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Stereoselective Synthesis of Allylic Alcohols via Substrate Control on Asymmetric Lithiation

Yannick Linne[+],[a] Daniel Lücke[+],[a] Kjeld Gerdes,[a] Kevin Bajerke,[a] and Markus Kalesse*[a, b]

Dedicated to Professor Ulf Diederichsen.

Allylic alcohols are a privileged motif in natural product synthesis and new methods that access them in a stereoselective fashion are highly sought after. Toward this goal, we found that chiral acetonide-protected polyketide fragments performing the Hoppe–Matteson–Aggarwal rearrangement in the absence of sparteine with high yields and diastereoselectivities rendering this protocol a highly valuable alternative to the Nozaki–Hiyama–Takai–Kishi reaction. Various stereodyads and -triads were investigated to determine their substrate induction. The mostly strong inherent stereoinduction was attributed to a combination of steric and electronic effects.

Introduction

The chemistry of lithiation and borylation developed by Hoppe, Matteson and Aggarwal has been successfully used more frequently in the total synthesis of polyketide natural products.[1] In contrast to the well-established approach via aldol reactions for accessing these kind of natural products[2] the effect of stereoinduction by substrate control has been very little elucidated. In this context the first examples were reported by Hoppe in the 1990s.[3] Starting with a 1,3- or 1,4-dicarbamate (**1** or **4**), the first methyl branching was introduced via deprotonation in the presence of (−)-sparteine and trapping of the generated anion with methyl iodide.[4] Upon introduction of the second methyl group, substrates **1** and **4** showed strong inherent stereoinduction (Scheme 1a).[3a] However, even in the absence of the second carbamate function, they observed diastereoselective alkylation controlled by the adjacent stereogenic center (Scheme 1b).[3b] Further development of their work was the use of chiral acetonide **8** for stereoinduction by coordination to the lithium atom, in which case the best selectivities were obtained without the addition of a diamine (Scheme 1c).[3c] We recently published two studies on the stereoselective synthesis of allylic alcohols by lithiation–borylation chemistry.[5] The first study (Scheme 1d)[5a] describes a general protocol for the synthesis of various chiral allylic alcohols by lithiation–borylation chemistry utilizing the chiral diamine sparteine for stereocontrol. In our second study we investigated on substrate- and reagent-induction in 1,2-metallate rearrangements of linear 2,4,6-triisopropylbenzoyl (TIB)- and *N,N*-diisopropylcarbamoyl (Cb)-derived diketides using vinyl boronic esters. Here, we observed the combination of TIB directing group and large (branched) vinyl boronic esters favoring the formal Felkin products. The Cb group on the other hand favors the formation of the formal *anti*-Felkin products (Scheme 1e).[5b] To further investigate on substrate controlled lithiation–borylation chemistry, acetonide-protected diketides were treated with different vinyl boronic esters. By this, the behavior of more rigid systems was analyzed and valuable polyketide building blocks were accessed.

Results and Discussion

In order to mimic the situation in polyketide frameworks as closely as possible, six-ring acetonides (1,3-distance of hydroxyl groups) and additional α-methyl branching (2 stereocenters) were used first. Both the acetonide-protected *syn*- and *anti*-diketides **14a**–**15b** were reacted with sterically different demanding vinyl boronic esters **16**–**19** (Figure 1).[6,7] In contrast to the work done by Hoppe[3c] all reactions were carried out in the presence of a diamine for better comparison with our previous study.[5b] Additionally, lithiation and borylation of the TIB and Cb derivatives of acetonide **8** with vinyl boronic ester **19** in the absence of TMEDA showed a massive drop in yield compared to the reactions carried out in the presence of the diamine (for more details see Supporting Information). The presence of a diamine ligand in lithiation–borylation chemistry was found to be crucial by Aggarwal as well.[8]

[a] Dr. Y. Linne,[+] Dr. D. Lücke,[+] K. Gerdes, K. Bajerke, Prof. Dr. M. Kalesse
Institute of Organic Chemistry
Gottfried Wilhelm Leibniz Universität Hannover
30167 Hannover (Germany)
E-mail: markus.kalesse@oci.uni-hannover.de
[b] Prof. Dr. M. Kalesse
Centre of Biomolecular Drug Research (BMWZ)
Wilhelm Leibniz Universität Hannover
30167 Hannover (Germany)

