Asymmetric Conjugate Reduction of $\alpha,\beta$–Unsaturated Ketones and Esters with Chiral Rhodium(2,6-bisoxazolylphenyl) Catalysts

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1. Preparation of the substrates, ketones and esters, and their spectroscopic data.

2. Spectroscopic data and chromatography for the products.
1. Preparation of the substrates, ketones and esters, and their spectroscopic data.

Representative example.

Preparation of (E)-4-phenyl-2-penten-2-one (6) and (E)-ethyl 3-phenylbut-3-enoate (22).

\[
\begin{align*}
\text{PhCO} & \quad + \quad \text{(EtO)}_2\text{P(O)CH}_2\text{CO}_2\text{Et} \quad \xrightarrow{\text{NaH, THF}} \quad \text{PhC} & \quad = & \quad \text{OEt} \\
\text{Me} & \quad \text{O} & \quad \text{OEt} & \quad \text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{O} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{PhC} & \quad \text{OEt} & \quad + \quad \text{MeONHMe\text{HCl}} & \quad \xrightarrow{i-\text{PrMgCl}} \quad \text{PhC} & \quad \text{N} & \quad \text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{PhC} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{N} & \quad \text{OMe} \\
\text{Me} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

To a suspension of NaH (26 mmol) in THF (10 mL), a solution of triethyl phosphonoacetate (5.83 g, 26 mmol) in THF was slowly added. The mixture was stirred at room temperature for 30 min. Then, acetophenone (2.4 g, 20 mmol) was added at 0°C, and the mixture was stirred at room temperature for 17 h. After confirmation of consumption of acetophenone, a solution of saturated aqueous sodium bicarbonate (15 mL) was added. The mixture was extracted with ethyl acetate (3x50 mL), was washed with brine (10 mL), and was dried over MgSO$_4$. After concentration of organic phase, the residue was purified by silica-gel column chromatography (hexane:ethyl acetate as eluent) to give 3.14 g (16.5 mmol, 82%) of (E)-ester (22) and 0.55 g (2.9 mmol, 14%) of (Z)-ester, (Z)-22.
To a solution of the (E)-ester (22) (2.85 g, 15 mmol) and N,O-dimethylhydroxyamine hydrochloride (2.93 g, 30 mmol) in THF (20 mL), a solution of i-PrMgCl (65 mL, 1M in THF) was slowly added at -5°C. The mixture was stirred for 30 min., and then the mixture was treated with a saturated aqueous NH₄Cl (10 mL). The mixture was extracted with ethyl acetate (3x50 mL), was washed with brine (10 mL), and was dried over MgSO₄. After concentration of organic phase, the residue was purified by silica-gel column chromatography (hexane:ethyl acetate as eluent) to give 3.04 g (14.8 mmol, 98%) of the N-methoxy amide: colorless oil; ¹H NMR (CDCl₃) δ = 7.46-7.50 (m, 2H), 7.32-7.41 (m, 3H), 6.57 (s, 1H), 3.71 (s, 3H), 3.27 (s, 3H), 2.53 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ = 18.10, 32.42, 61.60, 115.9, 126.2, 128.3, 128.4, 142.8, 152.1, 167.8 ppm; IR (KBr, film) ν = 1648 cm⁻¹.

At -30°C, 15 mL of a solution of MeMgBr (0.87 M, THF) was slowly added to a solution of the N-methoxy amide (2.05 g, 10 mmol). The mixture was stirred at -5°C for 30 min., and was treated with a saturated aqueous NH₄Cl (10 mL). The mixture was extracted with ethyl acetate (3x50 mL), was washed with brine (10 mL), and was dried over MgSO₄. After concentration of organic phase, the residue was purified by silica-gel column chromatography (hexane:ethyl acetate as eluent) to give 1.49 g (9.3 mmol, 93%) of (E)-4-phenyl-2-penten-2-one (6) as colorless oil; ¹H NMR (CDCl₃) δ = 7.46-7.50 (m, 2H), 7.35-7.42 (m, 3H), 6.51 (q, J = 1.2 Hz, 1H), 2.54 (d, J = 1.2 Hz, 3H), 2.30 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ = 18.45, 32.31, 124.4, 126.4, 128.4, 129.0, 142.4, 153.7, 198.7 ppm; IR (KBr, film) ν = 1680, 1600 cm⁻¹.
The other substrate ketones, 8, 10, 12, 14, 16, 18, 20, (Z)-6, and (Z)-16 were prepared by the same procedure. Procedure of Weinreb's amide formation and subsequent alkylation from the corresponding esters was performed according to the reported method.\[^{[S1]}\]

