Reductive Aldol Reaction

DOI: 10.1002/ange.201302535

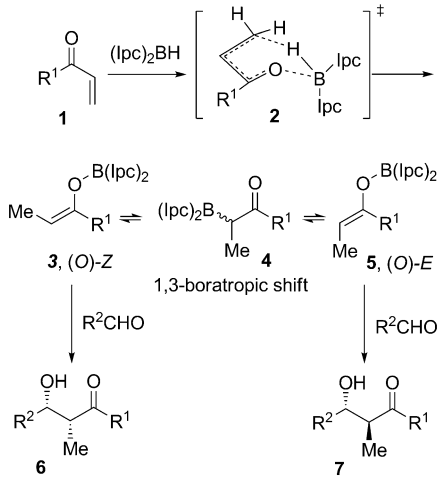
Diisopinocampheylborane-Mediated Reductive Aldol Reactions: Highly Enantio- and Diastereoselective Synthesis of *syn* Aldols from *N*-Acryloylmorpholine**

*Philippe Nuhant, Christophe Allais, and William R. Roush**

The reductive aldol reaction of α,β-unsaturated carbonyl compounds is an important emerging method for stereocontrolled C–C bond formation.[1] Numerous studies[2–6] have focused on reductive aldol reactions of enones and enoates catalyzed by transition-metal complexes. Many such reactions provide excellent levels of enantio- and diastereoselectivity with aromatic aldehyde substrates; however, reductive aldol reactions with aliphatic aldehydes have been generally less selective.[1,2a,b,d,i,3,4c,i,6] Very effective catalytic enantioselective aldol reactions have also been developed, including reactions with aliphatic aldehydes.[7]

It is well-established that boron enolates are exceptionally useful intermediates for asymmetric aldol reactions.[7] We reasoned that the synthetic utility of reductive aldol reactions could be enhanced by utilizing enolborinate intermediates, in view of the tight (B–O bond length 1.4–1.5 Å), closed, structurally well-defined transition states that are invoked to rationalize the enhanced stereochemical control in aldol reactions of enolborinates as compared to those of other metal enolates.[7] Although examples of borane-mediated 1,4-reductions of enone and enoate Michael acceptors have been reported (including the use of diisopinocampheylborane ($(Ipc)_2BH$) as the reducing agent),[8] as well as their subsequent reaction with aldehydes to give *syn* aldols, these processes have not yet been found to deliver the *syn* aldol products with synthetically useful enantioselectivity.[8b,c]

We report herein the development of a highly enantio- and diastereoselective boron-mediated reductive aldol reaction that delivers *syn* aldols with exceptionally high levels of stereoselectivity (≥96% *ee*; ≥20:1 d.r.). It was anticipated that the hydroboration of a Michael acceptor **1** with $(Ipc)_2BH$ would proceed via transition state **2** and lead directly to an (*O*)-*Z* enolate (Scheme 1).[8a–c] We suspected that *Z*–*E* enolborinate equilibration through a reversible 1,3-boratropic shift occurred in prior studies of this process to deliver



Scheme 1. Hydroboration of α,β-unsaturated carbonyl compounds with $(Ipc)_2BH$ and subsequent aldol reactions.

a mixture of *syn* and *anti* aldol adducts **6** and **7** from the (*O*)-*Z* and (*O*)-*E* enolborinate, respectively.[8c,9] Therefore, two major objectives of this study became 1) the identification of a substrate that would undergo 1,4-reduction to give the (*O*)-*Z* enolborinate **3** with high kinetic (if not thermodynamic) control, and 2) the identification of a chiral hydroboration reagent capable of inducing excellent enantioselectivity in the subsequent aldol reaction. We elected to pursue (diisopinocampheyl)enolborinates, which are known to be useful intermediates for enantioselective aldol reactions, although they frequently undergo aldol reactions with only moderate levels of enantioselectivity.[8c,10]

