Highly Diastereo- and Enantioselective Reagents for Aldehyde Crotylation

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Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. All reaction solvents were purified by degassing with argon and passage through an activated alumina column. *Z*- and *E*-crotyltrichlorosilane were prepared according to literature procedures.¹ ¹H NMR spectra were recorded on Bruker DPX-300 (300 MHz) or DPX-400 (400 MHz) spectrometers. ¹H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual protiated solvent (CDCl₃, 7.25; C₆D₆, 7.15). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dt = doublet of triplets, dd = doublet of doublets, ddd = doublet of doublet of doublets; coupling constant(s) in Hz; integration; assignment). Proton decoupled ¹³C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) and are reported in ppm from CDCl₃ internal standard (77.0 ppm). ¹³C resonances are singlets, unless otherwise specified. ³¹P NMR spectra were recorded on a Bruker DPX-300 (121.6 MHz) and are reported in ppm from H₃PO₄ (85% in H₂O) external standard (0.0 ppm). ¹⁹F NMR spectra were recorded on a Bruker DPX-300 (282 MHz) and are reported in ppm from internal CF₃-trifluorotoluene (0.00 ppm). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter; the concentration *c* is reported in g/100 mL. Low resolution mass spectra were obtained on a JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory.

(1) (a) Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143-2146. (b) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1-C3. (c) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099-1102. (d) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513-3526.

Preparation of reagent (*R,R*)-2: (*Note: Reagents 2 and 3 are moisture sensitive, and it is important that care be taken to exclude moisture especially during the workup procedure. The filtrations and crystallization are most effectively carried out in an inert atmosphere glovebox, especially in humid environments.*) To a cooled (0 °C) solution of *Z*-crotyltrichlorosilane (8.38 mL, 0.055 mol) in CH₂Cl₂ (100 mL) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (16.45g, 0.110 mol). A solution of (*R,R*)-*N,N'*-bis-(4-bromobenzyl)cyclohexane-1,2-diamine² (22.56 g, 0.050 mol) in CH₂Cl₂ (50 mL) was then added over 30 min. The reaction mixture was allowed to warm to room temperature. After 12 h the reaction mixture was concentrated by vacuum distillation (the use of a rotary evaporator is not recommended, as substantial decomposition can result). The residue was diluted with pentane (150 mL) and vigorously stirred for 3 h to ensure complete precipitation of all DBU salts. The suspension was filtered and the filtrate was placed in a freezer (-10 °C) for two days. The resulting pale yellow solid was isolated by filtration and dried under vacuum to give (*R,R*)-**2** (21.5 g, 76% yield). $[\alpha]_D = -46.1^\circ$ (*c* 1.46, CH₂Cl₂); ¹H NMR (300 MHz, C₆D₆) δ 7.38-7.35 (m, 4H, Ar-**H**), 7.14-7.10 (m, 4H, Ar-**H**), 5.49-5.36 (m, 2H, SiCH₂CH=CHMe), 3.99-3.92 (m, 2H, two of ArCH₂N), 3.64-3.52 (m, 2H, two of ArCH₂N), 2.72-2.61 (m, 2H, two CHN), 1.79-1.31 (m, 9H, SiCH₂, CH=CHCH₃, and 2 x CH₂), 0.96-0.84 (m, 4H, 2 x CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 141.6, 140.7, 131.6, 130.2, 129.3, 125.3, 122.3, 66.6, 65.8, 47.5, 31.1, 30.8, 25.1, 25.0, 18.9, 13.4; ²⁹Si NMR (60 MHz, CDCl₃) δ -4.0; IR (CH₂Cl₂) 3020, 2940, 2863, 1487, 1444, 1287, 1207, 1175, 1106, 1070, 1012 cm⁻¹.

