

# Chiral Counteranions in Asymmetric Transition Metal Catalysis: Highly Enantioselective Pd/Brønsted Acid-Catalyzed Direct $\alpha$ -Allylation of Aldehydes

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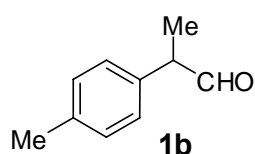
## Supporting Information

**General:** All reactions were carried out under argon atmosphere in oven-dried and/or flame-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agent prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel precoated glass plates (0.25 mm thickness, 60F-254, E. Merck) using UV light to visualize the course of reaction. Flash column chromatography was performed using E. Merck silica gel 60 (particle size 0.040–0.063 mm). Chemical yields refer to pure isolated substances.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained using either a Bruker DPX-300 or AV-400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet).

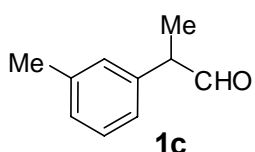
### Preparation of aldehyde substrates:

Aldehyde **1a** is commercially available. Other aldehydes were prepared from the corresponding ketones following the literature procedure and spectroscopic data are in agreement with the

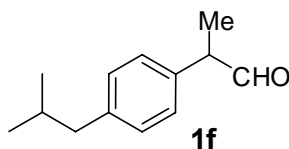
literature.<sup>1,2,3</sup> Characterization of the aldehydes **1b**, **1c**, **1f**, **1i** and **1j** are given below. For other aldehydes, see ref 3.



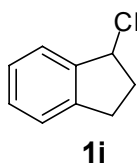
**2-(4-Methylphenyl)propanal (1b):** Aldehyde **1b** was obtained as a clear oil (12% yield) after bulb-to-bulb distillation (110 °C, 0 mbar). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.46 (d, *J* = 7.11 Hz, 3H), 2.38 (s, 3H), 3.59-3.66 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 9.69 (d, *J* = 1.44 Hz, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ = 14.5, 21.0, 52.5, 128.1, 129.7, 134.6, 137.2, 201.1. HRMS (EI) Calcd. for [C<sub>10</sub>H<sub>12</sub>O] ([M]<sup>+</sup>): 148.088814, found: 148.088875.



**2-(3-Methylphenyl)propanal (1c):** Aldehyde **1c** was obtained as a clear oil (34% yield) after bulb-to-bulb distillation (110 °C, 0 mbar). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.43 (d, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 3.56-3.62 (m, 1H), 7.00-7.02 (m, 2H), 7.10-7.12 (m, 1H), 7.25-7.29 (m, 1H), 9.67 (d, *J* = 1.44 Hz, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 14.6, 21.3, 52.9, 125.3, 128.2, 128.9, 129.0, 137.7, 138.8, 201.1. HRMS (EI) Calcd. for [C<sub>10</sub>H<sub>12</sub>O] ([M]<sup>+</sup>): 148.088814, found: 148.088919.



**2-(4-Isobutylphenyl)propanal (1f):** Aldehyde **1f** was obtained as a clear oil. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 0.92 (d, *J* = 6.64 Hz, 6H), 1.44 (d, *J* = 7.04 Hz, 3H), 1.82-1.92 (m, 1H), 2.48 (d, *J* = 7.20 Hz, 2H), 3.58-3.64 (m, 1H), 7.11-7.18 (m, 4H), 9.68 (d, *J* = 1.52 Hz, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 14.5, 22.3, 30.2, 45.0, 52.6, 128.0, 129.8, 134.8, 141.0, 201.2. HRMS (EI) Calcd. for [C<sub>13</sub>H<sub>18</sub>O] ([M]<sup>+</sup>): 190.135766, found: 190.135942.

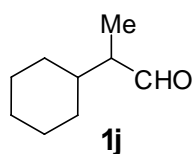


**2,3-Dihydro-1H-indene-1-carbaldehyde (1i):** Aldehyde **1i** was prepared according to the literature procedure and obtained as a thick colorless oil (80% yield) after bulb-to-bulb distillation (110 °C, 0.2 mbar). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.29-2.53 (m, 2H), 2.96-3.18 (m, 2H), 3.95-4.01 (m, 1H), 7.22-7.34 (m, 4H), 9.70 (d, *J* = 2.82 Hz, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ = 25.4, 31.7, 57.8, 124.9, 125.1, 126.7, 127.9, 138.4, 144.7, 200.6. HRMS (EI) Calcd. for [C<sub>10</sub>H<sub>10</sub>O] ([M]<sup>+</sup>): 146.073169, found: 146.073001.

<sup>1</sup> Svoboda, J.; Kocfeldova, Z.; Palecek, J. *Collection Czechoslovak Chem. Commun.* **1988**, *53*, 822-832.

<sup>2</sup> Kavadias, G.; Velkof, S. *Can. J. Chem.* **1978**, *56*, 730-732.

<sup>3</sup> Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074-13075.

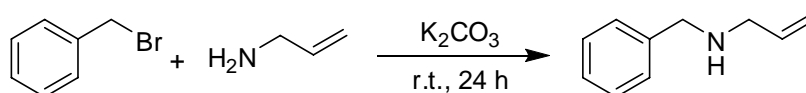


**2-(Cyclohexyl)propanal (1j):** Aldehyde **1j** was obtained as a clear oil (18% yield) after bulb-to-bulb distillation (100 °C, 4 mbar). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 0.99 (d, *J* = 7.0 Hz, 3H), 1.02-1.31 (m, 5H), 1.55-1.73 (m, 6H), 2.13-2.18 (m, 1H), 9.60 (d, *J* = 2.3 Hz, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ = 10.0, 26.2, 26.3, 26.4, 29.1, 31.1, 38.5, 51.8, 205.7. HRMS (CI) Calcd. for [C<sub>9</sub>H<sub>17</sub>O] ([M]<sup>+</sup>): 141.127938, found: 141.127778.

### Synthesis of *N*-allyl amine reagents:

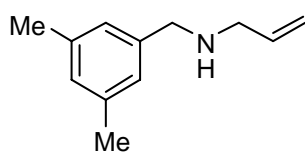
*N*-Allyl aniline is commercially available and used as received. Other reagents were prepared following the literature or modified literature procedures.<sup>4,5</sup>

#### *N*-Allyl-benzyl-amine:



To a suspension of K<sub>2</sub>CO<sub>3</sub> (6.98 g, 50.5 mmol) in allylamine (25.3 mL, 336.8 mmol), was added benzyl bromide (5 mL, 42.1 mmol) slowly via syringe addition over a period of 45 mins. The resulting suspension was stirred at room temperature for 24 hours. K<sub>2</sub>CO<sub>3</sub> was filtered off over a Celite<sup>®</sup> pad and washed with dichloromethane. Filtrate was concentrated in vacuo to obtain a clear oil. Purification by column chromatography on silicagel (hexane/EtOAc 10:1 to 2:1) afforded pure *N*-benzyl allylamine as a clear oil (5.81 g, 39.5 mmol, 94% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.39 (br s, 1H), 3.26-3.28 (m, 2H), 3.78 (s, 2H), 5.09-5.13 (m, 1H), 5.17-5.23 (m, 1H), 5.88-5.98 (m, 1H), 7.22-7.33 (m, 5H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 51.6, 53.1, 115.8, 126.8, 128.0, 128.2, 136.7, 140.2. HRMS (EI) Calcd. for [C<sub>10</sub>H<sub>13</sub>N] ([M]<sup>+</sup>): 147.104802, found: 147.104619.

