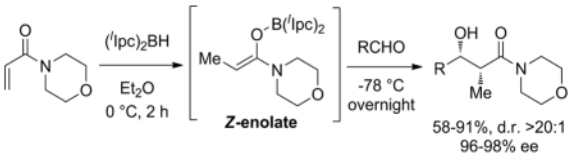
Published in final edited form as:
Angew Chem Int Ed Engl. 2013 August 12; 52(33): . doi:10.1002/anie.201302535.

(Diisopinocampheyl)borane-Mediated Reductive Aldol Reactions: Highly Enantio and Diastereoselective Synthesis of Syn-Aldols from *N*-Acryloylmorpholine**

Dr. Philippe Nuhant‡, **Dr. Christophe Allais**‡, and **Prof. Dr. William R. Roush**
Department of Chemistry The Scripps Research Institute 130 Scripps Way, 3A2, Jupiter FL 33458 (USA), Fax: (+1) (561)-228-3052, Homepage: http://www.scripps.edu/roush

William R. Roush: roush@scripps.edu

Abstract



An efficient and highly enantio- and diastereoselective synthesis of *syn* propionamide aldols is described. Formation of the *Z*-enolborinate via the hydroboration of 4-acryloylmorpholine with (diisopinocampheyl)borane followed by aldol reactions with representative achiral and chiral aldehydes provided *syn*-α-methyl-β-hydroxy morpholine carboxamides with excellent enantio- and diastereoselectivity (96–98% ee and d.r. >20:1).

Keywords

Diisopinocampheylborinate; aldol; enantioselective; diastereoselective; morpholine amide

The reductive aldol reaction of α,β-unsaturated carbonyl compounds is an important, emerging method for stereocontrolled C-C bond formation.[1] Numerous recent 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 in reductive aldol reactions with aromatic aldehydes, however reductive aldol reactions with aliphatic aldehydes have been generally less selective.[1,2a,b,d,i,3,4c,i,6] Catalytic enantioselective aldol reactions have also been developed that are very effective 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 Á), closed, structurally well-defined transition states that are invoked

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

Correspondence to: William R. Roush, roush@scripps.edu.

‡These authors contributed equally to this work.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

to rationalize the enhanced stereochemical control in aldol reactions of enolborinates compared to other metal enolates.[7] While examples of borane-mediated 1,4-reductions of enone and enoate Michael acceptors have been reported (including use of diisopinocampheylborane as the reducing agent),[8] with subsequent reactions with aldehydes leading to *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 stereocontrol (≥96% ee; ≥20:1 d.r). As depicted in Scheme 1, it was anticipated that hydroboration of a Michael acceptor **1** with $(Ipc)_2BH$ would proceed *via* transition state **2** and lead directly to a *Z(O)*-enolate.[8a–c] However, *Z-E* enolborinate equilibration through a reversible 1,3-boratropic shift was suspected to occur in prior studies of this process, thereby delivering a mixture of *syn* (**6**) and *anti* (**7**) aldol adducts from the *Z(O)* and *E(O)*-enolborinates, respectively.[8c,9] As such, two major objectives of this study became (1) the identification of a substrate that would undergo 1,4-reduction to give the *Z(O)*-enolborinate **3** with high kinetic (if not thermodynamic) control, and (2) identification of a chiral hydroborating 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, albeit frequently undergoing aldol reactions with only moderate levels of enantioselectivity.[8c,10]

We selected commercially available (and very inexpensive)[11] 4-acryloylmorpholine (**8**) as 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 0.85 equiv of aldehyde at −78 °C (Scheme 2). By using this procedure, the *syn*-α-methyl-β-hydroxy morpholine amides **11a–f** were obtained in good to excellent yields (68–91%) and with excellent enantio- and diastereoselectivities (96–98% ee, d.r. >20:1). Separation of aldols **11** from pinene-derived byproducts is trivial, essentially constituting a short column filtration, owing to the large polarity difference. The enantiofacial selectivity derived from $(^{t}Ipc)_2BH$ in these reactions is the same as in the very well studied allylboration reaction.[17]