Preparation of reagent (*R,R*)-3: Using *E*-crotyltrichlorosilane, the procedure is analogous to that for (*R,R*)-**2** with the following modification: After filtration of the DBU salts, 15 mL CH₂Cl₂ was added to the filtrate. The transparent, pale yellow solution was then placed in a freezer (-10 °C) for 2 days. The resulting pale white crystals were isolated by filtration and dried under vacuum to give (*R,R*)-**3** (4.92 g, 69% yield; a larger scale run gave 28.1 g, 62% yield). $[\alpha]_D = -43.5^\circ$ (*c* 1.25, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.42 (m, 4H, Ar-**H**), 7.24-7.20 (m, 4H, Ar-**H**), 5.31-5.24 (m, 2H, R₃SiCH₂CH=CHMe), 3.97 (AB q, 2H, *J* = 16.2 Hz, ArCH₂N), 3.92 (AB q, 2H, *J* = 15.1 Hz, ArCH₂N), 2.78-2.71 (m, 2H, two

(2) Kubota, K.; Leighton, J.L. *Angew. Chem. Int. Ed.* **2003**, 42, 946-948.

CHN), 1.81-1.53 (m, 9H, SiCH₂, CH=CHCH₃, and 2 x CH₂), 1.15-0.92 (m, 4H, 2 x CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 141.5, 140.8, 131.5, 130.2, 129.4, 127.3, 123.1, 66.5, 65.9, 47.5, 31.0, 30.8, 25.1, 25.0, 23.5, 18.4; ²⁹Si NMR (60 MHz, CDCl₃) δ -4.2; IR (CH₂Cl₂) 3019, 2939, 2862, 1592, 1487, 1175, 1106 cm⁻¹.

General Procedure for Aldehyde Crotylation Reactions Using (R,R)-2 and (R,R)-3: To a cooled (0 °C) solution of reagent **2** or reagent **3** (0.707 g, 1.26 mmol) in CH₂Cl₂ (12 mL) is added the aldehyde (1.14 mmol). After 20 h the reaction is quenched by the addition of 4 mL of a 1 M HCl solution, and the resulting mixture is stirred for 10 min. The layers are separated and the aqueous layer is extracted with ethyl acetate (2 x 10 mL). The combined organic layers are dried over MgSO₄, filtered, and concentrated. Purification of the residue by silica gel chromatography provides the pure homoallylic alcohol products.

Procedure for the Larger Scale Crotylation of Hydrocinnamaldehyde Using Reagent 2 with Recovery of the Diamine: To a cooled (0 °C) solution of reagent **2** (9.77 g, 17.1 mmol) in 150 mL was added hydrocinnamaldehyde (2.06 mL, 15.6 mmol). After 20 h the reaction was quenched with 100 mL of saturated aqueous NaHCO₃, and the mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. Purification of the residue by chromatography on silica gel (10% EtOAc:90% hexanes) afforded 2.34 g (79%) of (3*R*,4*R*)-4-methyl-1-phenyl-5-hexen-3-ol as an oil. The column was then eluted with hexanes/EtOAc/Et₃N (1:1:0.1) to provide 6.95 g (90%) of diamine **1**.

(3*R*,4*R*)-4-methyl-1-phenyl-5-hexen-3-ol (Table 1, entry 1) and **(3*R*,4*S*)-4-methyl-1-phenyl-5-hexen-3-ol** (Table 2, entry 1): These compounds are known.³ Enantiomeric excess was determined by chiral HPLC: Chiracel OD column; 97:3 hexane:isopropanol; 1.0 mL/min, 254 nm. The assay was developed using a 2.5:1 *syn:anti* mixture of racemic diastereomers.

(3) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, 59, 6620-6628.