***N*-Allyl-(3,5-dimethyl-benzyl)-amine:** This was prepared following the same procedure as above and



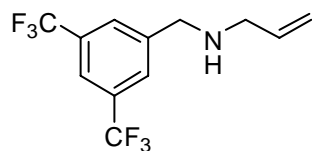
obtained as a clear oil (98% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.41 (br s, 1H), 2.30 (s, 6H), 3.27-3.29 (m, 2H), 3.71 (s, 2H), 5.09-5.13 (m, 1H), 5.17-5.22 (m, 1H), 5.89-5.99 (m, 1H), 6.88 (s, 1H), 6.94 (s, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 21.2, 51.9, 53.3, 115.9, 126.0, 128.5, 136.8, 137.9,

<sup>4</sup> Aurrecochea, J. M.; Fernandez, A.; Gorgojo, J. M.; Suero, R. *Synth. Commun.* **2003**, 33, 693-702.

<sup>5</sup> Rahman, O.; Kihlberg, T.; Långström, B. *Org. Biomol. Chem.* **2004**, 2, 1612-1616.

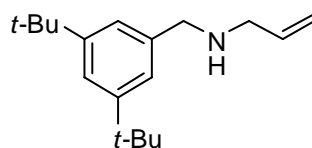
140.2. HRMS (EI) Calcd. for [C<sub>12</sub>H<sub>17</sub>N] ([M]<sup>+</sup>): 175.136097, found: 175.136005.

***N*-Allyl-(3,5-bis-trifluoromethyl-benzyl)-amine:** The same procedure as above was followed to



obtain the amine as a clear oil (>99% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.51 (br s, 1H), 3.26-3.28 (m, 2H), 3.90 (s, 2H), 5.11-5.22 (m, 2H), 5.85-5.95 (m, 1H), 7.74 (s, 1H), 7.81 (s, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 51.8, 52.1, 116.5, 121 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 271 Hz), 128.2, 131.6 (q, *J* = 33 Hz), 136.2, 143.2. HRMS (EI) Calcd. for [C<sub>12</sub>H<sub>11</sub>NF<sub>6</sub>] ([M]<sup>+</sup>): 283.079567, found: 283.079659.

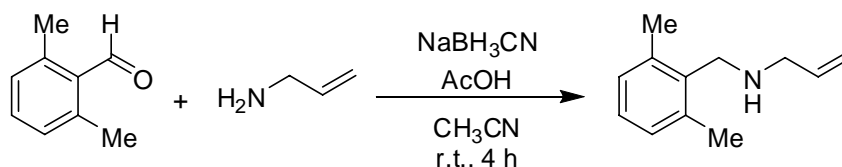
***N*-Allyl-(3,5-di-*tert*-butyl-benzyl)-amine:** The same procedure as above was followed to obtain the



product as a clear oil (70% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.33 (s, 18H), 1.49 (br s, 1H), 3.31-3.33 (m, 2H), 3.79 (s, 2H), 5.11-5.14 (m, 1H), 5.19-5.24 (m, 1H), 7.16 (s, 2H), 7.32 (s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 31.5, 34.8, 52.0, 54.0, 115.9, 121.0, 122.3, 137.0, 139.3, 150.8. HRMS

(EI) Calcd. for [C<sub>18</sub>H<sub>30</sub>N] ([M+H]<sup>+</sup>): 260.237276, found: 260.237123.

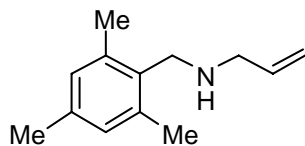
***N*-Allyl-(2,6-dimethyl-benzyl)-amine:**



To a solution of 2,6-dimethyl benzaldehyde (500 mg, 3.73 mmol) in 5 mL abs. CH<sub>3</sub>CN, allylamine (0.84 mL, 11.2 mmol) was added and the resulting solution was stirred at room temperature under argon for 30 mins. NaBH<sub>3</sub>CN (352 mg, 5.6 mmol) was then added followed 15 mins later by acetic acid (0.43 mL, 7.46 mmol). The resulting turbid solution was then stirred at room temperature for 4 hours. The reaction mixture was then diluted with dichloromethane (30 mL) and washed with 1N NaOH solution (2 × 25 mL). NaOH layer was extracted with dichloromethane (25 mL). Combined DCM layers were dried over anh. MgSO<sub>4</sub> and concentrated in vacuo to obtain a pale yellow oil. Purification by column chromatography on silicagel (hexane/EtOAc 10:1) afforded the desired product as a pale yellow oil (482 mg, 2.75 mmol, 74% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.14 (br s, 1H), 2.40 (s, 6H), 3.35-3.36 (m, 2H), 3.77 (s, 2H), 5.11-5.14 (m, 1H), 5.21-5.26 (m, 1H), 5.92-6.00 (m, 1H), 7.01-7.24 (m, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 19.5, 47.2, 52.8, 115.9,

126.9, 128.2, 136.7, 136.9, 137.1. HRMS (EI) Calcd. for  $[C_{12}H_{17}N]$  ( $[M]^+$ ): 175.136098, found: 175.135983.

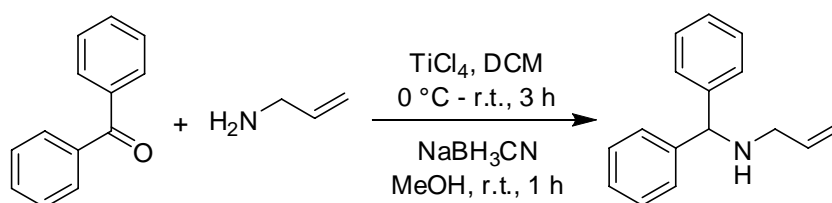
***N*-Allyl-(2,4,6-trimethyl-benzyl)-amine:** The same reductive amination procedure as above was followed to obtain the desired product as a pale yellow oil (74% yield).  $^1H$ -



NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 1.14 (br s, 1H), 2.27 (s, 3H), 2.37 (s, 6H), 3.34-3.36 (m, 2H), 3.74 (s, 2H), 5.11-5.14 (m, 1H), 5.21-5.26 (m, 1H), 5.92-6.02 (m, 1H), 6.85 (s, 2H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 19.4, 20.8,

46.9, 52.7, 115.8, 128.9, 133.7, 136.3, 136.8, 137.1. HRMS (EI) Calcd. for  $[C_{13}H_{19}N]$  ( $[M]^+$ ): 189.151751, found: 189.151629.

