JOC The Journal of Organic Chemistry

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Enantioselective Synthesis of Garner's Aldehyde by Asymmetric Hydroformylation

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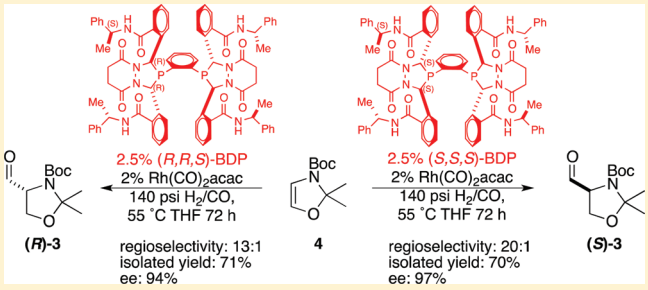
Supporting Information

ABSTRACT: Both enantiomers of Garner's aldehyde (**3**) are prepared from the same alkene **4** by catalytic asymmetric hydroformylation.



Asymmetric hydroformylation (AHF) is a powerful transformation, converting achiral and readily available alkenes into valuable and reactive α-chiral aldehydes with perfect atom economy.[1,2] Recently, the Landis group has reported bis(diazaphospholane) (BDP) ligands **1** and **2** (Figure 1) for AHF

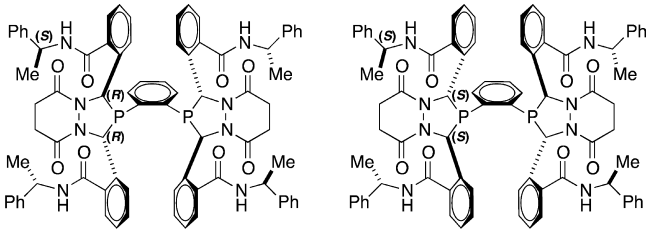


Figure 1. BDP ligands **1** and **2**.

that combine complete conversion, excellent regioselectivity, and high enantioselectivity with low catalyst and ligand loading to effect AHF on a variety of alkene substrates under mild reaction conditions.[3] Because ligands **1** and **2** are readily available[4] and provide excellent catalytic control comparable to or better than other reported ligands,[1,2] we endeavored to use them for the generation of chiral, enantioenriched aldehydes. Our attention was drawn to Garner's aldehyde (**3**, Figure 2), a popular synthetic building block,[5,6] as a useful example of the utility of AHF for the generation of these valuable synthetic intermediates. While both enantiomers of **3** can be prepared from commercially available D- or L-serine,[7] we surmised that achiral alkene **4**, reported by Funk,[8] could serve as a common precursor to both enantiomers of **3** if regioselective and facial selective hydroformylation could be accomplished (Figure 2). Although heteroatom substitution on or near an alkene has been shown to direct regioselectivity, the presence of two

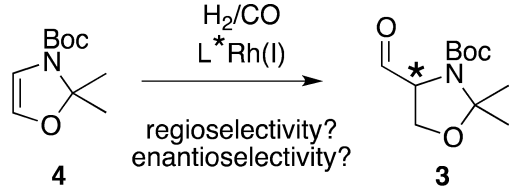
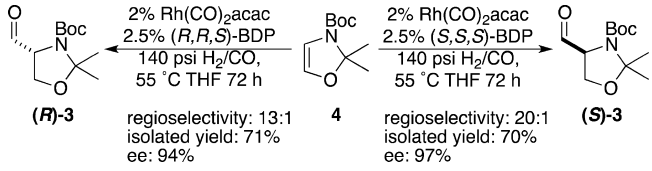


Figure 2. AHF-based synthesis of Garner's aldehyde from achiral alkene **4**.

possible directing heteroatoms on **4** had no precedent in AHF.[1−3,9] There have been several *N*-protecting groups reported for 4-formyl-2,2-dimethyl-3-oxazolidine, including Cbz,[10] benzyl,[11] methyl carbonate,[12] Fmoc,[13] and *o*-phenylbenzoyl,[14] but Boc-protected oxazolidine **3**, Garner's aldehyde, is by far the most common and was thus the focus of our efforts.

