Nickel-Catalyzed Hydroalumination of Oxabicyclic Alkenes. Ligand Effects on the Regio- and Enantioselectivity

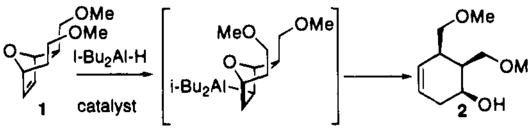
Mark Lautens,*[,1a] Pauline Chiu,[1b] Shihong Ma, and Tomislav Rovis

Department of Chemistry, University of Toronto
Toronto, Ontario, Canada M5S 1A1

Received June 13, 1994

Metal-catalyzed hydrometalations are of intense interest in organic synthesis because an increase in the rate of the hydrometalation is accompanied by dramatic changes in regio- and stereoselectivity.[2−4] For example, hydroboration promoted by rhodium or iridium catalysts and hydrosilylation using palladium complexes have emerged as important strategies for the stereo- and enantioselective syntheses of secondary alcohols.[5,6] By comparison, nickel-promoted hydroalumination has not gained wide use in synthesis despite the fact that nickel catalysts were among the first to be shown to accelerate the hydroalumination of alkenes and alkynes.[7,8]

We have been investigating the electrophilicity of the alkene in oxabicycloheptenes and octenes toward organolithium and hydridic reagents.[9] The highly substituted cyclohexenols and cycloheptenols are valuable intermediates in organic synthesis.[10] The studies described herein were initiated with the goal of developing a catalytic asymmetric ring opening. In considering new approaches for the reductive ring opening, we have examined a metal-catalyzed hydrometalation−β-elimination approach, eq 1.



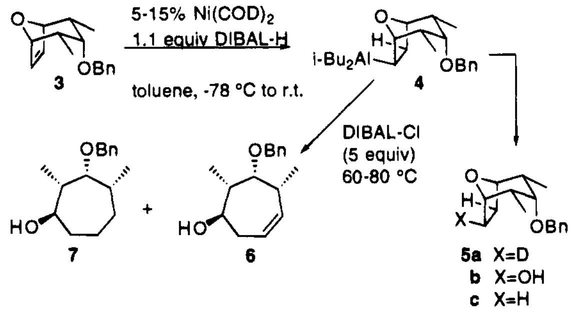
(1)

We now report that the nickel-catalyzed hydroalumination is the best method for achieving this transformation. As well as a significant increase in the rate and efficiency of the process, nickel catalysts and monodentate or chiral bidentate phosphine ligands control the regioselectivity and enantioselectivity culminating in the synthesis of cyclohexenol **2** in up to 97% enantiomeric excess (ee).

Hydroalumination of oxabicyclic alkenes occurs at temperatures as low as −78 °C in the presence of nickel catalysts. Reaction of **3** with DIBAL-H (1.1 equiv) in the presence of 5−15 mol % of $Ni(COD)_2$ is complete within a few minutes at room temperature, Scheme 1. By comparison, reaction of **3** with 5 equiv of DIBAL-H in the absence of nickel required extended heating at 50−70 °C.

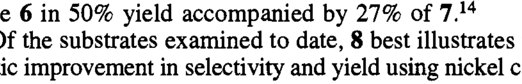
The hydroaluminated intermediate was identified by treating **4** with D_2O/D_2SO_4 to yield the monodeuterated product **5a** in 77% yield.[11] Exposure of the organoalane **4** to oxygen gave the exo alcohol **5b** in 42% yield. These experiments also confirmed the stereochemistry of the hydrometalation step.[12]

Scheme 1



The organoalane was converted to the ring-opened product **6** in one of two ways. Simply heating a solution of **4** at 70 °C for 12−16 h led to a mixture of **6**, **7**, and **5c**. Much better results were obtained when **4** was heated in the presence of a Lewis acid.[13] DIBAL-Cl (5 equiv) was the most efficient and gave **6** in high yield, with minimal formation of **7** (<5%) arising from hydroalumination of **6**. In contrast, reaction of **3** with 6 equiv of DIBAL-H in refluxing hexane in the absence of nickel gave **6** in 50% yield accompanied by 27% of **7**.[14]