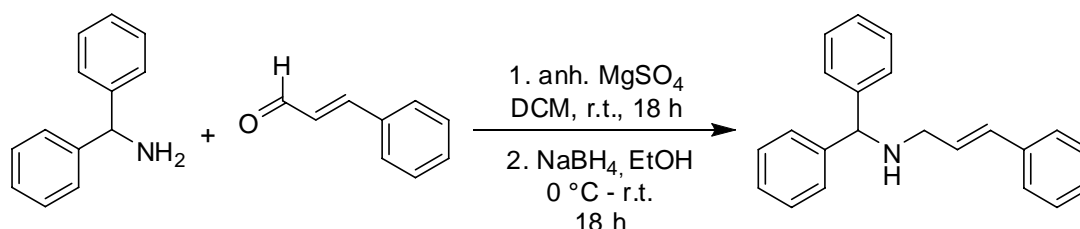
***N*-Allyl-benzhydryl-amine:**



To a solution of benzophenone (3.0 g, 16.5 mmol) in 90 mL abs. DCM under positive pressure of argon, was added a solution of  $TiCl_4$  in DCM (~1.0 M, 18.0 mL, 18.2 mmol) and the resulting bright yellow solution was cooled to 0 °C. Allylamine was then added and the resulting mixture was stirred at room temperature for 3 hours when a pale yellowish white precipitate appeared. A solution of  $NaBH_3CN$  (1.24 g, 19.8 mmol) in 30 mL abs. MeOH was then added when the yellow color disappeared. The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was basified with 5N NaOH solution until pH ~10 when a white precipitate formed. This white solid was filtered through a frit and the filtrate was taken in water (300 mL) and EtOAc (300 mL). The organic layer was separated and washed with water (2  $\times$  300 mL) and brine (300 mL). After drying over anh.  $MgSO_4$ , the organic layer was concentrated in vacuo to obtain a pale yellow oil. This was dissolved in  $Et_2O$  (50 mL) and acidified with conc. HCl until pH ~2. The mixture was washed with water (3  $\times$  50 mL). The ether layer was discarded and the aqueous layer was basified with 25%  $NH_4OH$  solution to pH ~10. The aqueous layer was extracted with  $Et_2O$  (3  $\times$  75 mL) and the ether layer was dried over anh.  $MgSO_4$ . Concentration of the ether layer in vacuo afforded pure product as a clear oil (3.61 g, 16.2 mmol, 98% yield).  $^1H$ -NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 1.54 (br s, 1H), 3.09-3.13

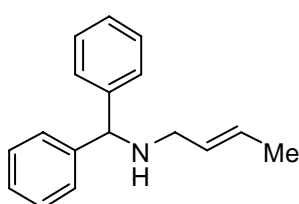
(m, 2H), 4.77 (s, 1H), 4.98-5.11 (m, 2H), 5.78-5.91 (m, 1H), 7.07-7.32 (m, 10H).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 50.4, 66.4, 115.8, 126.9, 127.3, 128.4, 136.8, 143.9$ . HRMS (EI) Calcd. for  $[\text{C}_{16}\text{H}_{17}\text{N}]$  ( $[\text{M}]^+$ ): 223.136100, found: 223.135894. Analytical data are in agreement with the literature.<sup>5</sup>

**Benzhydryl-(*N*-(*E*)-3-phenyl-allyl)-amine:**



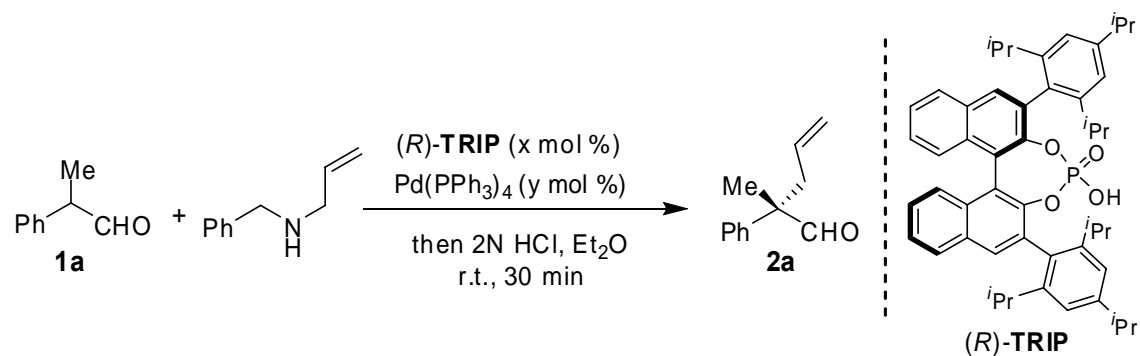
To a suspension of anh.  $\text{MgSO}_4$  in 7 mL of abs. DCM, *trans*-cinnamaldehyde (1.00 mL, 7.94 mmol) was added followed by benzhydryl amine (1.37 mL, 7.94 mmol) and the resulting mixture was stirred at room temperature for 18 hours.  $\text{MgSO}_4$  was then filtered off and the filtrate was concentrated in vacuo to obtain a yellow solid. To an ice cold suspension of this solid in 20 mL abs. EtOH, was added  $\text{NaBH}_4$  under argon. The resulting mixture was then allowed to attain room temperature and stirred at room temperature for 18 hours. The reaction mixture was cooled to 0 °C and quenched with water (30 mL). It was then extracted with  $\text{Et}_2\text{O}$  ( $2 \times 40$  mL). Combined ether layers were dried over anh.  $\text{MgSO}_4$  and concentrated in vacuo to obtain a thick yellow oil. Purification by column chromatography on silicagel (hexane/ $\text{EtOAc}$  10:1) afforded a clear oil (1.95 g, 6.51 mmol, 82% yield).  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.82$  (br s, 1H), 3.45-3.48 (m, 2H), 5.01 (s, 1H), 6.37-6.46 (m, 1H), 6.57-6.62 (m, 1H), 7.27-7.53 (m, 15H).  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 49.8, 66.5, 126.2, 127.0, 127.3, 128.46, 128.48, 131.2, 137.1, 143.9$ . HRMS (EI) Calcd. for  $[\text{C}_{22}\text{H}_{21}\text{N}]$  ( $[\text{M}]^+$ ): 299.167398, found: 299.167489.

**Benzhydryl-(*N*-but-2-enyl)-amine:** This was synthesized following the same method as above.



Product was obtained as a clear oil (35%).  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.60$  (br s, 1H), 1.70-1.74 (m, 3H), 3.15-3.16 (m, 2H), 4.87 (s, 1H), 5.58-5.61 (m, 2H), 7.19-7.24 (m, 2H), 7.28-7.32 (m, 4H), 7.40-7.44 (m, 4H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 17.8, 49.8, 66.6, 126.9, 127.2, 127.3, 128.4, 129.5, 144.1$ . Calcd. for  $[\text{C}_{17}\text{H}_{19}\text{N}]$  ( $[\text{M}]^+$ ): 237.151749, found: 237.151459.

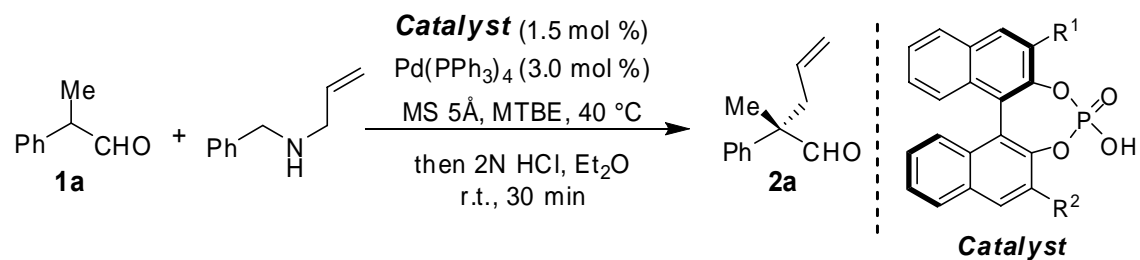
## Optimization of reaction conditions:



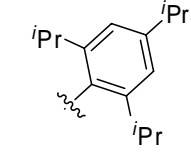
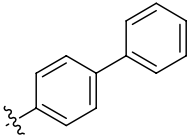
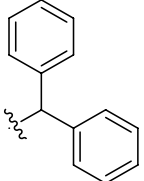
entry	solvent	x	y	temp (°C)	additive	time (h) <sup>a</sup>	er <sup>b</sup>
1	C <sub>6</sub> H <sub>6</sub>	1.5	3	80	none	3	85:15
2	C <sub>6</sub> H <sub>6</sub>	1.5	3	60	none	24	87:13
3	C <sub>6</sub> H <sub>6</sub>	1.5	3	60	5Å MS	2	88:12
4	C <sub>6</sub> H <sub>6</sub>	<b>1.5</b>	<b>3</b>	<b>40</b>	<b>5Å MS</b>	3	89:11
5	C <sub>6</sub> H <sub>6</sub>	1.5	3	r.t.	5Å MS	<sup>c</sup>	n.d.
6	C <sub>6</sub> H <sub>6</sub>	3	3	40	5Å MS	3	89:11
7	C <sub>6</sub> H <sub>6</sub>	1	2	40	5Å MS	6	89:11
8	C <sub>6</sub> H <sub>6</sub>	1.5	3	40	4Å MS	2	80:20
9	C <sub>6</sub> H <sub>6</sub>	1.5	3	40	3Å MS	<sup>c</sup>	n.d.
10	toluene	1.5	3	40	5Å MS	2	87:13
11	<i>c</i> -hexane	1.5	3	40	5Å MS	14	85:15
12	dioxane	1.5	3	40	5Å MS	2	86:14
13	<b>MTBE</b>	1.5	3	40	5Å MS	1.5	89:11
14	DCM	1.5	3	40	5Å MS	14 <sup>d</sup>	59:41

<sup>a</sup> Time for complete conversion. <sup>b</sup> Determined by GC using chiral column. <sup>c</sup> Trace of conversion after 24h. <sup>d</sup> ~90% conversion.

### Catalyst screening:

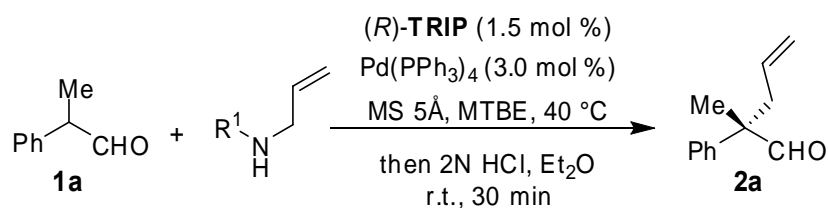


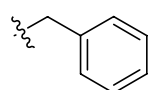
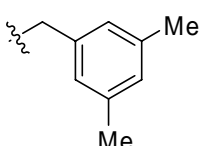
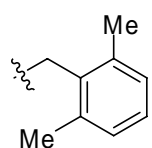
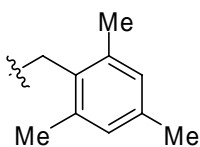
entry	R <sup>1</sup>	R <sup>2</sup>	time (h) <sup>a</sup>	er(ee) <sup>b</sup>
1			6	57.5:42.5 (15%)
2			3	55.5:44.5 (11%)
3			2	75:25 (50%)
4			3	50:50 (0%)
5			2	53.5:46.5 (7%)
6			<sup>c</sup>	n.d.
7			2	<b>89:11 (78%)</b>
8	<b>H<sub>8</sub>-TRIP</b>		2	82:18 (64%)

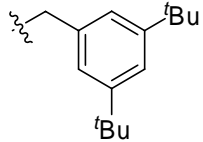
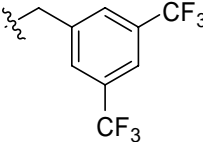
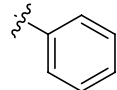
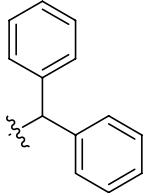
9	Br		2	69:31 (38%)
10			24 <sup>d</sup>	35.5:64.5 (-29%)
11			4	76:24 (52%)

<sup>a</sup> Time for complete conversion. <sup>b</sup> Determined by GC using chiral column. <sup>c</sup> Trace of conversion after 18h. <sup>d</sup> Conversion not complete.

### Reagent optimization:

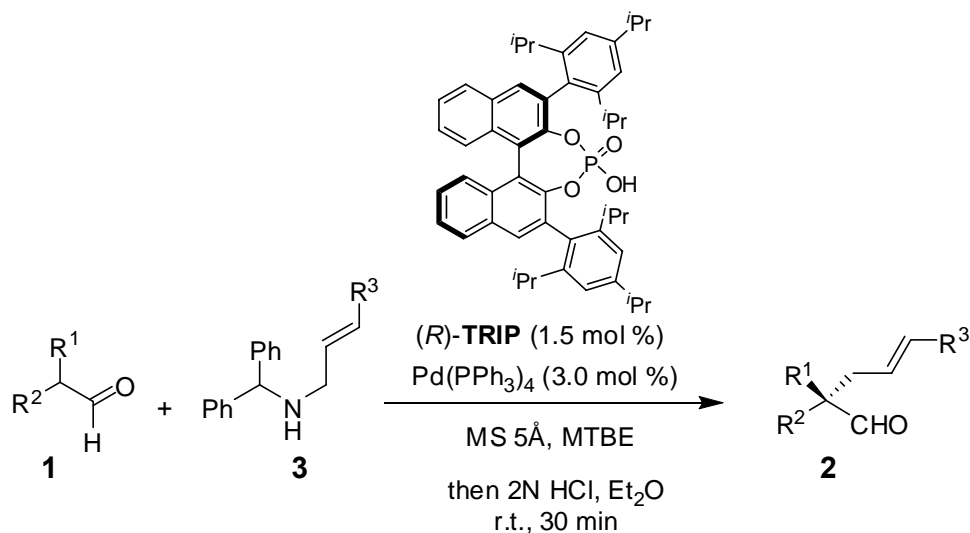


entry	R <sup>1</sup>	time (h) <sup>a</sup>	er(ee) <sup>b</sup>
1		2	89:11 (78%)
2		2	88.5:11.5 (77%)
3		3	89.5:10.5 (79%)
4		5	91:9 (82%)

5		2	91:9 (82%)
6		2	91.5:8.5 (83%)
7		2	68.5:31.5 (37%)
8		8	<b>98.5:1.5 (97%)</b>

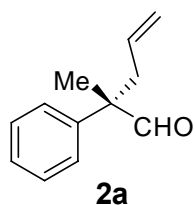
<sup>a</sup> Time for complete conversion. <sup>b</sup> Determined by GC using chiral column.

### General experimental procedure for the asymmetric $\alpha$ -allylation of aldehydes:

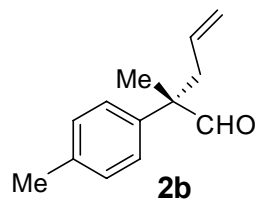
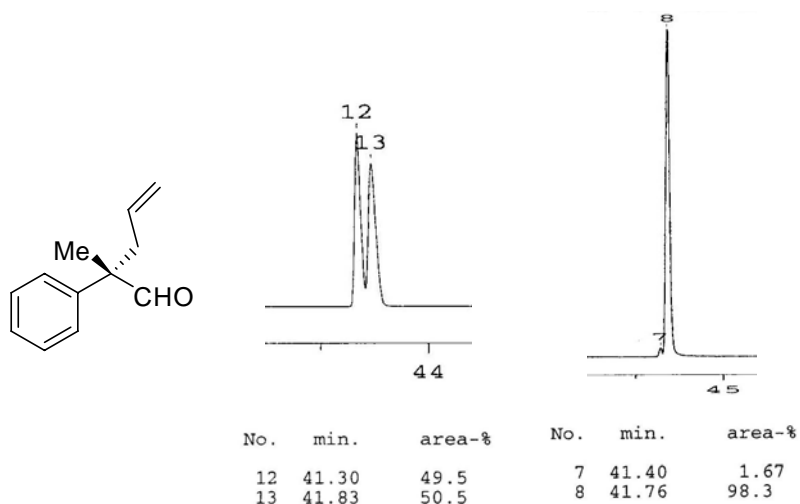


To a flame-dried Schlenk tube charged with 5Å activated molecular sieves and magnetic stirring bar, was added Pd(PPh<sub>3</sub>)<sub>4</sub> (12 mg, 0.01 mmol) and the catalyst **TRIP** (3.8 mg, 0.005 mmol) under a positive argon pressure. A solution of the aldehyde **1** (0.34 mmol) and the allyl reagent **3** (0.34 mmol) in 0.75 mL abs. MTBE was added and the resulting suspension was stirred at specified temperature under argon. Upon completion of the reaction (monitored by GC-MS), the reaction

mixture was diluted with diethyl ether (4 mL), 2N HCl (5 mL) was added and stirred vigorously for 30 mins. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O. The combined organic layers, after drying over anh. MgSO<sub>4</sub>, was concentrated in vacuo to obtain the crude product. Purification by column chromatography afforded the pure product **2**.

