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The Impact of the Mukaiyama Aldol Reaction in Total Synthesis

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*Dedicated to
Professor Teruaki Mukaiyama*

aldol reaction · enolates · natural products · polyketides · stereocontrol

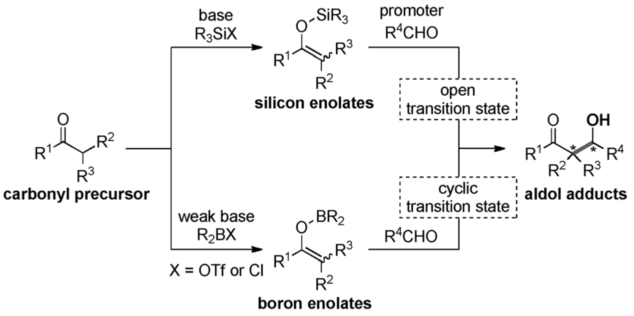
Four decades since Mukaiyama's first reports on the successful application of silicon and boron enolates in directed aldol reactions, the ability of this highly controlled carbon–carbon bond-forming method to simultaneously define stereochemistry, introduce complexity, and construct the carbon skeleton with a characteristic 1,3-oxygenation pattern has made it a powerful tool for natural product synthesis. This Minireview highlights a number of representative total syntheses that demonstrate the impact of the Mukaiyama aldol reaction and discusses the underlying mechanistic rationale that determines the stereochemical outcomes.

1. Introduction

The ability to forge new carbon–carbon bonds in a regio-, stereo-, and enantioselective manner is of paramount importance in organic synthesis. Since the seminal reports of the use of boron enolates[1] (1971) and silicon enolates[2] (1973) by Mukaiyama and co-workers, the aldol reaction has evolved into one of the most powerful methods, excelling especially in controlling acyclic stereochemistry.[3] The mild reaction conditions, along with the high levels of predictable stereocontrol, directly facilitate the efficient assembly of complex polyoxygenated natural products, particularly those of polyketide origin.[4]

The directed aldol reaction forms a bond between a preformed enolate and a carbonyl compound, such as an aldehyde or a ketone, to give rise to a β-hydroxy carbonyl compound and introduce one or two stereocenters (Scheme 1). Among the various protocols available, the most straightforward method to generate an enolate intermediate is from a carbonyl precursor. A silicon enolate can be obtained by deprotonating a suitable carbonyl compound with a strong base followed by treatment with a trialkylsilyl chloride. For ketones, a combination of tertiary amine and trimethylsilyl chloride or triflate is also effective for regiocontrolled enolization. Usually isolated, the silicon enolate can then participate in an aldol addition with another carbonyl compound in the presence of a suitable promoter (often a Lewis acid) via an open transition state.[5] A boron enolate is more reactive and is typically generated in situ by treatment of a carbonyl precursor with a boron Lewis acid and a weak amine base.[6] The ensuing enolate can then directly undergo an aldol addition with an aldehyde partner via a highly ordered cyclic transition state,[7] to result in a predictable stereochemical outcome that often complements the silicon-mediated aldol reaction. In particular, the close correlation between the enolate geometry and the product stereochemistry (*Z* enolates give *syn* aldol adducts, *E* enolates give *anti* aldol adducts) makes the boron-mediated aldol reaction particularly powerful.[8]

In their 1976 paper,[1d] Mukaiyama and Inoue foresaw that the boron-mediated aldol reaction "would provide a practically useful tool in organic synthesis, because of its mild



Scheme 1. The directed aldol reaction employing silicon or boron enolates. Tf = trifluoromethylsulfonyl.

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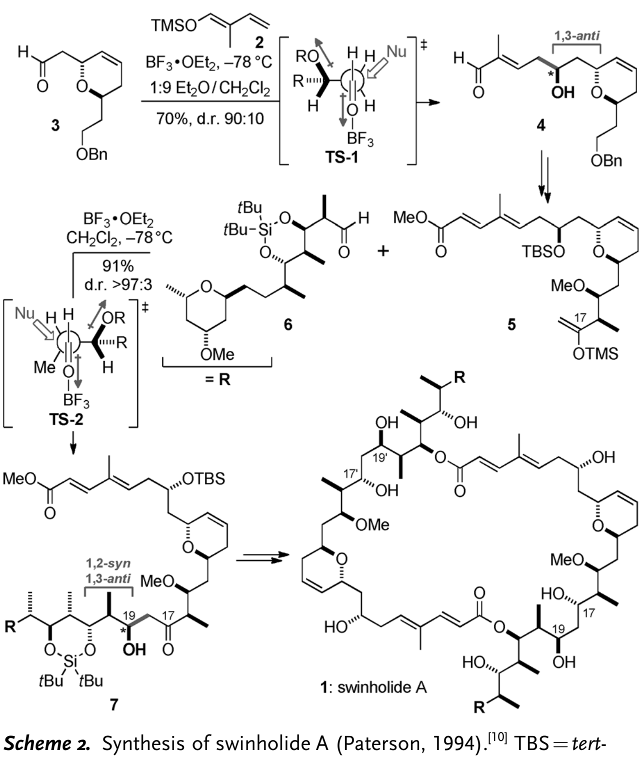
reaction conditions, the simplicity of the procedure and high regiospecificity". Indeed, the robustness of the transformation, together with mechanistic understanding, has allowed predictably high levels of stereocontrol to be achieved in complex settings. In this Minireview, we discuss the various controlling influences in silicon- and boron-mediated aldol reactions in the context of selected natural product total syntheses.

2. Diastereoselective Aldol Reactions with Silicon Enolates

2.1. Control by Chiral Aldehydes through 1,2- and 1,3-Stereoinduction

A powerful approach to achieve highly diastereoselective aldol reactions with silicon enolates is to use a chiral aldehyde partner to control the configuration of the newly generated stereocenters by 1,2- or 1,3-asymmetric induction.[9] Importantly, this strategy excels even in complex molecular settings, thus providing a predictable method for realizing key fragment couplings in challenging natural product syntheses. Two illustrative examples of this concept are apparent in the Paterson group's total synthesis of swinholide A (**1**, Scheme 2), a C_2-symmetrical marine macrodiolide that exhibits potent cytotoxic activity through disruption of the actin cytoskeleton.[10]

Firstly, a vinylogous Mukaiyama aldol reaction of dienolate **2** with β-alkoxy aldehyde **3** promoted by the monocoordinating Lewis acid $BF_3{\cdot}OEt_2$ gave adduct **4** (70%, 90:10 d.r.), which arose through 1,3-stereoinduction in open transition state **TS-1**, as rationalized by the Evans polar model based on opposed dipoles.[11] At a later stage, a pivotal Mukaiyama aldol fragment coupling established the full carbon backbone and oxygenation pattern of the monomeric swinholide seco acid. In the event, treatment of methyl ketone derived silicon enolate **5** and aldehyde **6** with $BF_3{\cdot}OEt_2$ at −78 °C led to a clean and rapid aldol addition, which provided adduct **7** in excellent yield and diastereoselectivity (91%, >97:3 d.r.). The efficient acyclic stereocontrol arises here from a cooperative inducing effect from the α- and β-stereocenters in aldehyde **6**; the combination of Felkin–Anh control and opposed dipoles results in complete π-facial bias in **TS-2**. The configuration of the newly generated hydroxy-substituted stereocenter was then relayed to the adjacent ketone by a 1,3-*syn* Narasaka reduction[12] to secure the C17 and C17′ stereocenters of swinholide A.