Of the substrates examined to date, **8** best illustrates the dramatic improvement in selectivity and yield using nickel catalysts, eq 2. In the absence of nickel, a 1:1 ratio of **9** and **10** was formed. Using 12 mol % $Ni(COD)_2$, a 1:1 ratio of **9** and **11** was obtained. The optimized conditions involved addition of DIBAL-Cl to the hydroaluminated intermediate followed by



(2)

---

(1) (a) E. W. R. Steacie Fellow 1994−1996, Alfred P. Sloan Foundation Fellow 1991−1994, NSERC (Canada) University Research Fellow 1987−1997, Bio-Mega Young Investigator 1990−1993, Eli Lilly Grantee 1992−1994. (b) NSERC Postgraduate Scholar 1989−1992, Ontario Graduate Scholar 1992−1993.

(2) For a recent review of metal-catalyzed hydrosilation, see: Hiyama, T.; Kusumoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, p 763 and references therein.

(3) Metal-catalyzed hydroboration: Mannig, D.; Noth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. For a review, see: Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. For discussions on the mechanism, see: Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679 and references therein.

(4) Hydrostannation: (a) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468. (b) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881. (c) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (d) Miyake, H.; Yamamura, K. *Chem. Lett.* **1992**, 1099. (e) Koerber, K.; Gore, J.; Vatele, J.-M. *Tetrahedron Lett.* **1991**, *32*, 1187. (f) Casson, S.; Kocienski, P. *Synthesis* **1993**, 1133.

(5) Enantioselective hydroboration: (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 231. (c) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5178.

(6) Enantioselective hydrosilation: (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Tamao, K.; Tohma, T.; Inui, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333. (c) Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2335.

(7) For a recent review of alkene and alkyne hydroalumination, see: Eisch, J. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, p 733. For seminal references, see: (a) Ziegler, K.; Holzkamp, E.; Breil, H.; Martin, H. *Angew. Chem.* **1955**, *67*, 543. (b) Eisch, J. J.; Foxton, M. W. *J. Organomet. Chem.* **1968**, *12*, 33. (c) Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 943. (d) Eisch, J. J.; Rhee, S.-G. *J. Am. Chem. Soc.* **1974**, *96*, 7276. (e) Eisch, J. J.; Fichter, K. C. *J. Organomet. Chem.* **1983**, *250*, 63 and ref 20.

(8) (a) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185. (b) For an early attempt at asymmetric hydroalumination, see: Giacomelli, G.; Bertero, L.; Lardicci, L. *Tetrahedron Lett.* **1981**, *22*, 883.

(9) For recent papers using oxabicyclic precursors, see: (a) Lautens, M. *Synlett* **1993**, 177. (b) Lautens, M. *Pure Appl. Chem.* **1992**, *64*, 1873 and references therein. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett.* **1990**, 173. For studies illustrating the utility of cyclohexenols, see: Arjona, O.; de Dios, A.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906.

(10) For examples of the importance of functionalized cyclohexanes in organic synthesis and the approaches to prepare them, see: (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779. (b) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129. (c) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715.

(11) The similar product was obtained using **3** (protected as the TBDMS ether), DIBAL-D/ $Ni(COD)_2$ followed by an H_2O/H_2SO_4 quench.

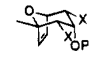
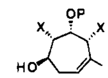
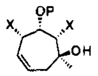
(12) In this reaction, the catalyst was $Ni(acac)_2$ rather than $Ni(COD)_2$. The remaining product was **5c**.

(13) Lewis acids have been reported to accelerate the fragmentation in the product following hydroboration of 2,5-dihydrofuran, see: (a) Zweifel, G.; Plamondon, J. *J. Org. Chem.* **1970**, *35*, 898. (b) Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 3002.

