Molybdenum-Catalyzed Asymmetric Allylic Alkylation

\[ \text{R-\(\text{\=C-H}X\)} \xrightarrow{\text{MoL}_n} \text{Nu} \rightarrow \text{Nu} \quad \text{R}\quad \text{*-\=C-H} \]
Asymmetric Allylic Alkylation from a Synthetic Viewpoint

- form a C-C bond with the creation of a new stereogenic center
- use readily accessible starting materials
- allow to an opportunity to perform dynamic kinetic transformation
- can be performed catalytically
- be able to predict the stereochemical outcome
- High regio-and enantioselectivity is achievable.

Tyranavir (phase II clinical trials)
a therapeutic agent used to combat HIV

advanced intermediate (Merck)
Allylic Alkylation from a Historical Viewpoint


Tsuji, J et al. J. Am. Chem. Soc. 1965, 84, 3275 (Addition of malonate Nu to cyclooctadiene activated by PdCl₂)

63% isolated yield

66% isolated yield

[] = -5.81 (20% optical yield)
Regioselective Issue in Metal-Catalyzed Allylic Alkylation


General Mechanism

Linear

Branched substrate

chiral racemic
Molybdenum-Catalyzed Asymmetric Allylic Alkylation

\[
\text{R} \text{OCO}_2\text{Me} \xrightarrow{\text{NaCH}_2(\text{CO}_2\text{Me})_2, (\text{EtCN})_3\text{Mo(CO)}_3 \text{ (10 mol%)}, \text{THF}} \text{MeO}_2\text{C}_2\text{CO}_2\text{Me} + \text{MeO}_2\text{C}_2\text{R}_1\text{CO}_2\text{Me}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R(_1)</th>
<th>T, °C</th>
<th>time, h</th>
<th>yield</th>
<th>4/5</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>reflux</td>
<td>3</td>
<td>88</td>
<td>32/1</td>
<td>99</td>
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<td>2</td>
<td>Ph</td>
<td>H</td>
<td>rt</td>
<td>3</td>
<td>70</td>
<td>49/1</td>
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<td>Me</td>
<td>reflux</td>
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<td>67</td>
<td>24/1</td>
<td>98</td>
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<tr>
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<td>Ph</td>
<td>Me</td>
<td>reflux</td>
<td>2</td>
<td>71</td>
<td>32/1</td>
<td>97</td>
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<table>
<thead>
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<th>R</th>
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<th>T, °C</th>
<th>time, h</th>
<th>yield</th>
<th>4/5</th>
<th>ee%</th>
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<td>2</td>
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<td>rt</td>
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<td>61</td>
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<td>78</td>
<td>19/1</td>
<td>88</td>
</tr>
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<td>2-pyridyl</td>
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<td>69</td>
<td>8/1</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>2-pyridyl</td>
<td>Me</td>
<td>reflux</td>
<td>2</td>
<td>71</td>
<td>5/1</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>2-thienyl</td>
<td>Me</td>
<td>reflux</td>
<td>2</td>
<td>71</td>
<td>13/1</td>
<td>75</td>
</tr>
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</table>

Linear versus Branched: Mechanistic Implication

![Diagram of chemical reaction]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R₁</th>
<th>T, °C</th>
<th>time, h</th>
<th>yield</th>
<th>4/5</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>reflux</td>
<td>3</td>
<td>88</td>
<td>32/1</td>
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<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>rt</td>
<td>3</td>
<td>70</td>
<td>49/1</td>
<td>99</td>
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<td>3</td>
<td>Ph</td>
<td>H</td>
<td>reflux</td>
<td>3</td>
<td>70</td>
<td>13/1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>H</td>
<td>rt</td>
<td>3</td>
<td>61</td>
<td>32/1</td>
<td>97</td>
</tr>
</tbody>
</table>

Whether p-allyl molybdenum complexation or the subsequent nucleophilic attack determines the stereochemical outcome of the product.

### Branched Substrates: Solvent Effects on Enantioselectivity

![Chemical structures and reaction scheme]

**Reaction Scheme:**

\[
\text{NaCHR(CO}_2\text{Me)}_2 (1.5 \text{ equiv}) \rightarrow \text{MeO}_2\text{C-CO}_2\text{Me} + \text{MeO}_2\text{C-CO}_2\text{Me}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>(T, \degree C)</th>
<th>(2/3)</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>48</td>
<td>25/1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>60</td>
<td>46/1</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>48</td>
<td>23/1</td>
<td>83</td>
</tr>
</tbody>
</table>

(S) isomer is the fast-reacting enantiomer, 98% ee and 35/1 branched/linear selectivity during the first half of the reaction according to chiral HPLC traces and independent synthesis of 1.