**(E)-5-Phenyl-4-hexen-3-one (8).**

$^1$H NMR (CDCl$_3$) $\delta = 7.45$-7.52 (m, 2H), 7.34-7.42 (m, 3H), 6.50 (q, $J = 1.5$ Hz, 1H), 2.57 (q, $J = 7.2$ Hz, 2H), 2.55 (d, $J = 1.5$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 8.31, 18.48, 38.03, 123.9, 126.3, 128.4, 128.9, 142.5, 153.4, 201.7$ ppm; IR (KBr, film) $\nu = 1685, 1604$ cm$^{-1}$.\[^{[S1]}\]

**(E)-2-Methyl-5-phenyl-4-hexen-3-one (10).**

$^1$H NMR (CDCl$_3$) $\delta = 7.46$-7.51 (m, 2H), 7.36-7.42 (m, 3H), 6.55 (d, $J = 1.5$ Hz, 1H), 2.72 (m, 1H), 2.55 (d, $J = 1.5$ Hz, 3H), 1.16 (d, $J = 6.9$ Hz, 6H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 18.50, 18.57, 42.15, 123.2, 126.3, 128.4, 128.8, 142.7, 154.2, 204.9$ ppm; IR (KBr, film) $\nu = 1682, 1601$ cm$^{-1}$.\[^{[S1]}\]

**(E)-1,3-Diphenyl-2-buten-1-one (12).**

$^1$H NMR (CDCl$_3$) $\delta = 7.99$-8.03 (m, 2H), 7.37-7.62 (m, 8H), 7.18 (q, $J = 1.2$ Hz, 1H), 2.61 (d, $J = 1.2$ Hz, 3H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 18.99, 122.0, 126.4, 128.2, 128.4, 128.5, 142.8, 153.1, 204.9$ ppm.\[^{[S1]}\]

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129.0, 132.4, 139.2, 142.6, 154.6, 191.6 ppm; IR (KBr, film) ν = 1656, 1600 cm⁻¹.

*(E)-5-Methyl-4-phenyl-3-hexen-2-one (14).*

\(^1^H\) NMR (CDCl\(_3\)) δ = 7.29-7.38 (m, 2H), 7.18-7.24 (m, 3H), 6.07 (s, 1H), 4.03 (m, 1H), 2.25 (s, 3H), 1.07 (d, J = 7.2 Hz, 6H) ppm; \(^{13}C\) NMR (CDCl\(_3\)) δ = 21.43, 29.57, 32.32, 125.8, 127.4, 127.5, 127.7, 140.7, 165.4, 198.6 ppm; IR (KBr, film) ν = 1681, 1592 cm⁻¹.

*(E)-4-Methyl-6-phenyl-3-hexen-2-one (16).*

\(^1^H\) NMR (CDCl\(_3\)) δ = 7.27-7.32 (m, 2H), 7.15-7.23 (m, 3H), 6.04 (s, 1H), 2.79 (m, 2H), 2.42 (m, 2H), 2.17 (s, 3H) ppm; \(^{13}C\) NMR (CDCl\(_3\)) δ = 19.44, 31.82, 34.04, 42.99, 123.9, 126.0, 128.2, 128.3, 140.9, 157.0, 198.6 ppm; IR (KBr, film) ν = 1686, 1617 cm⁻¹.

*(E)-4,8-Dimethyl-3,7-nonadien-2-one (18).*

\(^1^H\) NMR (CDCl\(_3\)) δ = 6.06 (s, 3H), 5.07 (m, 1H), 2.17 (s, 3H), 2.12-2.15 (m, 7H), 1.68 (s, 3H), 1.61 (s, 3H) ppm; \(^{13}C\) NMR (CDCl\(_3\)) δ = 17.76, 19.36, 25.72, 26.18, 31.83, 41.21, 122.9, 123.5, 132.4, 158.1, 198.6 ppm; IR (KBr, film) ν = 1687, 1617 cm⁻¹.

