Synthetic Methods

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Stereoarrays with an All-Carbon Quaternary Center: Diastereoselective Desymmetrization of Prochiral Malonaldehydes**

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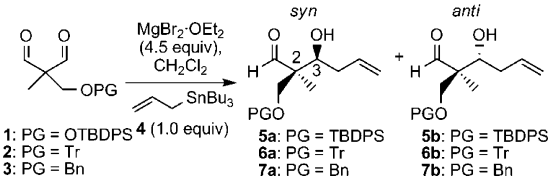
The stereocontrolled nucleophilic addition to aldehydes and ketones is a fundamental C–C bond-forming process in organic synthesis, with a number of models available to predict or explain facial selectivity.[1] Intermolecular nucleophilic addition reactions to 1,3-dicarbonyl groups are rare in comparison. Nevertheless, additions to α-formyl esters and amides under chelation control, with stereochemical bias provided by a central chiral center, have been shown to be highly diastereoselective.[2] A study by Prantz and Mulzer involving chiral α-formyl esters showed how the aldehyde facial selectivity could be reverted depending on whether the reaction was run under chelation control or not.[2a] Only a few examples of intermolecular additions to 1,3-dialdehydes are described, and they proceeded with modest or no diastereoselectivity.[3] In fact, Krische and co-workers described an ingenious transfer hydrogenation approach in which 1,3-propanediols were used as malonaldehyde synthons in a highly enantioselective and diastereoselective bidirectional allylation process.[4]

Herein we show the tremendous synthetic potential of prochiral non-enolizable malonaldehydes for the synthesis of acyclic compounds containing an all-carbon quaternary center as part of a stereoarray, the synthesis of which is subject to much contemporary interest.[5] Reactions of malonaldehydes having a methyl and protected hydroxymethyl group at the central position are described, and it is shown that under $MgBr_2$ chelation, these substituents are able to exert excellent diastereofacial control for addition reactions onto an aldehyde group, with complementary diastereoselection depending on the nature of the protecting group. Apart from monoadditions, one-pot bisaddition reactions are also described, wherein the second addition occurs with virtually complete stereocontrol. This unprecedented process allows the synthesis of nonsymmetric products containing up to five stereocenters. A model to explain the observed stereochemical outcomes is presented.

The malonaldehydes **1**–**3** (see Table 1) used in this study were synthesized in quantitative yield[6a,b] by IBX-mediated (IBX = *o*-iodoxybenzoic acid) oxidation[6c,d] of the corresponding 1,3-diols, which were easily obtained from exceedingly cheap tris-1,1,1-(hydroxymethyl)ethane.[6a,b]

The reaction of **1**–**3** with a variety of nucleophiles, including Grignard reagents, allyl boronates, and allyl boranes proceeded with low diastereoselectivity and low to moderate yield (not shown). Allylstannation under $BF_3{\cdot}OEt_2$ activation led to extensive decomposition, but the use of freshly prepared $MgBr_2{\cdot}OEt_2$ successfully led to the monoallylation products **5**–**7** (Table 1).

Table 1: Chelation-controlled allylstannation reactions of malonaldehydes.



Entry	*T* [°C]	Product	Yield [%][a]	**a**/**b**[b]
1	−25	**5a,b**	77	70:30
2	−25	**6a,b**	53	92:08
3	−78	**7a,b**	81	05:95

[a] Yield of product isolated after chromatography. [b] Determined by ^{1}H NMR analysis before chromatography. Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl, Tr = trityl.

The reaction of **1** with allyltributyl stannane led to the products **5a**/**b** in a modest ratio (Table 1, entry 1). The selectivity was much improved upon switching the protecting group from TBDPS to trityl (entry 2). In both cases, the 2,3-*syn* adduct was the major isomer. However, allylation of the benzyl-protected **3**, which proceeded in slightly higher diastereoselectivity compared to reaction with **2**, resulted in the 2,3-*anti* adduct **7b** as the major diastereoisomer (entry 3). Hence, the desymmetrization of the malonaldehyde starting material leads to the formation of a chiral, all-carbon quaternary stereocenter, and both diastereomeric products are accessible in high diastereoselectivity depending upon the protecting group present. The relative stereochemistry of these and the following products was determined by X-ray crystallographic analysis, chemical correlation, and NMR experiments.[6b]