Scheme 2. Synthesis of swinholide A (Paterson, 1994).[10] TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

Diastereoselective aldol reactions controlled by chiral aldehydes can also be achieved with silicon enolates derived from ethyl ketones. This was demonstrated by Taylor,

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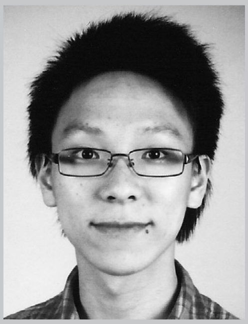
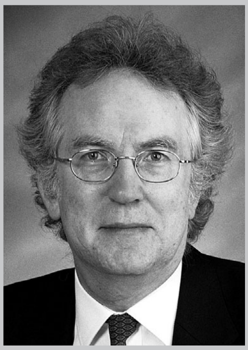
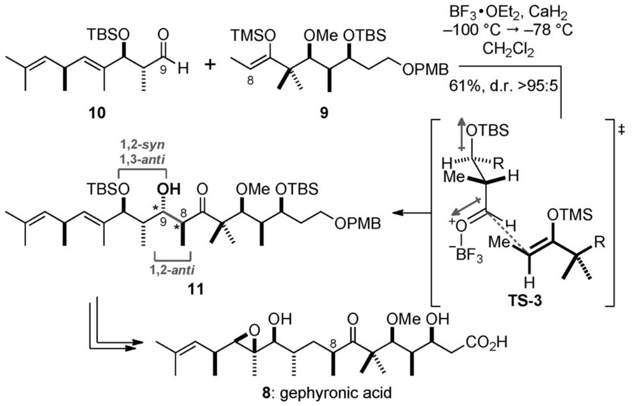


Kenneth Ng received his B.A. and M.Sc. degrees in 2010 from the University of Cambridge where he performed undergraduate research under the supervision of Dr. Christopher Cordier and Professor Ian Paterson. He is currently a third-year graduate student in the Paterson group where his studies focus on the total synthesis of bioactive natural products.



Ian Paterson received his B.Sc. degree from the University of St. Andrews and Ph.D. from the University of Cambridge, working with Professor Ian Fleming. After a postdoctoral period with Professor Gilbert Stork at Columbia University, he joined the faculty at University College London. In 1983, he returned to Cambridge, where he is now Professor of Organic Chemistry and a Fellow of Jesus College. His research interests are centered on novel synthetic methods for the efficient control of stereochemistry and the total synthesis of bioactive natural products, particularly anticancer agents. His research achievements have been recognized by various awards, and he was elected as a Fellow of the Royal Society (2005) and the Royal Society of Edinburgh (2010).

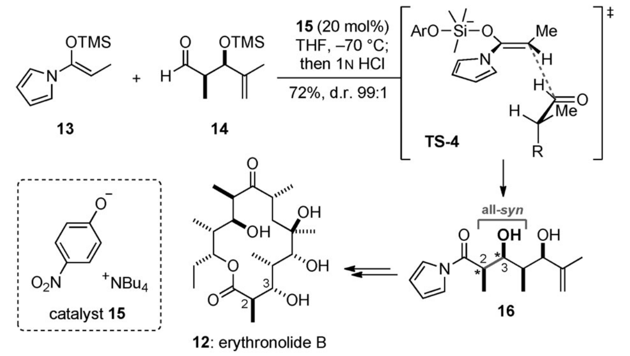
Laschat, and co-workers who reported the synthesis of gephyronic acid (**8**, Scheme 3), a potent inhibitor of eukaryotic protein synthesis.[13] In this context, *Z* silicon enolate **9** underwent a BF$_3$·OEt$_2$-mediated aldol reaction with aldehyde **10** to give C8,C9-*anti*-adduct **11** (> 95:5 d.r.). This outcome is consistent with the addition proceeding via **TS-3**, an open transition state based on the Felkin–Anh and Evans polar models. Reductive removal of the C9 alcohol by a Barton–McCombie deoxygenation then provided an intermediate suited to completing the synthesis of gephyronic acid.



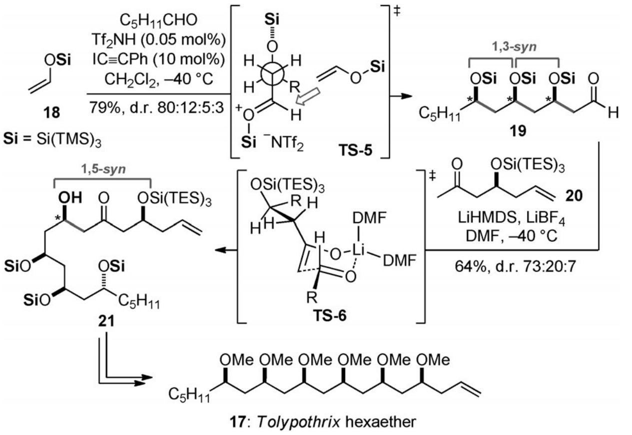
Scheme 3. Synthesis of gephyronic acid (Taylor and Laschat, 2011).[13] PMB = *para*-methoxybenzyl.

Diastereoselective aldol reactions of silicon enolates mediated by Lewis bases[14] have also found applications in complex polyketide synthesis, and are useful for configuring *syn* propionate units. Towards this end, Nelson and co-workers[15] have reported their use in the total synthesis of erythronolide B (**12**, Scheme 4). Thus, an aldol coupling between enolate **13** and α-chiral aldehyde **14** facilitated by Lewis base catalyst **15** cleanly provided all-*syn* adduct **16** (72 %, 99:1 d.r.) via open transition state **TS-4** with complete Felkin–Anh control. Tetrabutylammonium *p*-nitrophenoxide (**15**) possesses the optimal Lewis basicity to promote the desired aldol addition without epimerizing the α-chiral aldehyde **14**.

The π-facial selectivity of a β-oxygenated aldehyde can be fine-tuned or even overturned by a judicious choice of protecting group on the oxygen atom.[16] A reversal in the normal 1,3-stereoinduction is exemplified in the synthesis of *Tolypothrix* hexaether (**17**, Scheme 5) in racemic form by Yamamoto and co-workers. In the event, hexanal was treated with tris(trimethylsilyl)silicon enolate **18** in the presence of triflimide and iodophenylacetylene to preferentially provide the triple adduct **19** with an all-*syn* configuration (79 %, 80:12:5:3 d.r.) via postulated **TS-5**. To further demonstrate the utility of their "super-silyl" method, aldehyde **19** was subjected to a double-stereodifferentiating aldol reaction with the lithium enolate of the β-tris(triethylsilyl)siloxy methyl ketone **20** to give predominantly 1,5-*syn*-adduct **21** (64 %, 73:20:7 d.r.), whereby the stereochemical outcome was rationalized by **TS-6**.[16b]



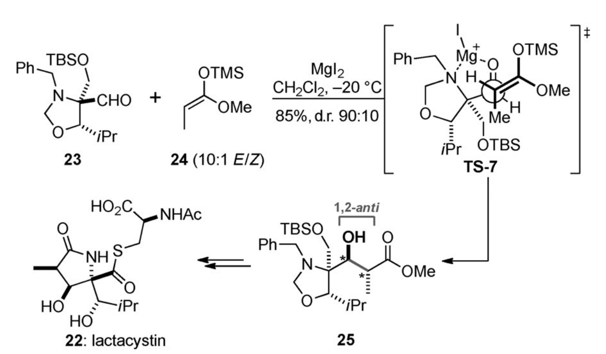
Scheme 4. Synthesis of erythronolide B (Nelson, 2010).[15]



Scheme 5. Synthesis of *Tolypothrix* hexaether (Yamamoto, 2011).[16] DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, TES = triethylsilyl.

