Brown Allylation and Crotylation Reactions

Reviews:

Synthesis of 2-Allyldiisopinocampheylborane

\[
\begin{align*}
\text{H}_3C & \quad \text{CH}_3 \\ + & \quad \text{H}_3B\text{S(CH}_3)_2 \\ \text{THF}, 0^\circ C & \quad 72 \text{ h}, 72\% \\
\text{CH}_3 & \quad \text{B}_2 \quad \text{H}_2 \\ \text{CH}_3O\text{H}, 1 \text{ h} & \quad 0^\circ C, 100\% \\
\end{align*}
\]

- Prolonged incubation at 0 °C affords enantiomerically enriched \text{Ipc}_2\text{BH}. This is due to equilibration of tetraisopinocampheyldiborane with \( \alpha \)-pinene and triisopinocampheyl-diborane; the symmetrical dimer crystallizes preferentially.
- Both enantiomers of \( \alpha \)-pinene are commercially available and inexpensive.
- 2-Allyldiisopinocampheylborane can be prepared and used in situ after filtration of the magnesium salts produced during its formation.


Enantioselective Allylboration

\[
\begin{align*}
\text{R} & \quad \text{yield} (\%) \quad \text{ee} (\%)^a \quad \text{ee} (\%)^b \\
\text{CH}_3 & \quad 74 \quad 93 \quad \geq 99 \\
n-C_3H_7 & \quad 71 \quad 86 \quad - \\
n-C_4H_9 & \quad 72 \quad 87 \quad 96 \\
t-C_4H_9 & \quad 88 \quad 83 \quad \geq 99 \\
C_6H_5 & \quad 81 \quad 96 \quad 96 \\
\end{align*}
\]

- Allylboration carried out without filtration of Mg salts. ^b Allylboration carried out at −100 °C under Mg-salt free conditions.
- The reaction is quite general; the stereochemistry of the addition is the same in all cases examined.
- Lower reaction temperatures (0 → −78 → −100 °C) lead to increased enantioselectivity.
- Only Mg-salt free reagent can be used at −100 °C because the reactive borane is sequestered by ate complex formation with CH\(_3\)OMgBr at this temperature.
- Allylboration of aldehydes is essentially instantaneous at −78 or −100 °C in the absence of Mg salts.
- Allylboration proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.


M. Movassaghi
Asymmetric Isoprenylation of Aldehydes

\[ (+)-\text{Ipc}_2\text{BH} + \text{CH}_3\equiv\text{CH} \rightarrow \text{THF} \rightarrow -25^\circ \text{C}, 6 \text{ h} \]

- Hydroboration of allenes is an efficient method for preparing B-prenyldiisopinocamphorboranes.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3</td>
<td>73</td>
<td>91</td>
</tr>
<tr>
<td>n-C_3H_7</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>CH_2=CH</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>(CH_3)_2C=CH</td>
<td>85</td>
<td>96</td>
</tr>
</tbody>
</table>


Methallylation of Aldehydes

\[ (+)-\text{Ipc}_2\text{BOCH}_3 + \text{LiEt}_2\text{O} \rightarrow -78^\circ \text{C}, 1 \text{ h} \]

- The yields for methallylation of aldehydes are generally lower than in simple allylation reactions.

Diastereoselective Allylboration of Chiral, \( \alpha \)-Substituted Aldehydes

- The diastereofacial selectivity of the B-allyldiisopinocampheylborane reagent typically overrides any facial preference of the aldehyde for nucleophilic attack.

\[ \text{H}_3\text{C}=\text{O} \rightarrow \text{allylboration} \rightarrow \text{H}_2\text{O}_2, \text{Et}_2\text{O}, -78^\circ \text{C} \]

\[ \text{MISMATCHED:} \quad (+)-\text{Ipc}_2\text{BCH}_2\text{CH} = \text{CH}_2 \quad 5 \quad 96 \quad 92\% \text{ de} \]

\[ \text{MATCHED:} \quad (-)-\text{Ipc}_2\text{BCH}_2\text{CH} = \text{CH}_2 \quad 96 \quad 4 \quad 92\% \text{ de} \]

Chair TS's Produce syn Adducts from (Z)-Crotylboranes and anti Adducts from (E)-Crotylboranes.