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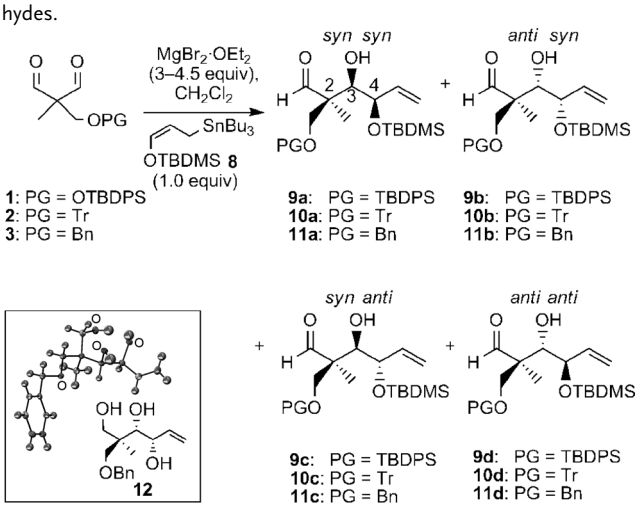
Table 2: Chelation-controlled hydroxyallylation reactions of malonaldehydes.



1: PG = OTBDPS
2: PG = Tr
3: PG = Bn

9a: PG = TBDPS **9b**: PG = TBDPS
10a: PG = Tr **10b**: PG = Tr
11a: PG = Bn **11b**: PG = Bn

9c: PG = TBDPS **9d**: PG = TBDPS
10c: PG = Tr **10d**: PG = Tr
11c: PG = Bn **11d**: PG = Bn

Entry	*T* [°C]	Product	Yield [%][a]	**a**/**b**/**c**/**d**[b]
1[c]	−20	**9a–d**	15[d]	–
2	−25	**9a–d**	64	86:14:0:0
3	−30	**10a–d**	65	95:05:0:0
4	−25	**11a–d**	83	0:91:0:9

[a] Yield of product isolated after chromatography. [b] Determined by ^{1}H NMR analysis. [c] 1 equiv $MgBr_2$. [d] 63% of **1** recovered. The thermal ellipsoids of the X-ray crystal are shown at 35% probability.

Encouraged by these results, the hydroxyallylation of **1**–**3** with (*Z*)-γ-(*tert*-butyldimethylsilyl-oxyallyl) tributylstannane (**8**)[7,8] was investigated next (Table 2). The hydroxyallylation of **1** and **2** with **8** gave the 2,3-*syn*- and 2,3-*anti*-addition products **9a**,**b** and **10a**,**b** (entries 2 and 3) in higher diastereoselectivity compared to that of the allylation described above. When one equivalent of $MgBr_2$ was used (entry 1), 63% of the starting malonaldehyde was recovered, thus indicating no decomposition is taking place under the reaction conditions. The hydroxyallylation of **3** led to the formation of **11b**,**d** in excellent yield and diastereoselectivity (entry 4). The crystal structure of a derivative of **11b** (**12**) is shown. In all cases, only monoaddition products were obtained. Interestingly, the stereochemical outcome of the hydroxyallylation of **1** and **2** differs from that of **3** on three accounts. First, the relative configuration at C2 and C3 of the major isomers obtained from reaction of **1** and **2** is different compared to that of the major isomer arising from **3**, which indicated that the respective major products were formed from reaction at opposite aldehyde faces (this is consistent with the allylation results described in Table 1). Secondly, the major and minor diastereoisomers from the reaction of **1** and **2** have a different relative configuration at C2 and C3, while the major and minor diastereoisomers **11b,d** from reaction of **3** possess the same relative configuration at C2 and C3. This indicates complete aldehyde facial selectivity for hydroxyallylation of **3** (this is not the case for the allylation of **3**, see Table 1). Thirdly, the major and minor isomers arising from **3** possess a C3/C4 *syn* and *anti* relationship, in contrast to the *syn* relationship found for both the major and minor isomers from hydroxyallylation of **1** and **2**. This outcome indicates that the isomers **11b**,**d** were formed by a different facial attack of the prochiral reagent **8**.

The models in Figure 1 are consistent with the observed stereochemical outcomes. Chelation of $MgBr_2$ with **2** leads to the flattened boat conformation **A**,[9] with the trityloxy

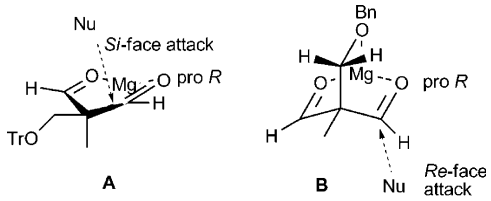
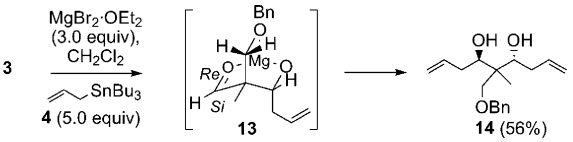


Figure 1. Proposed models for 1,3-dialdehyde addition.

substituent in a pseudoequatorial position, which we believe is due to electronic factors. Taking the pro-*R* aldehyde group as a reference, the major product isomer arises from attack on the least hindered *Si* face, and the minor isomer is presumed to arise from reaction of the ring-inverted boat conformation (not shown). In contrast to the bulky TBDPS and trityl ethers, benzyl ethers are able to engage in chelation[10] leading to formation of **B**. Now *Si*-face attack to the pro-*R* aldehyde group is hindered by the CH_2OBn bridge: the large reagent **8** reacts only at the *Re* face, but the smaller reagent **4** can also approach from the *Si* face, thus leading to the minor isomer **7a**. DFT calculations support the proposed model, and further investigations to fully explain the diastereoselection will be reported in due course.

