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Highly Diastereo- and Enantioselective Aldol Reactions of Stereochemically Defined Tetrasubstituted Enolborinates Generated By 1,4-Hydroboration of α,β-Unsaturated Morpholine Carboxamides with (Diisopinocampheyl)borane

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Keywords

reductive aldol; all-carbon quaternary centers; (diisopinocampheyl)borane; morpholine amides; enantioselective

The enantioselective synthesis of acyclic all-carbon quaternary centers remains a significant challenge in organic synthesis.[1] 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.[2,3] 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.[3.4] Thus, alternative methods for generation of acyclic tetrasubstituted enolates or their synthetic equivalents have been developed.[5–8] 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..[8] 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 via 1,4-hydroboration reactions[9,10] of unsaturated morpholine carboxamides with (diisopinocampheyl)borane ($(Ipc)_2BH$), 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 morpholine acrylamide **1** with $(^{l}Ipc)_2BH$ provides enolborinate *Z*(O)-**2** via **TS-I** (Scheme 1, where $R^2 = R^3 = H$).[11a] Treatment of *Z*(O)-**2** with aldehydes provided *syn*-aldols **3** with exceptional diastereo- and enantioselectivity (≥20:1 d.r. and 96–98% ee). By virtue of transition state **TS-I** proposed for the 1,4-hydroboration reaction,[9,12] we anticipated that this procedure could be used to generate stereodefined tetrasubstituted enolborinates **5** from substituted α,β-unsaturated

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

We began by using α-methylacryl carboxamide **7** as the substrate to probe the effect of an α-substituent on the 1,4-hydroboration and the following aldol reaction. Compounds bearing a α,α-dimethyl-β-hydroxy quaternary center are often generated by using Mukaiyama aldol methods.[15] 1,4-Hydroboration of **7** (1.1 equiv) with $(^{d}Ipc)_2BH$ (1 equiv) in Et_2O at ambient temperature for 3 h followed by addition of an aldehyde (0.85 equiv) and heating the reaction mixture at 50 °C in sealed tube for 16 h gave aldols **9** (see SI for 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 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 aldols **9a**–**9e** were obtained in good yield (66–84%) and with excellent enantioselectivity (91–96% ee). The absolute stereochemistry of aldols **9** was assigned by using the Mosher method,[16] and is consistent with product formation occurring via transition state **TS-IV**. The aldol reaction proved to be sensitive to steric effects, as aldols **9b** and **9c** deriving from aliphatic aldehydes were obtained in lower yield than those from aromatic or unsaturated aldehydes, and aldols derived from α-branched aldehydes such as cyclohexanecarboxaldehyde were obtained in much lower yield (<10%, not shown).[17]

Having established that α-substituted α,β-unsaturated carboxamide substrates are compatible with this reductive aldol procedure, we elected to study the 1,4-hydroboration and aldol reactions of α,β-dimethyl acrylamide **10** (tigloyl carboxamide). If both steps proceed with synthetically useful stereochemical control, aldol adducts **12** with an α-quarternary center bearing a methyl group *syn* and an ethyl group *anti* to the β-hydroxyl group would be obtained. Thus, 1,4-hydroboration of unsaturated amide **10** with $(^{l}Ipc)_2BH$ (Et_2O, 23 °C) followed by treatment of the intermediate enolborinate *Z*(O)-**11** with representative aliphatic and aromatic aldehydes provided β-hydroxy amides **12** (Scheme 3). The 1,4-hydroboration of **10** was slower than that of **7** and was 80–90% complete after 3 h at 23 °C, as determined by ^1H NMR analysis. Attempts to push the hydroboration to completion by using longer reaction times were not successful. This led us to decrease the amount of aldehyde used in the aldol step from 0.85 to 0.75 equiv in order to compensate for the incomplete hydroboration. Under these conditions, the reductive aldol reactions of **10** provided aldols **12a–12e** in moderate to good yields (40–90%). The least efficient aldol reaction of those presented in Scheme 3 was with hydrocinnamaldehyde, which gave **12b** in 40% yield. However, synthetically useful yields are obtained with α,β-unsaturated aldehydes (**12a**, **12d**), which can serve as surrogates for a saturated aldehyde substrate. Gratifyingly, aldols **12** with *syn*-relationships between the α-ethyl and the β-hydroxyl 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 aldols **12** were assigned by using the Mosher method (see SI).[16] Collectively, these data indicate that enolborinate **11** has *Z*(O) stereochemistry, which is consistent with 1,4-hydroboration of **10** via **TS-V**, and that aldols **12** arise via chair-like transition state **TS-VI**.

