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 A or B → E 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 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. 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.

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Moreover, we describe here a trapping of transient cyclization products $\Phi$ to form new carbon-carbon bonds, with concomitant regeneration of the catalyst $\Phi \rightarrow \Theta$ (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.

Scheme 4

This C-O $\rightarrow$ C-Pd $\rightarrow$ C-C chirality transfer also provides a selective route to either cis- or trans-fused hexahydroazulenes 11 and 14 (ref. 3, Scheme 5).
Scheme 6 exemplifies the enantiospecific preparation of hexahydropentalene 20 from readily available enantiomerically pure allyl acetate 16 (ref. 3).

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.

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).

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).
These enantiomeric reactions of (E)- and (Z)-acetoxydienes 25 and 29 indicate a predominant insertion of the olefinic bond into an (E)- u-allyl or syn-r-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 whereas with the dppp ligand no reaction took place (ref. 6, 7, Scheme 11).

Scheme 11

<table>
<thead>
<tr>
<th>Bridge</th>
<th>Ligand (mol %)</th>
<th>Reaction Time [h]</th>
<th>Yield of 36 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(SO$_2$Ph)$_2$</td>
<td>Ph$_3$P (40)</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>NC$_2$O$_2$Ph$_2$</td>
<td>Ph$_3$P-(CH$_2$)$_2$-Ph$_3$ (100)</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>NC$_2$O$_2$Ph$_2$</td>
<td>Ph$_3$P-(CH$_2$)$_3$-Ph$_3$ (100)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>C(SO$_2$Ph)$_2$</td>
<td>Ph$_3$P-(CH$_2$)$_2$-Ph$_3$ (10)</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>NC$_2$O$_2$Ph$_2$</td>
<td>Ph$_3$P-(CH$_2$)$_2$-Ph$_3$ (100)</td>
<td>12</td>
<td>81</td>
</tr>
</tbody>
</table>

$^{31}$P-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)$_2$/dppb = Ni(COD)$_2$ + Ni(dppp)$_2$ (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)$_2$PPh$_3$ (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 38 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).
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**

\[
\begin{align*}
0.25 \% \text{Ni(II)en} & \quad \text{THF/Methanol 4:1, CO (1 atm), RT} \\
& \quad \xrightarrow{\text{Ni(CO)₃PPh₃ or Ni(COD)₂/dppb}} \\
\text{41} & \quad \xrightarrow{\text{CO (1 atm), RT}} \quad \text{42} \\
& \quad \xrightarrow{\text{MeOOC}} \quad \text{43} \\
& \quad \xrightarrow{\text{H₂, CH}_3\text{N₂}} \quad \text{44}
\end{align*}
\]

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**

\[
\begin{align*}
1) 10\% \text{Pd(dba)₂, 30\% PPh₃, AcOH, 45°C, 12 h} & \quad \text{CO (1 atm), 2) CH₃N₂} \\
& \quad \xrightarrow{\text{Ni(II)en, AcOH, 45°C, 12 h, CO (1 atm), 2) CH₃N₂}} \\
\text{45} & \quad \xrightarrow{\text{PdL₅}} \quad \text{46} \\
& \quad \xrightarrow{\text{exclusively}} \quad \text{47}
\end{align*}
\]

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**

\[
\begin{align*}
(\text{Z}) \ - \ \text{ene} \\
\xrightarrow{\text{Pd} \ - \ \text{L}} \\
\text{trans} \ E
\end{align*}
\]

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 \(\text{Pd(dba)}_2/\text{PPh}_3\) under CO in \(\text{AcOH}\), 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

<table>
<thead>
<tr>
<th>Starting Dione</th>
<th>Y</th>
<th>R</th>
<th>Catalyst (^{a}))</th>
<th>Yield</th>
<th>Ratio (53/55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>O</td>
<td>(n-C_6H_{13})</td>
<td>Pd (10)</td>
<td>83</td>
<td>88 : 12</td>
</tr>
<tr>
<td>51</td>
<td>O</td>
<td>(n-C_6H_{13})</td>
<td>Ni (10)</td>
<td>85</td>
<td>97.4 : 2.6</td>
</tr>
<tr>
<td>52</td>
<td>CH(_2)</td>
<td>CH(_3)OBn</td>
<td>Pd (7)</td>
<td>72</td>
<td>92.6 : 7.4</td>
</tr>
<tr>
<td>52</td>
<td>CH(_2)</td>
<td>CH(_3)OBn</td>
<td>Ni (40)</td>
<td>74</td>
<td>97.7 : 2.3</td>
</tr>
</tbody>
</table>

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

Scheme 19

<table>
<thead>
<tr>
<th>Y</th>
<th>R</th>
<th>Catalyst (^{a}))</th>
<th>Yield</th>
<th>Ratio (56 / 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>(n-C_6H_{13})</td>
<td>Pd (5)</td>
<td>62</td>
<td>52 : 48</td>
</tr>
<tr>
<td>O</td>
<td>(n-C_6H_{13})</td>
<td>Ni (10)</td>
<td>79</td>
<td>&gt; 99 : &lt; 1</td>
</tr>
<tr>
<td>CH(_2)</td>
<td>CH(_3)OBn</td>
<td>Pd (10)</td>
<td>67</td>
<td>72 : 28</td>
</tr>
<tr>
<td>CH(_2)</td>
<td>CH(_3)OBn</td>
<td>Ni (10)</td>
<td>88</td>
<td>97.3 : 2.7</td>
</tr>
</tbody>
</table>

\(^{a})\) \(\text{Pd} = \text{Pd(dba)}_2/\text{PPh}_3 (1:3)\), \(\text{AcOH, 80°C}\); \(\text{Ni} = \text{Ni(COD)}_2, \text{dppb (1:1)}, \text{THF, 20 - 51°C}\)
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.

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 approach to the key intermediate 65 serves as an example (ref. 13, 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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REFERENCES


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