



Studies on pinacol chemistry
by Dan R Bruss

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

Montana State University

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Abstract:

Synthetic methodology employing pinacol chemistry is explored. An investigation of the stereochemical consequences of pinacol formation as related to the method of coupling is presented. Aluminum and titanium-mediated pinacol coupling of alkyl substituted cyclohexanones are shown to exhibit distinct stereoselectivity. It is found that the aluminum procedure produces primarily axial orientation of the alkyl groups, while the titanium coupling prefers equatorial orientation. A rapid method of separation and identification of the resulting diastereomers is discussed. A pronounced alkyl substituent effect on the course of the pinacol rearrangement of cyclohexyl-3-methylcyclohexane-1,1'-diol is noted. While the exact nature of the effect is unknown, MNDO studies indicate that it does not appear to be electronic in nature. Baeyer-Villiger oxidation of spiroketones and acid catalyzed rearrangement of spiroalcohols are presented. Rearrangement of spiro-[4,5]-6-methyldecan-6-ol to 9-methyl- Δ 4,10-octalin demonstrated the potential utility of this reaction as an entry into decalin based terpenes.

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of a thesis submitted by

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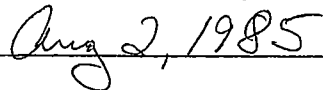
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Organic chemistry just now is enough to drive one mad. It gives me the impression of a primeval tropical forest, full of the most remarkable things; a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter.

--Friedrick Wöhler

If I have seen further than other men, it is because I stood on the shoulders of giants.

--Isaac Newton

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ABSTRACT

Synthetic methodology employing pinacol chemistry is explored. An investigation of the stereochemical consequences of pinacol formation as related to the method of coupling is presented. Aluminum and titanium-mediated pinacol coupling of alkyl substituted cyclohexanones are shown to exhibit distinct stereoselectivity. It is found that the aluminum procedure produces primarily axial orientation of the alkyl groups, while the titanium coupling prefers equatorial orientation. A rapid method of separation and identification of the resulting diastereomers is discussed. A pronounced alkyl substituent effect on the course of the pinacol rearrangement of cyclohexyl-3-methylcyclohexane-1,1'-diol is noted. While the exact nature of the effect is unknown, MNDO studies indicate that it does not appear to be electronic in nature. Baeyer-Villiger oxidation of spiroketones and acid catalyzed rearrangement of spiroalcohols are presented. Rearrangement of spiro-[4,5]-6-methyldecan-6-ol to 9-methyl- $\Delta^{4,10}$ -octalin demonstrated the potential utility of this reaction as an entry into decalin based terpenes.

CHAPTER 1

INTRODUCTION

A fundamental tenet of organic synthetic methodology is the ability to generate stereoselective formation of carbon-carbon bonds which readily allow further transformation. While few processes can approach the general applicability of a paradigm such as the Diels-Alder reaction, any process which generates more complex organic structures in a predictable way is highly desirable. As an outgrowth of the work previously carried out in our laboratory on several aspects of pinacol chemistry, it became evident that this chemistry possessed a number of attributes that could potentially expand its generality.

Since the first reported rearrangement of pinacol to pinacolone in the mid-nineteenth century,¹ this reaction has been studied extensively. At the same time, a host of methods have been developed to generate the requisite 1,2-diols. Our principal interest focused on the metal-mediated reductive coupling of cyclic ketones, followed by mineral acid rearrangement. Figure 1 summarizes this approach.

The rationale was straightforward. Coupling of the ketones afforded conversion from sp^2 hybridization to functionalized sp^3 centers. Rearrangement of the 1,2-diols would then provide

entry into functionalized quaternary centers, often a difficult synthetic task. Once formed, these spiroketones could further be modified or fully transformed.

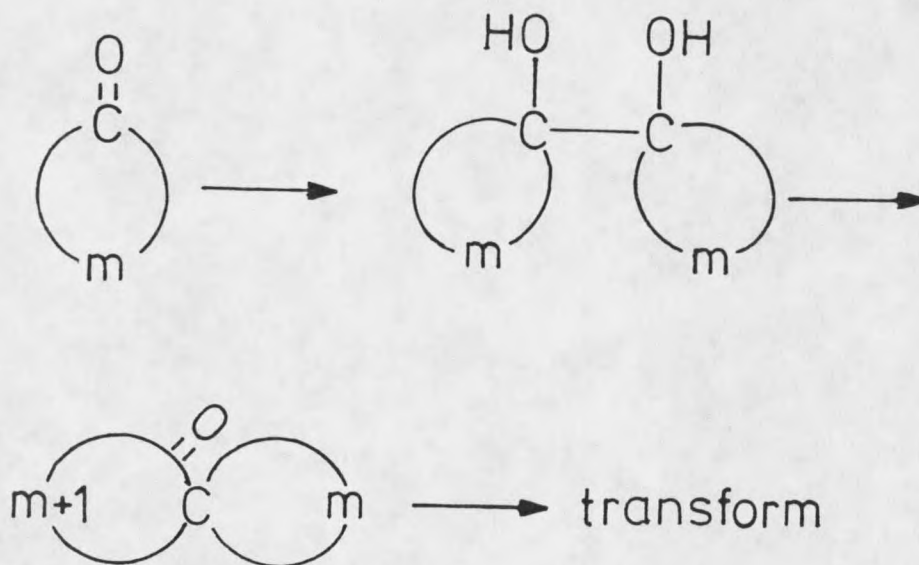


Figure 1. Generalized scheme for pinacol chemistry of cyclic ketones.