* (Z)-crotylborane*  "syn adduct"

* (E)-crotylborane*  "anti adduct"

- These adducts can be viewed as protected aldol products; "deprotection" is brought about by dihydroxylation/periodate cleavage or by ozonolysis.


(Z)-Crotylboranes

![Diagram of reactions involving (Z)-crotylboranes and (E)-crotylboranes](image)

<table>
<thead>
<tr>
<th>Ipc</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>A:B</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH₃CHO</td>
<td>75</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>CH₃CHO</td>
<td>72</td>
<td>4:96</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>C₂H₅CHO</td>
<td>70</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C₂H₅CHO</td>
<td>78</td>
<td>4:96</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>CH₂=CHCHO</td>
<td>63</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C₆H₅CHO</td>
<td>72</td>
<td>94:6</td>
<td>88</td>
</tr>
</tbody>
</table>

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by BF₃•OEt₂ at –78 °C to avoid crotyl isomerization.

"Superbases" for Organic Synthesis

- The "superbase" prepared by mixing n-butyllithium and potassium t-butoxide (1:1) can metalate hydrocarbons of low acidity, in particular olefins.
- Allylic methyl groups are much more readily metalated than allylic methylene or methine centers.
- cis-2-alkenes generally react faster than their trans-isomers.
- The large atomic radius of potassium favors π₃-bonding in allyl, crotyl and prenyl derivatives:

![Diagram of superbase structure](image)


M. Movassaghi
(E)-Crotylboranes

\[
\begin{align*}
\text{H}_3\text{C} & \text{CH}_3 & \text{n-BuLi, KOt-Bu} & \text{THF} & -45^\circ\text{C} & \rightarrow & \text{CH}_3\text{K}^+ \\
& & & \text{(-)-Ipc}_2\text{BOCH}_3 & -78^\circ\text{C} & \rightarrow & \text{CH}_3\text{B} \text{-OCH}_3 \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{CH}_3 & \text{C} & \text{D} & \text{RCHO, –78 °C; NaOH, H}_2\text{O}_2 & \rightarrow & \text{RCHO} \text{-78 °C} \\
& & & & & & \text{BF}_3\text{•OEt}_2 \text{-78 °C}
\end{align*}
\]

**Table:**

<table>
<thead>
<tr>
<th>Ipc</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>C:D</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>CH₃CHO</td>
<td>78</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td>+</td>
<td>CH₃CHO</td>
<td>76</td>
<td>4:96</td>
<td>92</td>
</tr>
<tr>
<td>–</td>
<td>C₂H₅CHO</td>
<td>70</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td>+</td>
<td>C₂H₅CHO</td>
<td>69</td>
<td>4:96</td>
<td>92</td>
</tr>
<tr>
<td>–</td>
<td>CH₂=CHCHO</td>
<td>65</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td>–</td>
<td>C₆H₅CHO</td>
<td>79</td>
<td>94:6</td>
<td>88</td>
</tr>
</tbody>
</table>

* The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by BF₃•OEt₂ at –78 °C to avoid crotyl isomerization.

Diastereo- and Enantioselective vic-Diol Synthesis

\[
\begin{align*}
\text{OCH}_3 & \text{OCH}_3 & \text{s-BuLi} & \text{THF, –78 °C} & \rightarrow & \text{(-)-Ipc}_2\text{BOCH}_3 \\
& & & -78^\circ\text{C} & \rightarrow & \text{CH}_3\text{B} \text{-OCH}_3 \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{CH}_3 & \text{R} & \text{RCHO} & \text{HOCH}_2\text{CH}_2\text{NH}_2 & \rightarrow & \text{RCHO, –78 °C; (crystalline)} \\
& & & & & & \text{BF}_3\text{•OEt}_2 \text{-78 °C}
\end{align*}
\]