[+] *These authors contributed equally to this work.*

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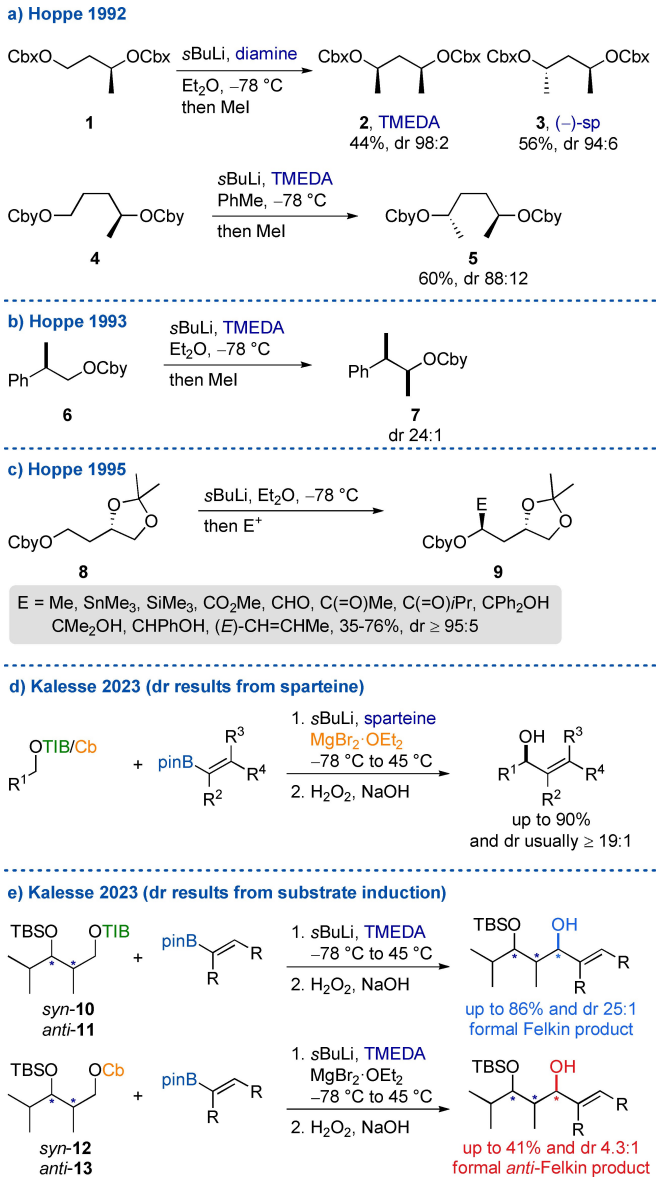


Scheme 1. Substrate controlled carbanion chemistry. Cbx: (3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decan-4-yl)carbonyl; Cby: (2,2,4,4-tetramethyloxazolidin-3-yl)carbonyl; E: electrophile; pin: pinacolato; TBS: *tert*-butyldimethylsilyl, TMEDA: *N,N,N′,N′*-tetramethylethylenediamine.

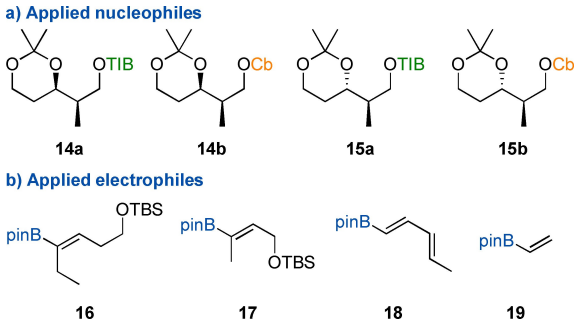
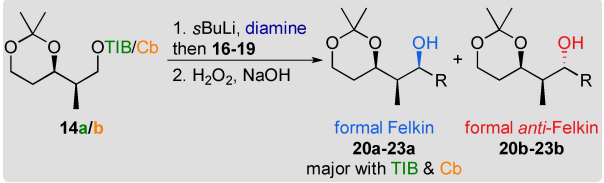
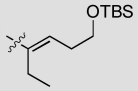
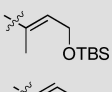


Figure 1. Applied nucleophiles and electrophiles.