2.2. Diastereoselectivity Arising from Chelation

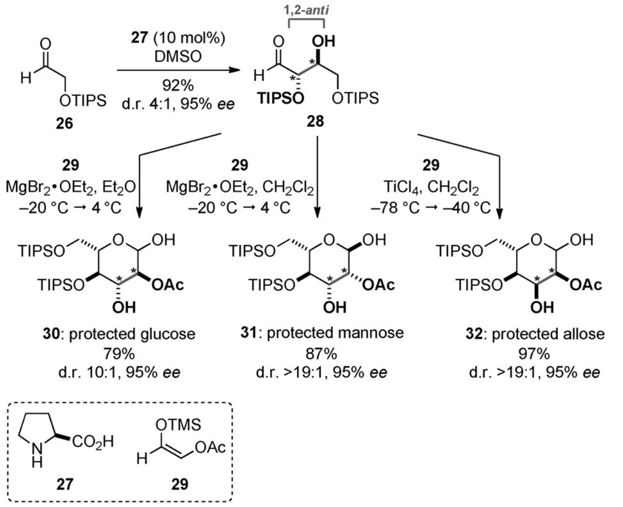
By using Lewis acids that possess multiple coordination sites, heteroatom-substituted substrates can undergo chelation-controlled aldol reactions to afford adducts with a reversal of π-facial selectivity compared to the nonchelation reaction.[2d] An example of this concept was shown by Corey and co-workers in their synthesis of lactacystin (**22**; Scheme 6),[17] a microbial natural product that affects the turnover of misfolded and denatured proteins. The aldol



Scheme 6. Synthesis of lactacystin (Corey, 1998).[17]

reaction of aldehyde **23** and *E* silicon enolate **24**, in the presence of MgI_2, proceeded with high diastereoselectivity in favor of the desired 1,2-*anti*-adduct **25** (85 %, 9:1 d.r.). This stereochemical outcome arises from chelation of the magnesium Lewis acid with the formyl oxygen atom and the neighboring benzylamino group that renders the aldehyde *Si* face more susceptible to nucleophilic attack by the enolate, as shown in **TS-7**.

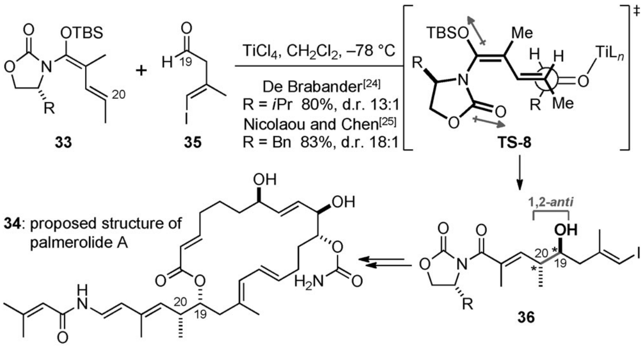
A two-step sequence that involves the proline-catalyzed aldol dimerization of α-siloxyaldehydes, and a subsequent tandem aldol addition/cyclization reaction, was used by the MacMillan group for the concise synthesis of differentially protected carbohydrates (Scheme 7).[18] Treatment of aldehyde **26** with L-proline (**27**) provided adduct **28** (92 %, 4:1 d.r., 95 % *ee*), which proved inert to further proline-catalyzed enolization or enamine addition under the reaction conditions. Subsequent Mukaiyama aldol reaction with silicon enolate **29** afforded protected versions of glucose (**30**), mannose (**31**), and allose (**32**); the selectivity was tuned by judicious choice of Lewis acid and reaction solvent. For example, the use of $MgBr_2{\cdot}OEt_2$ favors a chelation-controlled open transition state, wherein the facial selectivity of the silicon enolate is solvent dependent. Aldol coupling mediated by $TiCl_4$, on the other hand, is rationalized as proceeding through Felkin-selective titanium enolate addition to the aldehyde through a Zimmerman–Traxler transition state. Overall, the modular nature of this process makes it possible to independently derivatize (isotopically or functionally) the hexose, thus allowing for the rapid construction of a broad range of differentially protected building blocks in saccharide and polysaccharide synthesis.



Scheme 7. Two-step synthesis of protected hexose carbohydrates (MacMillan, 2004).[18] DMSO = dimethylsulfoxide, TIPS = triisopropylsilyl.

2.3. Control by Chiral Auxiliaries

The vinylogous version of the silicon enolate aldol reaction was first reported by Mukaiyama and Ishida in 1975.[19] After four decades of continued development, both diastereoselective and enantioselective versions of the reaction have evolved.[20] A practical auxiliary-based method was developed by the group of Kobayashi,[21] and later extended by the groups of Hosokawa[22] and Kalesse;[23] this method uses silicon dienolates of type **33** to simultaneously configure one double bond and up to two stereocenters. The efficiency of this vinylogous aldol addition was demonstrated independently by De Brabander and co-workers[24] and Nicolaou, Chen, and co-workers[25] in the total synthesis and structural revision of palmerolide A (**34**, Scheme 8), a marine macrolide that exhibits potent and selective activity against melanoma cancer cells. The reaction of dienolate **33** with aldehyde **35**, in the presence of $TiCl_4$, gave *anti* adduct **36** in high yield and excellent diastereoselectivity. The high degree of long-range acyclic stereocontrol may be ascribed to the open transition state depicted in **TS-8**. In this scenario, the addition proceeds on the less hindered π face of the preferred conformation of silicon dienolate **33**, in which dipoles are opposed, whereas the facial selectivity of the aldehyde is dictated by minimization of steric interactions between the nucleophile's α-methyl substituent and the R substituent of the aldehyde.



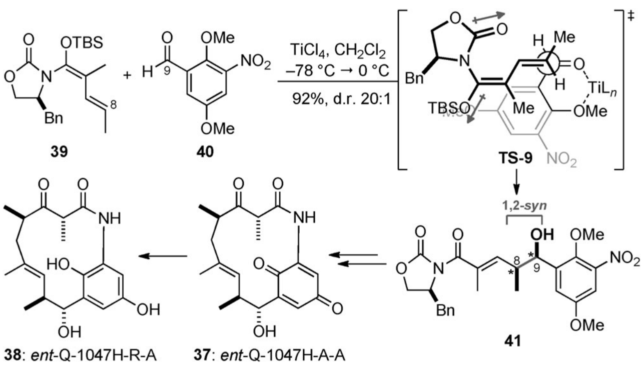
Scheme 8. Synthesis of the proposed structure of palmerolide A (De Brabander, 2007;[24] Nicolaou and Chen, 2007).[25]

Interestingly, a switch to *syn* diastereoselectivity can be attained when α- or β-heteroatom-substituted aldehydes are employed in this vinylogous aldol reaction. In the recent total synthesis of the antioxidant and antinephritis agents, Q-1047H-A-A and Q-1047H-R-A (**37** and **38**, respectively; Scheme 9), the C8 and C9 stereocenters were installed by Chen, Yang, and co-workers using this strategy.[26] Through the $TiCl_4$-mediated aldol coupling between dienolate **39** and methoxy-substituted aryl aldehyde **40**, *syn*-adduct **41** was obtained (92 %, 20:1 d.r.) via chelated transition state **TS-9**. The X-ray crystal structure of **37** enabled reassignment of the absolute configuration of the natural products.

