Metal catalyzed hydrometalations and their applications in synthesis

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Abstract: We report that palladium catalyzed hydrostannation of allenes leads to allylstannanes or vinylstannanes depending on the choice of catalyst. Hydrostannation of 1,6-diynes has also been investigated and shown to give 1,2-alkylidene-cyclopentanes bearing a tin group with (Z) stereochemistry. The effect of metal and ligand is discussed. Finally, an enantioselective nickel catalyzed reductive ring opening of three classes of oxabicyclic substrates has been developed and the methodology has been applied to the synthesis of sertraline, a commercially important antidepressant.

INTRODUCTION

Metal catalyzed hydrometalations are of significant interest due to the synthetic utility of the resulting organometallic products. We now describe two different transition metal catalyzed hydrometalation reactions. Palladium catalysts have been shown to promote the hydrostannation of allenes and diynes while nickel catalyzes the hydrometalation-ring opening of oxabicyclic substrates. These reactions open up new approaches to synthetically useful intermediates and precursors to bioactive compounds.

REGIOSELECTIVE HYDROSTANNATION OF ALLENES

We recently reported the palladium catalyzed hydrostannation of alkenes and showed that Pd(OH)2/C catalyzes the reaction of strained and unstrained alkenes whereas palladium complexes bearing phosphines react exclusively with strained alkenes (ref. 1).

The hydrostannation of allenes was of interest because there are two modes with which the H–Sn moiety can add across an allene (Scheme 1) and both classes of products are of significant synthetic utility. Addition of the tin to the central carbon of the allene gives a vinyl stannane, while addition to the terminal carbon gives an allyl stannane. Previous reports from the literature indicate that allylstannanes are the most commonly formed products (refs. 2,3).

SCHEME 1. Possible modes of addition of H-Sn to an allene

Hydrostannation of Allenic Alcohols and Ethers

A series of allenes were subjected to "ligandless" and ligand-containing palladium complexes and the results are shown in Tables 1 and 2 and equation 1. Remarkably the two catalysts give different products with Pd(Ph3P)4 favoring the production of allylstannanes and Pd(OH)2/C generating predominantly vinylstannanes. In both cases slow addition of Bu3SnH to a mixture of the allene and catalyst in THF gave the best yields. Neither the nature of the oxygen substituent nor the R group had any measurable effect on the outcome of the reactions. Reaction with a soluble catalyst lacking phosphine ligands, Pd2dba3, gave a very complex mixture of products containing several olefinic residues.
TABLE 1. Hydrostannation using Pd(PPh3)4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>P</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHx</td>
<td>H</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>CHx</td>
<td>MEM</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>t-Bu</td>
<td>2</td>
<td>67</td>
</tr>
</tbody>
</table>

* All reactions carried out at room temperature, 0.1 M in THF, syringe pump addition of HSnBu3 over 1.5h. * Isolated yield of a mixture of stereoisomers.

** TABLE 2. Hydrostannation using Pd(OH)2/C

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>P</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHx</td>
<td>H</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>CHx</td>
<td>MEM</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>CHx</td>
<td>TBDPS</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>n-C7H15</td>
<td>H</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>H</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>H</td>
<td>2</td>
<td>67</td>
</tr>
</tbody>
</table>

We also investigated the reactions of 1,6-diynes to determine if hydrostannation of the individual alkynes occurred or if a cyclization-hydrostannation would be possible. We see remarkable differences between ligandless catalysts and phosphine-containing palladium catalysts but have found conditions to generate synthetically useful 1,2-dialkylidene cyclopentanes containing a (Z)-tributylstannane moiety. 1,2-Dialkylidene cycloalkanes are useful building blocks in organic synthesis and other approaches including the cyclizations of 1,n-enynes or diynes using Zr, Ti, Ni or Pd have been reported (refs. 4-8).

The hydrostannation-cyclization is applicable to a range of substrate types (Table 3) including those with a heteroatom in the propargylic position (entries 4-7) giving in each case, good to excellent yields of the corresponding cyclized products 4a-g. Of particular note is the cyclization of dipropargyl sulfide 3f (entry 6) and sulfone 3g (entry 7) as it has been reported that substrates containing sulfur at the propargylic position are incompatible with homogeneous palladium catalysts (ref. 9).