*(E)-4-Cyclohexyl-3-penten-2-one (20).*

\(^1^H\) NMR (CDCl\(_3\)) δ = 6.05 (s, 1H), 2.17 (s, 3H), 1.96 (m, 1H), 1.68-1.81 (m, 5H), 1.08-1.36 (m, 5H) ppm; \(^{13}C\) NMR (CDCl\(_3\)) δ = 17.91, 26.21, 26.50, 31.45, 31.98, 48.97, 121.7, 163.2, 199.0 ppm; IR (KBr, film) ν = 1685, 1611 cm⁻¹.
(Z)-4-Phenyl-2-penten-2-one [(Z)-6].

$^1$H NMR (CDCl$_3$) $\delta = 7.34-7.41$ (m, 3H), 7.18-7.22 (m, 2H), 6.13 (q, $J = 1.5$ Hz, 1H), 2.19 (d, $J = 1.5$ Hz, 3H), 1.80 (s, 3H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 27.41, 30.23, 127.0, 128.2, 128.3, 128.4, 140.8, 152.7, 200.0$ ppm; IR (KBr, film) $\nu = 1665, 1619$ cm$^{-1}$.

(Z)-4-Methyl-6-phenyl-3-hexen-2-one [(Z)-16].

$^1$H NMR (CDCl$_3$) $\delta = ppm$: 7.15-7.32 (m, 5H), 6.10 (d, $J = 1.2$ Hz, 1H), 2.83-2.89 (m, 2H), 2.72 (m, 2H), 2.14 (s, 3H), 1.86 (d, $J = 1.2$ Hz, 3H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 25.73, 31.72, 34.48, 35.96, 124.3, 125.8, 128.2, 128.4, 141.5, 158.1, 197.9$ ppm; IR (KBr, film) $\nu = 1685, 1616$ cm$^{-1}$.

The other substrate esters, 24, 26, 28, 30, 32, and 34 were prepared by Horner-Wadsworth-Emmons reaction from the corresponding ketones according to previously reported procedure.\textsuperscript{[2b, 5a, 7]} Spectroscopic data: for 28, 30, see ref. 26; for 28, 32, and 34, see ref. 5a; for 32, see ref. 2b. The esters 24 and 26 could also be prepared from 22 by alkaline hydrolysis followed by esterification.

(E)-Isopropyl 3-phenylbut-2-enoate (24): $^1$H NMR (CDCl$_3$) $\delta = 7.50-7.54$ (m, 2H), 7.38-7.45 (m, 3H), 6.10 (q, $J = 1.2$ Hz, 1H), 5.10 (sept, $J = 6.3$ Hz, 1H), 2.57 (d, $J = 1.2$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 6H) ppm.

(E)-tert-Butyl 3-phenylbut-2-enoate (26): $^1$H NMR (CDCl$_3$) $\delta = 7.50-7.54$ (m, 2H),
7.38-7.45 (m, 3H), 6.12 (q, $J = 1.5$ Hz, 1H), 2.60 (d, $J = 1.5$ Hz, 3H), 1.58 (s, 9H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 17.86, 20.37, 79.96, 119.0, 126.2, 128.3, 128.6, 142.4, 153.9, 166.2$ ppm.

2. Spectroscopic data and chromatography for the products.

Racemic samples for all products were prepared by hydrogenation with Pd/C catalyst. Each peak for the enantiomers was correlated with that for the racemic sample in all cases.

Ketones:

(R)-4-Phenyl-2-pentanone (7) (Table 1).

$^1$H NMR (CDCl$_3$) $\delta = 7.27-7.32$ (m, 2H), 7.17-7.22 (m, 3H), 3.31 (m, 1H), 2.76 (dd, $J = 16.2$ Hz, 6.6 Hz, 1H), 2.66 (dd, $J = 16.2$ Hz, 7.5 Hz, 1H), 2.07 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H) ppm; $^{13}$C NMR (CDCl$_3$) $\delta = 207.6, 146.0, 128.4, 126.7, 126.2, 52.02, 35.50, 30.66, 22.10$ ppm; IR (neat) $\nu$ 1716 cm$^{-1}$. 
(R)-5-Phenyl-3-hexanone (9) (Table 2).

\[ \text{MeOEt} \]

^1H NMR (CDCl\textsubscript{3}) \( \delta = 7.26-7.32 \) (m, 2H), 7.16-7.22 (m, 3H), 3.32 (m, 1H), 2.73 (dd, \( J = 16.2 \) Hz, 6.6 Hz, 1H), 2.63 (dd, \( J = 16.2 \) Hz, 7.8 Hz, 1H), 2.32 (m, 2H), 1.26 (d, \( J = 7.2 \) Hz, 3H) ppm; ^13C NMR (CDCl\textsubscript{3}) \( \delta = 7.74, 22.03, 35.54, 36.70, 50.82, 126.1, 126.7, 128.4, 146.2, 210.2 \) ppm; IR (KBr, film) \( \nu = 1714 \) cm\(^{-1}\).