Complementary aldol diastereoselectivity is achieved by using α-ethyl acrylamide **13** as the substrate for the 1,4-hydroboration reaction (Scheme 4). Treatment of **13** with $(^{l}Ipc)_2BH$ in

Et_2O at ambient temperature for 3 h, followed by addition of an aldehyde and heating the resulting mixture at 50 °C overnight provided aldols **15** with high diastereoselectivity (d.r. >20:1) and excellent enantioselectivity (92–95% ee).

Aldols **15** so obtained have *anti*-relationships between the α-ethyl and β-hydroxyl groups and are diastereomers of **12**, which in most cases were not detected by ^{1}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 enolborinate *E*(O)-**14** stereoselectively, and with the aldol reaction of *E*(O)-**14** occurring preferentially via the chair-like 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 aldols **15** obtained from acrylamide **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^1" substituent (of R^1CHO).[18]

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.[9b,19] The results presented in Schemes 3 and 4 demonstrate that enolborinates *Z*(O)-**11** (from **10**, Scheme 3) and *E*(O)-**14** (from **13**, Scheme 4) are configurationally stable and do not isomerize via reversible formation of a C-boryl species (not shown), under the conditions of the hydroboration or the subsequent aldol reactions. The kinetic stability of these enolborinates[20] undoubtedly reflects the increase in nonbonded steric interactions that must develop in the (unobserved) O- to C- 1,3-boratropic 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 demonstate a simple solution to the stereoselective synthesis of tetrasubstituted enolates, which are not accessible with synthetically useful stereoselectivity by using conventional enolate forming reactions.[5]

Aldol reactions of **8** (deriving from **7**) with a panel of representative aldehydes provided α,α-dimethyl-β-hydroxy carboxamides **9** with excellent enantioselectivity (91–96 % ee, Scheme 2). *Syn* and *anti* α-methyl-α-ethyl-β-hydroxy amides **12** and **15** are obtained with excellent diastereoselectivity (d.r. >20:1) and high enantioselectivity (92->95% ee) from acrylamides **10** and **13** respectively (Schemes 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.[11a] Thus, this simple and experimentally convenient procedure for synthesis of tetrasubstituted enolborinates via 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

To a room temperature suspension of ($^{d\ or\ l}$Ipc)$_2$BH (weighed in the glovebox, 72 mg, 0.25 mmol, and then crushed into a fine powder) in Et_2O (1.0 mL) was added acryloylmorpholine derivative **7**, **10** or **13** (0.275 mmol). The solution was stirred for 3 h (at which point all of the (Ipc)$_2$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_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (CH_2Cl_2-ethyl acetate, 1:1) provided the aldol adducts **9**, **12** or **15**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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[17]. The low reactivity with α-branched aliphatic aldehydes is not viewed as a serious problem for eventual synthetic applications, since the majority of natural products with an all-carbon quaternary center in polypropionate/polyacetate segments have methylene substituents adjacent to the hydroxyl group. Moreover, the vast majority of natural products in this category have gem-dimethyl groups (e.g., would derive from aldol reactions of enolborinate 8 derived from 7), for which α-unbranched aliphatic aldehydes are acceptable substrates (see 9b, Scheme 2).

