Regio- and stereocontrolled catalytic palladium- and nickel 'ene-type' cyclizations

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Intramolecular Pd(0)- and Ni(0) catalyzed alkene allylations, coupled with β-eliminations or methoxycarbonylations efficiently provide various carbo- and heterocycles in one synthetic operation. Particularly, the nickel(0) catalyzed reaction of acyclic allylic substrates proceeds in a clean *'exo'*-manner with excellent topological control of pre-existing over developing stereogenic centers. Cyclic allyl precursors undergo exclusive *'endo'*-cyclizations permitting simple and selective *cis*- or *trans*-annulation processes *via* an almost 100% stereospecific C-O → C-Pd or C-Ni → C-C chirality transfer. Analogous chirality transfer was also observed starting from enantiomerically pure (*E*)- and (*Z*)- 4-acetoxy-6-aza-2,8-nonadienes.

In 1987 we introduced the combination of oxidative addition/intramolecular alkene allylation/β-elimination $\underline{A}$ or $\underline{B} \rightarrow \underline{F}$ as an efficient tool to prepare various carbo- and heterocycles in one synthetic operation (ref. 1, Scheme 1).
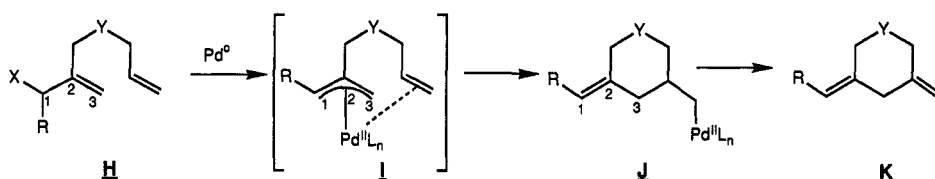
Scheme 1
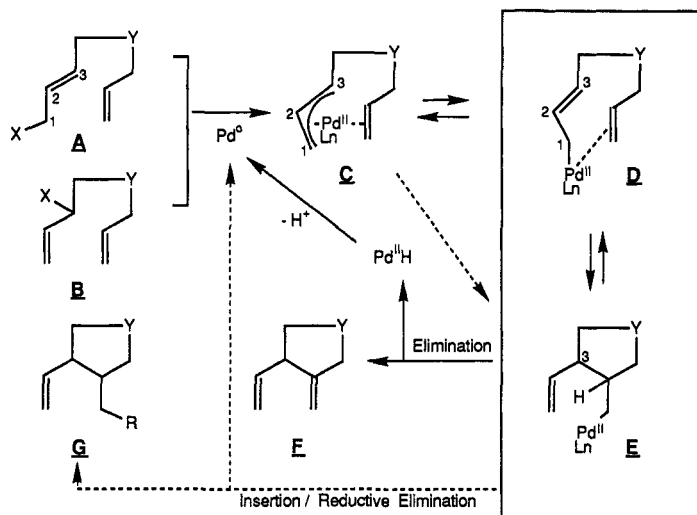
These transformations, where the olefinic bridge is tied to the the terminal (C-3) of the allyl unit, may be formally regarded as intramolecular type-I metallo-ene reactions involving the regioselective transfer of palladium to the more distal center of the 'enophile' unit and carbon-carbon bond formation between the proximal termini of the two reactive moieties (ref. 1).
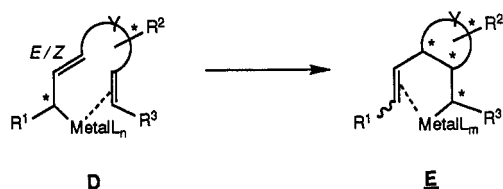
Analogous type-II cyclizations *i.e.* the insertion of an allyl-Pd species (*e.g.* $\underline{I}$) into an alkene, attached by a tether to C-2 have been also accomplished (ref. 2, Scheme 2).