Peak #	RetTime [min]	Type	Width [min]	Area mAU	*s	Height [mAU]	Area %
1	9.638	VV	0.2708	1289.93518		72.27089	14.5640
2	10.667	VV	0.3196	3137.76294		150.08788	35.4269
3	16.629	BP	0.4850	1274.28162		40.02996	14.3873
4	18.699	BV	0.6239	3155.03320		78.39735	35.6219

Peak #	RetTime [min]	Type	Width [min]	Area mAU	*s	Height [mAU]	Area %
1	9.654	VB	0.2733	82.97385		4.53125	1.3844
2	10.680	BB	0.3217	82.29893		3.76895	1.3731
3	16.705	PB	0.4675	120.95913		3.87541	2.0181
4	18.759	BB	0.6679	5707.39014		134.22169	95.2244

Peak #	RetTime [min]	Type	Width [min]	Area mAU	*s	Height [mAU]	Area %
1	10.238	BD	0.2740	32.86974		1.87892	0.8932
2	11.382	BV	0.3243	49.03228		2.31432	1.3324
3	18.482	BB	0.5854	3461.69873		91.23190	94.0654
4	20.940	BB	0.5974	136.49805		3.39328	3.7091

(3R,4R)-3,6-dimethyl-1-hepten-4-ol (Table 1, entry 2): $[\alpha]_D^{25} = +45.2^\circ$ (*c* 1.45, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) δ 5.85-5.74 (m, 1H, $\text{CH}=\text{CH}_2$), 5.13-5.05 (m, 2H, $\text{CH}=\text{CH}_2$), 3.61-3.58 (m, 1H, CHOH), 2.32-2.21 (m, 1H, CHCH_3), 1.87-1.74 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.45 (s, 1H, OH), 1.40-1.22 (m, 2H, $(\text{CH}_3)_2\text{CHCH}_2$), 1.05 (d, 3H, $J = 6.9$ Hz, CHCH_3), 0.95 (d, 3H, $J = 6.6$ Hz, one of $(\text{CH}_3)_2\text{CH}$), 0.92 (d, 3H, $J = 6.6$ Hz, one of $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (75 MHz, CDCl_3) δ 141.4, 115.7, 72.9, 44.2, 43.4, 25.1, 24.2, 22.1, 14.5; IR (CH_2Cl_2) 3368, 3082, 2959, 1638, 1461, 1373, 1259, 1088, 912 cm^{-1} .

Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiralcel AD-H column; 98.8:0.6:0.6 hexane:EtOH:MeOH; 1.0 mL/min, 254 nm.

Peak #	RetTime [min]	Type	Width [min]	Area mAU	*s	Height [mAU]	Area %
1	8.636	VB	0.3718	1.80570e4		718.68335	49.5495
2	10.999	BP	0.4606	1.83854e4		602.84534	50.4505

Peak #	RetTime [min]	Type	Width [min]	Area mAU	*s	Height [mAU]	Area %
1	8.154	PV	0.2997	593.14478		27.98173	1.9270
2	10.275	FP	0.4739	3.01672e4		961.82971	98.0730

(3R,4S)-3,6-dimethyl-1-hepten-4-ol (Table 2, entry 2): $[\alpha]_D^{25} = +15.9^\circ$ (*c* 1.025, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 5.82-5.70 (m, 1H, $\text{CH}=\text{CH}_2$), 5.17-5.08 (m, 2H, $\text{CH}=\text{CH}_2$), 3.51-3.45 (m, 1H, CHOH), 2.22-2.15 (m, 1H, CHCH_3), 1.86-1.81 (m, 1H, $(\text{CH}_3)_2\text{CH}$), 1.52 (s, 1H, OH), 1.39-1.22 (m, 2H, $(\text{CH}_3)_2\text{CHCH}_2$), 1.04 (d, 3H, $J = 6.9$ Hz, CHCH_3), 0.94 (d, 3H, $J = 6.8$ Hz, one of $(\text{CH}_3)_2\text{CH}$), 0.91 (d, 3H, $J = 6.8$ Hz, one of $(\text{CH}_3)_2\text{CH}$).

$J = 6.6$ Hz, one of the $(\text{CH}_3)_2\text{CH}$; ^{13}C NMR (75 MHz, CDCl_3) δ 140.7, 116.8, 73.0, 45.1, 43.9, 25.0, 24.2, 22.1, 16.6; IR (CH_2Cl_2) 3373, 2964, 2919, 1606, 1261, 1093, 1016 cm^{-1} .

Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 98.8:0.6:0.6 hexane:EtOH:MeOH; 1.0 mL/min, 254 nm.

(3R,4R)-4-cyclohexyl-3-methyl-1-buten-4-ol (Table 1, Entry 3): $[\alpha]_D = +39.2^\circ$ (c 0.67, CHCl_3). This is a known compound.³ Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 98:1:1 hexane:EtOH:MeOH; 1.0 mL/min, 254 nm.

(3S,4R)-4-cyclohexyl-3-methyl-1-buten-4-ol (Table 2, Entry 3): $[\alpha]_D = -16.8^\circ$ (c 1.10, CHCl_3). This is a known compound.³ Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 98:1:1 hexane:EtOH:MeOH; 1.0 mL/min, 254 nm.

(2R,3R)-1-benzyloxy-3-methyl-4-penten-2-ol (Table 1, Entry 4): $[\alpha]_D^{25} = +24.6^\circ$ (*c* 1.84, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.36 (m, 5H, Ar-H), 5.89-5.78 (m, 1H, CH=CH₂), 5.18-5.10 (m, 2H, CH=CH₂), 4.64 (s, 2H, PhCH₂O), 3.78-3.72 (m, 1H, CHOH), 3.55 (dd, 1H, *J* = 3.0 and 9.4 Hz, one of BnOCH₂), 3.40 (dd, 1H, *J* = 7.7 and 9.4 Hz, one of BnOCH₂), 2.50-2.40 (m, 2H, OH and CH₃CH), 1.19 (d, 3H, *J* = 6.8 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 140.7, 138.4, 128.9, 128.2, 128.1, 115.6, 73.8, 73.2, 41.5, 16.1; IR (CH₂Cl₂) 3449, 2916, 2865, 1640, 1454, 1103, 916 cm⁻¹; LRMS (FAB+) calc'd for C₁₃H₁₈O₂ 206.28, found (M+H⁺) 207.24. **(2R,3S)-1-benzyloxy-3-methyl-4-penten-2-ol** (Table 2, Entry 4): $[\alpha]_D^{25} = -5.6^\circ$ (*c* 1.23, CHCl₃). This is a known compound.⁴ Enantiomeric excess was determined by chiral HPLC: Chiracel AD-H column; 99:1 hexane:isopropanol; 1.0 mL/min, 254 nm. The assay was developed using a ~4:1 *anti:syn* mixture of racemic diastereomers.

⁴ Hoffmann, R. W.; Helbig, W. *Chem. Ber.* **1981**, *114*, 2802-2807.

(3*R*,4*R*)-1-(4'-methoxy-benzyloxy)-4-methyl-5-hexen-3-ol (Table 1, Entry 5): $[\alpha]_D^{25} = +9.8^\circ$ (*c* 0.79, CH₂Cl₂); ¹H NMR (300 MHz, C₆D₆) δ 7.19 (d, 2H, *J* = 6.5 Hz, 3',5'-ArH), 6.81 (d, 2H, *J* = 6.5 Hz, 2', 6'-ArH), 5.88-5.76 (m, 1H, CH=CH₂), 5.04 (t, 2H, *J* = 9.3 Hz, CH=CH₂), 3.95 (s, 2H, ArCH₂O), 3.69-3.63 (m, 1H, CHOH), 3.59-3.54 (m, 1H, one of ArCH₂OCH₂), 3.51-3.40 (m, 1H, one of ArCH₂OCH₂), 3.35 (s, 3H, OCH₃), 2.75 (d, 1H, *J* = 3.4 Hz, OH), 2.28 (m, 1H, CHCH₃), 1.68 (m, 2H, OCH₂CH₂), 1.16 (d, 3H, *J* = 6.8 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) 159.6, 141.4, 130.4, 129.7, 115.3, 114.2, 74.9, 73.4, 69.6, 55.6, 44.3, 33.9, 15.5; IR (CH₂Cl₂) 3456, 2958, 2864, 1613, 1514, 1462, 1302, 1249, 1088, 1036 cm⁻¹; LRMS (FAB+) calc'd for C₁₅H₂₂O₃ 250.33, found (M+H⁺) 251.25. **(3*R*, 4*S*)-1-(4'-methoxybenzyloxy)-4-methyl-5-hexen-3-ol** (Table 2, Entry 5): $[\alpha]_D^{25} = -2.38^\circ$ (*c* 0.80, CHCl₃). This is a known compound.⁵ Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 98:1:1 hexane:EtOH:MeOH; 1.0 mL/min, 254 nm. The assay was developed using a ~3:1 *anti:syn* mixture of racemic diastereomers.

