Organic Syntheses

Enantioselective Reductive *Syn*-Aldol Reactions of 4-Acryloylmorpholine: Preparation of (2*R*, 3*S*)-3-Hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one

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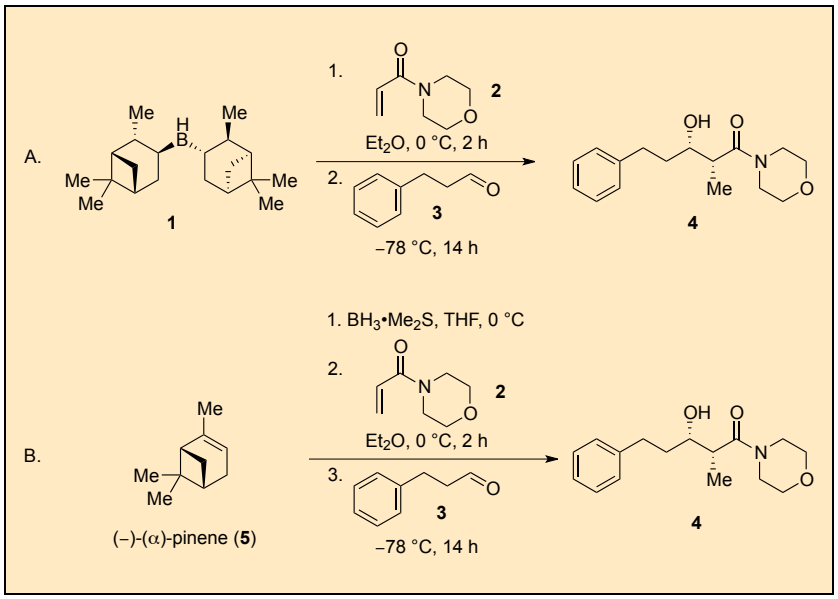
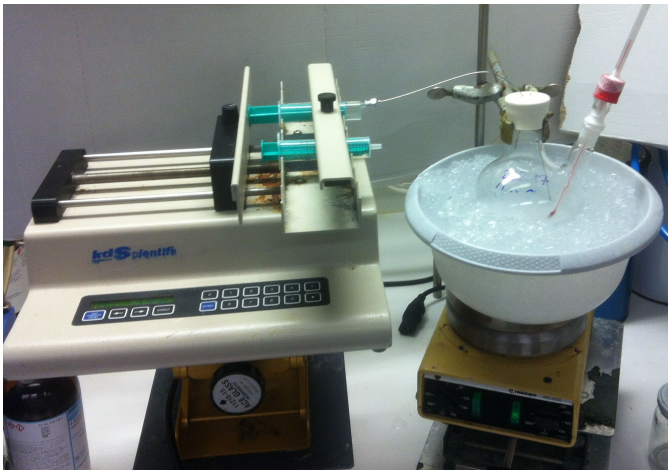
Checked by Simon Krautwald, Simon Breitler, and Erick M. Carreira



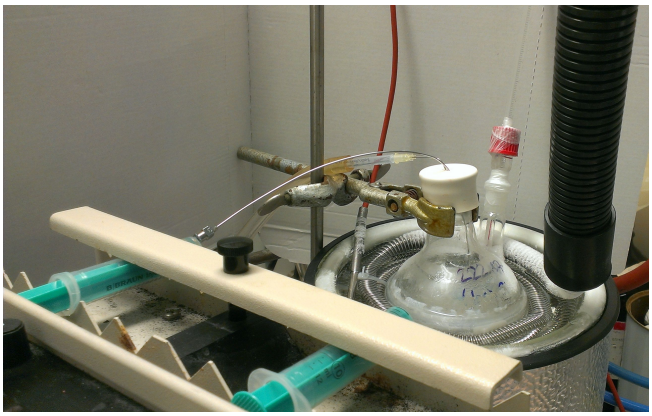
Procedure

A. *(2R, 3S)-3-Hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one (**4**) from Crystalline (Diisopinocampheyl)borane* (**1**). A flame-dried 500-mL, two-necked, round-bottomed flask is equipped with a 5-cm Teflon-coated egg-shaped magnetic stir bar and moved into a glovebox. The flask is charged with

crystalline (^{l}Ipc)$_2$BH (**1**) (13.5 g, 47.06 mmol, 1.18 equiv) (Note 1), and capped with rubber septa. The flask is then removed from the glovebox, equipped with an argon line and a thermometer (Note 2), and charged with diethyl ether (190 mL) (Note 3). The resulting white suspension is cooled to 0 °C (Note 4) with an ice/water bath and stirred for 15 min. 4-Acryloylmorpholine (**2**) (Note 3) (6.5 mL, 7.31 g, 51.76 mmol, 1.30 equiv) is added over 5 min using a syringe pump. Upon complete addition, the



mixture is stirred at 0 °C for 2 h. After 15 min the white suspension becomes a clear solution, which gradually gives way to a turbid white suspension (Note 4). The ice/water bath is then replaced with a dry ice/acetone bath and the mixture is cooled to –78 °C and stirred for 15 min at this temperature. Hydrocinnamaldehyde (**3**) (Note 3) (5.3 mL, 5.37 g, 40.00 mmol, 1.00 equiv) is added over 5 min using a syringe pump (Note 5). Upon complete addition, the mixture is stirred at –78 °C for 14 h before a premixed solution of THF/methanol/pH 7 potassium phosphate buffer (Note 3) (1:1:1 v/v/v, 135 mL total) is introduced via syringe. The reaction mixture is allowed to warm to 23 °C and, upon reaching that temperature, stirred vigorously for 6 h. During this period the color of the solution changes from clear to yellow. The mixture is then transferred to a 500-mL separatory funnel with the aid of diethyl ether. The organic layer is removed and the aqueous phase is extracted with two 50-mL portions of diethyl ether. The combined organic layers are washed with two 100-mL