** TABLE 3. The stannylative-cyclization of 1,6-diynes catalyzed by Pd(OH)2/C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X=C, Y'=Y2=MeO2C</td>
<td>3a</td>
<td>X=C, Y'=Y2=MeO2C</td>
</tr>
<tr>
<td>2</td>
<td>X=C, Y'=Y2=HOCH2</td>
<td>3b</td>
<td>X=C, Y'=Y2=HOCH2</td>
</tr>
<tr>
<td>3</td>
<td>X=C, Y'=Y2=PhCO2CH2</td>
<td>3c</td>
<td>X=C, Y'=Y2=PhCO2CH2</td>
</tr>
<tr>
<td>4</td>
<td>X=N, Y'=PhCH2</td>
<td>3d</td>
<td>X=N, Y'=PhCH2</td>
</tr>
<tr>
<td>5</td>
<td>X=O</td>
<td>3e</td>
<td>X=O</td>
</tr>
<tr>
<td>6</td>
<td>X=S</td>
<td>3f</td>
<td>X=S</td>
</tr>
<tr>
<td>7</td>
<td>X=S, Y'=Y2=O</td>
<td>3g</td>
<td>X=S, Y'=Y2=O</td>
</tr>
</tbody>
</table>

(a) Conditions: Reactions carried out with Bu3SnH (1.3 equiv, addition over 1 h), Pd(OH)2/C (5 mol%) in THF [0.1M], RT. (b) The [2] geometry of vinyl stannane 4 was proved by 1H-1H NOESY. (c) In addition to 4f, the product arising from mono-hydrostannation of 3f (with Sn terminal) was isolated in 9% yield.

When 1,6-diyne 3a was treated with various palladium catalysts several important observations were made. Phosphine-free catalysts such as Pd(OH)2/C, Pd/C, Pd(OAc)2 and Pd2(dba)3 all gave >75% yield of the cyclized product 4a. Conversely, the use of Pd2(dba)3 in the presence of 1 or 2 equivalents of PPh3 or 1 equivalent of dppb results in a complex reaction mixture containing less than 15% of 4a. Non-regioselective hydrostannylation of 3a was the major reaction pathway in the presence of phosphine ligands (hydrostannylation:stannylative-cyclization = approx. 7:1). These results suggest that the phosphine ligand occupies one of the coordination sites in a proposed Pd(II) intermediate thereby preventing formation of a chelate between the diyne and the metal bearing a hydride and tributylstannyl group.

Terminally substituted 1,6-diynes also undergo the cyclization although the nature of the substituent had a dramatic effect on the course of the reaction, Table 4. Thus, alkynone 5a undergoes hydrostannation-cyclization to furnish exclusively the α,β-unsaturated ketone 6a in 64% yield. In contrast, alkynol 5b gives a mixture of regioisomers 6b and 7b in 42% and 14% yield respectively (small quantities of 8b were also observed), pointing to electronic effects influencing the reaction pathway. Monosilylacetylene 5c undergoes regioselective hydrostannylation as the major reaction pathway to give terminal vinylstannane 8c in 59% yield (as opposed to stannyl-cyclization) while disilane 5d gave mostly recovered starting material.

**TABLE 4.** Terminally substituted 1,6-diynes as substrates for hydrostannation-cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Y=H, X=C(O)CH2CH3</td>
<td>5a</td>
<td>64%</td>
</tr>
<tr>
<td>2</td>
<td>Y=H, X=CH(OH)CH&amp;H&amp;H3</td>
<td>5b</td>
<td>6b:7b:8b = 9:2/1#</td>
</tr>
<tr>
<td>3</td>
<td>Y=H, X=TM3</td>
<td>5c</td>
<td>8c</td>
</tr>
<tr>
<td>4</td>
<td>Y=TM3, X=TM3</td>
<td>5d</td>
<td>Recovered 5d</td>
</tr>
</tbody>
</table>

(a) Ratio determined by 1H NMR of the crude reaction mixture. (b) Purification carried out by column chromatography on Et3N washed silica gel.

Dienyl stannanes 4 are useful synthetic intermediates as illustrated by the transformations shown in Scheme 2. Thus, Diels-Alder cycloaddition of 4a with N-phenylmaleimide gave 9 in 97% yield which upon treatment with BF3*Et2O underwent proto-destannylation with allylic rearrangement to give non-symmetrical tricycle 10 in 78% yield. A modified Stille-type coupling converted 4a into 11 in 60% yield although extended reaction times and low temperature were required to prevent isomerization of the aryl group to the thermodynamically favored (E)-stereoisomer (ref. 10). Homocoupling of stannyl diene 4a with Cu(NO3)2*3H2O gave 13 via a thermally allowed 8n electron conrotatory electrocyclization of 12 (ref. 11).

