Catalytic Asymmetric 1,4-Addition Reactions Using \(\alpha,\beta\)-Unsaturated N-Acylpyrroles as Highly Reactive Monodentate \(\alpha,\beta\)-Unsaturated Ester Surrogates

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*J. Am. Chem. Soc., ASAP Article 10.1021/ja0485917 S0002-7863(04)08591-9
Web Release Date: May 26, 2004
Introduction

- Catalytic asymmetric 1,4-additions to \( \alpha,\beta \)-unsaturated ketones.
- For \( \alpha,\beta \)-unsaturated esters lower reactivity is an issue.
- Monodentate Vs bidentate substrates.
- Objective: development of monodentate ester substitute.
1 \( R = \text{aryl, alkyl, alkenyl} \)

2

3 \((R)-H_8\text{-BINOL}\)

4

5 \((S,S)\text{-linked-BINOL}\)
Preparation of Ylide 2

Conditions: (i) 2,5-dimethoxytetrahydrofuran, AcOH, 100 C; (ii) PPh3, toluene, 100 C; (iii) 2 M aq NaOH, CH2Cl2/H2O; (iv) THF/Et2O, -78 to 25 C.
Proposed catalytic cycle for the epoxidation promoted by Ln-Binol complex.

- Ln-Binol complex favors monodentate coordination.
- Not applicable for α,β-unsaturated esters.
- Bidentate substrates, oxazolidinone, carboxylic acid imidazolide and α,β-unsaturated morpholinyl amide: not practical results.
- Poor conversion;
- High catalyst loading;
- Explosive TBHP;
- Unstable, low soluble and difficult to prepare substrates.
Table 2. Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated N-Acylpyrrole 1a

<table>
<thead>
<tr>
<th>entry</th>
<th>Sm(O-i-Pr)_3 (x mol %)</th>
<th>ligand (x mol %)</th>
<th>additive (y mol %)</th>
<th>solvent</th>
<th>oxidant</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>BINOL (10)</td>
<td>Ph_3As(O) (10)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>BINOL (5)</td>
<td>Ph_3As(O) (5)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3As(O) (5)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>H_8-BINOL(5)</td>
<td>Ph_3P(O) (15)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>84</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3P(O) (50)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3P(O) (100)</td>
<td>THF</td>
<td>TBHP</td>
<td>0.5</td>
<td>85</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3P(O) (15)</td>
<td>THF/toluene</td>
<td>TBHP</td>
<td>0.4</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>H_8-BINOL(5)</td>
<td>Ph_3P(O) (50)</td>
<td>THF/toluene</td>
<td>TBHP</td>
<td>0.5</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3P(O) (100)</td>
<td>THF/toluene</td>
<td>TBHP</td>
<td>0.2</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>H_8-BINOL (5)</td>
<td>Ph_3P(O) (100)</td>
<td>THF/toluene</td>
<td>CMHP</td>
<td>0.2</td>
<td>91</td>
<td>&gt;99.5</td>
</tr>
</tbody>
</table>

^a TBHP in decane or CMHP in toluene was used. ^b Isolated yield. ^c Determined by chiral HPLC analysis.

First tuning:
- Ligand: H8-BINOL 5 mol%;
- Lanthanide: Sm(O-i-Pr)_3 5 mol%;
- Additive: Ph_3P(O) 100 mol%;
- Oxidant: TBHP or CMHP
- Solvent: THF/toluene.
Second tuning:
- H8-BINOL/Sm(O-i-Pr)₃ as low as 0.1, 0.05 and 0.02 mol%;
- Keep the catalyst concentration within 1-5 mM for best ee’s;
- Practical aspects for large scale: reduced MS amounts, catalytic loading.
- Catalytic Ph₃As=O; equimolar Ph₃P=O.

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**Table 3. Trials to Reduce Catalyst Loading in Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated N-Acylpyrrole 1**

<table>
<thead>
<tr>
<th>entry</th>
<th>Sm(O-i-Pr)₃ (x mol %)</th>
<th>H₂-BINOL (x mol %)</th>
<th>additive (y mol %)</th>
<th>MS 4Å (mg/mmol of 1a)</th>
<th>concn of [1a] (M)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>5</td>
<td>5</td>
<td>Ph₃P(O) (100)</td>
<td>1000</td>
<td>0.1</td>
<td>0.2</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>2c</td>
<td>1</td>
<td>1</td>
<td>Ph₃P(O) (100)</td>
<td>500</td>
<td>1</td>
<td>0.3</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>3d</td>
<td>0.5</td>
<td>0.5</td>
<td>Ph₃P(O) (100)</td>
<td>250</td>
<td>1</td>
<td>0.6</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>4d</td>
<td>0.2</td>
<td>0.2</td>
<td>Ph₃P(O) (100)</td>
<td>100</td>
<td>2</td>
<td>1</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>5d</td>
<td>0.1</td>
<td>0.1</td>
<td>Ph₃P(O) (100)</td>
<td>100</td>
<td>2</td>
<td>2</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>6d</td>
<td>0.1</td>
<td>0.1</td>
<td>Ph₃As(O) (0.1)</td>
<td>100</td>
<td>3</td>
<td>0.6</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>7d</td>
<td>0.05</td>
<td>0.05</td>
<td>Ph₃As(O) (0.05)</td>
<td>100</td>
<td>3</td>
<td>1</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>8d</td>
<td>0.02</td>
<td>0.02</td>
<td>Ph₃As(O) (0.02)</td>
<td>100</td>
<td>3</td>
<td>1.5</td>
<td>94</td>
<td>99</td>
</tr>
</tbody>
</table>