In our previous study we observed a change in selectivity when the directing group was switched (TIB vs. Cb). To investigate whether a coordinating protecting group (acetonide) would lead to similar results TIB esters **14a**, **15a** and the corresponding Cb analogs **14b**, **15b** were used in each case. TIB ester **14a** gave the formal Felkin products **20a**–**23a** (Table 1, entries 1, 3, 5 and 7) with all vinyl boronic esters (**16**–**19**) in very good to excellent selectivities (10:1–14:1) and excellent yields (72%–97%), regardless of their steric demand. The use of Cb analog **14b** (Table 1, entries 2, 4, 6 and 8) did not lead to the corresponding formal *anti*-Felkin products **20b**–**23b** as main products, but instead also favored the formation of the formal Felkin products **20a**–**23a**, albeit in lower selectivities (2:1–7:1) and yields (24%–86%). To examine whether the presence of (+)-sparteine can overrule the strong substrate induction favoring the formal Felkin product, carbamate **14b** was treated with vinyl boronic ester **19**, giving formal *anti*-Felkin product **23b** in poor yield (17%) and moderate selectivity (4:1, Table 1, entry 9). In contrast to the previously described mismatched case (Table 1, entry 9), in presence of (−)-sparteine, substrate induction to formal Felkin product **23a** was significantly enhanced in a matched situation (≥ 19:1, Table 1, entry 10). For further investigation on the origin of the obtained selectivities the anions of **14a**/**b** were quenched with deuterated methanol (see Supporting Information). This should determine whether the lithiation or borylation step controls the stereochemistry. For **14a** a diastereomeric ratio of 6:1 was determined by ^{1}H NMR, indicating that the borylation proceeds

Table 1. Substrate induction of acetonide-protected *syn*-diketides.



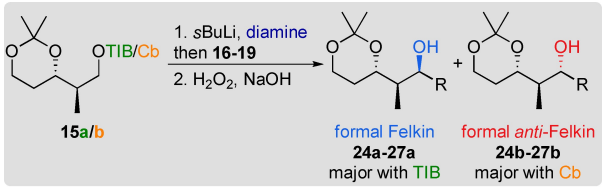
entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB		20a	≥ 95%	10:1
2	TMEDA	Cb		20a	79%	7:1
3	TMEDA	TIB		21a	72%	14:1
4	TMEDA	Cb		21a	86%	5:1
5	TMEDA	TIB		22a	86%	14:1
6	TMEDA	Cb		22a	59%	3:1
7	TMEDA	TIB		23a	76%	13:1
8	TMEDA	Cb		23a	24%	2:1
9	(+)-sp	Cb		23b	17%	1:4
10	(−)-sp	Cb		23a	31%	19:1[b]

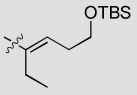
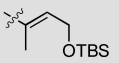
[a] General conditions: 1. TIB ester (1.5 equiv.), diamine (1.5 equiv.), *s*BuLi (1.4 equiv.), Et_2O, −78 °C, 5 h then vinyl boronic ester (1.0 equiv.), Et_2O, −78 °C, 3 h then 45 °C, o/n or carbamate (1.5 equiv.), diamine (1.5 equiv.), *s*BuLi (1.4 equiv.), Et_2O, −78 °C, 5 h then vinyl boronic ester (1.0 equiv.), Et_2O, −78 °C, 3 h then $MgBr_2{\cdot}OEt_2$ (2.0 equiv.), −78 °C, 30 min then 45 °C, o/n. 2. H_2O_2, NaOH, THF, −20 °C to rt. [b] Attributed to NMR-accuracy. sp: sparteine.

under retention and inversion. The occurance of inversion and retention during the borylation of TIB ester derived carbanions was also observed in our previous work and can be explained by a combination of accessibility of the anion and steric demand of the vinyl boronic ester.[5b] Deuterated **14b** was obtained as a diastereomeric mixture of 4:1. Assuming retention for the borylation step this result is in line with the obtained selectivities for **21a** and **22a** (Table 1, entries 4 and 6). However, the differing selectivities obtained for **20a** and **23a** (Table 1, entries 2 and 8) could then either arise from a higher preference of one carbanion reacting in the borylation step or partial inversion during this.