The very high selectivity realized in these reactions reflects, in part, the essentially exclusive (≥99%) formation of the *Z(O)*-enol diisopinocampheylborinate **9*Z*** (which we characterized by 1D and 2D NMR experiments; see SI). Isomerization of **9*Z*** to **9*E*** 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 realized in these reactions, which significantly exceeds that obtained in previous studies of enantioselective aldol reactions of (diisopinocampheyl)enolborinates.[8c,10] The relative and absolute stereochemistry determined for aldols **11** is consistent with transition state **10** being dominant in these reactions. That other aldol reactions[8c,10] using the $(Ipc)_2B$– auxiliary 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 **9*Z*** reported here.[19]

In order to test the utility of this reductive aldol procedure in more complex synthetic contexts, we examined the aldol reactions of **9*Z*** (generated *in situ* from acrylamide **8** and $(Ipc)_2BH$ as described for the reactions in Scheme 2) in the double asymmetric manfold[20] with four chiral aldehydes, **12a**, **12b**,[21a] **12c**,[21b] **12d** (Scheme 3). The intrinsic

diastereofacial preferences of these aldehydes was determined to be 1.5:1 (in favor of **13a**), 1:2 (in favor of **13d**), 3:1 (in favor of **13e**) and 1.3:1 (in favor of **13g**), respectively, by aldol reactions with the achiral enolborinate generated from **8** and dicyclohexylborane (see SI). Remarkably, the double asymmetric aldol reactions of **12a**, **12b**, **12c** and **12d** using the chiral *Z*-enolborinate **9*Z*** deriving from **8** with either $(^{l}\text{Ipc})_2\text{BH}$ or $(^{d}\text{Ipc})_2\text{BH}$ proceeded with excellent stereocontrol (d.r. >20:1; in each case, the minor diastereomer could not be detected in any of the experiments by ^{1}H NMR analysis of crude reaction mixtures) in both the stereochemically matched and mismatched combinations for each aldehyde substrate. The mismatched double asymmetric reaction of **2c** yielding **13f** (56% yield, 71% based on recovered **2c**) was very slow and had not reached completion even after 48 h at −78 °C; all other experiments were complete after overnight at −78 °C. Knowing the intrinsic facial selectivity of aldehyde **12c** (d.r. 3:1, see SI), the enantiofacial selectivity of the *Z*-enol diisopinocampheyborinate **9*Z***, expressed in energetic terms, must be at least 1.57 kcal/mol in order to override the intrinsic diastereofacial preference of **12c** to the extent of >20:1. This corresponds to a reagent enantioselectivity of 96.5% ee, fully consistent with the data provided in Scheme 1 for reactions of **9*Z*** with achiral aldehydes.

This method for synthesis of *syn*-α-methyl-β-hydroxy morpholine carboxamides **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 associated with prior studies of (diisopinocampheyl)enolborinates in enantioselective aldol transformations of achiral substrates.[8c,10]

The aldol reactions of **9*Z*** described here are performed under exceptionally mild and simple conditions, with no added bases. The results summarized in Schemes 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. 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 Weinreb amide-like ease of manipulation in subsequent steps.[13,14] Our procedure requires only two steps, starting with the straightforward synthesis of diisopinocampheylborane.[15] Strikingly, the cost of raw materials required for the synthesis of enolborinate **9*Z*** (including the synthesis of diisopinocampheylborane) is less than $0.25 per mmol scale aldol reaction (2012 Sigma-Aldrich prices for bulk quantities of reagents).[11] Integrating over cost, reagent accessibility, selectivity (both enantio- and diastereoselectivity), substrate scope and generality, and the ease of manipulation of the morpholine amide aldol products,[14] we submit that the new reductive aldol procedure described here is the least expensive[24] and ranks high among the most highly enantio- and diastereoselective, substrate-general methods for synthesis of *syn* aldols compared to all other currently available procedures.

In summary, we have developed a highly enantioselective synthesis of *syn*-α-methyl-β-hydroxy morpholine amides **11** and **13** from achiral and chiral aldehydes, respectively, *via* the hydroboration of 4-acryloylmorpholine (**8**) with diisopinocampheylborane. This reaction produces the *Z*-(diisopinocampheyl)enolborinate **9*Z*** with excellent selectivity, which 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 is also noteworthy, especially given that the vast majority of literature examples of aldol reactions of (diisopinocampheyl)enolborinates generally proceed with lower levels of enantioselectivity, which suggests that transition state control in the aldol reactions reported herein is more precise than with the previously studied aldol reactions of (diisopinocampheyl)enolborinates.[8c,10] Extensions of this methodology to other aldol

substrates, as well as applications in the synthesis of natural products are currently under investigation and will be reported in due course.