portions of deionized water, one 100-mL portion of brine, and dried over sodium sulfate (Na_2SO_4) (100 g). The drying agent is removed by vacuum filtration through a 150-mL fritted glass funnel and washed with three 25-mL portions of diethyl ether. The filtrate is concentrated by rotary evaporation (35 °C bath temperature, 460 mmHg initial pressure to 10 mmHg final pressure) to afford 25.0–25.1 g of a clear yellow oil. For purification, the crude product is solubilized in 10-mL of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) (Note 6) and loaded onto a 7.5 cm diameter column containing 200 g of silica gel that is prepacked with 30% EtOAc-hexanes (70:30 hexanes:EtOAc) (Note 7). The flask is washed with three 10-mL portions of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) and the washings are loaded onto the silica gel. Fraction collection (250-mL fractions) is begun and elution proceeds with 3000-mL of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) and then 1000-mL of 40% EtOAc-hexanes (60:40 hexanes:EtOAc). The product is finally eluted from the column using 2000-mL of EtOAc, with fractions 17-24 containing the desired material (Note 8). These fractions are combined and concentrated by rotary evaporation (35 °C bath temperature, 200 mmHg initial pressure to 10 mmHg final pressure) and subsequently dried for 12 h at <5 mmHg (Note 9) to provide 7.8–8.2 g (70–73%) of diastereomerically pure (Notes 10 and 11) (2*R*, 3*S*)-3-hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one (**4**), 97% ee (Note 12), as a white solid, mp 76–78 °C (Note 13).

B. *One-pot Synthesis of (2R, 3S)-3-Hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one (**4**) from (–)-(α)-pinene (**5**)*. A flame-dried 500-mL, two-necked, round-bottomed flask equipped with a 5-cm Teflon-coated egg-shaped magnetic stir bar and rubber septa is purged with argon, and its tare

weight is recorded. An argon line is inserted through one of the septa and the other one is replaced with a thermometer (Note 2). The flask is charged with tetrahydrofuran (THF) (80 mL) and borane-methyl sulfide complex (Note 3) (8.2 mL, 6.5 g, 80.1 mmol, 1.75 equiv) is added via syringe. The mixture is cooled to 0 °C (Note 4) with an ice/water bath and (–)-(α)-pinene (**5**) (25.5 mL, 22.3 g, 160.2 mmol, 3.50 equiv) (Note 14) is added over 30 min using a syringe pump. Upon complete addition, the stirring is terminated, the thermometer replaced with a rubber septum, the argon line removed, and the septa are wrapped thoroughly with Parafilm®. The reaction flask is then placed in a 0 °C ice/water bath in a 4 °C cold room for 46 h (Note 15).

After this time, the flask is allowed to warm to room temperature, the Parafilm® is discarded, and the supernatant is removed via cannula. Trituration of the residual chunks of $(^{l}Ipc)_2BH$ is performed by introduction of diethyl ether (50 mL) via syringe and subsequent decannulation of the supernatant. The trituration process is repeated two additional times before the cannula is removed and replaced with a needle attached to a vacuum line. The white crystals of $(^{l}Ipc)_2BH$ are allowed to dry at <5 mmHg for 3 h. At this time the flask is back-filled with argon, gently shaken to pulverize chunks of solid $(^{l}Ipc)_2BH$ with the aid of the magnetic stir bar, and then weighed. This procedure provides 13.0–13.9 g (57–60%, 45.4–48.2 mmol) of (+)-(diisopinocampheyl)borane ($(^{l}Ipc)_2BH$) (**1**) as a white solid (Note 16). The flask is then equipped with an argon line and a thermometer (Note 2), and charged with diethyl ether (215 mL) (Note 3). The resulting white suspension is cooled to 0 °C (Note 17) with an ice/water bath and stirred for

15 min. 4-Acryloylmorpholine (**2**) (Note 3) (6.3 mL, 7.1 g, 50.2 mmol, 1.30 equiv) is added over 5 min using a syringe pump. Upon complete

addition, the mixture is stirred at 0 °C for 2 h. After 15 min the white suspension becomes a clear solution, which gradually converts into a turbid white suspension. The ice/water bath is then replaced with a dry ice/acetone bath and the mixture is cooled to –78 °C and stirred for 15 min at this temperature. Hydrocinnamaldehyde (**3**) (Note 3) (5.1 mL, 5.2 g, 38.6 mmol, 1.00 equiv) is added over 5 min using a syringe pump (Note 5). Upon complete addition, the mixture is stirred at –78 °C for 14 h before a premixed solution of THF/methanol/pH 7 potassium phosphate buffer (Note 3) (1:1:1 v/v/v, 127 mL total) is introduced via syringe. The reaction mixture is allowed to warm to 23 °C and, upon reaching that temperature, stirred vigorously for 6 h. During this period the color of the solution changes from clear to yellow. The mixture is then transferred to a 500-mL separatory funnel with the aid of diethyl ether. The organic layer is removed and the aqueous phase is extracted with two 50-mL portions of diethyl ether. The combined organic layers are washed with two 100-mL portions of deionized water, one 100-mL portion of brine, and dried over sodium sulfate (Na_2SO_4) (100 g). The drying agent is removed by vacuum filtration through a 150-mL fritted glass funnel and washed with three 25-mL portions of diethyl ether. The filtrate is concentrated by rotary evaporation (35 °C bath temperature, 460 mmHg initial pressure to