In the event (Scheme 1), Rh(I)-catalyzed AHF of **4** (0.5 M in THF) using BDP ligand **1** and syngas at 55 °C at 140 psi

Scheme 1. Asymmetric Hydroformylation of 4



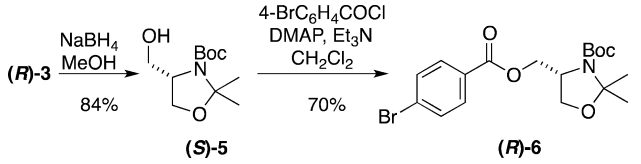
proceeded to afford (*R*)-**3** with 13:1 regioselectivity in 94% ee. AHF of **4** under the same conditions using BDP ligand **2** yielded (*S*)-**3** with 20:1 regioselectivity in 97% ee. Regioselectivities were determined by ^{1}H NMR.[15] Experiments with

Received: January 4, 2012
Published: February 27, 2012

dx.doi.org/10.1021/jo300025t | J. Org. Chem. 2012, 77, 2983−2985

lower temperatures (37 and 44 °C), lower catalyst loading (1%), and higher concentration (1.2 M) resulted in erosion of regioselectivity. Garner and co-workers have reported optical rotation data for (*R*)-**3** and (*S*)-**3**,[7] but for more accurate data enantioselectivities were determined by supercritical fluid chromatography (SFC) of esters (*R*)-**6** and (*S*)-**6**, prepared by reduction of (*R*)-**3** and (*S*)-**3** with $NaBH_4$ and acylation with 4-bromobenzoyl chloride to provide a good chromophore (Scheme 2). Absolute configuration was assigned on the basis

Scheme 2. Preparation of 6 for Enantiopurity Analysis



of SFC data for (*S*)-**6** prepared from L-serine methyl ester hydrochloride.

EXPERIMENTAL SECTION

1,1-Dimethylethyl (*S*)-4-Formyl-2,2-dimethyl-3-oxazolidinecarboxylate [(*S*)-3]. Under an inert atmosphere, (*S,S,S*)-BDP (**2**) (174 mg, 0.133 mmol) and $Rh(CO)_2acac$ (27 mg, 0.106 mmol) were dissolved in THF (3.64 mL) in a 40.5 cm long pressure bottle sealed with a custom head (equipped with a pressure gauge, filling/venting valve, and a septum-sealed valve) and pressurized to 140 psi with syngas. The solution was stirred at 55 °C for 20 min, the pressure reduced to about 15 psi, and alkene **4** (1.06 g, 5.32 mmol) added as a solution in THF (7 mL) via syringe. The pressure was increased to 140 psi, and the reaction mixture was stirred at 55 °C for 3 d. After the mixture was cooled to rt, the syngas was vented and the solution concentrated in vacuo. The regioselectivity was determined to be 20:1 by comparison of the aldehyde peaks in the ^1H NMR spectrum of the crude oil (minor regiomeric aldehyde δ 9.76 (d, J = 1.2 Hz). The crude oil was purified by flash column chromatography (20% EtOAc/hexane) to give a colorless to yellow oil (0.85 g, 70%): R_f 0.35 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (br s), 1.52 (br s), 1.56 (s), 1.61 (s), 1.66 (s) 4.00−4.16 (m, 2H), 4.16−4.40 (m 1H) 9.55 (d, J = 2.4 Hz), 9.61 (d, J = 0.9 Hz, rotamer); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 24.0 (CH_3), 24.9* (CH_3), 26.0 (CH_3), 26.9* (CH_3), 28.5 (CH_3), 63.7*(CH_2), 64.1 (CH_2), 64.9 (CH), 81.3 (C), 81.6* (C), 94.5 (C), 95.3* (C), 101.0 (C), 151.5 (C), 152.8* (C), 199.6 (CH); IR (neat) 2981, 1739, 1709, 1370 cm^{-1}; HRMS (ESI) m/z calcd for [$C_{11}H_{19}NO_4$ + Na] 252.1207, found 252.1194.

1,1-Dimethylethyl (*R*)-4-Formyl-2,2-dimethyl-3-oxazolidinecarboxylate [(*R*)-3]. Under an inert atmosphere, (*R,R,S*)-BDP (**1**) (160 mg, 0.122 mmol) and $Rh(CO)_2acac$ (25 mg, 0.097 mmol) were dissolved in THF (2.74 mL) in a 40.5 cm long pressure bottle sealed with a custom head (equipped with a pressure gauge, filling/venting valve, and a septum-sealed valve) and pressurized to 140 psi with syngas. The solution was stirred at 55 °C for 20 min, the pressure reduced to about 15 psi, and alkene **4** (0.97 g, 4.87 mmol) added as a solution in THF (7 mL) via syringe. The pressure was increased to 140 psi, and the reaction mixture was stirred at 55 °C for 3 d. After the mixture was cooled to rt, the syngas was vented and the solution concentrated in vacuo. The regioselectivity was determined to be 13:1 by comparison of the aldehyde peaks in the ^1H NMR spectrum of the crude oil (minor regiomeric aldehyde δ 9.76 (d, J = 1.2 Hz). The crude oil was purified by flash column chromatography (20% EtOAc/hexane) to give a colorless to yellow oil (0.79 g, 71%): R_f 0.35 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (br s), 1.52 (br s), 1.56 (s), 1.61 (s), 1.66 (s) 4.00−4.16 (m, 2H), 4.16−4.40 (m 1H) 9.55 (d, J = 2.4 Hz), 9.61 (d, J = 0.9 Hz, rotamer). ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ 24.0 (CH_3), 24.9* (CH_3), 26.0 (CH_3), 26.9* (CH_3), 28.5 (CH_3), 63.7*(CH_2), 64.1 (CH_2), 64.9 (CH), 81.3 (C), 81.6* (C), 94.5 (C), 95.3* (C), 101.0 (C), 151.5 (C), 152.8* (C), 199.6 (CH); IR (neat) 2981, 1739, 1709, 1370 cm^{-1}; HRMS (ESI) m/z calcd for [$C_{11}H_{19}NO_4$+Na] 252.1207. Found 252.1194.

