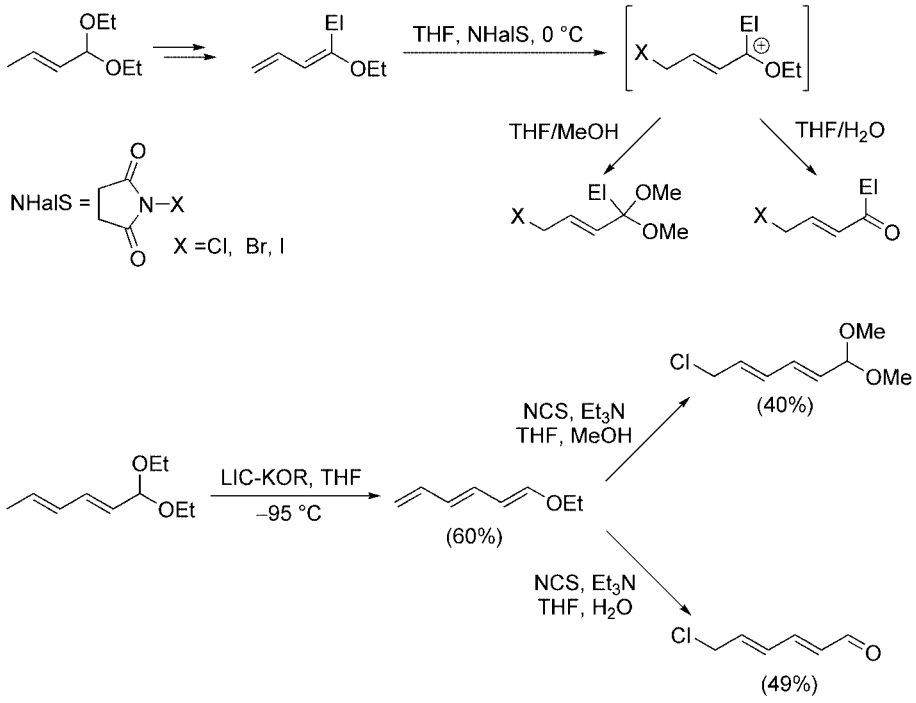
More recently, Maddaluno et al.[23] have shown that 1-(*Z*)-alkoxy-4-(*E*)-methoxybutadiene derivatives undergo a cycloaddition reaction with ethyl glyoxylate and diethyl ketomalonate under thermal or hyperbaric conditions to give dihydropyranic adducts, which were then converted into racemic pyranoses (Scheme 12).

4. Conjugated Dienes and Bifunctional Derivatives

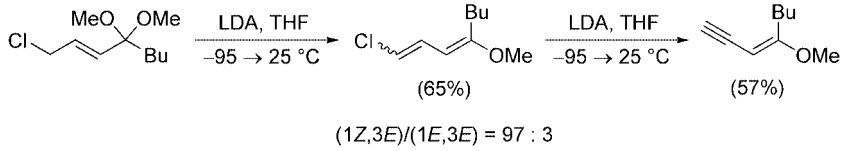
It is known that conjugated polyenes of the *all-E* variety constitute key subsections of many natural and unnatural products. Traditional routes to functionalize polyenes have relied on olefin elongation.[24] More recently, however, new approaches to the construction of *all-E* unsaturated structures based on bidirectional elaboration have been reported by the research groups of Lipshutz, Zu, Alexakis, Normant, Marek, Alami, and Duhamel,[4f,25] with attention focused on the use of halo-carbonyl intermediates in particular (Scheme 13). These compounds have emerged as model bifunctional precursors of the target compounds, as discussed by Ross and Schreiber, and by Magnusson, by elaboration of the carbonyl group (Wittig, Grignard, or oxidation) and subsequent cross-coupling of the halide substituent.[26]



Scheme 13. Synthesis of functionalized dienes.[27a,27b]



Scheme 14. Formation of α,β-unsaturated γ-halogenated carbonyl derivatives.



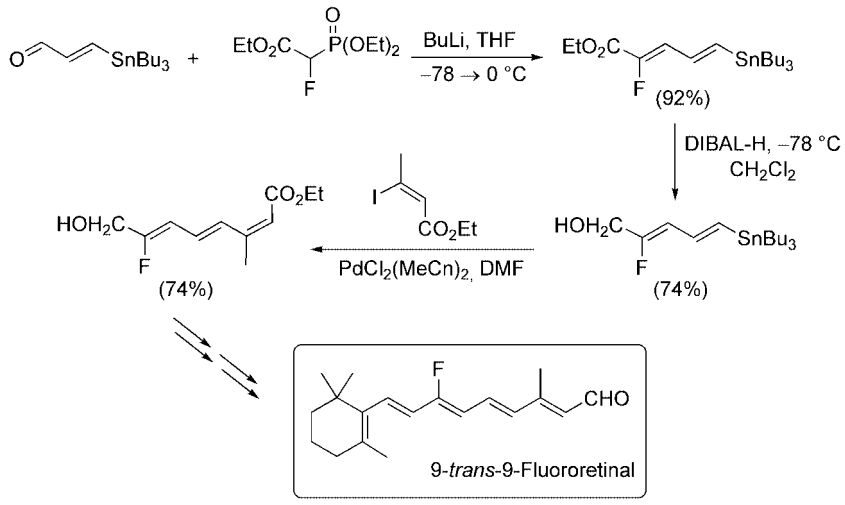
Scheme 15. Synthesis of vinyl chlorides and enynes.

We have reported that γ-halogenated α,β-unsaturated acetals and carbonyl derivatives can be prepared by reaction of alkoxy-functionalized dienes with *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS; Scheme 14).[28] The method starts with a LIC-KOR induced 1,4-conjugate elimination reaction, which gives functionalized 1-alkoxy-1,3-dienes. The halogenation step proceeds through electrophilic addition to the conjugated system and final quenching of the intermediate carbocation by the nucleophilic solvent: H_2O (which affords α,β-unsaturated γ-halogenated carbonyl derivatives) or MeOH (which affords acetal-protected α,β-unsaturated γ-halogenated carbonyl derivatives).

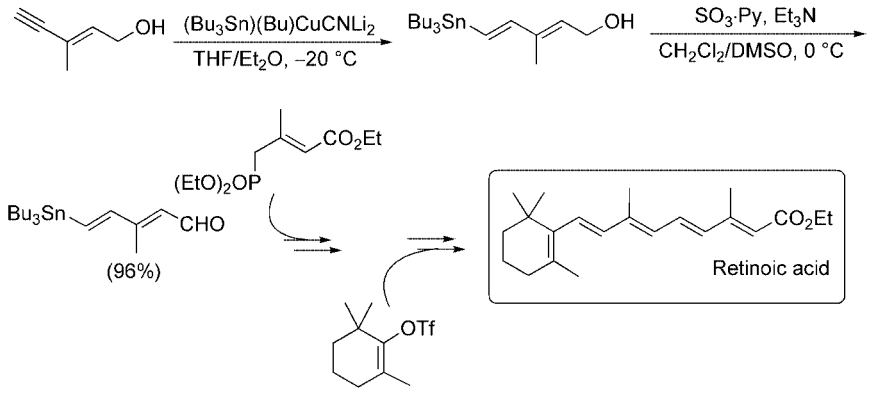
Halogenated bifunctional derivatives have been used for the synthesis of vinyl chlorides and enynes[27b] (Scheme 15).

