

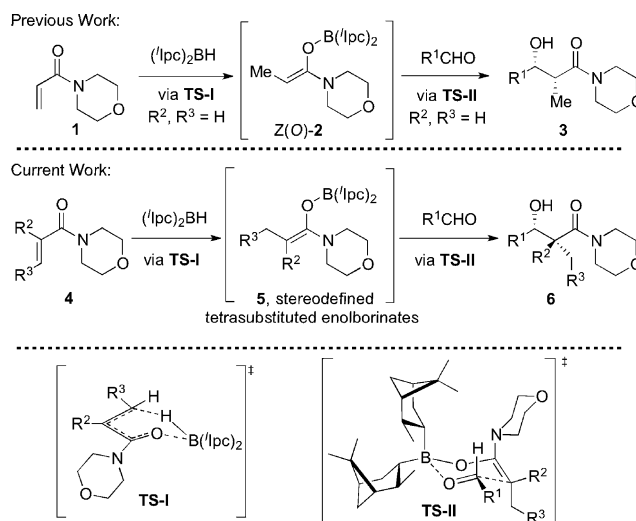
Synthetic Methods

# Generation of Stereochemically Defined Tetrasubstituted Enolborinates by 1,4-Hydroboration of $\alpha,\beta$ -Unsaturated Morpholine Carboxamides with (Diisopinocampheyl)borane\*\*

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The enantioselective synthesis of acyclic all-carbon quaternary centers remains a significant challenge in organic synthesis.<sup>[1]</sup> In view of the tremendous utility of enantioselective aldol reactions in organic synthesis, extension of this reaction to the enantioselective synthesis of all-carbon quaternary centers from stereochemically defined tetrasubstituted enolates would be highly valuable.<sup>[2,3]</sup> However, attempts to generate such enolates or enolate equivalents by deprotonation of acyclic carbonyl compounds in most cases lead to geometric mixtures, which translates to poor diastereoselectivity in the subsequent aldol reaction.<sup>[3,4]</sup> Thus, alternative methods for generation of acyclic tetrasubstituted enolates or their synthetic equivalents have been developed.<sup>[5–8]</sup> Noteworthy among these, a highly stereoselective carbocupration of chiral ynamides followed by oxidation of the resultant vinylcuprate has been developed by Marek and co-workers.<sup>[8]</sup> Nevertheless, the development of a simple, highly stereocontrolled method for synthesis of stereochemically defined tetrasubstituted enolates from readily available achiral starting materials remains an important objective. Toward this end, we report herein a simple procedure by which stereodefined tetrasubstituted enolborinates are generated with exceptional stereoselectivity by 1,4-hydroboration reactions<sup>[9,10]</sup> of unsaturated morpholine carboxamides with (diisopinocampheyl)borane [(Ipc)<sub>2</sub>BH], and demonstrate that the tetrasubstituted enolborinates undergo highly enantio- and diastereoselective aldol reactions with representative achiral aldehydes.

We recently reported that the 1,4-hydroboration of the morpholine acrylamide **1** with (Ipc)<sub>2</sub>BH provides the enolborinate **Z(O)-2** via **TS-I** (Scheme 1, where R<sup>2</sup> = R<sup>3</sup> = H).<sup>[11a]</sup> Treatment of **Z(O)-2** with aldehydes provided the *syn*-aldol products **3** with exceptional diastereo- and enantioselectivity ( $\geq 20:1$  d.r. and 96–98% *ee*). By virtue of the transition state **TS-I** proposed for the 1,4-hydroboration reaction,<sup>[9,12]</sup> we anticipated that this procedure could be used to generate stereodefined tetrasubstituted enolborinates (**5**) from substi-



**Scheme 1.** 1,4-Reductive aldol reactions of substituted  $\alpha,\beta$ -unsaturated amides with (Ipc)<sub>2</sub>BH.

tuted  $\alpha,\beta$ -unsaturated amides (**4**). Subsequent aldol reactions of **5** should faithfully relay the enolborinate geometry to the all-carbon quaternary stereocenter in **6** via the transition state **TS-II**.<sup>[2]</sup> To the best of our knowledge, stereodefined tetrasubstituted enolates have not been successfully generated with high stereochemical control by using alternative reductive aldol procedures,<sup>[9,10,12,13]</sup> but several have been generated by 1,4-addition of organometallic reagents to unsaturated carbonyl derivatives.<sup>[5a,m,q,r,14]</sup>