Scheme 2

This account will focus on several stereochemical aspects of the 'type-I' process as outlined in the Scheme 3.
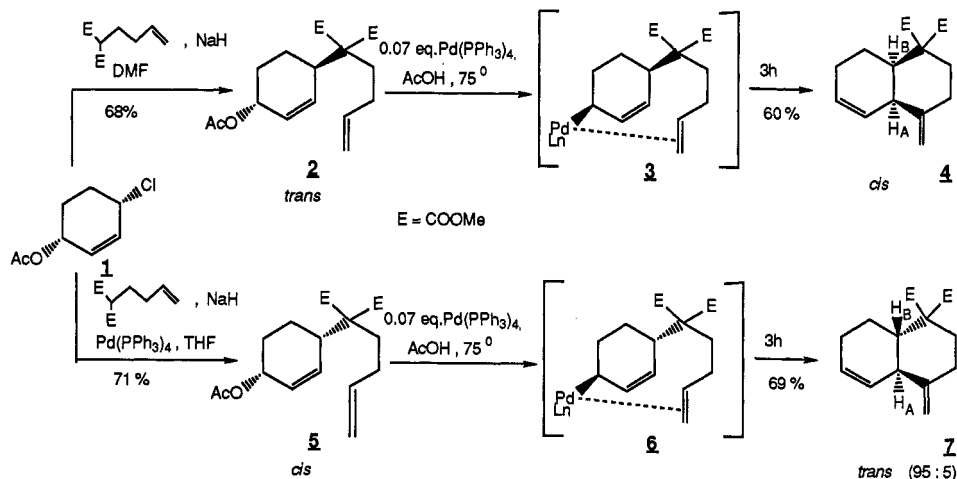
Scheme 3

1) $\overset{*}{C}$—Metal ⟶ $\overset{*}{C}$ - C : *Syn* - and / or *Anti* Displacement ?
2) Reactive (E) and / or (Z) - Allylmetal Configuration?
3) Exo and / or Endo Orientation?
4) Asymmetric Induction By Resident Stereogenic Centers?

Moreover, we describe here a trapping of transient cyclization products **E** to form new carbon-carbon bonds, with concomitant regeneration of the catalyst: **E** → **G** (Scheme 1).

As the first stereochemical issue we dealt with the question of whether the carbon-metal bond cleavage and carbon-carbon bond formation occur in a *supra-* or *antarafacial* manner (*syn-* or *anti* displacement) in the cyclization process.

Stereodivergent preparation of the *trans-* or *cis*-acetoxydienes **2** and **5** from the same precursor (±)-**1** followed by treatment with Pd(0) (7 mol%, AcOH) furnished *cis*-fused octahydronaphthalene **4** (~100% selectivity) from **2** or the *trans*-annulated product **7** (95% selectivity) from **5** (ref. 3, Scheme 4).
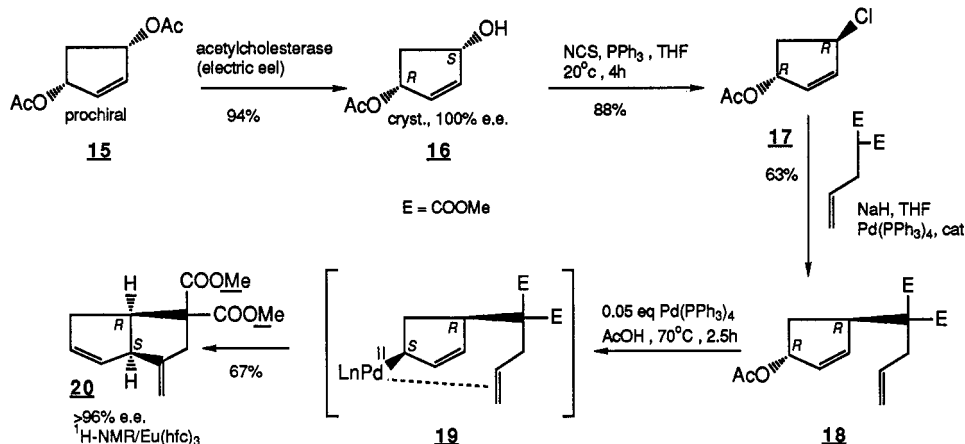
Scheme 4