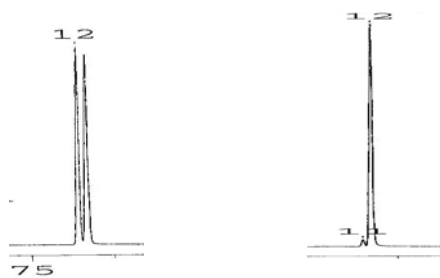
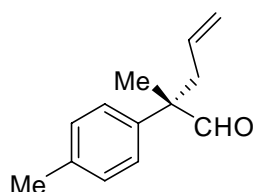


(**2a**): Compound **2a** was isolated as a clear oil (85% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $[\alpha]_D^{20} = +84.8^\circ$  ( $c = 1.08$ , MeOH, 20 °C) [Lit.<sup>6</sup>  $-38.0^\circ$  (MeOH) for the (*R*)-enantiomer]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.37$  (s, 3H), 2.52-2.66 (m, 2H), 4.94-5.02 (m, 2H), 5.41-5.55 (m, 1H), 7.17-7.34 (m, 5H), 9.45 (s, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 18.8, 40.6, 53.6, 118.6, 127.2, 127.3, 128.8, 133.2, 139.5, 201.9$ . HRMS (EI) Calcd. for [C<sub>12</sub>H<sub>14</sub>O] ([M]<sup>+</sup>): 174.104466, found: 174.104268. The enantiomeric ratio was determined to be >98:2 by GC using chiral Ivadex-7 / PS086 column 25m (80 °C, 0.4 °C/min until 140 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer:  $t_R = 41.76$  min, minor enantiomer:  $t_R = 41.40$  min.

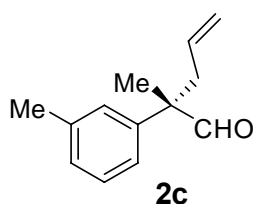


(**2b**): Compound **2b** was isolated as a pale yellow oil (89% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.41$  (s, 3H), 2.33 (s, 3H), 2.54-2.70 (m, 2H), 4.99-5.08 (m, 2H), 5.47-5.61 (m, 1H), 7.03-7.28 (m, 4H), 9.47 (s, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 18.8, 20.9, 40.5, 53.2, 118.5, 127.1, 129.6, 133.3, 136.3, 137.0, 202.0$ . HRMS (EI) Calcd. for [C<sub>13</sub>H<sub>16</sub>O] ([M]<sup>+</sup>): 188.120114, found: 188.120084. The enantiomeric ratio was determined to be 97:3 by GC using chiral Ivadex-7 / PS086 column 25m (60 °C, 0.7 °C/min until 220 °C, 15 min at 220 °C). Major enantiomer:  $t_R = 78.38$  min, minor enantiomer:  $t_R = 77.91$  min.

<sup>6</sup> Hiroi, K.; Abe, J.; Suya, K.; Sato, S. *Tetrahedron Lett.* **1989**, 30, 1543-1546.



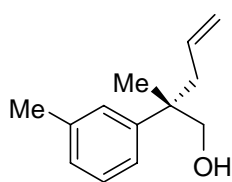
No.	min.	area-%	No.	min.	area-%
12	77.76	49.8	11	77.91	2.81
13	78.31	50.2	12	78.38	97.2



**2c**

(**2c**): Compound **2c** was isolated as a clear oil (84% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.43 (s, 3H), 2.36 (s, 3H), 2.60-2.70 (m, 2H), 5.02-5.09 (m, 2H), 5.51-5.61 (m, 1H), 7.05-7.12 (m, 3H), 7.26-7.29 (m, 1H), 9.51 (s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.8, 21.5, 40.5, 53.5, 118.4, 124.1, 127.9, 128.1, 128.7, 133.3, 138.5, 139.4, 202.0.

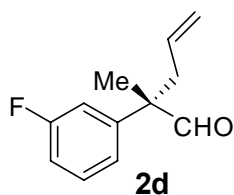
HRMS (EI) Calcd. for [C<sub>13</sub>H<sub>16</sub>O] ([M]<sup>+</sup>): 188.120114, found: 188.120328. The enantiomeric ratio was determined to be 98:2 (of the corresponding alcohol after reduction with NaBH<sub>4</sub>) by HPLC using chiral Chiralcel OD-H column 250 mm, 4.6 mm i.D. (98:2 *n*-heptane / *i*-PrOH, 0.5 ml/min). Major enantiomer: t<sub>R</sub> = 18.69 min, minor enantiomer: t<sub>R</sub> = 17.65 min.



Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	17.84	49.94
2	18.89	50.06
Total		100.00



Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	17.65	1.96
2	18.69	98.04
Total		100.00

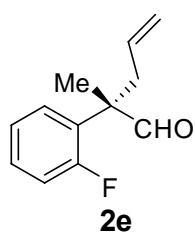
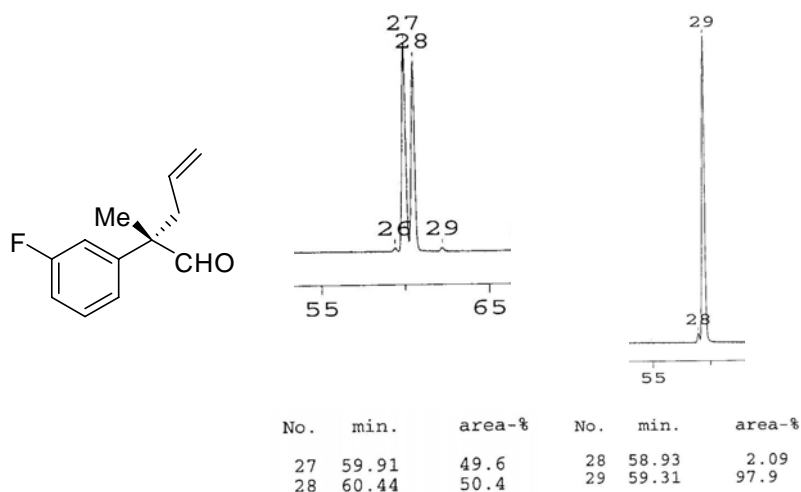