By employing an excess of the allyl stannane **4**, bidirectional addition products were obtained. Starting from malonaldehyde **3** [Eq. (1)], only one diastereoisomer **14** could be identified. Surprisingly, **14** was assigned (NMR) as the pseudo-C_2-symmetric stereoisomer, as opposed to the corresponding possible *meso* diastereomer(s), which in principle would have been expected from a substrate-directed bidirectional reaction process.[11] With dialdehyde **1**, the bisallylation product was isolated as a 94:6 mixture of *anti* and *meso* isomers.[6b] Bidirectional hydroxyallylation could not be achieved, which was attributed to the larger steric bulk of the less reactive reagent **8**.

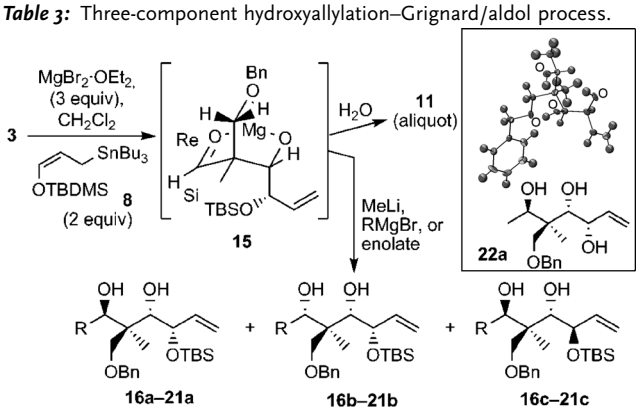


(1)

This stereochemical outcome is rationalized by formation of chelate **13** after initial allyl stannane attack, which can undergo a second reaction by a suitably small nucleophile such as allylstannane **4**, but not by a larger reagent such as **8**. From **13**, *Si*-face attack is prevented by steric hindrance from the allyl group.[12]

These insights led to exploiting the clean monohydroxyallylation process for the synthesis of nonsymmetric double addition products by subsequent addition of a more reactive

Table 3: Three-component hydroxyallylation–Grignard/aldol process.



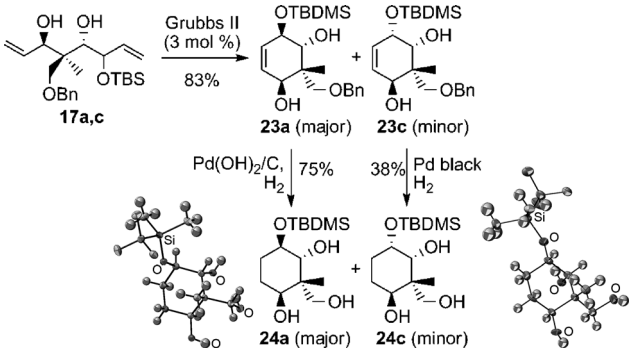
Entry	R	d.r. (**11**)[a]	Product	Yield [%][b]	**a**/**b**/**c**[c]
1	Me[d]	91:09	**16a–c**	51	79:9:12
2	Me[e]	93:07	**16a–c**	56	87:4:9
3	vinyl	90:10	**17a–c**	67	>9:0:<1[f]
4	Et	89:11	**18a–c**	59	88:0:12
5	Ph	90:10	**19a–c**	60	90:0:10
6	allyl	90:10	**20a–c**	51	>9:0:<1[f]
7	$CH_2COOtBu$	92:8	**21a–c**	64	94:0:6

[a] Ratio of hydroxyallylation product determined on an aliquot. [b] Yield of product isolated after chromatography. [c] Determined by ^{1}H NMR analysis. A fourth possible isomer was never observed. [d] MeLi. [e] MeMgBr. [f] Precise diastereomeric ratio could not be determined. The thermal ellipsoids of the X-ray crystal are shown at 35% probability.

