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Metal-Directed Stereoselective Functionalizations and Cyclizations of Alkenes in Organic Synthesis

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Over the past seven years we have systematically explored the intramolecular type I and type II magnesium-ene reactions (Scheme 1).

These cyclizations proceed under kinetic control with high regio- and diastereo-selectivities and the cyclized organomagnesium intermediates can be trapped by a variety of electrophiles.

Applications of type I and type II magnesium-ene reactions to the syntheses of an array of natural products demonstrate their potential in organic synthesis.

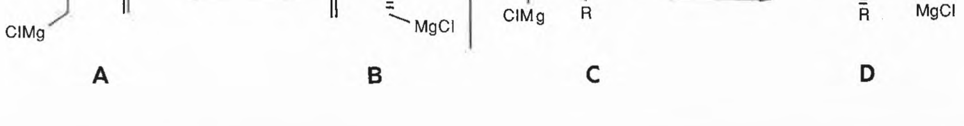
Nevertheless, these examples involve only terminal (or strained) olefinic enophile units since intramolecular allylmagnesium insertions into 1,2-dialkyl-, trialkyl-, and cyclic alkenes could not be achieved. Furthermore, all attempts to apply these cyclizations to the preparation of pyrrolidines have so far failed.

To overcome these and other limitations of magnesium-ene cyclizations we envisaged the exploration of *catalytic* intramolecular palladium-ene reactions. Whereas norbornadiene, norbornene, and 1,3-dienes were reported to insert into stoichiometric amounts of allylpalladium complexes, simple olefins (e.g. styrene, cyclohexene, 1,4-cyclohexadiene, and 1,5-cyclooctadiene) did not undergo this reaction.

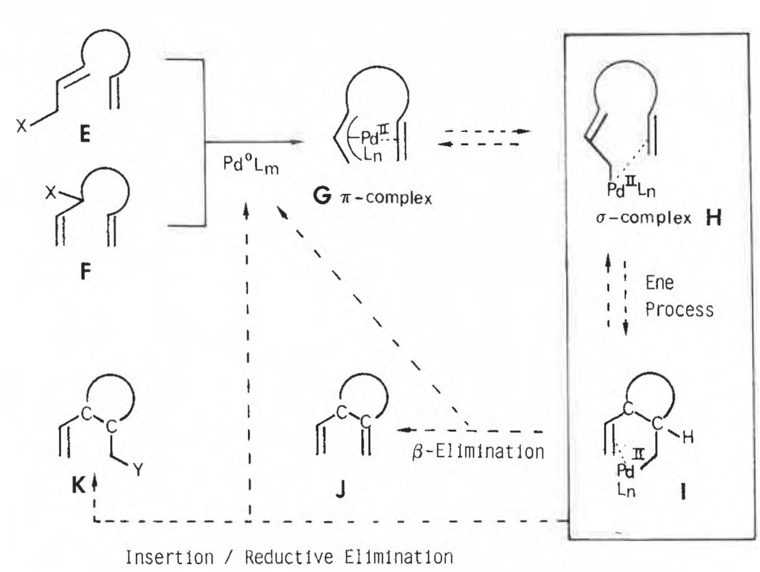
However, we assumed the intramolecular ene process **H** → **I** to be entropically favoured and a subsequent irreversible β-elimination **I** → **J** to withdraw the ene product **I** from the equilibrium **H** ⇌ **I**, thereby regenerating Pd^0 which continues the catalytic cycle (Scheme 2).

In situ preparation of the olefinic allylpalladium intermediates **G** was accomplished by oxidative addition of Pd^0-complexes to allylacetates **E**, **F**, X = OAc. To this end, acetoxydienes **2** were readily obtained, predominantly as their (*E*)-isomers, via $Pd(PPh_3)_4$-catalyzed alkylation of disulfones **1**, Y = SO_2Ar or malonates **1**, Y = COOMe with 4-acetoxy-2-butenyl methyl carbonate (Scheme 3).

