Stereoselective "Pinacol" Coupling of 2,3-*O*-Isopropylidene-D-glyceraldehyde

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The use of carbohydrate-derived aldehydes as building blocks for stereoselective synthesis of polyhydroxylated alkyl moieties[1,2] can be an important alternative to other methods which might involve sequential linking of hydroxymethylene units. Pinacol coupling of sugar-derived aldehydes represents one such general, alternative methodology. However, while various low-valent metallic complexes are capable of effecting pinacol coupling of aliphatic aldehydes,[3] few of these accomplish the desired transformation with high stereoselectivity, except where considerations of large steric bulk or remote substrate coordination are involved.[4] We recently reported[5] that the simple Ti(III) reagent $(Cp_2TiCl)_2$ (**1**)[6] can accomplish highly stereoselective pinacol coupling of aromatic and unsaturated aldehydes, likely *via* a reactive monomer (**2**), which is readily obtained by dimer dissociation.[7] However, this species was not effective for analogous coupling of aliphatic aldehydes. Both halogen atom abstraction from an aliphatic halide and pinacol coupling involve reduction of the substrate, and *in situ* generated $Cp_2Zr(III)Cl$[8] (**3**) is far more reactive than **2** for halogen atom abstraction from aliphatic halides.[9] Therefore, we examined the possibility that a Zr(III) reagent could effect pinacol coupling of a relatively unreactive aliphatic aldehyde. Indeed we find that $(Cp_2ZrCl)_2$[10] (**4**) can be used to pinacol couple a simple aliphatic aldehyde, for example 2,3-*O*-isopropylidene-D-glyceraldehyde, in good yield and with high diastereoselectivity, in a process which might involve reactive monomer **3**.

Reduction of Cp_2ZrCl_2 with 10% Na(Hg) gives **4** as a deep red, oxygen sensitive complex. While Ti(III) dimer **1** is easily dissociated to monomer **2** by reaction with a broad range of donor ligands or coordinating solvents,[7] these ligands (even in excess) failed to cleave **4** to monomeric **3** in any quantity readily detectable by EPR analysis; indeed, the observed diamagnetism of **4** has been postulated to derive from strong Zr−Zr bonding.[11] One electron reduction capability does exist for **4**. This was demonstrated by its reaction with 6-bromo-1-hexene, which gave, following D_2O workup, 1-hexene-*d* and methylcyclopentane-*d* (1:1), or with 4-(2-bromophenyl)-1-butene which gave, following D_2O workup, 1-methylindane-*d*, consistent with a radical mechanism for activation of the C−Br bond. Significantly, while *in situ* generated **3** reacts rapidly with 6-bromo-1-hexene (reaction time 1−10 min at room temperature[8]), **4** requires 7−10 h at room temperature for reaction completion. It may be that dissociation of **4** to **3**, or the creation of a vacant site on **4** by dissociation of a chloride ligand, is rate determining, overall, for reaction with the alkyl halide.

Ti(III) dimer **1** reacts rapidly with benzaldehyde, even below room temperature, to accomplish diastereoselective pinacol coupling;[5] however, a similar procedure using **4** and benzaldehyde occurred only slowly, even at room temperature, to give a mixture of hydrobenzoins (*dl*:meso = 65:35).[12] The low rate of reactivity of **4** compared with **1** and the consequently higher temperature required to effect pinacol coupling (with attendant lower coupling stereoselectivity) suggest that, as for alkyl halide activation, dissociation of **4** to **3**, or the creation of a vacant site by dissociation of a chloride ligand, might be rate determining for pinacol coupling, overall. The inherent reactivity of Zr(III) as a reducing agent, however, is greater than that of Ti(III): whereas **1** did not appreciably react with aliphatic aldehydes or ketones at room temperature, **4** readily coupled such species, albeit slowly. Significantly, **4** could accomplish pinacol coupling of 2,3-di-*O*-isopropylidene-D-glyceraldehyde with good stereoselectivity. Analysis by NMR showed a 1:1 mixture of the di-*O*-isopropylidene derivatives of mannitol[13] and iditol[13] if the reaction was performed at room temperature. However, if reagents were mixed at −78 °C, and then the mixture was allowed to warm only to 0 °C, then 1,2:5,6-di-*O*-isopropylidene-D-mannitol was the dominant product (mannitol:iditol > 7:1) (Scheme 1). The stereoselectivity of pinacol coupling observed for this simple carbohydrate suggests that similar procedures might be applicable for efficient preparation of higher carbohydrate derivatives, for use in synthesis of end products with interesting biological properties.[1,2] Accordingly, we are examining methods for the activation of the Zr(III) dimer.