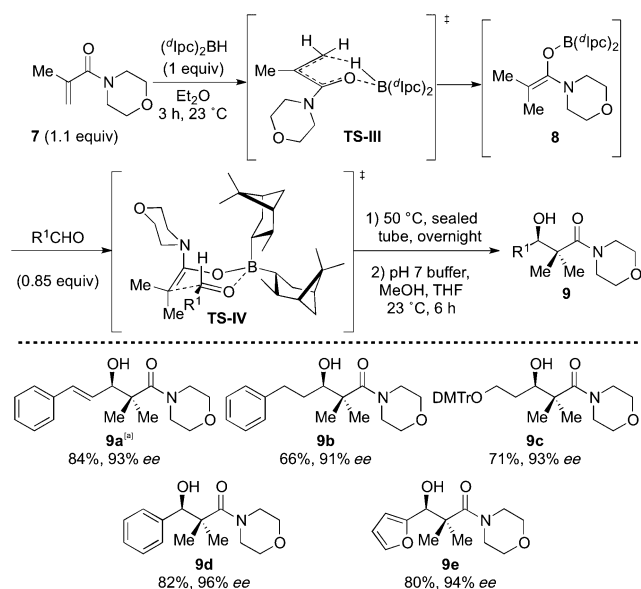
We began by using the  $\alpha$ -methylacryl carboxamide **7** as the substrate to probe the effect of an  $\alpha$  substituent on the 1,4-hydroboration and the subsequent aldol reaction. Compounds bearing a  $\alpha,\alpha$ -dimethyl- $\beta$ -hydroxy quaternary center are often generated by using Mukaiyama aldol methods.<sup>[15]</sup> 1,4-Hydroboration of **7** (1.1 equiv) with (Ipc)<sub>2</sub>BH (1 equiv) in Et<sub>2</sub>O at ambient temperature for 3 hours with subsequent addition of an aldehyde (0.85 equiv) and heating the reaction mixture at 50°C in sealed tube for 16 hours gave the aldol products **9** (Scheme 2; see the Supporting Information for the variables studied during the optimization of this reaction). Results of the reductive aldol reactions of **7** with a range of representative aldehydes are presented in Scheme 2. The aldol reactions of the enolborinate **8** are more sluggish than conventional aldol reactions of less substituted enolborinates owing to the hindered nature of **8**, and required heating at reflux overnight. Nevertheless **9a–e** were obtained in good yield (66–84%) and with excellent enantioselectivity (91–96% *ee*). The absolute stereochemistry of the products **9** was

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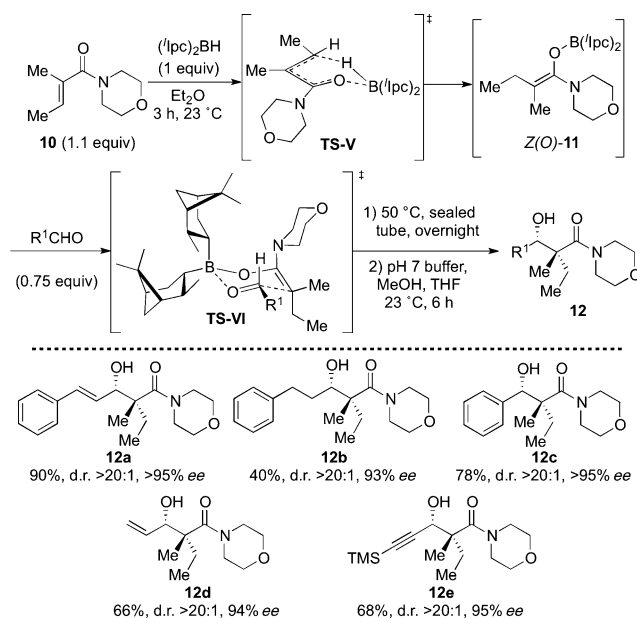
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201307302>.



**Scheme 2.** Reductive aldol reactions of **7**. Reactions were performed with 0.25 mmol of (*d*Ipc)<sub>2</sub>BH at a concentration of 0.25 m. Yields of isolated products are reported. Enantiomeric purity and absolute configuration of the C(3)-hydroxy group was determined by Mosher ester analysis.<sup>[16]</sup> [a] Reaction of **8** with cinnamaldehyde in Et<sub>2</sub>O at reflux using a standard cooling system yielded **9a** in similar efficiency (83 %, 92 % *ee*, performed on 1 mmol scale). DMTr = dimethoxytrityl, THF = tetrahydrofuran.

assigned by using the Mosher method,<sup>[16]</sup> and is consistent with product formation occurring via transition state **TS-IV**. The aldol reaction proved to be sensitive to steric effects as **9b** and **9c**, derived from aliphatic aldehydes, were obtained in lower yield than those from aromatic or unsaturated aldehydes, and products derived from  $\alpha$ -branched aldehydes such as cyclohexanecarboxaldehyde were obtained in much lower yield (< 10 %, not shown).<sup>[17]</sup>