10 mmHg final pressure) to afford 22.0 g of a clear yellow oil. For purification, the crude product is solubilized in 10-mL of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) (Note 6) and loaded onto a 7.5 cm diameter column containing 200 g of silica gel that is prepacked with 30% EtOAc-hexanes (70:30 hexanes:EtOAc) (Note 7). The flask is washed with three 10-mL portions of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) and the washings are loaded onto the silica gel. Fraction collection (250-mL fractions) is begun and elution proceeds with 3000-mL of 30% EtOAc-hexanes (70:30 hexanes:EtOAc) and then 1000-mL of 40% EtOAc-hexanes (60:40 hexanes:EtOAc). The product is finally eluted from the column using 2000-mL of EtOAc, with fractions 17-24 containing the desired material (Note 8). These fractions are combined and concentrated by rotary evaporation (35 °C bath temperature, 200 mmHg initial pressure to 10 mmHg final pressure) and subsequently dried for 12 h at <5 mmHg (Note 9) to provide 7.4–8.0 g (69–70%) of diastereomerically pure (Notes 10 and 11) (2*R*, 3*S*)-3-Hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one (**4**), 97% ee (Note 12), as white solid, mp 76–78 °C (Note 13).

Notes

1. Crystalline (+)-(diisopinocampheyl)borane (**1**) was synthesized and stored in a glovebox as described in the accompanying procedure.[2]
2. The submitters used a single-necked flask and monitored the internal temperature of the reaction mixture using an Oakton Instruments Temp JKT temperature meter with a Teflon-coated thermocouple probe (30.5 cm length, 3.2 mm outer diameter, temperature range –250 to 400 °C).
3. THF (HPLC Grade) and diethyl ether (Certified ACS, stabilized with BHT) were obtained from Fisher Scientific and purified by passage through activated alumina using a GlassContour solvent purification system.[3] Borane-methyl sulfide complex (94%) was obtained from Acros Organics and used as received. (−)-(α)-Pinene (**5**) (98%, ≥81% ee) was obtained from Aldrich Chemical Co., Inc. and used as received. 4-Acryloylmorpholine (**2**) (99%, stabilized with MEHQ) was obtained from TCI, used as received, and stored at −20 °C under argon. Hydrocinnamaldehyde (**3**) (90% technical grade) was obtained from Aldrich Chemical Co., Inc., distilled (13 mmHg, 99-101 °C), and stored

at −20 °C under argon. pH 7.0 Buffer Solution (catalog number SB108-1) was purchased from Fischer and used as received in the reaction workup.

4. The internal temperature of the reaction mixture remained between 0 and 1 °C throughout the course of the reaction.
5. The internal temperature of the reaction mixture remained between –79 °C and –75 °C throughout the course of the aldol reaction.
6. Sonication can be used to help completely solubilize the crude yellow oil.
7. Silica gel (SiliaFlash® F60, 230–400 mesh, 40–63 μm) was obtained from Silicycle. The checkers strongly recommend using this type of Silica gel since a product from Fluka containing calcium oxide led to two mixed fractions. This does not happen when the SiliaFlash gel is used.
8. Individual fractions were analyzed by TLC (Merck Kieselgel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel) using 50% EtOAc-hexanes (50:50 hexanes:EtOAc) and visualized first with a 254-nm UV lamp and then with an aqueous solution of cerium molybdate. In this solvent system, unidentified reaction impurities have Rf values of 0.89, 0.80, and 0.60. The reaction product, **4**, has an Rf value of 0.14 in 50% EtOAc-hexanes (50:50 hexanes:EtOAc) and 0.33 in 25% hexanes-EtOAc (25:75 hexanes:EtOAc).
9. If the product remains as a clear oil after drying for 12 h at <5 mmHg, it may be coevaporated with diethyl ether to induce solidification.
10. The purity of this material was confirmed by spectroscopic and elemental analysis. *Syn*-**4** exhibits the following properties: white solid; mp 76–78 °C; $[\alpha]_D^{22.8}$ = –10.7 (c = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (d, *J* = 7.2 Hz, 3 H), 1.51–1.62 (m, 1 H), 1.92 (dtd, *J* = 5.4, 9.3, 13.6 Hz, 1 H), 2.52 (dq, *J* = 2.1, 7.2 Hz, 1 H), 2.68 (ddd, *J* = 7.1, 9.2, 13.8 Hz, 1 H), 2.88 (ddd, *J* = 5.2, 9.4, 14.3 Hz, 1 H), 3.43 (br t, *J* = 4.8 Hz, 2 H), 3.51–3.71 (m, 6 H), 3.93 (ddd, *J* = 2.1, 3.8, 9.4 Hz, 1 H), 4.39 (s, 1 H), 7.16–7.24 (m, 3 H), 7.26–7.31 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.2, 32.5, 35.7, 39.0, 41.9, 46.2, 66.8, 66.9, 70.5, 126.0, 128.5 (2C), 128.7 (2C), 142.2, 176.3; IR (neat) 3428, 2921, 2857, 1616, 1454, 1434, 1224, 1114, 1025 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}NNaO_3$ $[M+Na]^+$ 300.1570. Found 300.1572; Anal. calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.15; H, 8.41; N, 5.07. The diastereomer ratio (*syn*-**4**/*anti*-**4**) was determined to be >20:1 from the ratio of resonance integrations at 1.13-1.17 ppm (methyl substituent of *syn* isomer) and 1.17-1.21 ppm

(methyl substituent of *anti* isomer—see Note 11). Both isomers co-elute by TLC analysis.