Control experiment:

\[
\text{R} \text{COC} \rightarrow \text{MeO}_2\text{C-CO}_2\text{Me} \quad 2/3 = 35/1, 97\% \text{ ee}
\]

Branched Substrates: Matched and Mismatched Cases

Matched case

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\text{N}-\text{CH} & \quad \text{CH}_2-\text{C} \\
\end{align*}
\]

\((\text{R})\)-ent. 1

\[
\begin{align*}
\text{NaCHR(CO}_2\text{Me})_2 & \quad (1.5 \text{ equiv}) \\
(C_7\text{H}_8)\text{Mo(CO)}_3 & \quad (10 \text{ mol}%) \\
\end{align*}
\]

\(\xrightarrow{(\text{R,R}) \ 4 \ (15 \text{ mol}%), \ 48 \degree \text{C}}\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CH} \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{CH} & \quad \text{CH}_2-\text{C} \\
\end{align*}
\]

\((\text{S}) \ 2 + \ (\text{R}) \ 3\)

\(2/3 = 55/1, > 99\% \text{ ee}\)

obtained by kinetic resolution

Mismatched case

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\text{N}-\text{CH} & \quad \text{CH}_2-\text{C} \\
\end{align*}
\]

\((\text{R})\)-ent. 1

\[
\begin{align*}
\text{same rxn conditions} \\
(\text{S,S}) \ 4 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CH} \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{CH} & \quad \text{CH}_2-\text{C} \\
\end{align*}
\]

\((\text{R}) \ 2 + \ (\text{R}) \ 3\)

\(2/3 = 12/1, 70\% \text{ ee}\)

“modest stereochemical memory effect”

Possible Explanation for Solvent Effects on Selectivity

Since both carbonate enantiomers give the same major alkylated product when the same catalyst enantiomer is used, diastereomeric equilibration must take place along the reaction path.

If $K_S$ and $K_R$ are fast relative to $k_1$, $k_2$, $k_3$, and $k_4$, then enantioselectivity is under Curtin-Hammett control. Thus, the concentration of II and II-epi diastereomers is not important.

Experimentally, the two carbonate enantiomers do not give the same ee and branched/linear ratio. This suggests that the rate of equilibration of II and II-epi must be competitive with the nucleophilic displacement steps.

Efforts towards Understanding Molybdenum-Ligand Interactions

Table 1: chelating effects

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
<th>2/3</th>
<th>ee%</th>
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<tbody>
<tr>
<td>1</td>
<td>(S,S) 1a</td>
<td>95</td>
<td>35/1</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>93</td>
<td>46/1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>90</td>
<td>60/1</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>35</td>
<td>1/1</td>
<td>24</td>
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**Variation in the Chiral Backbone of Ligands**

![Chemical structure of ligand](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>2/3</th>
<th>ee%</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image of ligand 1b" /></td>
<td>93</td>
<td>13/1</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image of ligand 8" /></td>
<td>84</td>
<td>10/1</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image of ligand 9" /></td>
<td>92</td>
<td>6/1</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Image of ligand 10" /></td>
<td>43</td>
<td>9/1</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Image of ligand 11" /></td>
<td>72</td>
<td>8/1</td>
<td>90</td>
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</table>

The Role of the Secondary Amide Nitrogens

The role of the secondary amide nitrogens is crucial for achieving catalytic activity. The reaction scheme shows the use of (C_7H_8)Mo(CO)_3 (10 mol%) and NaCHR(CO_2Me)_2 (2 equiv) to produce a mixture of products, with 2/3 = 35/1, 95% yield, and 97% ee for a specific ligand 1a. However, ligand 12 is 200-fold less active than 1a and shows poor enantioselectivity, while ligand 13 shows no observable reaction. The reaction conditions are 15 mol% ligand, 80-90 °C in THF.