This C-O → C-Pd → C-C chirality transfer also provides a selective route to either *cis-* or *trans*-fused hexahydroazulenes **11** and **14** (ref. 3, Scheme 5).
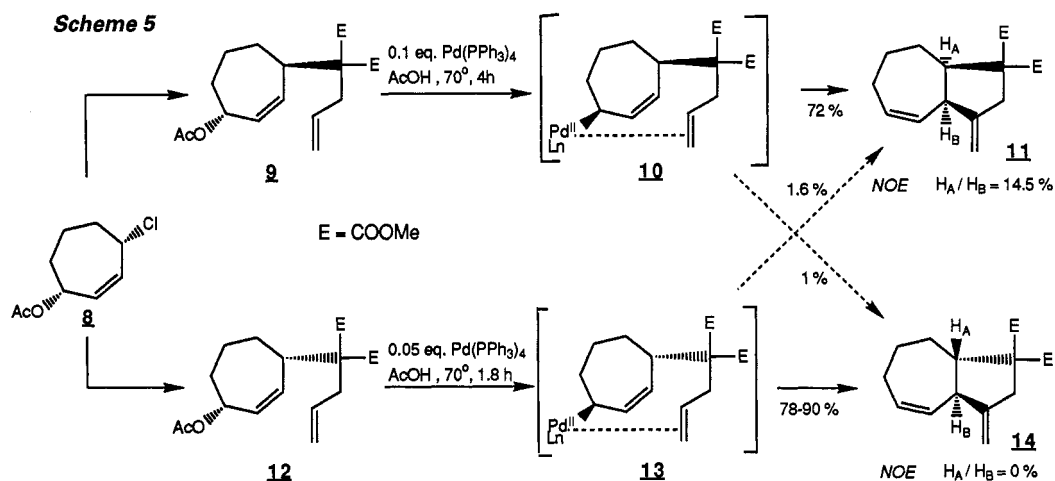
**Scheme 5**

Scheme 6 exemplifies the enantiospecific preparation of hexahydropentalene 20 from readily available enantiomerically pure allyl acetate 16 (ref. 3).

Scheme 6

acetylcholesterase (electric eel)

94%

cryst., 100% e.e.

16

NCS, PPh₃ , THF 20°c , 4h

88%

17

63%

E = COOMe

NaH, THF Pd(PPh₃)₄, cat

15 prochiral

0.05 eq Pd(PPh₃)₄ AcOH , 70°C , 2.5h

20
>96% e.e.
¹H-NMR/Eu(hfc)₃

67%

19

18

We thus conclude that the olefinic bond inserts into the allylpalladium unit *syn* relative to the Pd *i.e.* within the coordination sphere of the metal. This topicity, being opposite to the well-known *anti*-displacement of allylpalladium species by 'soft' nucleophiles (ref. 4), is consistent with the three hypothetical mechanisms depicted in the Scheme 7.

Scheme 7

Metallo-Ene Mechanism   OR   π- Allylmetal / Alkene Insertion   OR   "Heck" Insertion   ?
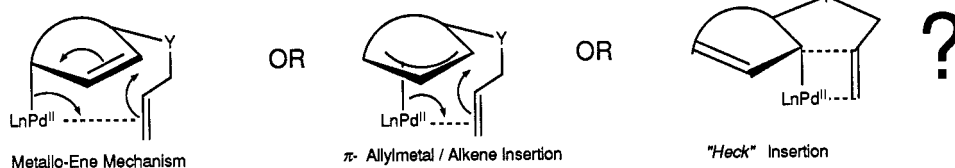
We then attempted to achieve a chirality transfer from enantiomerically pure acyclic acetoxydienes. Pd(0)-catalyzed cyclization/elimination of a terminally non-substituted allylacetate led to a complete loss of the stereochemical integrity: (S)-21 → (R,S)-24 (Scheme 8).
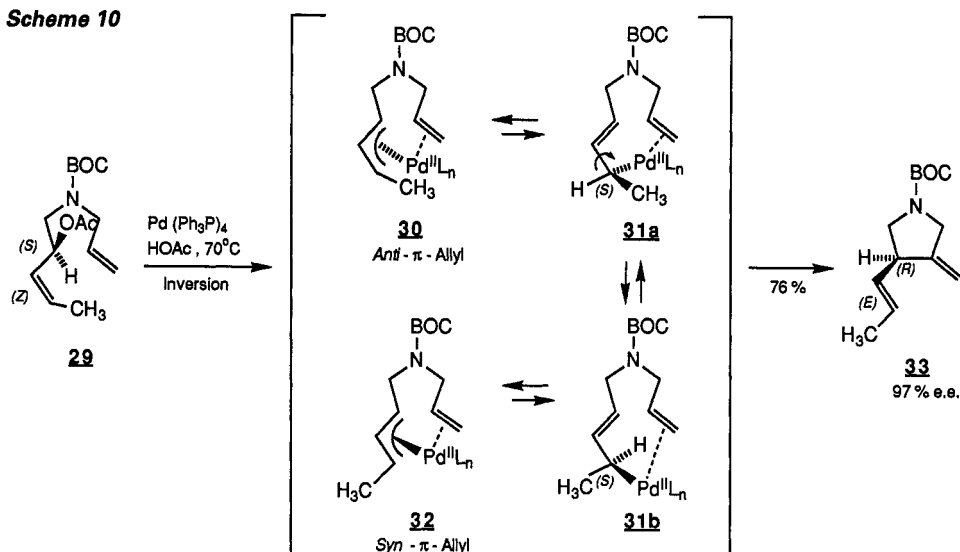
Scheme 8

