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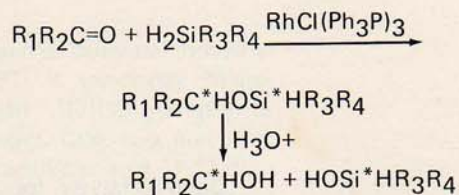
RECENT EXAMPLES OF SELECTIVITY IN CATALYSIS

by John H. MacMillan

Synthetic organic chemistry is in part a science of reactions of functional groups. Invariably the chemist will encounter synthesis where he wishes to react one functional group while keeping other active groups in the molecule intact. Chemists also desire "optical" selectivity, which is defined as preferential production of one enantiomer giving an optically active product. Stereoselective synthesis, i.e. preferential production of one structural isomer over another, and stereospecific synthesis, i.e. exclusive production of one isomer, are of obvious importance. In addition the selective incorporation of isotopes is important for mechanistic investigations. Transition metal catalysts have proven of enormous utility in these areas. This account will briefly summarize recent work, commenting on advantages over older procedures.

Recent work in asymmetric synthesis has involved the direct synthesis of optically active amines or alcohols. Corriu² has shown

$\text{RhCl}(\text{Ph}_3\text{P})_3$ to be a selective catalyst for hydrosilylation of carbonyl compounds.



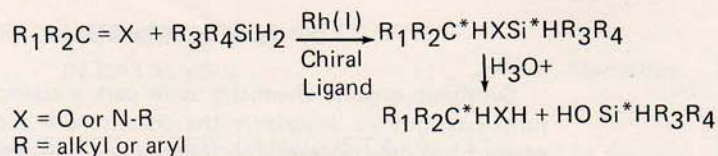
R = alkyl or aryl

Hydrosilylation is preferable to catalytic hydrogenation of the carbonyl group in cases where the product alcohol is a solid or is prone to hydrogenolysis. The liquid silylated derivatives are analizable by gas chromatography and are stable to further reduction. If $\text{R}_1 \neq \text{R}_2$ and $\text{R}_3 \neq \text{R}_4$, optical centers are produced on both carbon and silicon. Employing a Rh(I) catalyst and chiral ligand such as (+) or (-)DIOP (2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)^{3,4} or ⁵R-(+)-PhCH₂PCH₃Ph asymmetric syntheses have recently appeared which may be summarized as

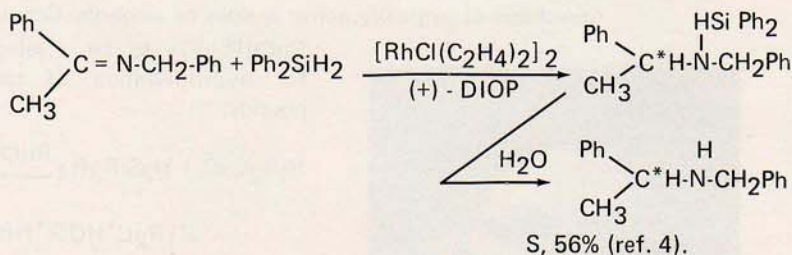


Dr. John H. MacMillan was born in Massachusetts in 1944. He received his B.S. from Tufts University in 1966 and Ph.D. in organic chemistry from Northeastern University in 1970. He has done postdoctoral work at the University of Utah in low temperature diazine chemistry and Temple University in organosilicon chemistry and lanthanide chemical shift reagents. Since July, 1973 he has acted as consultant to Strem Chemicals, Inc. in organic and organometallic synthesis and homogeneous and heterogeneous catalysis.