In the case of the acetonide-protected *anti*-diketides (Table 2), TIB ester **15a** afforded formal Felkin products **24a**–**27a** (Table 2, entries 1, 3, 5, and 7) with all four vinyl boronic esters (**16**–**19**) in excellent selectivities (≥14:1) and very good yields (62%–79%). Cb analog **15b**, in contrast to the acetonide-protected *syn*-diketides (Table 1), afforded the corresponding formal *anti*-Felkin products **24b**–**26b** (Table 2, entries 2, 4 and 6) with the sterically more demanding vinyl boronic esters **16**–**18**. **24b**–**26b** were obtained in good yields (52%–66%) but only in low to moderate selectivities (1.3:1–4:1). For the combination of carbamate **15b** and sterically undemanding vinyl boronic ester **19** a similar result as with the *syn*-analog was obtained (Table 2, entry 8). For this reason, carbamate **15b** was reacted in the presence of both sparteine enantiomers (Table 2, entries 9 and 10). (+)-Sparteine led to the formation of formal *anti*-Felkin product **27b** in an excellent selectivity (≥19:1) but poor yield (7%). In contrast, with (−)-sparteine no preference for either of the diastereoisomers was observed (Table 2, entry 10). Deuteration experiments provided a single diastereoisomer of deuterated **15a** (dr≥19:1), which is in line with the selectivities of **24a**, **25a** and **27a** (Table 2, entries 1, 3 and 7). The slightly lower diastereomeric ratio obtained for **26a** indicates some inversion during the borylation step. For **15b** nearly no selectivity was obtained (dr 1.1:1) during deuteration. The observed selectivity is consistent with the result of **24b** (Table 2, entry 2). In the cases of **25b**, **26b** and **27a** (Table 2, entries 4, 6 and 8) again partial inversion during the borylation or the preferred consumption of one diastereoisomer during this step could explain the differing selectivities. The latter might as well serve as an explanation for the lower yields obtained for **26b** and **27a**.

Table 2. Substrate induction of acetonide-protected *anti*-diketides.

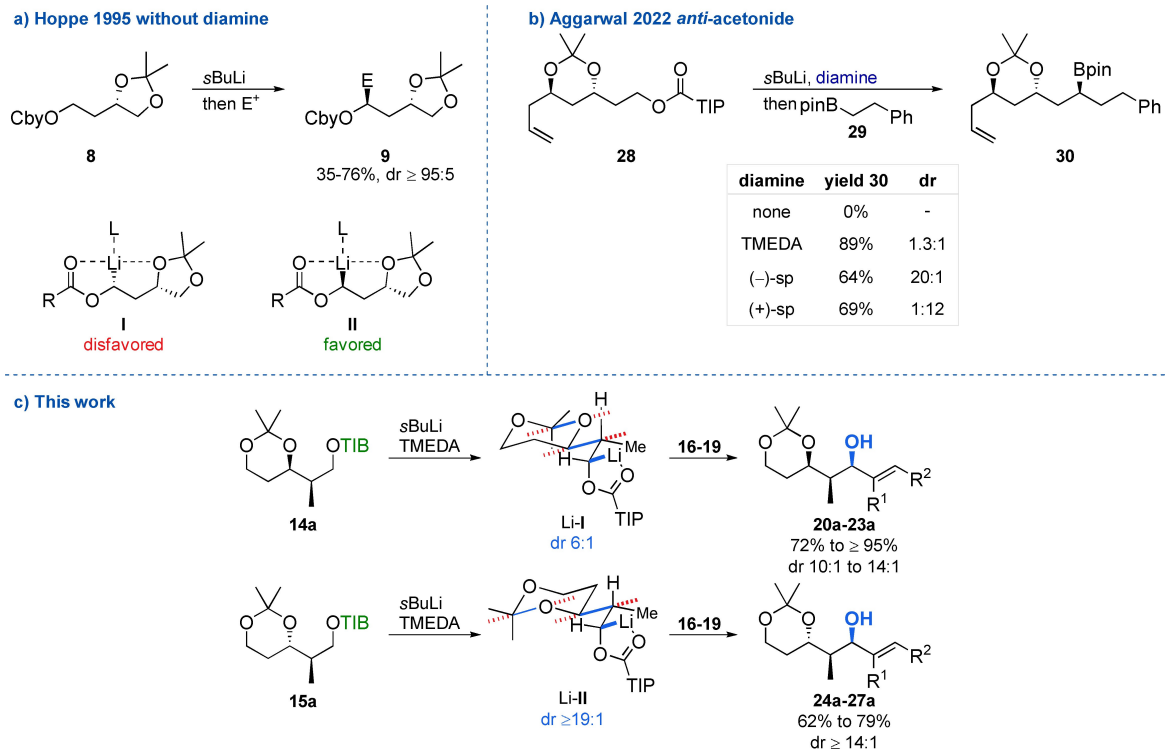


entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB		**24a**	79%	19:1[b]
2	TMEDA	Cb		**24b**	62%	1:1.3
3	TMEDA	TIB		**25a**	62%	19:1[b]
4	TMEDA	Cb		**25b**	66%	1:2
5	TMEDA	TIB		**26a**	69%	14:1
6	TMEDA	Cb		**26b**	52%	1:4
7	TMEDA	TIB		**27a**	72%	19:1[b]
8	TMEDA	Cb		**27a**	10%	2:1
9	(+)-sp	Cb		**27b**	7%	1:19[b]
10	(−)-sp	Cb			14%	1:1

[a] For general conditions see Table 1. [b] Attributed to NMR-accuracy.