Several methods exist for effecting the reductive coupling of carbonyl compounds by zero or low valent state metals. Traditionally, aluminum amalgam^{2,3,4} has been employed to generate the 1,2-diols. More recently, McMurry⁵ has found that TiCl_3/K is an effective reducing agent which yields not diols, but alkenes. Shortly after this report, Corey and co-workers⁶ found that high yields of 1,2-glycols were formed by reacting aldehydes and ketones with a low valent titanium source generated in situ from titanium tetrachloride and magnesium amalgam.

Additional reagents have since been examined. Porta and Clerici⁷ have successfully used the mild reaction conditions of aqueous TiCl_3 to produce diols directly instead of the aforementioned alkenes. Low valent cerium has been shown by Imamota⁸ to carry out effective coupling, while Cotton et al⁹ have successfully characterized a tungsten-alkoxide complex.

Two of these procedures, when applied to the same ketone, appeared to have distinctive stereochemical consequences. In 1978, Munoz-Madrid and Pasqual⁴ reported the formation of a single product, 3, from the aluminum mediated coupling of (R)-(+)-3-methylcyclohexanone. On the other hand, Kim¹⁰ characterized 2 as the sole product when the Corey method was employed to couple the same ketone. These results are summarized in Figure 2.

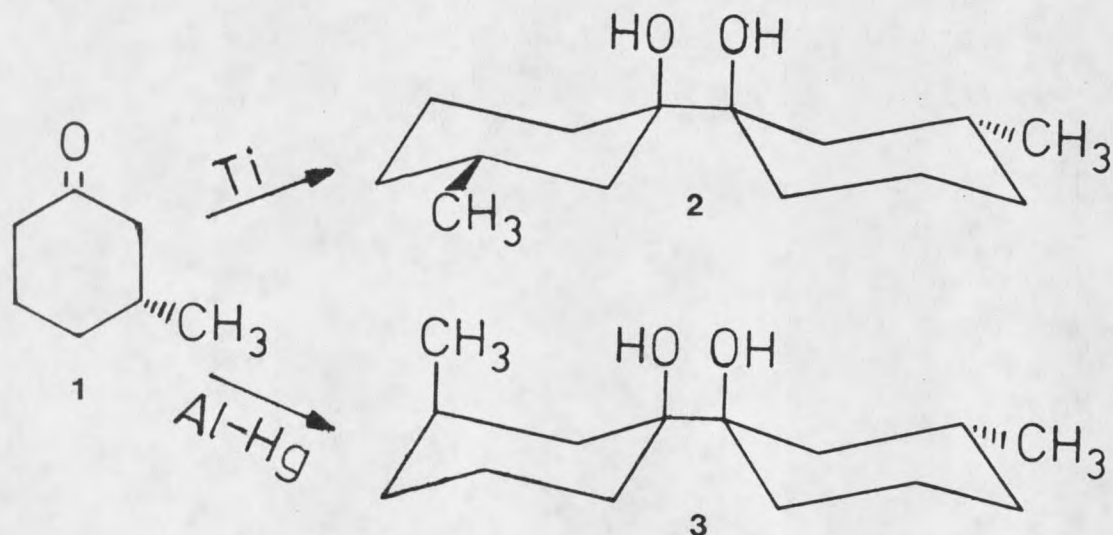


Figure 2. Reported stereospecificity in (R)-(+)-3-methylcyclohexanone self-coupling.

These results were certainly intriguing. Controlled stereochemical discrimination is a powerful asset in synthesis. This laid the groundwork for a portion of the present study.

While earlier works suggested a statistical distribution of products from a mixed reductive coupling, Mundy and co-workers¹⁰ demonstrated this not to be the case for various cycloalkanone coupling reactions. These results are summarized in Tables 1 and 2.

Table 1. Distribution of coupling products.