(R)-2-Methyl-5-phenyl-3-hexanone (11) (Table 2).

racemic sample
(R)-1,3-Diphenyl-1-butanone (13) (Table 2).

1H NMR (CDCl₃) δ = 7.93-7.97 (m, 2H), 7.56 (m, 1H), 7.42-7.48 (m, 2H), 7.28-7.35 (m, 4H), 7.21 (m, 1H), 3.53 (m, 1H), 3.33 (dd, J = 16.5 Hz, 5.7 Hz, 1H), 3.20 (dd, J = 16.5 Hz, 8.1 Hz, 1H), 1.36 (d, J = 6.6 Hz, 3H) ppm; 13C NMR (CDCl₃) δ = 21.94, 35.60, 47.03, 126.1, 126.7, 127.9 x2, 128.4, 132.8, 137.0, 146.4, 198.8 ppm; IR (KBr, film) ν 1684 cm⁻¹.

(S)-5-Methyl-4-phenyl-2-hexanone (15) (Table 2).

1H NMR (CDCl₃) δ = 7.24-7.29 (m, 2H), 7.11-7.21 (m, 3H), 2.91 (m, 1H), 2.80 (m, 2H), 1.98 (s, 3H), 1.83 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H) ppm; 13C NMR (CDCl₃) δ = 20.40, 20.79, 30.65, 33.33, 47.66, 48.07, 126.1, 128.0, 128.1, 143.1, 208.1 ppm; IR (KBr, film) ν 1715 cm⁻¹. Elemental analysis calcd (%) for C₁₃H₁₈O (190.28): C 82.06, H 9.53; found: C 81.97, H 9.62.
(S)-4-Methyl-6-phenyl-2-hexanone (17) (Table 2).

$^1$H NMR (CDCl$_3$) $\delta = 7.25-7.31$ (m, 2H), 7.15-7.20 (m, 3H), 2.53-2.72 (m, 2H), 2.46 (dd, $J = 15.9$ Hz, 5.7 Hz, 1H), 2.28 (dd, $J = 15.9$ Hz, 8.1 Hz, 1H), 2.11 (s, 3H), 2.07 (m, 1H), 1.63 (m, 1H), 1.47 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 3H) ppm; $^1$H NMR (CDCl$_3$) $\delta = 19.80$, 29.05, 30.46, 33.41, 38.73, 51.14, 125.6, 128.2 x2, 142.2, 208.5 ppm; IR (KBr, film) $\nu$ 1714 cm$^{-1}$. Elemental analysis calcd (%) for C$_{13}$H$_{18}$O (190.28): C 82.06, H 9.53; found: C 81.98, H 9.61.

(S)-4,8-Dimethyl-7-nonen-2-one (19) (Table 2).

$^1$H NMR (CDCl$_3$) $\delta = 5.08$ (m, 1H), 2.42 (dd, $J = 15.9$ Hz, 5.7 Hz, 1H), 2.22 (dd, $J = 15.9$ Hz, 8.1 Hz, 1H), 2.12 (s, 3H), 1.88-2.07 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.10-1.41 (m,
2H), 0.90 (d, J = 6.6 Hz, 3H) ppm; \(^{13}\text{C}\) NMR (CDCl\(_3\)) \(\delta = 17.74, 19.79, 25.51, 25.78, 29.04, 30.46, 37.00, 51.24, 124.2, 134.2, 208.9\) ppm; IR (KBr, film) \(\nu = 1716\) cm\(^{-1}\).

(R)-4-Cyclohexyl-2-pentanone (21) (Table 2).