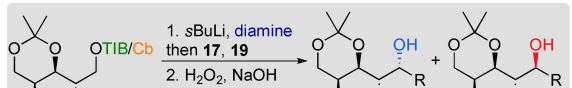
Hoppe explained the observed substrate induction in **8**, in the absence of a diamine, by an intramolecular coordination of the acetonide oxygen atom to the lithium ion (Scheme 2a). Due to steric interactions, the *trans*-annulated chelate complex **II** is favored.[3c] Since strong substrate induction was observed in our case in the presence of TMEDA which occupies the remaining coordination spheres, Hoppe's explanation cannot be applied to the examples reported herein. In 2022, the group of Aggarwal investigated a potential substrate control of an *anti*-configured six-ring acetonide in their bastimolide B synthesis (Scheme 2b). In their case the fragment coupling of TIB ester **28** and boronic ester **29** even required a diamine ligand for the lithiation–borylation chemistry to succeed. However, in contrast to our results, they did not observe a strong substrate induction when applying TMEDA (1.3:1). They only obtained high levels of selectivity (20:1 and 1:12) when sparteine was utilized.[8] To rationalize our observed high selectivities in the presence of TMEDA, we propose a model based on minimization of steric repulsion and stabilizing electronic effects[9] (Scheme 2c). For *syn*-TIB-modified diketide **14a** it is most likely that the less hindered proton, which points away from the acetonide, is removed, leading to a potential carbanion Li-**I**. Additionally, attractive interactions between the carbanion and σ*-orbitals of the neighboring C–C-bond and one O–C-bond of the acetonide could further stabilize this carbanion. Since the lithiation of **14a** is not fully selective (dr 6:1) the diastereomeric anion of Li-**I** (not shown) is partially formed. This carbanion points toward the acetonide, which could explain a preference for an inversion in the borylation step due to steric hindrance. Considering the same assumptions, Li-**II** is obtained for *anti*-diketide **15a**, which also explains the observed selectivity. The high level of stereoselectivity for the lithiation of **15a** (dr≥19:1) might be explained by the close proximity of the geminal dimethyl group to the methylene group, which forms the carbanion. This model could also serve as an explanation for the differences in the stereochemical outcome of this study compared to the work of Aggarwal. In their synthesis an *anti*-acetonide, which adopts a twist-boat conformation, was used as neighboring group. Due to the different conformation the substrate induction toward a defined carbanion might be less pronounced. Furthermore, the stabilizing electronic effects are not given in a twist-boat conformation.

As it is known that even remote stereocenters can control the stereochemical outcome of aldol reactions[10] we next investigated acetonides with an additional chiral center (Tables 3–6). For these investigations we used only one branched vinyl boronic ester since both branched boronic

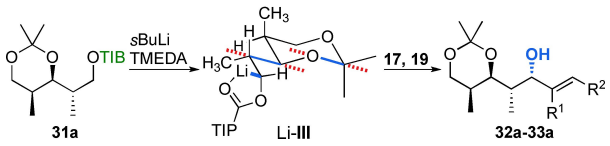


Scheme 2. Acetonides as neighboring groups in asymmetric lithiation. (a) Five-ring acetonide by Hoppe. (b) *anti*-Configured six-ring acetonide by Aggarwal. (c) Rationalization of our observed selectivity (σ*-orbitals are indicated by red dotted lines). TIP: 2,4,6-triisopropylphenyl.

Table 3. Substrate induction of acetonide-protected *anti, syn*-diketides (top). Rationalization of our observed selectivity (σ*-orbitals are indicated by red dotted lines) (bottom).