5. Conjugated Dienes and the Stille Cross-Coupling

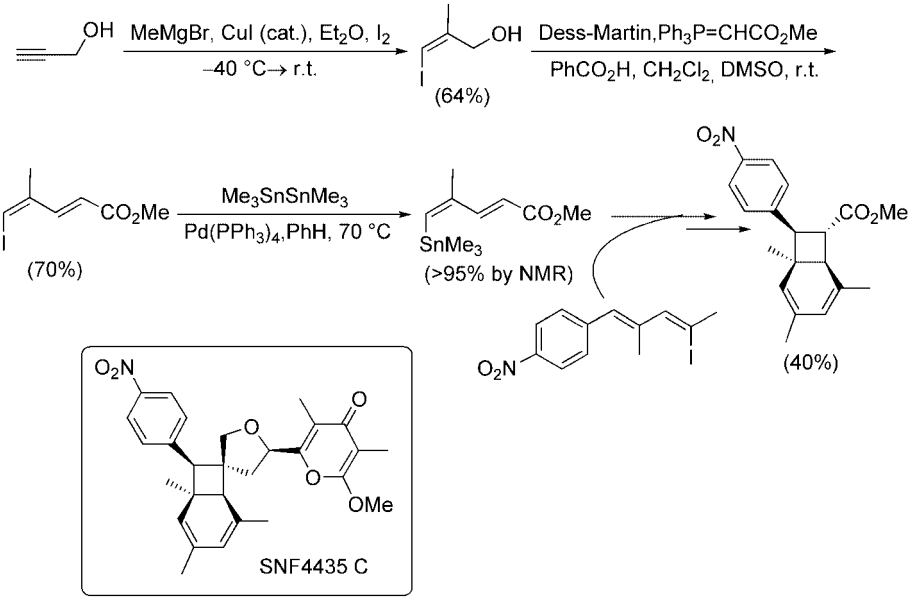
Synthetic routes to conjugated polyenes can be classified as double- or single-bond-forming reactions. The Wittig or Horner–Wadsworth–Emmons reaction[29] and the Julia olefination[30] are the most often used double-bond-forming processes. The synthesis involving single-bond formation usually takes advantage of a metal-catalyzed cross-coupling reaction between alkenyl organometallic reagents and alkenyl electrophiles. With regards to this, the palladium-catalyzed coupling of organostannanes with organic electrophiles, developed by Stille,[31] owes its success, amongst other aspects, to the stability and low cross-reactivity of organotin compounds and the compatibility of the reaction conditions with many types of functional groups. A variety of building blocks for the synthesis of conjugate polyenes present in many natural products have been studied using the Stille coupling. Some pertinent examples are, for example, the stereocontrolled synthesis of 9-*trans*-9-fluororetinal,[32] the synthesis of retinoic acid and analogs,[33] the synthesis of symmetrical carotenoids,[34] a synthetic approach to the immunosuppressants SNF4435 C and SNF4435 D[35] and towards viridenomycin,[36] and the total synthesis of dermostatin A.[37] Scheme 16 shows the strategy developed by Yoshihara and co-workers[31] for the stereocontrolled synthesis of 9-*trans*-9-fluororetinal, which involves a Pd-catalyzed cross-coupling reaction of a C_4 unit with a C_5 counterpart.



Scheme 16. Stereocontrolled synthesis of 9-*trans*-9-fluororetinal.



Scheme 17. Synthesis of retinoic acid and analogs.

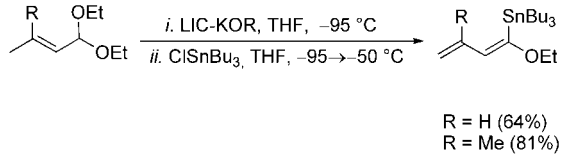


Scheme 18. Synthetic approach towards SNF4435.

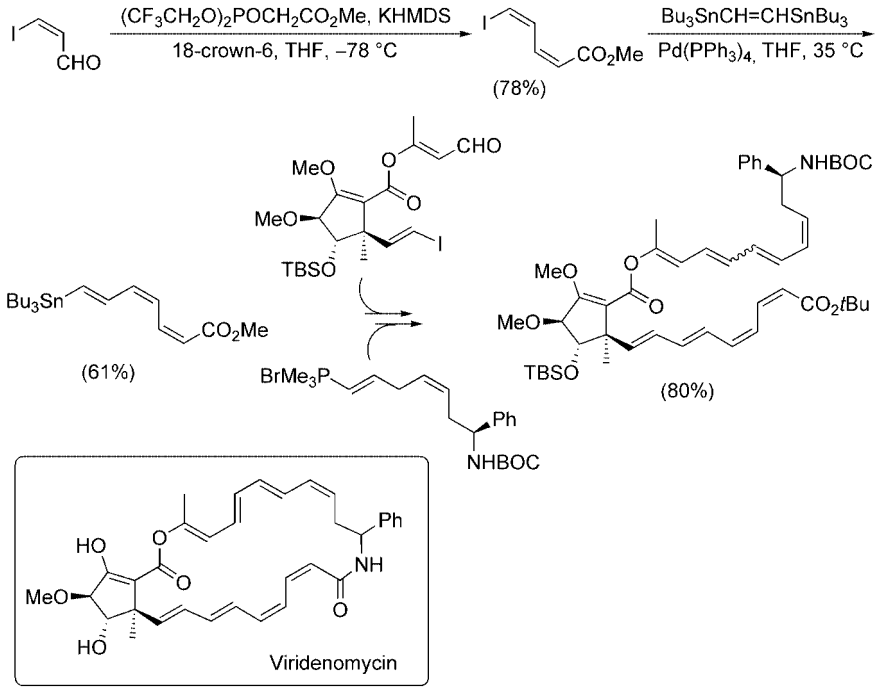
de Lera and colleagues have employed the experimental conditions developed by Farina [$Pd_2(dba)_3$, $AsPh_3$, NMP][38] for a Stille cross-coupling during the preparation of retinoic acid (Scheme 17),[32] and Trauner and Beaudry have carried out a tandem Stille coupling/electrocyclization cascade, in the presence of catalytic amounts of [$PdCl_2(MeCN)_2$], in order to prepare the precursor of the immunosuppressants SNF4435 C and SNF4435 D (Scheme 18).[34]

Mayers and colleagues have used a Stille coupling to instal the (*E*,*E*,*Z*,*Z*) tetraenic moiety during their studies directed towards the synthesis of viridenomycin (Scheme 19),[35] and Rychnovsky and Sinz have applied, for the first time, the Stille cross-coupling to the total synthesis of an oxo-polyene macrolide (Scheme 20).[36]

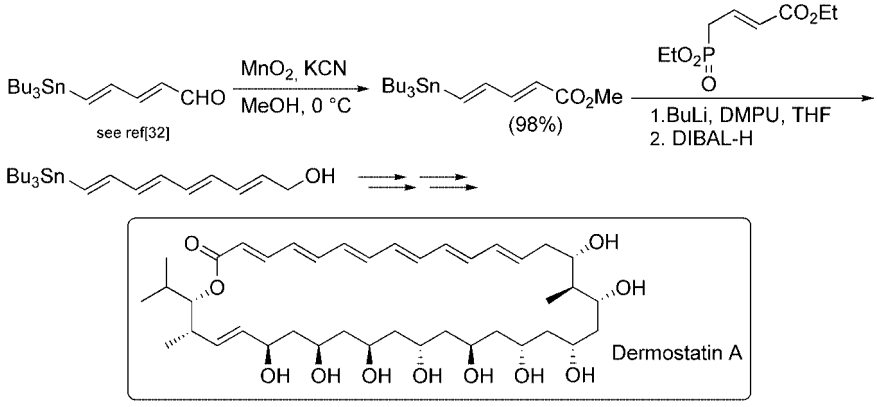
In our laboratory alkoxydienylstannanes have been obtained from the reaction between α-metalated alkoxy-1,3-dienes and chlorotributylstannane (Scheme 21).[39] The Stille reaction between these reactants and allyl bromide, iodobenzene, or benzoyl chloride has been performed, and