3. Enantioselective Aldol Reactions with Silicon Enolates

3.1. Chiral Tin Lewis Acid Mediated Aldol Reactions

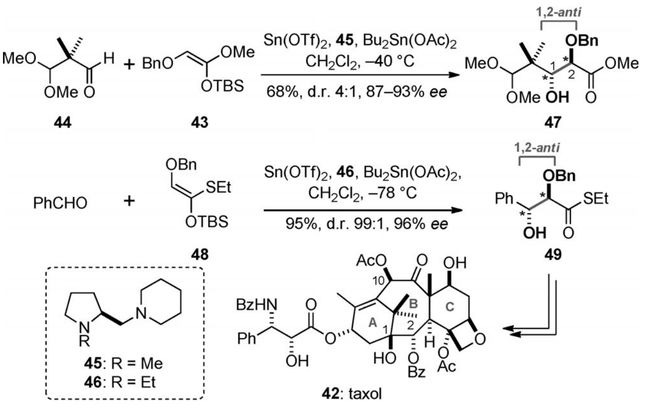
In 1989, Mukaiyama and Kobayashi first reported that enantioselective aldol reactions of silicon enolates can be



Scheme 9. Synthesis and structural revision of Q-1047H-A-A and Q-1047H-R-A (Chen and Yang, 2013).[26]

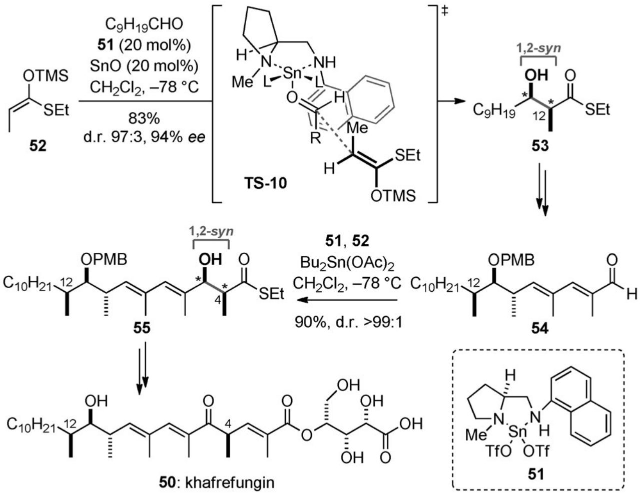
achieved by using a chiral diamine/tin(II) triflate complex as an aldehyde activator.[27] Moreover, this method can be rendered catalytic in the presence of tin by slow addition of the starting silicon enolate and aldehyde to the tin catalyst solution to suppress the racemic background reaction promoted by TMSOTf. Depending on the α substituent of the enolate, the reaction can afford either the *anti* or *syn* adduct, and thus constitutes a powerful method for controlling the absolute stereochemical outcome in directed aldol reactions.

In the total synthesis of the important anticancer agent taxol (**42**, Scheme 10), an *anti*-selective aldol reaction was employed by Mukaiyama and co-workers to define the side-chain stereochemistry, as well as to configure the C1 and C2 stereocenters in the B ring.[28] Silyl ketene acetal **43** underwent aldol coupling with aldehyde **44** in the presence of stoichiometric amounts of $Sn(OTf)_2$, chiral diamine **45**, and $Bu_2Sn(OAc)_2$ as a Lewis basic silicon enolate activator. This reaction gave *anti* adduct **47** in useful selectivity (68%, 4:1 d.r., 87–93% *ee*), thus enabling the stereochemistry of the C10 hydroxy-substituted stereocenter and the BC ring junctions to be controlled at a later stage. The aldol reaction between **48** and benzaldehyde took place under similar conditions to give *anti*-adduct **49** (95%, 99:1 d.r., 96% *ee*). The ensuing benzylic alcohol stereocenter was subsequently inverted by hydrogen azide under Mitsunobu conditions, reduced, and benzoylated to complete the taxol side chain.



Scheme 10. Synthesis of taxol (Mukaiyama, 1999).[28]

The tin-promoted aldol method can also provide access to *syn* adducts by changing the α substituent in the silyl ketene thioacetal, as demonstrated in Kobayashi's total synthesis and stereochemical assignment of the antifungal agent khafrefungin (**50**, Scheme 11).[29] In the presence of chiral tin(II)/diamine complex **51** as a Lewis acid catalyst and SnO as a Lewis base, an aldol reaction between decanal and **52** gave *syn*-adduct **53** with excellent selectivity (83%, 97:3 d.r., 94% *ee*). The reaction likely proceeds via a pentacoordinate, square pyramidal tin(II) intermediate, wherein the *Re* face of the aldehyde is shielded by the diamine naphthyl group, thus allowing the nucleophile to attack the aldehyde *Si* face via open transition state **TS-10**.[30] Intermediate **53** was next transformed to aldehyde **54** for a second aldol iteration under similar reaction conditions (albeit requiring a stoichiometric amount of tin(II)/diamine) to provide adduct **55** (90%, > 99:1 d.r.).

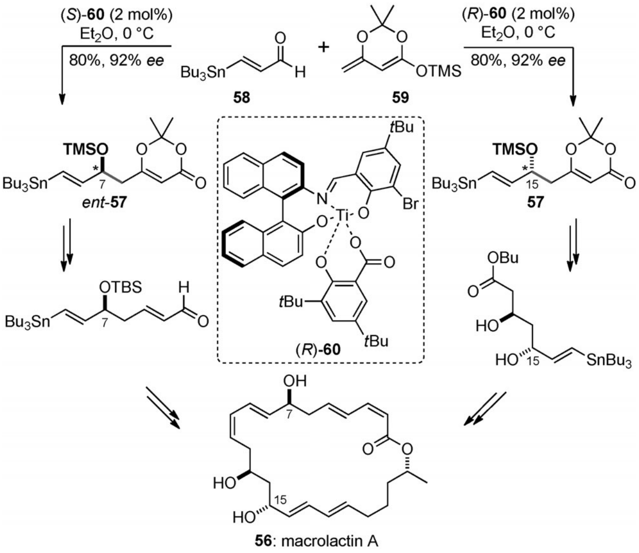


Scheme 11. Synthesis of khafrefungin (Kobayashi, 2001).[29]

3.2. Chiral Titanium and Copper Lewis Acid Catalyzed Aldol Reactions

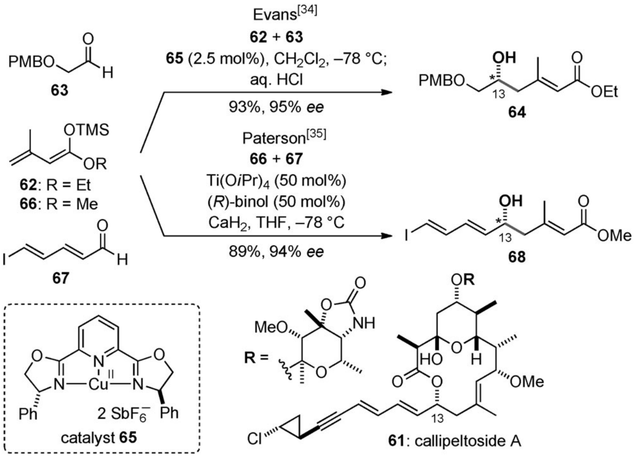
The use of chiral titanium Lewis acids to realize catalytic enantioselective Mukaiyama aldol reactions[31] was exemplified by Carreira and Singer in their total synthesis of macrolactin A (**56**, Scheme 12), a polyene macrolide that inhibits HIV replication in T-lymphoblast cells.[32] Recognizing the structural homology between the two dienyl alcohols within macrolactin A, enantiomeric fragments **57** and *ent*-**57** (80%, 92% *ee*) were prepared by the aldol reactions of common precursors **58** and **59**, in the presence of the appropriate enantiomer of the Ti^{IV} catalyst **60** to establish the C7 and C15 stereocenters.