Pd (Ph₃P)₄ HOAc , 70°C

Inversion

21

22
π – Allyl

23
σ – Allyl

64%

24
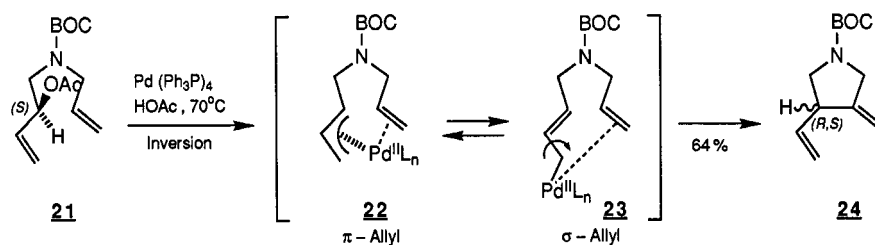
However, analogous cyclizations of terminally substituted substrates (S,E)-25 → (S,E)-28 and (S,Z)-29 → (R,E)-33 proceeded in a highly stereospecific manner (ref. 5, Schemes 9 and 10).

Scheme 9

Pd (Ph₃P)₄ HOAc , 70°C

Inversion

25

26
Syn - π - Allyl

27
E - σ - Allyl

64%

28
~ 100 % e.e.
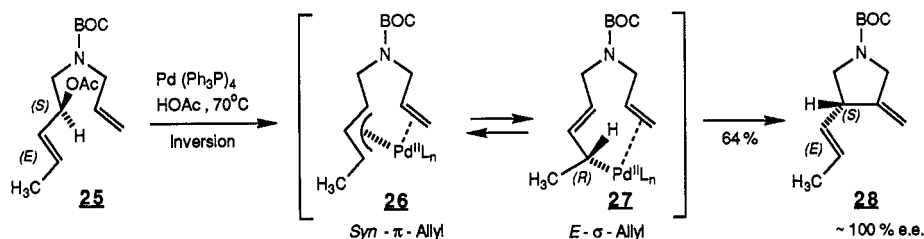
Scheme 10

These enantiodivergent reactions of (*E*)- and (*Z*)-acetoxydienes **25** and **29** indicate a predominant insertion of the olefinic bond into an (*E*)- σ-allyl or *syn*-π-allyl unit (*e.g.*, **27**, **32**).

The utility of Ni(0) complexes as catalysts for intramolecular 'metallo-ene' type reactions depends strongly on the metal ligands. Thus, a 1:1-mixture of Ni(COD)₂/dppb (10 mol%) catalyzed efficiently the allylation/elimination **34** → **35** → **36** whereas with the dppp ligand no reaction took place (ref. 6, 7, Scheme 11).