(5) Eggen, J.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem.* **2000**, *65*, 7792-7799.

(1*S*,2*R*)-2-methyl-1-phenyl-3-buten-1-ol (Table 1, Entry 6): $[\alpha]_D = -25.9^\circ$ (*c* 0.805, CHCl₃). This is a known compound.⁶ Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 95:5 hexane:isopropanol; 1.0 mL/min, 254 nm.

(1*S*,2*S*)-2-methyl-1-phenyl-3-buten-1-ol (Table 2, Entry 6): $[\alpha]_D = -101.4$ (*c* 0.85, CHCl₃). This is a known compound.⁶ Enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate ester: Chiracel AD-H column; 95:5 hexane:isopropanol; 1.0 mL/min, 254 nm.

(1*S*,2*R*)-2-methyl-1-(4'-trifluoromethylphenyl)-3-buten-1-ol (Table 1, Entry 7): $[\alpha]_D = -18.2^\circ$ (*c* 0.565, CH₂Cl₂). This is a known compound.⁷ Enantiomeric excess was determined by chiral GC: Chiraldex GTA column; 100 °C; 2.0 mL/min.

(6) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L.; *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.

(7) Denmark, S. E.; Fu, J.; *J. Am. Chem. Soc.* **2001**, *123*, 9488-9489.

(1*S*,2*S*)-2-methyl-1-(4'-trifluoromethylphenyl)-3-buten-1-ol (Table 2, Entry 7): $[\alpha]_D = -77.1^\circ$ (*c* 1.230, CHCl₃). This is a known compound.⁸ Enantiomeric excess was determined by chiral GC: Chiraldex GTA column; 100 °C; 2.0 mL/min.

(3*S*,4*R*)-4-Methyl-1-phenyl-hexa-1,5-dien-3-ol (Table 1, Entry 8): $[\alpha]_D = -7.1^\circ$ (*c* 0.59, CH₂Cl₂).
(3*S*,4*S*)-4-Methyl-1-phenyl-hexa-1,5-dien-3-ol (Table 2, Entry 8): $[\alpha]_D = +18.6^\circ$ (*c* 0.955, Et₂O). These are known compounds.⁷ Enantiomeric excess was determined by chiral HPLC: Chiralcel OD column; hexane to 98:2 hexane:isopropanol gradient over 1 h; 1.0 mL/min, 254 nm. The assay was developed using a 1.5:1 *syn:anti* mixture of racemic diastereomers.

(8) Malkov, A.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674-3677.

¹H NMR Spectrum of (R,R)-2 (300 MHz, CDCl₃):

¹H NMR Spectrum of (R,R)-3 (300 MHz, CDCl₃):

^1H NMR Spectrum of **(3*R*,4*R*)-3,6-dimethyl-1-hepten-4-ol** (Table 1, entry 2) (300 MHz, CDCl_3):

^1H NMR Spectrum of **(3*S*,4*R*)-3,6-dimethyl-1-hepten-4-ol** (Table 2, entry 2) (300 MHz, CDCl_3):

^1H NMR Spectrum of **(2*R*,3*R*)-1-benzyloxy-3-methyl-4-penten-2-ol** (Table 1, entry 4) (300 MHz, CDCl_3):

^1H NMR Spectrum of **(3*R*,4*R*)-1-(4'-methoxy-benzyloxy)-4-methyl-5-hexen-3-ol** (Table 1, entry 5) (300 MHz, CDCl_3):