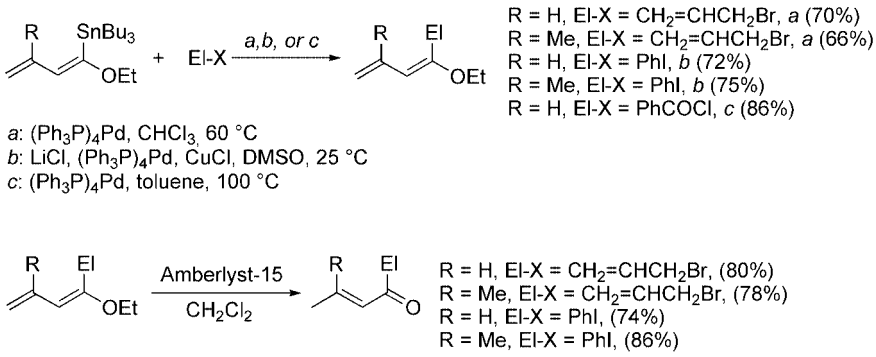
Scheme 21. Preparation of alkoxydienylstannanes.



Scheme 19. Synthetic approach towards viridenomycin.



Scheme 20. Total synthesis of dermostatin.

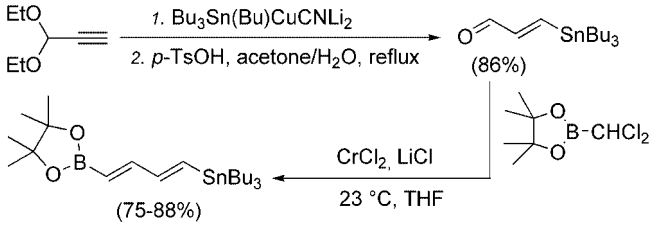


Scheme 22. Reactions of alkoxydienylstannanes with electrophiles.

the obtained cross-coupled derivatives have been further converted into carbonyl compounds (Scheme 22).

6. Conjugate Dienes and the Suzuki Cross-Coupling

Hetero-bis-metallo-1,3-dienes have recently been synthesized and used in a tandem Stille/Suzuki–Miyaura coupling.[40] Butadiene was effectively prepared from propargaldehyde diethyl acetal by stannylcupration followed directly by acetal hydrolysis to afford β-stannylacrolein. Takai olefination with dichloromethyl borinate then afforded the bis metalated diene in a 75% overall yield (Scheme 23).

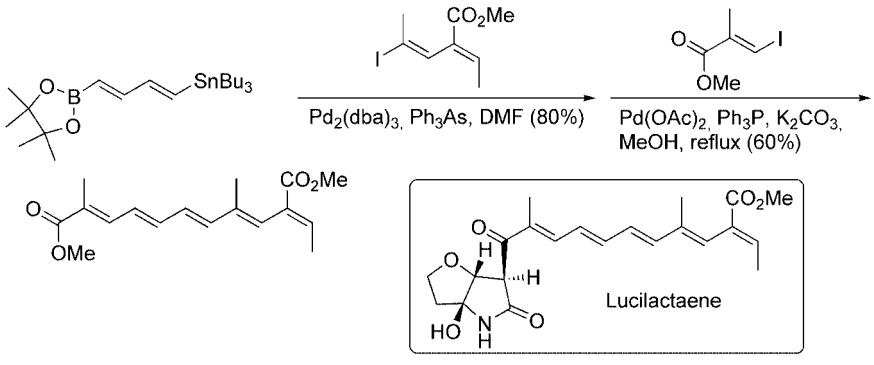


Scheme 23. Preparation of tin/boron 1,4-bis-metallo-1,3-butadiene.

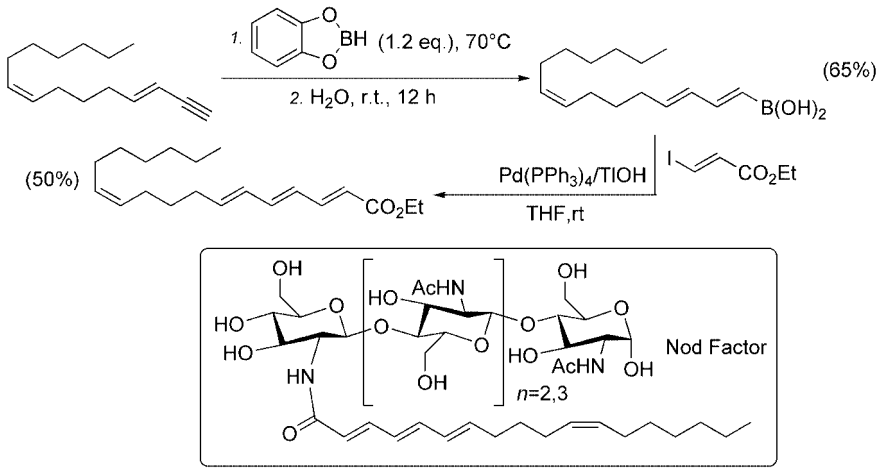
Selective coupling at the tin-bearing terminus of the bis-metallo-1,3-butadiene and at the boron-bearing end was possible as a consequence of the need for basic reaction conditions in the case of Suzuki cross-coupling. Moreover, tandem coupling was implemented in a sequential one-pot sequence, performing the Stille coupling with one partner followed by direct addition of CsF and the second Suzuki partner directly into the reaction flask. The authors performed an efficient two-step coupling to form the pentaene side-chain of the *Fusarium* metabolite lucilactaene (Scheme 24).

Nod factor is a lipochitooligosaccharide produced by *Rhizobium* bacteria that elicits the morphogenesis of plant root nodules in which atmospheric nitrogen is reduced to ammonia. Treilhou et al.[41] have synthesized the unsaturated fatty acid attached to the nonreducing terminal glucosamine, namely (2*E*,4*E*,6*E*,11*Z*)-octadecatetraenoic acid. To generate a trienic system by a highly stereoselective route, hydrometalation with catecholborane and cross-coupling reactions were used to obtain pure configuration (*E*)-olefins. The (*Z*) double bond was synthesized by a Wittig reaction (Scheme 25).

Bacteriorodopsin (BR), the light-harvesting protein found in the purple membrane of *Halobacterium salinarum*, uses *trans*-retinal as the chromophore responsible for light absorption. Upon replacing the native retinal by synthetic analogues, artificial protein–chromophore complexes are obtained. Two derivatives, both functionalized at C(13), show ground-state absorption spectra shifted to the red relative to native BR (λ_{max} = 568 nm), namely (13*Z*)-13-



Scheme 24. One-pot, two-step synthesis of the side-chain of the *Fusarium* metabolite lucilactene.



Scheme 25. Synthesis of (2*E*,4*E*,6*E*,11*Z*)-octadecatetraenoic acid.

bromo-13-desmethylretinal and (13*E*)-20,20,20-trifluororetinal. de Lera et al.[42] have performed the synthesis of the aforementioned retinal analogues by resorting to a convergent approach, which features Suzuki cross-coupling reactions involving the dienylboronic acid and the appropriate electrophiles as the key step.