Scheme 11
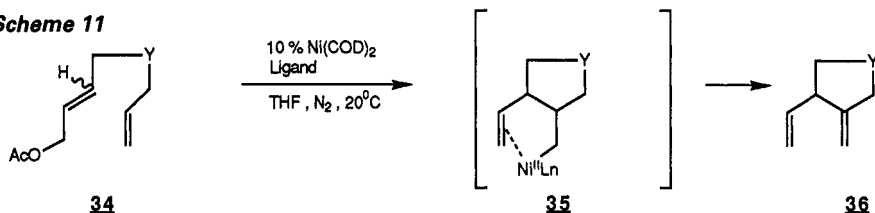
Bridge Y	Ligand (mol %)	Reaction Time [h]	Yield of **36** [%]
C(SO₂Ph)₂	PPh₃ (40)	18	55
NCO₂CH₂Ph	Ph₂P-(CH₂)₂-PPh₂ (100)	12	36
NCO₂CH₂Ph	Ph₂P-(CH₂)₃-PPh₂ (100)	12	0
C(SO₂Ph)₂	Ph₂P-(CH₂)₄-PPh₂ (10)	3	83
NCO₂CH₂Ph	Ph₂P-(CH₂)₅-PPh₂ (100)	12	81

³¹P-NMR measurements indicate the formation of a stable and inactive Ni(dppp)₂ complex. In contrast, we observed an equilibrium between the catalytically active and inactive species: 2 Ni(COD)dppb ⇌ Ni(COD)₂ + Ni(dppb)₂ (ref. 8).

Interesting stereochemical differences between nickel(0)- and palladium (0) catalyzed cyclizations were observed on trapping the cyclized alkylmetal intermediates with carbon monoxide (1 atm).

Ni(CO)₃PPh₃ (24 mol%) a stable, easy to handle solid (ref. 9) readily catalyzed the conversion of iodoenyne **37** to a 1:1-mixture of monocyclized (*Z*)-ester **39** and bicyclo [3.3.0] octenone **40**. Interestingly, complete bicyclization **37** → **40** could be achieved when using the bidentate ligand dppb (ref. 10, Scheme 12).
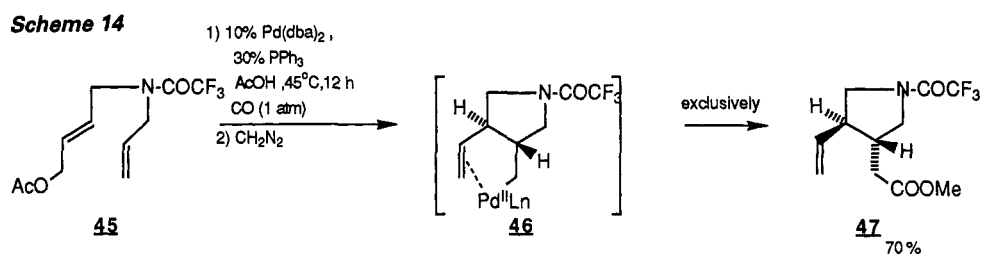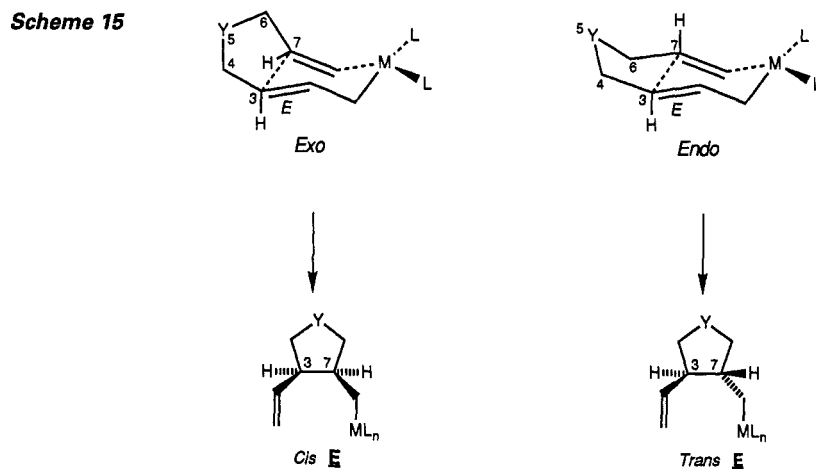
Scheme 12

