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Stereoselective Synthesis of β-Hydroxy Enamines, Aminocyclopropanes, and 1,3-Amino Alcohols via Asymmetric Catalysis

Petr Valenta, Patrick J. Carroll, and Patrick J. Walsh*

P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

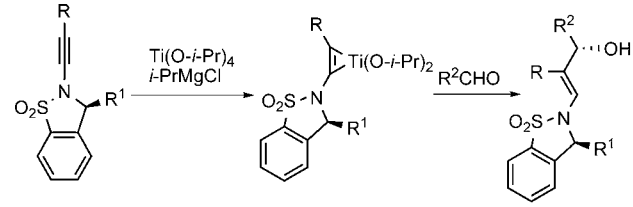
Received June 21, 2010; E-mail: pwalsh@sas.upenn.edu

Abstract: Tandem methods for the catalytic asymmetric preparation of enantioenriched β-hydroxy (*E*)-enamines and aminocyclopropanes are presented. The diastereoselective hydrogenation of enantioenriched (*E*)-trisubstituted hydroxy enamines to generate 1,2-disubstituted-1,3-amino alcohols is also outlined. These methods are initiated by highly regioselective hydroboration of *N*-tosyl-substituted ynamides with diethylborane to generate β-amino alkenyl boranes. In situ boron-to-zinc transmetalation generates β-amino alkenylzinc reagents. These functionalized vinylzinc intermediates are subsequently added to aldehydes in the presence of a catalyst derived from an enantioenriched amino alcohol (morpholino isoborneol, MIB). The catalyst promotes highly enantioselective C−C bond formation to provide β-hydroxy enamines in good isolated yields (68−86%) with 54−98% enantioselectivity. The intermediate zinc β-alkoxy enamines can be subjected to a tandem cyclopropanation to afford aminocyclopropyl carbinols with three continuous stereocenters in a one-pot procedure with good yields (72−82%), enantioselectivities of 76−94%, and >20:1 diastereomeric ratios. Diastereoselective hydrogenation of isolated enantioenriched β-hydroxy enamines over Pd/C furnished *syn*-1,2-disubstituted-1,3-amino alcohols in high yields (82−90%) with moderate to excellent diastereoselectivities. These methods were used in an efficient preparation of the enantioenriched precursor to PRC200-SS derivatives, which are potent serotonin−norepinephrine−dopamine reuptake inhibitors.

1. Introduction

β-Hydroxy enamines are present in several natural and unnatural products[1−5] and are valuable synthetic intermediates.[6−8] The absence of efficient catalytic enantioselective methods for their preparation, however, impedes their wider utilization in synthesis and drug discovery. Methods for the synthesis of racemic β-hydroxy enamines have been introduced. Meyer recently developed a five-step synthesis of β-hydroxy enamines from ynamides.[7,8] Derivatization followed by Wittig rearrangement afforded amino alcohols, highlighting the utility of β-hydroxy enamines. The only one-step method for the synthesis of β-hydroxy enamines is Urabe's reaction of ynamide−titanium complexes with aldehydes (Scheme 1).[6,9,10] Yields as high as 94% were achieved with moderate to excellent diastereoselectivities (2:1 to <20:1) and good substrate scope. However, the method requires the use of enantioenriched sulfonamide-based auxiliaries that were synthesized in four steps, one of which employed another chiral auxiliary.[11]

Scheme 1. Urabe's Addition of Ynamide−Titanium Complexes to Aldehydes To Form β-Hydroxy Enamines



Given the challenges associated with the development of a catalytic enantioselective version of this reaction, we considered an alternative strategy for the stereoselective synthesis of β-hydroxy enamines. Ynamides[12,13] were chosen as precursors

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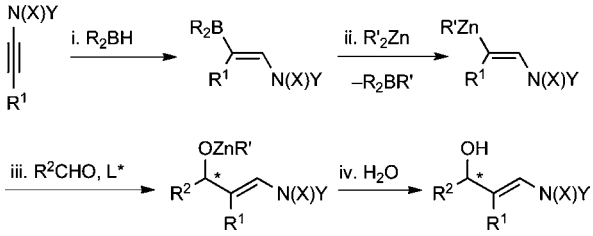
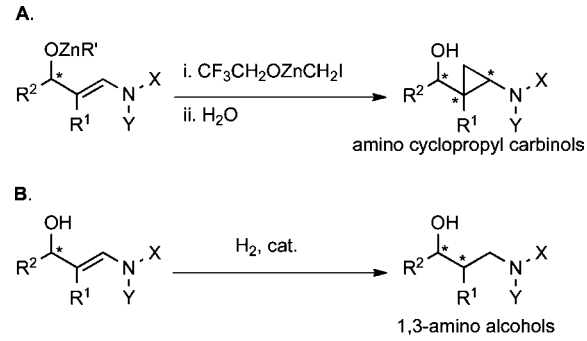
Scheme 2. One-Pot Generation of (*E*)-Trisubstituted β-Hydroxy Enamines



because they can be easily prepared in one step from terminal alkynes, amine derivatives, and copper catalysts in the presence of oxygen following the method of Stahl and co-workers.[14] As outlined in Scheme 2, we envisioned hydroboration of ynamides to generate β-amino vinyl boranes, boron-to-zinc transmetalation of the resulting vinyl group, and catalytic enantioselective carbonyl addition of the β-amino vinyl group to aldehydes to afford zinc alkoxides. Simple protonation of these intermediates was expected to provide β-hydroxy enamines as single double-bond isomers with high ee (Scheme 2). As the catalyst for the asymmetric addition of β-amino vinylzinc reagents to aldehydes, we anticipated using enantioenriched amino alcohol derivatives, which we[15−19] and others[20−29] have successfully employed in the asymmetric addition of vinylzinc reagents to aldehydes.

In addition to their intrinsic value, β-hydroxy enamines are also potentially important synthetic intermediates for further elaboration via alkoxide- and hydroxyl-directed diastereoselective reactions.[30] Alkoxide-directed cyclopropanation of β-alkoxide enamines could provide access to aminocyclopropyl alcohols (Scheme 3A). Enantioenriched aminocyclopropanes are pharmacophores that are present in many natural products and synthetic materials.[31−33] As a result, their synthesis has attracted significant attention.[34−54] β-Hydroxy enamines are anticipated to be useful precursors in the synthesis of enantioenriched 1,2-disubstituted-1,3-amino alcohols (Scheme 3B), a class of compounds that has garnered much interest because of their biological activity.[55−58]

Scheme 3. Application of β-Hydroxy Enamine Derivatives in the Synthesis of (A) Aminocyclopropyl Carbinols and (B) 1,3-Amino Alcohols



Herein we disclose the first one-pot catalytic asymmetric synthesis of β-hydroxy enamines starting from readily available ynamides. Through the approach outlined in Scheme 2, β-hydroxy enamines can be accessed in good to high yields with good to excellent enantioselectivity as single double-bond isomers. The intermediate β-alkoxide enamines can be subjected to a tandem diastereoselective cyclopropanation to afford aminocyclopropyl carbinols with high enantio- and diastereoselectivity. We have also developed an efficient diastereoselective hydrogenation of β-hydroxy enamines that leads to 1,2-disubstituted-1,3-amino alcohols with high enantio- and diastereoselectivities. This method has been applied to the synthesis of PRC200-SS and its derivatives, which are potent serotonin−norepinephrine−dopamine reuptake inhibitors.

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2. Experimental Section

Representative procedures and characterization of the products are described herein. Full experimental details and characterization of all compounds are provided in the Supporting Information.