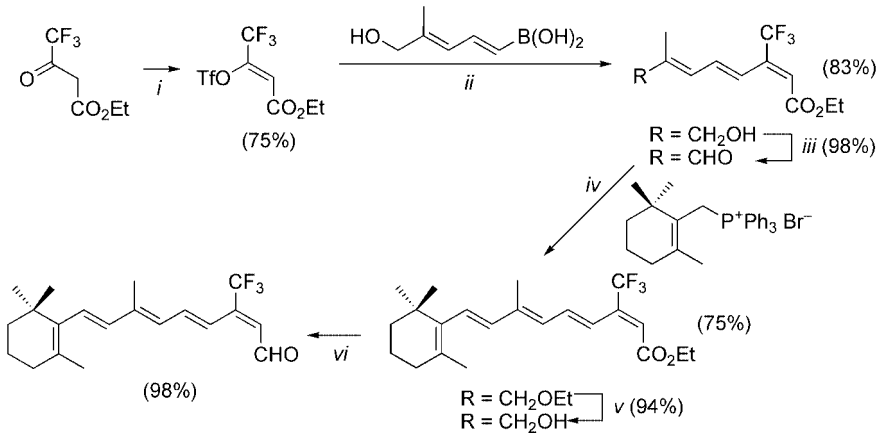
The Suzuki coupling of alkenyl-*gem*-dibromides has been shown to proceed stereoselectively due to the considerable rate difference between the bromide with (*Z*) or (*E*) configuration relative to the substituent, with the reaction proceeding in favour of the latter (Scheme 26).

As for the synthesis of (13*E*)-20,20,20-trifluoretinal, once more the key step is a Suzuki cross-coupling reaction between a dienylboronic acid and the appropriate vinyl triflate obtained from the corresponding β-keto ester. The right (*Z*) isomer triflate has been obtained in 75% using LiHMDS in THF/HMPA to generate the lithium enolate, followed by quenching of the reaction with Tf_2NPh (Scheme 27).

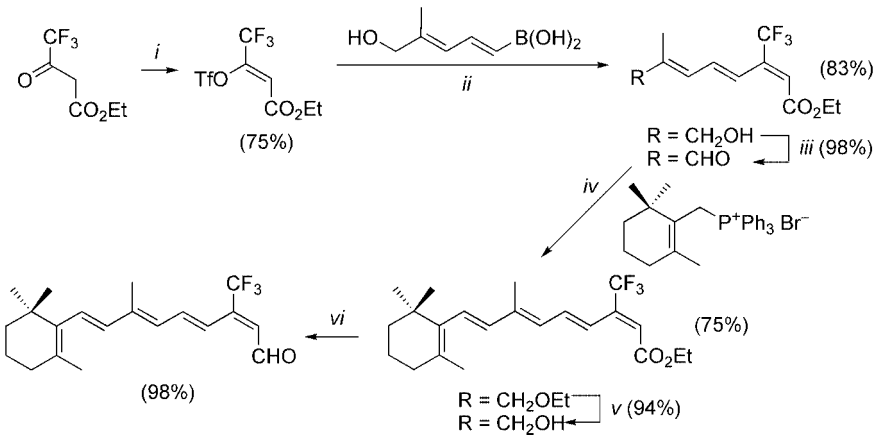
The highly selective nature of the Suzuki coupling allows the stereocontrolled synthesis of polyene skeletons. The trifluoromethylated building block, in particular, should prove useful in the preparation of trifluoromethylated organic molecules, which are known to have significantly different properties to the parent methylated compounds.

13-Aryl-substituted (11*Z*)-retinals have been prepared by a convergent methodology based on a Pd-catalyzed cross-coupling reaction between the appropriate aryl dienyliodide (Scheme 28 A) and a geometrically pure trienylboronic acid (Scheme 28 B).[43] The synthesis is shown in Scheme 29.

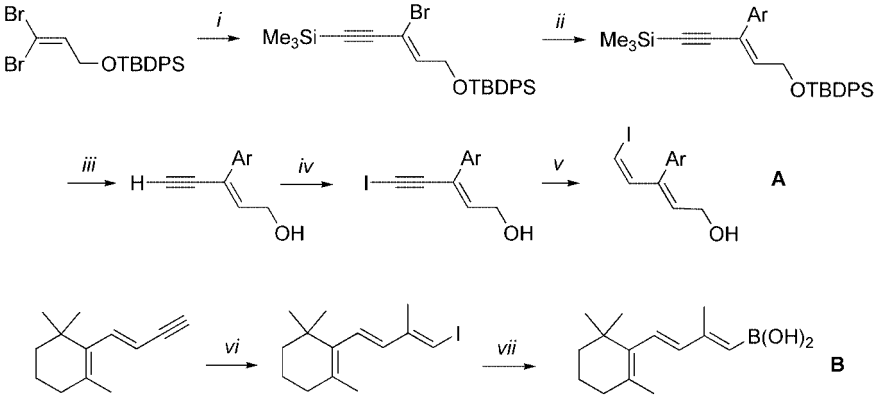
Barret et al.[44] have developed an efficient synthesis of restrictinol from commercially available starting materials in which the triene side-chain is introduced in a geometrically pure form in a Pd^0 coupling reaction (Scheme 30). This family of compounds have been the subject of considerable interest and several syntheses have been published, in all of which the triene side-chain is introduced by car-



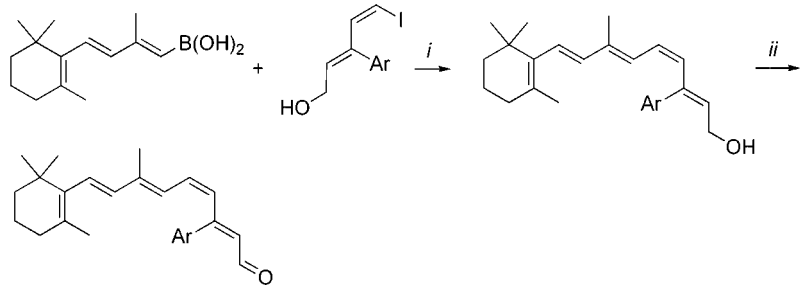
Scheme 26. Synthesis of (13*Z*)-13-bromo-13-desmethylretinal. Reagents and conditions: *i*. PPh_3, CBr_4, CH_2Cl_2, 25 °C (75%); *ii*. dienylboronic acid, [$Pd(PPh_3)_4$], 10% aq. TlOH, THF, 25 °C (88%); *iii*. MnO_2, CH_2Cl_2, 25 °C (98%); *iv*. phosphonium salt, BuLi, THF, –30→0 °C (87%); *v*. Bu_4NF, THF, 25 °C (80%); *vi*. MnO_2, CH_2Cl_2, 25 °C (98%).



Scheme 27. Synthesis of (13*E*)-20,20,20-trifluororetinal. Reagents and conditions: *i*. LiHMDS, Tf_2NPh (75%); *ii*. $[Pd(PPh_3)_4]$, Na_2CO_3, DME, 80 °C (83%); *iii*. MnO_2, DCM, 25 °C (98%); *iv*. BuLi, THF, –30 °C→0 °C (75%); *v*. DIBAL-H, THF, –78→0 °C (94%); *vi*. MnO_2, DCM, 25 °C (98%).



Scheme 28. Synthesis of dienyliodide (A) and trienylboronic acid (B). Reagents and conditions: *i*. trimethylsilylacetylene, cat. $[PdCl_2(dppf)]$, CuI, *i*PrNH, benzene; *ii*. $ArB(OH)_2$, cat. $[PdCl_2(dppf)]$, Na_2CO_3, THF; *iii*. TBAF, THF; *iv*. I_2, morpholine, benzene; *v*. KOOCN=NCOOK, AcOH, THF; *vi*. 1. $Bu_3SnMgMe$, cat. CuCN, THF then MeI; 2. I_2, DCM or 1. $[Cp_2ZrCl_2]$, $AlMe_3$, $ClCH_2CH_2Cl$ then I_2; *vii*. 1. BuLi, –78 °C, THF; 2. $B(OiPr)_3$, –20 °C, THF, room temp., then purification by silica gel column chromatography.