**Table:**

<table>
<thead>
<tr>
<th>Ipc</th>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>E:F</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>CH₃CHO</td>
<td>57</td>
<td>95:5</td>
<td>90</td>
</tr>
<tr>
<td>+</td>
<td>CH₃CHO</td>
<td>59</td>
<td>4:96</td>
<td>92</td>
</tr>
<tr>
<td>–</td>
<td>C₂H₅CHO</td>
<td>65</td>
<td>96:4</td>
<td>92</td>
</tr>
<tr>
<td>+</td>
<td>C₂H₅CHO</td>
<td>68</td>
<td>5:95</td>
<td>90</td>
</tr>
<tr>
<td>–</td>
<td>CH₂=CHCHO</td>
<td>63</td>
<td>94:6</td>
<td>88</td>
</tr>
<tr>
<td>–</td>
<td>C₆H₅CHO</td>
<td>72</td>
<td>95:5</td>
<td>90</td>
</tr>
</tbody>
</table>

* Treatment of the crude product mixture with ethanolamine allows for easy removal of the reagent by-product as a crystalline adduct; this is an alternative to oxidative work-up.

* Other vinyl ethers may be used, such as methoxymethyl vinyl ether (affording the MOM-protected vic-diol).


M. Movassaghi
Roush Allylation and Crotylation Reactions


Preparation of (E)- and (Z)-Crotylboration Reagents

1. B(Oi-Pr)3
   Et2O, –78 °C
2. 2N HCl, Et2O
3. (+)-DIPT, MgSO4

77%

• The stability of allylboration reagents permits their purification by distillation. Allyl diisopinocamphenyl reagents cannot be distilled.

1. B(OCH3)3
   Et2O, –78 °C
2. 1N HCl, Et2O
3. DIPT, MgSO4

70-75%

• Crotylborationates are configurationally stable at or slightly above room temperature.

• Tartrate-modified (E)- and (Z)-Crotylborationates can be stored for several months at –20 °C in neat form or in solution with little noticeable deterioration.

• Competition experiments have shown that (E)-crotylborationates react faster with aldehydes than the corresponding (Z)-isomers.

• Essentially identical results are obtained with a range of commercially available tartrate esters (CH3, Et, i-Pr).

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C6H5CHO</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>c-C6H5CHO</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>C6H5CHO</td>
<td>78</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C9H19CHO</td>
<td>90</td>
<td>95:5</td>
</tr>
<tr>
<td>n-C9H19CHO</td>
<td>70</td>
<td>1:99</td>
</tr>
<tr>
<td>n-C9H19CHO</td>
<td>94</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>n-C9H19CHO</td>
<td>90</td>
<td>2:98</td>
</tr>
<tr>
<td>TBSOCH2CH2</td>
<td>71</td>
<td>≥98:2</td>
</tr>
<tr>
<td>TBSOCH2CH2</td>
<td>68</td>
<td>2:98</td>
</tr>
</tbody>
</table>

• Enantioselectivities are typically moderate.
• 4Å-MS are necessary to achieve the highest levels of selectivity.

Proposed Origin of Selectivity in Tartrate Derived Allylboration Additions

• The favored transition state is believed to minimize unfavorable lone pair-lone pair interactions.


M. Movassaghi
Reaction of Tartrate-Derived Allyl- or Crotylboronates with Chiral Aldehydes

**MATCHED:**

\[
\text{CH}_3\text{OTBS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBS}
\]

71%, 78% de

**MISMATCHED:**

\[
\text{CH}_3\text{OTBDPS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBDPS}
\]

72%, 74% de

**MISMATCHED:**

\[
\text{CH}_3\text{OTBDPS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBDPS}
\]

80%, 94% de

**MISMATCHED:**

\[
\text{CH}_3\text{OTBDPS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBDPS}
\]

85%, 76% de

**MATCHED:**

\[
\text{CH}_3\text{OTBS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBS}
\]

71%, 90% de

**MISMATCHED:**

\[
\text{CH}_3\text{OTBS} + \text{OHC}^\bullet\text{CHO} \rightarrow \text{CH}_3\text{OTBS}
\]

28% de

* All reactions were performed in toluene at –78 °C in the presence of 4Å-MS.