Experimental Section

Reduction procedures were performed under inert atmosphere. Organic substrates were purchased from Aldrich Chemical and were purified prior to use. Solvents were distilled from sodium benzophenone ketyl. NMR spectra were recorded on a General Electric QE300 (300 MHz) spectrometer. EPR spectra were recorded on a Bruker ESP 300 spectrometer with *g*-values referenced to 2,2-di(4-*tert*-octylphenyl)-1-picrylhydrazyl (DOPH) as internal standard (sealed capillary, $g = 2.004$). The EPR spectrometer was routinely operated at microwave powers of 0.2−0.5 mW; no saturation was observed. Field modulations were kept below 0.2 G in order to ensure full resolution of the

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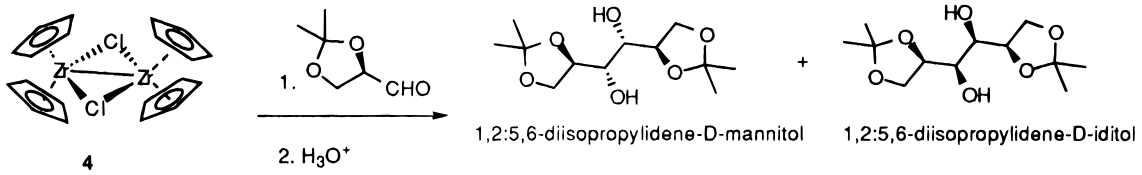
Scheme 1. Coupling of 2,3-Di-*O*-isopropylidene-D-glyceraldehyde



spectra. Flash chromatography was done using EM Science silica gel 62 (60−200 mesh).

Preparation of $(Cp_2ZrCl)_2$ (4).[10] Zirconocene dichloride 2.92 g (10 mmol) was dissolved in 250 mL of THF. A slight excess (1.05 equiv) of 10% Na(Hg) (2.40g, 10.5 mmol) was added to the colorless solution, and the reaction was stirred overnight. The resulting red mixture was filtered, and the solvent was removed *in vacuo*. After 24 h under vacuum, a red solid was collected to give 1.39 g of $(Cp_2ZrCl)_2$ as a dark red solid (54%). For **4**, ^{1}H NMR (300 MHz, C_6D_6): δ 5.13 (s, 10H). No EPR signal was visible for 1.56×10^{-3} M solutions in THF, pyridine (neat), or diphenylmethylphosphine (neat).

Pinacol Coupling of Benzaldehyde. Dimer **4** (0.515 g; 1.00 mmol, 2.04 equiv Zr) was dissolved in 10 mL of THF under inert atmosphere. Benzaldehyde (100 μL; 0.98 mmol) dissolved in 10 mL of THF was placed in a dropping funnel. The flask containing **4** was cooled to −78° C, and the benzaldehyde/THF solution was added dropwise over several minutes. After 1 h, the ice-bath was removed, and the reaction was allowed to slowly warm to room temperature. After 30 min, the resulting orange solution, containing a yellow precipitate, was quenched by pouring into 40 mL of 1 N NaOH and was extracted with ether. The organic fraction was dried over Na_2SO_4, filtered, and concentrated to give a slightly yellow solid. Chromatography on silica gel gave gives 84 mg of colorless solid (80% yield). ^{1}H NMR analysis (300 MHz, $CDCl_3$) showed a 65:35 mixture of *dl:meso* 1,2-diphenyl-1,2-ethanediols.[12] For the *dl* diastereomers: δ 7.36−7.19 (m, 10H); 4.66 (s, 2H); 2.79 (broad s, 2H). For *meso*-1,2-diphenyl-1,2-ethanediol, δ 7.36−7.19 (m, 10H); 4.82 (s, 2H); 2.79 (broad s, 2H).