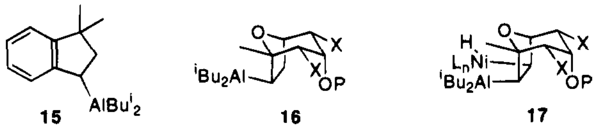
(14) A 65% yield of **6** could be obtained if the reaction was stopped prior to the complete consumption of the starting material.

0002-7863/95/1517-0532$09.00/0

Table 1. Effect of Ligand on the Regioselectivity

entry	substrate	products[a]		yield[b] (ratio)
				
1	**12a**, X = Me, P = TBS	**13a**	**14a**	72%[c] (1:6.4)
2	**12a**, X = Me, P = TBS	**13a**	**14a**	71%[d] (9.4:1)
3	**12b**, X = Me, P = H	**13b**	**14b**	75%[c] (1:1.3)
4	**12b**, X = Me, P = H	**13b**	**14b**	72% (28.5:1)
5	**12c**, X = H, P = H	**13c**	**14c**	74%[c] (1:1.1)
6	**12c**, X = H, P = H	**13c**	**14c**	87% (15.5:1)

[a] Typical conditions: 10 mol % $Ni(COD)_2$, 30 mol % Ph_3P, 1.1–2.5 equiv of DIBAL-H, toluene. [b] Isolated yield of the mixture of products; ratio determined by proton NMR. [c] Ratio in the absence of catalyst and ligand. [d] 35 mol % $Ni(COD)_2$, 1.35 equiv of DIBAL-H.



15 **16** **17**

Figure 1.

heating to 60 °C for 6 h to give **9** in 85% isolated yield. We have successfully converted **9** to a mevinic acid lactone derivative.[15]

The principal advantage of using metal catalysts in this transformation is the ability to modify the selectivity by the addition of ligands, Table 1. Control of this kind is not possible using DIBAL-H in the absence of nickel.[16] For example, whereas treatment of **12a** with DIBAL-H in refluxing hexanes favored the formation of **14a**, addition of catalytic $Ni(COD)_2$ and Ph_3P gave predominantly **13a**.[17a] Thus, reversal in the regioselectivity was achieved by the addition of phosphine to the nickel catalyst. Similar effects were also noted with alcohols **12b** and **12c**.[17b]

The preferential formation of **13a–c** is intriguing considering the earlier work of Eisch, who showed that dimethylindene undergoes regioselective hydroalumination in the presence of triphenylphosphine.[7d] Whereas **15** was formed with >99:1 regioselectivity, **13a–c** can only have arisen from **16**, in which the sense of the hydroalumination is opposite to that observed with dimethylindene (Figure 1). The regioselectivity results we obtained can be explained by considering that addition of the Al–Ni bond precedes reductive elimination of the Ni–H bond. By invoking the formation of **17**, the increase in regioselectivity which accompanies addition of phosphine can be explained since the more bulky nickel moiety is further removed from the bridgehead group.[18]

It is remarkable that the nickel which catalyzes the first hydroalumination does not catalyze a second hydroalumination of the product alkene in **2**, **6**, or **9**. Clearly the difference in the rate of hydroalumination vs fragmentation is an important factor.[19] Additionally, the excess DIBAL-H may be reacting with the displaced COD ligand to remove any traces of reducing agent prior to the ring opening. Furthermore, the nickel(II) species formed from the oxidative addition with DIBAL-H may be reacting with any excess DIBAL-H to form an inactive aluminum nickelide.[20] In both scenarios, there is neither an active catalyst nor any dialkylaluminum hydride available for a second hydroalumination, leading to improved yields of the desired products.

