Enantioselective Syntheses of (–)-(R)-Rolipram, (–)-(R)-Baclofen and Other GABA Analogues via Rhodium-Catalyzed Conjugate Addition of Arylboronic Acids

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Received 20 August 2003; revised 17 September 2003

Abstract: Highly enantioselective syntheses of two important γ-aminobutyric acid (GABA) analogues, the antispastic drug (–)-(R)-Baclofen and the antidepressant agent (–)-(R)-Rolipram, are reported. Key-steps in both syntheses are the Rh-catalyzed asymmetric 1,4-additions of arylboronic acids to 4-aminobut-2,3-enolic acid derivatives.

Key words: asymmetric synthesis, catalysis, conjugate addition, rhodium, arylboronic acid

Because of the crucial importance of γ-aminobutyric acid (GABA) in various nervous system functions, GABA analogues are of great interest in medicinal chemistry. For example, the strongly lipophilic β-substituted analogue 4-amino-3-(4-chlorophenyl)butyric acid (1, Baclofen) is until now the only available selective agonist of the GABA_B receptor. Of particular interest is the cyclic GABA analogue 4-(3-cyclopentenolxy-4-methoxyphenyl)pyrrolidin-2-one (2, Rolipram), known for its potent inhibitor activity of the cardiac cyclic AMP phosphodiesterase, found in brain tissue. It has been disclosed that for both compounds the (R)-enantiomers are responsible for the pharmacological activities. Therefore, short and efficient syntheses of the enantiomerically pure GABA analogues (R)-Baclofen and (R)-Rolipram are of great interest.

Several stereoselective syntheses of (R)-Baclofen^4 and (R)-Rolipram^3,5 have already been reported. Some of these syntheses require more than ten steps and proceed generally with a relatively low overall yield. In this paper, we describe shorter and more efficient syntheses of these compounds from a common precursor based on asymmetric catalysis (Scheme 1).^6 Key steps of our syntheses are Rh(I)-catalyzed asymmetric conjugate additions of arylboronic acids to the substrates 3a–c (Scheme 2).

**Scheme 1**

**Scheme 2**

syntheses of the enantiomerically pure GABA analogues (R)-Baclofen and (R)-Rolipram are of great interest. Several stereoselective syntheses of (R)-Baclofen^4 and (R)-Rolipram^3,5 have already been reported. Some of these syntheses require more than ten steps and proceed generally with a relatively low overall yield. In this paper, we describe shorter and more efficient syntheses of these compounds from a common precursor based on asymmetric catalysis (Scheme 1).^6 Key steps of our syntheses are Rh(I)-catalyzed asymmetric conjugate additions of arylboronic acids to the substrates 3a–c (Scheme 2).
This type of reaction was discovered by Miyaura et al. in 1997 and further developed into an enantioselective version in collaboration with Hayashi et al. The substrates (E)-3a-c were prepared in isolated overall yields of 57–82% from N-protected 2-aminoethanol derivatives 4a-c (Scheme 2) by oxidation with 2-iodoxybenzoic acid (IBX) followed by Horner–Wadsworth–Emmons (HWE) olefination.

The reaction conditions of the 1,4-addition were optimized for the synthesis of 7a using first standard reaction conditions, i.e. 3 mol% of [Rh(acac)(C₂H₄)₂], 4.5 mol% of (R)-BINAP and Na₂CO₃ at 100 °C for 48 hours (Table 1). Under these conditions, (S)-7a was obtained in 62% yield and 82% ee (entry 1). An improvement was achieved by using Cs₂CO₃ instead of Na₂CO₃ as base: 89% yield, 87% ee (entry 2). As the arylboronic acid is partially hydrolyzed under the standard reaction conditions, the amount of 6a was increased to 5 equivalents; using (S)-BINAP as ligand, the addition product (R)-7a was obtained in almost quantitative yield with 89% ee (entry 3).

The optimized procedure was then applied successfully to reactions of 3a with 4-fluorophenylboronic acid (7b) (entry 4) and phenylboronic acid (7c) (entry 5).