General Methods. Reactions involving dialkylzinc reagents were performed under nitrogen using standard Schlenk or vacuum-line techniques in oven-dried glassware. Hydrogenations were carried out in magnetically stirred glass test tubes placed in a Parr high-pressure hydrogenator. Chemicals were purchased from Aldrich or Acros unless otherwise specified, and solvents were purchased from Fisher Scientific. Toluene and hexanes were dried through alumina columns. Aldehydes were distilled prior to use and stored under nitrogen. Solutions of dimethylzinc and diethylzinc (2 M in toluene) were prepared and stored in a Vacuum Atmospheres drybox. Ynamides were synthesized according to Stahl's procedure.[14] *N*-Benzyl-*N*-ethynyl-4-methylbenzenesulfonamide was synthesized using the method of Bruckner.[59] Silica gel (230−400 mesh, Silicycle) was used for air-flashed chromatography. Deactivated silica gel was prepared by addition of 17 mL of Et_3N to 1 L of silica gel. The progress of reactions was monitored by thin-layer chromatography (TLC) on Whatman precoated silica gel F-254 plates and visualized by UV light or ceric ammonium molybdate stain. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained on Bruker 300, 360, 400, and 500 MHz Fourier transform spectrometers at the University of Pennsylvania NMR facility. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and coupling constants are reported in hertz. IR spectra were obtained using a PerkinElmer 1600 series spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters liquid chromatography−time-of-flight (LC−TOF) mass spectrometer (model LCT-XE Premier) using electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas−Hoover melting point apparatus and are uncorrected.

Caution! *Dialkylzinc reagents are pyrophoric. Care and proper laboratory attire must be used when handling them.*

General Procedure A. Asymmetric Aminovinylation of Aldehydes with β-Amino Vinylzinc Reagents: (*R*)-(*E*)-*N*-Benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpent-1-enyl)-4-methylbenzenesulfonamide (1a). A 10 mL Schlenk flask was charged with a solution of *N*-benzyl-*N*-(*p*-toluenesulfonyl)-2-phenylethynylamine (1.0 mL, 0.25 M in toluene, 0.25 mmol), and a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 20 min. The reaction flask was then cooled to −78 °C, and Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol) was added, after which the reaction mixture was stirred for 20 min. (−)-MIB (3.0 mg, 0.012 mmol, 5 mol %) was added, and then isobutyraldehyde (24 μL, 0.3 mmol) was added dropwise at −78 °C. The reaction flask was placed in a −30 °C cold bath and allowed to warm to 0 °C over several hours. The solution was stirred at 0 °C until vinyl addition was complete, as determined by TLC (typically 12 h). The reaction was then quenched by addition of brine (2 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were then washed with 50 mL of water and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 107 mg (82% yield) of **1a** as an amorphous solid. $[\alpha]_D^{20}$: −19.5 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.82 (d, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 7.0 Hz), 1.57 (sept., 1H, J = 7.0 Hz), 2.07 (s, 3H), 3.84 (d, 1H, J = 6.4 Hz), 4.27 (dd, 2H, J = 21.3, 15.0 Hz), 6.54 (s, 1H), 6.94−7.02 (m, 4H), 7.09−7.19 (m, 7H), 7.29 (s, 1H), 7.84−7.90 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 27.65, 28.66, 35.45, 44.95, 77.47, 127.52, 127.66, 127.89, 128.81, 129.09, 129.62, 129.91, 134.50, 136.20, 136.32, 156.2. IR (neat): 3537 (OH), 2961, 2870, 1723, 1643, 1598, 1494, 1455, 1343, 1162, 1092, 1026, 814 cm^{-1}; HRMS-CI: m/z 458.1766 [(M + Na)$^+$; calcd for $C_{26}H_{29}NO_3SNa$, 458.1766].

General Procedure B. Asymmetric Aminovinylation of Aldehydes/Diastereoselective Cyclopropanation: *N*-Benzyl-*N*-((1*R*,2*R*)-2-((*R*)-1-hydroxy-2-methylpropyl)cyclopropyl)-4-methylbenzenesulfonamide (2a). A 10 mL Schlenk flask was charged with a solution of *N*-benzyl-*N*-ethynyl-4-methylbenzenesulfonamide (1.0 mL, 0.25 M in toluene, 0.25 mmol), and a solution of diethylborane (0.25 mL, 1.0 M in toluene, 0.25 mmol) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 20 min. The reaction flask was then cooled to −78 °C, and Et_2Zn (0.25 mL, 2.0 M in toluene, 0.5 mmol) was added, after which the reaction mixture was stirred for 20 min. (−)-MIB (3.0 mg, 0.012 mmol, 5 mol %) was added, and then isobutyraldehyde (24 μL, 0.3 mmol) was added dropwise at −78 °C. The reaction flask was placed in a −30 °C isopropyl alcohol/dry ice cold bath and allowed to warm to 0 °C over 12 h. The solution was stirred at 0 °C until vinyl addition was complete, as determined by TLC (typically 12 h). The volatile materials, including the Et_3B byproduct, were removed in vacuo at 0 °C. After addition of hexanes (2 mL), the volatile materials were again removed under reduced pressure. This step was repeated two more times to ensure the complete removal of Et_3B. A solution of Et_2Zn (0.63 mL, 2.0 M in toluene, 1.25 mmol) and neat CF_3CH_2OH (91 μL, 1.25 mmol) was added slowly at 0 °C, and the Schlenk flask was wrapped in aluminum foil to exclude light. The resulting mixture was stirred at 0 °C for 5 min, and then diiodomethane (101 μL, 1.25 mmol) was added. The stirring was continued at 0 °C for 40 h, after which the reaction mixture was quenched with brine (2 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with 3 × 20 mL of diethyl ether. The combined organic layers were then washed with 50 mL of water and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on deactivated silica gel (10% ethyl acetate in hexanes) to afford 59 mg (80% yield) of **2a** as a yellow oil. $[\alpha]_D^{20}$: −28.1 (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.68 (dd, 1H, J = 14.32, 6.95 Hz), 0.74 (d, 3H, J = 6.7 Hz), 0.77 (d, 3H, J = 6.7 Hz), 1.00 (d, 1H, J = 5.2 Hz), 1.09 (m, 1H), 1.52 (m, 1H), 2.00 (m, 1H), 2.42 (s, 3H), 3.16 (q, 1H, J = 4.6 Hz), 4.18 (d, 1H, J = 14.6 Hz), 4.38 (d, 1H, J = 14.6 Hz), 7.20−7.38 (m, 7H), 7.67−7.76 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 9.90, 17.22, 18.94, 21.77, 23.69, 34.11, 34.44, 54.96, 74.52, 127.78, 127.86, 128.61, 128.65, 129.84, 135.68, 137.40, 143.67. IR (neat): 3538 (OH), 2960, 2873, 1598, 1495, 1455, 1341, 1163, 1093, 927, 815 cm^{-1}. HRMS-CI: m/z 396.1604 [(M + Na)$^+$; calcd for $C_{21}H_{27}NO_3SNa$, 396.1609].

General Procedure C. Diastereoselective Hydrogenation of β-Hydroxy Enamines with Aliphatic Substituents at the 3-Position: *N*-Benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpentyl)-4-methylbenzenesulfonamide (3a). In a 10 × 75 mm glass test tube, (*E*)-*N*-benzyl-*N*-(3-hydroxy-4-methyl-2-phenylpent-1-enyl)-4-methylbenzenesulfonamide (44 mg, 0.1 mmol) was dissolved in methanol (4 mL) at room temperature. The space above the solution was purged with nitrogen to remove most of the air, and 10% Pd/C (8 mg, 7 mol %) was added. The test tube was placed in a Parr hydrogenator, and good stirring was confirmed before the apparatus was closed. After the system was flushed three times with hydrogen, it was pressured with hydrogen (9.65 MPa, 1400 psi), and the reaction was stirred for 12 h at room temperature. After the apparatus was opened, the Pd catalyst was removed via filtration through a plug of Celite. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (10% ethyl acetate in hexanes) to afford 39 mg (90% yield) of **3a** as an amorphous solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.36 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.16 (sept., 1H, J = 7.2 Hz), 2.41 (s, 3H), 2.73 (dd, 1H, J = 14.3, 4.4 Hz), 3.08 (d, 1H, J = 5.4 Hz), 3.48 (m, 1H), 3.74 (d, 1H, J = 14.0 Hz), 3.96 (dd, 1H, J =

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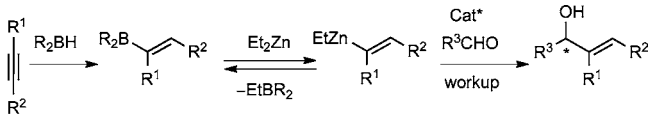
Scheme 4. Oppolzer's Alkenylation of Aldehydes



R^1 = H or alkyl
R^2 = alkyl or phenyl

14.8, 11.7 Hz), 4.73 (d, 1H, J = 14.0 Hz), 7.06−7.13 (m, 2H), 7.14−7.22 (m, 3H), 7.28−7.44 (m, 7H), 7.68−7.76 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 18.86, 20.21, 21.75, 31.15, 46.69, 53.51, 55.23, 75.25, 126.97, 127.43, 128.39, 128.48, 129.05, 129.24, 129.66, 130.11, 136.70, 139.05, 139.21, 143.80. IR (neat): 3532 (OH), 2924, 1599, 1494, 1330, 1156, 1094, 925, 814 cm^{-1}; HRMS-CI: m/z 438.2111 [$(M + H)^+$; calcd for $C_{26}H_{32}NO_3S$, 438.2103].

