ORGANO TIN NUCLEOPHILES III.[1] PALLADIUM CATALYZED REDUCTIVE CLEAVAGE OF ALLYLIC

HETEROSUBSTITUENTS WITH TIN HYDRIDE

Ehud Keinan* and Noam Greenspoon

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Abstract. Tributyl tin hydride, serving as an efficient hydride transfer agent, allows highly chemoselective palladium catalyzed reductions of allylic heterosubstituents even in presence of aldehydes, benzyl acetate and benzyl chloride.

The chemoselective removal of an allylic heterosubstituent is a synthetic problem which has yet to be satisfactorily solved. Nucleophilic displacement by hydride donors[2] is effective only when: a) the heterosubstituent is a good leaving group, and b) the hydride donor is a powerful nucleophile, such as $LiAlH_4$, a requirement incompatible with many functional groups.

Remarkable progress towards increased chemoselectivity was achieved by palladium activation of the allylic unit, thus allowing the use of milder hydride donors such as $NaBH_4$ and $NaBH_3CN$.[3] However, these two reagents are still incompatible with a considerable number of electrophilic functional groups such as ketones and aldehydes.

The recent observation that dimeric, neutral π-allyl palladium complexes are reduced by $LiAlH_4$ with endo stereochemistry,[4] leads us to speculate that a similar internal transfer of hydride from the transition metal to the allylic system will take place in cationic π-allyl palladium complexes as well (path b in Scheme I).

If such an assumption proved correct,[5] it may yield an interesting consequence: in order to reduce an allylic heterosubstituent via palladium catalysis, one should apply a reagent capable of transferring hydride to the transition metal, but not necessarily a nucleophilic hydride donor.

Scheme I
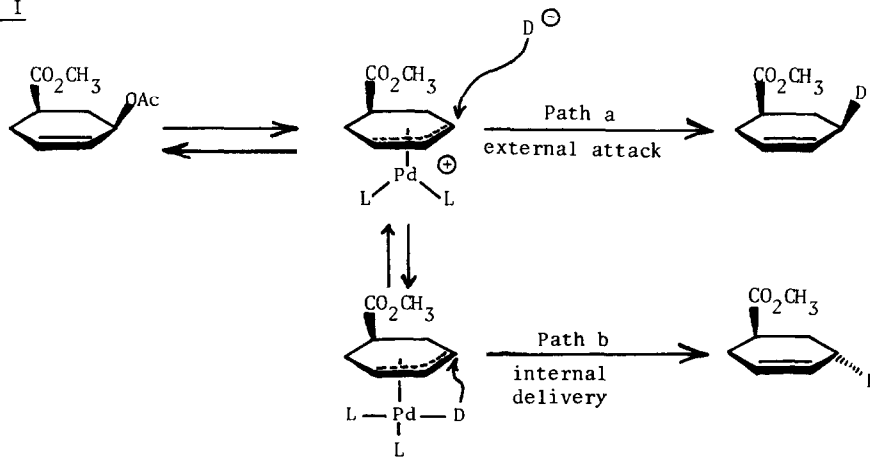
Our first assumption was easily confirmed by the stereospecific reduction of model compounds $\underline{1}$ and $\underline{2}^6$ by $NaBD_4/Pd(PPH_3)_4$ in THF at room temperature (eq. 1,2).

$$(1)$$

$$(2)$$
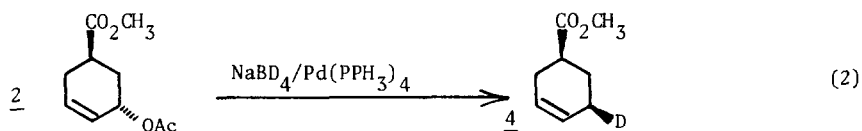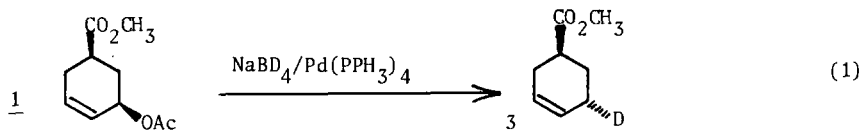
The complete inversion of the acetate's configuration was evident from the 270 MHz NMR spectra of both isomeric product $\underline{3}$ and $\underline{4}$.[7]

This internal delivery of the hydride, resulting in endo-reduction of cationic η^3-palladium complex is a unique exception to analogous reductions of other cationic polyene-transition metal complexes, where exo attack by the hydride is a general phenomenon.[8-12] A typical example[8b] is shown in Scheme II.