The influence of the protecting group at nitrogen was then studied. With phthalimide 3b, yield and ee were lower than with the Boc-derivative 3a (entries 6–8). The benzylcarbonyl derivative 3c gave addition product 7g in only 46% yield, but with 92% ee (entry 9). Upon reoptimization of reaction conditions for 3c it was found that with Et₃N instead of Cs₂CO₃ the product (R)-7g was obtained in 68% yield with 88% ee, using (S)-BINAP as ligand (entry 10). Similar improvements were generally obtained (entries 11,12). It is noteworthy that the use of Et₃N as base resulted in a rate enhancement and the starting material was consumed completely after 24 hours at 100 °C.

Deprotection of the addition product (R)-7a to give Bacloden hydrochloride was performed in 83% overall yield by treatment with 2 M NaOH in MeOH followed by addition of HCl in ether (Scheme 2). Comparison of the optical rotation of the product 1 ([α]D = 1.7 (c = 0.32, H₂O)) with literature data proved the absolute configuration to be R.² This methodology was then extended to the synthesis of (R)-Rolipram (Scheme 1). The requisite boronic acid 6d (Scheme 2) was prepared from 4-bromo-2-(cyclopentyl-oxy)anisole (8)³ by transformation to the corresponding Moc-derivatives which were separable, AD-H, n-hexane–i-PrOH (90:10) for 7a, n-hexane–i-PrOH (95:5), 4 °C for 7c.

### Table 1  Rh-Catalyzed Asymmetric 1,4-Additions of Arylboronic Acids to 4-Aminobut-2,3-enoic Acid Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Ester 3</th>
<th>Boronic Acid 6</th>
<th>Ligand</th>
<th>Base</th>
<th>Conditiona</th>
<th>Product 7</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E)-3a</td>
<td>6a</td>
<td>(R)-BINAP</td>
<td>Na₂CO₃</td>
<td>A</td>
<td>7a</td>
<td>62</td>
<td>82(4) (S)</td>
</tr>
<tr>
<td>2</td>
<td>(E)-3a</td>
<td>6a</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>A</td>
<td>7a</td>
<td>89</td>
<td>87(4) (S)</td>
</tr>
<tr>
<td>3</td>
<td>(E)-3a</td>
<td>6a</td>
<td>(S)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7a</td>
<td>96</td>
<td>89a (R)</td>
</tr>
<tr>
<td>4</td>
<td>(E)-3a</td>
<td>6b</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7b</td>
<td>56</td>
<td>90(6) (S)</td>
</tr>
<tr>
<td>5</td>
<td>(E)-3a</td>
<td>6c</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7c</td>
<td>98</td>
<td>65(5) (S)</td>
</tr>
<tr>
<td>6</td>
<td>(E)-3b</td>
<td>6a</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7d</td>
<td>59</td>
<td>80(5)</td>
</tr>
<tr>
<td>7</td>
<td>(E)-3b</td>
<td>6b</td>
<td>(S)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7e</td>
<td>55</td>
<td>85 (99) (R)</td>
</tr>
<tr>
<td>8</td>
<td>(E)-3b</td>
<td>6c</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7f</td>
<td>56</td>
<td>42 (S)</td>
</tr>
<tr>
<td>9</td>
<td>(E)-3c</td>
<td>6a</td>
<td>(R)-BINAP</td>
<td>Cs₂CO₃</td>
<td>B</td>
<td>7g</td>
<td>46</td>
<td>92 (S)</td>
</tr>
<tr>
<td>10</td>
<td>(E)-3c</td>
<td>6a</td>
<td>(S)-BINAP</td>
<td>Et₃N</td>
<td>C</td>
<td>7g</td>
<td>68</td>
<td>88 (R)</td>
</tr>
<tr>
<td>11</td>
<td>(E)-3c</td>
<td>6b</td>
<td>(R)-BINAP</td>
<td>Et₃N</td>
<td>C</td>
<td>7h</td>
<td>70</td>
<td>90 (S)</td>
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<tr>
<td>12</td>
<td>(E)-3c</td>
<td>6c</td>
<td>(R)-BINAP</td>
<td>Et₃N</td>
<td>C</td>
<td>7i</td>
<td>74</td>
<td>86 (S)</td>
</tr>
<tr>
<td>13</td>
<td>(E)-3a</td>
<td>6d</td>
<td>(S)-BINAP</td>
<td>Cs₂CO₃</td>
<td>A</td>
<td>7j</td>
<td>73</td>
<td>84 (99) (R)</td>
</tr>
</tbody>
</table>