11. The *anti*-**4** diastereomer was prepared in low yield (with d.r. ca. 8:1) from *syn*-**4** by Mitsunobu reaction (see discussion) and exhibits the following properties: colorless oil; $[\alpha]_D^{26.4}$ = –9.4 (c = 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (d, *J* = 7.1 Hz, 3 H), 1.70-1.85 (m, 2 H), 2.59-2.73 (m, 2 H), 2.92 (ddd, *J* = 5.4, 9.4, 13.7 Hz, 1 H), 3.44-3.49 (m, 2 H), 3.56-3.71 (m, 7 H), 3.94 (d, *J* = 6.4 Hz, 1 H), 7.16-7.23 (m, 3 H), 7.26-7.31 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.3, 32.3, 37.2, 40.2, 41.8, 46.1, 66.7, 66.9, 73.4, 125.8, 128.4 (2C), 128.5 (2C), 142.2, 175.1; IR (neat) 3426, 3026, 2922, 2857, 1614, 1496, 1454, 1435, 1361, 1301, 1268, 1220, 1113, 1069, 1026, 934, 846 cm^{-1}.
12. The enantiomeric purity and absolute configuration of *syn*-**4** were determined by Mosher ester analysis.[4] Thus, a mixture of aldol (–)-**4** (0.0064 g, 0.023 mmol, 1.0 equiv) in dichloromethane (0.5 mL, obtained from Fisher and Scientific and dried by passage through activated alumina using a GlassContour solvent purification system (see Note 3)), pyridine (0.0075 mL, 0.007 g, 0.092 mmol, 4 equiv; obtained from EMD and distilled from CaH_2 under Ar) and a catalytic amount of dimethylaminopyridine (DMAP; one small crystal; obtained from Sigma-Aldrich and used as obtained) was stirred under Ar at ambient temperature. (*R*)-(–)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.0086 mL, 0.012 g, 0.046 mmol, 2 equiv; obtained from Matrix Scientific and used as received) was added via microliter syringe. The mixture was stirred at ambient temperature for 18 h, at which point TLC analysis (1:1, CH_2Cl_2-EtOAc; R_f **4** = 0.40; R_f for Mosher ester product = 0.79) indicated that the reaction was complete. The mixture was diluted with hexanes (1 mL), filtered to remove the white precipitate, then directly filtered through a short column of silica gel (in a Pasteur pipette) using 15 mL of 4:1 hexanes-EtOAc. The filtrate was collected as a single fraction and concentrated on a rotary evaporator to give the (*S*)-MTPA ester as an oil. By using the same procedure, the (*R*)-MPTA ester was prepared (using (*S*)-(+)-α- methoxy-α-(trifluoromethyl)phenylacetyl chloride, obtained from Alfa Aesar). Key resonances in the ^{19}F and ^{1}H NMR spectra of the diastereomeric MTPA esters that may be used in making enantiomeric purity determinations are as follows. Partial data for the (*S*)-MTPA ester of (–)-**4**: ^{19}F ($CDCl_3$) δ: –70.88; ^{1}H (400 MHz, $CDCl_3$) δ: 1.14 (d, *J* = 6.9 Hz, 3H), 1.96 (m, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 2.91 (quint, *J* = 6.8 Hz, 1H), 3.32 (m, 2H), 5.42 (m,

1H). Partial data for the (*R*)-MTPA ester of (–)-**4**: ^{19}F ($CDCl_3$) δ: −70.81; ^{1}H (400 MHz, $CDCl_3$) δ: 1.06 (d, *J* = 6.9 Hz, 3 H), 2.00 (m, 2 H), 2.61 (m, 2 H), 2.89 (quint, *J* = 6.9 Hz, 1 H), 3.29 (m, 2H), 5.46 (m, 1 H).