Scheme II
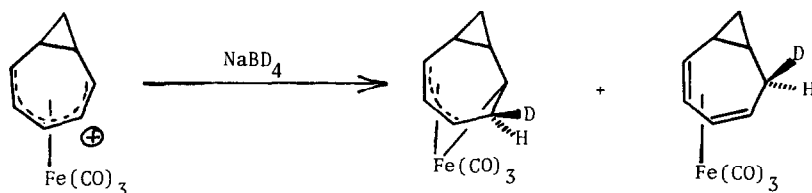
Based on the above stereochemical results, we turned our attention to tributyl tin hydride as a potential hydride donor. Its poor nucleophilicity[13] promises an attractive chemoselectivity while its propensity to undergo transmetallation and oxidative addition reactions[14] makes it a qualified partner for palladium catalyzed reductions.

Indeed, when tributyl tin hydride was added to a THF solution of cyanohydrin acetate $\underline{5}$ in presence of 1% $Pd(PPh_3)_4$ (eq. 3), a rapid and regioselective reduction took place, yielding the allylic nitrile $\underline{6}$.


$$(3)$$
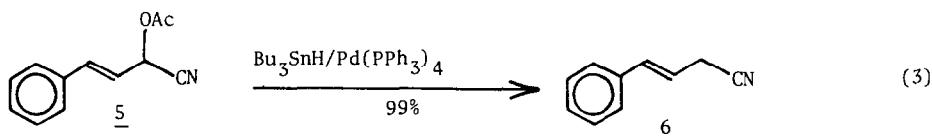
Surprisingly,[15] less than 1% of the other isomeric product could be observed. Under similar conditions, cinnamyl acetate was quantitatively reduced to β-methyl styrene.

When trying to reduce less reactive allylic acetates, we encountered disappointingly unclean reductions and low yields. Suspecting these difficulties to arise from the known tendency of tin hydrides to participate in free-radical chain processes,[13] we tried to suppress such undesired side reactions. Thus, addition of a radical scavenger[16] and slow addition of tributyl tin hydride caused a striking yield increase as illustrated by eq. 4,5.

$$\text{(4)}$$

THF 70%

THF + 20% 90%

$$\text{(5)}$$

THF 49%

THF + 1% H_2O 98%
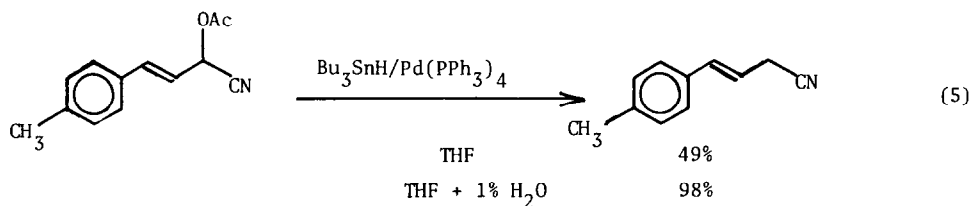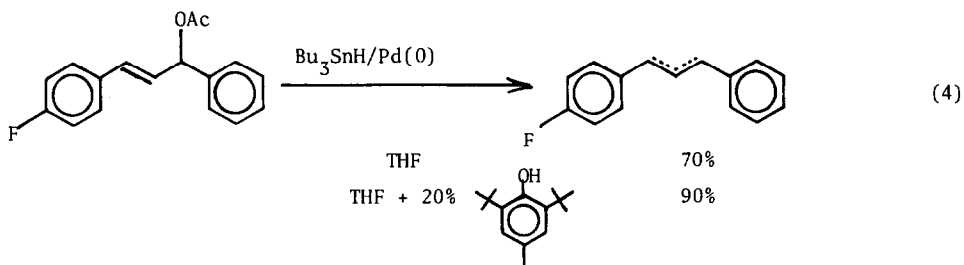
Obviously the special chemoselectivity offered by this method[17] is its major advantage as demonstrated by eq. 6-8. Allylic acetates can be selectively reduced in the presence of a benzylic acetate, aldehydes and various halides. The addition of a radical scavenger allows tributyl tin hydride to leave even benzyl chloride unaffected.