nucleophile (Table 3). When using methyl lithium (entry 1), reaction of the remaining (chelated) aldehyde group led to stereotetrads **16a–c** in a 79:9:12 ratio. X-ray crystallographic analysis of a derivative of **16a** (**22a**) confirmed the stereoselection was as observed for the diallylation reaction to give **14**. As a control, an aliquot of the reaction mixture was subjected to aqueous workup before MeLi addition, and resulted in a 91:9 ratio of **11b**/**11d**. Hence it was concluded that the second addition proceeded with good (ca. 9:1) diastereoselectivity. When **15** was reacted with MeMgBr (entry 2), the second addition was more selective, and larger Grignard reagents (entries 3–6), reacted with virtually complete selectivity, thus giving stereotetrads in good yields. Reaction of intermediate **15** with the lithium enolate derived from *tert*-butyl acetate also led to complete selectivity for the second addition step, with **21** formed in excellent diastereoselectivity (entry 7).

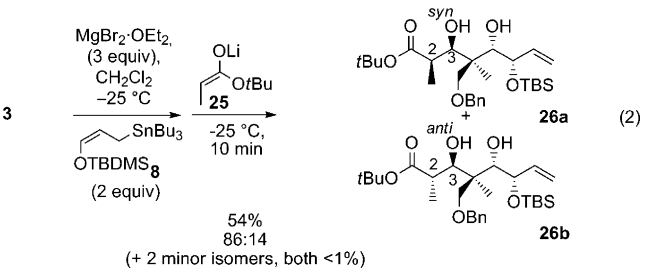
A short synthesis of polysubstituted cyclohexenes was carried out by a facile ring-closing metathesis reaction of the **17a**,**c** mixture (Scheme 1). The resulting separable cyclohexenes **23a**,**c** were each submitted to catalytic hydrogenation to obtain the corresponding crystalline derivatives **24a** and **24c**. X-ray crystallographic analysis in both cases clearly reveals the *anti* configuration of the 1,3-diol unit flanking the quaternary center, as well as the different relative configurations at the 1,2-OH and 1,2-OTBDMS centers, which further confirms the complete stereoselectivity of the second addition reaction.

Finally, the synthesis of stereopentads was investigated by a hydroxyallylation propionate aldol sequence [Eq. (2)]. To



Scheme 1. Confirmation of the relative stereochemistry of the hydroxyallylation vinyl magnesium bromide double-addition product. The hydrogen atoms of the *tert*-butyl group in the X-ray crystal structure are omitted for clarity; the thermal ellipsoids are shown at 35% probability.

our delight, the process resulted in the formation of **26** in good yield and stereoselectivity. Only two major isomers could be isolated from the crude reaction mixture, along with very small quantities of two minor diastereomers[6b] (<1%, not shown). Both isomers were derived from the major hydroxyallylation intermediate. Clearly, compared to the allyl stannane **8**, which also reacts through a secondary carbon atom, the enhanced reactivity of enolate **25** is sufficient to overcome the hindered nature of intermediate **15** for second addition. Interestingly, the major isomer was identified as the 2,3-*syn* product, thus suggesting that the aldol reaction with the *E*-enolate **25** (>95% *E*)[13] occurred via an acyclic transition state enforced by the chelation of the aldehyde group.[14] The formation of the minor 2,3-*anti* adduct could be the result of a competing Zimmerman–Traxler or retro-aldol isomerization pathway.[13]



(2)

Hence this malonaldehyde three-component bisaddition process allows rapid access (3 steps) to acyclic stereoarrays including an all-carbon quaternary stereocenter from cheap and simple tris-1,1,1-(hydroxymethyl)ethane. The scope of this process will be easily extended by employing different malonaldehydes and nucleophiles. The short de novo synthesis of polysubstituted cyclohexenes **23**, which are highly functionalized building blocks for novel carbasugar and inositol analogues containing a quaternary center, is an illustration of the synthetic usefulness of the method. While the aforementioned enantioselective bidirectional process developed by Krishe and co-workers[4] is a superior way to obtain pseudo-C_2-symmetric allylation products, our current

focus is on the three-component sequential bisaddition process to give nonsymmetric adducts. The requirement of a chelate intermediate for this process suggests a chiral auxiliary approach is preferable for obtaining enantioenriched compounds (addition on the isolated monoaddition product occurs with significantly lower diastereoselectivity).[6b] Additional investigations to achieve these goals are currently ongoing.

In conclusion, chelation of non-enolizable 1,3-dialdehydes allows diastereoselective monoaddition reactions with the relative stereochemistry dependent on the choice of protecting group of a pendent hydroxymethyl group. Furthermore, a second addition reaction is also possible with very high diastereoselectivity. This work introduces prochiral 2,2-disubstituted malonaldehydes as versatile substrates for the synthesis of stereochemically dense acyclic systems including all-carbon quaternary centers, which is an area of significant current interest.[5]

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