\(^1\text{H}\) NMR (CDCl\(_3\)) \(\delta = 2.47 (\text{dd}, J = 15.6\) Hz, 4.8 Hz, 1H), 2.19 (dd, J = 15.6 Hz, 9.3 Hz, 1H), 2.13 (s, 3H), 1.90 (m, 1H), 1.71-1.76 (m, 2H), 1.58-1.67 (m, 3H), 1.10-1.28 (m, 4H), 0.88-1.08 (m, 2H), 0.84 (d, J = 6.6 Hz, 3H) ppm; \(^{13}\text{C}\) NMR (CDCl\(_3\)) \(\delta = 16.62, 26.63, 26.68, 26.72, 29.05, 30.34, 30.37, 34.21, 42.74, 48.55, 209.2\) ppm; IR (KBr, film) \(\nu = 1715\) cm\(^{-1}\).

(S)-4-Phenyl-2-pentanone (7) (Table 2).

\(^1\text{H}\) NMR (CDCl\(_3\)) \(\delta = 7.16\) ppm; \(^{13}\text{C}\) NMR (CDCl\(_3\)) \(\delta = 17.74, 19.79, 25.51, 25.78, 29.04, 30.46, 37.00, 51.24, 124.2, 134.2, 208.9\) ppm; IR (KBr, film) \(\nu = 1716\) cm\(^{-1}\).
(R)-4-Methyl-6-phenyl-2-hexanone (17) (Table 2).

Esters:

Ethyl (R)-3-phenylbutanoate (23) (Table 3).

1H NMR (300MHz, CDCl₃) δ = 7.17-7.32 (m, 5H), 4.08 (q, J = 7.2 Hz, 2H), 3.28 (ddq, J = 15.3 Hz, 15.0 Hz, 7.2 Hz, 1H), 2.62 (dd, J = 15.3Hz, 7.2 Hz, 1H), 2.53 (dd, J = 15.0Hz, 7.2 Hz, 1H), 1.31 (d, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (75 MHz, CDCl₃) δ = 9.89, 17.51, 32.24, 38.66, 55.88, 121.9, 122.3, 124.0, 141.2, 167.8 ppm.

Isopropyl (R)-3-phenylbutanoate (25) (Table 4).
**tert-Butyl (**R**)-3-phenylbutanoate (27) (Table 4).**

**racemic sample:**

**Ethyl (**R**)-3-phenylpentanoate (29) (Table 4).**
$^1$H NMR (300MHz, CDCl$_3$) $\delta = 7.17$-$7.31$ (m, 5H), 4.03 (q, $J = 7.2$ Hz, 2H), 3.00 (ddq, $J = 15.3$ Hz, 15.0 Hz, 7.2 Hz, 1H), 2.65 (dd, $J = 15.3$Hz, 7.2 Hz, 1H), 2.55 (dd, $J = 15.0$ Hz, 7.2 Hz, 1H), 1.78-$1.56$ (m, 2H), 1.13 (t, $J = 7.2$ Hz, 3H), 0.79 (t, $J = 7.2$ Hz, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta = 12.23$, 14.43, 29.41, 41.77, 44.20, 60.40, 126.5, 127.6, 128.4, 144.0, 172.5 ppm.

**Ethyl (S)-4-methyl-3-phenylpentanoate (31) (Table 4).**

racemic sample:

**Ethyl (S)-3-methyl-5-phenylpentanoate (33) (Table 4).**
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.14-7.31\) (m, 5H), 4.13 (q, \(J = 7.2\) Hz, 2H), 2.63 (m, 2H), 2.35 (dd, \(J = 14.7\) Hz, 6.0 Hz, 1H), 2.17 (dd, \(J = 14.6\) Hz, 7.8 Hz, 1H), 2.02 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.25 (t, \(J = 7.2\) Hz, 3H), 1.01 (d, \(J = 6.6\) Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 14.36, 19.71, 30.29, 33.36, 38.57, 41.81, 60.13, 125.6, 128.2\) x2, 142.2, 172.9 ppm.

**Ethyl (S)-3,7-dimethyloct-6-enoate (35) (Table 4).**

\(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta = 5.04-5.13\) (m, 1H), 4.13 (q, \(J = 7.2\) Hz, 2H), 2.30 (dd, \(J = 14.7\) Hz, 6.3 Hz, 1H), 1.85-2.16 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.18-1.40 (m, 5H), 0.94 (d, \(J = 6.9\) Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 14.39, 17.24, 19.70, 25.50, 25.78, 30.12, 36.85, 41.95, 60.09, 124.2, 131.4, 173.1\) ppm.