\[\text{(-)-Bafilomycin A}_1\:
\]

\[
\text{H}_3\text{C}^\bullet\text{CHO} + \text{H}_3\text{C}^\bullet\text{B(OH)}_2 \rightarrow \text{H}_3\text{C}^\bullet\text{CHO} \rightarrow \text{H}_3\text{C}^\bullet\text{CHO}
\]

1. (S,S)-2, Toluene –78 °C  
2. TBSOTf

85%, >96% de

\[
\text{H}_3\text{C}^\bullet\text{B(OH)}_2 + \text{H}_3\text{C}^\bullet\text{CHO} \rightarrow \text{H}_3\text{C}^\bullet\text{B(OH)}_2
\]

1. Pd(PPh$_3$)$_4$, TIOH  
THF, 23 °C, 30 min  
65%

2. KOH, 1,4-dioxane;  
2,4,6-trichlorobenzoyl chloride,  
$i$-Pr$_2$NEt, THF;  
DMAP, toluene, reflux  
52%

M. Movassaghi
Catalytic, Enantioselective Addition of Allylsilanes to Aldehydes

\[
\text{R} - \text{H} + \text{Si}((\text{CH}_3)_3) \rightarrow \text{R} - \text{Si}((\text{CH}_3)_3) \text{CHO}
\]

1. (S)-(−)-BINOL (20 mol%) TiF\(_4\) (10 mol%) CH\(_2\)Cl\(_2\), CH\(_3\)CN, 0 °C
2. Bu\(_4\)NF, THF

<table>
<thead>
<tr>
<th>aldehyde</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH(_3))(_3)CHO</td>
<td>4</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>TIPSOCHO</td>
<td>20</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>(CH(_3))(_3)CCHO</td>
<td>4</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>PhCHO</td>
<td>20</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>PhCHO</td>
<td>20</td>
<td>81(^a)</td>
<td>74</td>
</tr>
<tr>
<td>o-C(_6)H(_4)CHO</td>
<td>4</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>PhCH(_2)CH(_2)CHO</td>
<td>4</td>
<td>69</td>
<td>61</td>
</tr>
</tbody>
</table>

\(^a\)Based on 25% recovered aldehyde.

- Allyltrimethylsilane initially reacts with the HF produced during catalyst preparation to give propene and (CH\(_3\))\(_3\)SiF.
- It is important that the reaction be conducted in the presence of small amounts of CH\(_3\)CN to solubilize the polymeric TiF\(_4\).
- \(\alpha,\alpha\)-Disubstituted aldehydes afford the highest enantioselectivities.


M. Movassagi
Catalytic, Enantioselective Addition of Allyltin Reagents to Aldehydes

\[
\text{R}_1 \text{CHO} + \text{R}_2 \text{Sn}(\text{n-Bu})_3 \rightleftharpoons \text{R}_1 \text{C} = \text{CHR}_2 \text{OH}
\]

- Addition occurs to the \( \text{re} \) face of the aldehyde with the catalyst prepared from (\( S \))-\( (\pm) \)-BINOL.
- This procedure allows for the efficient asymmetric methallylation of aldehydes, typically a difficult transformation.

<table>
<thead>
<tr>
<th>( \text{R}_1 )</th>
<th>( \text{R}_2 )</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( \text{CH}_3 )</td>
<td>60</td>
<td>75</td>
<td>91</td>
</tr>
<tr>
<td>( \text{c-C}<em>6\text{H}</em>{11} )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>66</td>
<td>94</td>
</tr>
<tr>
<td>( \text{c-C}<em>6\text{H}</em>{11} )</td>
<td>( \text{CH}_3 )</td>
<td>48</td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>( \text{(E)}-\text{C}_6\text{H}_5\text{CH} = \text{CH} )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>42</td>
<td>89</td>
</tr>
<tr>
<td>( \text{(E)}-\text{C}_6\text{H}_5\text{CH} = \text{CH} )</td>
<td>( \text{CH}_3 )</td>
<td>12</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2 )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2 )</td>
<td>( \text{CH}_3 )</td>
<td>40</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>( \text{i-C}_3\text{H}_7 )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>furyl</td>
<td>( \text{H} )</td>
<td>70</td>
<td>73</td>
<td>96</td>
</tr>
<tr>
<td>furyl</td>
<td>( \text{CH}_3 )</td>
<td>12</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>( p-\text{CH}_3\text{OC}_6\text{H}_4 )</td>
<td>( \text{CH}_3 )</td>
<td>48</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>( p-\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{OCH}_2 )</td>
<td>( \text{H} )</td>
<td>70</td>
<td>81</td>
<td>96</td>
</tr>
<tr>
<td>BnOCH( _2 )</td>
<td>( \text{H} )</td>
<td>60</td>
<td>84</td>
<td>95</td>
</tr>
</tbody>
</table>