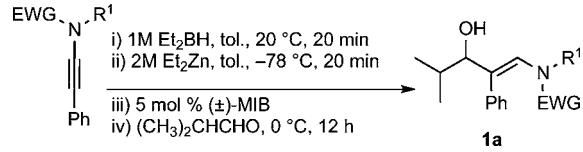
General Procedure D. Diastereoselective Hydrogenation of *β*-Hydroxy Enamines with Aromatic Substituents at the 3-Position: *N*-Benzyl-*N*-(3-hydroxy-2,3-diphenylpropyl)-4-methylbenzenesulfonamide (3d). In a 10 × 75 mm glass test tube, (*E*)-*N*-benzyl-*N*-(3-hydroxy-2,3-diphenylprop-1-enyl)-4-methylbenzenesulfonamide (47 mg, 0.1 mmol) was dissolved in ethyl acetate (3 mL) at room temperature, and 10% Pd/C (8 mg, 7 mol %) was added. The test tube was placed in a Parr hydrogenator at room temperature, and good stirring was confirmed before the apparatus was closed. After the system was flushed three times with hydrogen, it was pressured with hydrogen (9.65 MPa, 1400 psi), and the reaction was stirred for 12 h at room temperature. After the apparatus was opened, the Pd catalyst was removed via filtration through a plug of Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (10% ethyl acetate in hexanes) to afford 43 mg (92% yield) of **3d** as an amorphous solid. ^1H NMR ($CDCl_3$, 360 MHz): δ 2.42 (s, 3H), 2.65 (m, 1H), 2.79 (d, 1H, J = 4.3 Hz), 2.99 (dd, 1H, J = 14.3, 6.1 Hz), 3.88 (d, 1H, J = 14.5 Hz), 4.55 (d, 1H, J = 14.5 Hz), 4.96 (t, 1H, J = 4.3 Hz), 6.59−6.70 (m, 4H), 6.82−6.89 (m, 2H), 7.04−7.13 (m, 3H), 7.25−7.36 (m, 8H), 7.61−7.66 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 21.78, 52.15, 54.66, 55.36, 72.28, 127.09, 127.32, 127.53, 128.16, 128.33, 129.03, 129.10, 129.62, 130.05, 134.51, 136.12, 136.79, 138.21, 143.83, 158.61. IR (neat): 3519 (OH), 2919, 1611, 1513, 1454, 1331, 1246, 1156, 1103, 1034, 928 cm^{-1}. HRMS-CI: m/z 494.1760 [$(M + Na)^+$; calcd for $C_{29}H_{29}NO_3SNa$, 494.1766].

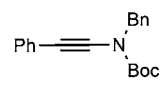
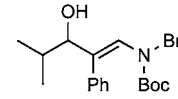
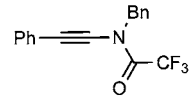
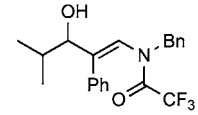
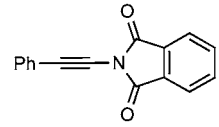
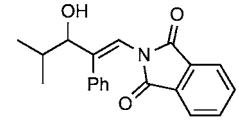
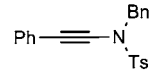
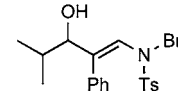
3. Results and Discussion

3.1. Asymmetric Synthesis of *β*-Hydroxy Enamines. Our interest in enantiomerically enriched β-hydroxy enamines with stereodefined double bonds stems from their potential utility in medicinal chemistry and as synthetic intermediates. We therefore set out to develop a highly enantioselective, practical, and efficient one-pot method for their generation.

3.1.1. Optimization of Enantioselective *β*-Aminovinylation of Aldehydes. For the synthesis of enantioenriched β-hydroxy enamines, we envisaged use of Oppolzer's method[20] for the key C−C bond-forming step. On the basis of Srebnik's observation[60] that alkenyl boranes undergo reversible transmetalation with dialkylzinc reagents to generate vinylzinc intermediates, Oppolzer[20] developed a catalytic asymmetric synthesis of allylic alcohols involving hydroboration of alkynes, transmetalation of the vinyl group to zinc, and enantioselective addition to aldehydes to afford enantioenriched allylic alcohols (Scheme 4). We[15−19] and others[20−29] have used this method to make

Table 1. Examination of Various Electron-Withdrawing Groups on the Ynamide



entry	ynamide	(*E*)-trisubstituted hydroxy enamine	isolated yield (%)
1			25
2			0
3			0
4			**82**

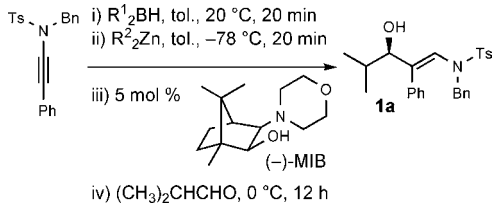
allylic alcohols, and we have applied it to the synthesis of α- and β-amino acid derivatives,[61,62] epoxy alcohols,[16,17,63] and cyclopropyl and vinylcyclopropyl alcohols.[19,64,65] This method works well with terminal and internal alkynes, and we have shown that ethoxy ethynyl ether can also be employed.[18,66] It was not clear at the outset whether the uncatalyzed hydroboration of internal ynamides would proceed with high regioselectivity; only hydroboration of terminal ynamides had previously been reported to proceed with good regioselectivity.[67,68]

Our synthesis of β-hydroxy enamines involves the application of Oppolzer's procedure to ynamides, which are readily available using Stahl's copper-catalyzed oxidative coupling of alkynes with amines.[14] The phenyl-substituted ynamides shown in Table 1 were synthesized using amines with an electron-withdrawing group (EWG) on the nitrogen. The presence of the EWG is important for the synthesis and stabilization of the ynamides and the resulting β-hydroxy enamines.

The β-hydroxy enamine synthesis begins with hydroboration of an ynamide using diethylborane and transmetalation of the vinylborane with Et_2Zn to generate the β-amino vinylzinc intermediate. The aldehyde alkenylation is then performed in

(60) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449.
(61) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225.
(62) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677.
(63) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13608.
(64) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 954.
(65) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 402.
(66) Valenta, P.; Drucker, N. A.; Bode, J. W.; Walsh, P. J. *Org. Lett.* **2009**, *11*, 2117.
(67) Witulski, B.; Buschmann, N.; Bergstraser, U. *Tetrahedron* **2000**, *56*, 8473.
(68) Hoffmann, R. W.; Bruckner, D. *New J. Chem.* **2001**, *25*, 369.