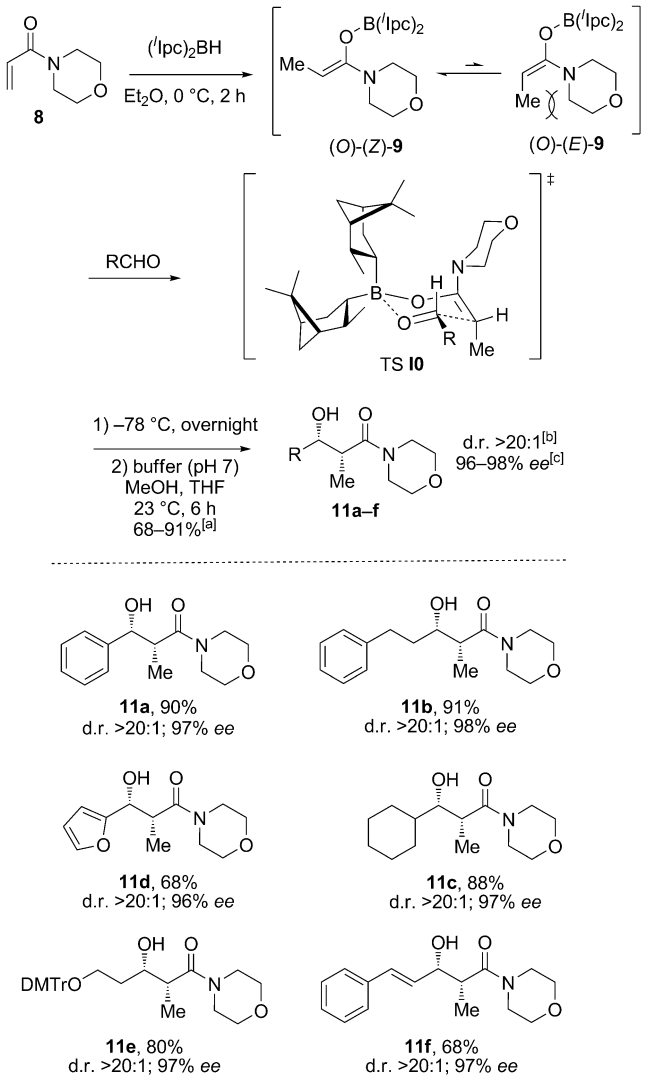
We selected commercially available (and very inexpensive)[11] 4-acryloylmorpholine (**8**) as the substrate for the studies reported herein.[12] Morpholine amides are a safe alternative[13] to Weinreb amides but have similar modes of reactivity and comparable ease of manipulation.[14] We quickly found that excellent results were obtained when the hydroboration of **8** with $(^{t}Ipc)_2BH$[15] was performed in Et_2O at 0 °C for 2 h, followed by addition of the aldehyde (0.85 equiv) at −78 °C (Scheme 2). By using this procedure, we obtained the *syn*-α-methyl-β-hydroxymorpholine amides **11a–f** in good to excellent yields (68–91%) and with excellent enantio- and diastereoselectivities (96–98% *ee*, d.r. > 20:1). The separation of aldols **11** from pinene-derived by-products is trivial owing to the large polarity difference and essentially involved filtration through a short column of silica gel. The enantiofacial selectivity derived from $(^{t}Ipc)_2BH$ in these reactions is the same as in the very well studied allylboration reaction.[17]

[*] Dr. P. Nuhant,[+] Dr. C. Allais,[+] Prof. Dr. W. R. Roush
Department of Chemistry, The Scripps Research Institute
130 Scripps Way, 3A2, Jupiter, FL 33458 (USA)
E-mail: roush@scripps.edu
Homepage: http://www.scripps.edu/roush

[+] These authors contributed equally.

[**] We thank the National Institutes of Health (GM038436) for support of this research. We also sincerely thank Prof. Glenn Micalizio and Dr. Daniel Canterbury for fruitful discussions and comments on this work.