13. The melting point was recorded on a Stuart SMP 40 apparatus.
14. Due to the viscosity of (–)-(α)-pinene, it is recommended that a large-gauge (16-18) needle be used.
15. As reported by Brown and Singaram[5] it is imperative that the crystallization be carried out at 0 °C. The submitters observed a significant decrease in yield (from 64–66% at 0 °C to 31% at –18.5 °C) with no discernable increase in reagent purity when the crystallization was carried out at –18.5 °C for 46 h.[2]
16. Crystalline (^{l}Ipc)$_2$BH (**2**) exhibits the following properties: mp 95-98 °C; ^{1}H NMR (500 MHz, d^8–THF) δ: 0.85 (s), 0.87 (s), 0.89 (s), 0.91 (s), 0.92 (s), 0.93 (s), 0.94 (s), 0.96 (s), 0.97 (s), 0.99 (s), 1.00 (s), 1.02 (s), 1.04 (s), 1.05 (s), 1.06 (s), 1.07 (s), 1.09 (s), 1.12 (s), 1.13 (s), 1.14 (s), 1.15 (s), 1.17 (s), 1.17 (s), 1.19 (s), 1.21 (s), 1.23 (s), 1.24 (s), 1.27 (s), 1.64 (m), 1.65–2.45 (m), 5.18 (m); ^{13}C NMR (125 MHz, d^8–THF) δ: 21.3, 22.6, 22.9, 23.1, 23.2, 23.28, 23.3, 23.4 (2), 23.7, 25.5, 26.8, 26.9, 27.6, 29.0, 29.2, 29.4, 30.1, 31.9, 32.2, 32.3, 32.6, 34.0, 34.7, 35.1, 35.6, 37.0, 38.9, 39.7, 39.8, 40.2, 40.3, 40.9, 41.6, 41.9, 42.6, 43.1, 43.1, 43.2, 43.3, 48.1, 49.6, 49.7, 49.9, 50.2, 117.0, 145.4. The sample for melting point determination was sealed in a capillary tube under Ar. The NMR sample was prepared under inert atmosphere and it is important to use anhydrous d^8–THF. See in particular Note 7 of the accompanying procedure.[2]
17. The internal temperature of the reaction mixture remained between 0 and 2 °C throughout the course of the hydroboration.

Working with Hazardous Chemicals

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Discussion

Development of highly diastereo- and enantioselective aldol reactions has captured the attention of numerous research groups for decades.[6,7] Enantioselective reductive aldol reactions[7] are attractive alternatives to conventional aldol, organocatalytic, chiral Lewis acid or chiral Lewis base mediated procedures because bases are not required to generate a reactive enol or metal enolate derivative; instead, the reactive intermediate is generated directly by the 1,4-reduction of the α,β-unsaturated carbonyl substrate. While the vast majority of reductive aldol reactions that have been developed to date use chiral transition metal catalysts, turnover numbers are modest (typically <50) and the reagents (both the metal catalysts as well as the chiral ligands) used in these experiments are expensive or require multi-step syntheses if not commercially available. Cost issues also apply to the vast majority of auxiliary-driven, organocatalytic, and chiral Lewis acid or chiral Lewis base mediated aldol processes.[6] Thus, a significant objective of research in this field increasingly will be on the development of highly cost effective aldol reactions that

proceed with exceptional diastereo- and enantioselectivity, that have broad substrate scope (i.e., are not limited to any particular sub-group of substrates such as aromatic aldehydes), and which function with excellent selectivity in the context of aldol reactions with chiral aldehyde substrates (e.g., double asymmetric reactions).[8]

Both enantiomers of α-pinene are widely available in bulk quantities at very low cost. Consequently, a variety of chiral reagents have been developed using α-pinene as the starting material. First among these is (diisopinocampheyl)borane ($(Ipc)_2BH$) which can be generated with excellent enantiomeric purity via the hydroboration of either (–)-(α)-pinene (**5**) (≥81% ee) or (+)-(α)-pinene (≥91% ee) with borane-dimethylsulfide complex followed by crystallization from the reaction mixture.[2,5] The enantiomeric purity enhancement derives from the fact that the minor enantiomer present in the commercial (α)-pinenes is preferentially converted during the hydroboration into the diastereomeric *meso*-$(Ipc)_2BH$ which is not crystalline and which is separated during the crystallization step.[2]

$(Ipc)_2BH$ is a precursor of a range of chiral reagents such as $(Ipc)_2BOTf$ and $(Ipc)_2BCl$ that have been employed in asymmetric aldol reactions by Paterson.[9] $(Ipc)_2BOMe$, a starting material used for the synthesis of chiral allylborane[10] and crotylborane[10c,11] reagents, is prepared by methanolysis of $(Ipc)_2BH$. Generation of chiral allylboron reagents via hydroboration of allenes[12] with $(Ipc)_2BH$ has also been reported. Enantioenriched secondary alcohols are generated by hydroboration of alkenes with $(Ipc)_2BH$.[13] Finally, enolborinates can be generated by the formal 1,4-reduction of α,β-unsaturated carbonyl compounds with $(Ipc)_2BH$.[14,15]

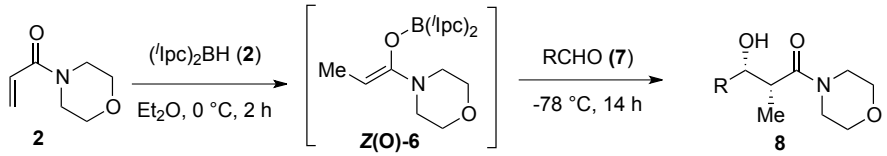
Hydroboration of 4-acryloylmorpholine (**2**) with ($^{l}Ipc)_2BH$ (**1**) is performed in diethyl ether at 0 °C for 2 h. The resulting turbid solution contains exclusively the *Z*(O)-enolborinate (**6**).[15a] The *Z*(O)-enolborinate solution is cooled to –78 °C and neat hydrocinnamaldehyde (**3**) is added. Mild hydrolytic workup liberates the *syn*-aldol adduct **4**, which is obtained, after purification on silica gel, in 74–76% yield (8.21–8.38 g, Procedure A) or 72% yield (9.08 g, Procedure B), calculated based on aldehyde as the limiting reagent, with complete control of the diastereoselectivity (d.r. >20:1) and excellent enantiomeric purity (97% ee by Mosher ester analysis[4]). The diastereomeric purity of **4** was established by comparison of the spectroscopic data (see Note 11) with those of a sample of the *anti*-diastereomer prepared by Mitsunobu reaction of **4** (*p*-nitrobenzoic acid,

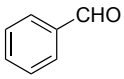
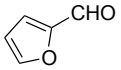
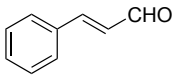
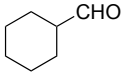
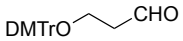
diethyl azodicarboxylate, triphenylphosphine) followed by nitrobenzoate ester hydrolysis (potassium carbonate, methanol).