Enantioselective Allylation Using a Stoichiometric Chiral Controller Group

\[
\text{R}_1 \text{CHO} + \text{R}_2 \text{Sn}(\text{n-Bu})_3 \rightleftharpoons \text{R}_1 \text{C} = \text{CHR}_2 \text{OH}
\]

- Reagent 1 is produced from the corresponding (\( R \))-\( (R) \)-bis-sulfonamide by reaction with BBr\( _3 \) in CH\( _2\text{Cl}_2 \).
- Transmetallation of allyltin reagents with the chiral B-bromoboron reagent 1 in toluene is complete in 3-20 h.
- The (\( R \))-\( (R) \)-bis-sulfonamide can be recovered from the reaction mixture.

Enantioselective Allyltitanation of Aldehydes

![Enantioselective Allyltitanation of Aldehydes](image)

- The chiral diol is readily available in both enantiomeric forms from the corresponding tartrate esters.
- Complex formation is driven to completion by neutralization of HCl with Et$_3$N, or by removal of HCl by heating.
- The complex may be used in crude form, as prepared in solution, or the complex may be crystallized and isolated.

(E)-Crotyltitaniunm reagents are produced from (E)- or (Z)-crotyl anion precursors.

Diastereoselective Allyltitanation of Chiral Aldehydes

![Diastereoselective Allyltitanation of Chiral Aldehydes](image)

- Exceptionally high reagent selectivity is observed in the mismatched allylation of (R)-2-phenylbutyraldehyde (90% de) (cf., (–)-Ipc$_2$BCH$_2$CH=CH$_2$: 34% de).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCpL$_{(R,R)}$</td>
<td>93</td>
<td>98.1</td>
<td>1.9</td>
</tr>
<tr>
<td>TiCpL$_{(S,S)}$</td>
<td>95</td>
<td>0.5</td>
<td>99.5</td>
</tr>
<tr>
<td>TiCp(O$_2$Pr)$_2$</td>
<td>89</td>
<td>37.3</td>
<td>62.7</td>
</tr>
<tr>
<td>MgCl</td>
<td>86</td>
<td>55.1</td>
<td>44.9</td>
</tr>
</tbody>
</table>

(E)-Crotyltitanation of aldehydes affords anti products, presumably by a chair-like TS.


M. Movassagi
**Asymmetric Allylation Reactions**

**Krische Allylation and Crotylation Reactions:**


**General Allylation Reaction:**

\[
\text{OAc} + \text{OH} \rightarrow \text{R} \quad [\text{Ir(cod)Cl}_2 \times 2.5 \text{ mol } \%] (R)-\text{BINAP} \times 5 \text{ mol } \% \quad m\text{-NO}_2\text{BzOH} \times 10 \text{ mol } \%
\]

\[
\text{Cs}_2\text{CO}_3 \times 20 \text{ mol } \% \quad \text{THF, 100 °C}
\]

R = aryl, alkyl 55-80% yield 90-93% ee

**General Crotylation Reaction:**

\[
\text{CH}_3 \text{OAc} + \text{OH} \rightarrow \text{R} \quad [\text{Ir(cod)Cl}_2 \times 2.5 \text{ mol } \%] (-)-\text{TMBTP} \times 5 \text{ mol } \%
\]

\[
4\text{-CN-3-NO}_2\text{BzOH} \times 10 \text{ mol } \% \quad \text{Cs}_2\text{CO}_3 \times 20 \text{ mol } \% \quad \text{i-ProOH} \times 200 \text{ mol } \%
\]

\[
\text{THF, 90 °C}
\]

R = aryl, alkyl 66-82% yield 96-98% ee 6:1 to 13:1 dr

**Proposed Catalytic Cycle:**

1. The Ir catalyst 1 (generated in situ) undergoes addition to aldehyde 2 via a 6-membered chair-like transition state to generate the IrIII alkoxide 3. This does not undergo further dehydrogenation as the olefin is thought to occupy a coordination site, blocking β-hydride elimination.