Experimental Section

At 0 °C, to a suspension of (^{l} or ^{d}Ipc)$_2$BH (weighed in a glovebox, 72 mg, 0.25 mmol) or (Cy)$_2$BH (weighed in a glovebox, 45 mg, 0.25 mmol) in Et_2O (1.0 mL) was added 4-acryloylmorpholine (**8**) (35 μL, 0.275 mmol). The solution was stirred 2 h at 0 °C at which time it became homogeneous. The resulting mixture was cooled to −78 °C, aldehyde (0.213 mmol) was added, and the solution was stirred overnight at −78 °C. 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 three times with CH_2Cl_2 (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 through a short plug of silica gel (1:1 CH_2Cl_2-ethyl acetate) provided the corresponding β–hydroxymorpholine amide **11** or **13**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Guo HC, Ma JA. Angew Chem Int Ed. 2006; 45:354–366.b) Nishiyama H, Shiomi T. Top Curr Chem. 2007; 279:105–137.c) Han SB, Hassan A, Krische MJ. Synthesis. 2008; 17:2669–2679. [PubMed: 21866204] d) Garner, SA.; Han, SB.; Krische, MJ. Metal Catalyzed Reductive Aldol Coupling. In: Andersson, P.; Munslow, I., editors. Modern Reduction Methods. Wiley-VCH; Weinheim: 2008. p. 387-408.
2. Rhodium catalyzed asymmetric reductive aldol reactions: Taylor SJ, Duffey MO, Morken JP. J Am Chem Soc. 2000; 122:4528–4529.Russell AE, Fuller NO, Taylor SJ, Aurriset P, Morken JP. Org Lett. 2004; 6:2309–2312. [PubMed: 15228266] Bocknack BM, Wang L-C, Krische MJ. Proc Natl Acad Sci. 2004; 101:5421–5424. [PubMed: 15024093] Fuller NO, Morken JP. Synlett. 2005:1459–1461.Nishiyama H, Shiomi T, Tsuchiya Y, Matsuda I. J Am Chem Soc. 2005; 127:6972–6973. [PubMed: 15884939] Jung C-K, Krische MJ. J Am Chem Soc. 2006; 128:17051–17056. [PubMed: 17177457] Han SB, Krische MJ. Org Lett. 2006; 8:5657–5660. [PubMed: 17107096] Ito J, Shiomi T, Nishiyama H. Adv Synth Catal. 2006; 348:1235–1240.Shiomi T, Ito J, Yamamoto Y, Nishiyama H. Eur J Org Chem. 2006:5594–5600.Shiomi T, Nishiyama H. Org Lett. 2007; 9:1651–1654. [PubMed: 17385871] Hashimoto T, Shiomi T, Ito J, Nishiyama H. Tetrahedron. 2007; 63:12883–12887.Hashimoto T, Ito J, Nishiyama H. Tetrahedron. 2008; 64:9408–9412.Bee C, Han SB, Hassan A, Iida H, Krische MJ. J Am Chem Soc. 2008; 130:2746–2747. [PubMed: 18266373] Shiomi T, Adachi T, Ito J, Nishiyama H. Org Lett. 2009; 11:1011–1014. [PubMed: 19161317] Sugiura M, Sato N, Sonoda Y, Kotani S, Nakajima M. Chem–Asian J. 2010; 5:478–481. [PubMed: 20033980]
3. Iridium catalyzed asymmetric reductive aldol reactions: Zhao CX, Duffey MO, Taylor SJ, Morken JP. Org Lett. 2001; 3:1829–1831. [PubMed: 11405722]
4. Copper catalyzed asymmetric reductive aldol reactions: Lam H, Murray GJ, Firth JD. Org Lett. 2005; 7:5743–5746. [PubMed: 16321037] Lam H, Joensuu PM. Org Lett. 2005; 7:4225–4228. [PubMed: 16146393] Chuzel O, Deschamp J, Chausteur C, Riant O. Org Lett. 2006; 8:5943–5946. [PubMed: 17165900] Deschamp J, Chuzel O, Hannedouche J, Riant O. Angew Chem Int Ed. 2006; 45:1292–1297.Zhao D, Oisaki K, Kanai M, Shibasaki M. Tetrahedron Lett. 2006; 47:1403–1407.Zhao D, Oisaki K, Kanai M, Shibasaki M. J Am Chem Soc. 2006; 128:14440–14441. [PubMed: 17090010] Lipshutz BH, Amorelli B, Unger JB. J Am Chem Soc. 2008; 130:14378–14379. [PubMed: 18847266] Deschamp J, Riant O. Org Lett. 2009; 11:1217–1220. [PubMed: 19220061] Kato M, Oki H, Ogata K, Fukuzawa S. Synlett. 2009:1299–1302.Ou J, Wong WT, Chiu P. Tetrahedron. 2012; 68:3450–3456.