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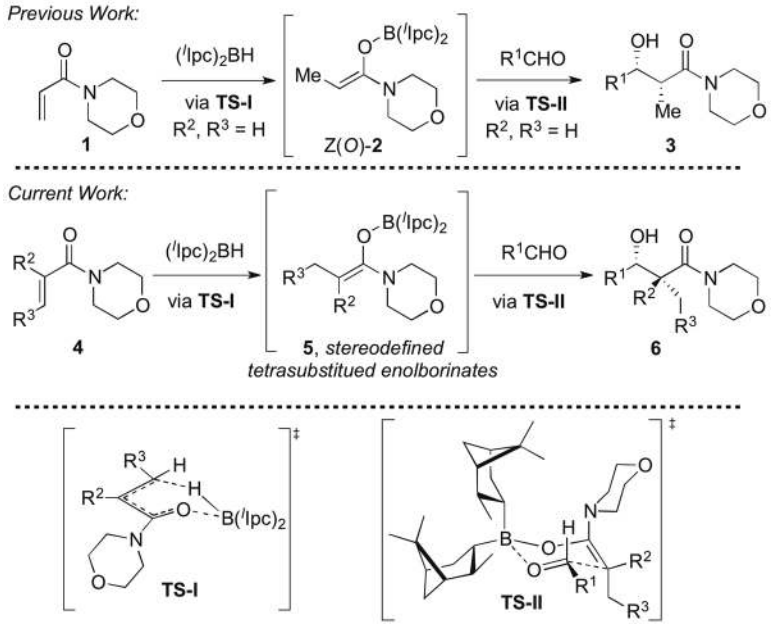
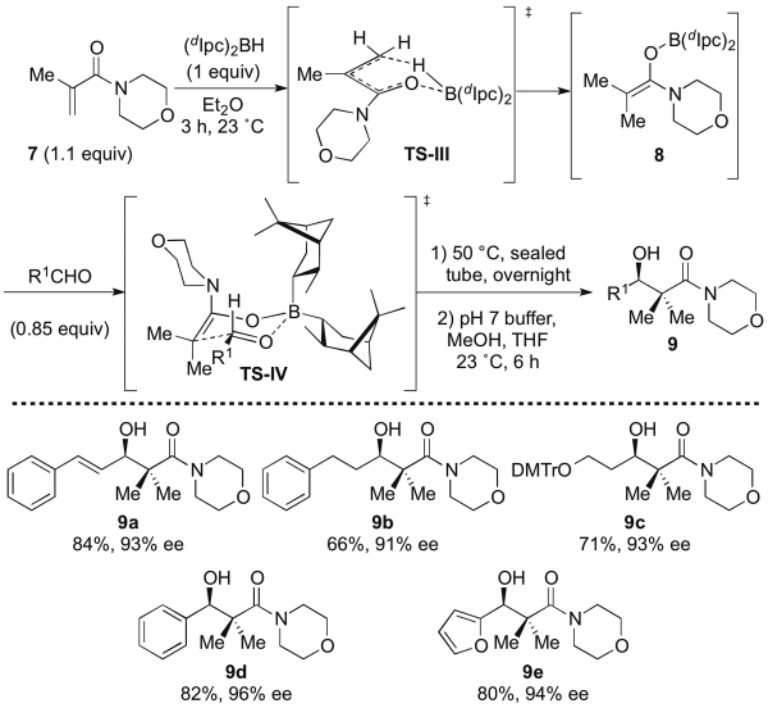
[20]. The exceptional stability of these (diisopinocampheyl)enolborinates is similar and might be related to the stability of previously reported stereodefined tetrasubstituted copper enolates; see reference [8].



Scheme 1.

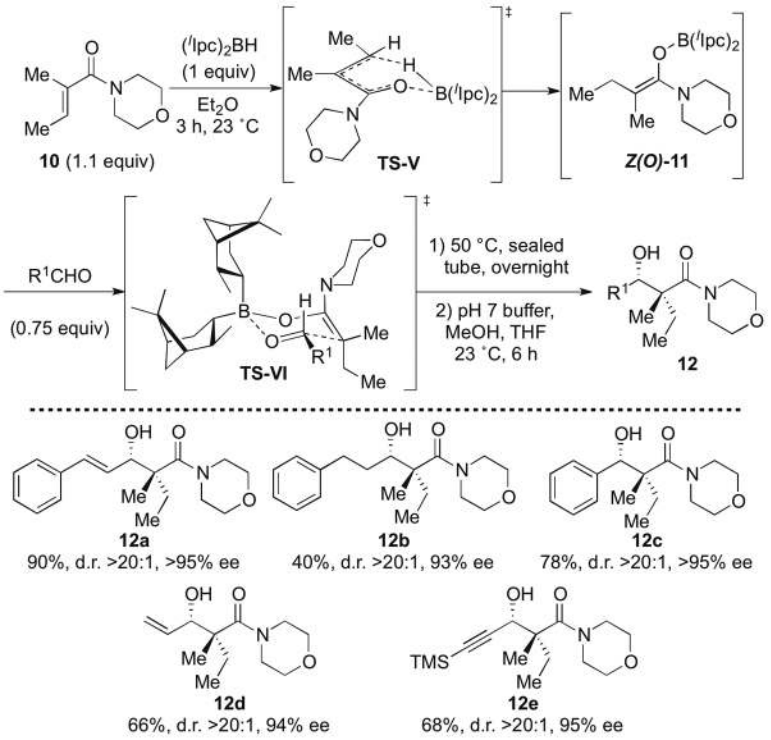
1,4-Reductive aldol reactions of substituted α,β-unsaturated amides with (^{l}Ipc)$_2$BH.