The submitters store crystalline $(Ipc)_2BH$ in a glovebox, and transfer this reagent as described in Procedure A. However, recognizing that many investigators may not have access to a glovebox, we developed Procedure B to illustrate that crystalline $(Ipc)_2BH$ may be generated in situ by hydroboration of (–)-(α)-pinene and used in a one-pot sequence, with virtually the same efficiency as compared to Procedure A. It should be noted as well, that we intentionally illustrated Procedure B by using the less enantiomerically pure (–)-(α)-pinene (≥81% ee). It stands to reason, that the efficiency of the one-pot procedure (calculated based on pinene) will be greater if (+)-(α)-pinene (≥91 ee) is used.

As summarized in Table 1, the $(^{l}Ipc)_2BH$-mediated reductive aldol reactions of 4-acryloylmorpholine (**2**) with achiral aldehydes furnishes the *syn*-α-methyl-β-hydroxy carboxamides **8** with excellent diastereocontrol (d.r. >20:1) and >96% enantiomeric excess.[15a] The substrate scope spans aliphatic, aromatic and α,β-unsaturated aldehydes.

Table 1. (^{l}Ipc)$_2$BH-mediated reductive aldol reactions of acryloylmorpholine (2) with achiral aldehydes 7

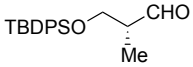
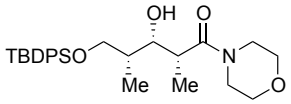
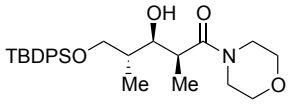
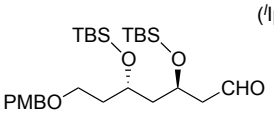
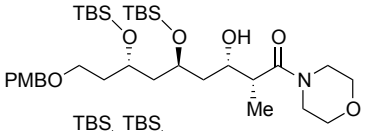
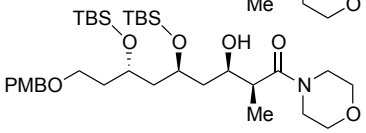
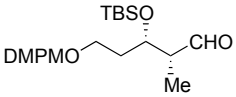
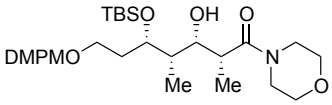
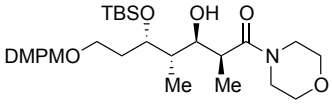
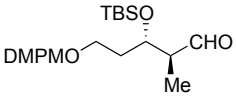
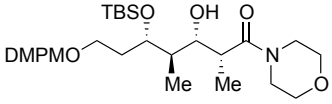
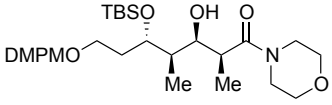


entry	aldehyde **7**	yield[a]	d.r. (*syn*:*anti*)[b]	ee[c]
1		90%	>20:1	97%
2		68%	>20:1	96%
3		68%	>20:1	97%
4		88%	>20:1	97%
5[d]		80%	>20:1	97%

[a] isolated yield; [b] determined by ^{1}H NMR of the crude reaction mixture;
[c] determined by Mosher ester analysis;[4] [d] DMTr = dimethoxytrityl.

Double asymmetric reactions of the chiral *Z*(O)-enolborinate [derived from **2** and either (^{l}Ipc)$_2$BH (**1**) or (^{d}Ipc)$_2$BH (*ent*-**1**)] with a panel of representative chiral, non-racemic aldehydes have also been reported.[15a] Excellent diastereoselectivity (>20:1) is achieved in both the stereochemically matched and mismatched cases for each aldehyde substrate, as shown in Table 2.

Table 2. Double asymmetric reactions of chiral aldehydes with the chiral *Z*(O)-enolborinates derived from (^{l}Ipc)$_2$BH (1) or (^{d}Ipc)$_2$BH (*ent*-1)

entry	aldehyde **7**[a]	(Ipc)$_2$BH	product **8**	yield[b] (d.r.)[c]
1		(^{l}Ipc)$_2$BH (**1**)		69% >20:1
2		(^{d}Ipc)$_2$BH (*ent*-**1**)		85% >20:1
3		(^{l}Ipc)$_2$BH (**1**)		82% >20:1
4		(^{d}Ipc)$_2$BH (*ent*-**1**)		78% >20:1
5		(^{l}Ipc)$_2$BH (**1**)		71% >20:1
6		(^{d}Ipc)$_2$BH (*ent*-**1**)		56% >20:1
7		(^{l}Ipc)$_2$BH (**1**)		74% >20:1
8		(^{d}Ipc)$_2$BH (*ent*-**1**)		72% >20:1