Pinacol Coupling of Valeraldehyde. Valeraldehyde (220 μL, 2.07 mmol) dissolved in 10 mL of THF was added slowly at −78 °C to 1.24 g of $(Cp_2ZrCl)_2$ (2.41 mmol) in 10 mL of THF, and the mixture was allowed to stir overnight as it slowly warmed to room temperature. The clear, golden-colored solution was quenched with 40 mL of 1 N HCl and was extracted with ether. The organic fraction was dried and concentrated to give a pale yellow residue. Recrystallization gave 119 mg (66%) of colorless crystals, which ^{1}H NMR analysis (300 MHz, acetone-d_6; 1 drop of D_2O added) showed to be a *dl:meso* mixture (88:12).[14] For *dl*-decane-5,6-diol: δ 3.28 (d, 2H); 1.47−1.24 (m, 12H); 0.85 (t, 6H); for *meso*-decane-5,6-diol: δ 3.35 (d, 2H); 1.51−1.25 (m, 12H); 0.86 (t, 6H).

Pinacol Coupling of Acetophenone. Acetophenone (120 μL; 1.03 mmol) dissolved in 5 mL of THF was added dropwise to a solution of 0.582 g (1.13 mmol) $(Cp_2ZrCl)_2$ in 10 mL of THF. The reaction mixture was allowed to stir at room temperature over 3 days during which time the red color changed to orange. The product, containing a white precipitate, was quenched with 1 N NaOH and was extracted with ether. The organic fraction was dried, filtered, and concentrated to give an orange residue. Chromatography (silica gel), eluting first with 20:1 hexanes:Et_2O followed by (1:1) hexanes:Et_2O, gave 97 mg (78%) colorless solid. ^{1}H NMR analysis (300 MHz; acetone-d_6) showed a 1:1 mixture of *dl:meso* diastereomers.[12] For *dl*-2,3-diphenyl-2,3-butanediol: δ 7.17−7.12 (m, 10H); 1.49 (s, 6H). For *meso*-2,3-diphenyl-2,3-butanediol: δ 7.17−7.12 (m, 10H); 1.46 (s, 6H).

Pinacol Coupling of 1,2-Di-*O*-isopropylidene-D-glyceraldehyde. A solution of 0.26 g (2.00 mmol) of 1,2-di-*O*-isopropylidene-D-glyceraldehyde in 10 mL of THF was added dropwise to a solution of 1.20 g of $(Cp_2ZrCl)_2$ (2.34 mmol, 1.17 equiv Zr) in 20 mL of THF at −78 °C. The red solution was allowed to stir overnight while the ice-bath warmed to room temperature. The orange mixture was hydrolyzed with 40 mL of 1 N NaOH and was extracted with ether. The organic fraction was dried and concentrated to give a pale yellow residue. ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the product showed a mixture of diastereomers. The glycols were converted to the corresponding tri-*O*-isopropylidene derivatives (Amberlite IR-120[plus] ion-exchange resin, acetone, $CuSO_4$) and were analyzed by GC, which showed a 7.3:1 (88:12) mixture of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol and 1,2:3,4;5,6-tri-*O*-isopropylidene-L-iditol (combined yield 51%) by comparison with authentic materials. (The standard for 1,2:3,4:5,6-tri-*O*-isopropylidene-L-iditol was prepared from L-iditol, acetone, Amberlite IR-120[plus], and $CuSO_4$. 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol was commercially available [Aldrich].) For 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol:[13] δ 4.22−4.17 (m, 2H), 4.11−4.06 (m, 2H), 4.01−3.94 (m, 4H), 1.50 (s, 6H); 1.43 (s, 6H, Me) 1.36 (s, 6H). For 1,2:3,4:5,6-Tri-*O*-isopropylidene-L-iditol:[13] 4.22−4.17 (m, 2H); 4.09−4.01 (m, 4H); 3.97−3.88 (m, 2H); 1.47 (s, 12H); 1.39 (s, 6H).

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