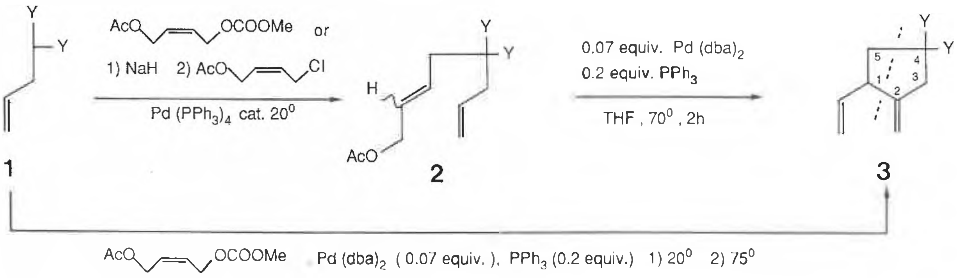
Scheme 1



Scheme 2



Scheme 3



Heating diene **2**, Y = Ts with $Pd(dba)_2$ (0.07 equiv.)/PPh_3 (0.2 equiv.) in tetrahydrofuran (THF) at +70 °C for 2 h gave the expected cyclized 1,4-diene **3**, Y = Ts in 83% yield. Even more conveniently, product **3**, Y = Ts was obtained (76% yield) in *one* operation from **1** via Pd^0-catalyzed alkylation/cyclization.

Solvent effects significantly influence this novel ene process as illustrated by the cyclization of the malonate **2**→**3**, Y = COOMe. Whereas no reaction took place in toluene, dichloromethane or *N,N*-dimethylformamide, the rate and yield increased on proceeding from THF (20%) to methanol (65%) to acetic acid (77%). Interestingly, the presence of the phosphane turned out to be indispensable.

In striking contrast to 8-alkyl-substituted 2,7-dienylmagnesium halides which did not cyclize, the allylpalladium unit of **H′** inserted readily into a terminally mono- and even dimethyl-substituted olefinic bond (**H′**→**I′**) (Scheme 4).

The efficient Pd^0-catalyzed cyclizations (AcOH, 75 °C, 1.5 h) of acetoxydienes **4** and **6** gave, in each case, a single 1,5-diene product **5** (91%) and **7** (71%), respectively. It follows that the transient ene product **I′** eliminates the exocyclic H_b preferentially over H_a in agreement with the conformational constraints of a *syn*-β-elimination process.

As expected, $Pd(PPh_3)_4$ (0.07 equiv.) turned out to be an equally efficient catalyst for intramolecular palladium-ene reactions (Scheme 5).

Acetoxydiene **8**, containing a cyclic «enophile» unit, furnished stereoselectively the bicyclic product **9** in 86% yield. The analogous conversion **12**→**13** illustrates the feasibility of this method for 6-membered ring formation.

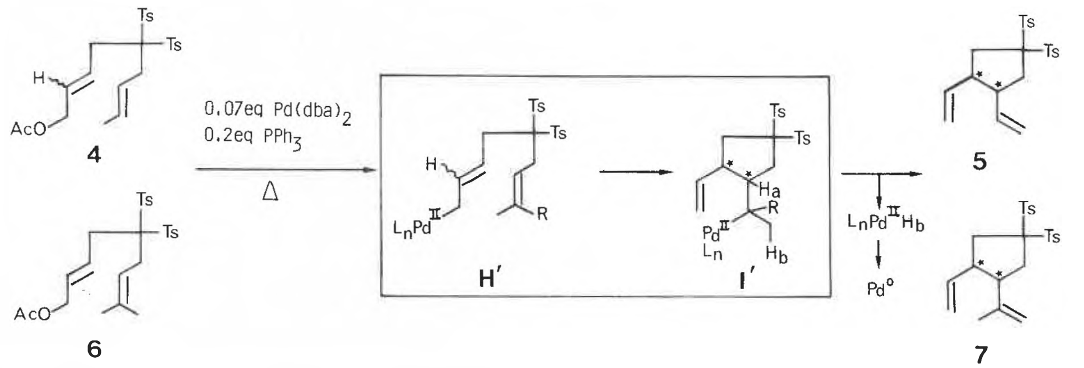
The palladium-ene unit may be also part of a ring as shown by the stereoselective formation of a spiro system (**10**→**11**).

Stereochemically even more striking are the cyclizations depicted in Scheme 6.

