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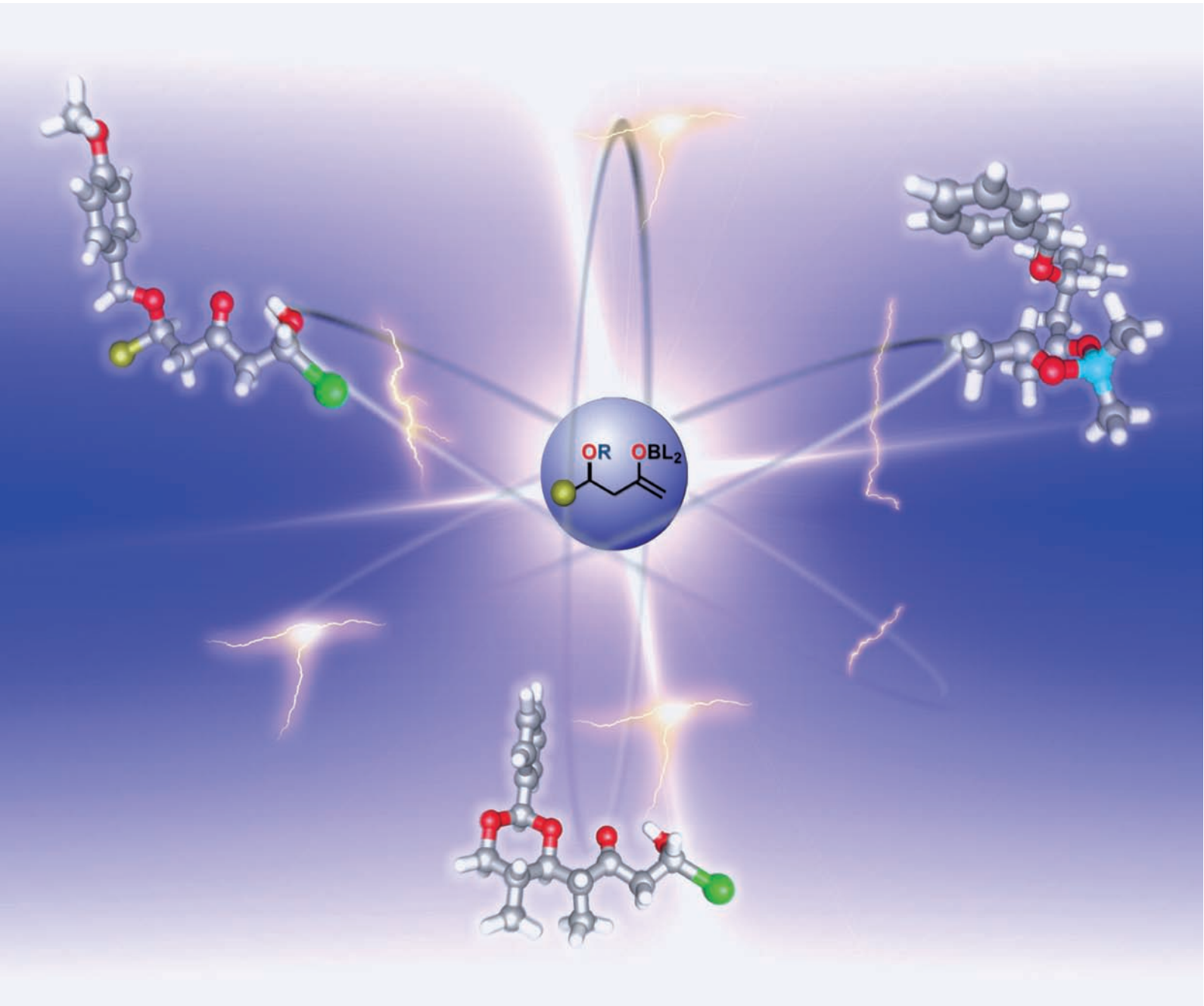

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1,5-Asymmetric induction in boron-mediated aldol reactions of β-oxygenated methyl ketones†

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This *tutorial review* describes that high levels of substrate-controlled, 1,5-stereoinduction are obtained in the boron-mediated aldol reactions of β-oxygenated methyl ketones with achiral and chiral aldehydes. Remote induction from the boron enolates gives the 1,5-*anti* adducts, with the enolate π-facial selectivity critically dependent upon the nature of the β-alkoxy protecting group. This 1,5-*anti* aldol methodology has been strategically employed in the total synthesis of several natural products with remarkable pharmacological activities. At present, the origin of the high level of 1,5-*anti* induction obtained with the boron enolates is unclear, although a model based on hydrogen bonding between the β-alkoxy oxygen and the formyl aldehyde hydrogen has recently been proposed.

Introduction

The aldol reaction is one of the most powerful and fundamental methods for carbon–carbon bond formation as well as for the creation of 1,3-dioxygen relationships in organic molecules and has been applied for the synthesis of a wide variety of natural products with biological and pharmacological significance.[1] The incorporation of convergence into the construction of complex polyketides requires that large fragments must be joined at some point in the synthesis and the aldol reaction provides an attractive method for such a convergent assembly. The use of boron enolates derived from α-methyl methyl ketones for asymmetric aldol reactions usually give low levels of diastereoselectivity, when compared with the high selectivities observed with the use of boron

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† The HTML version of this review has been enhanced with colour images.

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Luiz Carlos Dias was born in Balneário Camboriú, SC (Brazil). He received his undergraduate degree from the Federal University of Santa Catarina (UFSC), Florianópolis, SC, in 1988 and his PhD, in 1993 at the State University of Campinas (UNICAMP). In 1992 he joined the faculty at the Department of Chemistry at UNICAMP as an Instructor. In 1993 he was promoted to Assistant Professor and in 1999 to Associate Professor. He spent two years as a postdoctoral fellow with Prof. David A. Evans at Harvard University, USA (1994–1995) where he worked on the total synthesis of spongistatin A. He is interested in the study of the control elements that influence the stereochemical outcome of double stereodifferentiating chiral allylsilane, allylstannane and boron enolates of methyl ketones additions to aldehydes. These methodological studies are being applied to the asymmetric synthesis of a wide variety of important natural and synthetic products of biological significance. Short, efficient and flexible synthetic routes to biologically important compounds like HIV-1 inhibitors, immunosuppressant agents, plant toxins, herpes virus inhibitors, antibiotics, antitumor agents and neurotransmitters are being developed in his laboratory. He was the General Secretary of the Brazilian Chemical Society (SBQ) from 2000 to 2004. Since 2005 Prof. Dias has been the Editor of the Journal of the Brazilian Chemical Society (JBCS). (Further information: http://www.lqos.iqm.unicamp.br/en)

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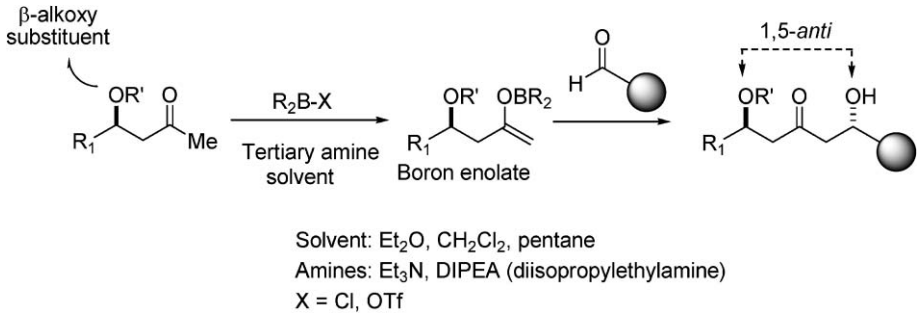


Fig. 1 General scheme for 1,5-*anti* aldol reactions.

enolates prepared from ethyl ketones.[1] Usually, reagent control using chiral ligands on boron is required to obtain useful levels of asymmetric induction in the addition of boron enolates of α-methyl β-alkoxy ketones to achiral aldehydes.[2] However, the presence of a β-heteroatom substituent in the boron enolates of methyl ketones influences the stereochemical outcome of the corresponding aldol reactions and high levels of 1,5-*anti* asymmetric induction are observed. With very important contributions, the research groups of Paterson, at Cambridge, and of Evans, at Harvard, were responsible for the development of this area of remote 1,5-asymmetric induction where a β-alkoxy substituent on the boron enolate controls the overall diastereoselectivity of the process.[3–5]

This review discusses the influence of a β-alkoxy substituent in the boron enolates in aldol reactions of β-alkoxy methyl ketones and α-methyl-β-alkoxy methyl ketones with both achiral and chiral aldehydes leading to 1,5-*anti* aldol adducts. The general scheme for this boron enolate aldol addition reaction is presented in Fig. 1. In this review we are going to discuss the effect of the nature of the protecting group at the β-alkoxy oxygen (R′), and the best reaction conditions leading to the 1,5-*anti* aldol adduct. In these examples, the kinetic boron enolate (less substituted enolate) is generated after treatment of the methyl ketone with the corresponding diakylborane (boron triflates or diakyl chloro boranes), followed by addition of a tertiary amine (usually Et_3N or DIPEA). The solvents are CH_2Cl_2, Et_2O or pentane.

1,5-*anti* Asymmetric induction in aldol reactions

The first evidence for 1,5-*anti* asymmetric induction in aldol reactions was described in 1989 by Masamune and co-workers.[6] This protocol was used in the synthesis of the AB fragment [C1–C16] of bryostatin 1 (Scheme 1). Addition of the kinetic boron enolate generated from methyl ketone **1** to aldehyde **2** gave aldol adduct **3**. The observed levels of diastereoselectivity were shown to be dependent on the boron reagent, as can be observed in Scheme 1. The use of diethyl boron triflate led to a 66 : 33 mixture favoring the 1,5-*anti* aldol, with the sense of diastereoselectivity being controlled by the chiral boron enolate. However, reaction of the boron enolate prepared with chiral boron reagent **4** led to a 33 : 66 (1,5-*anti* : 1,5-*syn*) mixture of aldol adducts. The use of enantiomeric chiral boron reagent **5** led to the aldol adduct **3** with 86 : 14 diastereoselectivity. In this case, the combination of facial selectivity of methyl ketone **1** with boron reagent **5** represents a matched case of diastereoselection.[7–11]

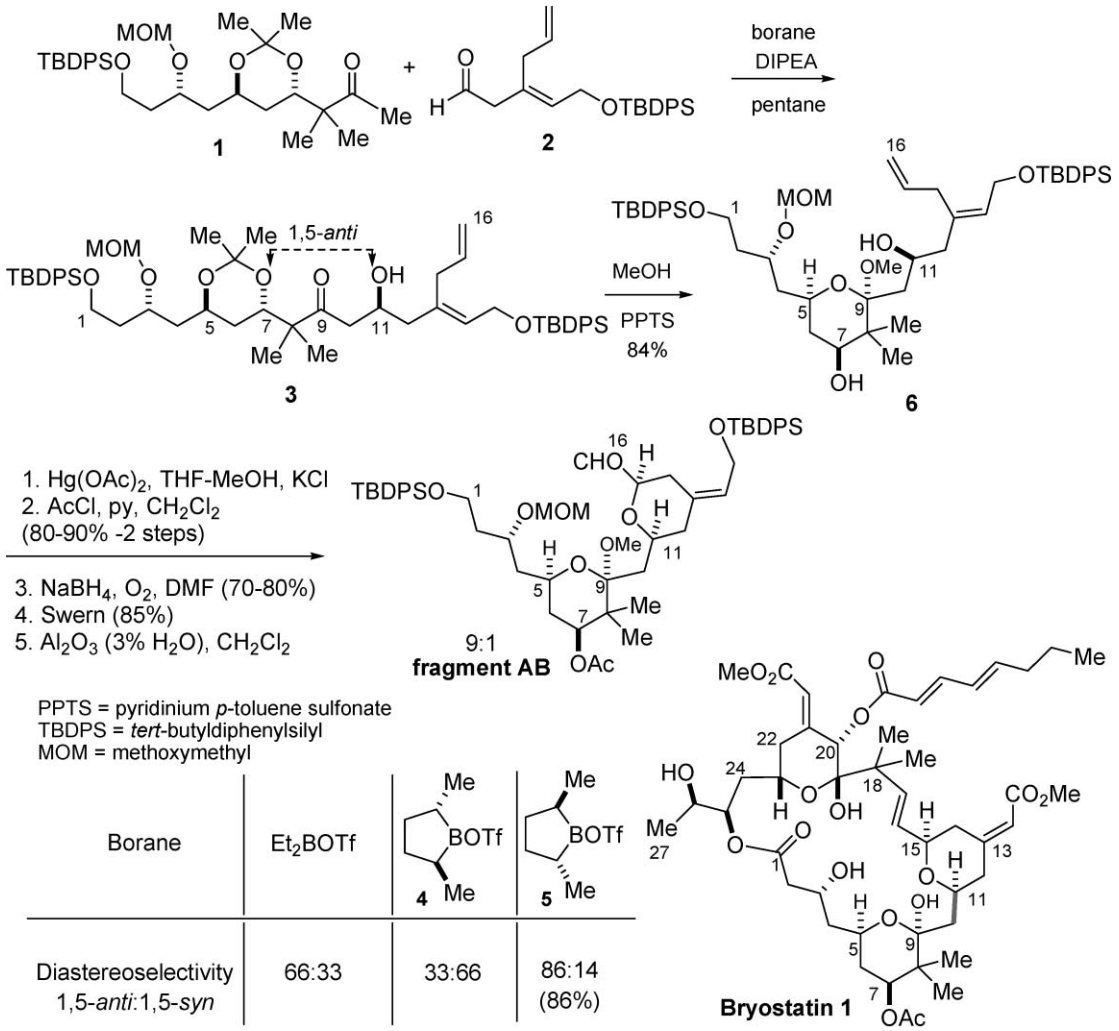
The relative stereochemistry for aldol **3** was confirmed after preparation of acetal **6** (MeOH, PPTS, 84%), followed by coupling constant analysis in the ^{1}H-NMR spectra. In addition, the diastereoisomeric ratio is based on the formation of acetal **6** and the reaction yield (86%) is specified only for borane **5**. After a few steps acetal **6** was transformed into the AB fragment of bryostatin 1 (Scheme 1).[6]