1,1-Dimethylethyl (*S*)-4-Hydroxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate [(*S*)-5]. $NaBH_4$ (0.18 g, 4.83 mmol) was added to a solution of aldehyde (*R*)-**3** (0.79 g, 3.45 mmol) in MeOH (35 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, quenched with aq satd NH_4Cl, warmed to rt, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil (0.67 g, 84%) that required no further purification: R_f 0.51 (50% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (br s, 12H), 1.55 (br s, 3H), 3.5−3.7 (m, 1H), 3.7−4.2 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) 23.2* (CH_3), 24.7 (CH_3), 26.9* (CH_3), 27.3 (CH_3), 28.6 (CH_3), 58.5* (CH), 59.6 (CH), 63.1* (CH_2), 65.2 (CH_2), 65.4 (CH_2), 80.2* (C), 81.3 (C), 94.2 (C), 152.0* (C), 154.2 (C); IR (film) 3011, 1656, 1405 cm^{-1}; HRMS (ESI) m/z calcd for [$C_{11}H_{21}NO_4$ + Na] 254.1363, found 254.1359.

1,1-Dimethylethyl (*R*)-4-(4-Bromobenzoyloxymethyl)-2,2-dimethyl-3-oxazolidinecarboxylate [(*R*)-6]. To a solution of alcohol (*S*)-**5** (0.30 g, 1.30 mmol) in CH_2Cl_2 (3.0 mL) were added 4-bromobenzoyl chloride (0.43 g, 1.95 mmol), DMAP (16 mg, 0.13 mmol), and Et_3N (0.27 mL, 1.95 mmol), and the solution was stirred overnight. The reaction mixture was diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude oil was purified by flash column chromatography (5% EtOAc/hexane to 10% EtOAc/hexane) to give 0.38 g (70%) of a light yellow to colorless oil that solidified with cold storage: mp 48−49 °C; R_f 0.53 (20% EtOAc/hexane); SFC (2% MeOH) 3.97 min (major enantiomer), 5.31 min (minor enantiomer); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s), 1.50 (s), 1.53 (s), 1.57 (s), 1.62 (s), 3.90−4.10 (m, 3H), 4.20−4.50 (m, 3H), 7.59 (m, 2H), 7.91 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer*) δ, 23.3* (CH_3), 24.5 (CH_3), 26.9* (CH_3), 27.8 (CH_3), 28.6 (CH_3), 55.8 (CH), 56.0* (CH), 64.2 (CH_2), 65.3 (CH_2), 65.5* (CH_2), 77.5 (C), 80.5 (C), 80.8* (C), 93.9 (C), 94.5* (C), 128.3* (C), 128.5 (C), 129.0* (C), 129.1 (C), 131.4 (CH), 131.9* (CH), 132.0 (CH), 151.8* (C), 152.5 (C), 165.7* (C), 165.8 (C); IR (film) 2979, 1725, 1697, 1591 cm^{-1}; HRMS (ESI) m/z calcd for [$C_{18}H_{24}BrNO_5$ + H] 414.0911, found 414.0919; $[\alpha]^{22}_D$ = +31.3 (c = 1.0, $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information

^1H NMR spectrum for **4**, ^1H NMR spectra for crude AHF reactions, ^1H and ^{13}C NMR spectra for (*R*)-**6**, and SFC traces of (*R*)-**6** and (*S*)-**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this research from the National Science Foundation (NSF CHE 0848616) and from a Wisconsin Distinguished Graduate Fellowship (A.J.L.C.) is gratefully acknowledged.

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