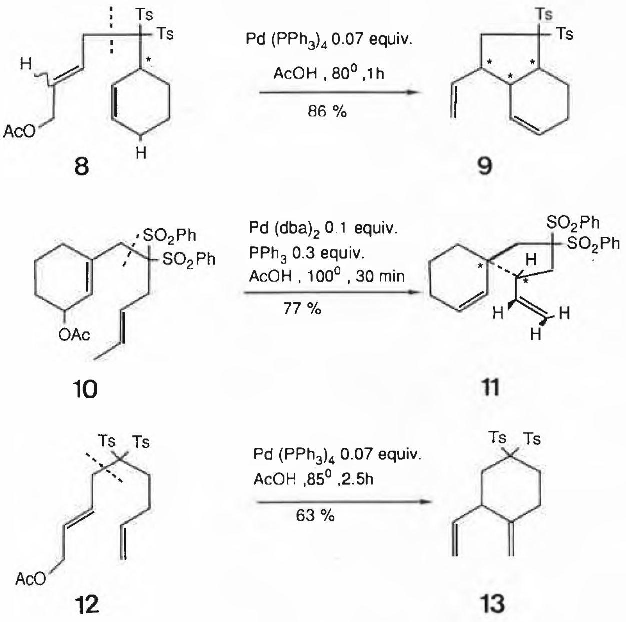
Thus, the *trans*-acetoxydiene **15** furnished exclusively the *cis*-fused octahydronaphthalene **17**, whereas the *cis*-acetoxydiene **18** gave with 95% stereospecificity the *trans*-annulated product **20**. These results indicate that the olefin inserts into either the σ- (**H**) or, directly, into the π-allylpalladium unit (**G**) *syn* relative to the Pd (**16**→**17** and **19**→**20**) and represent an interesting C-O→C-Pd→C-C chirality transfer.

Scheme 7 illustrates the feasibility of carrying out catalytic type II palladium-ene cyclizations, for example, the transformation **24**→**25** (8 h at 118 °C, 66% yield). Cyclization of **27** (lacking the bis-sulfone moiety) proceeded more efficiently to give **28** (87%) under milder conditions (80 °C, 6.5 h). Moreover, the latter reaction showed a high regio- and stereo-selectivity *both in the opposite sense*