Ni(CO)₃PPh₃ :	41 %	36 % (>26 : 1)
Ni(COD)₂/dppb :	-	87 % (27 : 1)
"[Ni(CO)₂dppb]" :		
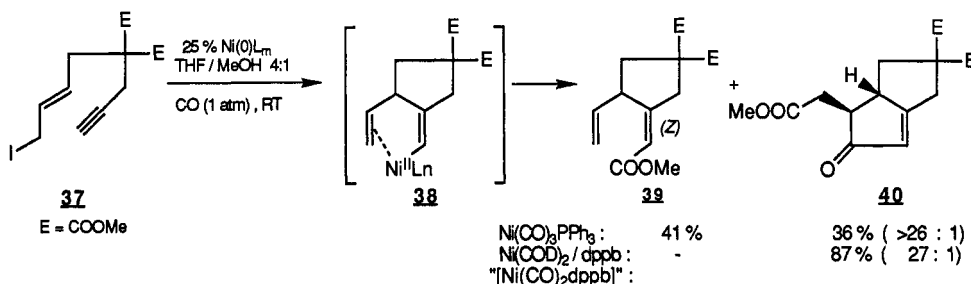
Similar treatment of dienyl iodide **41** with Ni(CO)₃PPh₃ or Ni(COD)₂/dppb led either to a mixture of **43 + 44** or exclusively to the bicyclic cyclopentanone **44**, respectively. It is worth noting that the *cis*-stereoisomer **42** was formed selectively and that carbonylation of **42** is faster than β-elimination (ref. 10, 11, Scheme 13).

Scheme 13

Ni(CO)₃PPh₃ :   28 %   47 % (4 : 1)
Ni(COD)₂ / dppb :   -   80 % (10 : 1)
"[Ni(CO)₂dppb]" :
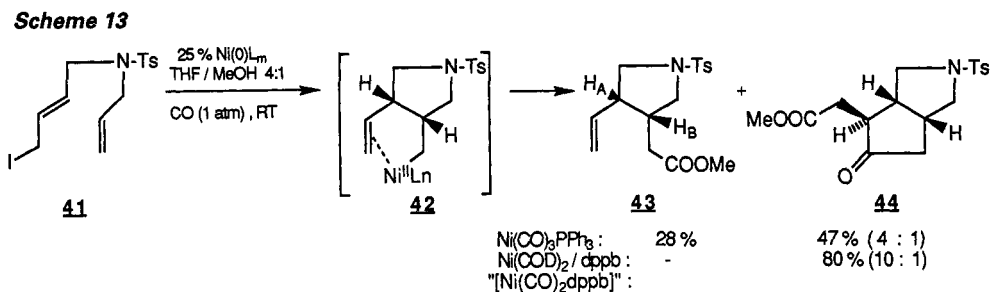
The opposite topicity was found on palladium(0)-catalyzed allylation/carbonylation of acetoxydiene **45** which provided (after esterification) only the *trans*-methyl ester **47** (ref. 11, 12, Scheme 14).

Scheme 14

Scheme 15 denominates this different orientation of the two involved π-faces in the transition state (analogous to the better-known Diels-Alder reaction) as *exo* or *endo* leading to *cis*- or *trans*- related metal donor and acceptor sites in the initial cyclization products **E**.