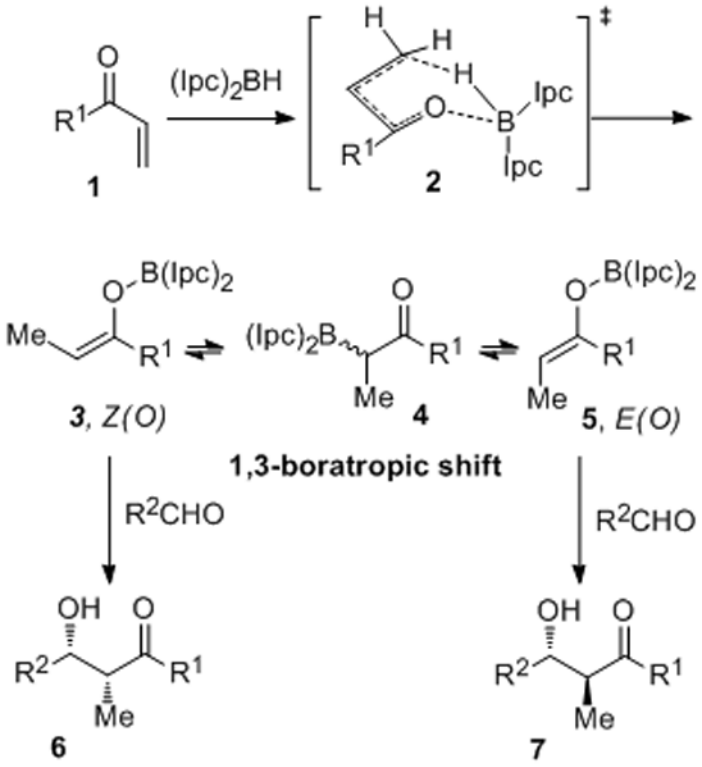
5. Cobalt catalyzed asymmetric reductive aldol reaction: Lumby RJ, Joensuu PM, Lam HW. Tetrahedron. 2008; 64:7729–7740.
6. Tertiary amine as a hydride donor for asymmetric reductive aldol reactions: Osakama K, Sugiura M, Nakajima M, Kotani S. Tetrahedron Lett. 2012; 53:4199–4201.
7. Selected reviews of enantioselective aldol reactions: Heathcock CH. Comprehensive Organic Synthesis. 2 Trost BM, Fleming I. Pergamon PressNew York1991; :181–238.Kim BM, Williams SF, Masamune S. Comprehensive Organic Synthesis. 2Trost BM, Fleming I. Pergamon PressNew York1991; :239–275.Cowden CJ, Paterson I. Org React. 1997; 51:1–200.Mahrwald R. Modern Aldol Reactions. 2Mahrwald R. Wiley-VCHWeinheim2004; Denmark SE, Fiujimori S. Modern Aldol Reactions. 2Mahrwald R. Wiley-VCHWeinheim2004; :229–326.Shibasaki M, Matsunaga S, Kumagai N. Modern Aldol Reactions. 2Mahrwald R. Wiley-VCHWeinheim2004; :197–227.Johnson JS, Nicewicz DA. Modern Aldol Reactions. 2Mahrwald R. Wiley-VCHWeinheim2004; :69–103.Bisai V, Bisai A, Singh VK. Tetrahedron. 2012; 68:4541–4580.
8. a) Evans DA, Fu GC. J Org Chem. 1990; 55:5678–5680.b) Boldrini GP, Mancini F, Tagliavini E, Trombini C, Umani-Ronchi A. J Chem Soc, Chem Commun. 1990:1680–1681.c) Boldrini GP, Bortolotti M, Mancini F, Tagliavini E, Trombini C, Umani-Ronchi A. J Org Chem. 1991; 56:5820–5826.d) Matsumoto Y, Hayashi T. Synlett. 1991:349–350.e) Ghosh AK, Kass J, Anderson DD, Xu X, Marian C. Org Lett. 2008; 10:4811–4814. [PubMed: 18831554] f) Huddleston RR, Cauble DF, Krische MJ. J Org Chem. 2003; 68:11–14. [PubMed: 12515454]
9. a) Masamune S, Mori S, van Horn D, Brooks SW. Tetrahedron Lett. 1979; 20:1665–1668.b) Duffy JL, Yoon TP, Evans DA. Tetrahedron Lett. 1995; 36:9245–9248.c) Abiko A, Inoue T, Masamune S. J Am Chem Soc. 2002; 124:10759–10764. [PubMed: 12207531]
10. a) Paterson I, Goodman JM, Lister MA, Schumann RC, McClure CK, Norcross RD. Tetrahedron. 1990; 46:4663–4684.b) Ramachandran PV, Pratihar D. Org Lett. 2009; 11:1467–1470. Ramachandran reports the synthesis of syn aldols with ≥94:6 d.r. and 90–98% ee from the Ipc_2BOTf mediated aldol reactions of methyl propionate. However, after repeated attempts, the best selectivity we have achieved is 2:1 d.r. and 79% ee for the syn aldol from the reaction of methyl propionate and cinnamaldehyde using Ramachandran's procedure. [PubMed: 19265395]