follows,



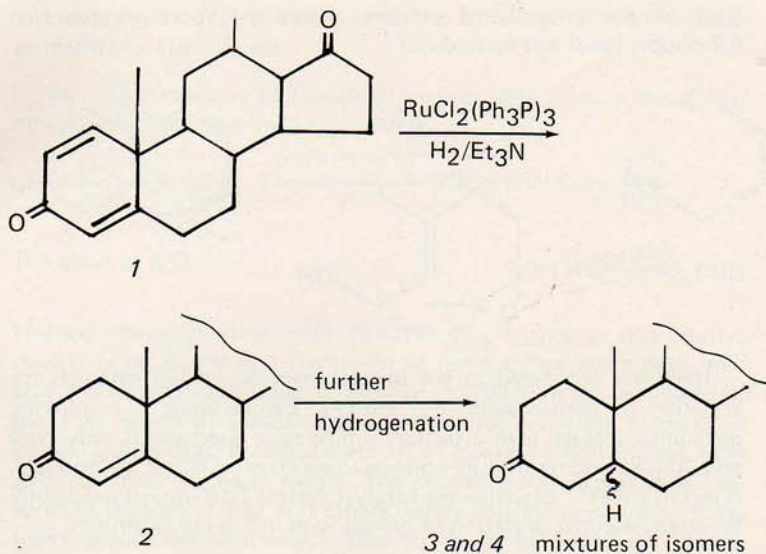
If X = oxygen, optically active silylated alcohol derivatives are produced which give optically active alcohols on hydrolysis^{3,5}. Optical yields are quite variable, intimately depending on steric size of the R groups for both carbon and silicon, but yields of 30-50% are common. A good example⁵ is t-butylphenylketone which with Rh(I) and RPhCH₂PCH₃Ph gives the S-carbinol in 62% optical yield after hydrolysis. Induced asymmetry at silicon³ gives an optical yield of 31-55%. For X = N-R (imino groups) asymmetric hydrosilylation gives derivatives from which optically active amines are produced on hydrolysis in ca 40-50% optical yields.



Good catalysts for the above reactions include RhCl(Ph₃P)₃, [RhCl(C₈H₁₄)₂]₂ or [RhCl(C₂H₄)₂]₂. Homogeneous Rh(I) catalyst systems such as RhHCO(Ph₃P)₃ with (-) DIOP also effect asymmetric hydroformylation of olefins to aldehydes with ca 20-30% optical yields⁶. Kagan and coworkers⁷ have complexed a chiral phosphine on a polymer with [RhCl(C₂H₄)₂]₂, giving a heterogeneous type catalyst for asymmetric synthesis which may be filtered from the reaction and used again. This catalyst proved less efficient for hydrogenation of olefins to optically active alkanes than the non-bound catalyst, but of comparable efficiency for asymmetric hydrosilylation of carbonyl groups.

These new catalyst systems give enantiomerically enriched products directly in contrast to the classical procedures which involve complexation of the racemate with a chiral natural product, separation and chemical degradation of the resulting diastereomers.

Steroid chemists will find Nishimura's recent work⁸ of interest. Selective hydrogenation of steroid 1 with RuCl₂(Ph₃P)₃ and base gives 2 with less than 4% fully saturated isomers 3 and 4.



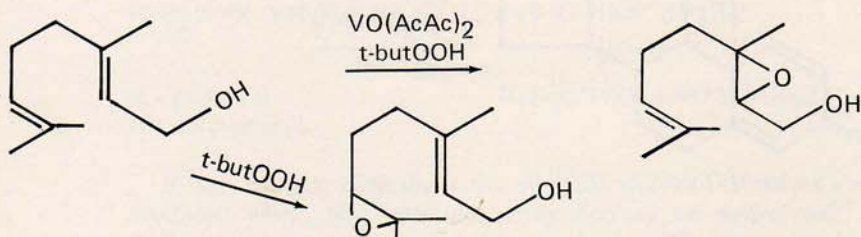
Tris-(*p*-methoxyphenyl)phosphine or tri-(*p*-tolyl)phosphine in place of triphenylphosphine in the ruthenium catalyst produced catalysts which greatly accelerated the hydrogenation rate with little loss of selectivity. These new catalysts offer exciting possibilities for fast selective hydrogenations.

Fahey⁹ describes a selective hydrogenation of potential industrial application. 1,5,9-Cyclododecatriene (CDT) is selectively hydrogenated to cyclododecene (CDE) with $\text{Ru}(\text{CO})_2(\text{Ph}_3\text{P})_2$ or $\text{Ru}(\text{Et}_2\text{S})_3\text{Cl}_3$. Up to 98% CDE is produced. CDE is a precursor for the polyamide monomers 1,12-dodecanedioic acid, 1,12-diaminododecane and 12-aminododecanoic acid lactam. CDE cannot be separated from cyclododecadiene or cyclododecane by distillation.

