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SYNTHESIS OF 1,2-CYCLOALKANEDIOLS BY INTRAMOLECULAR TITANIUM-INDUCED PINACOL COUPLING

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Abstract: Seven representative 1,2-cycloalkanediols of ring size 6-14 were prepared in high yield by titanium-induced pinacol coupling of dialdehydes. Cis stereochemistry predominated in six- and eight-membered rings, but trans products were formed in ring sizes ten and above.

Although known since 1859,[1] the pinacol reductive coupling of ketones and aldehydes remains one of the least well understood and least studied of all carbon-carbon bond-forming reactions. One measure of the reaction's obscurity is that no general review has ever been published as far as we are aware.

Our own interest in the pinacol coupling reaction stems from our 1974 report[2] that ketones and aldehydes undergo deoxygenative dimerization to yield alkenes on reaction with low-valent titanium. As we demonstrated in our early paper, pinacols are intermediates in the alkene-forming process and can be isolated if the reaction is carried out under mild conditions.[3]

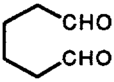
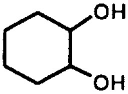
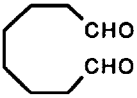
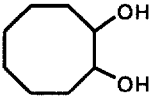
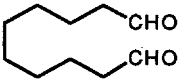
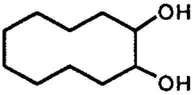
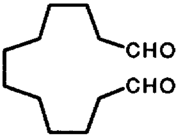
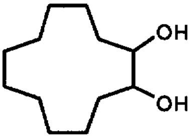
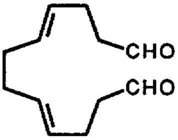
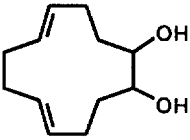
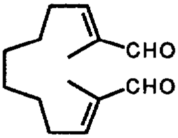
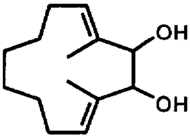
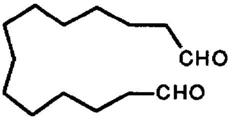
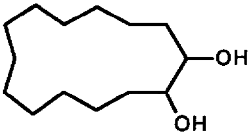
We and others have shown on numerous occasions that the real synthetic value of the titanium-induced dicarbonyl coupling lies in its ability to form *cyclo*alkenes by intramolecular reaction of dicarbonyl compounds.[4] Small-, medium-, and large-ring cycloalkenes can all be obtained in high yield. We therefore thought that it might be of synthetic interest to see if the intermediate cyclic pinacols could be isolated in useful yields. There are several such reports already in the literature,[3a,5,6,7] but no systematic study with respect to ring size and product stereochemistry has been undertaken.

The reaction does in fact work, and we now report a titanium-induced pinacol procedure for the synthesis of 1,2-cycloalkanediols. As indicated in the Table, high isolated yields of pinacol products were obtained in all cases from ring size 6 through 14. The stereochemistry of each product was determined by conversion of the diols into their acetonides and comparison of their NMR spectral data with those of authentic samples.[8] In all cases, cis acetonides showed the -CH(OR)- methine hydrogens near 4.1 δ and the acetonide methyl groups as two singlets at 1.2-1.4 δ; trans acetonides showed the -CH(OR)- methine hydrogens near 3.9 δ and the acetonide methyl groups as a singlet at 1.2 δ.

Several points need mention. First, it appears that cis stereochemistry of the product diol results when smaller rings are formed but that trans stereochemistry predominates for ring sizes ten and above. Second, it has been our experience that readily reducible functional groups such as nitro, epoxide, and sulfoxide are not compatible with low-valent titanium reactions, but that less readily reducible groups such as nitrile, ester, and amide often will survive the mild conditions.[5,9] Thus, the synthesis of highly oxygenated products via titanium-induced pinacol reaction is possible. Third, we find that the use of other titanium-based reagents such as $TiCl_4$/Mg-Hg[3a] and $TiCl_3/C_8/K$[10] results in much lower yields of pinacol products than the $TiCl_3$/Zn-Cu reagent. Third, we find that coupling of α,β-unsaturated aldehydes (entry 6) takes place with extraordinary ease and requires the use of low reaction temperatures (-50°C) to prevent deoxygenation and alkene formation.

