Solvent-Dependent Stereoselectivity in a Still-Wittig Rearrangement: An Experimental and Ab Initio Study

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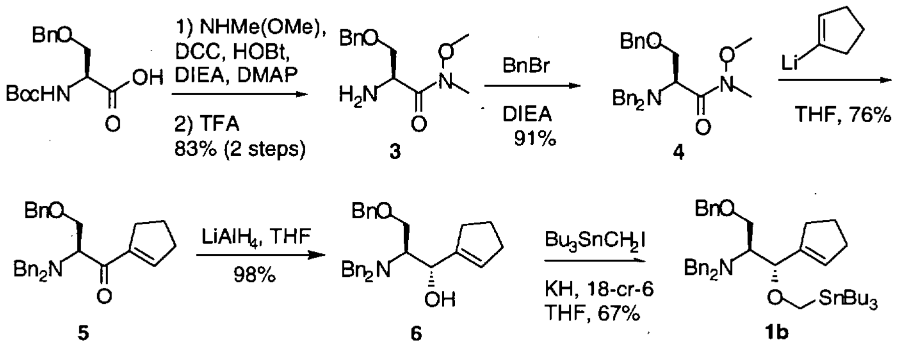
Supporting Information

Supporting Scheme 1. Synthesis of (S,S) stannane **1b**.



Experimental Section. Unless otherwise indicated, all reactions were carried out under N_2 in flame dried glassware. THF, toluene, and CH_2Cl_2 were dried by passage through alumina.[1] Anhydrous (99.8%) DMF was purchased from Aldrich and used directly from SureSeal™ bottles. Diisopropylethylamine (DIEA) was distilled from CaH_2 under a N_2 atmosphere. Brine (NaCl), $NaHCO_3$ and NH_4Cl refer to saturated aqueous solutions. Chromatography was performed on 32-63 μm silica gel with reagent grade solvents. Melting points are uncorrected. Proton (300 MHz) and carbon-13 (75 MHz) NMR spectral data were recorded on a General Electric spectrometer using deuterated solvents at rt.

Serine(OBn) Weinreb amide (3). Boc-Serine(OBn)-OH, (20 g, 71.2 mmol), N,O-dimethylhydroxylamine hydrochloride (13.9 g, 142.3 mmol), and DIEA (36.7 g, 284.7 mmol) were dissolved in 1:1 CH_2Cl_2:DMF (500 mL) and cooled to 0°C. N-hydroxybenzotriazole (HOBt) (11.5 g, 85.4 mmol), DCC (17.6 g, 85.4 mmol), and DMAP (ca. 200 mg) were added and the reaction was stirred 5 days. The reaction was filtered to remove dicyclohexyl urea and concentrated. The resulting slurry was diluted with 700 mL EtOAc and washed with water (4x 200 mL), NH_4Cl (2x 100 mL), $NaHCO_3$ (2x 100 mL), and brine again (100 mL). The organic layer was dried on $MgSO_4$ and concentrated. ^1H NMR ($CDCl_3$): δ 7.36-7.23 (m, 5H), 5.43 (br d, J=8.8, 1H), 4.88 (m, 1H), 4.57 (d, J=12.3, 1H), 4.49 (d, J=12.3, 1H), 3.71 (s, 3H), 3.67 (m, 2H), 3.21 (s, 3H), 1.44 (s, 9H). The resulting oil was dissolved in CH_2Cl_2 (400 mL) and TFA (125 mL) was added and stirred 30 min. The mixture was concentrated, then quenched with $NaHCO_3$ until gas evolution ceased. The aqueous mixture was extracted with CH_2Cl_2 (8 x 300 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 50% EtOAc in petroleum ether to remove impurities, followed by product elution with 10% MeOH in EtOAc yielded 13.12 g (83%) of the amine **3** as a clear oil. ^1H NMR ($CDCl_3$): δ 7.40-7.20 (m, 5H), 4.57 (d, J=12.1, 1H), 4.52 (d, J=12.1, 1H), 4.06 (m, 1H), 3.67 (s, 3H), 3.66-3.45 (m, 2H), 3.20 (s, 3H), 1.88 (br s, 2H).

N,N,O-Tribenzyl Serine Weinreb amide (4). Weinreb amide **3** (13 g, 58 mmol) was dissolved in CH_2Cl_2 (50 mL), then benzyl bromide (24.8 g, 145.1 mmol) and DIEA (37.4 g, 290 mmol) were added. After 4 days at rt, the reaction was diluted with EtOAc (600 mL), washed with NH_4Cl (4x 200 mL) and brine (200 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 10% EtOAc in petroleum ether to remove benzyl bromide, then 50% EtOAc in petroleum ether to elute the product yielded 21.37 g (91%) of the fully protected Weinreb amide **4** as a clear oil. ^1H NMR ($CDCl_3$): δ 7.40-7.17 (m, 15H), 4.56 (d, J=11.9, 1H), 4.48 (d, J=11.9, 1H), 4.13 (m, 1H), 3.98-3.84 (m, 4H), 3.76 (d, J=14.1, 2H), 3.28 (br s, 3H), 3.20 (br s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.5, 140.0, 138.2, 128.7, 128.1, 127.9, 127.3, 126.6, 73.0, 68.6, 60.8, 56.4, 55.0, 30.9. Anal. Calcd for: $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.40. Found: C, 74.31; H, 7.32; N, 6.40.

