A New Route to the Enantioselective Synthesis of Cycloheptenols. Temperature Effects in the Asymmetric Reductive Ring Opening of [3.2.1] Oxabicycloalkenes

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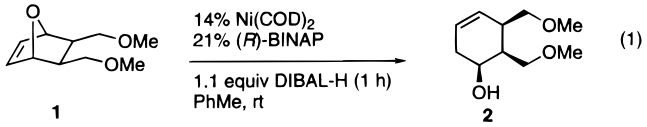
We recently reported that nickel−phosphine complexes catalyze the regioselective and enantioselective reductive ring opening of oxabicyclo[2.2.1] alkenes.[1] For example, the reaction of **1** with a DIBAL-H and $Ni(COD)_2$/BINAP system gave the substituted cyclohexenol **2** in 95% yield and 97% ee (eq 1). We have also shown that this reaction is applicable to

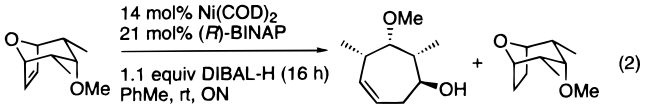


1 **2** (1)

the labile oxabenzonorbornadiene class of substrates and reported the first application of the enantioselective ring opening in a synthesis of sertraline, a medicinally important agent used to treat depression.[2]

Oxabicyclo[3.2.1] alkenes are also valuable building blocks for the construction of highly functionalized cycloheptenols which are useful precursors to polypropionate or polyacetate subunits.[3] Since there are far fewer methods reported for the enantioselective synthesis of seven-membered rings[4] we decided to investigate the applicability of the $Ni(COD)_2$/BINAP + DIBAL-H reaction to the ring opening of [3.2.1] compounds. We now report that a variety of cycloheptenols can be prepared in >90% ee by carrying out the reaction at elevated temperatures. In addition to the synthetic utility of this reaction, these results have provided new insights into the reaction pathway.

Our initial attempts at an enantioselective ring opening of [3.2.1] systems such as **3** under our standard conditions revealed two fundamental problems: while hydroalumination of the alkene was efficient, the organoalane undergoes sluggish ring opening under the reaction conditions exemplified by low chemical yields of cycloheptenol **4**, eq 2. Furthermore, the



3 **4** 20%, 56% ee **5** 70% (2)

product is obtained in 56% ee. The yield could be improved by adding a Lewis acid and heating the reaction to 80 °C following the hydroalumination step, but this typically gave the product in even lower ee (44%).[5]

After examining several parameters including solvent, additives, and the ligand, we found that the reaction gives improved yields and ee's at 60 °C rather than room temperature. For example, treatment of **3** with DIBAL-H, added slowly in the presence of 14 mol % $Ni(COD)_2$ and 24 mol % (*R*)-BINAP at 60 °C, gave **4** in 83% isolated yield with 97% ee (Table 1, entry 1). While ee vs temperature effects of this kind have previously been observed in other catalytic asymmetric processes,[6] this effect was particularly dramatic with these substrates. Possible causes for the increase in selectivity are discussed below following a survey of the scope of the reaction.

The data in Table 1 illustrate several features of the reaction. A variety of commonly used protecting groups are tolerated, entries 1, 2, and 8. While the initial conditions we examined utilized 14 mol % $Ni(COD)_2$, as little as 1−4 mol % of the catalyst is sufficient to achieve good enantioselectivities if the DIBAL-H is added more slowly (Table 1, entries 3, 5, and 6). Protection of the hydroxyl group is unnecessary as shown by the reaction with **8**, which also gives the highest enantioselectivity we have obtained to date (99.5%) with 3.0 mol % of catalyst (entry 5). Oxabicyclic **10** undergoes ring opening with similar enantioselectivity as does the epimeric substrate **12** (P = Bn) showing that both exo and endo substitution (and likely conformational changes) are well tolerated in the reaction. Compound **13** (P = Bn) is closely related to a key intermediate in our synthesis of the mevinic acid lactone.[7] We previously acetylated the meso diol **13** (P = H) then used an enantioselective enzymatic hydrolysis reaction, but our new methodology achieves the same ultimate goal in four fewer steps.

The improvement in ee with increasing temperature was particularly noticeable with the tricyclic alkene **14** (Table 2). Conducting the hydroalumination at 60 °C gave **15** in 81% ee, which was better than the result at room temperature, but was still significantly lower than the results presented in Table 1. Raising the temperature to 75 or 80 °C led to further improvement in the ee, but at 85 °C the ee began to decrease.