*a Condition A: 1 equiv of 3, 2 equiv of 6, 2 equiv of the base, 100 °C, 48 h. Condition B: 1 equiv of 3, 5 equiv of 6, 2 equiv of the base, 100 °C, 48 h. Condition C: 1 equiv of 3, 5 equiv of 6, 4 equiv of the base, 100 °C, 24 h.*

* Isolated yields after flash chromatography.

* Determined by HPLC, using a Daicel AD-H column, eluent n-hexane–i-PrOH, ratio 70:30 for 7d-f, 90:10 for 7g-h and 7j, 95:5, 4 °C for 7i.

* Separation of the enantiomers of 7a-c was not possible; these compounds were treated with HCl/Et₃O and then (MeOCO)₂O/Et₃N to form the corresponding Moc-derivatives which were separable, AD-H, n-hexane–i-PrOH (90:10) for 7a,b, n-hexane–i-PrOH (95:5), 4 °C for 7c.

* 97% ee after one crystallization, 99% ee after two crystallizations from CH₂Cl₂–n-hexane.

* 90% ee after one crystallization, 99% ee after two crystallizations from CH₂Cl₂–n-hexane.

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It is noteworthy that the classical halogen–metal exchange reactions followed by reaction with B(OMe)₃, and acidic hydrolysis, were not successful for the synthesis of 6d starting from 8; all attempts gave multicomponent reaction mixtures.

The boronic acid 6d (2 equivalents) was reacted with 3a under the optimized reaction conditions (Table 1, entry 13). The expected addition product 8j was obtained in 73% yield with 84% ee. Material of 99% ee was obtained by two-fold recrystallization from CH₂Cl₂–hexane. Using the substrate 3c, both lower yield and ee were obtained. In contrast, even after extensive experimentation, the reaction of the boronic ester 9 with 3a gave less than 30% isolated yield because of competing hydrolysis.

Deprotection to obtain (R)-Rolipram was performed in 78% overall yield by treatment of 7j (90% ee) with TFA–CH₂Cl₂ (1:1), followed by heating with Et₂N in toluene solution at reflux (Scheme 2). Comparison of the optical rotation of the product 2 [(1)D = −27.4 (c = 0.1, MeOH)] with literature data proved the absolute configuration to be R. In conclusion, we have developed straightforward and efficient enantioselective syntheses of (--)-(R)-Baclofen and (--)-(R)-Rolipram using as key steps Rh-catalyzed additions of arylboronic acids to 4-aminobut-2,3-enolic acid derivatives.

TLC: Macherey & Nagel Polygram Sil G/U/V precoated sheets, treatment with aqueous K₃[Fe(CN)₆] solution for visualization of spots. Column chromatography: Fluka silica gel, grade 60 (0.04–0.063 mm). ¹H and ¹³C NMR spectra were recorded on Bruker DRX 300, AMX 400 or DRX 500 instruments. ¹H NMR chemical shifts are relative to residual deuterated solvent in CDCl₃ (δ = 7.26). The ¹³C NMR shifts relate to solvent CDCl₃ (δ = 77.0). High-resolution mass spectra were determined on a JMS 700 mass spectrometer. HPLC: Hewlett Packard HP 1100 with DAICEL Chiralpak AD-H column (25 cm × 0.46 cm) in combination with DAICEL Chiralpak AD-H precolumn (1 cm × 0.4 cm); separation of the enantiomers of 7a–c was not possible; these compounds were treated with HCl/Et₂O and then (MeOCO)₂O/NEt₃ to form the corresponding Modervatives which were separable. Elemental analyses: Mikroanalytische Abteilung des Organisch-Chemischen Instituts, Universität Heidelberg. Optical rotations were measured on a Perkin-Elmer P 241 polarimeter. Compound 4c was prepared according to published methods.¹⁵