Attempt to identify the Catalytically Active Species

\[
\begin{align*}
\text{10} & \rightarrow \text{11} \\
\text{11} & \rightarrow \text{12} \\
\text{12} & \rightarrow \text{12, situ generated} \\
\text{12} & \rightarrow \text{12, isolated}
\end{align*}
\]

\[\text{Amide nitrogens: 133 ppm, 123 ppm} \]
\[118 \text{ ppm, 119 ppm (free ligand)} \]
\[\text{Pyridine nitrogen: 273 ppm} \]
\[304 \text{ ppm (free ligand)} \]

A CO source is needed for achieving catalytic activity.

Solution and Solid State Studies of the Reactive Intermediate

11

situ generated

1-H

or

THF-d8, NaCHR(CO2Me)2 (1 equiv)

as above

12

Amide N: 130 ppm, 175 ppm
118 ppm, 119 ppm (free ligand)
Pyridine N: 263 ppm
304 ppm (free ligand)

Other structures:

A

B

A B

Possible Pathways for [■]-allyl Intermediates to Interconvert

Mechanistic possibilities:
1. Mo*1S2S isomer recrystallizes preferentially and Nu attacks Mo*1R2R isomer with inversion.
2. Mo*1S2S and Mo*1R2R are in rapid equilibrium, and Mo*1R2R is the more reactive intermediate and reacts by inversion (selectivity is under Curtin-Hammett control).
3. Mo*1S2S isomer in solution and crystal and the nucleophilic addition occurs with retention of configuration.

Deterium-Labeling Experiments

1. In reaction [1] about 3% of trans-4-D corresponds well with the 4% enantiomer present in the SM. This means that little or no scrambling of the deuterium occurs in the reaction.

2. In reaction [2], about 7% nontransposed product indicates that no more than 3% of the reaction can occur with scrambling of the label since the SM has 96/4 er. and reacts by inversion (selectivity is under Curtin-Hammett control).

\( ^1 \text{H NMR Studies of } \alpha\text{-Allyl Molybdenum Complexes} \)

Stoichiometric reactions:

\[
\begin{align*}
\text{1-H} & \quad \text{or} \quad \text{2-H} \quad \text{or} \quad \text{3-H} \\
\text{MeO}_2\text{CO} & \quad \text{Ph} \quad \text{or} \quad \text{Ph} \quad \text{or} \quad \text{Ph} \\
\text{1-D (S)} & \quad 96/4 \text{ er} \\
\text{2-D (R)} & \quad 96/4 \text{ er} \\
\end{align*}
\]

\[
\begin{align*}
\text{[Mo] ligand 10} & \quad \text{THF-d8, rt} \\
\text{12} & \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{cis-4-D (R)} & \quad \text{NaCH(CO}_2\text{Me)}_2 \\
\text{trans-4-D (R)} & \quad \text{NaCH(CO}_2\text{Me)}_2
\end{align*}
\]

\( ^1 \text{H NMR Studies of } \alpha\text{-Allyl Molybdenum Complexes} \)

The results of experiments 1 & 2 confirm that the reaction proceeds by retention-retention pathway.

Mechanistic Pathways for the Formation of Cis-4-D and Trans-4-D Products

Linear Chiral Allylic Substrates

Catalytic reaction:

\[ \text{Catalytic reaction:} \]

\[
\begin{align*}
\text{Ph} \text{HOCO}_2\text{Me} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{trans-4-D} & 96\% \text{ ee} \\
\text{Ph} \text{HOCO}_2\text{Me} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{cis-4-D} & 96\% \text{ ee} \\
\text{Ph} \text{HOCO}_2\text{Me} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{cis-ent-4-D} & 4.5\% \\
\text{Ph} \text{HOCO}_2\text{Me} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{13-D} & 4.5\% \\
\end{align*}
\]

Less than 2% of oxidative addition occurred with inverted stereochemistry.

Stoichiometric reaction:

\[ \text{Stoichiometric reaction:} \]

\[
\begin{align*}
\text{PhHOCO}_2\text{Me} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{2-D (R) 96/4 er} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{NaCH(CO}_2\text{Me})_2 & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{trans-4-D (R)} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\text{10} & \rightarrow \text{MeO}_2\text{C}\text{CO}_2\text{Me} \\
\end{align*}
\]

Again, the reaction proceeds by a double retention pathway.

The X-ray Structure of the Protio Complex vs its Solution Structure

Competition experiments:

If 12 was the minor isomer and required equilibration to the major isomer (7) before undergoing nucleophilic addition, then both the 3-F substituted and unsubstituted products should exhibit a memory effect and have similar, low ee.

