# On the Stereochemistry of the Titanium-Induced Intramolecular Pinacol Coupling Reaction

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Abstract: We have devised and tested a simple model for predicting the stereochemistry of the titanium-induced intramolecular pinacol coupling reaction. The model is based on molecular mechanics calculations of the dimethylsilyl acetals of the potential pinacol products.

The pinacol coupling reaction of a ketone or aldehyde to yield a 1,2-diol is one of the oldest known carbon-carbon bond-forming reactions,[1] yet few studies of the reaction have been carried out, and no major review of the reaction has been published. The intramolecular variant of the reaction has received even less attention, even though the cyclic 1,2-diol products are valuable intermediates for further transformation into epoxides, ketones, allylic alcohols, and alkenes.
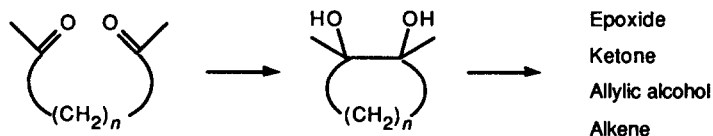
We have previously reported[2] experimental conditions for carrying out mild and high-yielding intramolecular pinacol coupling reactions to give diol products with a variety of ring sizes and with a variety of functional groups present in the substrate. There remains, however, the problem of stereochemistry. In the absence of any stereogenic centers in the substrate, two diol products are possible – cis and trans. In the presence of other stereocenters, however, four products can be formed. We encountered just such four-component mixtures in our reported syntheses of crassin[3,4] and isolobophytolide,[4] although in both of those instances we were able to purify and use the major diol product. Related work on the SmI_2-induced pinacol coupling of substituted 1,6-dialdehydes has also been reported by Hanessian.[5]

We have now carried out a program aimed at predicting the stereochemistry of titanium-induced diol formation in complex molecules. From our own previous mechanistic work[6] and that of others,[7] we know that the titanium-induced pinacol reaction occurs by a radical coupling on a titanium particle, probably at an edge so that steric interactions are minimized.
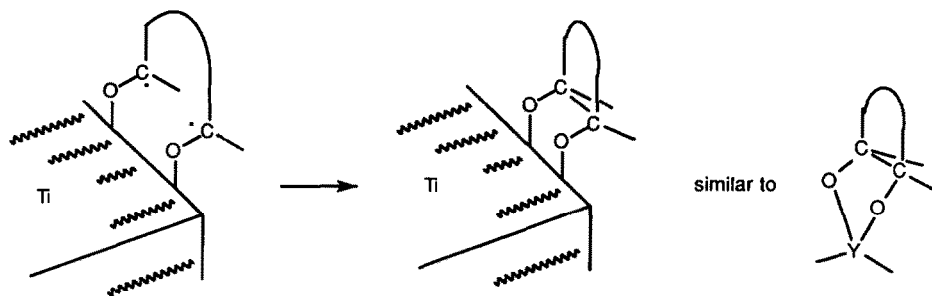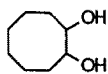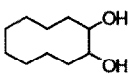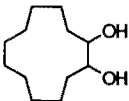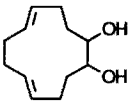
Thinking about this rough picture, we realized that the titanium/oxygen part of the cyclization is probably similar in all coupling reactions and that the product stereochemistry might therefore be controlled by steric interactions in the newly formed ring. If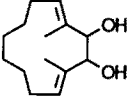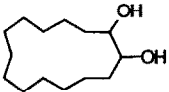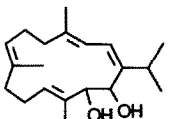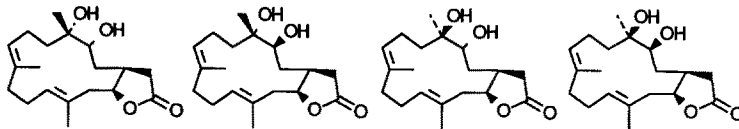 so, it might be possible to mimic the crucial steric features of different pinacol-forming transition states by carrying out molecular mechanics calculations on simple bicyclic molecules that hold the two oxygen atoms in a rigid, well-defined relationship. We cannot, of course, calculate the energies of the transition states themselves, but we have concluded after studying numerous bicyclic possibilities that the *relative* energies of the different transition states, and therefore the relative amounts of the different diol products, can be predicted by calculating the energies of the corresponding dimethylsilyl acetals. For example, using Still's MacroModel program,[89] the calculated energy difference between the minimum energy conformations of the dimethylsilyl acetals of *cis*- and *trans*-cyclodecane-1,2-diols is 3.66 kJ/mol, which predicts a cis:trans isomer ratio of 19:81 for the coupling of decanedial. The ratio of isomers actually obtained in the coupling reaction is 25:75 (Table, entry 3). Additional examples are given in the Table,[10] including the results for our published synthesis of the naturally occurring cembrane diterpene, sarcophytol B (entry 8). As predicted, the trans 14-membered diol was formed exclusively.[11]