**Scheme 3**

tert-Butyl 2-Hydroxyethylcarbamate (4a)
A solution of Boc₂O (33.6 g, 154 mmol, 1.1 equiv) in anhyd CH₂Cl₂ (40 mL) was added dropwise to a solution of 2-amin ethanol (8.55 g, 140 mmol, 1 equiv) in anhyd CH₂Cl₂ (180 mL) at r.t. under argon. The reaction mixture was stirred at r.t. for 5 h, then washed with an aq. sat. solution of NaHCO₃ (3 × 200 mL). The organic layer was dried and concentrated in vacuo. The crude reaction mixture was distilled under reduced pressure to give 4a in quantitative yield. NMR data were in accordance with those reported.¹⁶

**N-Protected But-2-enolic Acid Ethyl Ester Derivatives 3a–c; General Procedure**
2-Iodoxybenzoic acid (IBX, 12.3 g, 44.8 mmol, 1.4 equiv) was added to a solution of 4 (32.0 mmol, 1 equiv) in DME (100 mL). The reaction mixture was heated at 80 °C for 1 h, then cooled to r.t. and filtered. The solid residue was washed with Et₂O (50 mL), and the filtrate was concentrated in vacuo. The residue was dried and concentrated in vacuo. Flash chromatography (silica gel, EtOAc–petroleum ether, 5:95) furnished 3a–c.

**Ethyl (2E)-4-[[tert-Butoxycarbonyl]amino]but-2-enoate (3a)**
Yellowish oil; yield: 57%.

**Ethyl (2E)-4-[[1,3-Dioxo-1,3-dihydro-2H-isooindol-2-yl]but-2-enoate (3b)**
Colorless crystals; yield: 82%; mp 93–94 °C.

**Ethyl (2E)-4-[[Benzyloxycarbonyl]amino]but-2-enoate (3c)**
Yellowish oil; yield: 69%.

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Ethyl 3-Aryl-4-[(tert-butoxycarbonyl)amino]butanoates 7a–c and Ethyl 3-Aryl-4-1,3-dioxo-1,3-dihydro-2H-isindol-2-yl)butanoates 7d–f; General Procedure
A solution of [Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}] (1.00 mg, 3.87 \mu mol, 0.03 equiv) and (R)- or (S)-(S)-BINAP (3.62 mg, 5.81 \mu mol, 0.045 equiv) in anhyd dioxane (2 mL) was stirred for 90 min at r.t. under argon. Cs\textsubscript{2}CO\textsubscript{3} (84.1 mg, 258 \mu mol, 2 equiv), arylboronic acid (645 \mu mol, 5 equiv), 3 (129 \mu mol, 1 equiv) and H\textsubscript{2}O (0.2 mL) were successively added at r.t. and the mixture was heated at 100 °C for 48 h. Then EtOAc (15 mL) was added and the mixture was extracted with H\textsubscript{2}O (10 mL). The organic layer was dried and concentrated in vacuo. Flash chromatography (silica gel, EtOAc–petroleum ether, 15:85) furnished 7a–f.

(R)-Ethyl 4-[(tert-Butoxycarbonyl)amino]-3-(4-chlorophenyl)butanoate (7a)
Colorless crystals; yield: 96%; mp 85–88 °C.
HPLC of Moc derivative: DAICEL Chiralpak AD-H column; length: 25 cm + 1 cm precolumn; flow: 0.5 mL/min; eluent: n-hexane–i-ProH (90:10); \(t\text{R}(S)\) 23.5 min, \(t\text{R}(R)\) 24.8 min.

1H NMR (CDCl\textsubscript{3}): \(\delta = 1.12 \text{ (t, } J = 7.2 \text{ Hz, 3 H)}, 1.41 \text{ (s, } 9 \text{ H}), 2.63 \text{ (m, 2 H)}, 3.24 \text{ (m, 2 H)}, 3.41 \text{ (m, 1 H)}, 4.05 \text{ (q, } J = 7.2 \text{ Hz, 2 H)}, 4.45 \text{ (s, 1 H)}, 7.11 \text{ (d, } J = 4.8 \text{ Hz, 2 H)}, 7.24 \text{ (d, } J = 8.4 \text{ Hz, 2 H}).