2. Ligand exchange with the reactant alcohol (or isopropanol) generates the homoallylic alcohol 4.

3. The Ir alkoxide 5 undergoes β-hydride elimination to produce the IrIII hydride 6. Dissociation of the aldehyde 2 produces an IrIII hydride which undergoes deprotonation by the base to provide the IrI anion 7.

4. Oxidative addition of allyl acetate to 7 regenerates α-allyl IrIII catalyst 1.

5. To use aldehydes as substrates in lieu of an alcohol, the use of a terminal reductant (isopropanol) is necessary for the catalytic cycle to proceed.

6. Enantioselectivities are high for both alcohol and aldehyde reactants.


Anne-Marie Schmitt, Fan Liu

**TMBTP** = 2,2',5,5'-Tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene
Stereochemical Model in Asymmetric Crotolation Reactions:

- Couplings of aldehydes display higher diastereoselectivities than with alcohols, as higher concentrations of aldehyde promote rapid capture of the kinetically formed trans-crotyl iridium complex.
- Equilibration to the cis-crotyl iridium complex causes erosion in diastereoselectivity.


Other allyl donors have been used with alcohols and aldehydes as reactants:

<table>
<thead>
<tr>
<th>Allyl Donor</th>
<th>Products Generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBz</td>
<td>R = aryl, alkyl 62-77% Yield 96-99% ee</td>
</tr>
<tr>
<td>OAc</td>
<td>R = aryl, alkyl 58-74% Yield 93-99% ee</td>
</tr>
<tr>
<td>CF3</td>
<td>R = aryl, alkyl 57-80% Yield 87-99% ee</td>
</tr>
<tr>
<td>SiMe3</td>
<td>R = aryl, alkyl 58-78% Yield 90-99% ee</td>
</tr>
<tr>
<td>EtO</td>
<td>R = aryl, alkyl 58-79% Yield 92-99% ee</td>
</tr>
</tbody>
</table>


Bis Allylation and Crotylation of Glycols

\[
\begin{align*}
&\text{[Ir(cod)Cl]_2 (5 mol %)} \\
&\text{(S)-Cl,MeO-BIPHEP (10 mol %)} \\
&\text{Cs_2CO_3 (40 mol %)} \\
&\text{4-Cl-3-NO_2-BzOH (20 mol %)} \\
&\text{Dioxane (0.2 M)} \\
&\text{90 °C}
\end{align*}
\]

70%, >30:1 dr >99% ee

- Equivalent bis aldehyde counterparts are unstable or unknown.
- Predominantly 1 of 16 possible stereoisomers was formed.
- Chromatographic isolation of the pre-formed iridium catalyst allows crotylations to be run at lower temperatures.

Application to the Total Synthesis of Roxaticin

- Catalyst Generation:

Application to the Synthesis of Roxaticin, continued.

Allylation of Epimerizable Aldehydes from the Alcohol Oxidation Level:

- Allylation of α-chiral aldehydes and β-chiral alcohols: the transiently generated aldehyde is prone to epimerization under the reaction conditions:

\[
\text{Allylation of } \alpha\text{-chiral aldehydes and } \beta\text{-chiral alcohols: the transiently generated aldehyde is prone to epimerization under the reaction conditions:}
\]

\[
\text{Allylation of } \alpha\text{-chiral aldehydes and } \beta\text{-chiral alcohols: the transiently generated aldehyde is prone to epimerization under the reaction conditions:}
\]

- Optimized Reaction Conditions:

\[
\text{Optimized Reaction Conditions:}
\]

- Increased loadings of base improve the yield of A while suppressing epimerization of the transient α-chiral aldehyde.