**2d**

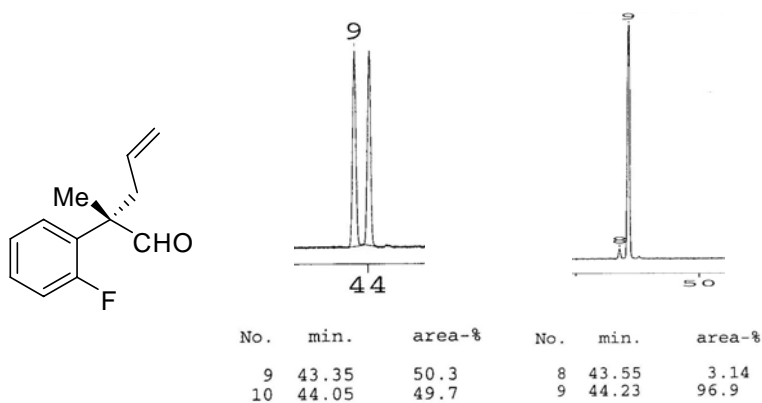
(**2d**): Compound **2d** was isolated as a clear oil (85% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.42 (s, 3H), 2.55-2.69 (m, 2H), 5.01-5.08 (m, 2H), 5.44-5.58 (m, 1H), 6.94-7.02 (m, 3H), 7.29-7.36 (m, 1H), 9.47 (s, 1H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ = 18.8, 40.6, 53.5,

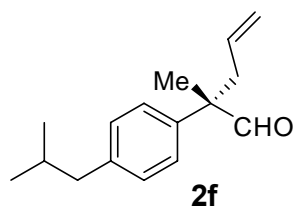
114.1 (d, *J* = 3.52 Hz), 114.4 (d, *J* = 4.98 Hz), 118.9, 122.8 (d, *J* = 2.98 Hz), 130.3 (d, *J* = 8.25 Hz),

132.6, 142.2 (d,  $J = 6.80$  Hz), 163.1 (d,  $J = 245.3$  Hz), 201.2. HRMS (EI) Calcd. for  $[C_{12}H_{13}OF]$  ( $[M]^+$ ): 192.095043, found: 192.094875. The enantiomeric ratio was determined to be 98:2 by GC using chiral Ivadex-7 / PS086 column 25m (10 min at 70 °C, 0.5 °C/min until 110 °C, 18 °C/min until 220 °C, 10 min at 220°C). Major enantiomer:  $t_R = 59.31$  min, minor enantiomer:  $t_R = 58.93$  min.

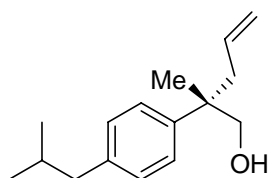


(**2e**): Compound **2e** was isolated as a clear oil (74% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $^1H$ -NMR (300 MHz,  $CDCl_3$ ):  $\delta = 1.48$  (s, 3H), 2.65-2.86 (m, 2H), 5.06-5.13 (m, 1H), 7.10-7.40 (m, 4H), 9.74 (d,  $J = 5.07$  Hz, 1H).  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ ):  $\delta = 19.1$ , 39.2 (d,  $J = 2.57$  Hz), 51.8 (d,  $J = 3.16$  Hz), 116.1 (d,  $J = 22.6$  Hz), 118.8, 124.4 (d,  $J = 3.17$  Hz), 127.9 (d,  $J = 12.98$  Hz), 128.6 (d,  $J = 5.04$  Hz), 129.4 (d,  $J = 8.75$  Hz), 132.7, 160.9 (d,  $J = 245.5$  Hz), 201.7 (d,  $J = 2.15$  Hz). HRMS (EI) Calcd. for  $[C_{12}H_{13}OF]$  ( $[M]^+$ ): 192.095043, found: 192.095078. The enantiomeric ratio was determined to be 97:3 by GC using chiral Ivadex-1 / OV1701 column 28m (80 °C, 0.7 °C/min until 200 °C, 10 min at 200 °C). Major enantiomer:  $t_R = 44.23$  min, minor enantiomer:  $t_R = 43.55$  min.



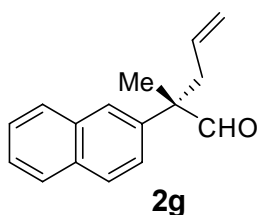


**(2f)** Compound **2f** was isolated as a pale yellow oil (76% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.89$  (d,  $J = 6.64$  Hz, 6H), 1.41 (s, 3H), 1.79-1.90 (m, 1H), 2.45 (d,  $J = 7.20$  Hz, 2H), 2.58-2.69 (m, 2H), 5.00-5.07 (m, 2H), 5.49-5.60 (m, 1H), 7.13-7.14 (m, 4H), 9.49 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 18.8, 22.3, 30.1, 40.5, 44.9, 53.3, 118.4, 126.9, 129.6, 133.4, 136.6, 140.8, 202.0$ . HRMS (EI) Calcd. for  $[\text{C}_{16}\text{H}_{22}\text{O}]$  ( $[\text{M}]^+$ ): 230.167063, found: 230.166911. The enantiomeric ratio was determined to be 97.5:2.5 (of the corresponding alcohol after reduction with  $\text{NaBH}_4$ ) by HPLC using chiral Sepapak-2 column 250 mm, 4.6 mm i.D. (99:1 *n*-heptane / *i*-PrOH, 0.5 ml/min). Major enantiomer:  $t_{\text{R}} = 28.83$  min, minor enantiomer:  $t_{\text{R}} = 25.16$  min.

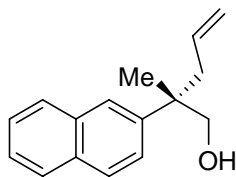


Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	24.91	49.35
2	27.56	0.31
3	28.64	50.34
Total		100.00

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	25.16	2.42
2	28.83	97.58
Total		100.00

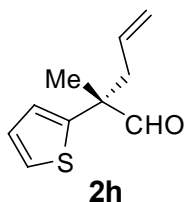


**(2g)**: Compound **2g** was isolated as a pale yellow oil (71% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.55$  (s, 3H), 2.67-2.85 (m, 2H), 5.00-5.11 (m, 2H), 5.50-5.61 (m, 1H), 7.34-7.38 (m, 1H), 7.47-7.52 (m, 2H), 7.70-7.71 (m, 1H), 7.80-7.86 (m, 3H), 9.59 (s, 1H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 18.9, 40.5, 53.7, 118.6, 124.9, 126.2, 126.3, 127.5, 128.0, 128.5, 132.4, 133.1, 133.4, 136.8, 201.9$ . HRMS (EI) Calcd. for  $[\text{C}_{16}\text{H}_{16}\text{O}]$  ( $[\text{M}]^+$ ): 224.120113, found: 224.119846. The enantiomeric ratio was determined to be 97:3 (of the corresponding alcohol after reduction with  $\text{NaBH}_4$ ) by HPLC using chiral Chiralcel OD-H column 250 mm, 4.6 mm i.D. (95:5 *n*-heptane / *i*-PrOH, 0.5 ml/min). Major enantiomer:  $t_{\text{R}} = 223.41$  min, minor enantiomer:  $t_{\text{R}} = 25.69$  min.