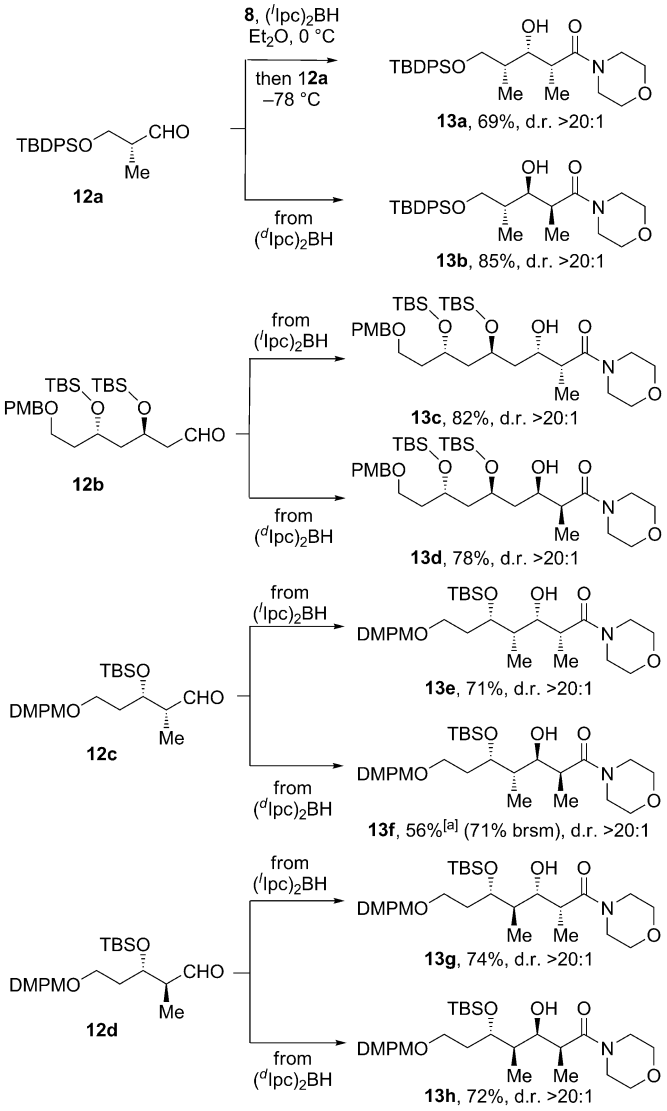
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302535.



Scheme 2. Enantioselective synthesis of *syn*-α-methyl-β-hydroxymorpholine amides **11** from achiral aldehydes. [a] Yield of the isolated aldol **11** after column chromatography. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] The *ee* value and absolute configuration were determined by Mosher ester analysis.[16] DMtr = dimethoxytrityl.

The very high selectivity observed in these reactions reflects, in part, the essentially exclusive (≥ 99 %) formation of the (*O*)-*Z* enol diisopinocampheylborinate (*Z*)-**9** (which we characterized by 1D and 2D NMR spectroscopy; see the Supporting Information). Isomerization of (*Z*)-**9** to (*E*)-**9** evidently does not occur to any significant extent owing to $A^{1,3}$ strain between the morpholine unit and the terminal methyl substituent of the enolborinate.[18] Most remarkable, however, is the exceptional level of enantioselectivity of these reactions, which significantly exceeds that observed in previous studies of enantioselective aldol reactions of (diisopinocampheyl)enolborinates.[8c,10] The relative and absolute configuration determined for aldols **11** is consistent with transition state **10** being dominant in these reactions. That other aldol reactions[8c,10] in which the $(Ipc)_2B$ auxiliary is used proceed with significantly lower levels of enantioselectivity implies that at least one heterochirally related transition state is competitive in those cases, but significantly less so in the reactions of (*Z*)-**9** reported herein.[19]

To test the utility of this reductive aldol procedure in more complex synthetic contexts, we examined the possibility of double asymmetric induction[20] in aldol reactions of (*Z*)-**9** (generated in situ from acrylamide **8** and $(Ipc)_2BH$ as described for the reactions in Scheme 2) with four chiral aldehydes, **12a**, **12b**,[21a] **12c**,[21b] **12d**[21b] (Scheme 3). The intrinsic diastereofacial preference of these aldehydes was determined to be 1.5:1 (in favor of **13a**), 1:2 (in favor of **13d**),