**SCHEME 2.** Synthetic elaboration of dienyl stannanes 4.
DEVELOPMENT OF AN ASYMMETRIC REDUCTIVE RING OPENING

As part of our efforts to control stereochemistry using rigid bicyclic precursors as templates (ref. 12), we sought a method of performing an enantioselective hydrometallation-ring opening on oxabicyclic substrates. Meso oxabicyclic alkenes are readily available via [4+3] or [4+2] cycloaddition reactions between furan and a suitable partner, and hydrometallation-ring opening would regenerate the alkene in enantiomerically enriched cycloalkenols, eq. 2.

\[
\begin{array}{c}
\text{O} \\
\text{H-M} \\
\text{M/L}^* \\
\text{O} \\
\end{array}
\xrightarrow{\text{H-M}}
\begin{array}{c}
\text{M} \\
\text{O} \\
\text{H} \\
\end{array}
\xrightarrow{\text{Ni(COD)2/BINAP}}
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{Me} \\
\end{array}
\]  
(2)

Cyclohexenes from [2.2.1] Systems

We have reported that diisobutylaluminum hydride (DIBAL-H) and heat or DIBAL-H and nickel complexes at room temperature catalyzes the reductive ring opening of oxabicyclic compounds (ref. 13). In the presence of a chiral phosphine such as BINAP, Ni(COD)\textsubscript{2} efficiently catalyzed the reductive cleavage reaction and gave enantiomerically enriched products. Interestingly, we found that the rate of addition of DIBAL-H to be crucial to the outcome of the reaction. When DIBAL-H was added over 1-2 min to 14 in the presence of a catalytic amount of Ni(COD)\textsubscript{2}/BINAP, the ee of 15 was 56%. When the rate of addition was slowed to 1 hour, the product was isolated in 97% yield and 97% ee, eq. 3.

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{OMe} \\
\end{array}
\xrightarrow{14 \text{ mol\% Ni(COD)2}}
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{OMe} \\
\end{array}
\xrightarrow{21 \text{ mol\% (R)-BINAP}}
\begin{array}{c}
\text{OH} \\
\text{OMe} \\
\text{OMe} \\
\end{array}
\]  
(3)

We have recently extended this investigation to the labile oxabenzonorbornadiene class of substrates which are much more sensitive than previously examined substrates. For example, reaction of 16 under our optimized conditions in toluene gave 6 in a 33% yield and 60% ee in addition to naphthalene and naphthol, Table 5 entry 1. By changing the solvent to THF, which would reduce the Lewis acidity of DIBAL-H, 16 could be ring opened to give 17 in 98% ee and 88% yield. A number of other oxabenzonorbornadienes were similarly studied to determine the scope of the reaction. The reaction was found to be quite sensitive to steric but insensitive to electronic effects. Both the electron donating dioxolane, entry 5, and the electron withdrawing difluoro compound, entry 6, gave the products in 94% and 96% ee respectively.

TABLE 5. Enantioselective Ring Opening Oxabenzonorbornadienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Time\textsuperscript{a}</th>
<th>Product</th>
<th>Yield\textsuperscript{b}</th>
<th>ee\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16 R,X,Y=H</td>
<td>PhMe</td>
<td>1</td>
<td>17 R,X,Y=H</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>THF</td>
<td>2</td>
<td>17</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>18 R=Me, X,Y=H</td>
<td>THF</td>
<td>16</td>
<td>18 R=Me, X,Y=H</td>
<td>66</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>20 R,Y=H, X=Me</td>
<td>THF</td>
<td>2</td>
<td>21 R,Y=H, X=Me</td>
<td>73</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>22 R,X=H, Y=OCH\textsubscript{2}O</td>
<td>THF</td>
<td>3</td>
<td>23 R,X=H, Y=OCH\textsubscript{2}O</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>24 R,X=H, Y=F</td>
<td>THF</td>
<td>3</td>
<td>25 R,X=H, Y=F</td>
<td>84</td>
<td>98</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Addition of DIBAL-H to a solution of Ni(COD)\textsubscript{2} (R)-BINAP and the alkene via syringe pump. \textsuperscript{b} Isolated yield. \textsuperscript{c} Measured by capillary GC (ChiralDEX G-TA or B-TA column) or chiral HPLC (Chiracel OD or OJ column).