Reductive opening of the oxabicyclic **12** illustrates the combined effects of high temperature *and* added phosphine most clearly (Scheme 1). Alkene **12** was treated in toluene at 60 °C with DIBAL-H (added over 4 h) in the presence of $Ni(COD)_2$, $Ni(COD)_2$ and BINAP (entry 7 in Table 1), and $Ni(COD)_2$ and dppb (1,4-bis(diphenylphosphino)butane). In the absence of a phosphine the major product was **17** accompanied by **13** and some overreduced material **16**. With an achiral or chiral phosphine, **13** was the only product observed. Adding a phosphine to the reaction after hydroalumination was complete had no effect on the ratio of products.

In our original report, we provided clear evidence to support a two-step process involving nickel-catalyzed hydroalumination

(1) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532.

(2) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246.

(3) For a comprehensive discussion of the use of oxabicyclic substrates in synthesis, see: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

(4) For selected references to the synthesis of seven-membered carbocycles, see: Maier, M. E.; Langenbacher, D.; Rebien, F. *Liebigs Ann.* **1995**, 1843 and references therein. Lautens, M. *Synlett* **1993**, 177 and references therein. Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, p 41. For enantioselective routes toward functionalized seven-membered carbocycles, see: Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615. Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831. Enders, D.; Wiedemann, J.; Bettray, W. *Synlett* **1995**, 369. Lautens, M.; Gajda, C. *J. Chem. Soc., Chem. Commun.* **1993**, 1193. Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320. Yoshizaki, H.; Yoshioka, K.; Sato, Y.; Mori, M. *Tetrahedron* **1997**, *53*, 5433.

(5) We found that splitting a solution of the product from an asymmetric hydroalumination (carried at room temperature) into two portions, quenching one fraction under typical conditions while heating the second to 80 °C in the presence of an excess of DIBAL-Cl, gave the ring opened product but with different ee's. In the fraction that was immediately quenched, the cycloheptenol was isolated in low yield but with 56% ee. In the half that was heated before it was quenched, the cylcoheptenol was isolated as the major product but the ee was only 44%. Clearly heating would not lead to the increases in ee we now report, further supporting the proposal that a trialkylalane is not produced during the reaction at 60 °C.

(6) (a) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329. (b) Marko, I. E.; Chesney, A.; Hollinshead, D. M. *Tetrahedron Asym.* **1994**, *5*, 569. (c) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515. (d) Vigneron, J. P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939. (e) Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163. (f) Heller, D.; Buschmann, H.; Scharf, H.-D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1852. (g) For a review discussing the isoinversion principle, see: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

(7) Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, *36*, 4185.

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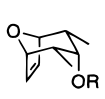
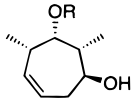
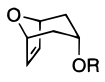
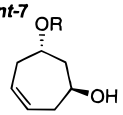
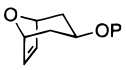
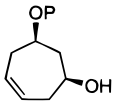
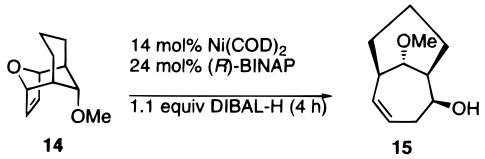
Table 1. Enantioselective Ring Opening of Oxabicycloalkenes

Entry[a]	Subtrate	Product	Yield[c]	ee[d]
				
1	**3** R=Me	**4** R=Me	83-95	97
2	**6** R=TIPS	**7** R=TIPS	87	>95
3[e]	**6**	***ent*-7**	95	91
				
4	**8** R=H	**9** R=H	89	96
5[f,g]	**8**	**9**	99	99.5
6[f,h]	**8**	**9**	83	98
7	**10** R=Me	**11** R=Me	67	95
				
8	**12** P = Bn	**13** P = Bn	88	95

[a] Reactions were run in the presence of 14 mol % $Ni(COD)_2$ and 24 mol % (*R*)-BINAP with slow addition of DIBAL-H to a solution of $Ni(COD)_2$, (*R*)-BINAP, and the alkene in toluene *via* syringe pump over 4 h at 60 °C (oil bath), unless otherwise noted. [b] DIBAL-H added over 16 h. [c] Isolated yield. [d] Determined by capillary GC (Chiraldex G-TA or B-TA column) or HPLC (Chiralcel OD or OJ column) or Mosher's method. [e] 4 mol % $Ni(COD)_2$, 8 mol % (*S*)-BINAP was used and DIBAL-H was added over 12 h at 65 °C. [f] The alcohol was pretreated with 1 equiv of DIBAL-H. [g] 3.0 mol % $Ni(COD)_2$, 5.4 mol % (*R*)-BINAP with DIBAL-H added over 12 h at 65 °C. [h] Reaction on 9 mmol scale using 1 mol % $Ni(COD)_2$ and 1.9 mol % BINAP.