Later on, the groups of Paterson and of Evans disclosed very interesting results dealing with the addition of boron enolates generated from β-alkoxy methyl ketones to aldehydes, leading to the corresponding aldol adducts with high levels of 1,5-*anti* diastereoselectivity.[12–15]

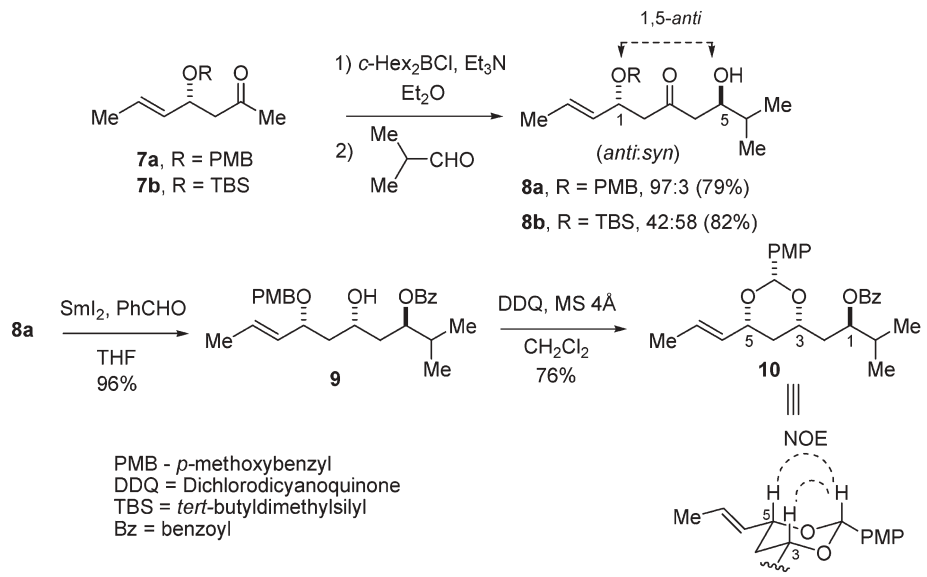
Paterson and co-workers prepared the boron enolate from methyl ketone **7** (c-Hex_2BCl, Et_3N, Et_2O) with different protecting groups at the oxygen β to the carbonyl group (Scheme 2).[12] Interestingly, the boron-mediated aldol reaction of **7a** (R = PMB) with isobutyraldehyde gave diastereoisomer 1,5-*anti* **8a** with 97 : 3 diastereoselectivity, in 79% yield (Scheme 2). Especially noteworthy is that changing the protecting group at the β-oxygen to TBS (*tert*-butyldimethylsilyl) led to a lower diastereoselectivity (**8b**, ds 42 : 58). This result shows that the π-facial selectivity of the boron enolate depends heavily on the nature of the protecting group at the β-oxygen.

The relative stereochemistry for aldol adduct **8a** was confirmed after selective 1,3-*anti* Evans–Tischenko reduction to give **9**, followed by conversion into benzylidene acetal **10**. The NOE enhancements illustrated in **10** provide strong evidence to support the 1,5-*anti* asymmetric induction in this aldol reaction.

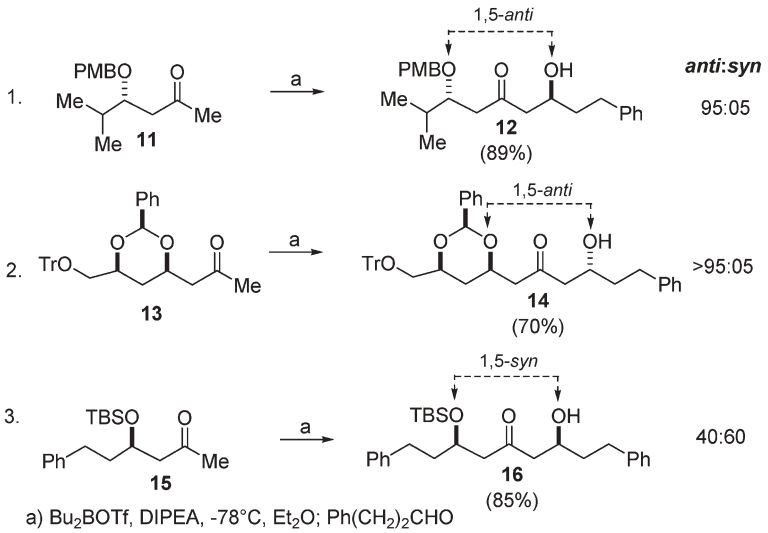
Another highly diastereoselective 1,5-*anti* asymmetric induction in methyl ketone aldol addition reactions of boron enolates was described by Evans and co-workers.[13,14] In this work, the aldols 1,5-*anti* **12** and **14** were obtained in good yields and with high levels of diastereoselection after n-Bu_2BOTf-mediated reactions of methyl ketones **11** and **13**, respectively, with dihydrocinammaldehyde (Scheme 3, entries 1 and 2).[15] The aldol reaction of the boron enolate from methyl ketone **15**, containing a β-OTBS (Scheme 3, entry 3), was nonselective (ds 40 : 60). This result indicates that the nature of the protecting group at the β-oxygen is critical in determining the level of induction, as observed also by Paterson and co-workers (Scheme 2).[12] Evans and co-workers suggested that the electronic nature of the β-alkoxy substituent at the boron enolate is responsible for the observed sense of



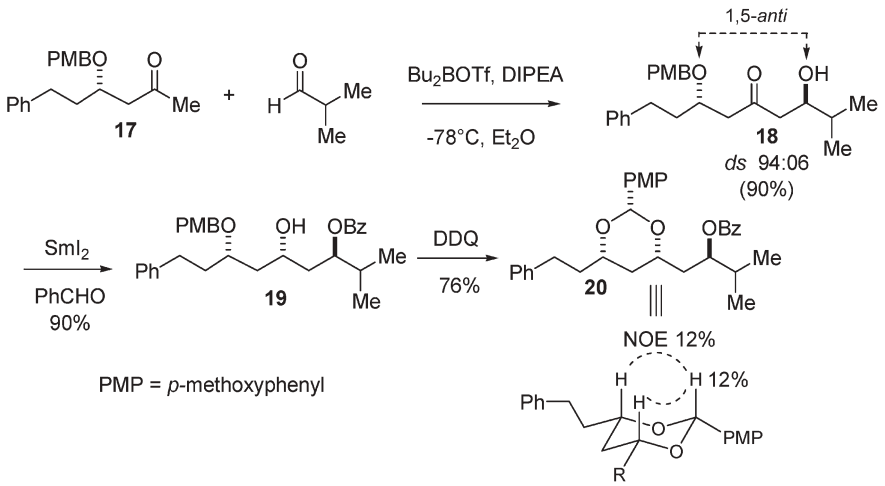
Scheme 1



Scheme 2



Scheme 3

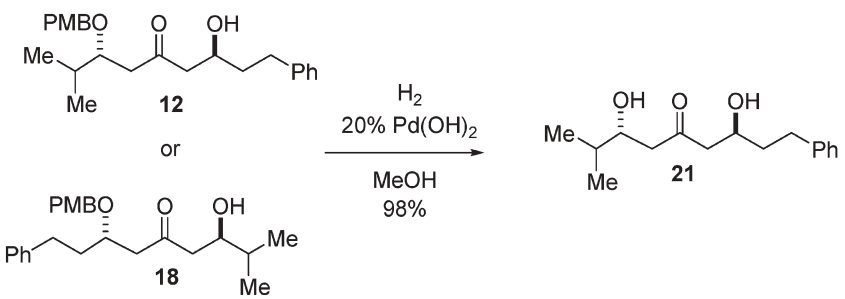


Scheme 4

induction, although no model to support this proposal was suggested.[13,14]

Evans and co-workers also indicated that the n-Bu_2BOTf-mediated aldol reaction of methyl ketone **17** with isobutyraldehyde served to confirm the anticipated role of the β-OPMB group in securing the 1,5-*anti* relationship, giving ketone **18** in 94 : 06 diastereoselectivity (Scheme 4). At this point, the relative stereochemistry for **18** was proved by NOE analysis of benzylidene acetal **20**, easily prepared from **18** by a sequence, which involved selective Evans–Tischenko reduction (SmI_2, PhCHO) of **18** to **19**, followed by treatment with DDQ.[13,14]

The relative stereochemistry of aldol adduct **12** (Scheme 3, entry 1) was confirmed after hydrogenolysis of the PMB group and comparison with the same diol **21** prepared from removal of the PMB group in **18** (Scheme 5). For 1,5-*syn* aldol adduct



Scheme 5

16 (Scheme 3), the relative stereochemistry was determined by comparison with the same compound obtained by using different methodologies.

The possibility of double stereodifferentiation or double asymmetric synthesis in the boron enolate aldol reactions arises when both aldehyde and boron enolates are chiral entities.[7–11] The stereochemical preference of the aldehyde could then either oppose or reinforce the selectivity that the boron enolate would express in a reaction with an achiral aldehyde. Cases that involve the combination of two chiral species, which are of competing selectivities, are called ''mismatched'' and those in which both species influence the newly formed stereocenter toward the same configuration are called ''matched''. In the mismatched case, the stereoselectivity observed can provide an indication of the relative influence of the directing groups on each reactant. By using chiral boron enolates, chiral aldehydes and chiral boranes, we have three elements of diastereocontrol which may influence the stereochemical outcome of aldol addition reactions, and again, double stereodifferentiation can be observed.[7–11]

Evans and co-workers also reported that with n-Bu_2BOTf/DIPEA the coupling of methyl ketone **22** with enantiomeric aldehydes (*R*)-**23** and (*S*)-**23** proceeded, as expected, with excellent levels of remote 1,5-*anti* stereocontrol in favor of the desired aldol adducts **24** and **25**, respectively, in good yields (Scheme 6).[16–18] It is clear from these results (entries 1 and 2) that the stereochemical outcome of these reactions is controlled mainly by the β-alkoxy substituent of the boron enolate. In both cases, the 1,5-*anti* diastereoisomer is obtained as the major product. The observed 1,5-*anti* diastereoselectivity is higher at lower temperatures (ds 96 : 04 at −110 °C *vs* ds 91 : 09 at −78 °C), although with lower yields. A similar result can be observed in entry 3, Scheme 6, using aldehyde **28**, with aldol **29** being isolated in 96 : 04 diastereoselectivity.

The intermediate **25** was applied in the total synthesis of the spongipyran macrolide altohyrtin C (spongistatin 2), a potent antitumor natural product. The relative stereochemistry for aldol adduct **25** was confirmed after spiroketalization, providing a 14 : 86 mixture of spiroketals **26** and **27**, respectively.[16–18] Coupling constant analysis in the ^{1}H-NMR spectra as well as NOE experiments unambiguously confirmed the 1,5-*anti* relationship. For aldol adduct **29**, the relative stereochemistry was determined by the observed NOE interactions in benzylidene acetal **30** (Scheme 6).