In a representative procedure, $TiCl_3(DME)_2$[11] (4.38 g, 13.1 mmol) and Zn-Cu couple[12] (2.6 g, 40.0 mmol) were placed under argon in a flame-dried flask via a Schlenk tube. Anhydrous dimethoxyethane (DME; 50 mL) was added, the mixture was refluxed for 5 h, and tetradecanedial (0.20 g, 0.88 mol) in 50 mL DME was added at 25°C over a period of 30 h using a syringe pump. After the mixture was stirred an additional 8 h, the reaction was hydrolyzed with 70 mL of 20% aqueous K_2CO_3 for 3 h, and extracted with 1:1 ether/ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to leave pinacol product. Acetone (25 mL) and Amberlyst ion-exchange resin (0.30 g) were added, and the mixtures was stirred for 1 h. Filtration, concentration, and chromatography of the residue on silica gel gave the pinacol acetonide (210 mg, 89%) as a clear, colorless oil. Analysis by high-field NMR[13] and capillary gas chromatography indicated a cis/trans ratio of 30:70. The other examples in the Table were carried out similarly, except that the unsaturated dialdehyde in entry 6 underwent coupling at -50° rather than room temperature.

Table. Titanium-Induced Intramolecular Pinacol Coupling

Entry	*Dialdehyde*	*Pinacol*	*cis/trans Ratio*[a]	*Yield (%)*
1			100 : 0	85
2			70 : 30	82
3			25 : 75	80
4			25 : 75	75
5			5 : 95	83
6			5 : 95	84
7			30 : 70	89

[a] cis/trans ratios determined by capillary gas chromatography

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References

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2. McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708-4709.
3. The synthesis of pinacols by low-valent titanium reactions has subsequently been studied by several groups: (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; *J. Org. Chem.*, **1976**, *41*, 260-265. (b) Mundy, B. P.; Srinivasa, R.; Kim, Y.; Dolph, T.; Warnet, R. J.; *J. Org. Chem.***1982**, *47*, 1657-1661.
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5. Ghiringhelli, D. *Tetrahedron Lett.* **1983**, *24*, 287-291.
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7. Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *Chem. Commun.* **1988**, 354-356.
8. Authentic samples of cis acetonides were prepared by OsO_4 hydroxylation of the appropriate cis alkene, followed by reaction with acetone. Authentic trans acetonides were prepared similarly by hydrolysis of the corresponding epoxides.
9. We have carried out the coupling of a 1,14-ketoaldehyde to yield a 14-membered-ring pinacol product in the presence of a lactone: J. E. McMurry and R. Dushin, unpublished results.
10. (a) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1985**, *280*, 307-312; (b) Fürstner, A.; Weidman, H. *Synthesis* **1987**, 1071-1075.
11. $TiCl_3(DME)_2$ was prepared by refluxing commercially available $TiCl_3$ (25.0 g) in 350 mL dry dimethoxyethane for two days, followed by cooling and subsequent filtration of the crystalline complex under argon.
12. Zn-Cu couple was prepared by adding zinc dust (17.4 g, 266 mmol) to 75 mL of water, purging the slurry with argon (via gas-dispersion tube for 15 min), and adding $CuSO_4$ pentahydrate (2.20 g, 8.8 mmol). The black slurry was then stirred for 30 min with continued argon purging, filtered under argon, washed with argon-purged water, acetone and ether, and then dried under vacuum. The couple can be stored indefinitely under argon.
13. *Cis*-1,2-cyclotetradecanediol: ^{1}H NMR δ 1.15 (s, 3 H), 1.2 (m, 24 H), 1.25 (s, 3 H), 4.02 (d of t, 2 H, J = 9.1, 4.5 Hz); ^{13}C NMR δ 79.10 for -CH(OR)-. *Trans*-1,2-cyclotetradecanediol: ^{1}H NMR 1.2 (s, 3 H), 1.25 (m, 24 H), 3.73 (d of t, 2 H, J = 6.1, 3.3 Hz); ^{13}C NMR δ 79.52 for -CH(OR)-.

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