Cycloheptenes from [3.2.1] Systems

We found that the corresponding oxabicyclo[3.2.1]octenes were significantly more difficult to open than the [2.2.1] systems. For example, treatment of 26 with DIBAL-H in the presence of the

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Ni(COD)$_2$/BINAP complex gave the cycloheptene 27 in only 20% yield and 56% ee. The major product was typically the oxabicyclo[3.2.1]octene 28, eq. 4.

We made the surprising discovery that conducting the reaction at 60 °C rather than at room temperature had a profound effect on the yield and enantioselectivity of the reaction. The ee's improved to 91-99.35% and the yields were in excess of 80% with many different substrates, Table 6. While inverse temperature effects of this kind have previously been observed in catalytic asymmetric processes (ref. 14), the effect was particularly dramatic effect with these substrates.

**TABLE 6. Enantioselective Ring Opening of Oxabicyclo[3.2.1]alkenes**

<table>
<thead>
<tr>
<th>Entry$^a$</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^c$</th>
<th>ee$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26 R=Me, X=H, Y=OMe</td>
<td>27 R=Me, X=H, Y=OMe</td>
<td>83-95</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>29 R=Me, X=H, Y=OTIPS</td>
<td>30 R=Me, X=H, Y=OTIPS</td>
<td>87</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3$^o$</td>
<td>31 R,X=H, Y=OMe</td>
<td>32 R,X=H, Y=OMe</td>
<td>67</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>33 R,X=H, Y=OH</td>
<td>ent-34 R,X=H, Y=OH</td>
<td>89</td>
<td>99.3</td>
</tr>
<tr>
<td>5$^f$</td>
<td>35 R,Y=H, X=OBn</td>
<td>36 R,Y=H, X=OBn</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ For all reactions, DIBAL-H was added over 4 h at 60 °C (oil bath), unless otherwise noted. DIBAL-H added over 16 h. $^b$ Isolated yield. $^c$ Measured by GC (Chiraldex G-TA or B-TA column) or HPLC (Chiralcel OD or OJ column) or Mosher’s ester. $^d$ 4 mol% Ni(COD)$_2$, 8 mol% (S)-BINAP was used and DIBAL-H was added over 12 h at 65 °C. $^f$ 4 mol% Ni(COD)$_2$, 8 mol% (S)-BINAP was used and the substrate was pretreated with one equiv. of DIBAL-H.

The effect of temperature on the ee in [3.2.1] systems is most dramatically illustrated by substrate 37. At ambient temperature, the ee of the product 38 is 56%. At 60 °C, the ee improves to 81% while at 80 °C 38 is obtained in 97% ee.

This temperature effect is not limited to the asymmetric reaction, but it does require the presence of a phosphine, Scheme 3. Reaction of 35 at 60 °C in the absence of a phosphine ligand has no effect on the ring opening as compared to the reaction at room temperature. However, in the presence of either dppb or BINAP, the hydrogenated alkene is not observed.

**SCHEME 3. Comparison of ring opening in presence and absence of phosphine.**

Total Synthesis of Sertraline

We have applied the enantioselective reductive ring opening reaction in the synthesis of the clinically important antidepressant agent sertraline (ref. 15). Silylation, bromination and dehydrobromination of the alcohol 41 gave the vinyl bromide 42 in >85% yield over three steps. A Stille coupling under Farina’s conditions (ref. 16) followed by desilylation provided the alcohol 43 in 64% yield over two steps. Crabtree’s catalyst (ref. 17) was employed to effect a directed reduction of the olefin providing the desired epimer with 28:1 selectivity and 88% isolated yield. The alcohol was converted to the azide 44 (ref. 18) in 88% yield and reduction and methylation provided sertraline in 86% yield over three steps. The synthesis required 8 steps and gave an overall yield of 33%, Scheme 4.

SCHEME 4. The Synthesis of sertraline

CONCLUSIONS

Palladium catalyzed hydrostannation reactions of allenes and 1,6-diynes have been shown to lead to synthetically useful tin-containing products in moderate to excellent yields. Issues relating to mechanism and the nature of the catalytically important species are the subjects of our ongoing experiments. Our work on nickel catalyzed hydrometalation reactions has yielded a new approach to enantiomerically pure cyclohexenols, cycloheptenols and hydroxydihydronaphthalenes. We continue to search for information on the sequence of events which lead to the final ring opened products.

References