Evans and Connell have applied a stereoselective 1,5-*anti* asymmetric aldol bond construction in the total synthesis of the antifungal macrolide antibiotic (+)-roxaticin (Scheme 7).[19] Addition of the di-n-butylboron enolate derived from ketone **31** to aldehyde **32** (Scheme 7) proceeded smoothly to give aldol adduct **33**, corresponding to the C12–C30 fragment of roxaticin in excellent diastereoselectivity (ds > 95 : 5, 79% yield). This fragment contains all the stereocenters of the natural product and, in this case, the boron enolate generated from methyl ketone **31** (Bu_2BOTf, DIPEA, Et_2O) plays a dominant role in controlling the facial diastereoselectivity in the reaction with chiral aldehyde **32**.

Paterson and co-workers applied a similar strategy in the synthesis of the C11–C30 fragment of (+)-roxaticin (Scheme 8).[20] As can be seen in Scheme 8, entry 1, the c-Hex_2BCl-mediated aldol coupling between methyl ketone **34** and aldehyde **35** gave aldol adduct **36** in excellent diastereoselectivity (ds 97 : 3), with the β-stereocenter of the enolate controlling the absolute configuration of the newly formed stereocenter. After a number of steps, this aldol adduct was converted to aldehyde **38**. The absolute stereochemistry at C26 in aldol product **36** was determined by using Mosher's method as well as by analysis of the ^{13}C-NMR spectra of the corresponding acetonide **38**, using the method of Rychnovsky.[20] The aldol reaction between aldehyde **38** and the boron enolate generated from methyl ketone **37** (Scheme 8, entry 2) gave aldol adduct **39** with moderate diastereoselectivity (ds 87 : 13). This fragment contains all the stereocenters of roxaticin.

In order to check the facial selectivity of the boron enolate derived from **37**, the authors investigated the aldol addition to achiral aldehyde **40** (Scheme 8, entry 3). This reaction led to aldol adduct **41** with moderate diastereoselectivity (ds 84 : 16).

This shows that the observed level of 1,5-*anti* diastereoselectivity in entry 2 is attributed only to the β-carbonyl stereocenter of the boron enolate, and it is believed that the bulky OTIPS at C14 in the boron enolate from methyl ketone **37** should influence the molecule conformation, lowering the stereoinduction coming from OPMB at C16 (Scheme 8).[20]

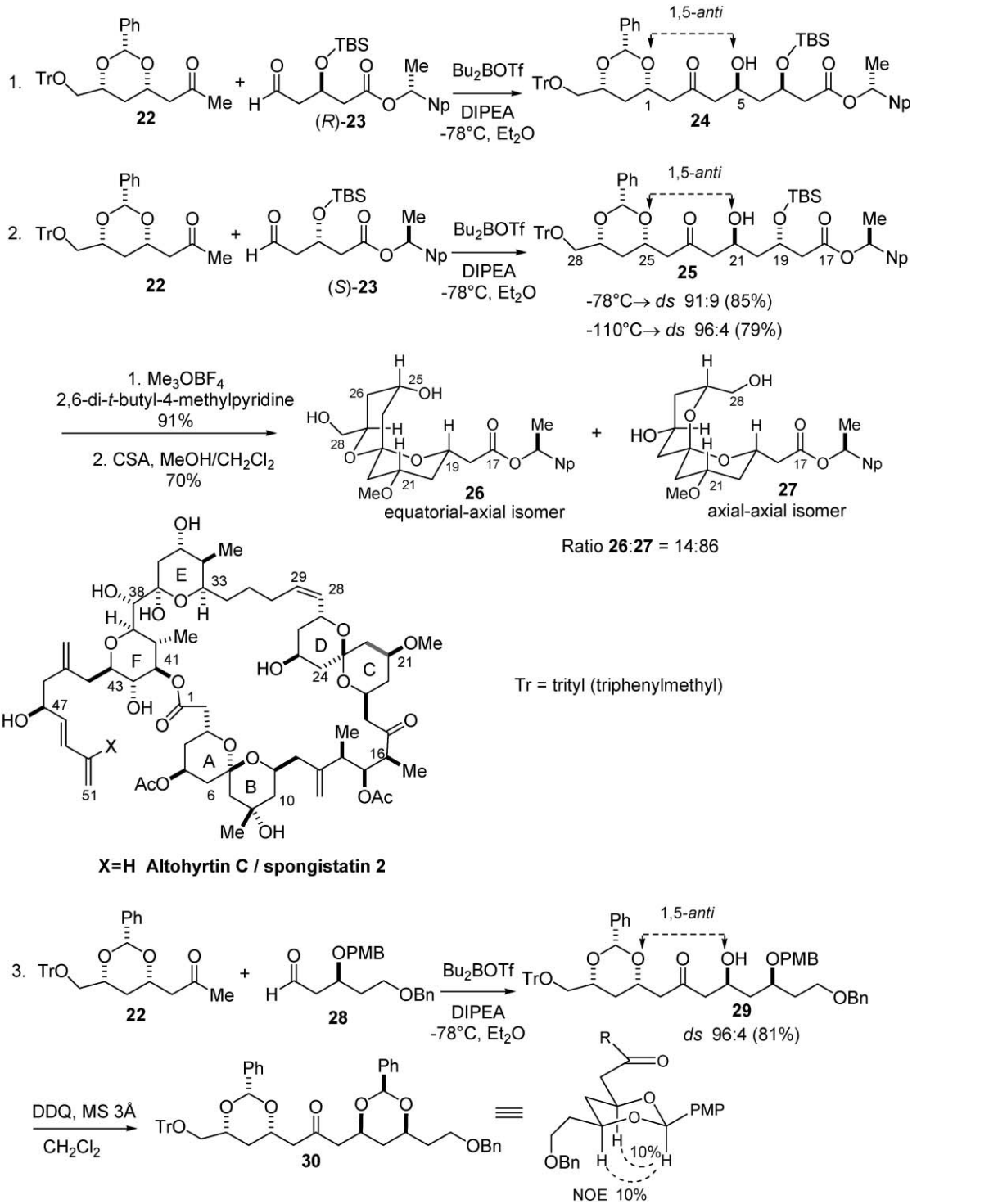
The stereochemistry at C20 in aldol **39** was confirmed after conversion to the PMB acetal **42** followed by NOE analysis (Scheme 9). The corresponding epimer at C20 (**43**) was also isolated and its relative stereochemistry was confirmed by NOE analysis.

By using the same aldol coupling strategy between **34** and **35** followed by *in situ* reduction with $LiBH_4$ the reaction proved to be exceptionally diastereoselective (ds 97 : 3) in favor of the the corresponding diol **44** (Scheme 10).[20]

In their very fascinating work directed towards the total synthesis of the spongipyran macrolide altohyrtin A (spongistatin 1), Paterson and co-workers described remarkable examples of double and triple asymmetric induction in boron-mediated aldol reactions of β-alkoxy methyl ketones (Scheme 11).[21–25]

In their approach to the AB-spiroketal of spongistatin 1, the authors have used different combinations between β-alkoxy aldehydes and β-alkoxy methyl ketones together with achiral and chiral boranes (Scheme 11).[21–25] First, the authors checked the facial selectivity of chiral aldehyde **46**. The aldol union of β-alkoxy-substituted aldehyde **46** with the boron enolate generated from acetone in the presence of (−)-diisopinocampheylboron chloride (entry 1, Scheme 11) gave 1,3-*syn* aldol adduct **47** in excellent diastereoselectivity (ds 93 : 7). By using c-Hex_2BCl they observed a lower selectivity for the 1,3-*syn* isomer (ds 75 : 25), and the use of (+)-Ipc_2BCl led to the 1,3-*anti* isomer in a very low diastereoselectivity (ds 43 : 57), which clearly shows that the β-alkoxy stereocenter of the aldehyde plays a secondary role in these aldol reactions, with (−)-Ipc_2BCl being the key control element.

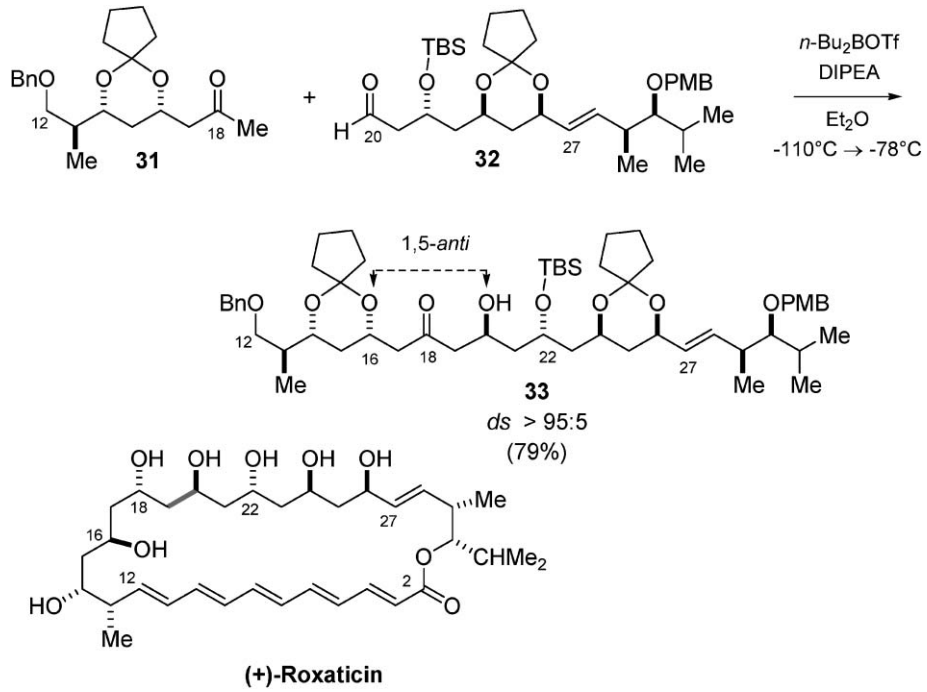
The facial selectivity of chiral methyl ketone **48** was determined by reaction of the corresponding enol borinate with isobutyraldehyde (entry 2), providing the aldol adduct 1,5-*anti* **49** in excellent diastereoselectivity (ds 95 : 5) in the presence of (−)-Ipc_2BCl, but with disappointing levels of diastereoselectivity (ds 77 : 23) in the presence of c-Hex_2BCl.[21–25] Clearly, as observed before, the (−)-Ipc_2BCl is controlling the



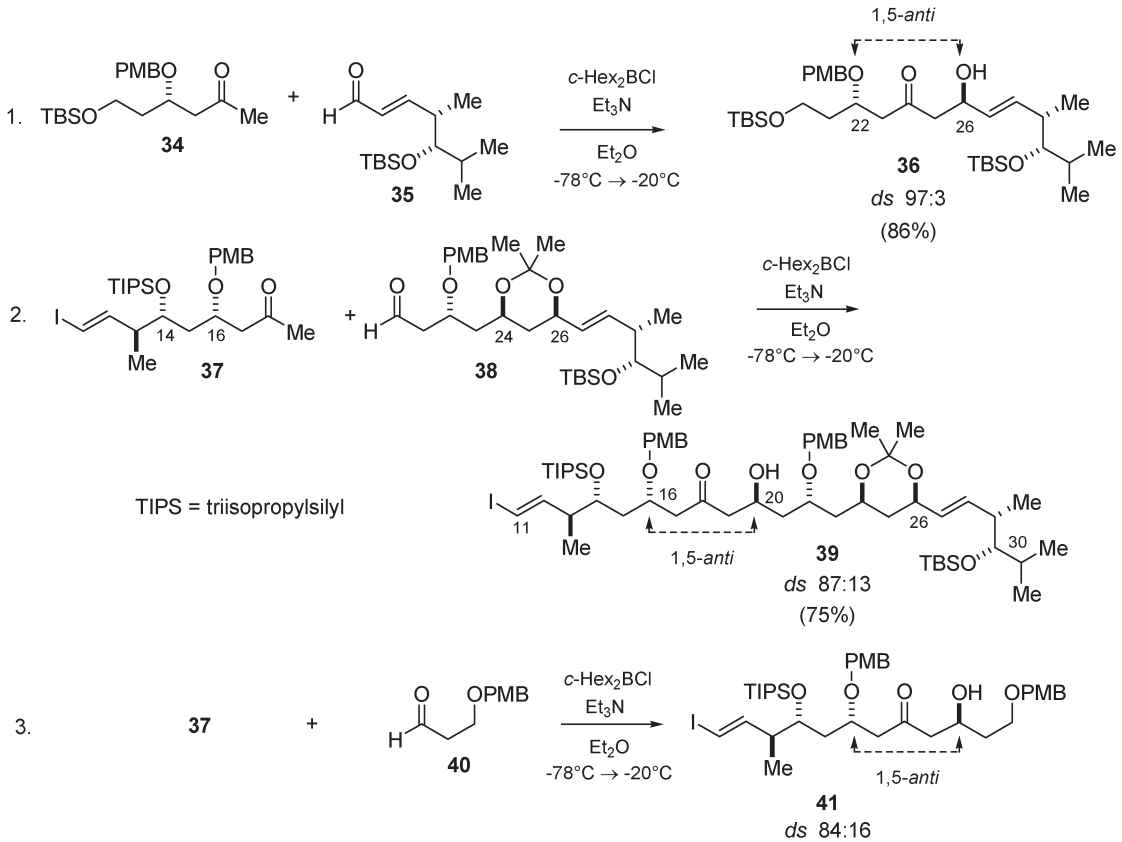
Scheme 6

overall diastereoselection of the process with the β-OTBS playing a secondary role. The combination of three chiral components (ketone **48** + aldehyde **46** + (−)-Ipc_2BCl) in the next aldol reaction (entry 3, Scheme 11) gave aldol adduct **50** in excellent diastereoselectivity (ds 98 : 2). In this case, the facial selectivity of aldehyde **46** together with the chiral induction promoted by the enol borinate from methyl ketone **48**, as well as the asymmetric induction promoted by (−)-Ipc_2BCl, were combined, providing the observed high level of diastereoselectivity. By employing c-Hex_2BCl the 1,5-*anti* aldol product was isolated in similar levels of diastereoselectivity (ds 96 : 4).