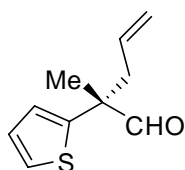


Peak #	Ret. Time	Area %
1	16.64	3.74
2	19.43	3.85
3	20.95	46.17
4	22.88	46.24
Total		100.00

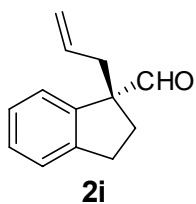
Peak #	Ret. Time	Area %
1	23.41	96.98
2	25.69	3.02
Total		100.00



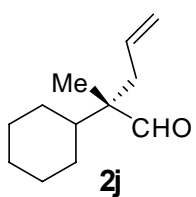
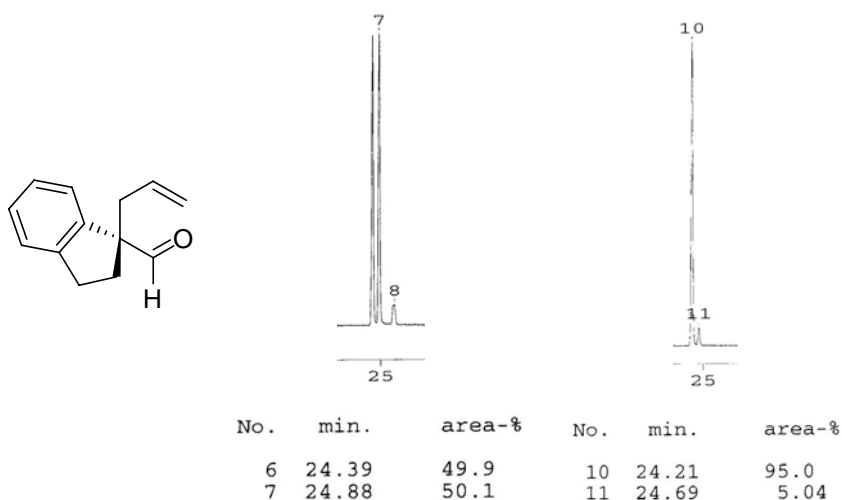
(**2h**): Compound **2h** was isolated as a pale yellow oil (80% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.51 (s, 3H), 2.68-2.70 (m, 2H), 5.08-5.15 (m, 2H), 5.62-5.69 (m, 1H), 6.91-6.92 (m, 1H), 7.03-7.05 (m, 1H), 7.29-7.31 (m, 1H), 9.49 (m, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 20.0, 41.4, 52.1, 119.2, 125.1, 125.4, 127.4, 132.5, 144.1, 199.5. HRMS (EI) Calcd. for  $[\text{C}_{10}\text{H}_{12}\text{OS}]$  ( $[\text{M}]^+$ ): 180.060888, found: 180.060804. The enantiomeric ratio was determined to be 93:7 by GC using chiral BGB-176 / SE-52 column 30m (80 °C, 1.2 °C/min until 130 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer:  $t_{\text{R}}$  = 28.09 min, minor enantiomer:  $t_{\text{R}}$  = 27.86 min.



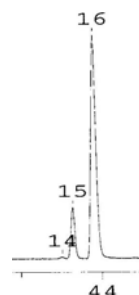
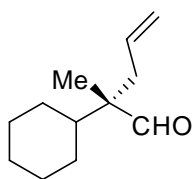
No.	min.	area-%	No.	min.	area-%
19	27.96	49.9	20	27.86	7.13
20	28.38	50.1	21	28.09	92.9



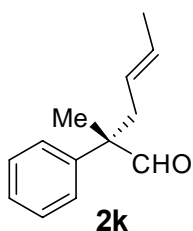
**(2i):** Compound **2i** was isolated as a pale yellow oil (45% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.07-2.14 (m, 1H), 2.52-2.60 (m, 2H), 2.73-2.79 (m, 1H), 3.02 (t, *J* = 7.52 Hz, 2H), 5.06-5.15 (m, 2H), 5.60-5.71 (m, 1H), 7.20-7.31 (m, 4H), 9.58 (s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 30.4, 30.9, 38.8, 63.3, 118.5, 124.2, 125.1, 126.8, 128.2, 133.3, 141.4, 145.0, 200.7. HRMS (EI) Calcd. for [C<sub>13</sub>H<sub>14</sub>O] ([M]<sup>+</sup>): 186.104466, found: 186.104367. The enantiomeric ratio was determined to be 95:5 by GC using chiral Ivadex-7 / PS086 column 25m (100 °C, 0.8 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: *t*<sub>R</sub> = 24.21 min, minor enantiomer: *t*<sub>R</sub> = 24.69 min.



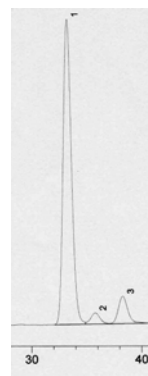
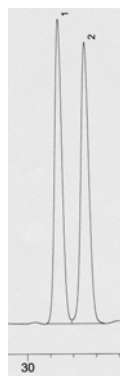
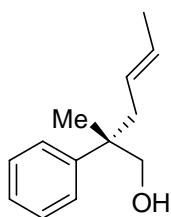
**(2j):** Compound **2j** was isolated as a pale yellow oil (65% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 0.95 (s, 3H), 0.97-1.28 (m, 5H), 1.49-1.82 (m, 6H), 2.17-2.22 (m, 1H), 2.30-2.35 (m, 1H), 5.00-5.05 (m, 2H), 5.60-5.71 (m, 1H), 9.47 (s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 14.9, 26.4, 26.7, 26.8, 28.0, 38.5, 42.3, 51.8, 118.1, 133.5, 207.1. HRMS (CI) Calcd. for [C<sub>12</sub>H<sub>21</sub>O] ([M+H]<sup>+</sup>): 181.159240, found: 181.159316. The enantiomeric ratio was determined to be 85:15 by GC using chiral Ivadex-7 / PS086 column 25m (80 °C, 0.4 °C/min until 100 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: *t*<sub>R</sub> = 43.48 min, minor enantiomer: *t*<sub>R</sub> = 42.52 min.



No.	min.	area-%	No.	min.	area-%
15	42.24	50.1	15	42.52	15.1
16	43.37	49.9	16	43.48	84.9

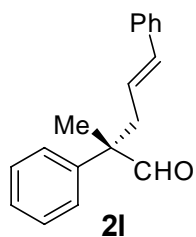


(**2k**): Compound **2k** was isolated as a pale yellow oil (40% yield) after silica gel column chromatography (10:1 hexane/EtOAc).  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.35 (s, 3H), 1.51-1.55 (m, 3H), 5.07-5.18 (m, 1H), 5.37-5.46 (m, 1H), 7.17-7.25 (m, 3H), 7.27-7.34 (m, 2H), 9.46 (s, 1H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 17.9, 19.1, 39.3, 53.8, 125.3, 127.1, 127.2, 128.8, 129.2, 139.9, 202.4. HRMS (CI) Calcd. for  $[\text{C}_{13}\text{H}_{17}\text{O}]$  ( $[\text{M}+\text{H}]^+$ ): 189.127941, found: 189.128063. The enantiomeric ratio was determined to be 96:4 (of the corresponding alcohol after reduction with  $\text{NaBH}_4$ ) by HPLC using chiral Chiralcel OD-H column 250 mm, 4.6 mm i.D. (99:1 *n*-heptane / *i*-PrOH, 0.5 ml/min). Major enantiomer:  $t_R$  = 33.24 min, minor enantiomer:  $t_R$  = 35.76 min. (Chromatogram was obtained using (*S*)-**TRIP** as the catalyst)