Scheme 3. Double asymmetric aldol reactions of chiral aldehydes and the chiral *Z* enolborinate generated from **8**. Yields of the isolated aldol adducts after column chromatography are given. Diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The absolute and relative configurations of **13a–h** were determined by Mosher ester analysis[16] and the Rychnovsky acetonide method[22] (see the Supporting Information). [a] Very slow reaction, incomplete after 48 h at −78 °C. brsm = based on recovered starting material, DMPM = 3,4-dimethoxybenzyl, PMB = *p*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

3:1 (in favor of **13e**), and 1.3:1 (in favor of **13g**), respectively, in aldol reactions with the achiral enolborinate generated from **8** and dicyclohexylborane (see the Supporting Information). Remarkably, the double asymmetric aldol reactions of **12a–d** with the chiral *Z* enolborinate (*Z*)-**9** derived from **8** and either $(^{l}Ipc)_2BH$ or $(^{d}Ipc)_2BH$ proceeded with excellent stereoselectivity (d.r. > 20:1; in each case, the minor diastereomer was not detected by ^1H NMR spectroscopic analysis of the crude reaction mixture) in both the stereochemically matched and mismatched combinations for each aldehyde substrate. The mismatched double asymmetric reaction of **12c** to give **13f** (56% yield, 71% based on recovered **12c**) was very slow and had not reached completion even after 48 h at −78 °C; all other reactions reached completion overnight at −78 °C. Given the intrinsic facial selectivity of aldehyde **12c** (d.r. 3:1; see the Supporting Information), the enantiofacial selectivity of the *Z* enol diisopinocampheyborinate (*Z*)-**9**, expressed in energetic terms, must be at least 1.57 kcal mol^{-1} to override the intrinsic diastereofacial preference of **12c** to the extent of > 20:1. This selectivity corresponds to a reagent enantioselectivity of 96.5% *ee*, which is fully consistent with the results in Scheme 1 for reactions of (*Z*)-**9** with achiral aldehydes.

This method for the synthesis of *syn*-α-methyl-β-hydroxymorpholinecarboxamides **11** and **13** is a highly attractive and highly competitive alternative to existing methods for the enantioselective synthesis of *syn* aldols.[1–7,23] It also sheds light on the great potential of boron-mediated reductive aldol reactions, despite the less than stellar history of the use of (diisopinocampheyl)enolborinates in enantioselective aldol transformations of achiral substrates.[8c,10]

The aldol reactions of (*Z*)-**9** described herein were performed under exceptionally mild and simple conditions, with no added bases. The results summarized in Scheme 2 and 3 demonstrate that standard (e.g., TBDPS, PMB, DMPM) as well as potentially sensitive protecting groups, such as dimethoxytrityl (DMTr; see **11e**), are fully compatible with the reaction. The diastereo- and enantioselectivity of this procedure rivals that of the very best technology currently available.[1–7,23] The morpholine amide unit in the aldol products exhibits ease of manipulation resembling that of Weinreb amides in subsequent steps.[13,14] Our procedure requires only two steps and begins with the straightforward synthesis of diisopinocampheylborane.[15] Strikingly, the cost of the raw materials required for the synthesis of enolborinate (*Z*)-**9** (including the synthesis of diisopinocampheylborane) is less than $0.25 per mmol scale of the aldol reaction (2012 Sigma–Aldrich prices for bulk quantities of reagents).[11] If the cost, reagent accessibility, selectivity (both enantio- and diastereoselectivity), substrate scope, and generality are considered, as well as the ease of manipulation of the morpholine amide aldol products,[14] we propose that the reductive aldol procedure described herein is not only the least expensive[24] but also among the most enantio- and diastereoselective and generally applicable of currently available procedures for the synthesis of *syn* aldols.