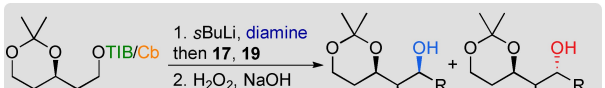


entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB	OTBS	32a	79%	19:1[b]
2	TMEDA	Cb	OTBS	32a	77%	5:1
3	TMEDA	TIB		33a	76%	19:1[b]
4	TMEDA	Cb		33b	22%	1:1.3

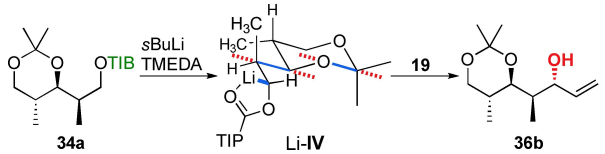


[a] For general conditions see Table 1. [b] Attributed to NMR-accuracy.

Table 4. Substrate induction of acetonide-protected *syn, anti*-diketides (top). Rationalization of our observed selectivity (σ*-orbitals are indicated by red dotted lines) (bottom).



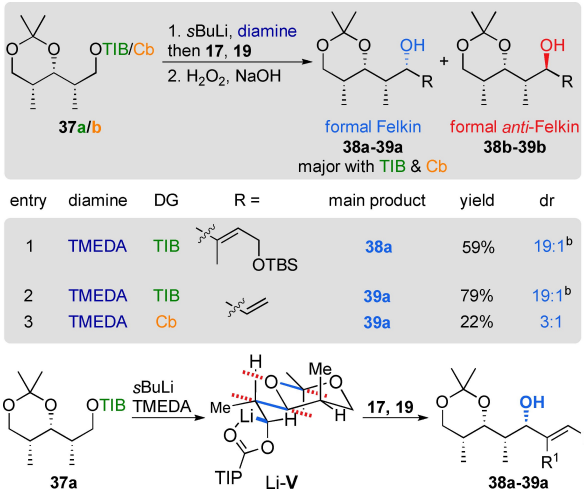
entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB	OTBS	nd	76%	1.5:1
2	TMEDA	TIB		36b	72%	1:6
3	TMEDA	Cb		36b	14%	1:2
4	(+)-sp	TIB			nr	
5	(+)-sps	TIB		36b	30%	1:7



[a] For general conditions see Table 1. sps: sparteine surrogate.

esters (**16**, **17**) provided comparable yields and selectivities in previous experiments (Tables 1 and 2). In addition, unsubstituted vinyl boronic ester **19** was used, as a drop in selectivity was observed in our previous work when no substituent was present.[5b] The TIB-modified *anti*, *syn*-acetonide **31 a** showed good yields and selectivities for the formal Felkin product with both vinyl boronic esters (Table 3, entries 1 and 3). The use of the Cb group decreased the yield and selectivity for branched vinyl boronic ester **17** (Table 3, entry 2) and provided the formal *anti*-Felkin isomer in low yield and selectivity for

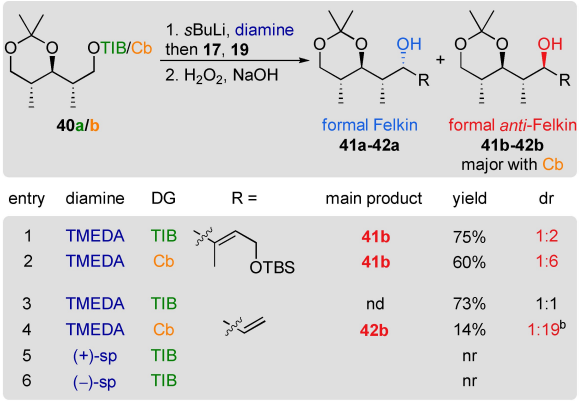
Table 5. Substrate induction of acetonide-protected all-*syn*-diketides (top). Rationalization of our observed selectivity (σ*-orbitals are indicated by red dotted lines) (bottom).



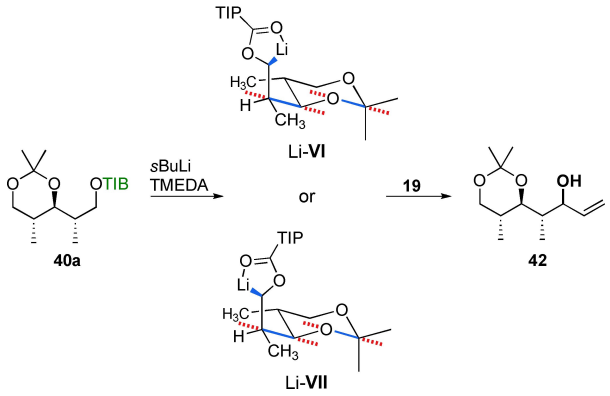
entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB	OTBS	38a	59%	19:1[b]
2	TMEDA	TIB		39a	79%	19:1[b]
3	TMEDA	Cb		39a	22%	3:1

[a] For general conditions see Table 1. [b] Attributed to NMR-accuracy.