The configuration at the newly formed stereocenter at C-9 in aldol **50** was confirmed after protection of the hydroxyl group at C9 with TBS, leading to a compound with C_2-symmetry (Scheme 11). After treatment with MeOH and PPTS, aldol

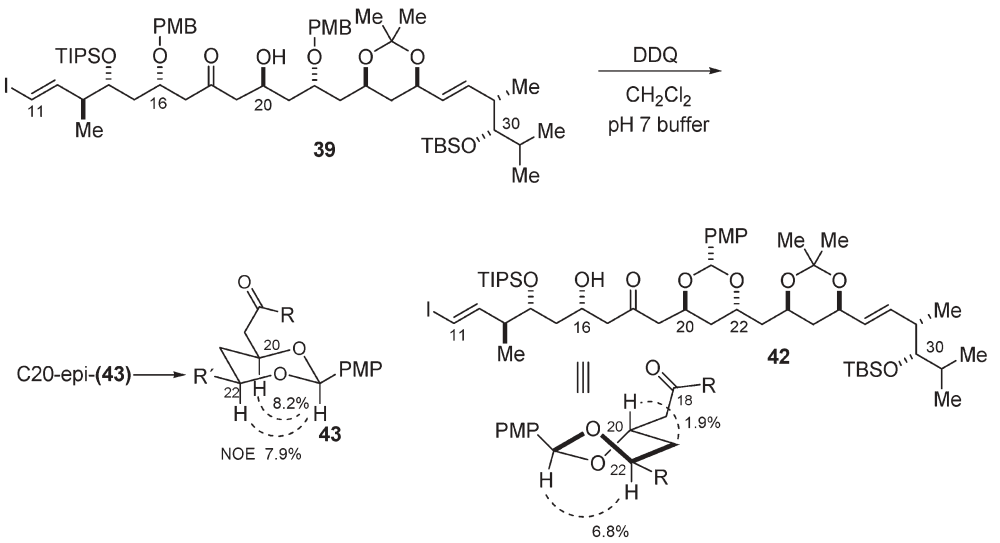


Scheme 7



Scheme 8

adduct **50** was transformed to spiroketal **51**, which corresponds to the AB spiroketal core of spongistatin 1.[21] Besides the fact this spiroketal contains two anomeric stabilizations, the hydrogen bonding with the hydroxyl group at C9 probably helps in the formation of the thermodynamic isomer. This spiroketal was latter converted to spiroketals **52** and **53**. The relative stereochemistry for spiroketal **53** was proved by the illustrated NOE enhancements (Scheme 11).



Scheme 9

In Scheme 12, the combination of chiral aldehyde **54**, methyl ketone **48** and (−)-Ipc$_2$BCl led to aldol adduct **55** with excellent levels of 1,5-*anti* diastereoselectivity (ds 97 : 3). In a very interesting synthetic application of this methodology, aldol **55** was converted to the AB spiroketal **56**, which corresponds to the C1–C15 fragment of spongistatin 1.[22]

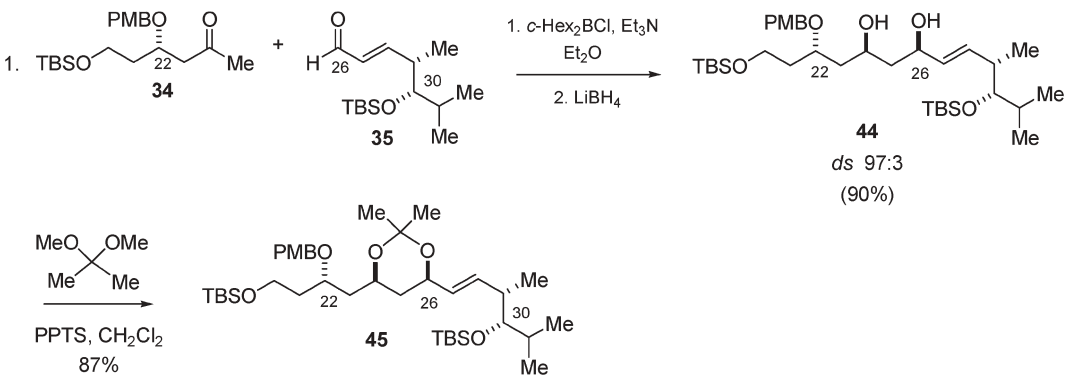
In another very interesting synthetic application of the 1,5-*anti* aldol reaction, Paterson and co-workers investigated the use of methyl ketones with β-OPMB, β-OMe and β-OBn substituents in order to prepare the C16–C28 spiroketal fragment of spongistatin 1 (Scheme 13).[23–25] The enol borinate prepared from methyl ketone **7a** and c-Hex$_2$BCl (Scheme 13, entry 1) reacted with aldehyde **57** to give β-hydroxy ketone **58** in moderate diastereoselectivity (ds 84 : 16).

In entries 2 and 3 of Scheme 13 we have examples of triple asymmetric induction in matched combinations. Treatment of methyl ketone **59** (β-OMe) with (−)-Ipc$_2$BCl followed by addition of chiral aldehyde **60** gave aldol adduct **61** with 97 : 03 diastereoselectivity. The use of methyl ketone **62** under the same conditions with aldehyde **60** led to aldol **63** with similar levels of diastereoselectivity. In entry 4, the reaction of the boron enolate prepared from chiral methyl ketone **64** and (+)-Ipc$_2$BCl reacted with achiral aldehyde **65** to give aldol **66** with 91 : 09 diastereoselectivity. The aldol products described in Scheme 13 were applied in the synthesis of the CD spiroketal core of spongistatin 1.[21–25]

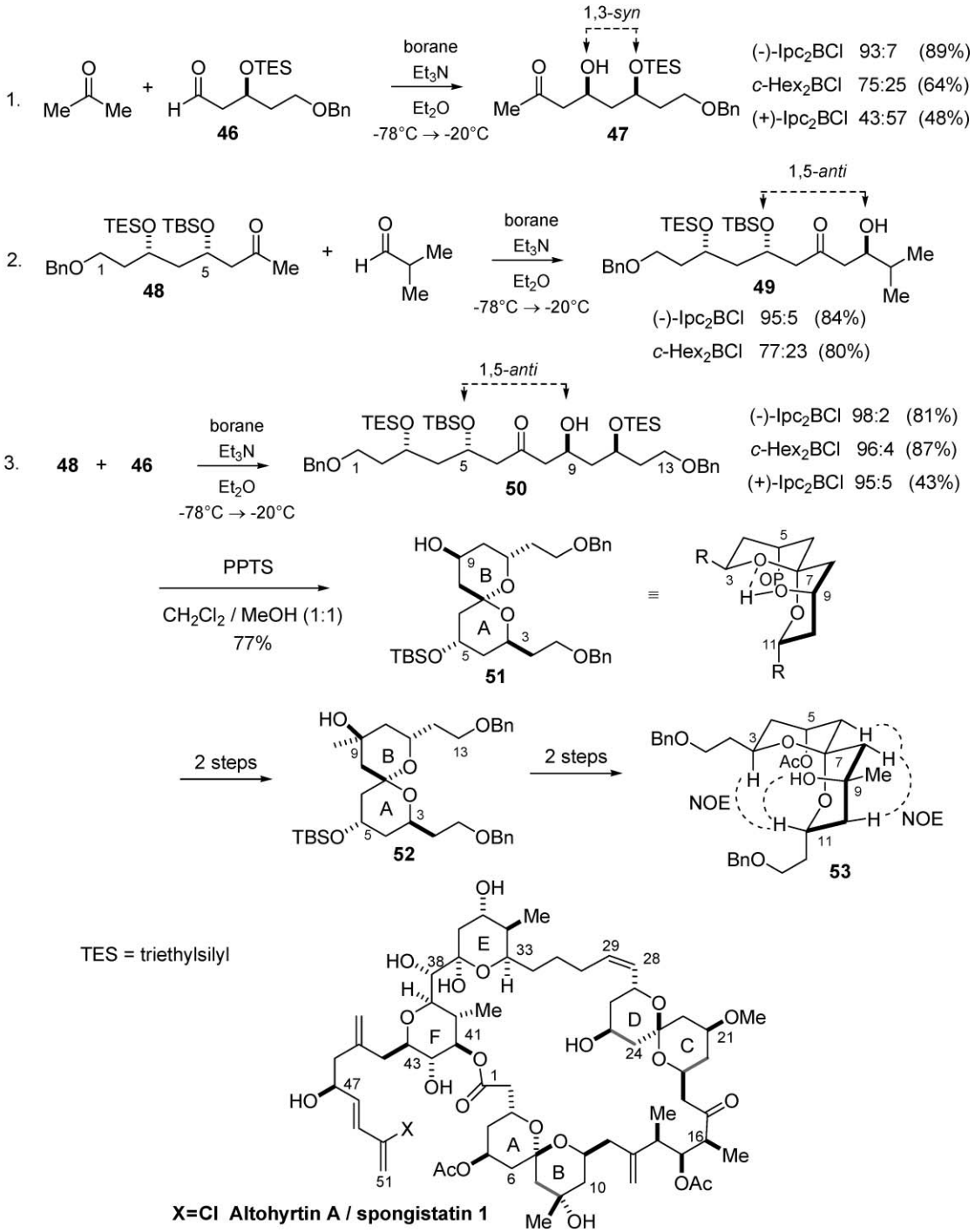
It is worthy of note that the Paterson group concluded the total synthesis of spongistatin 1 in 33 steps with the boron aldol reaction of methyl ketones with 1,5-*anti* induction being applied in 3 steps.[21–25]

The usefulness of this methodology was again displayed by the Paterson group in the asymmetric synthesis of the macrolide (+)-leucascandrolide A.[26,27] Remarkable levels of 1,5-*anti* diastereoselectivity were obatined after reaction of the less substituted dicyclohexylboron enolate prepared from methyl ketone **67** with aldehyde **68** leading to the *anti*-Felkin aldol **69** in 94 : 06 diastereoselectivity (Scheme 14). In addition, the authors used a tetrahydropyran moiety at the β-position to give an analogous directing effect compared to the more traditional OPMB, OBn and OMe groups. This aldol product corresponds to the C1–C15 fragment of (+)-leucascandrolide A.