Having established that  $\alpha$ -substituted  $\alpha,\beta$ -unsaturated carboxamide substrates are compatible with this reductive aldol procedure, we elected to study the 1,4-hydroboration and aldol reactions of the  $\alpha,\beta$ -dimethyl acrylamide **10** (tigloyl carboxamide; Scheme 3). If both steps proceed with synthetically useful stereochemical control, the aldol adducts **12** with an  $\alpha$ -quaternary center bearing a methyl group *syn* and an ethyl group *anti* to the  $\beta$ -hydroxy group would be obtained. Thus, 1,4-hydroboration of the unsaturated amide **10** with (*l*Ipc)<sub>2</sub>BH (Et<sub>2</sub>O, 23 °C) with subsequent treatment of the intermediate enolborinate **Z(O)-11** with representative aliphatic and aromatic aldehydes provided the  $\beta$ -hydroxy amides **12** (Scheme 3). The 1,4-hydroboration of **10** was slower than that of **7** and was 80–90 % complete after 3 hours at 23 °C, as determined by <sup>1</sup>H NMR analysis. Attempts to push the hydroboration to completion by using longer reaction times were not successful. This outcome led us to decrease the amount of aldehyde used in the aldol step from 0.85 to 0.75 equivalents to compensate for the incomplete hydroboration. Under these reaction conditions, the reductive aldol reactions of **10** provided the products **12a–e** in moderate to good yields (40–90 %). The least efficient aldol reaction of

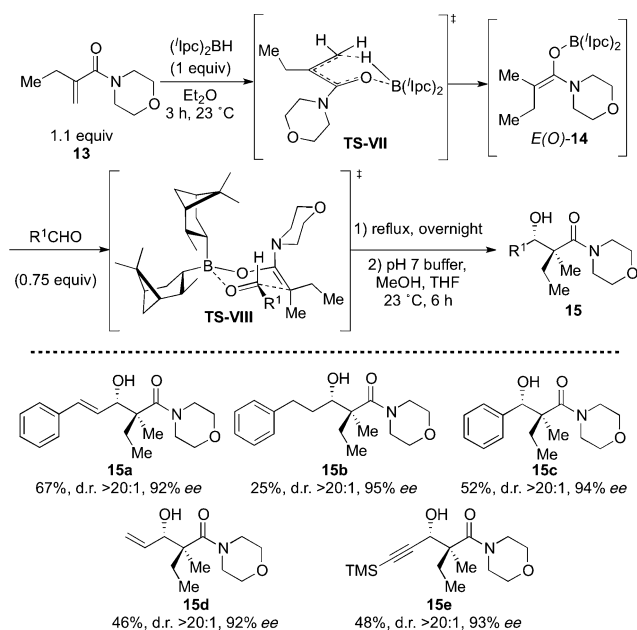


**Scheme 3.** Reductive aldol reactions of **10**. Reactions were performed with 0.25 mmol of (*l*Ipc)<sub>2</sub>BH at a concentration of 0.25 m. Aldol diastereomer ratios were determined by <sup>1</sup>H NMR analysis of crude reaction mixtures. Only **12** was usually observed. Yields of the isolated products are reported. Enantiomeric purity and absolute configuration of the C(3)-hydroxy group was determined by Mosher ester analysis.<sup>[16]</sup> TMS = trimethylsilyl.

those presented in Scheme 3 was that with hydrocinnamaldehyde, which gave **12b** in 40 % yield. However, synthetically useful yields are obtained with  $\alpha,\beta$ -unsaturated aldehydes (**12a**, **12d**), which can serve as surrogates for a saturated aldehyde substrate. Gratifyingly, the products **12** with *syn* relationships between the  $\alpha$ -ethyl and the  $\beta$ -hydroxy groups were obtained with high diastereoselectivity in all cases (d.r. > 20:1), and excellent enantioselectivity (93–95 % *ee*). The relative stereochemistry of **12a** was assigned as described in the Supporting Information, and absolute configurations of **12** were assigned by using the Mosher method.<sup>[16]</sup> Collectively, these data indicate that the enolborinate **11** has *Z*(O) stereochemistry, which is consistent with 1,4-hydroboration of **10** via **TS-V**, and that the products **12** arise via the chairlike transition state **TS-VI**.

Complementary aldol diastereoselectivity is achieved by using the  $\alpha$ -ethyl acrylamide **13** as the substrate for the 1,4-hydroboration reaction (Scheme 4). Treatment of **13** with (*l*Ipc)<sub>2</sub>BH in Et<sub>2</sub>O at ambient temperature for 3 hours, with subsequent addition of an aldehyde, and heating the resulting mixture at 50 °C overnight provided the products **15** with high diastereoselectivity (d.r. > 20:1) and excellent enantioselectivity (92–95 % *ee*).