The Cu^{II}/PyBox-promoted Mukaiyama aldol reaction developed by the Evans group, relies on bidentate coordina-



Scheme 12. Synthesis of macrolactin A (Carreira, 1998).[32]

tion of the reacting aldehyde to the catalyst to achieve π-facial bias in the carbon–carbon bond-forming step.[33] This powerful method was used by Evans and co-workers in the total synthesis of the cytotoxic marine macrolide, callipeltoside A (**61**, Scheme 13).[34] In the event, a Cu^{II}/PyBox catalyzed vinylogous aldol reaction between silicon dienolate **62** and aldehyde **63** afforded adduct **64** (93 %, 95 % *ee*). The observed asymmetric induction can be rationalized by chelation of the benzyloxy group on the aldehyde to the Lewis acidic copper center in **65**, thus imposing facial bias in the enolate addition. Notably, this enantioselective aldol reaction tolerates variation in both the nucleophilic and electrophilic components while maintaining low catalyst loading.

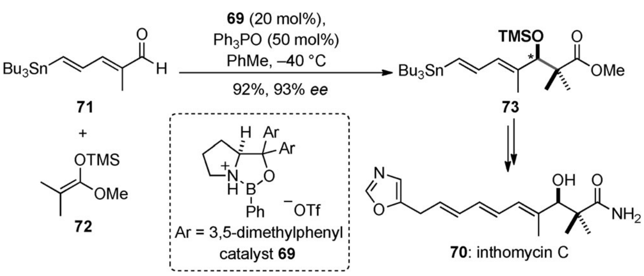


Scheme 13. Synthesis of callipeltoside A (Evans, 2002;[34] Paterson, 2003).[35] (*R*)-binol = (*R*)-(+)-1,1′-Bi(2-naphthol).

In contrast, a titanium-promoted aldol addition was preferred by Paterson and co-workers in their synthesis of callipeltoside A.[35] An asymmetric vinylogous Mukaiyama aldol reaction between **66** and iododienal **67** with Ti^{IV}/binol as a chiral Lewis acid gave adduct **68** (89 %, 94 % *ee*). Although high catalyst loadings are required in this transformation, the sensitive iododiene moiety was tolerated, thus enabling the later attachment of the cyclopropyl alkyne side chain of callipeltoside by a Sonogashira cross-coupling.

3.3. Chiral Boron Lewis Acid Catalyzed Aldol Reactions

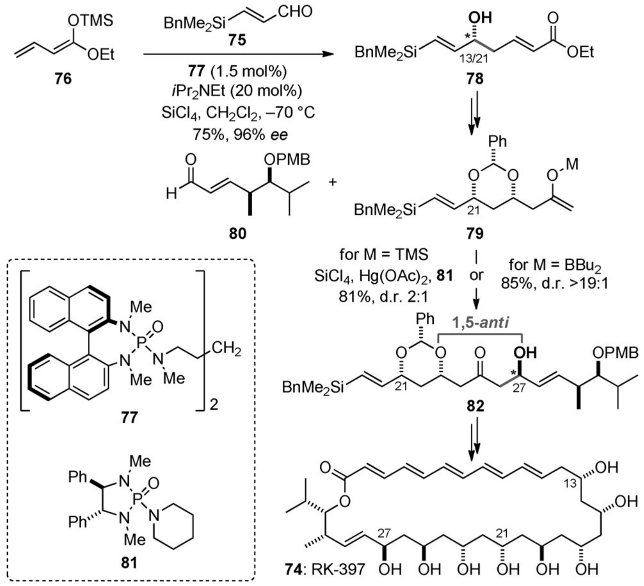
Chiral oxazaborolidinium salts, such as **69**, are also effective Lewis acids for aldehyde activation in aldol reactions with silicon enolates.[36] In the total synthesis of the antimicrobial and anticancer agent inthomycin C (**70**, Scheme 14) of Ryu and co-workers, the aldol reaction of the stannyl aldehyde **71** with silicon enolate **72** proceeded smoothly in the presence of catalyst **69** to give adduct **73** (92 %, 93 % *ee*), and retaining the sensitive dienylstannane moiety.



Scheme 14. Synthesis of inthomycin C (Ryu, 2010).[36]

3.4. Chiral Lewis Base Catalyzed Aldol Reactions

Chiral Lewis base catalyzed Mukaiyama aldol reactions[37] feature as key steps in the total synthesis of the antifungal polyene macrolide RK-397 (**74**, Scheme 15) by the group of



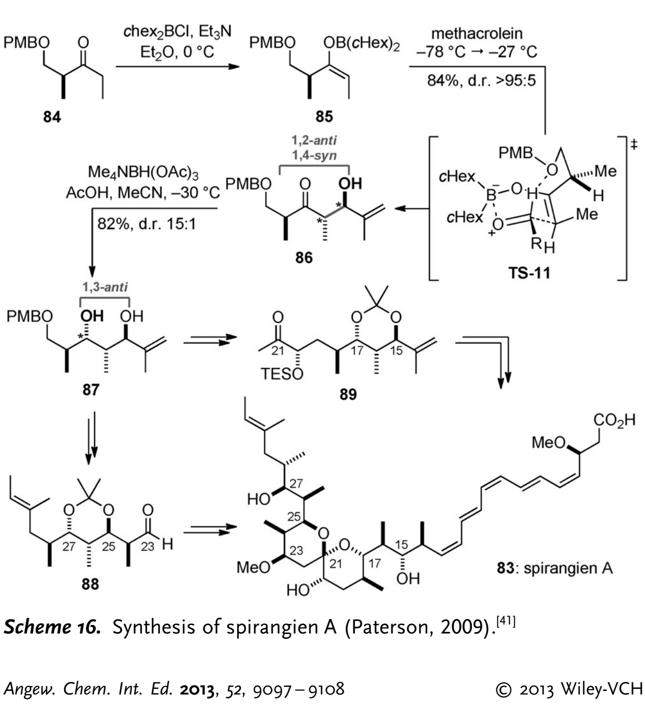
Scheme 15. Synthesis of RK-397 (Denmark, 2005).[38]

Denmark.[38] In this context, the reaction between aldehyde **75** and trichlorosilyl enolate, which was generated in situ from ketene acetal **76**, was promoted by Lewis base catalyst **77**. This reaction provided vinylogous adduct **78** (75 %, 96 % *ee*), and simultaneously defined the C13 and C21 stereocenters, which were then used to configure an additional six of the 10 stereocenters in RK-397 by substrate control. After conversion into a methyl ketone, a second aldol reaction of the derived enolate **79** with aldehyde **80** was needed to configure the C27 stereocenter. In this scenario, the use of catalyst **81** with the derived silicon enolate gave adduct **82** with moderate diastereoselectivity (2:1 d.r.), whereas the corresponding boron enolate gave **82** with a characteristically high level of 1,5-*anti* stereoinduction (19:1 d.r.),[39] as discussed later in section 4.1.