If 12 is the major complex (7) and requires no equilibration, then a high ee should result.

Proposed Mechanism for Product Formation

- The ligand binds to Mo in a tridentate fashion
- CO is imperative for the reaction to take place
- Allyl substrates react with overall retention of configuration
- S,S catalyst gives product with R configuration
- Independent synthesis of 16 which has activity the same as that of 12

Heating $(\text{EtCN})_3\text{Mo(CO)_3}$ can generate ethylene and HCN, thus raising a safety issue.

Searching for Different Molybdenum Precatalysts

![Diagram]

1.5 equiv

\[
\text{N} \quad \text{NH} \quad \text{O} \quad \text{HN} \quad \text{O} \quad \text{N}^{1}(\text{S,S}) + \text{Mo(CO)}_{6} \quad \overset{85-90 \, ^{0}\text{C}}{\longrightarrow} \quad \text{LnMo(CO)}_{4}
\]

1.5 equiv

\[
\text{MeO}_{2}C \quad \text{O} \quad \text{NaCH}_{2}(\text{CO}_{2}\text{Me})_{2} \quad [\text{Mo}] \quad (10 \, \text{mol}\%)
\]

\[
\text{MeO}_{2}C \quad \text{CO}_{2}\text{Me} \quad \overset{1 \, (15 \, \text{mol}\%), \text{toluene}}{\longrightarrow} \quad \text{F}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Activation Time (h)</th>
<th>Activation Temp(°C)[c]</th>
<th>% ee of 3[b]</th>
<th>Branched:Linear</th>
<th>% Assay Yield[d]</th>
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</thead>
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<tr>
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<td>0.75</td>
<td>85</td>
<td>95</td>
<td>95:5</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>4</td>
<td>85</td>
<td>97</td>
<td>95:5</td>
<td>91(84)</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>15</td>
<td>89</td>
<td>89</td>
<td>92:8</td>
<td>91</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 10 mol% Mo(CO)$_{6}$, 15 mol% ligand 1, 2.0 equiv dimethyl sodiomalonate, 0.15 M substrate 2, reaction time: 8–12 h.

[b] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 µm particle diameter).

[c] The activation temperature [Mo(CO)$_{6}$ + ligand 1 in solvent] is also the alkylation reaction temperature.

[d] Yield in parentheses represent isolated product yield with purity >95% as determined by HPLC and $^1$H NMR.

---

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mo-precataltyst[b]</th>
<th>Solvent</th>
<th>Activation Time (h)</th>
<th>Activation Temp(°C)[c]</th>
<th>% ee of 3[d]</th>
<th>Branched:Linear</th>
<th>% Assay Yield of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(EtCN)$<em>{3}$Mo(CO)$</em>{5}$</td>
<td>toluene</td>
<td>0.5</td>
<td>85</td>
<td>95</td>
<td>95:7</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>(C$<em>{2}$H$</em>{8}$)Mo(CO)$_{5}$</td>
<td>toluene</td>
<td>0.5</td>
<td>85</td>
<td>96</td>
<td>96:4</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Mo(CO)$_{6}$</td>
<td>toluene</td>
<td>4</td>
<td>85</td>
<td>97</td>
<td>95:5</td>
<td>91</td>
</tr>
</tbody>
</table>

[a] Results represent the average of two or more runs.

[b] (EtCN)$_{3}$Mo(CO)$_{5}$ was prepared using a literature procedure, see reference 7.

[c] The activation temperature [Mo(CO)$_{6}$ + ligand 1 in solvent] is also the subsequent alkylation reaction temperature.

[d] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 µm particle diameter).

Molybdenum-Catalyzed Asymmetric Allylic Alkylation in Large Scale Synthesis

Completion of the Synthesis

1.5 kg scale

56% overall yield starting from 3-fluorobenzaldehyde.

Summary

- Molybdenum-catalyzed allylic alkylation is a general reaction.
- Ligands and solvents can greatly influence both regio- and enantioselectivity.
- The reaction proceeds by a retention-retention pathway.
- Modest stereochemical memory effect is observed in the case of chiral racemic substrates.
- Labeling, solution, and solid state studies have shed light on the identity of the catalytically active species.
- The reaction has great potential for synthetic application.