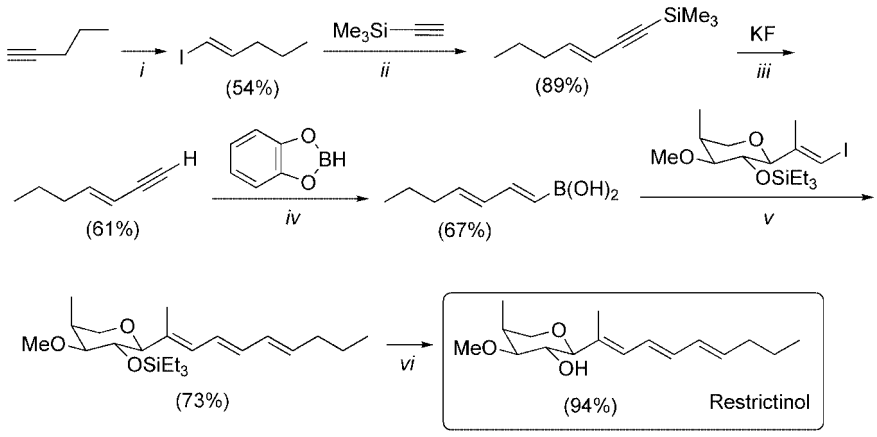


Scheme 29. Synthesis of 13-aryl-(11*Z*)-retinal. Reagents and conditions: *i*. cat. $[Pd(PPh_3)_4]$, aq. KOH, Ag_2CO_3, THF; *ii*. $Ba(MnO_4)_2$, DCM.

bonyl olefination chemistry (Wittig, Horner–Emmons, or Julia olefination) to afford mixtures of geometric isomers.

The key step is a Suzuki cross-coupling where a mixture of vinyl iodide and boronic acid is allowed to react with TlOH (10% aq) and $[Pd(PPh_3)_4]$ in THF to afford the coupling products in 73% yield. Subsequent deprotection with Bu_4NF afforded restrictinol.

A dienylboronic acid has been used in a Suzuki reaction with a range of vinyl and aryl halides in the presence of TlOEt, which proved to be an excellent alternative to TlOH



Scheme 30. Synthesis of restrictinol. Reagents and conditions: *i*. 1. DIBAL-H, hexane, 55–60 °C, 4 h; 2. I_2, THF, –78 → 0 °C; *ii*. BuLi, $ZnCl_2$, $[Pd(PPh_3)_4]$, THF, –78 → 20 °C; *iii*. KF, DMF, H_2O, 2 h; *iv*. catecholborane, THF, 70 °C, 24 h; *v*. TlOH 10% aq., $[Pd(PPh_3)_4]$, THF, 12 h; *vi*. Bu_4NF, THF, 2 h.

in terms of stability and ease of use. These reaction conditions seem to be less effective with arylboronic acids (Scheme 31).[45]

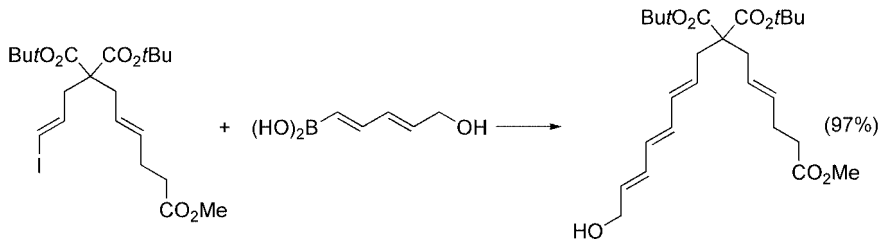
Spinosyn A is a member of a group of natural products that possess perhydro-*as*-indacene ring systems. The spinosyn family displays very potent insecticidal activity. Their synthesis was inspired by the hypothesis that the biosynthetic pathway involves a transannular Diels–Alder reaction of an appropriately substituted (*E*,*E*,*E*)-cyclodeca-1,6,8-triene.[46] The authors proposed the synthesis of the tricyclic core of spinosyn A by a route involving the tandem ring contraction/transannular Diels–Alder reaction of a macrolactone whose synthesis involves a Pd^0-catalysed cross-coupling between a dienylboronic acid and a substituted vinyl dibromide (Scheme 32). The boronic acid was prepared in 81% yield by hydroboration of the corresponding acetylene with 2.2 equivalents of catecholborane and used immediately in the following step. The dibromoalkene was then treated with three equivalents of boronic acid, 1.8 equivalents of TlOEt, and a catalytic amount of $[Pd(PPh_3)_4]$ in aqueous THF (3:1) to afford the desired conjugate (*Z*)-triene with excellent stereoselectivity.

Dienylboronates have been used in a three-component tandem Vaultier sequence in the diastereoselective synthesis of an advanced Clerodin intermediate (Scheme 33).[47] Clerodin is one of the most active members of an important class of diterpenes, Clerodanes, and has potential use in the protection of crops. The establishment of the correct relative configurations at centres C(9) and C(11) is the major problem in the choice of the synthetic strategy. The sequence proposed by the authors allows the preparation of the alcohol intermediate with complete control over the relative configuration at C(9) and C(11).

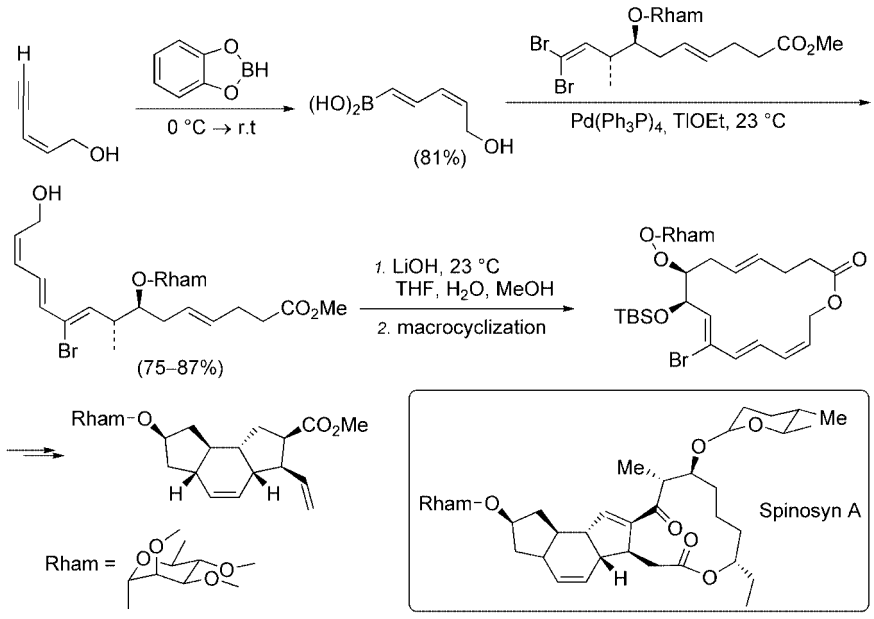
Stereochemically pure (*E*)-alkoxydienylboronates could be easily prepared from α,β-unsaturated acetals through a conjugate eliminative process promoted by LIC-KOR superbase.[48] Thus, in a typical procedure treatment of crotonaldehyde diethyl acetal at –95 °C with LIC-KOR readily gives the α-metalated alkoxy alkene. Triisopropylborate was then added as electrophile. Aqueous workup of the reaction mixture afforded the boronic acid intermediate, which was converted into the more stable cyclic derivative by esterification in the presence of 2,2-dimethyl-1,3-propandiol or pinacol (Scheme 34).