Cycloalkanones	Alkenes			Pinacols		
C ₅ + C ₆	C ₅ -C ₅	C ₅ -C ₆	C ₆ -C ₆	C ₅ -C ₅	C ₅ -C ₆	C ₆ -C ₆
	10.2	14.1	4.1	11.4	42.0	18.2
	<u>+0.4</u>	1.6	0.6	0.3	2.4	3.8
C ₅ + C ₇	C ₅ -C ₅	C ₅ -C ₇	C ₇ -C ₇	C ₅ -C ₅	C ₅ -C ₇	C ₇ -C ₇
	8.0	4.2	16.7	27.8	33.9	10.8
	<u>+3.7</u>	2.9	4.7	4.3	1.6	3.7
C ₆ + C ₇	C ₆ -C ₆	C ₆ -C ₇	C ₇ -C ₇	C ₆ -C ₆	C ₆ -C ₇	C ₇ -C ₇
	1.8	7.2	4.8	28.7	48.8	8.7
	<u>+1.0</u>	5.5	5.9	6.5	3.6	6.4

As mentioned earlier, acid-catalyzed rearrangement of these diols provides direct entry into the spirane skeletons. A growing number of naturally occurring spiro-compounds, several of which are illustrated in Figure 3, has prompted vigorous research in this area.¹¹

Table 2. Product distribution in the methylcyclohexanone studies.

	Olefin ^a			Pinacol ^a		
	AA	AB	BB	AA	AB	BB
2-Me-B ^C + A ^b	8.82 +0.16 <u>8.66</u>	0.83 0.16 <u>0.67</u>	11.82 0.29 <u>11.53</u>	59.13 4.36 <u>63.49</u>	20.39 1.27 <u>19.12</u>	8.01 2.15 <u>10.16</u>
3-Me-B + A	2.05 +0.90 <u>1.15</u>	4.74 1.18 <u>3.56</u>	1.75 0.76 <u>0.99</u>	26.21 2.33 <u>23.88</u>	49.61 2.12 <u>47.49</u>	15.62 5.54 <u>10.08</u>
4-Me-B + A				39.10 +7.51 <u>46.61</u>	51.97 11.88 <u>39.09</u>	8.93 5.85 <u>3.08</u>

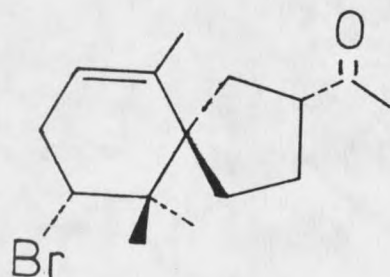
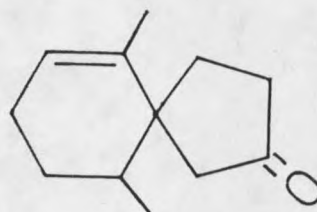
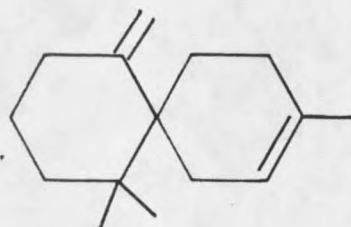
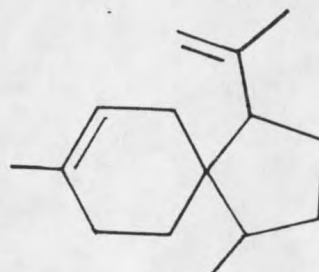
^aIn percent^bA = Cyclohexanone^cB = Methylcyclohexanonespiro[3.3]heptanone¹²spiro[3.3]heptanone¹³Chamigrene¹⁴Acoradiene¹⁵

Figure 3. Typical naturally occurring spirocompounds.

Considerable effort has been expended on understanding the pinacol rearrangement in general. Factors such as migratory aptitude of the substituents, diol stereochemistry, reaction media, product and intermediate stability, and ring effects have been studied extensively. Much of this early work has been cogently discussed.¹⁶

The effects of ring size on the course of the pinacol rearrangement have been approached from several points of view. Meerwein¹⁷ examined the rearrangement of cyclopentyl and cyclohexyl diols (Figure 4), concluding that ring expansion occurred more readily for the cyclopentyl precursors.

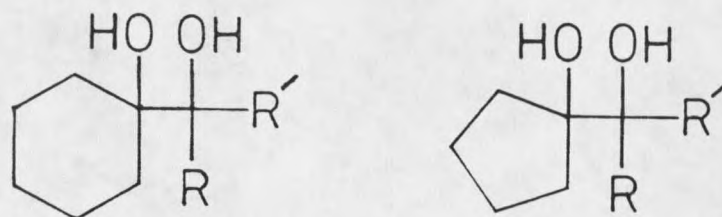


Figure 4. Cyclopentyl and cyclohexyl diols.

Botteron and Wood³ and more recently Mundy and Srinivasa¹⁸ examined the ring size effect on the rearrangement of the mixed diol, 4. Srinivasa found the reaction to be highly dependent on temperature and acid concentration. A summary of this and additional mixed diols is shown in Figure 5. Mundy and Srinivasa concluded that the formation of the initial carbocation directed the course of rearrangement. The variability of the product ratio for 4 was thought to be a matter of thermodynamic vs. kinetic control.