Table 2. Optimization of Yield and Enantioselectivity in the Synthesis of β-Hydroxy Enamines



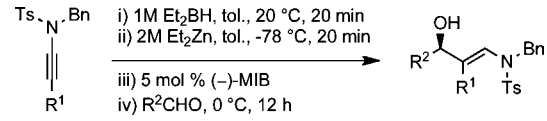
entry	$R^1{}_2BH$	$R^2{}_2Zn$	isolated yield (%)	ee (%)
1	$BH_3 \cdot SMe_2$	Et_2Zn	trace	–
2	9-BBN	Et_2Zn	44	82
3	Cy_2BH	Et_2Zn	78	92
4	Et_2BH	Et_2Zn	**82**	**92**
5	Et_2BH	Me_2Zn	80	91

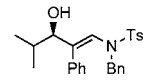
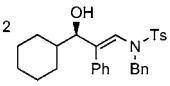
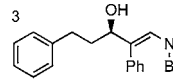
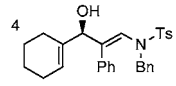
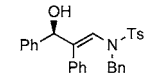
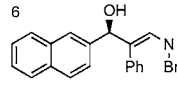
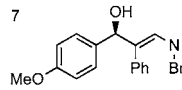
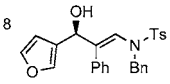
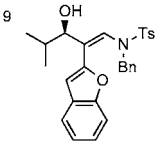
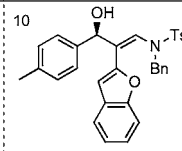
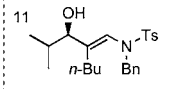
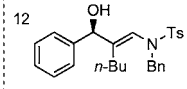
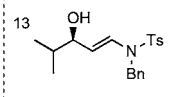
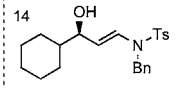
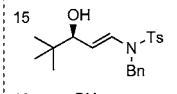
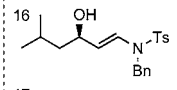
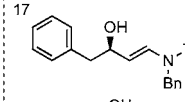
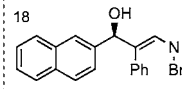
the presence of a catalyst derived from Nugent's isoborneol-based amino alcohol ligand MIB.[69] As illustrated in Table 1, the yield of the addition product is strongly dependent on the nature of the EWG. Although the Boc group resulted in formation of the desired addition product, the isolated yield did not exceed 25% (entry 1). Use of more strongly electron-withdrawing carbonyl groups on the nitrogen, such as trifluoroacetyl or imide, did not result in formation of the β-hydroxy enamine product (entries 2 and 3), perhaps because the borohydride added to the carbonyl group. In contrast, the more robust tosyl group led to formation of the β-hydroxy enamine in 82% yield (entry 4). The tosyl group serves a dual role in the chemistry: it both enables the generation of the product in good yield and prevents elimination of the β-hydroxy enamine. Decomposition via elimination eventually affords α,β-unsaturated aldehydes after reaction with water.

To perform the analogous asymmetric addition, we used a catalyst derived from enantiomerically pure (−)-MIB (Table 2), which is readily prepared in three steps or can be purchased.[70] With the general procedure for entry 4 of Table 1, several hydroborating agents were examined (Table 2). After the hydroboration and addition of the dialkylzinc reagent, (−)-MIB (5 mol %) and isobutyraldehyde were added. When $BH_3 \cdot SMe_2$ was used in the hydroboration, only trace addition product was observed (entry 1). Use of 9-BBN resulted in formation of the β-hydroxy enamine in 44% yield with 82% ee (entry 2). Screening combinations of diethyl- and dicyclohexylborane with diethyl- and dimethylzinc (entries 3−5) led to the identification of diethylborane and diethylzinc as the optimal combination, with formation of the β-hydroxy enamine in 82% yield and 92% ee. It is noteworthy that under the reaction conditions the addition of Et_2Zn to the aldehyde was very slow relative to the reaction of the vinylzinc species and that a yield of less than 5% for the ethyl addition product was observed. The optimized conditions in Table 2 were then used to determine the substrate scope, as outlined in the following section.

3.1.2. Substrate Scope of the Synthesis of β-Hydroxy Enamines. To determine the scope and limitations of our one-pot synthesis of enantioenriched β-hydroxy enamines, a series of aldehydes and ynamides were tested using the conditions from entry 4 of Table 2. As shown in Table 3, the asymmetric vinylation reaction is compatible with a range of ynamides and aldehydes. Initially, ynamides derived from phenylacetylene

Table 3. Substrate Scope of the Asymmetric One-Pot Generation of (*E*)-Trisubstituted β-Hydroxy Enamines



entry	β-hydroxy enamine	isolated yield (%)	ee (%)[a]
1		**1a**	82	92
2		**1b**	73	91
3		**1c**	78	54
4		**1d**	70	92
5		**1e**	85	91
6		**1f**	81	98
7		**1g**	86	96
8		**1h**	68	89
9		**1i**	82	91
10		**1j**	85	98
11		**1k**	81	93
12		**1l**	85	96
13		**1m**	80	93
14		**1n**	77	94
15		**1o**	67	93
16		**1p**	81	76
17		**1q**	79	83
18		**1r**	25	97

[a] Enantioselectivities were determined by HPLC.

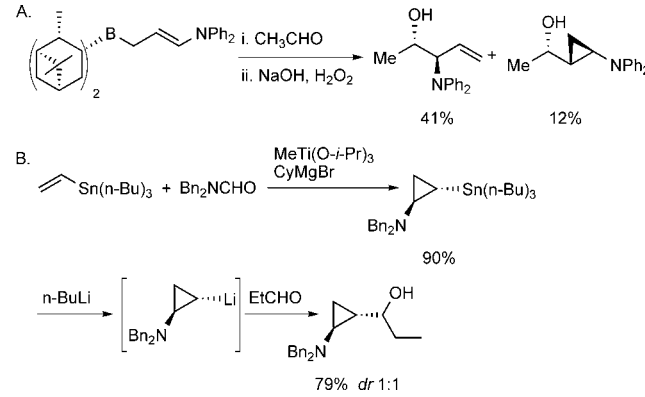
were employed (entries 1−8). With this coupling partner, aliphatic aldehydes with α-branching underwent additions with enantioselectivities of >90% and yields of 73−82% (entries 1 and 2). With dihydrocinnamaldehyde, which lacks α-branching, a significant decrease in enantioselectivity to 54% was observed (entry 3). The α,β-unsaturated aldehyde cyclohexenecarboxaldehyde afforded the corresponding β-hydroxy enamine in 70% yield with 92% enantioselectivity (entry 4). This product also contains an allylic alcohol, which is a useful functional group for further elaboration.[30] Aromatic aldehydes proved to be excellent substrates, undergoing the reaction with enantioselectivities of 91−98% and yields >80% (entries 5−7). The heteroaromatic 3-furancarboxaldehyde resulted in formation of the product in 68% yield with 89% enantioselectivity (entry 8). The ynamide with a 2-benzofuranyl substituent also exhibited excellent enantioselectivities in the asymmetric addition to isobutyraldehyde (91% ee; entry 9) and 4-methylbenzaldehyde (98% ee; entry 10). Yields of >80% were achieved in both cases. Comparison of the enantioselectivities for phenyl- and 2-benzofuranyl-substituted ynamides (entries 1−8 vs entries 9 and 10) suggests that the addition does not strongly depend on the nature of the aryl group.

(69) Nugent, W. A. *Chem. Commun.* **1999**, 1369.
(70) Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87.

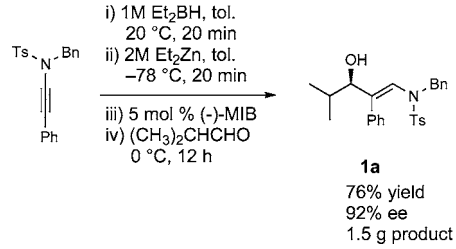
The *n*-Bu-substituted ynamide underwent addition with representative aliphatic and aromatic aldehydes with high levels of enantioselectivity. Thus, with isobutyraldehyde and benzaldehyde, the addition products were obtained with 93 and 96% enantioselectivity, respectively (entries 11 and 12). The yields were >80% in both cases. The parent ynamide (R = H) was also a useful coupling partner, as shown in entries 13−17. With the aliphatic aldehydes isobutyraldehyde and cyclohexanecarboxaldehyde, the yields were 80 and 77%, respectively, and the corresponding enantioselectivities were ≥93% (entries 13 and 14). Bulky pivaldehyde reacted with high enantioselectivity (93%), albeit in decreased yield (67%; entry 15). Not surprisingly, aliphatic aldehydes lacking α-branching were difficult substrates with (−)-MIB (entries 16 and 17), as with most amino alcohol catalysts.[71−82] Isovaleraldehyde and phenylacetaldehyde gave enantioselectivities of 76 and 83%, respectively. Presumably, the advent of more enantioselective catalysts will enable additions to these challenging substrates to occur with higher stereoselectivities. As indicated in entry 1 of Table 1, the Boc-protected ynamide gave a low yield. Nonetheless, the product formed upon addition to 2-naphthaldehyde in the presence of (−)-MIB had an ee of 97% (Table 3, entry 18).