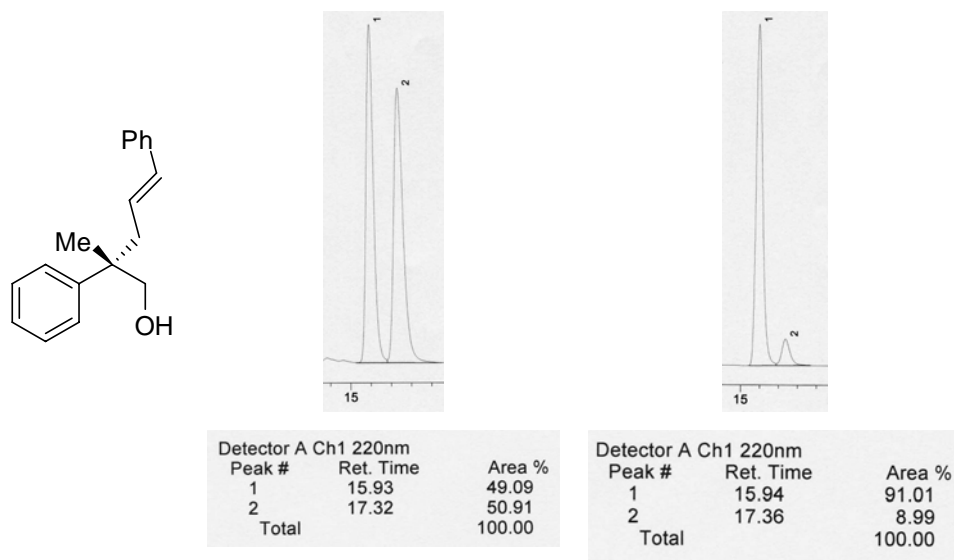


Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	32.77	49.83
2	35.07	50.17
Total		100.00

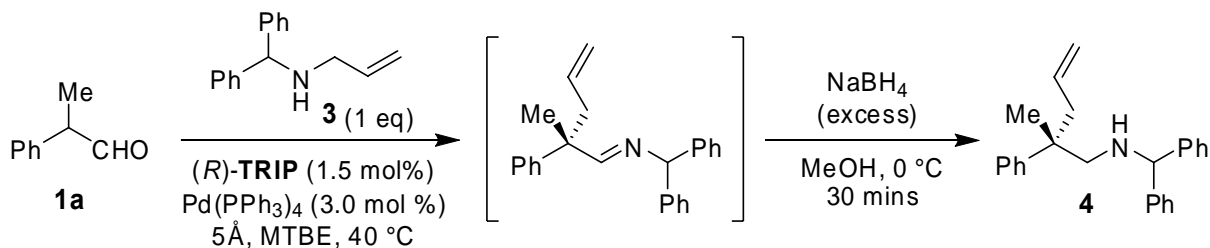
Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	33.24	87.75
2	35.76	3.48
3	38.27	8.77
Total		100.00



(**2I**): Compound **2I** was isolated as a pale yellow oil (82% yield) after silica gel column chromatography (10:1 hexane/EtOAc). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.40 (s, 3H), 2.70-2.74 (m, 2H), 5.81-5.89 (m, 1H), 6.29-6.33 (m, 1H), 7.08-7.11 (m, 1H), 7.14-7.24 (m, 7H), 7.29-7.33 (m, 2H), 9.48 (s, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.9, 39.9, 54.1, 124.9, 126.1, 127.1, 127.2, 127.4, 128.4, 128.9, 133.6, 137.2, 139.4, 201.9. HRMS (EI) Calcd. for [C<sub>18</sub>H<sub>18</sub>O] ([M]<sup>+</sup>): 250.135764, found: 250.136009. The enantiomeric ratio was determined to be 91:9 (of the corresponding alcohol after reduction with NaBH<sub>4</sub>) by HPLC using chiral Chiralpak AS-H column 250 mm, 4.6 mm i.D. (95:5 *n*-heptane / *i*-PrOH, 0.5 ml/min). Major enantiomer: t<sub>R</sub> = 15.94 min, minor enantiomer: t<sub>R</sub> = 17.36 min. (Chromatogram was obtained using (*S*)-**TRIP** as the catalyst)



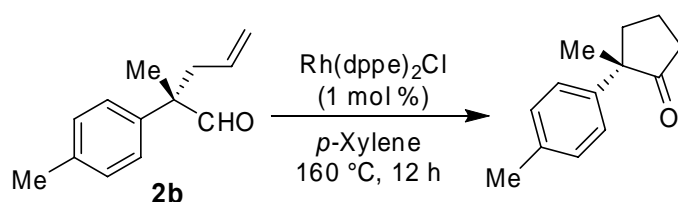
### Reductive work-up:



After the reaction was complete (monitored by GCMS), the reaction mixture (0.68 mmol scale) was diluted with abs. MeOH (3 mL) and cooled to 0 °C. Excess of NaBH<sub>4</sub> was added and the resulting mixture was stirred at 0 °C for 30 mins. The reaction mixture was quenched with water (5 mL) and

extracted with diethyl ether (3 × 10 mL). Combined ether layers were washed with brine and dried over anhydrous MgSO<sub>4</sub>. Concentration afforded a pale brown oil which was purified by silica gel column chromatography (10:1 hexane/EtOAc) to obtain the amine **4** as a pale yellow oil (190 mg, 0.56 mmol, 82%). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.21 (br s, 1H), 1.30 (s, 3H), 2.24-2.31 (m, 1H), 2.43-2.50 (m, 1H), 2.56 (d, *J* = 11.4 Hz, 1H), 2.72 (d, *J* = 11.4 Hz, 1H), 4.58 (s, 1H), 4.82-4.86 (m, 1H), 4.91-4.92 (m, 1H), 5.38-5.50 (m, 1H), 7.04-7.25 (m, 15H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ = 23.3, 41.9, 44.9, 58.9, 67.7, 117.1, 125.8, 126.5, 126.8, 126.9, 127.2, 128.2, 128.3, 135.0, 144.3, 144.4, 146.0. HRMS (EI) Calcd. for [C<sub>25</sub>H<sub>27</sub>N] ([M]<sup>+</sup>): 341.214347, found: 341.214240.

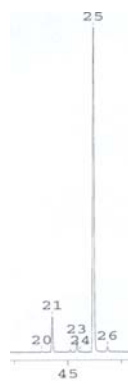
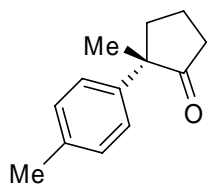
### Synthesis of cuparenone:



In a flame-dried schlenk tube charged with a magnetic stirring bar, aldehyde **2b** (100 mg, 0.53 mmol) was taken along with Rh(dppe)<sub>2</sub>Cl<sup>7</sup> (5.0 mg, 0.0053 mmol) under positive argon pressure. 0.5 mL abs *p*-xylene was added and the resulting mixture was heated at 160 °C under argon for 12 hours. The crude product was purified by silica gel chromatography (hexane/EtOAc 15:1 to 10:1) to obtain cuparenone as a pale yellow oil (30 mg, 0.16 mmol, 30%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.37 (s, 3H), 1.85-2.03 (m, 3H), 2.32-2.35 (m, 5H), 2.52-2.57 (m, 1H), 7.12-7.14 (m, 2H), 7.22-7.26 (m, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.7, 20.9, 25.0, 37.5, 38.0, 52.8, 126.2, 129.3, 136.3, 139.5, 220.8. HRMS (EI) Calcd. for [C<sub>13</sub>H<sub>16</sub>O] ([M]<sup>+</sup>): 188.120118, found: 188.119897. Analytical data are in agreement with the literature.<sup>8</sup>

<sup>7</sup> James, B. R.; Young, C. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1215-1216.

<sup>8</sup> Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, 47, 5455-5458.



No.	min.	area-%	No.	min.	area-%
20	42.52	4.15	20	42.55	0.17
21	43.52	4.14	21	43.53	8.30
22	45.71	45.8	23	45.84	2.75
23	47.29	45.9	25	47.34	88.8

Enantiomers 20 & 21  
corresponds to 3'-Me isomer