- Water improves the yield of A, possibly by facilitating the exchange between product and reactant alkoxide and by increasing the amount of Cs₂CO₃ in solution.

- The enhanced Lewis acidity at iridium may strengthen the agostic interaction between the iridium center and the carbinol C-H bond, facilitating alcohol dehydrogenation. It may also accelerate carbonyl addition with respect to aldehyde epimerization.

- Inductive electron withdrawal by the 3,4-dinitro benzoate ligand may facilitate deprotonation of the Ir(III) hydride intermediate, allowing for faster catalyst turnover.


Anne-Marie Schmitt, Fan Liu
Leighton Silicon Allylation Chemistry:

**Background:**

- In 2000, Leighton reported an allylation reaction where a Lewis acidic silicon atom is embedded in a strained five-membered ring:

\[
\begin{align*}
\text{PhCHO (6 equiv)} & \quad \text{sealed tube, 130 °C} \\
\text{HCl, 87%}
\end{align*}
\]


- By incorporating another electronegative element bound to silicon, the reaction takes place at room temperature. With a chiral ligand, the reaction becomes enantioselective:

\[
\begin{align*}
\text{t-BuCHO} & \quad \text{PhH_3, –10 °C} \\
\text{HCl, 80%, 96% ee}
\end{align*}
\]


**Preparation of Allylsilane**

- Two diastereomers are generated upon complexation with pseudoephedrine, which converge on a common complex prior to allyl transfer:

\[
\begin{align*}
\text{PhH_3, CH_2Cl_2, 23 ºC, 15min} & \quad \text{PhH_3, 23 ºC, 12h} \\
\text{OSiNPh} & \quad 1. \text{HCl, Et_2O} \\
\text{Recrystallize} & \quad 3. \text{SmI_2, THF}
\end{align*}
\]


**Mechanism:**

- A 5-coordinate trigonal bipyramidal silicon species is proposed.
- The strained silacyclopentane increases the Lewis acidity of silicon.
- Aldehydes and acylhydrazones react, but not ketones, aldimes, or ketimines.

Angela Puchlopek-Dermenci, Fan Liu

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**Enantioselective Addition to Acylhydrazones:**

![Chemical equations and reactions showing enantioselective addition to acylhydrazones.](attachment:image.png)
A C$_2$-symmetric Chiral Controller for Aldehyde Allylation and Crotylation:

- The C$_2$-symmetric N,N'-dialkylcyclohexanediamine silane shown below shows improved selectivities in the allylation and crotylation of aldehydes:

\[
\text{N} \quad \text{Si} \quad \text{N} \quad \begin{array}{c} 4-\text{BrC}_6\text{H}_4 \\ 4-\text{BrC}_6\text{H}_4 \end{array} + \text{Ph} = \text{CH}_2 \quad \text{CH}_2\text{Cl}_2, -10^\circ C \quad 90\%, 98\% \text{ ee}
\]

\[
\text{N} \quad \text{Si} \quad \text{N} \quad \begin{array}{c} 4-\text{BrC}_6\text{H}_4 \\ 4-\text{BrC}_6\text{H}_4 \end{array} + \text{BnO} = \text{CH}_2 \quad \text{CH}_2\text{Cl}_2, 0^\circ C \quad 83\%, 99\% \text{ ee}
\]

\[
\text{N} \quad \text{Si} \quad \text{N} \quad \begin{array}{c} 4-\text{BrC}_6\text{H}_4 \\ 4-\text{BrC}_6\text{H}_4 \end{array} + \text{Ph} = \text{CH}_2 \quad \text{CH}_2\text{Cl}_2, 0^\circ C \quad 79\%, 97\% \text{ ee}
\]

(2.09 g)


- Using 2-hydroxybenzene as an activating group, imines can be allylated or crotylated with high selectivity:

\[
\text{Ph} \quad \text{O} \quad \text{Si} \quad \text{O} \quad \text{Cl} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} + \text{Ph} = \text{H} \quad \text{CH}_2\text{Cl}_2, 23^\circ C \quad 74\%, 99\% \text{ ee} \\
\quad \text{dr} = 96 : 4
\]