The absolute stereochemistry of a derivative of **1b** was determined by single-crystal X-ray diffraction (see the Supporting Information and section 3.2). Accordingly, the (−)-MIB-based catalyst promoted the formation of (*R*)-hydroxy enamines, consistent with the transition state proposed by Noyori[83,84] for the asymmetric alkylation of aldehydes with dialkylzinc reagents and the amino alcohol-based catalyst derived from DAIB. The stereochemistry of the remaining entries in Table 3 was assigned by analogy. It is noteworthy that coordination to zinc by the heteroatoms, such as the nitrogens present in the ynamides and the oxygens of the sulfonamides and benzofuryl groups (entries 9 and 10), was not problematic in the enantioselective vinyl addition step. Finally, only the *E* isomer of the β-hydroxy enamine was observed in each case by ^{1}H NMR spectroscopy, indicating that isomerization of the double bond does not occur during the transmetalation, addition, workup, and purification steps. As will be seen in subsequent sections, the conservation of the double-bond geometry of the enamine is essential for diastereoselective elaboration of these products.

Scheme 5. (A) Barrett's and (B) de Meijere's Syntheses of Aminocyclopropyl Carbinols



In order for a method to be useful, scalability must be demonstrated. As shown in eq 1, the phenyl-substituted ynamide and isobutyraldehyde were used in the catalytic asymmetric β-amimo vinylation to afford 1.5 g of β-hydroxy enamine **1a** (92% ee).



(1)

3.2. Tandem Asymmetric β-Aminovinylation of Aldehydes/Diastereoselective Cyclopropanation. Cyclopropylamines continue to attract interest because of their abundance in natural products and biologically active compounds,[31] including several commercial medications.[85−93] As a result, many methods for synthesizing the aminocyclopropyl moiety have been developed.[34−54] Direct methods for the effective synthesis of functionalized enantio- and diastereoenriched cyclopropylamines remain elusive, however. Existing routes for preparing aminocyclopropyl carbinols suffer from either low yields[94] (Scheme 5A) or low diastereoselectivities[95,96] (Scheme 5B) or are not enantioselective.[97−99]

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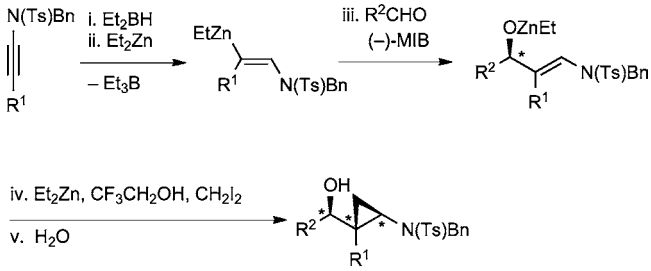
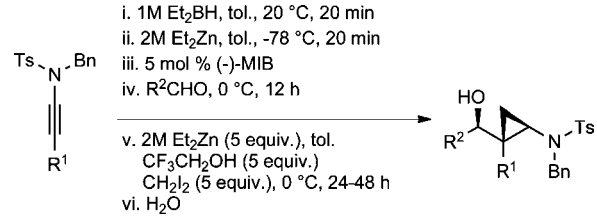
Scheme 6. Asymmetric and Diastereoselective One-Pot Generation of Aminocyclopropyl Carbinols

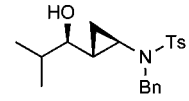
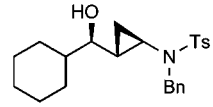
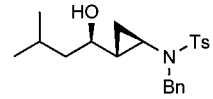
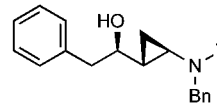
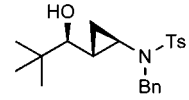
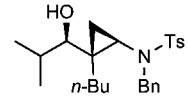


Because aminocyclopropyl carbinols can serve as precursors to compounds of biological relevance,[52,100−102] their direct enantio- and diastereoselective synthesis is desirable. Our approach to the catalytic enantio- and diastereoselective synthesis of aminocyclopropyl carbinols is based on our prior efforts involving the diastereoselective directed cyclopropanation of allylic alcohols.[19,64,65] At the outset of this study, however, it was not clear how the nitrogen of the enamine would impact the reactivity of the double bond toward cyclopropanation or whether it would affect the diastereoselectivity. A search of the literature revealed very few examples of Simmons−Smith cyclopropanations of enamines.[50,103] Nonetheless, we attempted the tandem asymmetric aminovinylation/diastereoselective cyclopropanation. Hydroboration of the ynamide, transmetalation, and asymmetric addition to the aldehyde according to our synthesis of β-hydroxy enamines generated the zinc β-alkoxy enamine intermediate (Scheme 6). The alkoxide complex was then subjected to a directed Simmons−Smith cyclopropanation using a carbenoid introduced by Shi.[104,105]

The generation of the Shi modified carbenoid involves the reaction of CF_3CH_2OH with diethylzinc to form the monoalkoxide complex CF_3CH_2OZnEt. Reaction of this intermediate with diiodomethane results in the formation of the Shi carbenoid, $CF_3CH_2OZnCH_2I$. Upon combining $CF_3CH_2OZnCH_2I$ with zinc β-alkoxy enamine intermediates, we were pleased to see the formation of the desired cyclopropyl amines as single diastereomers, although the yields were moderate. As we have observed with other systems,[19,64,65] the cyclopropanation proceeds in low to moderate yield in the presence of triethylborane, a byproduct formed during transmetalation of the β-aminovinyl group from boron to zinc (Scheme 6). To achieve high yields, the triethyborane was removed from the reaction mixture before the cyclopropanation step. Removal of the volatile triethylborane was accomplished by subjecting the reaction mixture to reduced pressure. The best results were obtained with addition of hexanes to the residue followed by removal of the volatile materials under reduced pressure. This procedure was performed three times. Under these conditions, aliphatic aldehydes (entries 1−5, Table 4) underwent the addition/cyclopropanation sequence with the terminal ynamide in 72−82% isolated yields, 76−94% enantioselectivities, and excellent diastereoselectivities (>20:1 in all cases).

Table 4. Enantio- and Diastereoselective One-Pot Generation of Aminocyclopropyl Carbinols



entry	product		isolated yield (%)	ee (%)[a]	dr[b]
1		**2a**	80	93	>20:1
2		**2b**	76	94	>20:1
3		**2c**	78	76	>20:1
4		**2d**	78	83	>20:1
5		**2e**	72	93	>20:1
6		**2f**	28[c]	93	>20:1

[a] Determined by HPLC of the intermediate enamines. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Reaction time 60 h.

Under our current conditions, the tandem reaction is capricious when the sequence is initiated with substituted ynamides. Although we were able to generate a trisubstituted aminocyclopropyl carbinol (entry 6), the isolated yield was low (28%) and the reaction time long (60 h). Cyclopropanation of β-alkoxy enamines generated from aromatic aldehydes or aryl-substituted ynamides did not proceed; instead, β-hydroxy enamines were isolated.