[a] TBDPS = *tert*-butyldiphenylsilyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; DMPM = 3,4-dimethoxybenzyl; [b] isolated yields; [c] determined by ^{1}H NMR of the crude reaction mixture. [d] DMTr = dimethoxytrity

In view of the very low cost of all reagents used for the synthesis of either enantiomer of crystalline (Ipc)$_2$BH, the very low cost of 4-acryloylmorpholine (**2**), and the ease of manipulation of the morpholine amide functionality of the aldol products (which have Weinreb amide-like

reactivity),[16] the procedure described here for the synthesis of *syn*-aldols **4** and **8** ranks among the least expensive and most selective *syn*-aldol procedures currently available in the literature.[6,7,14,15a] For laboratory scale experiments, the cost of the raw materials used to generate enolborinate *Z*(O)-**6** according to this procedure is less than $0.25 per mmol for each aldol reaction.

Extensions of this methodology to the stereocontrolled synthesis of stereochemically defined tetrasubstituted enolborinates (Figure 1),[15b] and to the synthesis of *anti*-aldols from acrylate esters (Figure 2)[15c] have been reported.

Figure 1. Generation of quaternary centers with high enantioselectivity via stereocontrolled generation of tetrasubstituted enolborinate intermediates

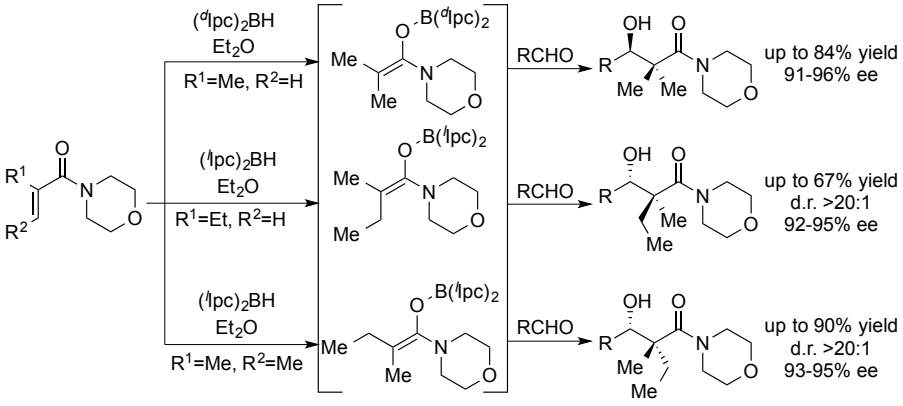
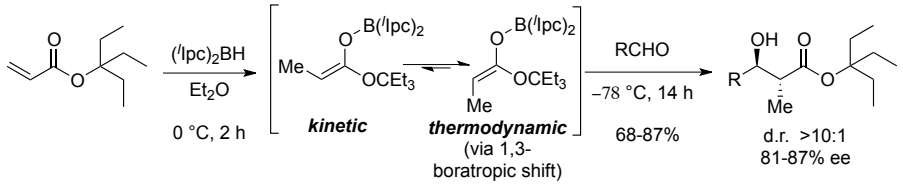


Figure 2. Reductive *anti*-aldol reactions of acrylate esters



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Appendix
Chemical Abstracts Nomenclature (Registry Number)

(+)-(Diisopinocampheyl)borane ((+)-$(Ipc)_2BH$) or ($(^{l}Ipc)_2BH$: borane, bis[(1*S*,2*R*,3*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]; (21947-87-5)
(–)-(Diisopinocampheyl)borane ((–)-$(Ipc)_2BH$) or ($(^{d}Ipc)_2BH$: borane, bis[(1*R*,2*S*,3*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]; (21932-54-7)
Borane-methyl sulfide complex: boron, trihydro[thiobis[methane]]-(T-4)-; (13292-87-0)
(–)-(α)-Pinene: (1*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene; (7785-26-4)
(2*R*, 3*S*)-3-Hydroxy-2-methyl-1-morpholino-5-phenylpentan-1-one; (1529772-55-1)
4-Acryloylmorpholine: 2-Propen-1-one, 1-(4-morpholinyl)-; (5117-12-4)
Hydrocinnamaldehyde: 3-Phenylpropionaldehyde; (104-53-0)
Sodium perborate monohydrate; (10332-33-9)

William R. Roush is Professor of Chemistry, Executive Director of Medicinal Chemistry, and Associate Dean of the Kellogg School of Science and Technology at the Scripps Research Institute–Florida. His research interests focus on the total synthesis of natural products and the development of new synthetic methodology. Since moving to Scripps Florida in 2005, his research program has expanded into new areas of chemical biology and medicinal chemistry. Dr. Roush was a member of the *Organic Syntheses* Board of Editors from 1993-2002 and was Editor of Volume 78. He currently serves on the *Organic Syntheses* Board of Directors (2003-present).