11. Cost of reagents used in the synthesis of $(Ipc)_2BH$ and enolborinate **9*Z*** (2012 Sigma Aldrich prices): N-acryloyl morpholine ($168 per 250 mL, or $0.008 per mmol); (+)-pinene ($72 per Kg, or $0.01 per mmol); (−)-pinene is less expensive than the (+)-enantiomer; borane-dimethyl sulfide ($550 for 800 mL of 10.0 M solution; or $0.07 per mmol).
12. The Weinreb amide of acrylic acid failed to undergo the reductive aldol reaction, presumably owing to chelation of boron by the N-methoxy group after the 1,4-reduction.
13. a) Jackson MM, Leverett C, Toczko JF, Roberts JC. J Org Chem. 2002; 67:5032–5035. [PubMed: 12098333] b) Peters R, Waldmeier P, Joncour A. Org Process Res Dev. 2005; 9:508–512.
14. a) Martin R, Romea P, Tey C, Urpi F, Vilarrasa J. Synlett. 1997; 49:1414–1416.b) Concellón JM, Rodríguez-Solla H, Méjica C, Blanco EG. Org Lett. 2007; 9:2981–2984. [PubMed: 17629282] c) Dhoro F, Kristensen TE, Stockmann V, Yap GPA, Tius MA. J Am Chem Soc. 2007; 129:7256–7257. [PubMed: 17508753] d) Concellón JM, Rodríguez-Solla H, Díaz P. J Org Chem. 2007; 72:7974–7979. [PubMed: 17887705] e) Lin KW, Tsai C-H, Hsieh I-L, Yan TH. Org Lett. 2008; 10:1927–1930. [PubMed: 18407645] f) Concellón JM, Rodríguez-Solla H, del Amo V, Díaz P. Synthesis. 2009:2634–2645.g) Rye C, Barker D. Synlett. 2009:3315–3319.
15. Brown HC, Singaram B. J Org Chem. 1984; 49:945–947.
16. a) Dale JA, Mosher HS. J Am Chem Soc. 1973; 95:512–519.b) Ohtani I, Kusumi T, Kashman Y, Kakisawa H. J Am Chem Soc. 1991; 113:4092–4096.
17. a) Jadhav PK, Bhat KS, Perumal PT, Brown HC. J Org Chem. 1986; 51:432–439.b) Brown HC, Bhat KS, Randad RS. J Org Chem. 1989; 54:1570–1576.c) Racherla US, Brown HC. J Org Chem. 1991; 56:401–404.
18. Hoffmann RW. Chem Rev. 1989; 89:1841–1860.
19. Computational studies of aldol reactions of enolborinate intermediates: Bernardi A, Capelli AM, Gennari C, Goodman JM, Paterson I. J Org Chem. 1990; 55:3576–3581.Li Y, Paddon-Row MN, Houk KN. J Org Chem. 1990; 55:481–493.Bernardi F, Robb MA, Suzzi-Valli G, Tagliavini E, Tromboni C, Umani-Ronchi A. J Org Chem. 1991; 56:6472–6475.
20. Masamune S, Choy W, Petersen JS, Sita LR. Angew Chem Int Ed. 1985; 24:1–30.