In these papers the authors described that high levels of 1,5-*anti* induction were also obtained after reaction of **67** with achiral aldehydes. These data are consistent with the α-methyl stereocenter at the aldehyde playing only a secondary role in these aldol reactions.[12,13,20,28]



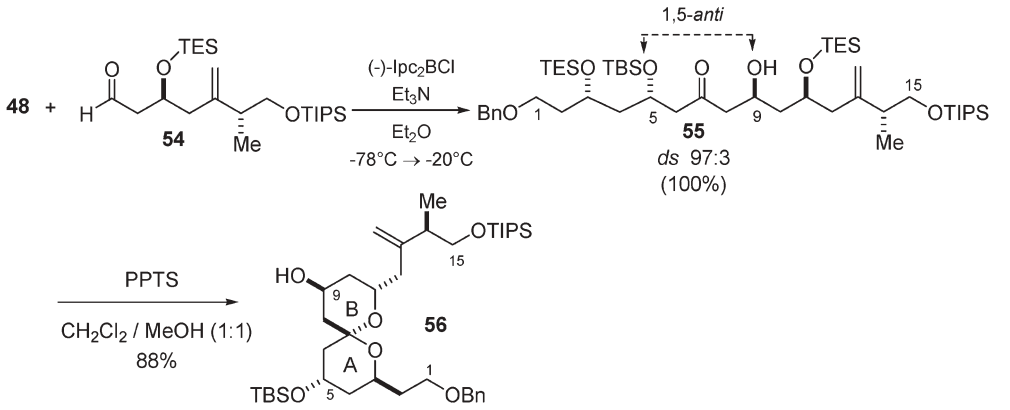
Scheme 10



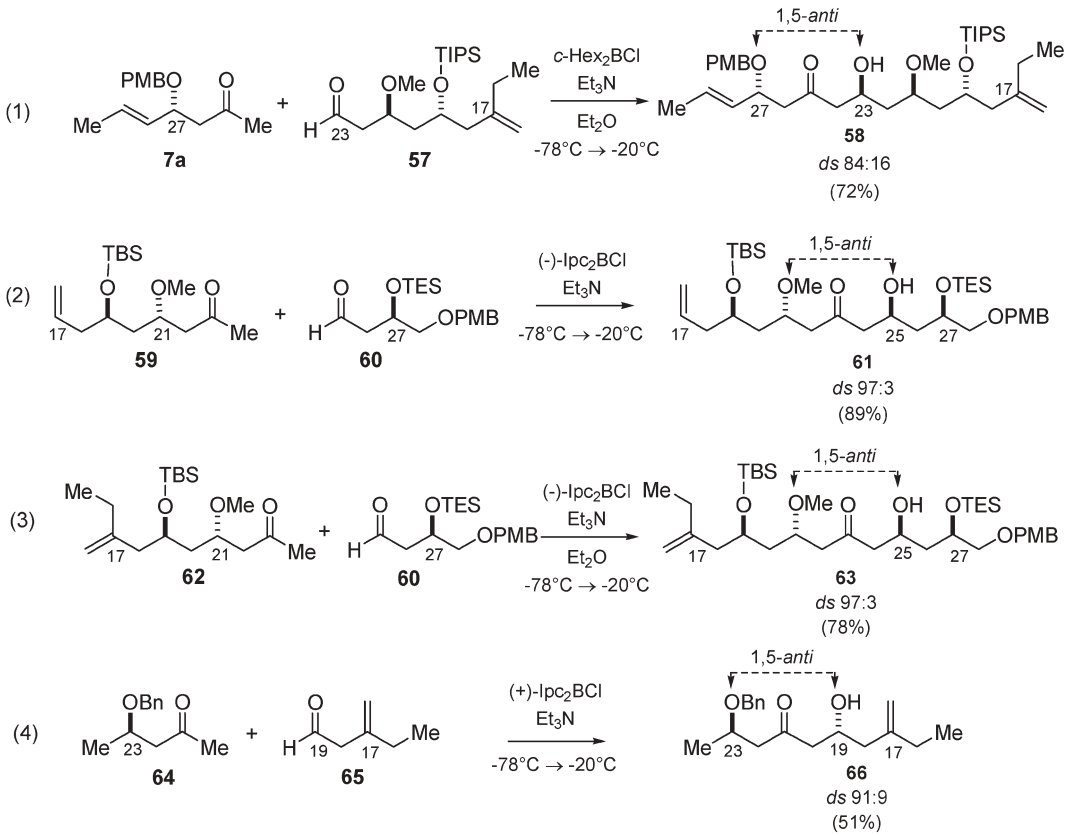
Scheme 11

A very similar approach has been used by Kozmim in his route to the C1–C15 fragment of leucascandrolide A (Scheme 15). He observed 1,5-*anti* induction from the β-oxygen-bearing stereocenter in the c-Hex$_2$BCl-mediated aldol reaction of methyl ketone **70** with aldehyde **71**, providing aldol **72** in >95 : 05 diastereoselectivity.[29]

High levels of 1,5-*anti* asymmetric induction using boron enolates containing a β-tetrahydropyran ring were also described by the Evans group (Scheme 16). This protocol has been used as a key step in the total synthesis of phorboxazole B.[30] In this case, the facial selectivity of the less substituted dibutylboron enolate prepared from methyl ketone **73** was determined by reaction with achiral aldehyde **74**, providing 1,5-*anti* aldol **75** with >95 : 05 diastereoselectivity (entry 1). The relative stereochemistry for **75** was established by X-Ray analysis. Reaction of the same boron enolate with chiral aldehyde **76** led to product **77** with similar levels of diastereoselectivity (entry 2). Aldol **77** was converted to bis-tetrahydropyran **78**, which corresponds to the C4–C19 fragment of phorboxazole B, after a sequence involving 5 steps. The



Scheme 12



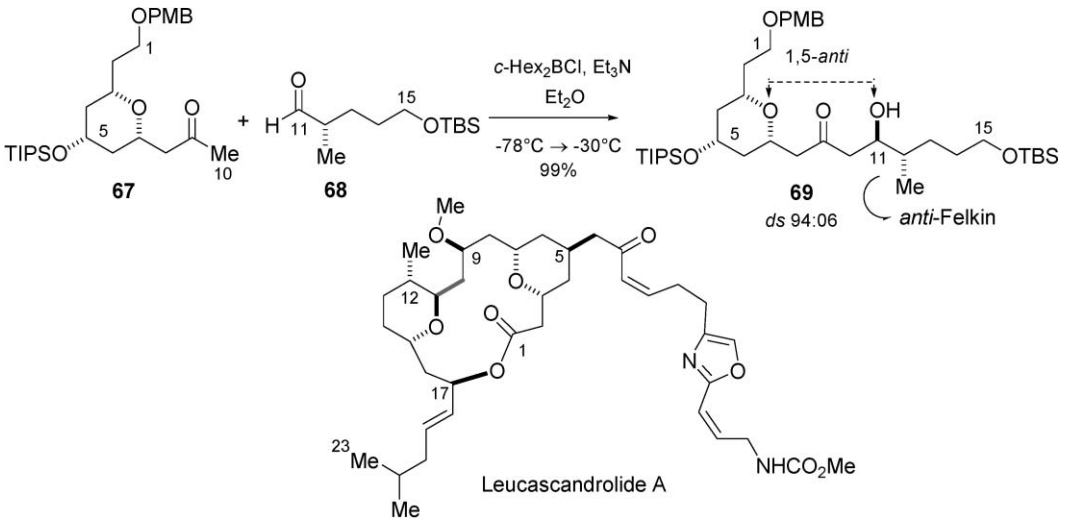
Scheme 13

relative stereochemistry was confirmed at this point by using NOE and ROESY experiments.[30]

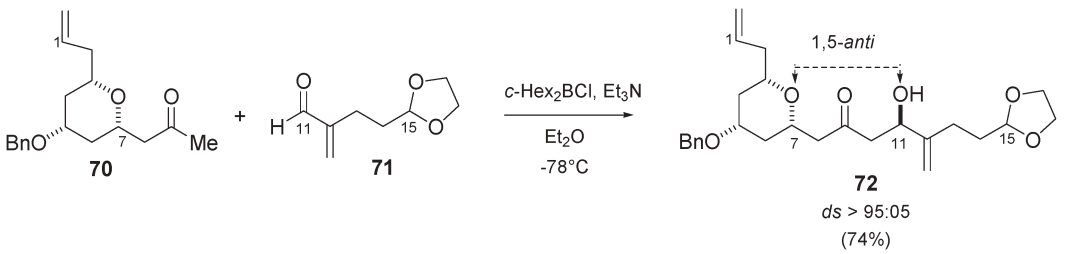
In another good example, Paterson and co-workers applied the 1,5-*anti* aldol methodology in the synthesis of the C9–C19 fragment of peloruside (Scheme 17).[31] Reaction of the dicyclohexylboron enolate derived from methyl ketone **79** with aldehyde **80** gave aldol **81** with >95 : 05 diastereoselectivity. The configuration at the newly formed stereocenter at C11 was determined by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters.

The authors also investigated the aldol addition reaction of the kinetic boron enolate of methyl ketone **82** with isobutyraldehyde. Surprisingly, 1,5-*anti* aldol adduct **83** was obtained with only 75 : 25 diastereoselectivity. They believe this is due to the γ-OTBS substituent adversely affecting the stereodirecting effect of the β-OMe group, in accordance with previous observations from the same group.[20,32]

In another application of this aldol coupling strategy, Keck and McLaws described their preliminary results towards the total synthesis of dolabelide B (Scheme 18).[33] In entry 1, the dicyclohexylboron enolate of ketone **84** reacted with a threefold excess of aldehyde **85** providing 1,5-*anti* aldol **86** in 93% yield and 92:08 diastereoselectivity. In entry 2 the authors investigated the coupling of the dicyclohexylboron enolate of methyl ketone **87** with achiral aldehydes **88–90**. Boron aldol reactions of ketone **87** with aldehydes **89** and **90** gave the



Scheme 14



Scheme 15

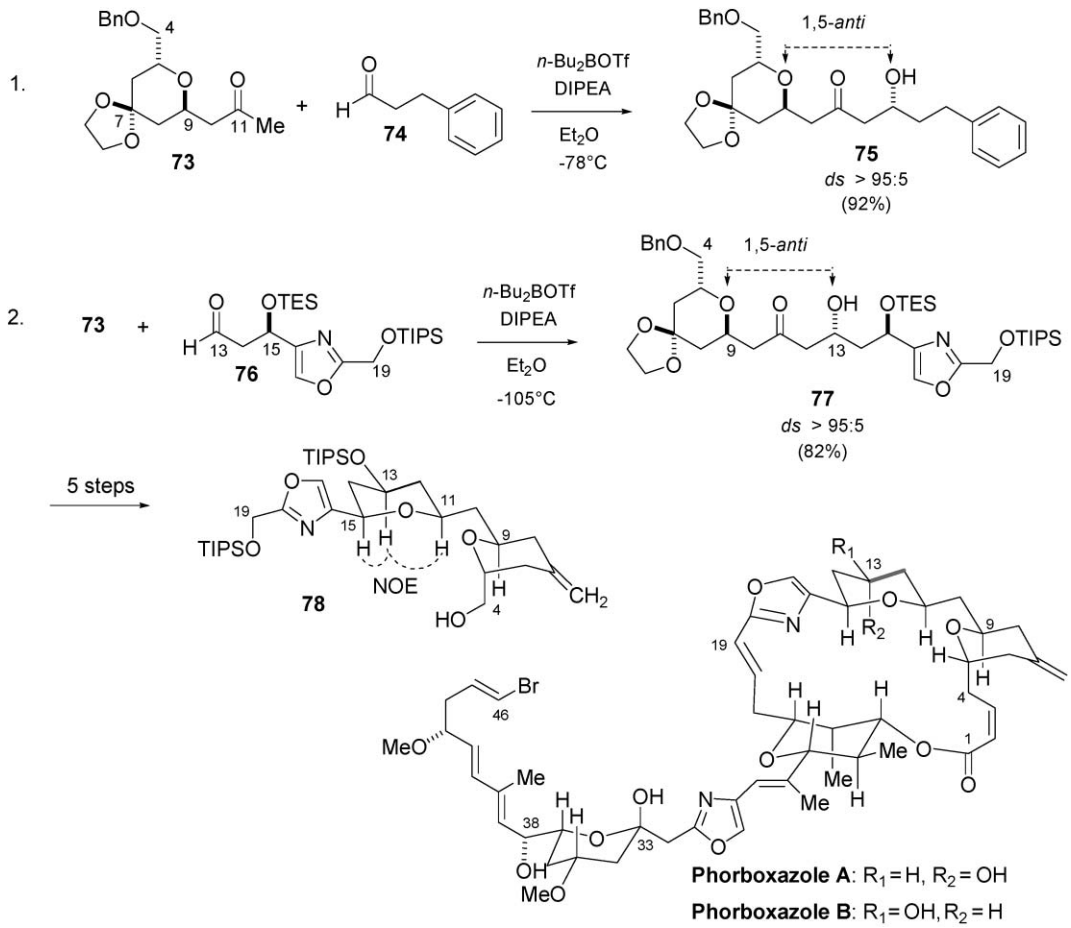
desired aldol adducts **92** and **93**, respectively, in good yields and high levels of diastereoselectivities. The relative stereochemistry for aldol adduct **92**, which corresponds to the C1–C13 fragment of dolabelide B, was confirmed by ^{1}H NMR analysis of the C11 Mosher ester as well as from the C7–C9 and C9–C11 acetonides using the Rychnovsky method.

In a more recent work, Leighton and co-workers described a 1,5-*anti* aldol coupling reaction applied in the total synthesis of dolabelide D (Scheme 19).[34] The n-Bu_2BOTf-mediated aldol coupling between ketone **94** and aldehyde **95** led to aldol **96**, which corresponds to the C1–C13 fragment of dolabelide D, in 79% yield and 91 : 09 diastereoselectivity.