Scheme 15

Examination of models allowed us to predict that a (Z)-palladium-allyl unit is unlikely to yield a *trans*-substituted product **E** (Scheme 16).
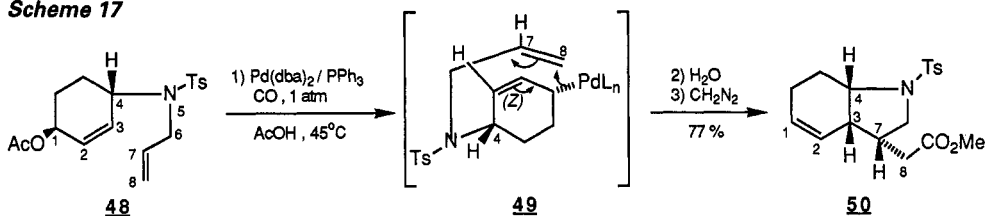
Scheme 16
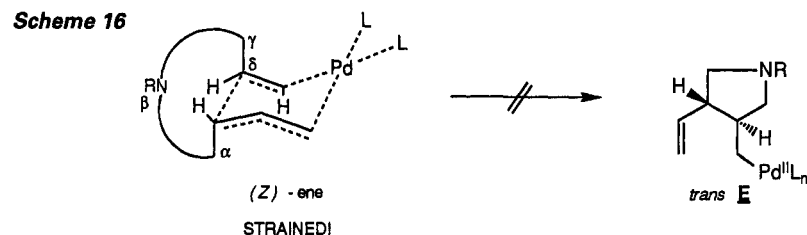
Hypothesis : Ene - cyclization of a *(Z)* - allyl - Pd unit does not give trans - substituted - five - membered rings.
Open - chain allyl - Pd - units insert *via* their *(E)* - configuration

Consequently, if the (Z)-configuration of the allylpalladium unit is enforced by incorporation into a ring (e.g. in 49) only cis-substituted products should be expected. Indeed, treatment of acetate 48 with Pd(dba)$_2$/PPh$_3$ under CO in AcOH, addition of water and esterification afforded exclusively all-cis-hexahydroindole 50 (ref. 11, Scheme 17).

Scheme 17

Another stereochemical issue concerns the topological influence of pre-existing over developing stereogenic centers in the carbometalation step. Schemes 18 to 20 deal with this topological control as to the formation of five-membered rings (ref. 11).
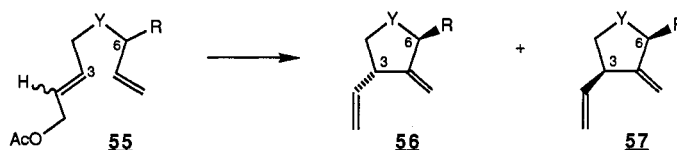
Scheme 18
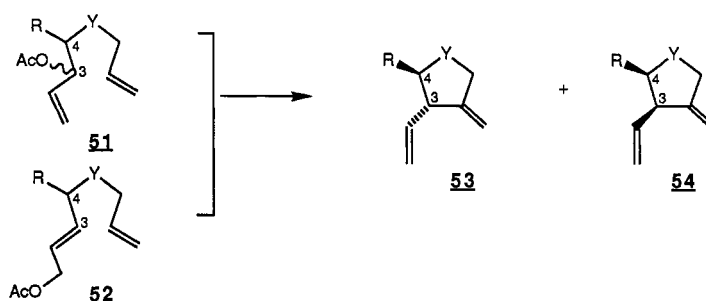
Starting Diene	Y	R	Catalyst [a] (mol %)	Yield 53 + 54	Ratio 53 / 54
51	O	n-C$_6$H$_{13}$	Pd (10)	83	88 : 12
51	O	n-C$_6$H$_{13}$	Ni (10)	85	97.4 : 2.6
52	CH$_2$	CH$_2$OBn	Pd (7)	72	92.6 : 7.4
52	CH$_2$	CH$_2$OBn	Ni (40)	74	97.7 : 2.3

a) Pd = Pd(dba)$_2$ / PPh$_3$ (1:3), AcOH, 80°C ; Ni = Ni(COD)$_2$, dppb (1:1),THF, 20 - 53°C

Scheme 19

Y	R	Catalyst [a] (mol %)	Yield 56 + 57	Ratio 56 / 57
O	n-C$_6$H$_{13}$	Pd (5)	62	52 : 48
O	n-C$_6$H$_{13}$	Ni (10)	79	> 99 : < 1
CH$_2$	CH$_2$OBn	Pd (10)	67	72 : 28
CH$_2$	CH$_2$OBn	Ni (10)	88	97.3 : 2.7

a) Pd = Pd(dba)$_2$ / PPh$_3$ (1:3), AcOH, 80°C ; Ni = Ni(COD)$_2$, dppb (1:1),THF, 20 - 51°C

Compared to the palladium(0) catalyzed cyclizations/eliminations of 51, 52 and 55, Ni(0) catalysis provided a significantly higher '1,2'- and '1,3' stereodirecting effect yielding almost exclusively *trans*-products 53 (from 51, 52) and 56 (from 55).