Dienylboronates have proved to be useful substrates for the Suzuki–Miyaura cross-coupling reaction, and various aryl halides and triflates have been successfully coupled under very mild experimental conditions. Furthermore, the method proposed allows additional synthetic modifications such that the sequence "cross-coupling and hydrolysis" corresponds to a two-step carbonylative coupling (Scheme 35).

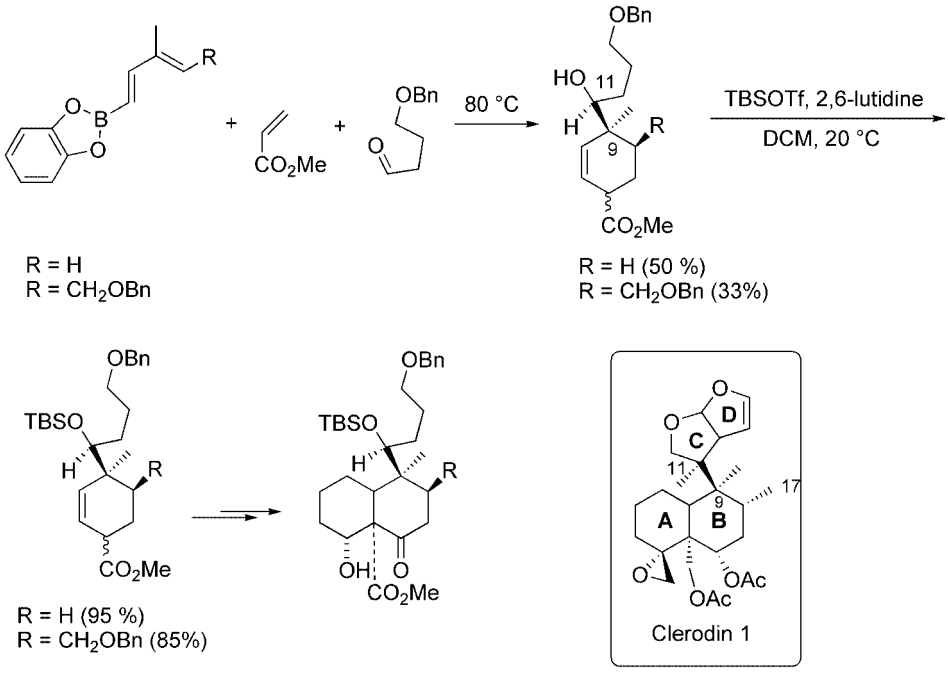
Alkoxydienylboronates have been coupled with *N*-alkoxycarbonyl triflates derived from six- and seven-membered lactams in order to introduce masked acyl functionality to the heterocyclic moiety.[49] Hydrolysis of the coupling products, performed with Amberlyst-15, resulted in a Nazarov-type[50] cyclization that afforded hexahydro[1]pyri-



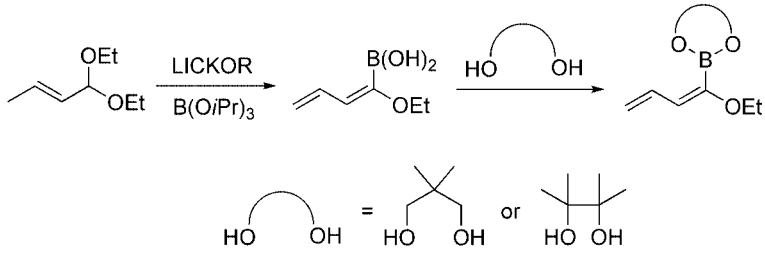
Scheme 31. Suzuki cross-coupling in the presence of TlOEt. Reagents and conditions: boronic acid (5 equiv.), 10% $[Pd(PPh_3)_4]$, TlOEt (1.8 equiv.), THF/H_2O (3:1).



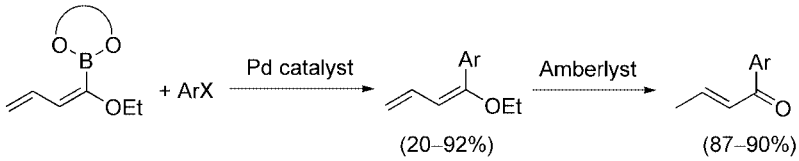
Scheme 32. Synthesis of the perhydro-*as*-indacene nucleus of spinosyn A.



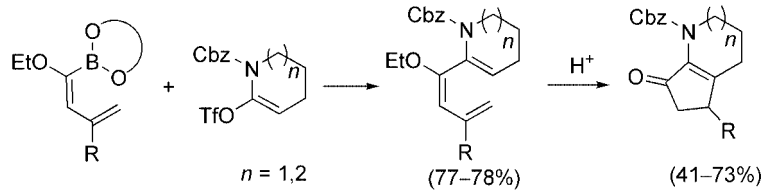
Scheme 33. Three-component tandem Vaultier cyclization towards Clerodin 1.



Scheme 34. Synthesis of alkoxyboronates.



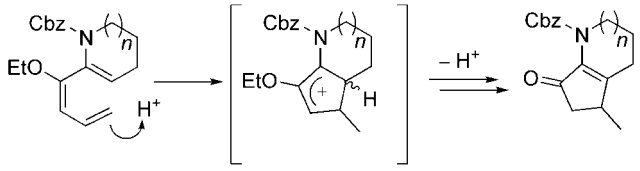
Scheme 35. Suzuki–Miyaura cross-coupling reactions of dienylboronates.



Scheme 36. Pd-catalyzed cross-coupling between alkoxyboronates and lactam-derived triflates.

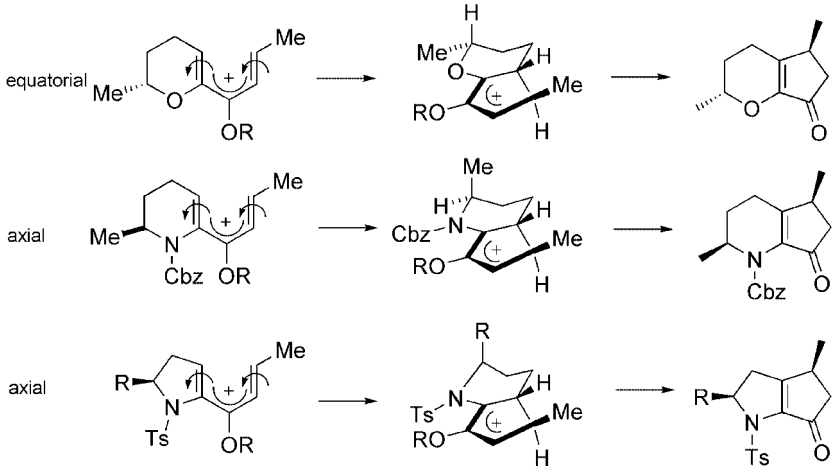
din-7-ones and 3,4,5,6,7,8-hexahydro-(2*H*)-cyclopenta[*b*]-azepin-8-ones (Scheme 36).

The formation of the cyclic structure can be accounted for by the initial protonation of the distal double bond, followed by an immediate Nazarov-type electrocyclization (Scheme 37).

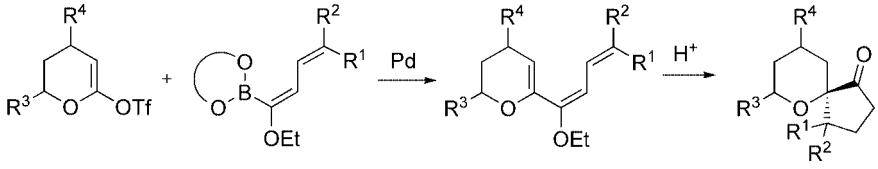


Scheme 37. Nazarov cyclization of ethoxydienyl derivatives.