$$\text{(6)}$$

$$\text{(7)}$$

$$\text{(8)}$$
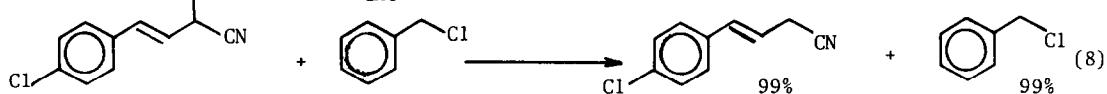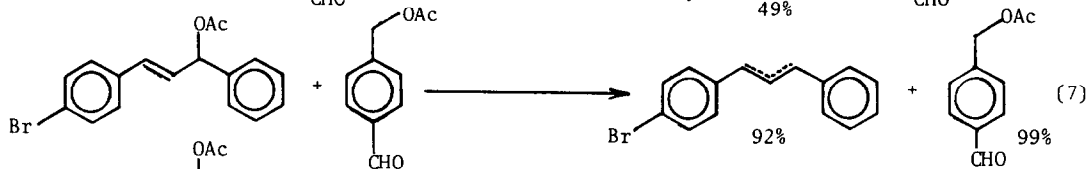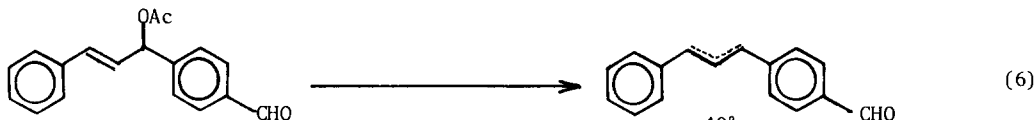
In view of the rapidly growing number of heterosubstituted allyl compounds which can easily form π-allyl palladium complexes, it is now possible to reductively cleave such heterosubstituents. Allylic amines[18] are a representative example:[19]

$$\text{(9)}$$
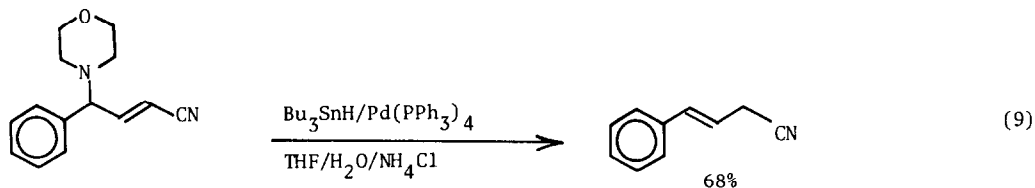
Tributyl tin hydride, being a stable, organically soluble, heavy liquid, is advantageous over solid insoluble metallic hydrides of low molecular weight in that it can be measured accurately and conveniently, especially in small scale preparations.

Utilization of this reduction method for chemoselective transformations in the Withanolide series[20] is in progress. One selected example is shown in eq. 10.
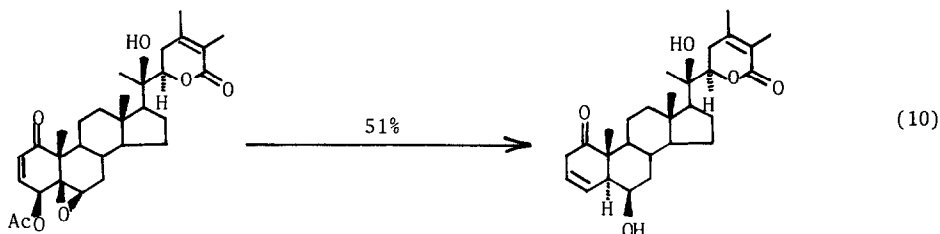
(10)