*a* Isolated yield. *b* Determined by chiral HPLC analysis. *c* TBHP in decane was used. *d* Anhydrous TBHP in toluene (dried with MS 4Å) was used.
Sequential Wittig Olefination-Catalytic Asymmetric Epoxidation

(A) One-pot Sequential Wittig-Catalytic Asymmetric Epoxidation Process

Ph<sub>H</sub> 10a

```
Ph
```

100 °C, 36 h

```
toluene
```

ylide 2

```
Ph
```

1a

+ Ph<sub>3</sub>P(O)

(without work-up)

(R)-H<sub>3</sub>-BINOL (5 mol %)

Sm(O-i-Pr)<sub>3</sub> (5 mol %)

CMHP (1.5 equiv)

```
toluene:THF = 1:1
```

25 °C, 0.5 h

Ph

11a

y. 96%

99.8% ee

(B) Step-by-step Wittig-Catalytic Asymmetric Epoxidation Process

Ph<sub>H</sub> 10a

```
Ph
```

100 °C, 36 h

```
toluene
```

ylide 2

```
Ph
```

1a

(isolated)

(R)-H<sub>3</sub>-BINOL (5 mol %)

Sm(O-i-Pr)<sub>3</sub> (5 mol %)

CMHP (1.5 equiv)

Ph<sub>3</sub>P(O) (x mol %)

```
toluene:THF = 1:1
```

25 °C, 0.5-2 h

Ph

11a

Ph<sub>3</sub>P(O) (waste)

none

y. 87%, 75.2% ee

15 mol % y. 88%, 96.8% ee

50 mol % y. 95%, 98.8% ee
**Scheme 3.** Catalytic Asymmetric Epoxidation of Z-α,β-Unsaturated N-Acylpyrrole

\[
\begin{align*}
&\text{Ph} \quad \text{12} \quad \text{K} \\
&\begin{array}{cccc}
&\text{(R)-H}_8\text{-BINOL (5 mol %)} & \text{Sm(O-i-Pr)}_3 (5 \text{ mol %}) & \text{Ph}_3\text{As(O) (5 mol %)} & \text{TBHP (1.5 equiv)} \\
&\text{THF/toluene} & 25^\circ\text{C}, 1 \text{ h} & & \\
&\text{y. 32\%, 86\% ee} \\
\end{array}
\end{align*}
\]

**Table 5.** Sequential Wittig–Catalytic Asymmetric Epoxidation Reaction with Chiral Aldehyde

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>time (h)</th>
<th>oxidant</th>
<th>yield* (%)</th>
<th>dr* (14/15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-H\textsubscript{8}-BINOL</td>
<td>0.7</td>
<td>CMHP</td>
<td>80</td>
<td>&gt; 99/1</td>
</tr>
<tr>
<td>2</td>
<td>(S)-H\textsubscript{8}-BINOL</td>
<td>0.9</td>
<td>CMHP</td>
<td>60</td>
<td>1/56</td>
</tr>
<tr>
<td>3</td>
<td>(S)-H\textsubscript{8}-BINOL</td>
<td>0.7</td>
<td>TBHP</td>
<td>78</td>
<td>1/36</td>
</tr>
</tbody>
</table>

*Isolated yield. *Determined by HPLC analysis.
Electronic properties of \(a,b\)-unsaturated N-acylpyrrole

(a) enones

- Benzophenone: -2.09 eV
- Phenylacetone: -1.88 eV

(b) carboxylic acid derivatives

- Pyrazole: -2.37 eV
- Iminazole: -2.06 eV
- Pyrrole: -2.05 eV
- Oxazoline: -1.72 eV
- Pyrrolidinone: -1.56 eV
Epoxidation profile of α,β-unsaturated ketones and α,β-unsaturated carboxylic acid derivatives.

- Imidazoline 17 > phenyl enone 18 > N-acyl pyrrole 1a > methyl enone 19 >> amide 20.
Scheme 4. Catalytic Asymmetric Epoxidation Reaction of (a) Unsaturated N-Acylpyrrole 1a and (b) N-Acylimidazolide 17 with 5 and 1 Mol % Sm Catalyst
Better solubility than the N-acylimidazolide 17.

- **monodentate**
- **cat**
- **Nu**
- **low LUMO energy**

- **aromaticity**
- **relatively robust C-N bond**
Transformations of Pyrrolyl Epoxides. Conditions: (i) tert-butyl acetate, BuLi, -78 C; then DBU, 25 C, (74%); (ii) PhLi, then DBU, 25 C, (88%); (iii) BuLi, 1-pentyne, -78 C, then DBU, 0 C, (84%); (iv) LiBH₄, 0 to 25 C; then NaBH₄, 25 C, (72%); (v) LiBH₄, 25 C, then (EtO)₂P(O)CH₂CO₂Et, LiCl, DBU, 25 C, (69%).
Transformation of Michael Adduct. Conditions: (i) EtSLi, EtOH, 25 C, 2 h, y. 96%.

Preparation of Synthetic Intermediate for Antifungal Natural Product. Conditions: (i) ylide 2, toluene, 85 C, then Sm(O-i-Pr)3 (5 mol %), (S)-H8-BINOL (5 mol %), MS 4A, THF/toluene, CMHP, 25 C, 0.8 h, y. 83% (from 10n), 96% ee; (ii) CH3C(O)N(OCH3)CH3, LHMDS, THF, -78 C, 20 min; then DBU, CH2Cl2, 25 C, 40 min, y. 63% (two steps).
Synthesis of Intermediate 33 in Smith's Total Synthesis of Phorboxazole A.

Conclusion

• Modentate ester surrogate α,β-unsaturated N-acylpyrrole;
• Good to excellent yields and ee’s for epoxidation;
• Good results for the first asymmetric Michael additions, but still limited;
• One spot transformation aldehyde to epoxide;
• Further investigations.