Ketone 5. Cyclopentenyllithium (39 mmol) was generated by adding *s*-BuLi (1.3 M, 60 mL, 78 mmol) to 1-iodocyclopentene[2,3] (7.6 g, 39 mmol) at -40°C in THF (450 mL) and stirring for 3 h. The Weinreb amide of N,N,O-tribenzyl Serine **4** (9.5 g, 23.5 mmol) in 50 mL THF, dried over 3 Å molecular sieves 3 h under N_2, was added slowly via canula. The mixture was stirred 2 h at -40°C, then warmed to rt and stirred an additional 16 h. The reaction was quenched with NH_4Cl (200 mL), diluted with 1 L EtOAc, washed with NH_4Cl (2x 200 mL), $NaHCO_3$ (2x 200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated. Chromatography on silica with 10% EtOAc in petroleum ether yielded 7.5 g (76%) of the ketone **5**. ^{1}H NMR ($CDCl_3$): δ 7.39-7.20 (m, 15H), 6.11 (m, 1H), 4.55 (d, J=12.3, 1H), 4.48 (d, J=12.3, 1H), 4.24 (app. t, J= 6.6, 1H), 3.90 (d, J=6.6, 2H), 3.79 (d, J=13.6, 2H), 3.71 (d, J=14.1, 2H), 2.59-2.39 (m, 4H), 1.98-1.84 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 197.8, 145.5, 144.7, 139.7, 138.2, 128.8, 128.2, 128.1, 127.5, 126.9, 73.3, 67.6, 60.6, 54.8, 33.9, 30.5, 22.6. Anal. Calcd for: $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29. Found: C, 81.51; H, 7.42; N, 3.52.

(*S,S*)-Alcohol 6. Ketone **5** (6.8 g, 16 mmol) was dissolved in 250 mL THF and $LiAlH_4$ (6 g, 160 mmol) was added. After 1 h, the reaction was quenched with MeOH (50 mL), then NH_4Cl (50 mL), diluted with EtOAc (500 mL), washed with NH_4Cl (150 mL), and 1 M sodium potassium tartrate (2x 150 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3x 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield 6.68 g (98%) of alcohol **6** as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.49-7.24 (m, 15H), 5.65 (m, 1H), 4.62 (d, J=11.9, 1H), 4.53 (d, J=11.9, 1H), 4.48 (s, 1H), 4.26 (d, J=10.1, 1H), 4.02 (d, J=13.2, 2H), 3.80-3.70 (m, 3H), 3.58 (dd, J=10.6, 3.1, 1H), 3.07 (m, 1H), 2.43-2.17 (m, 3H), 2.00-1.75 (m, 3H). ^{13}C NMR (CDCl$_3$): δ 144.1, 139.0, 138.2, 129.2, 129.0, 128.3, 127.5, 127.4, 127.1, 73.2, 67.5, 66.4, 59.7, 54.3, 32.0, 29.5, 23.0. Anal. Calcd for: $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.25; H, 7.66; N, 3.11.

(*S,S*)-Stannane 1b. Alcohol **6** (2.5 g, 5.85 mmol) was dissolved in 120 mL THF, and KH (ca. 1 g of a 35% suspension in mineral oil), 18-crown-6 (4.63 g, 17.55 mmol), and Bu_3SnCH_2I[4] (3.8 g, 8.78 mmol) were added and stirred 1 h. An additional equivalent of Bu_3SnCH_2I (2.5 g, 5.85 mmol) was added and stirred 16 h. The reaction was quenched with MeOH and diluted with EtOAc (400 mL), washed with NH_4Cl (2x 150 mL), $NaHCO_3$ (2x 150 mL), brine (150 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with petreoleum ether to remove nonpolar impurities, followed by 3% EtOAc in petroleum ether to elute the product, yielded 2.88 g (67%) of stannane **1b** as a clear liquid. ^{1}H NMR (CDCl$_3$): δ 7.40-7.13 (m, 15H), 5.58 (m, 1H), 4.44 (d, J=11.9, 1H), 4.35 (d, J=11.9, 1H), 4.03 (d, J=7.5, 1H), 3.97 (d, J=13.6, 2H), 3.82 (d, J=13.6, 2H), 3.72 (d, J=9.7, 1H), 3.58 (dd, J=9.7, 5.7, 1H), 3.51 (dd, J=9.7, 4.4, 1H), 3.39 (d, J=9.7, 1H), 2.97 (m, 1H), 2.45-2.19 (m, 2H), 1.98 (m, 2H), 1.79 (m, 2H), 1.53 (m, 6H), 1.30 (m, 6H), 0.97-0.79 (m, 15H).