Allylation and Crotylation of β-Diketones:
- The first example of enantioselective nucleophilic addition to β-diketones was achieved using the C$_2$-symmetric N,N'-dialkylcyclohexanediamine silane reagent:

\[
\begin{array}{c}
\text{N} \quad \text{Si} \quad \text{N} \quad \begin{array}{c} 4-\text{BrC}_6\text{H}_4 \\ 4-\text{BrC}_6\text{H}_4 \end{array} \\
\end{array} + \begin{array}{c} \text{Br} \quad \text{O} \quad \text{O} \quad \text{CH}_3 \\
\text{Ph} \quad \text{O} \quad \text{HO} \quad \text{CH}_3
\end{array} \quad \text{CHCl}_3, 23^\circ C \quad 89\%, 92\% \text{ ee} \quad \text{regioselectivity} > 20 : 1
\]

\[
\begin{array}{c}
\text{N} \quad \text{Si} \quad \text{N} \quad \begin{array}{c} 4-\text{BrC}_6\text{H}_4 \\ 4-\text{BrC}_6\text{H}_4 \end{array} \\
\end{array} + \begin{array}{c} \text{Ph} \quad \text{O} \quad \text{O} \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{O} \quad \text{HO} \quad \text{CH}_3
\end{array} \quad \text{CHCl}_3, 23^\circ C \quad 75\%, 97\% \text{ ee} \quad \text{dr} > 20 : 1 \quad \text{regioselectivity} > 20 : 1
\]

- Four possible diastereomers undergo fast interconversion.
- Regioselectivity is determined by Curtin-Hammett kinetics. Steric interactions are minimized and conjugation is maximized in the lower energy transition state.


Angela Puchlopek-Dermenci, Fan Liu
Hoveyda Boron Allylation Chemistry:

- The Hoveyda group demonstrated that Cu-complexed $C_1$-symmetric ligands I and II, can effect enantioselective allylation of phosphinoylimines:

  I (5.0 mol%)
  CuCl (5 mol%)
  NaOtf-Bu (12 mol%)
  MeOH, THF, –50 °C
  92%, 97% ee

  II (5 mol%)
  CuCl (5 mol%)
  NaOtf-Bu (12 mol%)
  MeOH, THF, –50 °C
  96%, 90% ee

- Allylation is driven by the formation of an energetically favorable B–O bond.

- Methanol releases the product alkoxide from the NHC–Cu complex. <5% conversion was observed in the absence of methanol.

- The product phosphinoylamides can be converted to free amines under aqueous acidic conditions.

- High selectivity is observed with aromatic, heteroaromatic, conjugated, and some aliphatic phosphinoylimines. Crotylation reactions proceed with modest yield and enantioselectivity but low diastereoselectivity.

Mechanism:

Simple amino alcohol catalysts III and IV were found to promote stereoselective boron allylation of phosphinoyl imines and isatins:

- **Mechanism:**
  - III (3.0 mol%)
    - NaO\(_\text{t-Bu}\) (2.5 mol%)
    - MeOH, PhCH\(_3\), 22 ºC
    - 75%, 96% ee
  - III (6.0 mol%)
    - NaO\(_\text{t-Bu}\) (8.5 mol%)
    - MeOH, PhCH\(_3\), 22 ºC
    - 71%, 95% ee
  - IV (6.0 mol%)
    - Zn(O\text{t-Bu})\(_2\) (8.5 mol%)
    - MeOH, PhCH\(_3\), 22 ºC
    - 70%, 90% ee
    - dr = 8 : 1
  - IV (3 mol%)
    - NaO\(_\text{t-Bu}\) (20 mol%)
    - MeOH, PhCH\(_3\), 22 ºC
    - 86%, 91% ee
    - dr = 39 : 1

- <2% conversion was observed in the absence of methanol.
- The internal hydrogen bond between the protonated amine and the amide carbonyl rigidifies the complex and increases the Lewis acidity of the boron center to facilitate substrate binding.
- Substrate release is accelerated by intramolecular protonation.


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