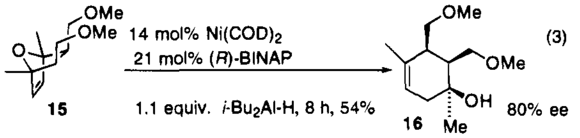
Table 2. Enantioselective Ring Opening of 1 to 2

entry	amount (mol %) $Ni(COD)_2$	amount (*R*)-BINAP (mol %)	time[a]	ee[b] (%)
1	14	21	<1 min	56
2	14	21	7 min	82[c]
3	14	21	1 h	97[d]
4	7	10.5	2 h	92
5	7	9	2 h	87
6	4	6	8 h	92

[a] Addition time to add DIBAL-H to a solution of **1**, $Ni(COD)_2$, and BINAP. Workup after 1–3 h. [b] Measured by preparing the Mosher ester or by capillary GC (Chiraldex G-TA column). [c] Isolated yield of pure product, 78%. [d] Isolated yield of pure product, 97%.

Catalytic asymmetric hydrometalation was achieved when DIBAL-H (1.1 equiv) was added via syringe pump to a mixture of the catalyst, (*R*)-BINAP, and substrate **1** at room temperature. A delicate balance between the amount of catalyst and the rate of addition must be maintained in order to maximize the ee. Under the optimized conditions, ring opening occurred smoothly to give **2** in up to 97% yield with 97% ee (Table 2).[21] The ee diminished if the ratio of BINAP:$Ni(COD)_2$ was <1.5:1 , entry 4 vs 5.

Substrate **15**, bearing additional substitution at the bridgehead position, also undergoes enantioselective hydrometalation–elimination to give **16** in 80% ee (unoptimized), eq 3.



(3)

In conclusion, we have shown that nickel catalysts offer several new opportunities for selective reductive ring opening of oxabicyclic compounds. Excellent yields with little or no overreduction of the ring-opened product can be achieved with only a slight excess of the reducing agent. Lewis acids accelerate the β-elimination in the [3.2.1] series. Higher regioselectivity and new regioisomers are possible through the addition of triphenylphosphine. Most significantly, this methodology is also appropriate for the asymmetric synthesis of cyclohexenols. Further studies are in progress to expand the scope of the enantioselective process.

Acknowledgment. The A. P. Sloan Foundation, E. W. R. Steacie Memorial Fund, (NSERC) Canada, Bio-Mega/Boehringer Ingelheim Inc., Eli Lilly Grantee Program, and the Petroleum Research Fund (administered by the ACS) are thanked for financial support. We thank Adrian Yee for preliminary experiments with **8**. We thank Professor T. Hayashi for helpful discussion.

Supplementary Material Available: Experimental procedures and ^1H and ^{13}C NMR, IR, and mass spectral data for the products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JA941827U

---

(15) Unpublished work of S. Ma and A. Yee. For a related approach with a cycloheptene triol, see: Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735. For a review, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(16) Lautens, M.; Chiu, P.; Colucci, J. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281; *Angew. Chem.* **1993**, *105*, 267.

(17) (a) A good yield of **13b** was obtained even without the addition of DIBAL-Cl. This reaction was more capricious than any of the others and gave variable ratios ranging from 6.4:1 to 9.4:1. (b) The phosphine and $Ni(COD)_2$ were premixed and stirred for 30 min prior to addition of the alkoxyalane (formed by mixing the oxabicyclic alcohol with 1.4 equiv of DIBAL-H). Addition of 1.1 equiv of DIBAL-H via a syringe pump over 6–16 h and the usual workup gave the product. The addition of DIBAL-H via syringe pump leads to improved yields and selectivity.

(18) For a recent discussion of the mechanism of hydrosilation, see: (a) Brookhart, M.; Grant, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 2151. (b) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121.

(19) For a study of relative rates of hydroalumination, see: Ziegler, K.; Gellert, H. G.; Martin, H.; Nagel, K.; Schneider, J. *Justus Liebigs Ann. Chem.* **1954**, *589*, 91.

(20) Eisch, J. J.; Sexsmith, S. R.; Fichter, K. C. *J. Organomet. Chem.* **1990**, *382*, 273.

(21) As measured by the Mosher method (a) Dale, J. E.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. E.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512] and CGC (Chiraldex G-TA, Advanced Separation Technologies Inc.). (c) The absolute stereochemistry is as indicated and was proven by comparison with an authentic sample of the enantiomer prepared by an alternative route.