The diastereomeric ratios in Table 4 were determined by ^{1}H NMR analysis of the crude reaction products. The absolute and relative configurations of **2f** were determined by X-ray diffraction (see the Supporting Information). The structure revealed that cyclopropanation occurred syn to the carbinol, as observed in the cyclopropanation of allylic alcohols via the Simmons−Smith cyclopropanation.[19,64,65,106,107] A possible transition state for the directed cyclopropanation is illustrated in Figure 1.[106,107]

The aminovinylation/cyclopropanation method introduced above affords aminocyclopropyl carbinols containing trans-

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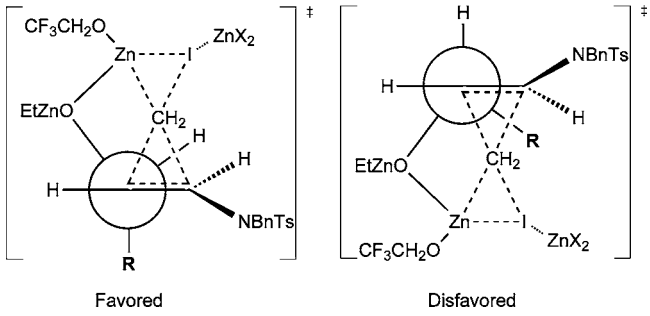

Figure 1. Proposed transition states for diastereoselective cyclopropanation of β-alkoxy enamines. The interaction of R with the substituents is responsible for the diastereoselectivity.

disubstituted cyclopropane motifs. The products are formed in good yields with good to excellent enantioselectivities and very high diastereoselectivities. This one-pot procedure results in the generation of three C−C bonds and three continuous stereocenters and is conducted without isolation of any intermediates.

3.3. Synthesis of Amino Alcohols. 1,3-Amino alcohols are common structural motifs in many biologically active compounds[55−58] and are extensively used in asymmetric synthesis as both chiral ligands and auxiliaries.[108] Many methods for the synthesis of enantio- and diastereoenriched 1,3-disubstituted-1,3-amino alcohols are available.[109−113] In contrast, the stereoselective synthesis 1,2-disubstituted-1,3-amino alcohols remains a significant challenge.[6,114−122] The best approach to enantioenriched 1,2-disubstituted-1,3-amino alcohols is addition of lithium arylacetonitriles to aldehydes,[123] which leads to β-hydroxy nitriles with moderate enantio- and diastereoselectivities. This method employs greater than stoichiometric amounts of chiral ligand. Efficient methods for the synthesis of enantio- and diastereoenriched 1,2-disubstituted-1,3-amino alcohols would facilitate their use in medicinal chemistry and asymmetric catalysis. We envisioned a catalytic diastereoselective hydrogenation of β-hydroxy enamines as a straightforward route to 1,2-disubstituted-1,3-amino alcohols.

3.3.1. Diastereoselective Hydrogenation of β-Hydroxy Enamines. Our initial efforts to reduce β-hydroxy enamines focused on homogeneous hydrogenation catalysts and variation of the solvent, hydrogen pressure, and reaction time (Table 5). Both Crabtree's[124] and Wilkinson's[125] catalysts resulted in loss of the hydroxyl group, probably by elimination to form an α,β-unsaturated iminium intermediate. This intermediate could then undergo subsequent hydrogenation, resulting in formation of the observed alkyl sulfonamide **4** (entries 1−6). These examples illustrate the sensitivity of β-hydroxy enamines to elimination even under very mild conditions. We next turned to common heterogeneous catalysts. PtO_2 did not catalyze the hydrogenation at room temperature but caused decomposition of the hydroxy enamine at elevated temperature or pressure (entries 7−9). On the other hand, rhodium on alumina (5 mol %) was completely inactive (entry 10). Palladium on carbon (10 mol %) was the most promising catalyst, providing the desired 1,3-amino alcohol as the major product. Atmospheric pressure at room temperature (entry 11) or above (entry 12) was not sufficient for full conversion, so a higher pressure was used (entries 13 and 14). With 10 mol % Pd/C catalyst in methanol at a hydrogen pressure of 8 MPa, the reaction provided an isolated yield of 90% with excellent diastereoselectivity (>20:1; entry 14). Unlike the β-hydroxy enamines with aliphatic carbinols, which undergo highly diastereoselective reductions in methanol, we found that the enamine hydrogenation of substrates with benzylic hydroxyl groups led to elimination/reduction in methanol. Therefore, the choice of the solvent was crucial and dependent on the substituent attached to the carbinol. We reasoned that protic solvents would hydrogen bond to the hydroxyl group of the β-hydroxy enamine and facilitate the elimination pathway. To reduce elimination, β-hydroxy enamines with aromatic carbinols were hydrogenated in aprotic solvents. After a screen of several solvents, ethyl acetate was determined to be the most effective. Interestingly, hydrogenation of β-hydroxy enamines with aliphatic carbinols in ethyl acetate resulted in lower conversions (entry 15) than in methanol.

3.3.2. Substrate Scope of the Diastereoselective Hydrogenation of β-Hydroxy Enamines. The results of the diastereoselective hydrogenation of β-hydroxy enamines are shown in Table 6. Catalytic hydrogenation of β-hydroxy enamines with aliphatic (entries 1, 2, 3, 7, and 9) or aromatic (entries 4, 5, 6, 8, and 10) carbinol substituents and aromatic (entries 1−6) or heteroaromatic (entries 7 and 8) substituents at the 2-position led to 1,2-disubstituted-1,3-aminoalcohols in good isolated yields (80−92%) with excellent diastereoselectivities (>20:1). With an alkyl group at the 2-position of the β-hydroxy enamine, however, the diastereoselectivity was only moderate (entries 9 and 10). The diastereomeric ratios in Table 6 were determined by ^{1}H NMR analysis of the crude reaction products. The ee's of the β-hydroxy enamines **1a**, **1e**, and **1j** were determined before the hydrogenation to be 92, 91, and 98%, respectively. Their hydrogenation products **3a**, **3e**, and **3j** were found to have ee's of 91, 90, and 95%, respectively. The absolute and relative stereochemistries in Table 6 are based on the X-ray structural determination of **3a**, which revealed that the hydrogenation is syn-selective (see the Supporting Information).

The diastereoselective outcome of the hydrogenation can be rationalized by conformational analysis of the β-hydroxy enamine when it is associated with the surface of the palladium catalyst (Figure 2, left). The β-hydroxy enamine binds to the surface of the catalyst through coordination of the hydroxyl group. The substrate then adopts a conformation that minimizes

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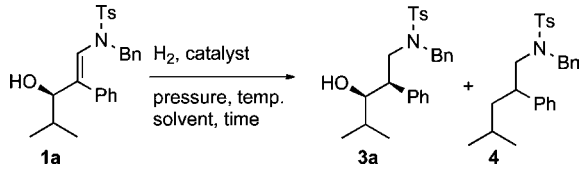
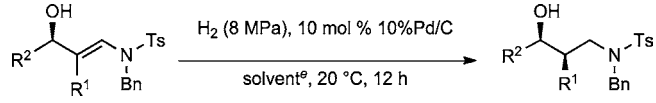
Table 5. Optimization of the Diastereoselective Hydrogenation of β-Hydroxy Enamines