21. a) Nuhant P, Kister J, Lira R, Sorg A, Roush WR. Tetrahedron. 2011; 67:6497–6512. [PubMed: 21857752] b) Lira R, Roush WR. Org Lett. 2007; 9:4315–4318. [PubMed: 17867698]

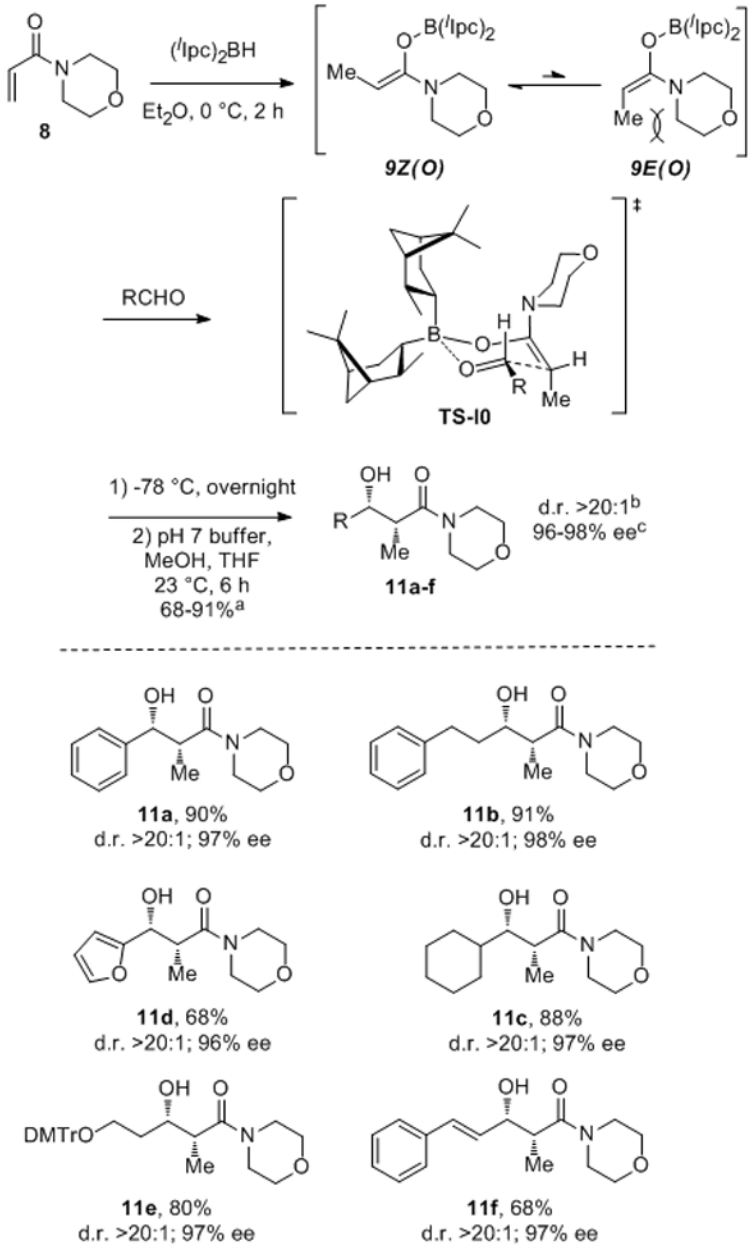
22. Rychnovsky SD, Skalitzky DJ. Tetrahedron Lett. 1990; 31:945–948.

23. a) Evans DA, Bartroli J, Shih TL. J Am Chem Soc. 1981; 103:2127–2129.b) Crimmins MT, King BW, Tabet AE. J Am Chem Soc. 1997; 119:7883–7884.c) Crimmins MT, Chaudhary K. Org Lett. 2000; 2:775–777. [PubMed: 10754681]