In summary, we have developed a highly enantioselective synthesis of *syn*-α-methyl-β-hydroxymorpholine amides **11** and **13** from achiral and chiral aldehydes, respectively, through the hydroboration of 4-acryloylmorpholine (**8**) with diisopinocampheylborane. This reaction produces the *Z* (diisopinocampheyl)enolborinate (*Z*)-**9** with excellent selectivity, and intermediate (*Z*)-**9** then undergoes highly enantioselective aldol reactions with achiral aldehydes (96–98% *ee*, Scheme 2) and equally highly diastereoselective double asymmetric reactions with a range of chiral aldehydes (Scheme 3). The exceptional enantioselectivity of this process distinguishes it from the vast majority of previously reported examples of aldol reactions of (diisopinocampheyl)enolborinates, which generally proceed with lower levels of enantioselectivity. This difference suggests that the transition-state control in the aldol reactions reported herein is more precise than in the previously studied aldol reactions of (diisopinocampheyl)enolborinates.[8c,10] The extension of this methodology to other aldol substrates and the synthesis of natural products is currently under investigation and will be reported in due course.

Experimental Section

4-Acryloylmorpholine (**8**; 35 μL, 0.275 mmol) was added to a suspension of $(^{l}Ipc)_2BH$ or $(^{d}Ipc)_2BH$ (weighed in a glovebox; 72 mg, 0.25 mmol) or dicyclohexylborane (weighed in a glovebox; 45 mg, 0.25 mmol) in Et_2O (1.0 mL) at 0 °C, and the resulting mixture was stirred for 2 h at 0 °C, during which time it became homogeneous. The mixture was then cooled to −78 °C, the aldehyde (0.213 mmol) was added, and the mixture was stirred overnight at −78 °C. An aqueous buffer solution (pH 7, 0.5 mL), MeOH (0.5 mL), and THF (0.5 mL) were then added, and the reaction mixture was stirred for 6 h at room temperature. The aqueous phase was extracted three times with CH_2Cl_2 (10 mL), and 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 through a short plug of silica gel (1:1 CH_2Cl_2/ethyl acetate) provided the corresponding β-hydroxymorpholine amide **11** or **13**.

Received: March 26, 2013
Published online: July 1, 2013

Keywords: aldol reaction · boranes · diastereoselectivity · enantioselectivity · morpholine amides

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[11] Cost of reagents used in the synthesis of $(Ipc)_2$BH and enolborinate (*Z*)-**9** (2012 Sigma–Aldrich prices): *N*-acryloyl morpholine ($168 per 250 mL, or $0.008 per mmol); (+)-pinene ($72 per kilogram, or $0.01 per mmol); (−)-pinene is less expensive than (+)-pinene; borane–dimethyl sulfide ($550 for 800 mL of a 10.0 M solution, or $0.07 per mmol).

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[24] By comparison, the cost of valine-derived *N*-propionyl oxazolidinone (e.g., Evans aldol reagent)[23] is $20 per mmol (2012 Sigma–Aldrich). The current cost of the chiral oxazolidinone (the use of which requires an N-acylation step prior to the aldol reaction) is $6.80 per mmol. The cost of the parent (*S*)-valinol (the less expensive of the two valinol enantiomers), common to both the Evans and Crimmins aldol methods, is $1.90 per mmol, but two additional synthetic steps are required to generate the reagents used in the aldol experiments. Virtually all of the catalytic enantioselective methods[1–7] currently available require

expensive transition-metal catalysts and/or expensive chiral ligands (many of which require multistep synthesis if not commercially available). For example, $Rh(cod)_2OTf$ and $[\{Rh(cod)Cl\}_2]$ (cod = 1,5-cyclooctadiene), two of the least expensive and most accessible Rh^I catalyst starting materials used in catalytic enantioselective reductive aldol reactions,[2] cost \$62 and \$86 per mmol, respectively (a 5% Rh^I loading is used in many of the reported examples; therefore, the cost of the Rh^I catalyst is \$3–5 for an aldol reaction on a 1 mmol scale). (*R*)-Binap, one of the least expensive widely available chiral phosphine ligands, costs \$80 per mmol; hence, the cost of this ligand when used with a 5 mol% catalyst loading in a catalytic enantioselective reductive aldol reaction is approximately \$5 per mmol scale of the aldol reaction.