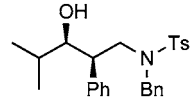
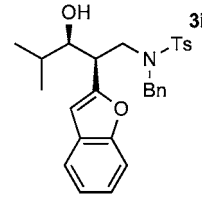
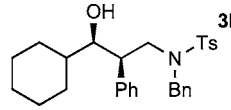
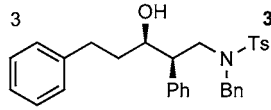
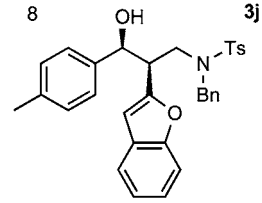
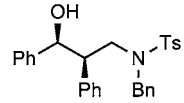
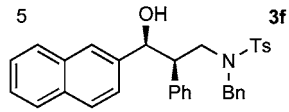
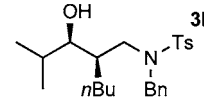
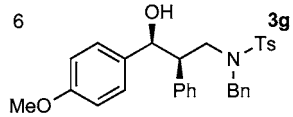
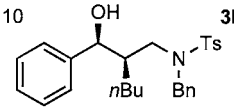


entry	catalyst (mol %)/solvent	pressure (MPa)	temp. (°C)	time (h)	product[a]	isolated yield (%)	dr[b]
1	Crabtree's cat. (10)/CH_2Cl_2	0.1	20	12	**4**	40	–
2	Crabtree's cat. (10)/1:1 MeOH:CH_2Cl_2	0.1	20	12	**4**	50	–
3	Crabtree's cat. (10)/1:1 MeOH:CH_2Cl_2	1.0	20	5	**4**	50	–
4	Crabtree's cat. (10)/1:1 MeOH:CH_2Cl_2	8.0	20	12	**4**	60	–
5	Wilkinson's cat. (1.0)/benzene	0.1	20	12	NR	0	–
6	Wilkinson's cat. (10)/benzene	1.0	20	12	**4**	60	–
7	PtO_2 (10)/MeOH	0.1	20	12	NR	0	–
8	PtO_2 (10)/MeOH	0.1	50	12	dec	0	–
9	PtO_2 (10)/MeOH	8.0	20	12	dec	0	–
10	5% Rh/Al_2O_3 (10)/AcOEt	1.0	20	12	NR	0	–
11	10% Pd/C (10)/MeOH	0.1	20	12	**3a**	10	>20:1
12	10% Pd/C (10)/MeOH	0.1	50	5	**3a**	14	>20:1
13	10% Pd/C (10)/MeOH	1.0	20	12	**3a**	55	>20:1
14	10% Pd/C (10)/MeOH	8.0	20	12	**3a**	90	>20:1
15	10% Pd/C (10)/AcOEt	8.0	20	12	**3a**	14	>20:1

[a] NR, only starting material recovered; dec, starting material decomposed to an inseparable mixture. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Table 6. Diastereoselective Hydrogenation of β-Hydroxy Enamines



entry	product	isolated yield (%)	dr[a]	entry	product	isolated yield (%)	dr[a]
1		**3a** 90	>20:1[b]	7		**3i** 88	>20:1
2		**3b** 80	>20:1				
3		**3c** 80	>20:1	8		**3j** 82	>20:1[d]
4		**3e** 92	>20:1[c]				
5		**3f** 86	>20:1	9		**3k** 85	3:1
6		**3g** 90	>20:1	10		**3l** 90	4:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] 91% ee (HPLC). [c] 90% ee (HPLC). [d] 95% ee. [e] For aliphatic R^1, MeOH; for aromatic R^1, EtOAc.

unfavorable interactions between R^1 and the hydroxyl group, as would be predicted for the free substrate in solution. The dihydrogen is then delivered to give the syn product. It is possible to disfavor the association of the hydroxyl group with the metal catalyst by introduction of a bulky protecting group. In this case, the two conformers differ in steric interactions, one having *i*Pr−Ph interactions and the other OTBS−Ph interactions (Figure 2, right). The difference in the energies of

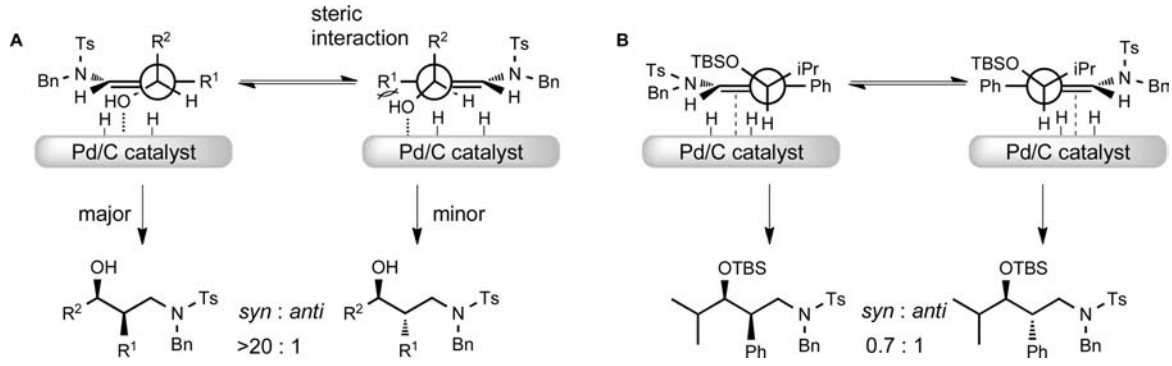
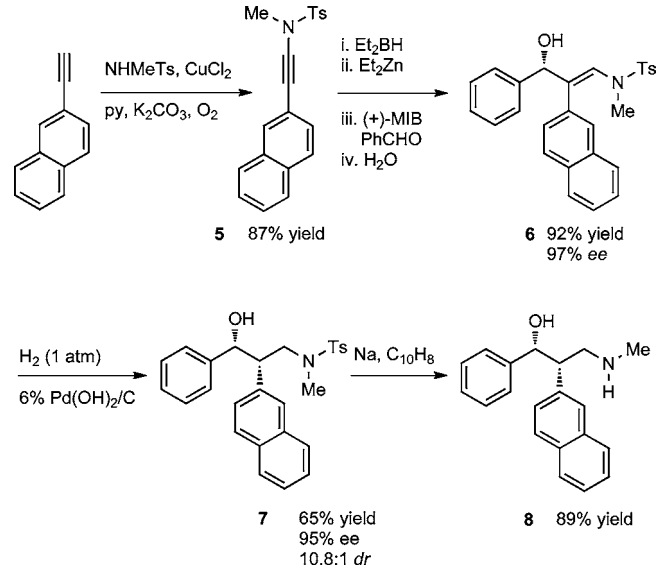


Figure 2. (A) Proposed conformation of hydroxy enamines on the surface of the catalyst to rationalize the syn-selective hydrogenation. (B) The conformation of the TBS-protected β-hydroxy enamine slightly favors the anti diastereomer.

the conformers is not sufficient for good diastereoselection, resulting in a 0.7:1 syn/anti mixture of diastereomers in case of TBS and an 1:1 mixture in case of TIPS. It is noteworthy that the *N*-benzyl group is not hydrogenolysed under these reaction conditions.

3.3.3. Enantio- and Diastereoselective Formal Synthesis of Derivatives of PRC200-SS. The 1,2-disubstituted-1,3-amino alcohol moiety is present in many biologically active compounds, such as the antidepressants venlafaxine (Effexor, Wyeth) and desvenlafaxine (Pristiq, Wyeth), which are both serotonin−norepinephrine reuptake inhibitors (SNRIs). Most antidepressants prescribed at the present time target serotonergic and noradrenergic neurotransmission, resulting in enhanced dopamine neurotransmission. Inhibitors that influence the combination of serotonergic, noradrenergic, and dopaminergic neurotransmission (SNDRIs) can result in significant improvement of depressive symptoms. There are no approved SNDRIs on the market to date, but several are in development. One family of SNDRIs includes PRC200-SS[126−129] and its derivatives.[130] To demonstrate the utility of our methods, we performed a short formal enantio- and diastereoselective synthesis of derivatives of PRC200-SS.[130] Our synthesis (Scheme 7) starts with the copper-catalyzed oxidative coupling of commercially available 2-naphthylacetylene with *N*-methyltoluene sulfonamide, which proceeded in 87% yield. Hydroboration of the resulting 2-naphthyl ynamide **5** with diethylborane followed by transmetalation to zinc and enantioselective addition to benzaldehyde promoted by the (+)-MIB-based catalyst provided β-hydroxy enamine **6** in high yield (92%) with excellent enantioselectivity (97%). Because of the presence of the *N*-methyl group in place of the *N*-benzyl group that appears in the examples in Tables 1−5, the hydrogenation of β-hydroxy enamine **6** under the original conditions (Table 7, entry 1) or related conditions (entries 2 and 3) provided only mediocre diastereoselectivity for **7** (2:1). However, an additional screen of heterogeneous catalysts revealded that use of 20% $Pd(OH)_2/C$ (6 mol %) in methanol

Scheme 7. Synthesis of the Key Intermediate **8** in the Synthesis of PRC200-SS and Derivatives



under 1 atm hydrogen provided the syn product **7** with high diastereoselectivity (dr = 10.8:1 by ^{1}H NMR analysis) in 65% yield with 95% ee (entry 4). When a higher hydrogen pressure (entry 5) or higher catalyst loading (entry 6) was applied, partial hydrogenation of the 2-naphthyl group was observed, and **7′** was the major product. The structure of **7′** was confirmed by X-ray diffraction (see the Supporting Information). The diastereomers formed in entry 4 were easily separable by column chromatography, allowing isolation of the pure syn isomer. Detosylation with sodium naphthalenide afforded **8** in 89% yield. Biologically active chloride, fluoride, and azide derivatives can be obtained from the common intermediate **8**, as shown in Scheme 8.[130] Mitsunobu reaction of **7** and subsequent hydrolysis afforded **9** in 79% yield with 95% ee (Scheme 9). After the detosylation, PRC200-SS was isolated in 76% yield.