The products **15** so obtained have *anti* relationships between the  $\alpha$ -ethyl and  $\beta$ -hydroxy groups and are diastereomers of **12**, which in most cases were not detected by <sup>1</sup>H NMR analysis of the crude reaction mixtures. These results are consistent with the 1,4-hydroboration reaction of **13** proceeding via **TS-VII** to give the enolborinate *E*(O)-**14** stereoselectively, and with the aldol reaction of *E*(O)-**14**



**Scheme 4.** 1 Reductive aldol reactions of **13**. Reactions were performed with 0.25 mmol of  $(^d \text{ or } ^l)\text{Ipc}_2\text{BH}$  at a concentration of 0.25 M. Aldol diastereomer ratios were determined by  $^1\text{H}$  NMR analysis of crude reaction mixture. Only **15** was usually observed. Yields of isolated products are reported. Enantiomeric purity and absolute configuration of the C(3)-hydroxy group was determined by Mosher ester analysis.<sup>[16]</sup> TMS = trimethylsilyl.

occurring preferentially via the chairlike transition state **TS-VIII**. The chemical efficiency of these sterically demanding aldol reactions is acceptable (46–67%) with aromatic and unsaturated aldehydes. The lower yields of **15** obtained from **13**, compared to the better yields for the reductive aldol reactions of **7** (Scheme 2) and **10** (Scheme 3) can be attributed to a destabilizing *syn*-pentane interaction in **TS-VIII** between the enolborinate equatorial ethyl substituent and the aldehyde “R<sup>1</sup>” substituent (R<sup>1</sup>CHO).<sup>[18]</sup>

The exceptional diastereoselectivity of these reactions is remarkable, especially in view of the fact that enolborinates are known to isomerize by reversible 1,3-shifts.<sup>[9b,11b,19]</sup> The results presented demonstrate that the enolborinates **Z(O)-11** (from **10**, Scheme 3) and **E(O)-14** (from **13**, Scheme 4) are configurationally stable and do not isomerize by reversible formation of a C-boryl species (not shown), under the reaction conditions of the hydroboration or the subsequent aldol reactions. The kinetic stability of these enolborinates<sup>[20]</sup> undoubtedly reflects the increase in nonbonded steric interactions that must develop in the (unobserved) O-to-C 1,3-borotropic isomerization reaction.

In summary, 1,4-hydroboration reactions of substituted morpholine acrylamides with (diisopinocampheyl)borane provide stereodefined tetrasubstituted enolborinates with exceptional stereochemical control. As such, the results presented here demonstrate a simple solution to the stereoselective synthesis of tetrasubstituted enolates, which are not accessible with synthetically useful stereoselectivity by using conventional enolate-forming reactions.<sup>[5]</sup>

Aldol reactions of **8** (deriving from **7**) with a panel of representative aldehydes provided  $\alpha,\alpha$ -dimethyl- $\beta$ -hydroxy carboxamides **9** with excellent enantioselectivity (91–96% *ee*, Scheme 2). The *syn* and *anti*  $\alpha$ -methyl- $\alpha$ -ethyl- $\beta$ -hydroxy amides **12** and **15**, respectively, are obtained with excellent diastereoselectivity (d.r. >20:1) and high enantioselectivity (92 to >95% *ee*) from the corresponding acrylamides **10** and **13** (Scheme 3 and 4). Morpholine carboxamides are known to have reactivity analogous to Weinreb amides and are valuable intermediates for a variety of subsequent synthetically useful transformations.<sup>[11a]</sup> Thus, this simple and experimentally convenient procedure for synthesis of tetrasubstituted enolborinates by highly stereoselective 1,4-hydroboration of unsaturated morpholine carboxamides and subsequent aldol reactions provide a useful, new method for stereocontrolled synthesis of all-carbon quaternary stereocenters.

## Experimental Section

Acryloylmorpholine derivative **7**, **10**, or **13** (0.275 mmol) was added to a room temperature suspension of  $(^d \text{ or } ^l)\text{Ipc}_2\text{BH}$  (weighed in the glovebox, 72 mg, 0.25 mmol, and then crushed into a fine powder) in Et<sub>2</sub>O (1.0 mL). The solution was stirred for 3 h [at which point all of the  $(\text{Ipc})_2\text{BH}$  had dissolved] and then aldehyde (0.213 mmol) was added. The solution was heated at 50 °C in a sealed tube overnight and then was allowed to cool to room temperature. An aqueous pH 7 buffer solution (0.5 mL), MeOH (0.5 mL) and THF (0.5 mL) were added and the reaction was stirred for 6 h at room temperature. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate, 1:1) provided the aldol adducts **9**, **12**, or **15**.

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