Scheme 20 illustrates the advantageous coincidence of high *exo-* and substituent-derived stereocontrol in such Ni(0)-catalyzed reactions.

Scheme 20

89 : 11
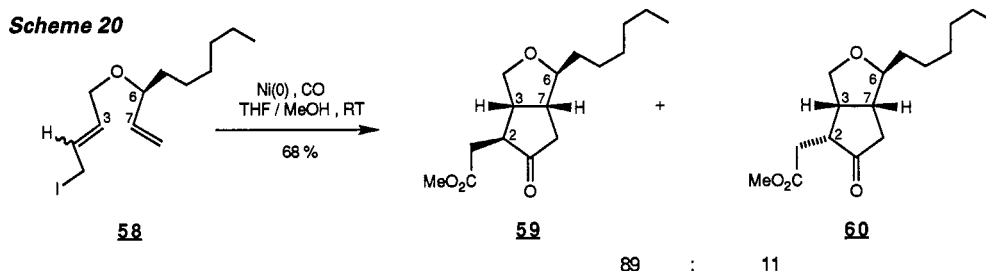
Thus, carbometalation/methoxycarbonylation of acyclic iododiene 58 furnished bicyclic ketoester 59 with ~100% control over centers C-3 and C-7 and 89% selectivity over center C-2.

This easy and stereocontrolled preparation of systems containing two annulated five-membered rings can be of value in natural products synthesis.

A formal synthesis of (±)-pentalenolactone E methylester 66 *via* a simple aproach to the key intermediate 65 serves as an example (ref. 13, Scheme 21).

Scheme 21
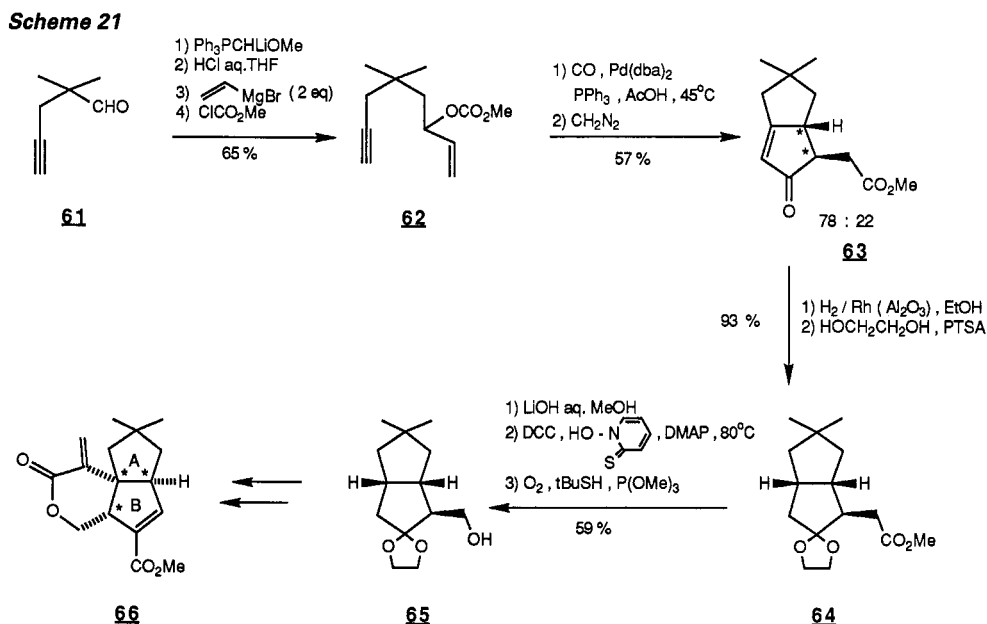
The conversions of (±)-65 into (±)-66 (ref. 14) and of (+)-65 into (-)-66 (ref. 15) have been previously described.

Further stereochemical aspects of such transition-metal catalyzed 'ene-type' cyclizations (*e.g.*, asymmetric induction by chiral ligands) as well as applications in synthesis are under current investigation.

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