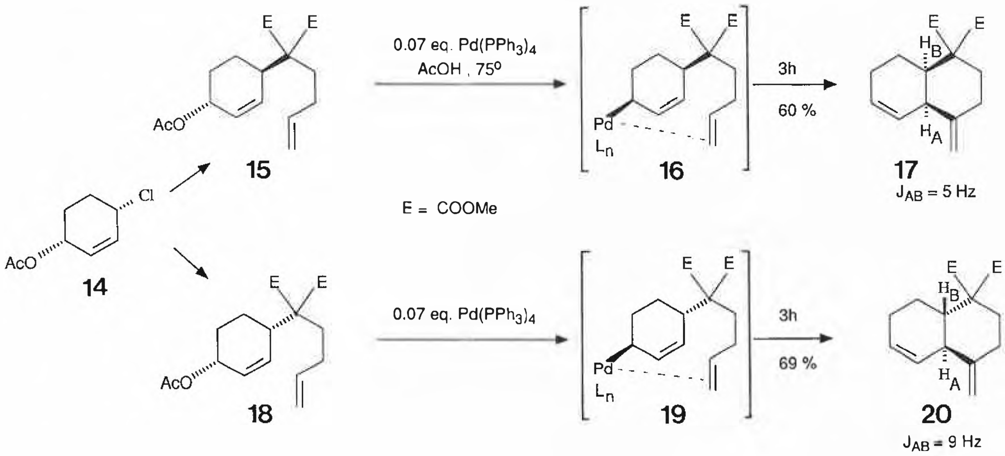
Scheme 4



Scheme 5

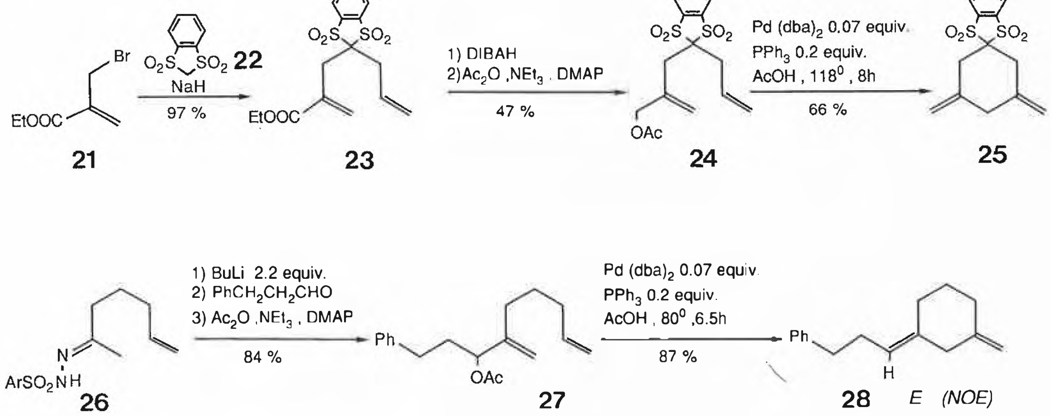


Scheme 6



Efficient C-O → C-Pd → C-C Chirality Transfer

Scheme 7



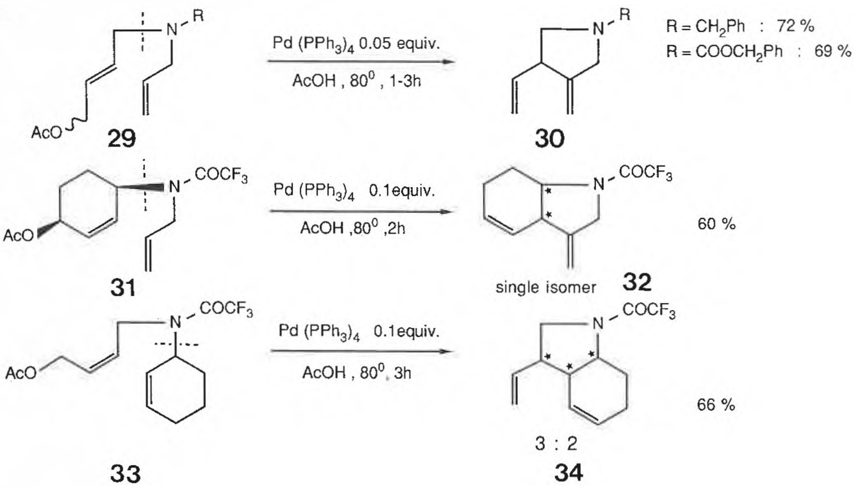
as the corresponding magnesium-ene process **C** → **D**.

Catalytic palladium-ene cyclizations may also open new perspectives in alkaloid synthesis considering the smooth formation of pyrrolidines (Scheme 8).

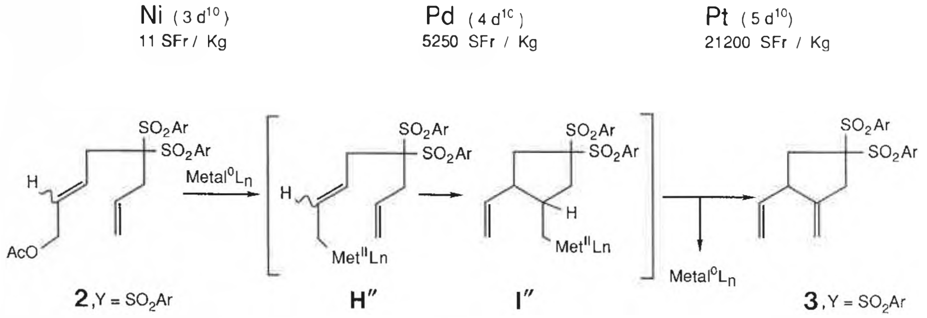
It is interesting to note that the cyclization **2** → **3**, Y = SO_2Ar can be also catalyzed by Pt^0- and Ni^0-phosphane complexes (Scheme 9).

In summary, we have shown that catalytic intramolecular d^{10}-transition metal ene reactions are simple to carry out, compatible with various functional groups, as well as applicable to 1,2-dialkyl, trialkyl-, and cycloalkenyl enophiles thereby complementing advantageously the analogous magnesium-ene process. Further extensions and applications of this novel methodology are presently under investigation in our laboratory.

Scheme 8



Scheme 9



Catalyst (Equiv.)	Solvent	Reaction Temp./ Time	Yield of **3**, Y = SO_2Ar
Pd(dba)$_2$ (0.09), PPh_3 (0.36)	THF	70° / 1h	82 %
Pt (PPh_3)$_4$ (0.035)	AcOH	80° / 5h	85 %
Ni(COD)$_2$ (0.1), Ph_2P–Ph_2P (0.1)	THF	20° / 3h	**85 %**

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