(*Z*)- and (*E*)-Alkenes 2 in THF. Stannane **1b** (1.8 g, 2.3 mmol) was dissolved in THF and cooled to -78°C. *n*-BuLi (2.5 M, 1.4 mL, 3.5 mmol) was added slowly and stirred 1 h at -78°C. The reaction was quenched with NH_4Cl and diluted with EtOAc (100 mL), washed with NH_4Cl (2x 50 mL), brine (50 mL), dried on $MgSO_4$ and concentrated. Chromatography on silica with 15% EtOAc in petroleum ether yielded 690 mg (68%) of (*Z*)-alkene **2**, and 248 mg (25%) of (*E*)-alkene **2** as clear oils. See NOE spectra included for stereochemical assignments. **(*E*)-2**: ^{1}H

NMR ($CDCl_3$): δ 7.40-7.16 (m, 15H), 5.40 (m, 1H), 4.49 (d, J=12.3, 1H), 4.44 (d, J=12.3, 1H), 3.83 (d, J=13.6, 2H), 3.73 (m, 1H), 3.66-3.42 (m, 6H), 2.62 (m, 1H), 2.03 (m, 2H), 2.00-1.55 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 148.6, 140.3, 138.5, 129.4, 128.5, 128.2, 128.0, 127.5, 127.3, 126.6, 117.6, 72.6, 71.7, 65.4, 57.3, 54.7, 47.0, 29.6, 29.2, 24.1. **(*Z*)-2**: ^1H NMR ($CDCl_3$): δ 7.45-7.19 (m, 15H), 5.59 (br d, J=7.9, 1H), 4.60 (d, J=12.3, 1H), 4.55 (d, J=12.3, 1H), 4.15 (br s, 1H), 3.91 (d, J=13.6, 2H), 3.82 (m, 1H), 3.76-3.64 (m, 4H), 3.41-3.24 (m, 2H), 2.57 (m, 1H), 2.40-2.18 (m, 2H), 1.80-1.44 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 149.0, 139.2, 138.4, 129.4, 128.3, 128.0, 127.5, 126.8, 120.9, 73.2, 69.7, 64.8, 57.3, 55.0, 43.5, 33.1, 29.4, 23.1. Anal. Calcd for: $C_{30}H_{35}NO_2$: C, 81.59; H, 7.99; N, 3.17. Found: C, 81.42; H, 8.27; N, 3.25.

(*Z*)- and (*E*)-Alkenes 2 in toluene. Stannane **1b** (75 mg, 0.10 mmol) was dissolved in toluene (3 mL) and cooled to -78°C. *n*-BuLi (2.5 M, 82 μL, 0.21 mmol) was added slowly and stirred 1 h at -78°C, after which TLC (10% EtOAc/hexanes) indicated the reaction was incomplete. An additional 41 μL *n*-BuLi was added and the reaction was stirred at -78°C for 1 h. The reaction was quenched with NH_4Cl (5 mL) and diluted with EtOAc (100 mL), washed with NH_4Cl (2x 30 mL), brine (30 mL), dried on $MgSO_4$ and concentrated. Chromatography on silica with 20% EtOAc in petroleum ether yielded 6 mg (13%) of **(*Z*)-2** and 18 mg (40%) of **(*E*)-2**.

Calculations. Chem3D Pro v.5.0[5] was used to sketch transition states for the reactions, and to locate transition state structures with the semi-empirical method MNDO. We refined these structures with Gaussian 98 ab initio software[6] on a Windows/Intel PC system. In the molecular modeling, the transition state is recognized by a single negative root in the curvature matrix and an associated eigenvector passing from reactant to product, at a point where all energy gradient components vanish.

Supplement Table 1. Results from 3-21G* calculations. Data for the lower energy pairs of transition states pictured in Figure 1 are shown in bold.