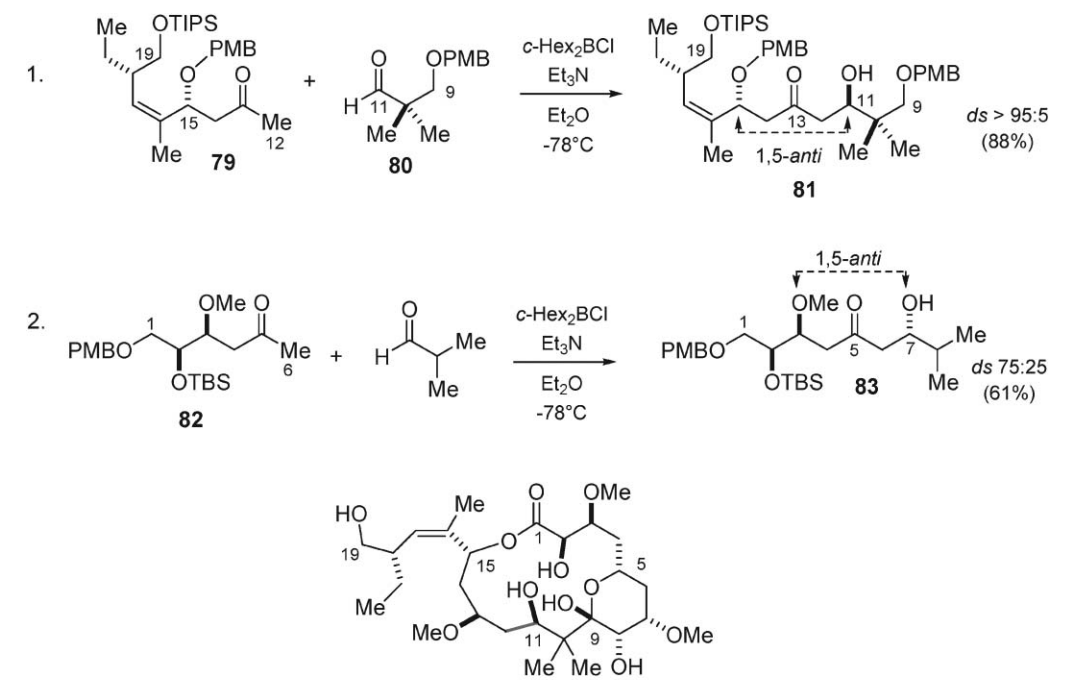
Marco and co-workers applied the 1,5-*anti* aldol methodology in their recent synthesis of aculeatins A, B, D and 6-*epi*-D (Scheme 20).[35] The aldol addition reaction of the enolborinate of β-alkoxy methyl ketone **97** with aldehyde **98** takes place with essentially complete diastereoselectivity to provide aldol **99** in 70% yield (ds >95 : 05). After reduction with $LiBH_4$ they were able to isolate diol **100** as a single diastereoisomer. However, even better results (65%, 2 steps) were obtained after *in situ* reduction of the aldol intermediate with $LiBH_4$. Finally, treatment of acetonide **102** with phenyliodonium bis(trifluoroacetate) gave an 84 : 16 mixture of aculeatins A and B. A similar approach involving aldol **99** was used in the synthesis of aculeatins D and 6-*epi*-D. In addition, the authors have determined the absolute configurations and corrected the previously assigned relative stereochemistry for the natural products.

In a very interesting work, Trieselmann and Hoffmann described bis-directional synthetic strategies in the stereoselective synthesis of stereodefined skipped polyols (Scheme 21).[36] Addition of the bis-enolborinate derived from methyl ketone **103** (c-Hex_2BCl, Et_3N, Et_2O) with aldehyde **104** gave the doubly extended aldol adduct **105** in 65% yield and 80 : 20 (*anti*,*anti*:*anti*,*syn*) diastereoselectivity. Addition of the boron enolate derived from the more complex dimethyl ketone **106** to the same aldehyde **104** led to *anti*,*anti* aldol **107** as the major isomer in 72% yield and 83 : 17 diastereoselectivity. The major isomers in these reactions were easily identified by their symmetry (Scheme 21).

In the examples already cited, the methyl ketone components have lacked substitution at the α-position to the ketone carbonyl group. At this point, the Dias group decided to investigate the levels and sense of selectivity of boron enolates derived from α-methyl-β-alkoxy methyl ketones in reactions with achiral as well as chiral aldehydes.[37] The double-diastereodifferentiating aldol addition reactions of chiral enolborinates prepared from α-methyl-β-alkoxy methyl ketones with achiral and chiral aldehydes were examined, leading to the corresponding aldol adducts with excellent levels of 1,5-*anti* diastereoselection. First, the c-Hex_2BCl-mediated aldol reaction of methyl ketone **108** containing a β-OTBS with aldehyde **109** gave a 52 : 48 mixture of aldol adducts **110** and **111** (Scheme 22). This is in accordance with previous results from the Paterson and Evans groups.[12,13] The contribution of the α-methyl stereocenter was reduced and this led to the

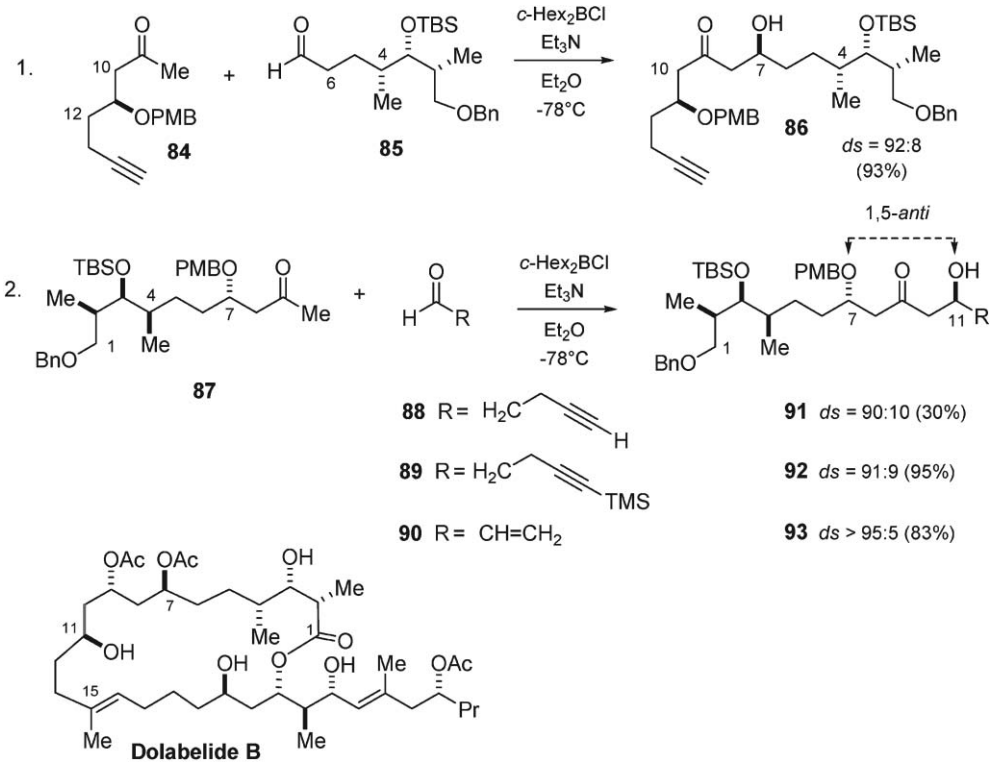


Scheme 16

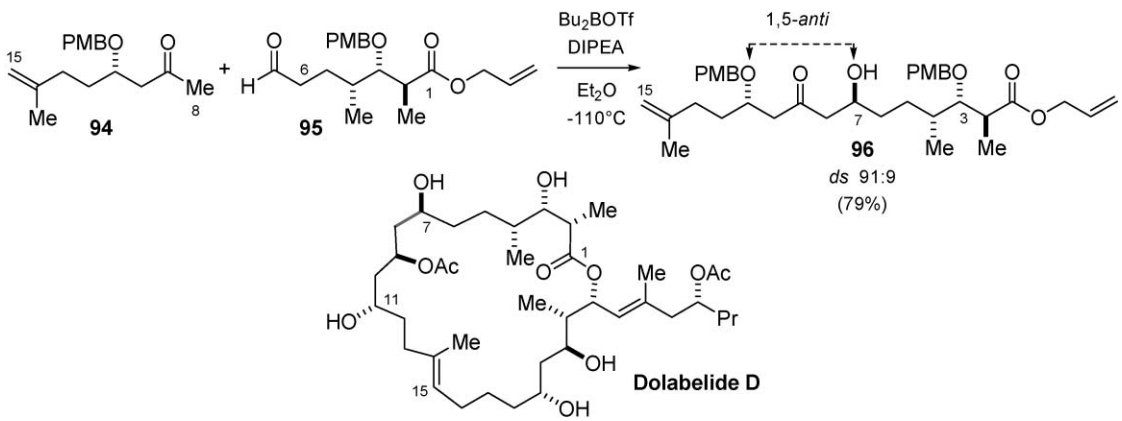


Peloruside A

Scheme 17



Scheme 18



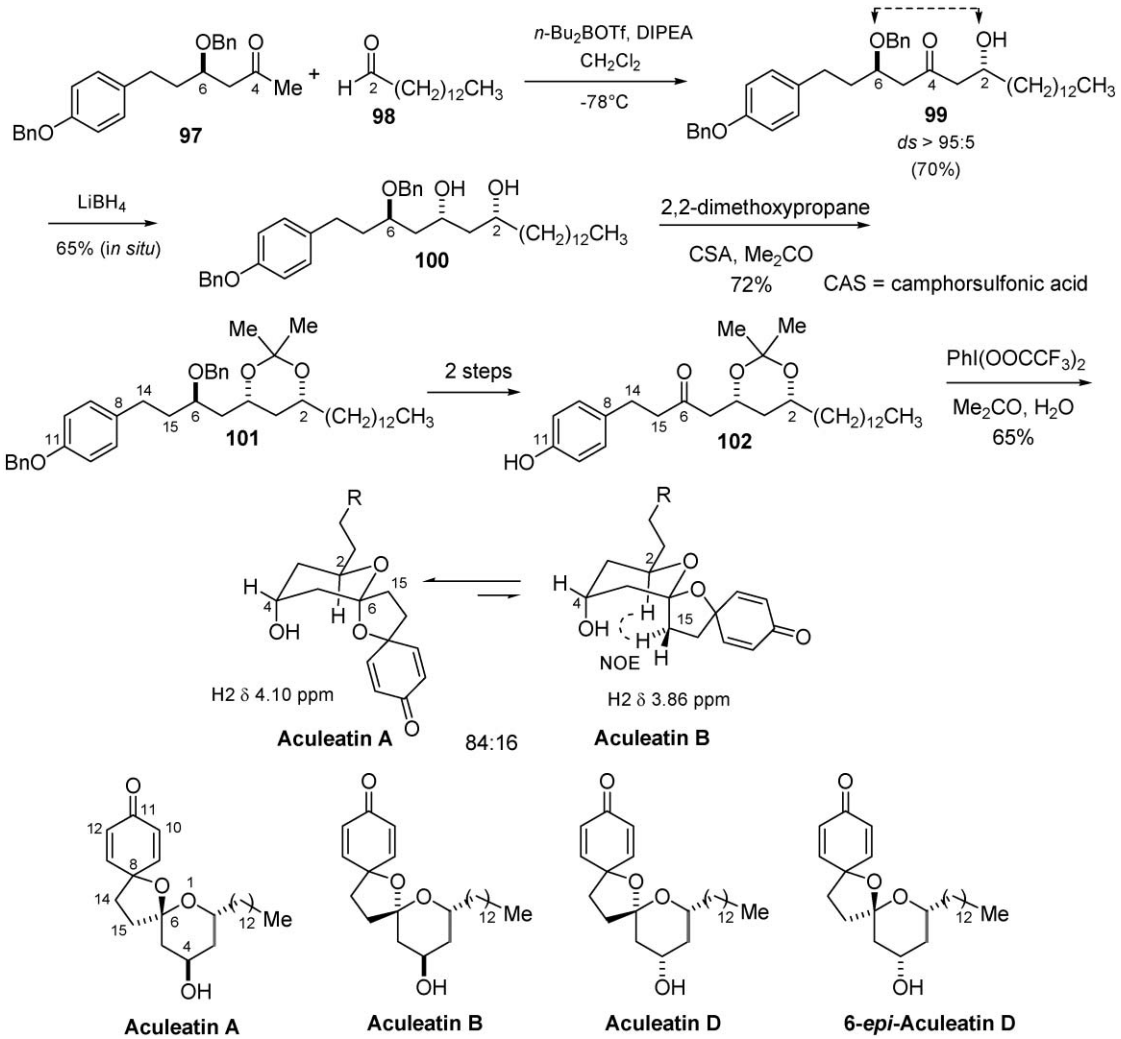
Scheme 19

conclusion that the stereogenic center α to the carbonyl group does not play a very important role in these aldol reactions.[13,38] In fact, it is known that, usually, reagent control using chiral ligands on boron is required to obtain useful levels of asymmetric induction in the addition of boron enolates of α-methyl ketones to achiral aldehydes.[38]