4. Diastereoselective Aldol Reactions with Boron Enolates

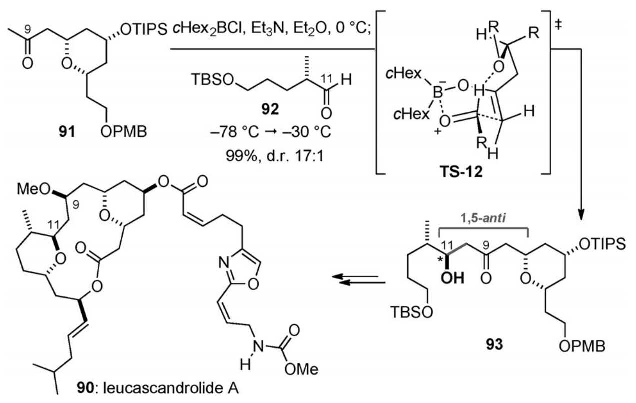
4.1. Control by Chiral Enolates through 1,4- and 1,5-Stereoinduction

For boron-mediated aldol reactions, a powerful approach to achieve highly diastereoselective additions to aldehydes is to use a chiral enolate partner to control the configuration of the newly generated stereocenters by 1,4-[40] or 1,5-asymmetric induction[39] through a highly ordered cyclic transition state. Notably, computational analysis of the transition state is well-developed in this context.[7] As discussed already in the case of silicon enolates, this strategy excels even in complex settings, and provides a predictable method for accomplishing key fragment couplings in challenging total syntheses. The synthesis of the antifungal and cytotoxic agent spirangien A (**83**, Scheme 16) by the group of Paterson showcases the use of boron-mediated 1,4-asymmetric induction[41] as a key step to define the majority of the stereocenters.[42] Selective enolization[5] of ketone **84**, derived from the Roche ester, with *c*Hex$_2$BCl and Et$_3$N gave *E* boron enolate **85**, which upon addition to methacrolein gave 1,4-*syn* adduct **86** (84 %, > 95:5 d.r.). Subsequent Evans–Saksena 1,3-*anti* reduction[43] then provided **87**, containing four stereocenters with equally high diastereoselectivity (82 %, 15:1 d.r.). The aldol stereocontrol arises from the preferred bicyclic boat transition state **TS-11**, which invokes minimization of 1,3-allylic strain and a stabilizing hydrogen bond between the formyl group and the oxygen atom of the PMB ether of the boron enolate.[7] The common building block **87** was then elaborated into aldehyde **88** and methyl ketone **89**, which were submitted to aldol coupling controlled by a chiral boron reagent (see section 5.1)[44] to introduce the C23 stereocenter in the spiroacetal core of spirangien A.



Scheme 16. Synthesis of spirangien A (Paterson, 2009).[41]

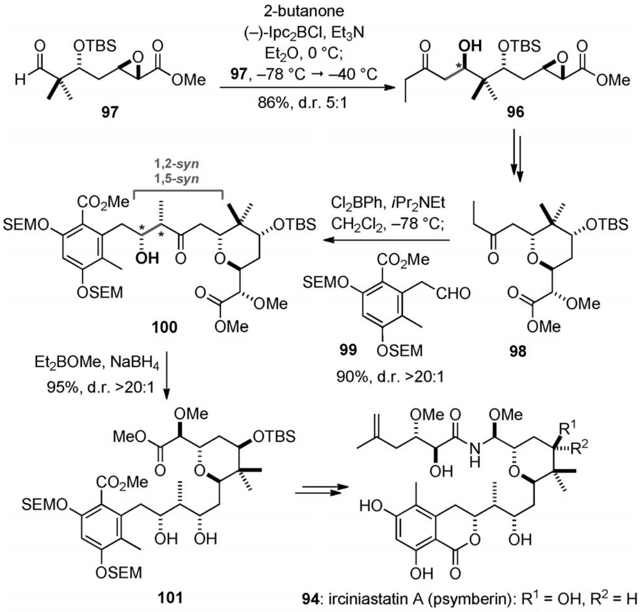
In comparison to boron-mediated aldol reactions involving α-substituted enolates, the use of boron enolates derived from methyl ketones often gives lower levels of stereoselectivity in both substrate- and chiral-reagent-controlled reactions.[3b,44b] This outcome is likely due to a preference of such acetate-type aldol reactions to proceed via boat-type transition states, as opposed to the chair transition states favored for *syn* aldol additions with *Z* enolates.[7] Interestingly, when boron enolates derived from methyl ketones and bearing suitably substituted β′-alkoxy groups are employed, remarkably high levels of 1,5-*anti* stereoinduction can be achieved,[45] as independently discovered by the groups of Paterson[39a] and Evans.[39b,c] The efficiency of this powerful fragment coupling strategy was demonstrated by the group of Paterson in their synthesis of leucascandrolide A (**90**, Scheme 17),[46] a marine macrolide that exhibits potent cytotoxic activity. Addition of the dicyclohexylboron enolate prepared from methyl ketone **91** to α-chiral aldehyde **92** afforded 1,5-*anti*-adduct **93** (99 %, 17:1 d.r.), thus overriding any inherent Felkin–Anh 1,2-*syn* preference of the aldehyde. In fact, equally high levels of 1,5-*anti* induction were also obtained with achiral aldehydes, thus indicating that **92** contributed only negligibly to 1,2-induction. The stereochemical outcome arises from bicyclic boat transition state **TS-12**, which involves a hydrogen bond between the formyl group and the tetrahydropyranyl oxygen atom of the boron enolate, and minimization of steric interactions



Scheme 17. Synthesis of leucascandrolide A (Paterson, 2003).[46]

between the enolate β′-alkyl substituent and one of the boron ligands.[7b,d]

Remarkably, the intrinsic π-facial selectivity of certain *Z* enolates derived from β′-alkoxy ethyl ketones may be reversed relative to the methyl ketone case, thus giving rise to 1,5-*syn* aldol adducts through a chair transition state. This effect was first described by Evans and Calter in their total synthesis of bafilomycin A_1[47] and subsequently used as a key step in other natural product syntheses,[48] as illustrated by the approach of Smith and co-workers towards the irciniastatins/psymberin (**94** and **95**, Scheme 18).[49] Here, the ethyl ketone



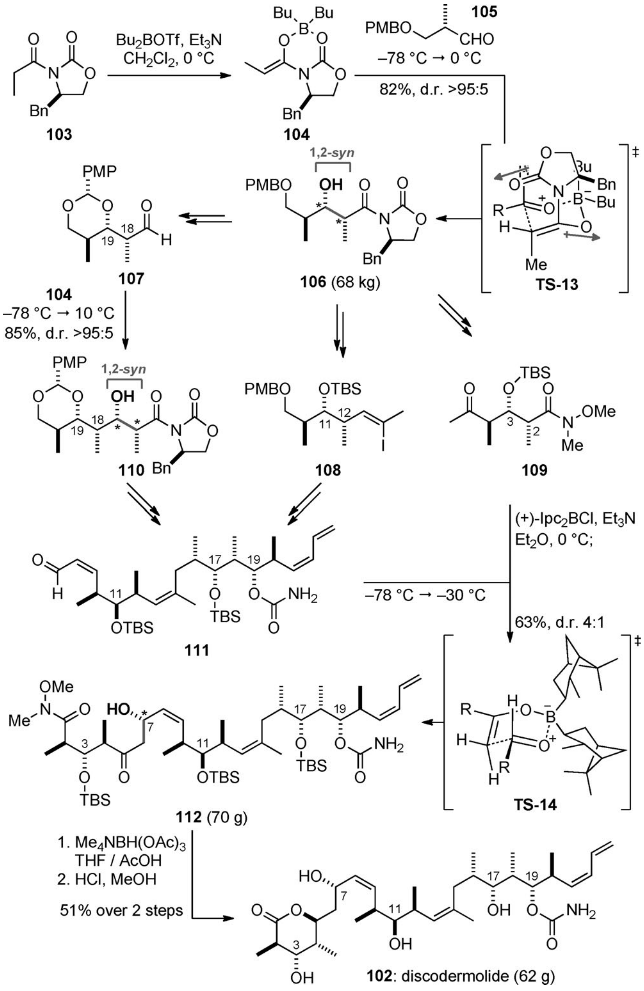
Scheme 18. Synthesis of irciniastatin A (psymberin) and irciniastatin B (Smith, 2008, 2013).[49] Ipc = isopinocampheyl, SEM = 2-trimethylsilylethoxymethoxy.