References
1. For previous work in this area see: B.M. Trost and E. Keinan, Tetrahedron Lett., 2591, 2595 (1980).
2. a. E.R.H. Walker, Chem. Soc. Rev., 5, 23 (1976); b. H.O. House, "Modern Synthetic reactions", Chapter 2, W.A. Benjamin, N.Y. (1972).
3. R.O. Hutchins, K. Learn and R.P. Fulton, Tetrahedron Lett., 27 (1980).
4. a. D.N. Jones and S.D. Knox, J. Chem. Soc. Chem. Comm., 165 (1975); b. J.E. Backvall, R.E. Nordberg, E.E. Bjorkman and C. Moberg, J. Chem. Soc. Chem. Comm., 943 (1980).
5. It was recently shown that nucleophilic attacks on neutral and on cationic π-allyl palladium complexes do not proceed via the same mechanism: B. Åkermark, G. Åkermark, L.S. Hegedus, and K. Zetterberg, J. Amer. Chem. Soc., 103, 3037 (1981).
6. B.M. Trost and E. Keinan, J. Amer. Chem. Soc., 100, 7779 (1978).
7. The relative configuration was assigned by 270 MHz NMR spectra based on the upfield signal of the axial proton H_a

which appears as a broad triplet in the trans isomer 3 and as a broad quartet in the cis isomer 4. Further support for structure 3 was evident from the large vicinal H_a-D coupling constant (1.73 Hz). For previous structure assignment to similar compounds see ref. 6.
8. For NaBH$_4$ reduction of cationic η^5 iron complexes see: a. A.J. Birch, K.B. Chamberlain, M.A. Haas and D.J. Thompson, J. Chem. Soc. Perkin I, 1882 (1973); b. A. Eisenstadt, J. Org. Met. Chem., 113, 147 (1976).
9. For reduction of analogous η^5ruthenium complexes see: a. B.A. Sosinsky, S.A.R. Knox and F.G.A. Stone, J.Chem.Soc., Dalton, 1633 (1975); b. A.J.P. Domingos, B.F.G. Johnson and J. Lewis, J. Chem. Soc. Dalton, 228 (1975).
10. For similar reduction of η^5 rhodium complexes see: B.F.G. Johnson, J. Lewis and D.J. Yarrow, J. Chem. Soc. Dalton, 2084 (1972).
11. For similar reduction of η^5 cobalt complexes see: a. P.H. Bird and M.R. Churchill, J. Chem. Soc. Chem. Comm., 777 (1967); b. E.D. Sternberg and K.P.C. Vollhardt, J. Amer. Chem. Soc., 102, 4839 (1980).
12. For reduction of η^6 rhenium complex see: G. Winkhous and H. Singer, Z. Naturforsch., 18b, 418 (1963).
13. H.G. Kuivila, Syn., 499 (1970).
14. a. J. Grobe and R. Rau, J. Org. Met. Chem., 157, 281 (1978); b. J.P. Fawcett and J.F. Harrod, Can. J. Chem., 54, 3102 (1976); c. F. Guibe, P. Four and H. Riviere, J. Chem. Soc. Chem. Comm., 432 (1980).
15. The reported thermodynamic ratio of the two allylic isomers:

G. Descotes, and P. Laconche, Bull. Soc. Chim. Fr., 2149 (1968).
16. E. Keinan and P.A. Gleize, accompanying paper in this issue.
17. Similar reductions using formate salts and palladium catalysts were not proved to be highly chemoselective. a. N.A. Cortese and R.F. Heck, J. Org. Chem., 42, 3491 (1977); b. J. Tsuji and T. Yamakawa, Tetrahedron Lett., 613 (1979).
18. For allylic amine as a leaving group see B.M. Trost and E. Keinan, J. Org. Chem., 45, 274 (1980).
19. The allylic morpholine derivative was obtained from Pd(0) catalysed reaction of compound 5 with morpholine.
20. E. Keinan, N. Greenspoon and I. Kirson, unpublished results.