A much more difficult test than predicting the stereochemistry of dialdehyde couplings is to predict the results obtained by coupling a complex, multifunctional molecule such as the keto aldehyde we used previously in our crassin synthesis.[4] Even here, though, the results are reasonably good. As shown in entry 9 of the Table, molecular mechanics calculations on the dimethylsilyl acetals corresponding to the four diol products correctly predict the relative amounts of three of the four.

Finally, our model accounts for the results of a recently reported *acyclic* pinacol coupling on a chiral aldehyde (entry 10) used for the synthesis of C_2 symmetric HIV protease inhibitors.[12] Three products were formed in the approximate ratio 2:1:1, and our model qualitatively predicts the product distribution.

Table: Stereochemistry of the Titanium-Induced Intramolecular Pinacol Reaction[a]

Entry	Diol	Observed ratio		ΔE (kJ/mol) (cis − trans)	Calculated ratio
1		cis trans	99 1	−4.02	83 17
2		cis trans	70 30	−1.22	41 59
3		cis trans	25 75	3.66	11 89
4		cis trans	25 75	7 02	5 95
5		cis trans	5 95	9.52	1 99
6		cis trans	5 95	3.14	1 99
7		cis trans	30 70	1.51	24 76
8		cis trans	<2 >98	10.40	2 98

9				
Observed ratio	41	37	20	2
Calculated ratio (silyl acetal)	3	74	18	5
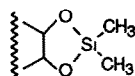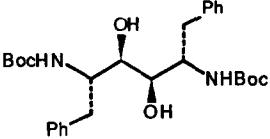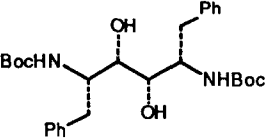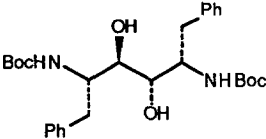
Table (continued)

10			
Observed ratio	50	25	25
Calculated ratio (Silyl acetal)	70	28	2

[a] The cis/trans energy differences (ΔE) refer to global minimum-energy conformations. The calculated ratios are based on Boltzmann distributions for all conformations with 10 kJ/mol of the global minimum.

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9. Calculations were carried out on a Silicon Graphics Crimson workstation. Global minimum energy conformations for each structure were found using the Monte Carlo torsional search algorithm of Still [Lipton, M.; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343-355] with MacroModel's implementation of the MM2 force field. All structures were inspected for isomerized double bonds and stereogenic centers. The number of conformations evaluated for each structure varied from several hundred for the small rings to 3000 for the 14-membered rings. In addition, several structures were tested using three-fold larger searches without a change in results. The ΔE values in the table refer to the cis–trans energy differences between global minima. The calculated predictions cited in the Table are based on Boltzmann distributions for all conformations with 10 kJ/mol of the global minimum.

10. We have not yet carried out coupling reactions to form 7-, 9-, and 11-membered rings, but our model predicts a 48:52 cis/trans mixture for 1,2-cycloheptanediol, a 31:69 cis/trans mixture for 1,2-cyclononane, and a 21:79 cis/trans mixture for 1,2-cycloundecanediol

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