Table 2. Temperature Effects on Enantioselective Opening of **14**



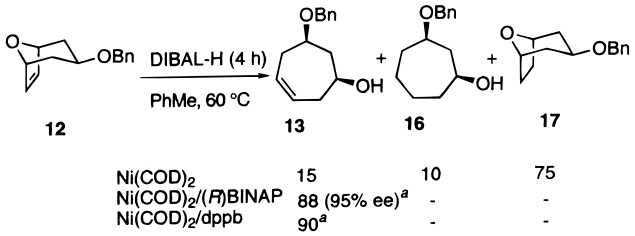
14 **15**

entry	solvent	temp, °C	yield[a]	ee[b]
1	PhMe	rt	20	56
2	PhMe	60	87	81
3	PhMe	75	67	90
4	PhMe	80	74	94
5	PhH	80	74	97
6	PhMe	85		76

[a] Isolated yield. [b] Measured by capillary GC (Chiraldex G-TA).

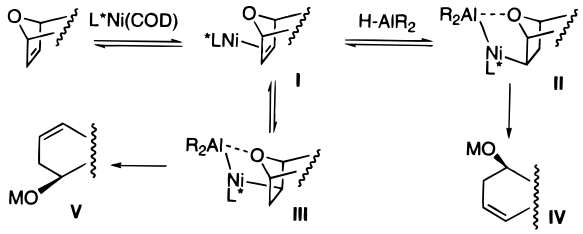
followed by a ring opening of the organoalane. For example, we could show the organoalane was formed by converting the C−Al bond to a C−O or C−D bond. Addition of an excess of a Lewis acid to the organoalane assisted in the ring-opening step, and in some cases the Lewis acid was essential to achieve high yields of ring-opened products.[1,7] However, we now find that by adding DIBAL-H slowly to $Ni(COD)_2$/BINAP in the presence of the alkene at 60 °C we fail to observe any products indicative of the formation of the organoalane. It is not simply that the organoalane opens too quickly under the reaction conditions to be observed since we have previously shown that if we generate the organoalane at room temperature in the absence of a phosphine ligand and then warm it to 60 °C (in the presence or absence of the phosphine), the ring-opened product is formed more slowly and in lower yield and ee than

Scheme 1



[a] Isolated yield. No other products visible in crude by 400-MHz NMR.

Scheme 2



we observe under our modified conditions. We must conclude that the organoalane is not along the pathway when the reaction is carried out at elevated temperatures in the presence of a phosphine.

The effect of added phosphine and ee vs temperature can be explained if the hydronickelation step is reversible at higher temperature, i.e. **II** and **III** interconvert through **I** faster than reductive elimination to the organoalane (Scheme 2). We then assume β-elimination of the oxygen from an organonickel species occurs at a rate that is also faster than reductive elimination. The precise location of the aluminum during these events is not known. Coordination to the bridging oxygen might be possible, which would trigger the β-elimination thereby playing the same role as externally added Lewis acids to the organoalane.[8]

In conclusion, we have observed a temperature and ligand effect in the enantioselective reduction reaction that has important synthetic and mechanistic consequences in our development of a highly enantioselective route to cycloheptenols. The use of achiral phosphines and higher temperatures provides a much improved method of reductive ring opening of oxabicyclic compounds. Further mechanistic investigations and application of this methodology in natural product synthesis are currently underway.

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Supporting Information Available: Experimental details and full characterization are available for all compounds (20 pages). See any current masthead page for ordering and Internet access instructions.

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(8) For a discussion of the various mechanistic possibilities we have considered and the uncertainties surrounding the existence of a Ni−Al species, see: (a) Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478. (b) Eisch, J. J.; Ma, X.; Singh, M.; Wilke, G. *J. Organomet. Chem.* **1997**, *527*, 301. (c) Pörschke, K.-R.; Kleimann, W.; Tsay, Y.-H.; Krüger, C.; Wilke, G. *Chem. Ber.* **1990**, *123*, 1267. At this point we have no evidence to preclude a pathway involving enantioselective insertion of the nickel into the bridging C−O bond.