24. By comparison, the cost of the valine-derived N-propionyl oxazolidinone (e.g., Evans' aldol reagent)[23] is $20/mmol (2012 Sigma-Aldrich). The current cost of the chiral oxazolidinone (use of which requires an N-acylation step prior to the aldol reaction) is $6.80/mmol. The cost of the parent (*S*)-valinol (the less expensive of the two valinol enantiomers), common to both the Evans and Crimmin's aldol methods, is $1.90/mmol, but two additional synthetic steps are required to generate the reagents used in the aldol rexperiments. Virtually all of the catalytic enantioselective methods[1–7] currently available use of expensive transition metal catalysts and/or expensive chiral ligands (many of which require multi-step synthesis if not commercially available). For example, $Rh(COD)_2OTf$ and $[Rh(COD)Cl]_2$, two of the least expensive and most accessible Rh(I) catalyst starting materials used in catalytic enantioselective reductive aldol reactions,[2] cost $62–$86 per mmol, respectively (5% Rh(I) loading is used in many of the published examples, therefore the Rh(I) cost is $3–$5 for a 1 mmol aldol experiment). (R)-BINAP, one of the least expensive and widely available chiral phosphine ligands, costs $80/mmol; hence the cost of this ligand when used at the 5 mol% level in a catalytic enantioselective reductive aldol experiment is approximately $5 per mmol aldol experiment.

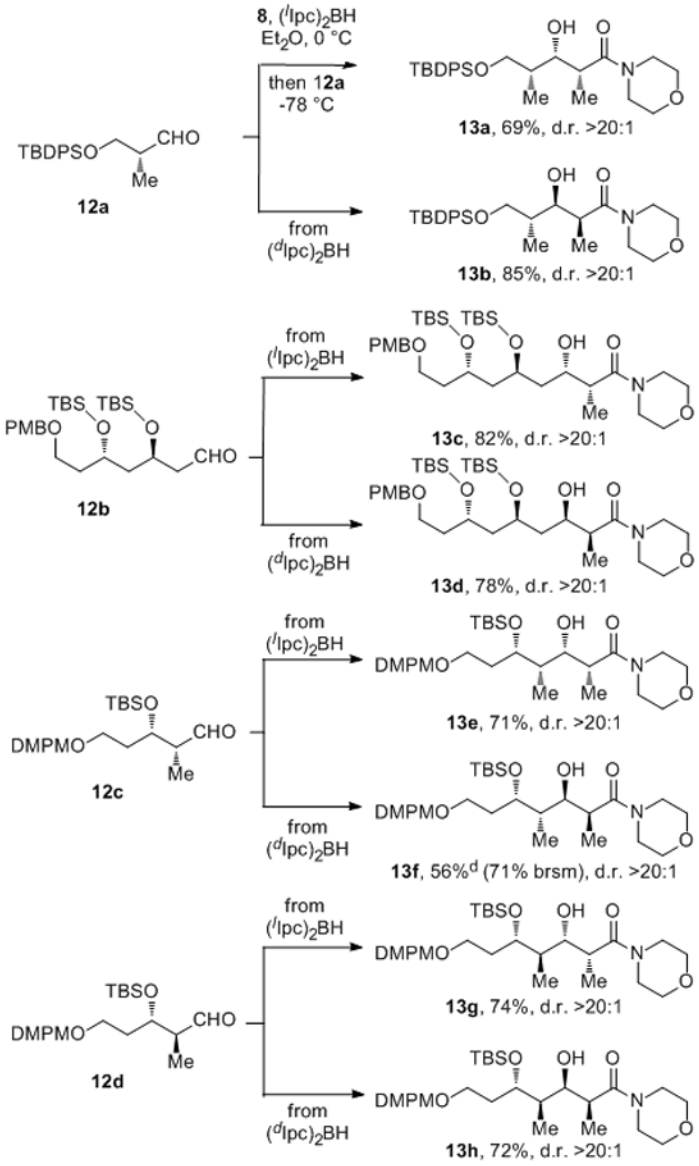


Scheme 1.
Hydroboration of α,β-unsaturated carbonyl compounds with (Ipc)2BH and subsequent aldol reactions.



Scheme 2.

Enantioselective synthesis of *syn*-α-methyl-β-hydroxy morpholine amides **11** from achiral aldehydes. [a] Isolated yields of aldols **11** obtained after column chromatography. [b] Diastereomer ratios (d.r.) determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Enantiomeric excess (% ee) and absolute configurations determined by using the Mosher ester analysis.[16]



Scheme 3.

Double asymmetric aldol reactions of chiral aldehydes and the chiral *Z*-enolborinate generated from **8**. [a] Yields of aldol adducts are for isolated products obtained by column chromatography. [b] Diastereomer ratios (d.r.) determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Absolute and relative configurations of **13a–13h** determined by using Mosher ester analysis[16] and the Rychnovsky acetonide method[22] (see SI). [d] Very slow reaction, not complete after 48 h at −78 °C.