96 (86 %, 5:1 d.r.) was readily prepared by a Paterson boron-mediated aldol addition (see section 5.1) between 2-butanone and aldehyde **97**, and then underwent epoxide ring opening and methylation to give tetrahydropyran **98**. Selective *Z* enolization of ketone **98** was carried out with Cl_2BPh and iPr_2NEt,[50] where addition to aldehyde **99** gave the 1,5-*syn*-adduct **100** (90 %, > 20:1 d.r.). A Narasaka reduction[12] then established the all-*syn* configuration of the three stereocenters at C15–C17 in 1,3-diol **101**.

5. Asymmetric Aldol Reactions with Boron Enolates

5.1. Control by Chiral Auxiliaries and Reagents

The versatile Evans *syn* aldol reaction involving boron enolates substituted by a chiral oxazolidinone auxiliary was first reported in 1981.[8d] This has subsequently proved to be a very dependable method for the stereocontrolled synthesis of complex polyketide natural products. A complementary approach is to use a chiral boron reagent for enolization of carbonyl compounds, for enantioselective aldol additions with aldehydes, where Ipc_2BX (X = OTf or Cl) reagents have proved particularly valuable.[44] The use of these two asymmetric boron-mediated aldol reactions on a large scale was demonstrated by the Novartis process chemistry group in their synthesis of discodermolide (**102**; Scheme 19), a marine sponge-derived microtubule-stabilizing agent that entered clinical trials as an anticancer drug candidate. This impressive campaign produced more than 60 g of this architecturally complex polyketide through total synthesis, by using a hybridized Novartis–Smith[51]–Paterson[52] approach.[53]



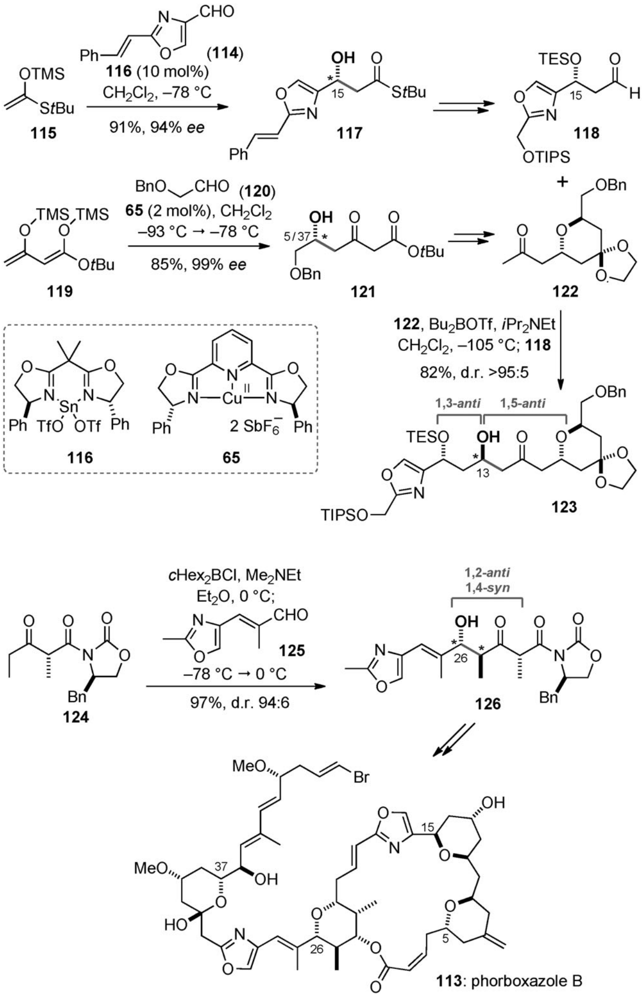
Scheme 19. Large-scale synthesis of discodermolide for phase 1 clinical trials (Novartis, 2004).[53] PMP = *para*-methoxyphenyl.

In the route developed by the Novartis group, boron-mediated aldol chemistry, featuring Evans oxazolidinone *syn* aldol and Paterson Ipc aldol methods, was employed to define nine of the 13 stereocenters in discodermolide. In this context, enolization of propionimide **103** with Bu_2BOTf and Et_3N followed by addition of the resulting *Z* enolate **104** to aldehyde **105**, derived from the Roche ester, gave *syn* adduct **106** as a single diastereomer (68 kg); the reaction proceeds through the chair transition state **TS-13**.[7c] Common intermediate **106** was next elaborated into the three subunits **107**, **108**, and **109**. A second Evans aldol reaction gave adduct **110** (85 %) with no minor diastereomers observed. Following elaboration, including reductive cleavage of the auxiliary and iodination of the ensuing alcohol, a Suzuki cross-coupling with fragment **108** was realized, which later led to aldehyde **111**. In the final reagent-controlled aldol reaction, enolization of **109** with (+)-Ipc$_2$BCl and Et$_3$N, followed by addition of aldehyde **111** led to adduct **112** (63 %, 4:1 d.r.) via the boat transition state **TS-14**.[7a,c] Finally, an Evans–Saksena reduction[43] of **112** and complete deprotection gave 62 g of crystalline discodermolide (**102**), as a single polymorphic form (monohydrate).

6. Combined Use of Silicon and Boron Enolates in Total Synthesis

6.1. Synthesis of Phorboxazole B

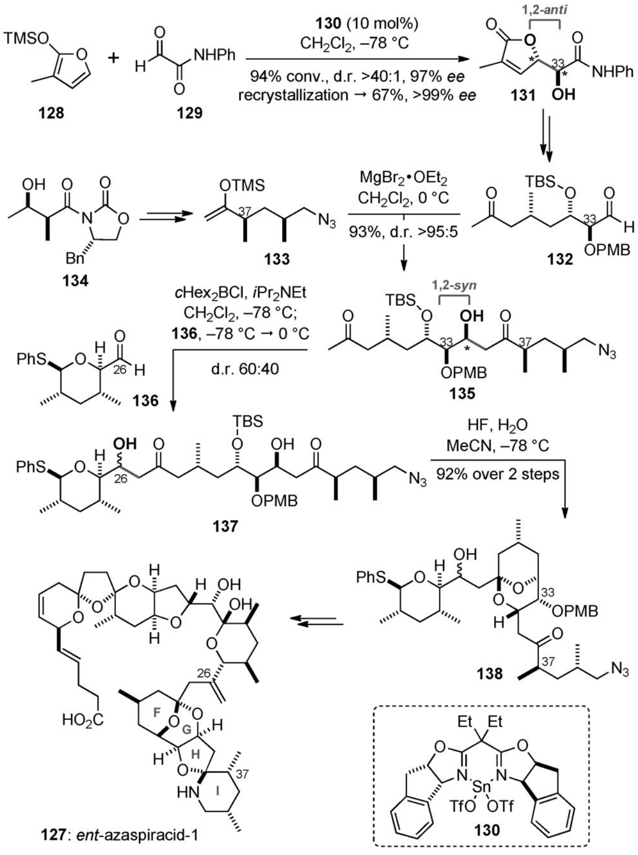
The total synthesis of the marine anticancer agent phorboxazole B (**113**, Scheme 20) by Evans and co-workers nicely showcases the application of both silicon- and boron-mediated aldol chemistry in the assembly of this architecturally complex polyketide.[54] Using α-oxazole aldehyde **114** as a bidentate electrophile, the Sn^{II}-catalyzed asymmetric aldol addition of silicon enolate **115** to **114** provided adduct **117** (91 %, 94 % *ee*), which was converted into aldehyde **118**. The aldol reaction of silicon enolate **119** with benzyloxyacetaldehyde (**120**), in the presence of Cu^{II}/PyBox catalyst **65**, gave δ-hydroxy-β-ketoester **121** (85 %, 99 % *ee*). **121** was converted into ketone **122**, which was subjected to a 1,5-*anti* boron-mediated aldol coupling with aldehyde **118** (performed at −105 °C) to give adduct **123** (82 %, > 95:5 d.r.). A second fragment was constructed using a boron-mediated aldol reaction[55] between the *E* enolate derived from β-ketoimide **124** and aldehyde **125** to give *anti*-adduct **126** (97 %, 94:6 d.r.).