In contrast to the original nine-step synthesis of **8** (Scheme 10), which involves resolution of racemic intermediate **10** and late-stage separation of diastereomers (Scheme 10, step 8), our procedure is highly efficient and both enantio- and diastereoselective, affording **8** in four steps from commercially available materials in 46% overall yield. Although the original anti-selective nitrile aldol method allows the synthesis of PRC200-SS, the absolute configuration of the carbinol must be inverted to prepare the bioactive chloride, fluoride, and azide derivatives.

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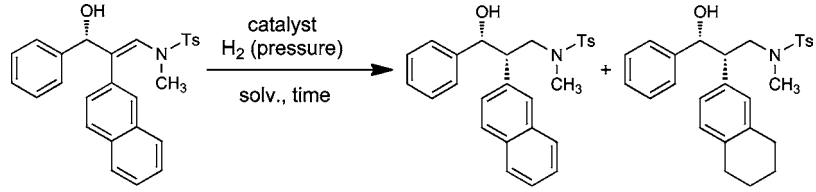
(129) Richelson, E.; Carlier, P. R. *PCT Int. Appl.* **2003**, *45*, WO 2003007929.
(130) Richelson, E.; Fauq, A. H. *PCT Int. Appl.* **2009**, *107*, WO 2009089479.

Table 7. Optimization of Diastereoselective Hydrogenation of β-Hydroxy Enamine **6**

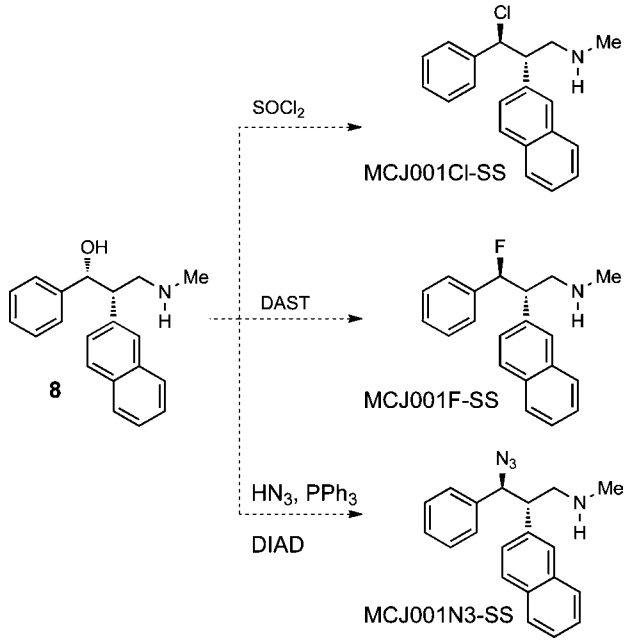


6 **7** **7'**

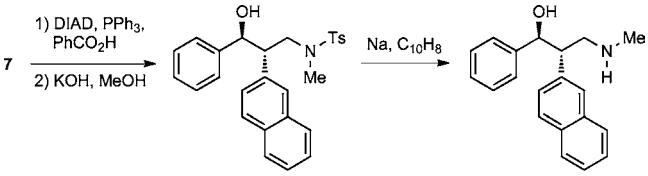
entry	catalyst (mol %)/solvent	pressure (MPa)	time (h)	major product	isolated yield (%)	dr[a]
1	10% Pd/C (10)/AcOEt	8.0	5	**7**	48	2:1
2	10% Pd/C (10)/MeOH	0.1	48	**7**	64	4:1
3	10% Pd/C (10)/MeOH	8.0	5	**7**	83	2:1
4	**10% $Pd(OH)_2$/C (6)/MeOH**	**0.1**	**48**	**7**	**65**	**10.8:1**
5	10% $Pd(OH)_2$/C (10)/MeOH	8.0	8	**7′**	78	2:1
6	10% $Pd(OH)_2$/C (20)/MeOH	0.1	48	**7′**	68	3:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Scheme 8. Known Conversion of **8** to Bioactive Derivatives



Scheme 9. Conversion of **7** to **9** and PCR200-SS

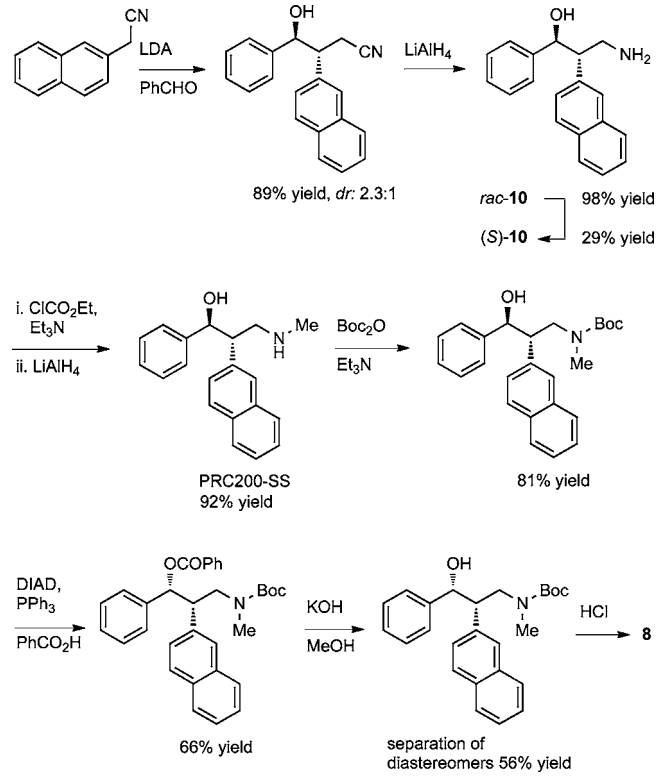


Our syn-selective method opens the door to the direct synthesis of PRC200-SS derivatives without the need for a Mitsunobu reaction.

4. Summary and Outlook

Herein has been presented the first general catalytic and highly enantioselective method of synthesis of β-hydroxy enamines. The versatility of this method is demonstrated by its wide substrate scope, as it can be used to combine aliphatic, α,β-unsaturated, aromatic, or heteroaromatic aldehydes with aliphatic, aromatic, or heteroaromatic ynamides. The resulting

Scheme 10. Carlier's Synthesis of PRC200-SS and Derivatives



β-hydroxy enamines are obtained in high yields with good to excellent ee's. We have shown that β-hydroxy enamines are viable substrates for alkoxy- and hydroxyl-directed reactions. An efficient catalytic enantio- and diastereoselective method for the synthesis of aminocyclopropyl carbinols has also been outlined. This convenient one-pot method enables the synthesis of aminocyclopropyl carbinols in good yields with good to excellent enantioselectivities and excellent diastereoselectivities. Additionally, an efficient syn-diastereoselective hydrogenation of β-hydroxy enamines has been developed that leads to 1,2-disubstituted-1,3-amino alcohols, a common structural motif in many biologically active compounds. This method has made possible the efficient synthesis of the precursor to PRC200-SS derivatives, which are potent serotonin−norepinephrine−dopamine reuptake inhibitors.

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Supporting Information Available: Experimental procedures, synthesis and full characterization of new compounds, conditions for resolution of racemates, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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