The proposed methodology has been extended to lactone-derived triflates and phosphates, thereby allowing the synthesis of cyclopenta-fused N- and O-containing heterocycles.[51,52] In particular, the role of the heteroatom and the size of the ring have been investigated. Five-membered azacycles require more drastic conditions to give 5-5 fused systems: the electrocyclization process, in fact, takes place only on the divinyl ketone intermediate in the presence of TFA. However, six- and seven-membered heterocycles undergo cyclization under very mild conditions. An interesting aspect of this synthetic route is the torquoselectivity of the Nazarov cyclization. The reaction is highly diastereoselective: 2-substituted five-membered lactams and 2- and 4-substituted six-membered derivatives lead to *cis* disubstituted cyclopentafused systems. In the case of 2-methyl-δ-valerolactone the authors observed high diastereoselectivity, but in this case the *trans* product was predominantly formed. The cyclization may be accounted for by a conrotatory process that involves the less-hindered face of the endocyclic double bond. As shown in the scheme, the experimental results obtained are explained by assuming that a counterclockwise conrotation is favoured. Stereoelectronic effects could presumably play a role through a better orbital overlap in the transition state, even though this involves a boat-like conformation of the heterocyclic six-membered ring. The mechanism is the same both for 2-methyl lactam and for 2-methyl lactone, with different diastereoisomers arising from the different conformation of the pentadienyl cation intermediate: for lactam derivatives the methyl in the 2-po-



Scheme 38. Torquoselectivity in the Nazarov cyclization.



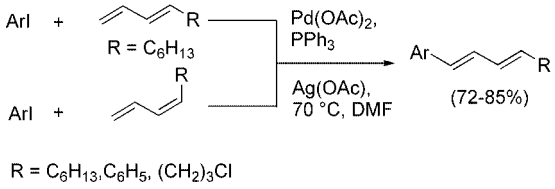
Scheme 39. Synthesis of spirocyclic ketones by a Nazarov reaction.

sition is forced to assume an axial orientation due to the presence of the bulky protecting group on N, whereas in the case of the δ-lactone the methyl in the 2-position is equatorial (Scheme 38).

Alkoxydienyl lactone derivatives *gem*-disubstituted on C(4) exhibit a different mode of Nazarov cyclization that leads to spirocyclic ketones (Scheme 39).[53] The formation of the spiro compounds can be explained by initial protonation of the endocyclic double bond to give a pentadienyl cation with the electronic arrangement necessary to give a Nazarov reaction. In this case the reaction also proved to be highly diastereoselective. With 2-alkyl-substituted dihydropyran rings, diastereopure compounds were obtained. The stereochemistry was assigned by NMR NOE experiments and by X-ray analysis.

7. Conjugated Dienes and the Heck Reaction

Few examples of conjugated polyenes prepared by arylation and vinylation of dienes have been reported in the literature. Normally, low yields and/or low stereoselectivity are encountered when the diene does not bear an activating substituent due to the formation of stable π-allylpalladium complexes in the presence of tertiary amines. A synthesis of (*E*,*E*) conjugated dienic aromatics has been proposed by Jeffery.[54] The reaction was reported to be highly chemo- and regiocontrolled: various functionalized aromatic halides and dienes were used and the bond formation occurred at the diene terminal carbon (Scheme 40).

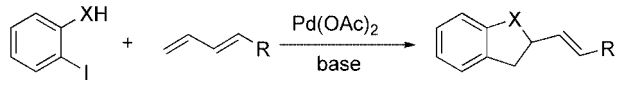


Scheme 40. Arylation of 1,3-dienes.

The coupling reaction is not stereospecific with respect to the diene, but, interestingly, it leads to a highly selective formation of (*E*,*E*) dienes irrespective of the (*E*) or (*Z*) geometry of the starting diene. These results have been rationalized by proposing the formation of unstable cationic palladium intermediates with a rapid interchange between *anti* and *syn* π-allyl cationic palladium complexes. The subsequent β-hydrogen elimination step proceeds selectively from the σ-palladium complex derived from the *syn* π-allyl complex, irrespective of the configuration of the starting diene.

The arylation of 1,3 dienes has also been described by Mane et al., using Amberlite IRA-400 (basic) as a base (Scheme 41).[55]

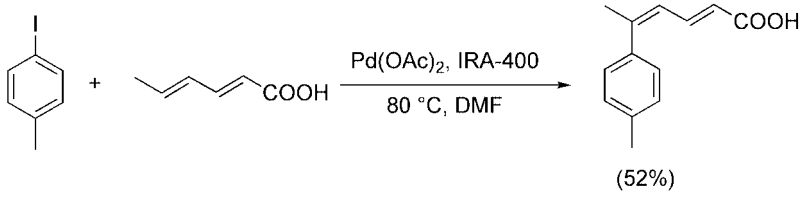
Conjugated 1,3-dienes react with aryl halides and nucleophiles by a cascade process, and many examples of palladium-catalyzed annulations of dienes have been reported by the Larock group (Scheme 42).[56]



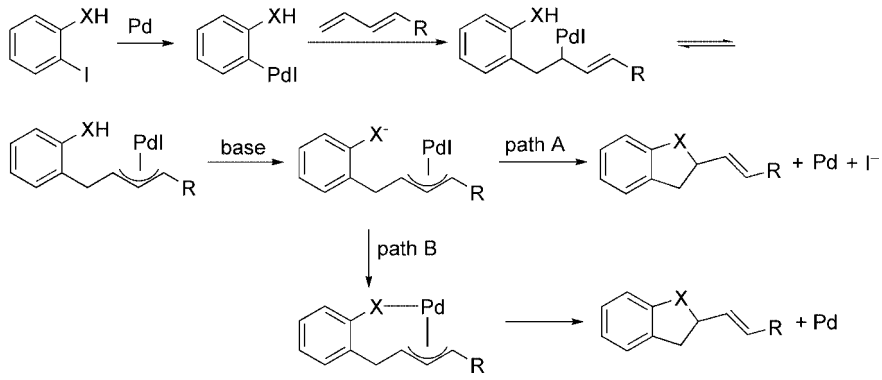
Scheme 42. Pd-catalyzed annulation.

The annulation proceeds by: (i) reduction of the Pd^{II} salt to Pd^0; (ii) oxidative addition of the aryl halide to Pd^0; (iii) arylpalladation of the carbon–carbon double bond to initially produce a σ-allylpalladium intermediate, which rapidly rearranges to the more stable π-allylpalladium intermediate; and (iv) nucleophilic displacement of palladium by the internal nucleophile (Scheme 43). The authors have proposed that the displacement step might involve either backside attack of the nucleophile on the π-allylpalladium carbon, or frontal attack at the metal, followed by reductive elimination of Pd^0. Both mechanisms for π-allylpalladium substitution are well known, and the actual pathway depends on the geometry of the intermediates and the nature of the nucleophile effecting the substitution.

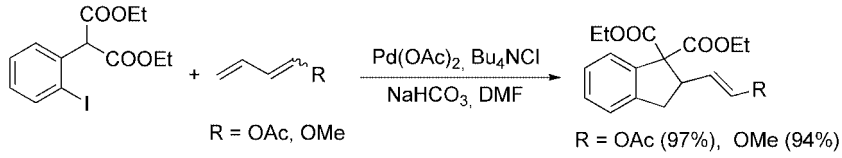
This reaction has been widely exploited in order to prepare carbonyl compounds starting from oxygen-substituted 1,3-dienes (an example is shown in Scheme 44), and many biologically and pharmaceutically important substances,



Scheme 41. Coupling in the presence of IRA-400 as a base.