Scheme 20. Synthesis of phorboxazole B (Evans, 2000).[54]

6.2. Synthesis of Azaspiracid-1

The total synthesis of the marine neurotoxin azaspiracid-1 (**127**, Scheme 21) by the group of Evans features a series of highly efficient silicon- and boron-mediated aldol reactions to build the FGHI-ring system and meet the challenging stereochemical requirements in this region.[56,57] Siloxyfuran **128** underwent a vinylogous Mukaiyama aldol reaction with glyoxamide **129** in the presence of Sn^{II} catalyst **130** to give γ-lactone **131** (94 %, > 40:1 d.r., 97 % *ee*). After elaboration to aldehyde **132**, a chelation-controlled aldol reaction promoted by MgBr$_2$·OEt$_2$ with silicon enolate **133**, derived from

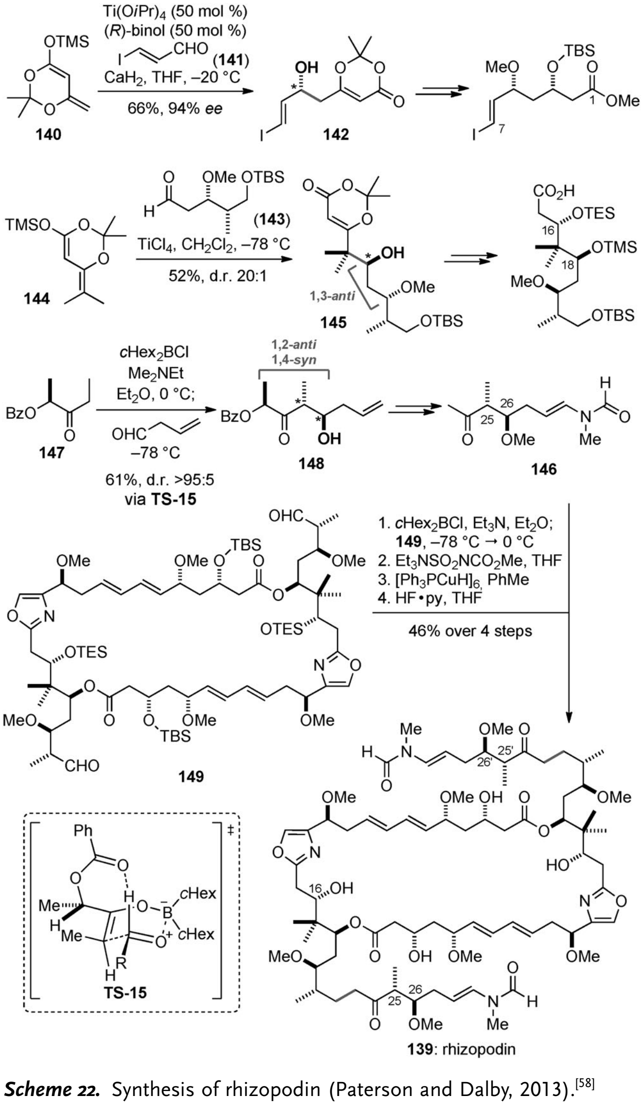


Scheme 21. Synthesis of *ent*-azaspiracid-1 (Evans, 2008).[56]

oxazolidinone-based aldol product **134**, cleanly provided adduct **135** (93 %, > 95:5 d.r.). Regioselective enolization of methyl ketone **135** with *c*Hex_2BCl and *i*Pr_2NEt, and a subsequent aldol addition to aldehyde **136** led to the formation of **137**; the low diastereoselectivity of this reaction was inconsequential because the C26 alcohol was later converted into an olefin. When diol **137** was exposed to aqueous HF in MeCN, cleavage of the TBS group at C32 was accompanied by spontaneous acetalization to afford **138** (92 % over 2 steps), thus efficiently generating a key intermediate suited to completing the total synthesis of *ent*-azaspiracid-1.

6.3. Synthesis of Rhizopodin

The recent total synthesis of the actin-targeting macrodiolide rhizopodin (**139**, Scheme 22) by the Paterson group[58] relies on both silicon- and boron-mediated aldol methods to install most of the stereocenters. A vinylogous aldol addition of silicon dienolate **140** to aldehyde **141** catalyzed by a chiral titanium Lewis acid afforded adduct **142** (66 %, 94 % *ee*). Using chelation-control with $TiCl_4$ and β-methoxyaldehyde **143**, aldol addition of dienolate **144** proceeded to give 1,3-*anti* product **145** (52 %, > 20:1 d.r.). The 1,2-*anti* related stereocenters in the remaining fragment **146** were configured by addition of the *E* boron enolate from lactate-derived ethyl ketone **147** to 3-butenal to give adduct **148** (91 %, > 20:1 d.r.) via the formyl hydrogen-bonded bicyclic transition state **TS-15**.[59] Completion of the total synthesis required a challenging two-directional aldol coupling between the methyl ketone **146** and macrocyclic dialdehyde **149**. In the event, this critical carbon–carbon bond formation[60] was best accomplished by enolization of **146** with *c*Hex_2BCl and Et_3N under mild conditions, and subsequent controlled addition to **149**, to give the bis(β-hydroxyketone), which was transformed into rhizopodin (**139**).



Scheme 22. Synthesis of rhizopodin (Paterson and Dalby, 2013).[58]

7. Summary and Outlook

The foregoing representative examples serve to highlight the impact of silicon- and boron-mediated aldol chemistry in contemporary total synthesis. In particular, creative solutions have been devised to render these aldol reactions highly stereoselective, efficient and reliable in complex settings, in which the sensitivity of densely functionalized substrates often provides only limited scope for successful chemoselective manipulations. The development of practical stoichiometric and catalytic asymmetric aldol reactions has also been achieved, and their scope and versatility are being continuously enhanced. These aldol reactions enable the preparation of chiral building blocks suited for the assembly of more elaborate molecular frameworks, as well as for allowing reagent control of stereochemistry and overturning the inherent substrate preference while defining new stereocenters. Total synthesis empowered by Mukaiyama's aldol chemistry has rapidly grown into a vibrant area of research over the past forty years, and will no doubt continue to serve as a fertile ground for the advancement of the field of organic synthesis in the future.

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