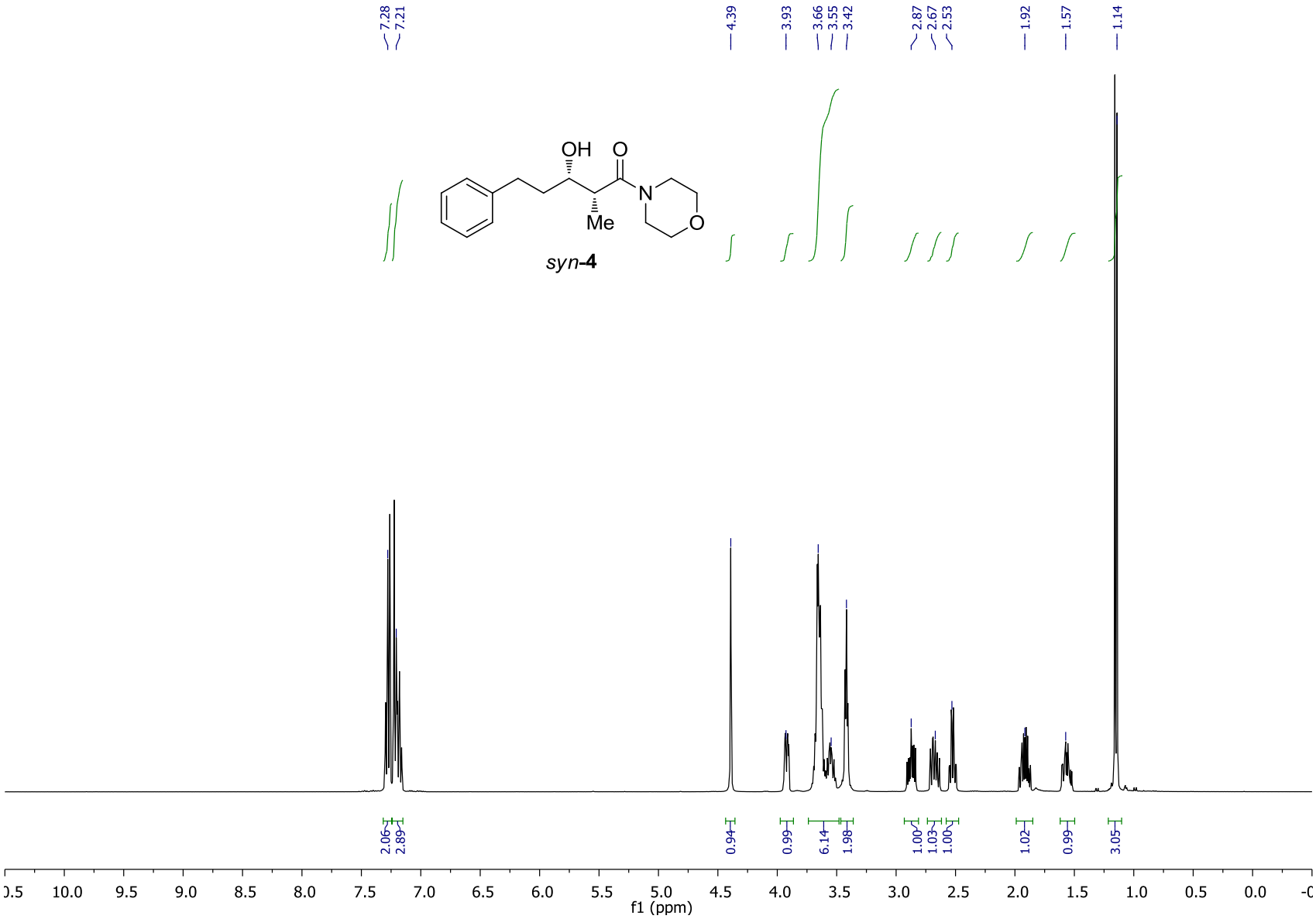
Jason R. Abbott received his B.S. in Chemistry from Northeastern University in Boston, MA. In 2008, Mr. Abbott enrolled in the Kellogg School of Science and Technology at the Scripps Research Institute–Florida to pursue his Ph. D. in Organic Chemistry. He joined the Roush Group shortly thereafter and defended his Ph. D. in early 2014.

Christophe Allais obtained his Ph. D. in 2010 from Université Paul Cézanne (Marseille, France), under the supervision of Prof. Constantieux and Prof. Rodriguez where he focused on the development of convergent and selective methods to access various heterocycles. In 2011, he joined Prof. Roush's Group as a research associate, expanding his research into the areas of medicinal chemistry, natural product synthesis, and the development of boron-mediated asymmetric methodologies. In March 2014, he joined Pfizer (Groton, CT) as a Senior Scientist.

Simon Krautwald was born in Aachen, Germany, in 1986. He received a M. Sci. degree in Chemistry from Imperial College London in 2010. Simon is currently a Ph.D. candidate in Professor Erick M. Carreira's research laboratory at ETH Zurich, where he is studying iridium-catalyzed enantioselective allylic substitution reactions.

Simon Breitler, born in Basadingen, Switzerland, studied chemistry at ETH Zurich, which he concluded with a M.Sc. degree in 2011. During his undergraduate education, he carried out research projects in the laboratories of Prof. Erick M. Carreira and Prof. Antonio Togni. After an internship as a research trainee at Syngenta Crop Protection, Stein, Switzerland, he completed his studies with a Master's thesis in the laboratories of Prof. Stephen L. Buchwald at Massachusetts Institute of Technology, Cambridge MA, USA. Currently pursuing a Ph.D. in synthetic organic chemistry with Prof. Erick M. Carreira, his research focuses on natural product synthesis and asymmetric catalysis.

^{1}H NMR (400 MHz, $CDCl_3$) of compound *syn*-**4**



^{13}C NMR (101 MHz, $CDCl_3$) of compound *syn*-**4**