Solvent	Internal Li$^+$ chelation and outcome	Hartrees	ΔΔG favored-unfavored (mH)	ΔΔG favored-unfavored (kcal)	Expected ratio at -78°C
with THF	**O-Li-N leads to (*Z*)**	**-904.72194**	**-0.89**	**-0.60**	**4.7**
with THF	**O-Li-N leads to (*E*)**	**-904.72105**			1
with THF	O-Li-O leads to (*Z*)	-904.7099276			
with THF	O-Li-O leads to (*E*)	-904.7121128	-2.19	-1.47	(44.3)
No THF	O-Li-N leads to (*E*)	-674.96285	-2.96	-1.99	(169.3)
No THF	O-Li-N leads to (*Z*)	-674.95989			
No THF	**O-Li-O leads to (*E*)**	**-674.97202**	**-0.67**	**-0.45**	**3.2**
No THF	**O-Li-O leads to (*Z*)**	**-674.97135**			1

References

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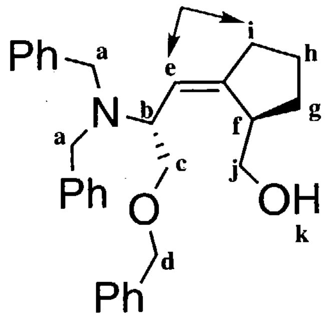
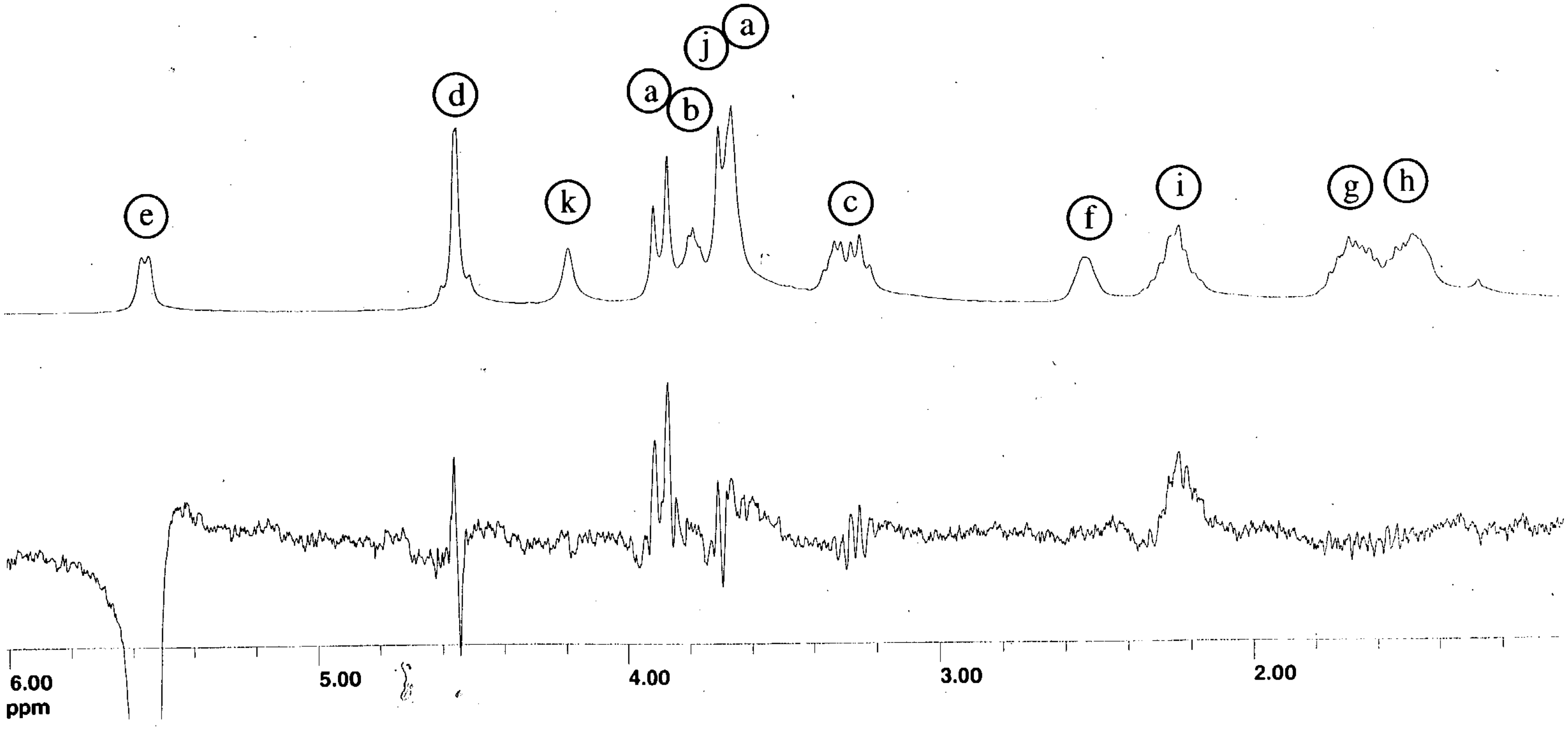
1D NOE experiment confirming geometry of (Z)-2.

Top: Control spectrum
Bottom: Difference spectrum, irradiation at H_e, enhancement at H_i





1D NOE experiment confirming geometry of (*E*)-2.

Top: Control spectrum
Bottom: Difference spectrum, irradiation at H_f, enhancement at H_e