Based on this result the Dias group decided to investigate the use of methyl ketone **112** (Scheme 23). The c-Hex_2BCl-mediated aldol coupling between methyl ketone **112** with achiral aldehydes gave 1,4-*syn*-1,5-*anti* aldol adducts **113–117** in excellent diastereoselectivities (ds >95 : 05). The relative stereochemistry was confirmed by X-Ray analysis of aldol adduct **113**.[37]

They also observed better yields by using the dicyclohexylboron enolate instead of the corresponding dibutylboron enolates,[37] in agreement with results published later by Sinha and co-workers.[39]

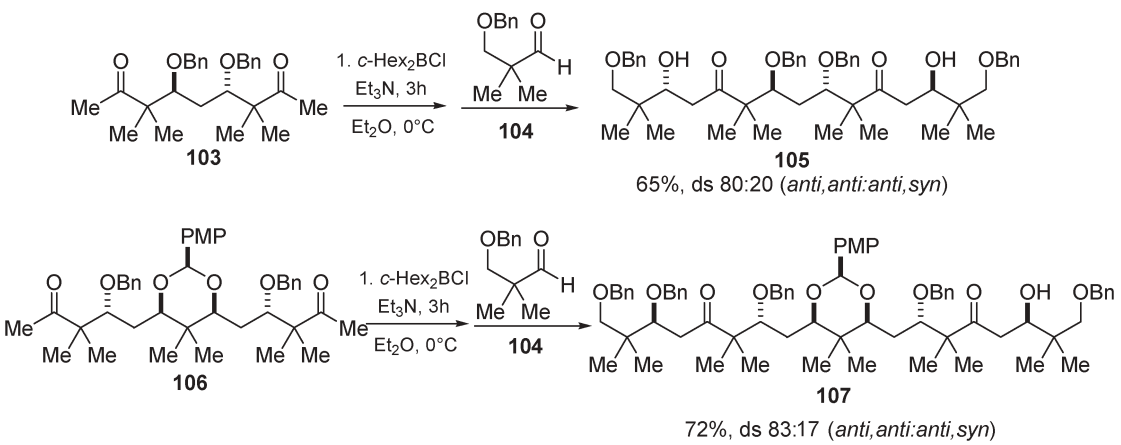
In 2002, Arefolov and Panek published their results related to the asymmetric synthesis of the C1–C14 fragment of discodermolide (Scheme 24).[40,41] The n-Bu_2BOTf-mediated aldol reaction of methyl ketone **118** with aldehyde **119** provided the corresponding 1,4-*syn*-1,5-*anti* product **120** in high diastereoselectivities. On the basis of the results presented in Scheme 23 and those described by Arefolov and Panek, it was proposed that the α-methyl stereocenter in these methyl ketones plays only a secondary role in these aldol reactions, with the β-alkoxy substituent being responsible for the enolate facial bias. Depending on the relative stereochemistry of the α-methyl-β-alkoxy methyl ketone used, both 1,4-*syn* and 1,4-*anti* aldol adducts could be obtained without the need to use a chiral auxiliary.



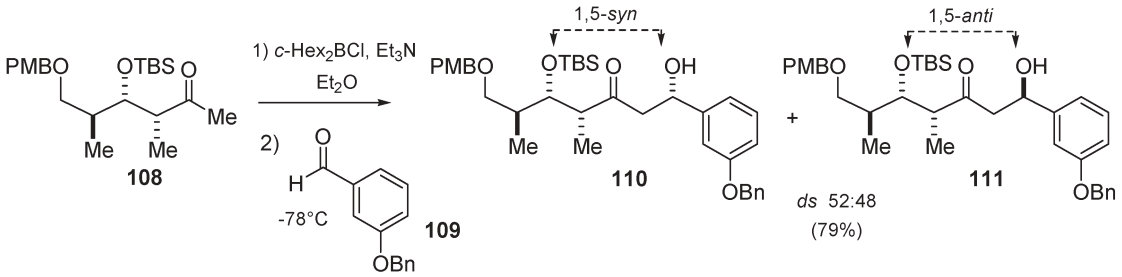
Scheme 20

It is interesting to point out that the dibutylboron enolates were more selective than the dicyclohexylboron enolates and the use of ethyl ether as solvent in combination with lower temperatures (−110 °C) led to better yields.[40,41] The relative stereochemistry for aldol **120** was determined by the NOE analysis of benzylidene acetal **121**.

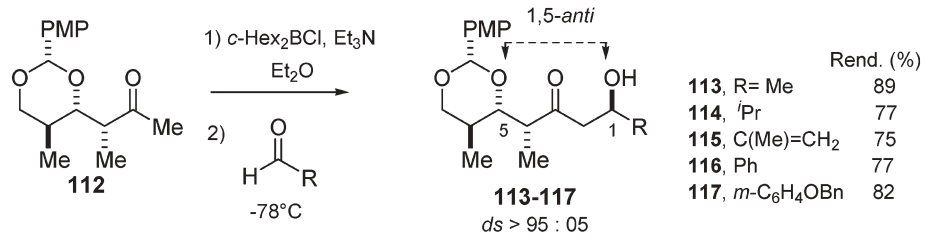
The Dias research group has also investigated the aldol reactions of the boron enolate derived from treatment of



Scheme 21



Scheme 22

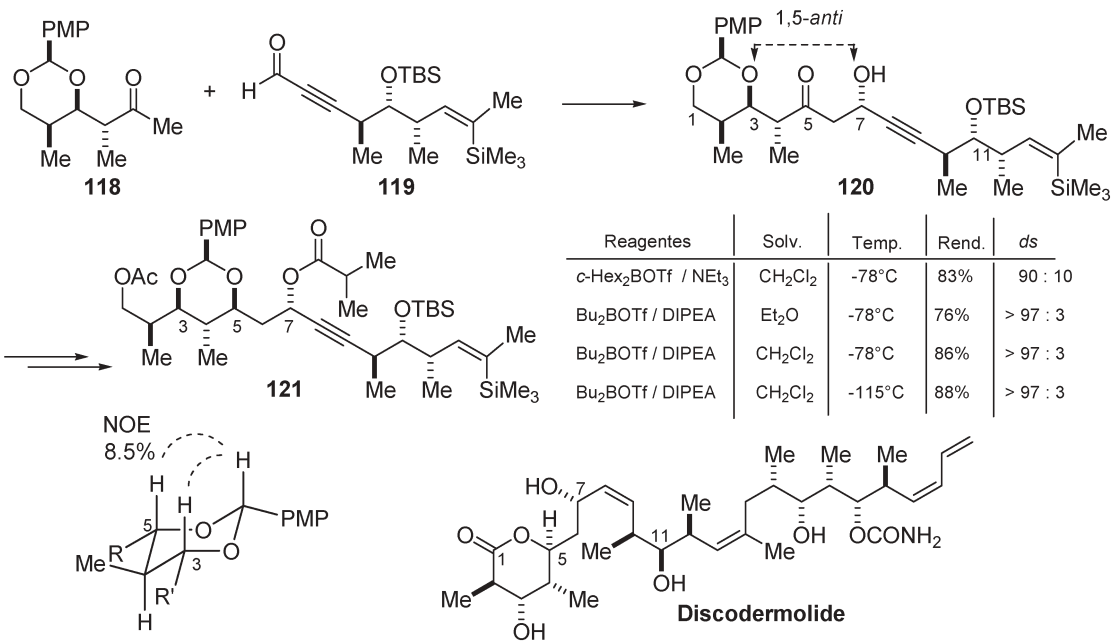


Scheme 23

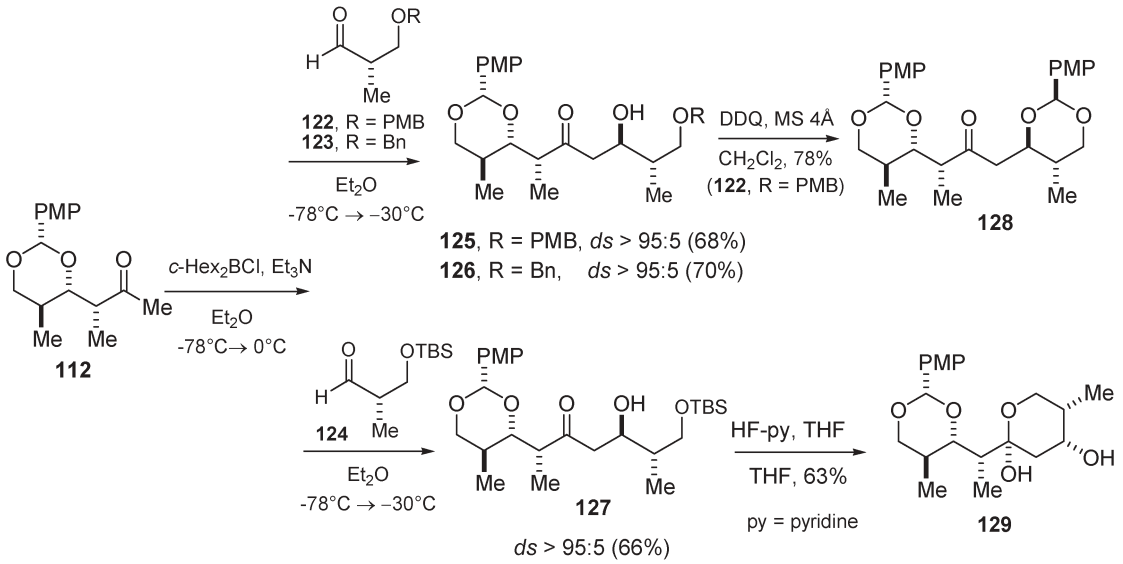
methyl ketone **112** (c-Hex_2BCl/DIPEA) with chiral aldehydes **122–124** (Scheme 25).[42] These substrates were chosen to be representative of the complex fragments that might be coupled in polyacetate and polypropionate-derived aldol-type reactions. Aldehydes with *tert*-butyldimethylsilyl (TBS), benzyl (Bn) and *p*-methoxybenzyl (PMB) protecting groups were employed to evaluate the potential steric and electronic impact of the protecting group. The boron-mediated aldol reaction with chiral aldehydes **122–124** led to the *anti*-Felkin products **125–127** with extremely high levels of diastereoselectivity (Scheme 25). The relative stereochemistries for 1,5-*anti* aldols **125** and **127** were unambiguously established by ^{1}H NMR analysis of benzylidene acetal **128** and hemiacetal **129**, respectively.

Addition of the same boron enolate to the enantiomeric aldehydes **130** and **131** led to the Felkin products **132** and **133**, respectively, with good levels of diastereoselectivity (Scheme 26). These are examples of partially matched relationships as these aldehydes have a small preference for *anti*-Felkin addition.[42] The relative stereochemistries for 1,5-*anti* aldols **132** and **133** were assigned by ^{1}H NMR analysis of benzylidene acetal **134** and acetal **135**, respectively (Scheme 26).