Table 6. Substrate induction of acetonide-protected *anti, anti*-diketides (top). Rationalization of our observed selectivity (σ*-orbitals are indicated by red dotted lines) (bottom).



entry	diamine	DG	R =	main product	yield	dr
1	TMEDA	TIB	OTBS	41b	75%	1:2
2	TMEDA	Cb	OTBS	41b	60%	1:6
3	TMEDA	TIB		nd	73%	1:1
4	TMEDA	Cb		42b	14%	1:19[b]
5	(+)-sp	TIB			nr	
6	(–)-sp	TIB			nr	



[a] For general conditions see Table 1. [b] Attributed to NMR-accuracy.

unsubstituted vinyl boronic ester **19** (Table 3, entry 4). The observed selectivities can be explained with Li-**III**, which minimizes steric repulsion for the deprotonation and shows the abovementioned attractive interactions between the carbanion and the σ*-orbitals. Additionally, further stabilization is gained by minimization of *syn*-pentane interactions between the two methyl groups.

The TIB-modified *syn, anti*-acetonide **34a** generated formal *anti*-Felkin product **36b** in 72% yield and a ratio of 6:1 if vinyl boronic ester **19** was used (Table 4, entry 2). The inherent selectivity was even increased to 7:1 by employing the (+)-sparteine surrogate (Table 4, entry 5) instead of TMEDA whereas in the presence of the larger (+)-sparteine (Table 4, entry 4) the desired product was not formed. In certain cases no product formation in the presence of sparteine was also observed in our previous study. There most likely the borylation did not occur due to steric hindrance of the carbanion, which was supported by the possibility of anion trapping with trimethyltin chloride.[5b] On the other hand, branched vinyl boronic ester **17** provided almost no selectivity for TIB-derivatized acetonide **34a**. Minimization of *syn*-pentane interactions and removal of the less hindered proton as well as maximization of stabilizing electronic effects lead to Li-**IV** as the most stable carbanion, which is in line with the observed *anti*-Felkin selectivity. In addition, the pseudo-axial methyl group adjacent to the carbanion might explain the low selectivity for the reaction with branched vinyl boronic ester **17** (Table 4, entry 1) due to steric repulsion.

The all-*syn*-acetonides **37a** and **37b** provided the formal Felkin product in all cases (Table 5). Again the TIB-directing group provided the highest yields and selectivities. As with the other acetonides removal of the less hindered proton and analysis of the *syn*-pentane interactions as well as the electronic effects provided a preferred structure, in this case Li-**V**, which illustrates the strong formal Felkin selectivity.

Surprisingly, the *anti*, *anti*-acetonide gave no or poor selectivities for TIB-derivatized acetonide **40a** (1:1, 1:2). The Cb-analog **40b** on the other hand provided good selectivities and low to moderate yields for the formal *anti*-Felkin products **41b** and **42b**. Minimization of *syn*-pentane interactions and a possible delocalization of the carbanion into the neighboring σ*-orbital would result in Li-**VII**. In this orientation, however, the directing group points toward the acetonide, leading to steric repulsion. If the directing group is turned away from the acetonide, these steric interactions are minimized, but the delocalization of the carbanion into the neighboring σ*-orbital is suppressed either. Li-**VI** explains the formal *anti*-Felkin selectivity, whereas Li-**VII** would lead to the formal Felkin product of *anti*, *anti*-acetonide **40a**. Based on the preferred formation of the formal *anti*-Felkin products steric hindrance seems to slightly override electronic stabilization in this example.