Scheme 2.

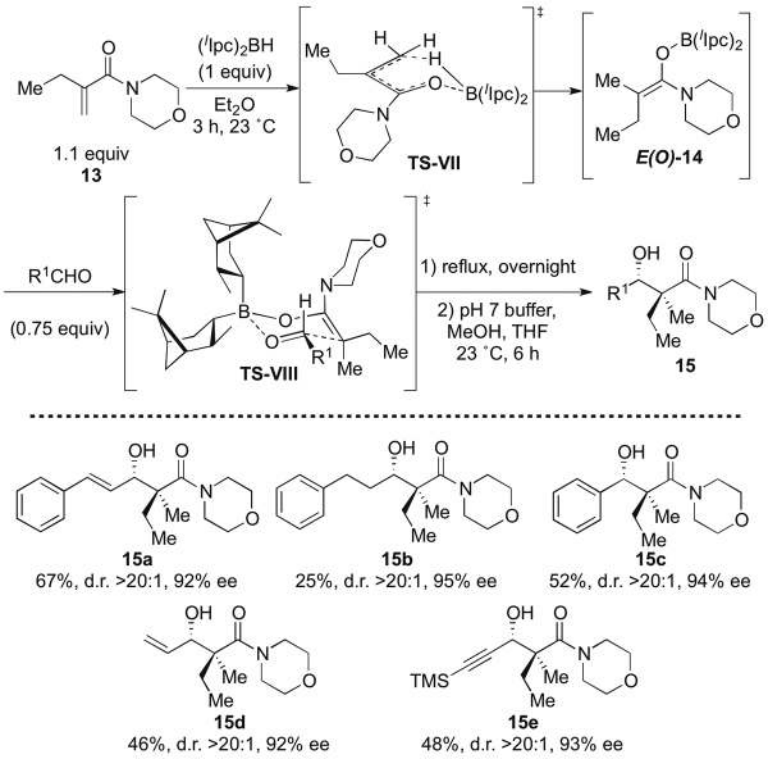
Reductive aldol reactions of α-methacrylamide **7**. [a] Reactions were performed with 0.25 mmol of $(^{d}Ipc)_2BH$ at a concentration of 0.25 M. [b] Isolated yields are reported. [c] Enantiomeric purity and absolute configuration of the hydroxyl stereocenter was determined by Mosher ester analysis.[16] [d]

Reaction of enolate **8** with cinnamaldehyde in Et_2O at reflux using a standard cooling system yielded product **9a** in similar efficiency (83%, 92% ee, performed on 1 mmol scale). DMTr = dimethoxytrityl.



Scheme 3.

Reductive aldol reactions of (*E*)-α,β-dimethylacrylamide **10**. [a] Reactions were performed with 0.25 mmol of (^{l}Ipc)2BH at a concentration of 0.25 M. [b] Aldol diastereomer ratios were determined by ^{1}H NMR analysis of crude products; only **12** was usually observed. [c] Isolated yields are reported. [d] Enantiomeric purity and absolute configuration of the hydroxyl stereocenter was determined by Mosher ester analysis.[16] TMS = trimethylsilyl.



Scheme 4.

1 Reductive aldol reactions of α-ethyl acrylamide **13**. [a] Reactions were performed with 0.25 mmol of (^{l}Ipc)2BH at a concentration of 0.25 M. [b] Aldol diastereomer ratios were determined by ^{1}H NMR analysis of crude products; only **15** was usually observed. [c] Isolated yields are reported. [d] Enantiomeric purity and absolute configuration of the hydroxyl stereocenter was determined by Mosher ester analysis.[16] TMS = trimethylsilyl.