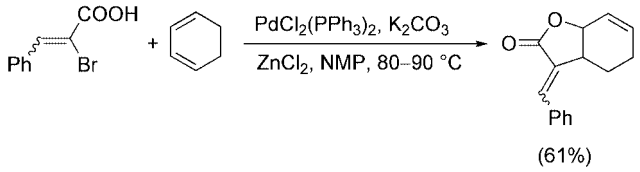
Scheme 43. Mechanism of annulation.



Scheme 44. Annulation of oxygen-substituted 1,3-dienes.

such as dihydrofurocoumarins and dihydrofuroflavonoids, have been synthesized according to this method.[57]

Iyer, Larock, and co-workers have reported that the heteroannulation of 1,3-dienes with α-halo acrylic acids affords α-alkylidene-γ-butyrolactones in a regio- and stereoselective manner (Scheme 45).[58] The reaction occurs predominantly at the less-hindered terminus of the diene, and when acyclic dienes were used the (*E*) isomer was the major product. The bicyclic lactones formed from cyclohexadiene show a *cis* junction. The role of sterically hindered, electron-rich phosphane ligands such as D-*t*-BPF [(di-*tert*-butylphosphanyl)-ferrocene] is very important. The exact role of this ligand is uncertain, but it is likely to prevent any unwanted coordination between the vinylpalladium species and the neighbouring carboxylic acid.



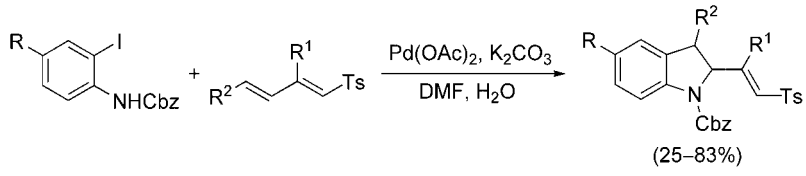
Scheme 45. Synthesis of γ-butyrolactones.

When unsaturated sulfones were coupled with *N*-Cbz-*o*-iodoanilines, 2-substituted indolines have been produced (Scheme 46).[59] The products are potential intermediates for synthetic routes to a variety of biologically interesting target compounds containing the indoline or, after oxidation, the corresponding indole moiety. The reaction tolerates both electron donating and withdrawing groups at the 4-position of the aniline, although the most rapid rate was observed with the electron-withdrawing ester substituent.

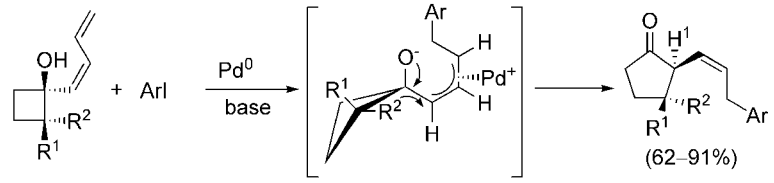
The ring rearrangement of vinylcyclobutanol derivatives, promoted by transition metals has been described as a valuable method for the construction of substituted five-membered ring systems. When the Pd-catalyzed cascade insertion-ring expansion involve 1,3-dienylcyclobutanols and aryl iodides, various substituted cyclopentanones were synthesized in a stereospecific manner, as shown in Scheme 47.[60]

Shibasaki and co-workers exploited a cascade asymmetric Heck reaction-carbanion capture process in order to synthesize various capnellenols and for the total synthesis of capnellene. They have developed a method for the catalytic asymmetric synthesis of bicyclo[3.3.0]octane derivatives with asymmetric induction up to 94% *ee*.[61] A catalytic asymmetric cyclization of a prochiral alkenyl triflate in the presence of a variety of carbanion was described (Scheme 48).

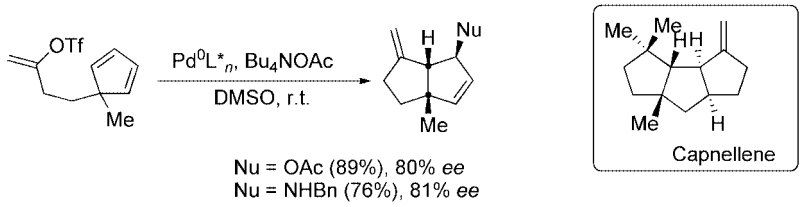
An enantioselective domino Heck-allylic amination reaction with α,ω-amino-1,3-dienes was proposed by Helmchen et al.[62] Phosphanyl-oxazolines were used as chiral ligands. (Scheme 49).



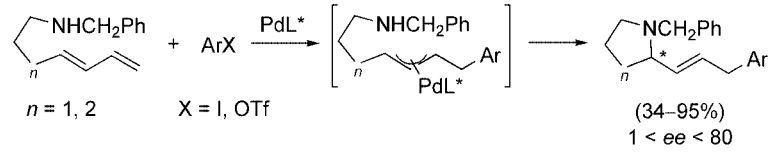
Scheme 46. Palladium catalyzed cyclization of 1- sulfonyl-1,3-dienes.



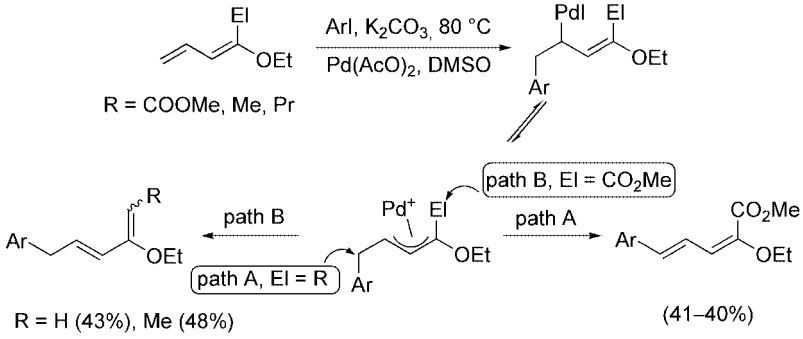
Scheme 47. Ring expansion of dienylcyclobutanols.



Scheme 48. Synthesis of capnellenols.



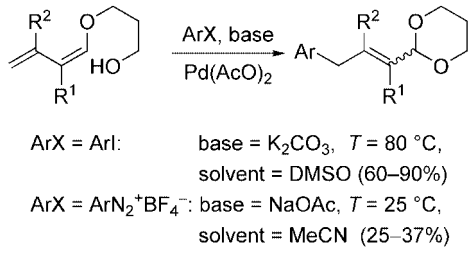
Scheme 49. Enantioselective domino Heck-allylic amination.



Scheme 50. Arylation of 1-alkoxy-1,3-dienes.

We have reported that 1-alkoxybuta-1,3-dienes can be arylated in the presence of a Pd^0 catalyst affording, after hydrolysis, γ-arylated carbonyl derivatives in a regio- and stereoselective manner.[63] The cross coupling reaction can produce the arylated products via path A or via path B, depending on the nature of the substituent bonded to the C(1) of the dienic system (Scheme 50).

When the coupling reaction was carried out on the alkoxy dienes obtained from cyclic acetals, a domino Heck-nucleophilic substitution promoted by the hydroxy group present in the molecule is the favourite pathway (Scheme 51). The process formally leads to the γ-arylation of the α,β-unsaturated protected carbonyl compound with good yields (60–90%). Alkoxy dienes have also been placed to react with arenediazonium salts to give the Heck arylation products (Scheme 51).[64] The use of these reagents could be in many cases synthetically convenient, since aryl iodides are prepared from diazonium salts.



Scheme 51. Domino Heck-nucleophilic substitution.

The suggested mechanism involves the addition of the arylpalladium intermediate to the terminal bond of the diene followed by the arrangement to the π-allylic complex and the iodide–acetate ligand exchange. Finally, the attack of the hydroxy group upon the complex displaces the palladium complex affording the cyclic acetal.

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