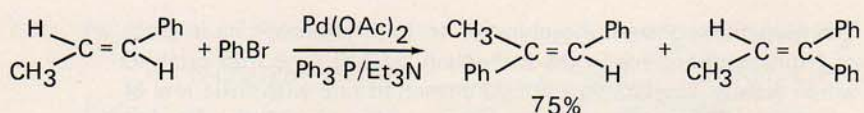
Two recent examples of deuterium incorporation with transition metal catalysts show greatly improved selectivity. Friedmann *et al*¹⁰ report that $\text{Co}_2(\text{CO})_8$ selectively deuterates the 9, 10 position of anthracene giving tetradeuterated product. Also Regen¹¹ describes $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ as a selective catalyst with D_2O for deuterium incorporation at C_1 of primary alcohols. Alcohols dideuterated at C_1 are valuable precursors to many materials such as 1-deuterated aldehydes, deuterated halides, organometallics or olefins. This method is one step under neutral conditions in contrast to older methods involving oxidation of alcohol to acid and reduction with LiAlD_4 .

Recent reports of stereoselective and stereospecific syntheses include the stereospecific epoxidation of geraniol (5) and related compounds with $\text{VO}(\text{AcAc})_2$ or $\text{Mo}(\text{CO})_6$ catalysts.¹² Epoxidation occurred at the olefinic site closest to the hydroxyl group in con-

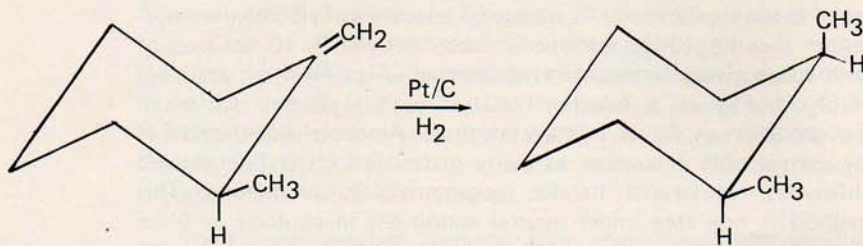
trast to the uncatalyzed process, where the more electron-rich 6,7-double bond was epoxidized.



Heck has pioneered in the development of Pd (II) catalysts for arylation of olefins with aryl iodides. Earlier work¹³ employing palladium acetate with a tertiary amine gave good yields only with aryl iodides and resulted in non-stereoselective mixtures of products. A recent paper¹⁴ describes the catalyst system Pd(OAc)₂/Ph₃P/Et₃N for stereoselective arylation of olefins with iodides or bromides.



Heterogeneous catalysts are less frequently employed for selective synthesis due to uncertainties regarding surface effects, pretreating, aging etc. However, significant work is continuing. Mitsui *et al*¹⁵ report stereoselective hydrogenations of dialkylcyclohexanones to axial alcohols with Raney nickel or platinum black and to equatorial alcohols with PtO₂. They also report 2,3 and 4-alkyl-substituted methylenecyclohexanes hydrogenate stereoselectively with Pt or Rh on C giving axial dimethylcyclohexanes¹⁶ (cis isomers from 2 and 4-substituted, trans from 3-substituted methylenecyclohexanes).

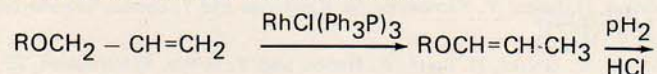


Palladium gives axial/equatorial ratios depending on catalyst concentration and reaction time while Raney nickel gives more axial than equatorial only on aged catalysts.

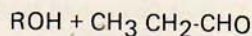
These stereoselective syntheses in substituted cyclohexanes are of interest not only for fundamental conformational studies but also

as model systems for selective syntheses from natural products such as menthols, steroids etc.

As a final example of selectivity we may note Corey's use of allyl ethers as protecting groups for alcohols.¹⁷



R = alkyl or aryl



Heating the allyl ether with $\text{RhCl}(\text{Ph}_3\text{P})_3$ results in quantitative double bond migration. Treatment at room temperature with mild acid cleaves the vinyl ether to alcohol in >90% yields. As examples the allyl ethers of 1-decanol and cholesterol form the alcohols in 96 and 90% yields. Previous methods of cleavage involved heating in strongly acidic or basic media. The present reaction conditions are so mild that alkyl and aryl ethers, esters and many common functional groups are unaffected. This technique may find application in natural product work, where often phenolic groups sensitive to oxidation must be protected.

In conclusion it is obvious that vigorous research activity in catalysis is continuing unabated. Perhaps the chemists' need for a specific catalyst for every desired reaction is no longer a dream and may approach reality within the next decade.

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