Moving to the more complex aldehydes **136–139**, excellent diastereoselectivities favoring the 1,5-*anti* products **140–143**



Scheme 24



Scheme 25

were observed in reactions with the dicyclohexylboron enolate derived from **112** (Scheme 27).[42]

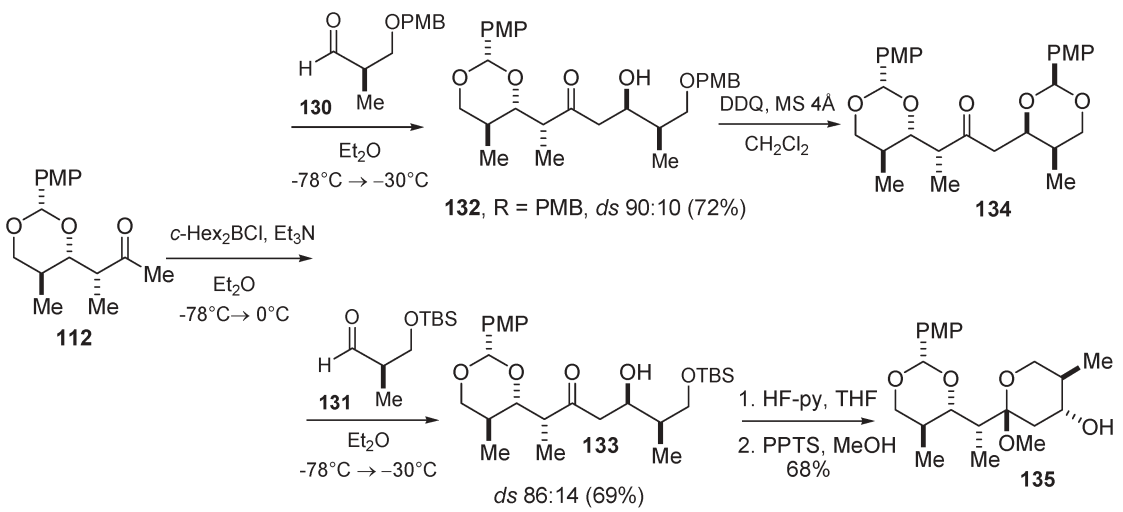
In the case of aldol adducts **140–143**, the relative stereochemistry was determined by using the very simple method developed by Roush and co-workers, which consists in coupling constant analysis for the methylenic hydrogens α to the carbonyl groups.[43–45]

As can be seen from these examples, the β-alkoxy stereocenter controls the asymmetric induction, even overriding the aldehyde facial bias for *anti*-Felkin addition. These examples show that high levels of substrate-based 1,5-*anti*-stereocontrol could be achieved in the boron-mediated aldol reactions of α-methyl-β-alkoxy methyl ketones with chiral aldehydes, leading to both Felkin and *anti*-Felkin aldol addition products. The levels of facial selection are independent of the absolute stereochemistries of the aldehydes although dependent on the absolute stereochemistry of the chiral boron enolate.[42]

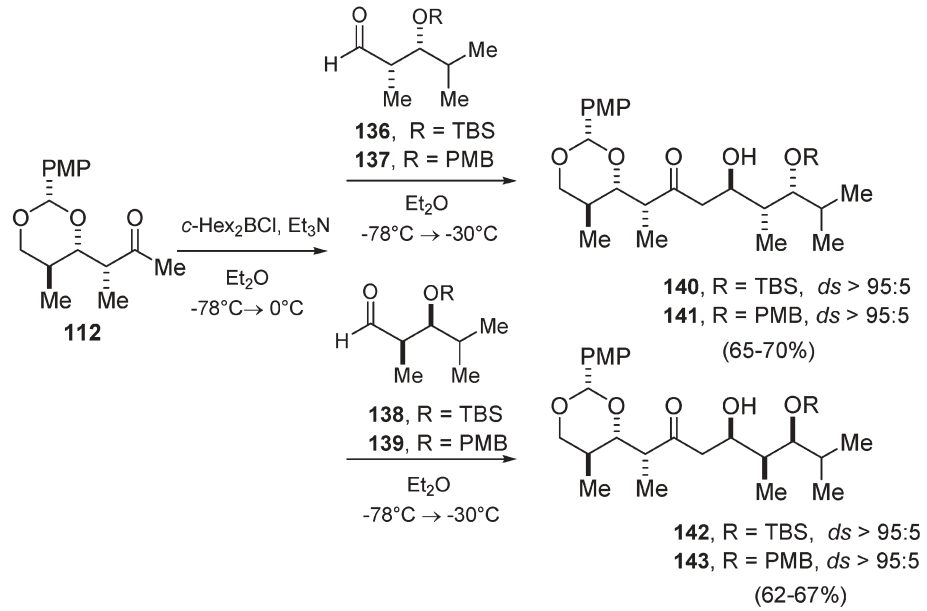
Dias and Salles also applied this 1,5-*anti* strategy in their approach to the C29–C39 fragment of sanglifehrin A (Scheme 28).[46] Aldol addition of the boron enolate derived from ketone **144** (c-He_2BCl/Et_3N) with aldehyde **124** gave *anti* aldol **145** with Felkin addition in >95 : 05 diastereoselectivity. The stereochemistry of **145** was assigned by coupling constant analysis in the ^1H NMR spectra of acetal **146**.

Very recently, Sinha and co-workers applied this strategy in the synthesis of the macrolactone precursors of sorangiolides and their analogues (Scheme 29).[47] The n-Bu_2BOTf-mediated aldol reaction of methyl ketone **147** with aldehydes **148** and **149** proceeded successfully to provide aldols **150** and **151**, respectively, with 92 : 08 diastereoselectivity. After a few steps, aldols **150** and **151** were converted to macrocyclic lactones **152** and **153**, respectively.

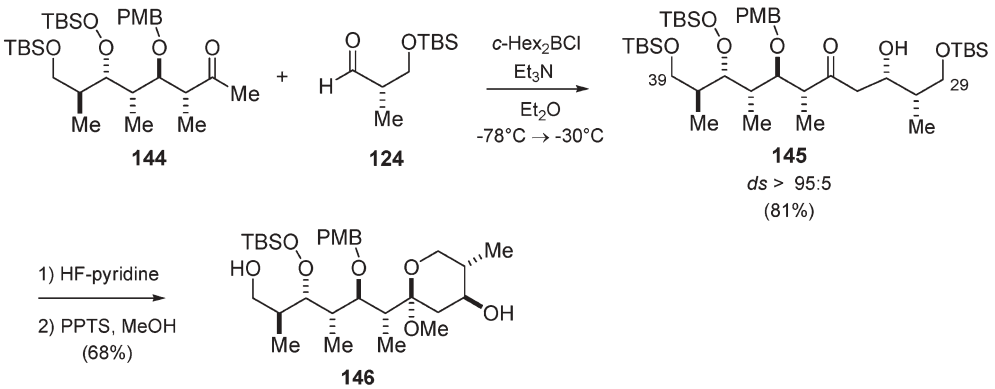
In a more recent work, Dias and co-workers disclosed their results in which good levels of substrate-based, 1,5-*syn*-stereocontrol were achieved in the boron-mediated aldol



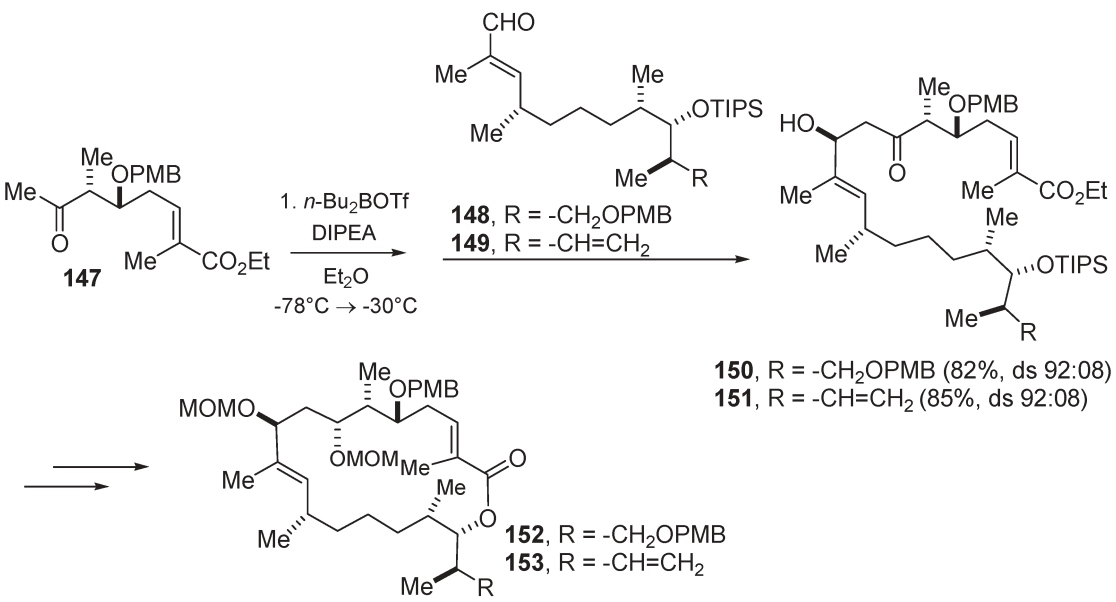
Scheme 26



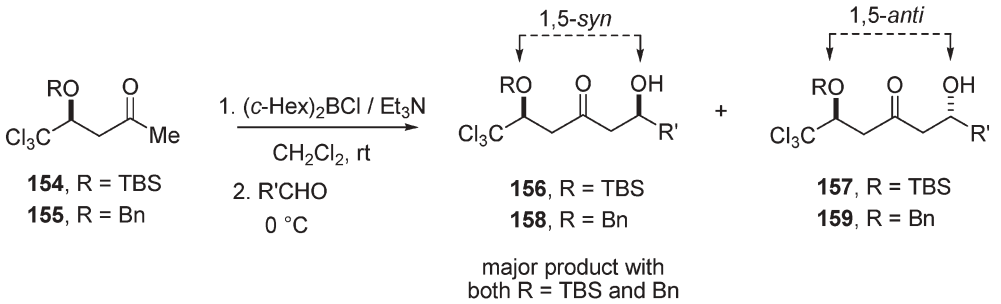
Scheme 27



Scheme 28



Scheme 29



Scheme 30

reactions of β-trichloromethyl methyl ketones with achiral aldehydes (Scheme 30).[48] Independent of the nature of the β-protecting group, the 1,5-*syn* diastereoisomer was always isolated as the major product when boron enolates generated from β-trichloromethyl methyl ketones were used. This aldol reaction gives the 1,5-*syn* isomer, opposite to 1,5-*anti* stereoinduction observed for boron aldol reactions of simple β-alkoxy methylketones, indicating the overriding contribution in this special case from the very strong electron withdrawing group at the β-position.

Origin of the 1,5-*anti* selectivity

It was suggested earlier by Hoberg and co-workers that a π-stacking interaction between benzylic protecting groups and the boron enolate would be important in the cyclic transition state.[49] However, even with β-alkoxy substituents like OMe, and cyclic ethers, like tetrahydropyranyl rings, high levels of 1,5-*anti* induction are obtained.

In 2006, Paton and Goodman published very interesting theoretical studies in order to try to understand the origins of the 1,5-*anti* asymmetric induction in boron-mediated aldol reactions of methyl ketones.[50] They concluded that the boron-mediated aldol reactions of methyl ketones proceed *via* boat-like transition states. In fact, several computational studies indicate that chair-like and boat-like transition states in methyl ketone aldol reactions are relatively close in energy.[51–54] For boron enolates with a β-alkoxy substituent, it is proposed that a stabilizing formyl hydrogen bond favors the 1,5-*anti* aldol adduct by minimizing steric interactions between the β-alkyl group and one of the ligands on boron (Fig. 2). Due to the lower intrinsic basicity of the oxygen, silyl protecting groups prevent this formyl hydrogen bonding and probably this is the reason for the low selectivity observed with silicon protecting groups at the β-oxygen.[54] The magnitude of this hydrogen bonding has been established by Natural Bond Order (NBO) analysis.[55]

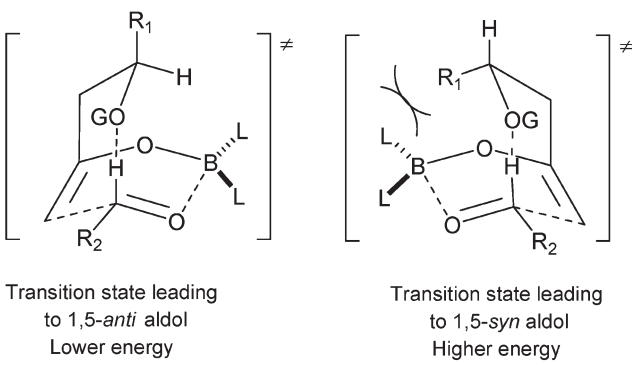


Fig. 2 Transition state models showing the formyl hydrogen bond.

Conclusions

High selectivities are obtained in aldol reactions of β-substituted methyl ketones when the β-alkoxy protecting group is benzylic (OBn, OPMB) or a benzylidene acetal. The nature of the β-alkoxy substituent is critical in determining the level of induction as usually, the use of a β-silicon protecting group gives rise to little or no selectivity. The strong internal stereoinduction of the β-alkoxy stereocenter of the boron enolates dominates the overall stereochemical outcome of the corresponding aldol addition reactions, leading to the 1,5-*anti* products with high diastereoselectivities. Even with the use of α-methyl-β-alkoxy methyl ketones, the β-stereocenter plays a dominant role in determining the sense of 1,5-*anti* asymmetric induction. It is also interesting to point out that a decrease in solvent polarity results in higher selectivity.[14] This 1,5-*anti* aldol methodology has been used in several key steps in the total synthesis of several natural products with interesting pharmacological significance.

Acknowledgements

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