Conclusions

In conclusion, we demonstrated that the use of acetonide-protected ketide motifs enables strong substrate induction in asymmetric lithiation–borylation chemistry. We observed out-

standing selectivities in the absence of sparteine and noticed that also in case of the acetonides altering the directing group from TIB to Cb influenced the diastereoselectivity. The general trend of TIB favoring the formal Felkin product whereas Cb shows a formal *anti*-Felkin induction was observed as well. However, in this case the influence of the chosen directing group was less pronounced than in our previous study. This is rationalized by the rigidity of the substrates. In addition, the conformation of the acetonide-derived substrates did decrease the effect of the vinyl boronic ester (branched vs unbranched). In cases where this directing group alteration did not produce the desired selectivities, the use of either (+)- or (−)-sparteine often gave improved selectivities. In addition, a model based on deprotonation of the less hindered proton, *syn*-pentane interactions and stabilizing electronic effects was suggested. As already described for aldol reactions by Paterson,[10] the stereochemical outcome depends very much on the overall conformation and even remote chiral centers can have substantial impact on the yields and selectivities. Considering the abovementioned points, the presented protocol serves as a highly valuable alternative to the Nozaki–Hiyama–Takai–Kishi reaction and can contribute to total syntheses of natural products in the future.

Experimental Section

Substrate-Controlled 1,2-Metallate Rearrangement of Vinyl Boronates

General procedure for the conversion of TIB esters

To a stirred solution of TIB ester (1.5 equiv.) and diamine (1.5 equiv.) in Et_2O (0.2 M) at −78 °C was added *s*BuLi (1.3 M in hexanes, 1.4 equiv.). The reaction mixture was stirred for 5 h at that temperature before a solution of vinyl boronic ester (1.0 equiv.) in Et_2O (0.5 M) was added. After stirring for further 3 h at −78 °C, the reaction mixture was warmed to 45 °C and stirred overnight. The reaction mixture was cooled to rt, sat. aq. NH_4Cl was added, and the biphasic mixture was stirred for 15 min. The phases were separated, the organic layer was washed with sat. aq. NH_4Cl (3×) and the combined aqueous phases were extracted with MTBE (3×). The combined organic phases were dried over Na_2SO_4, concentrated in vacuo and the crude material was purified by a short flash column chromatography (to remove TIBOH).[5]

The residue was dissolved in THF (0.2 M) and cooled to −20 °C. A premixed, ice-cooled solution of NaOH (2.0 M)/H_2O_2 (35 %, 2/1 v/v, 0.12 M) was added dropwise. The reaction mixture was stirred at rt before being diluted with MTBE and quenched by the slow addition of sat. aq. $Na_2S_2O_3$ at 0 °C after TLC showed full conversion. The solution was diluted with MTBE, the phases were separated, and the aqueous phase was extracted with MTBE (3x). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography to afford allylic alcohol.[5]

General procedure for the conversion of carbamates

To a stirred solution of carbamate (1.5 equiv.) and diamine (1.5 equiv.) in Et_2O (0.2 M) at −78 °C was added *s*BuLi (1.3 M in hexanes, 1.4 equiv.). The reaction mixture was stirred for 5 h at that temperature before a solution of vinyl boronic ester (1.0 equiv) in Et_2O (0.5 M) was added. The reaction mixture was stirred for 3 h at −78 °C.[5]

In parallel, magnesium turnings were activated (2x 1.0 M HCl, 2x H_2O, 2x acetone, drying under high vacuum). The required amount (2.0 equiv.) was dissolved in Et_2O (0.8 M) and 1,2-dibromoethane (2.0 equiv.) was added under water bath cooling. The reaction mixture was stirred for 2 h at this temperature.[5] The biphasic $MgBr_2{\cdot}OEt_2$ solution was added dropwise to the main reaction mixture, which was then stirred for another 30 min at −78 °C before being warmed to 45 °C and stirred overnight. The reaction mixture was cooled to rt, sat. aq. NH_4Cl was added, and the biphasic mixture was stirred for 15 min. The phases were separated, the organic layer was washed with sat. aq. NH_4Cl (3x) and the combined aqueous phases were extracted with MTBE (3x). The combined organic phases were dried over Na_2SO_4, concentrated in vacuo and the crude material was purified by a short flash column chromatography (to remove excess of the carbamate).[5]

The residue was dissolved in THF (0.2 M) and cooled to −20 °C. A premixed, ice-cooled solution of NaOH (2.0 M)/H_2O_2 (35 %, 2/1 v/v, 0.12 M) was added dropwise. The reaction mixture was stirred at rt before being diluted with MTBE and quenched by the slow addition of sat. aq. $Na_2S_2O_3$ at 0 °C after TLC showed full conversion. The solution was diluted with MTBE, the phases were separated, and the aqueous phase was extracted with MTBE (3x). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography to afford allylic alcohol.[5]

Supporting Information

The authors have cited additional references within the Supporting Information.[11-18]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: allylic alcohols · boron · NHTK · 1,2-metallate rearrangement · substrate control

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