13C NMR (CDCl\textsubscript{3}): \(\delta = 13.9, 28.7, 38.1, 41.7, 45.3, 60.3, 80.1, 128.6, 128.8, 132.6, 133.9, 139.6, 171.4.

Anal. Calcd for C\textsubscript{17}H\textsubscript{25}NO\textsubscript{4}: C, 66.43; H, 8.20; N, 4.56. Found: C, 65.98; H, 7.19; N, 4.20.

(S)-Ethyl 4-[(tert-Butoxycarbonyl)amino]-3-(fluorophenyl)butanoate (7b)
Colorless crystals; yield: 56%; mp 76–78 °C.
HPLC of Moc derivative: DAICEL Chiralpak AD-H column; length: 25 cm + 1 cm precolumn; flow: 0.5 mL/min; eluent: n-hexane–i-ProH (90:10); \(t\text{R}(S)\) 17.4 min, \(t\text{R}(R)\) 18.8 min.

1H NMR (CDCl\textsubscript{3}): \(\delta = 1.11 \text{ (t, } J = 7.2 \text{ Hz, 3 H)}, 1.36 \text{ (s, } 9 \text{ H}), 2.62 \text{ (m, 2 H)}, 3.29 \text{ (m, 3 H)}, 4.03 \text{ (q, } J = 7.2 \text{ Hz, 2 H}), 4.44 \text{ (s, 1 H)}, 7.08 \text{ (m, 2 H)}, 7.15 \text{ (m, 2 H)}.

13C NMR (CDCl\textsubscript{3}): \(\delta = 14.1, 28.3, 38.6, 41.8, 45.7, 60.5, 79.4, 115.4, 115.6, 129.0, 129.1, 136.9, 160.2, 163.5, 171.8.

Anal. Calcd for C\textsubscript{20}H\textsubscript{22}ClNO\textsubscript{4}: C, 64.61; H, 4.88; N, 3.77. Found: C, 64.93; H, 4.87; N, 3.75.

(S)-Ethyl 4-[(tert-Butoxycarbonyl)amino]-3-(4-fluorophenyl)butanoate (7c)
Colorless crystals; yield: 96%; mp 96–98 °C.
HPLC: DAICEL Chiralpak AD-H column; length: 25 cm + 1 cm precolumn; flow: 0.5 mL/min; eluent: n-hexane–i-ProH (70:30); \(t\text{R}(S)\) 20.1 min, \(t\text{R}(R)\) 22.7 min.

1H NMR (CDCl\textsubscript{3}): \(\delta = 1.07 \text{ (t, } J = 7.2 \text{ Hz, 3 H)}, 2.73 \text{ (d, } J = 7.4 \text{ Hz, 2 H)}, 3.75 \text{ (m, 1 H)}, 3.93 \text{ (m, 4 H)}, 7.23 \text{ (m, 4 H)}, 7.74 \text{ (m, 4 H)}.

13C NMR (CDCl\textsubscript{3}): \(\delta = 14.0, 38.6, 40.8, 43.2, 60.4, 123.2, 127.7, 128.6, 131.9, 133.9, 140.4, 168.1, 171.5.

HRMS: m/z calcd for C\textsubscript{20}H\textsubscript{18}F\textsubscript{4}NO\textsubscript{4} (M\textsuperscript{+}): 355.1220; found: 355.1201.

Ethyl 3-Aryl-4-[(benzoxyl]carbonyl]amino)butanoates 7g–i; General Procedure
A solution of [Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}] (1.00 mg, 3.87 \mu mol, 0.03 equiv) and (R)- or (S)-(S)-BINAP (3.62 mg, 5.81 \mu mol, 0.045 equiv) in anhyd dioxane (1 mL) was stirred for 90 min at r.t. under argon. Et,N (52.0 mg, 516 \mu mol, 4 equiv), arylboronic acid (645 \mu mol, 5 equiv), 3c (34.0 mg, 129 \mu mol, 1 equiv) and H\textsubscript{2}O (0.1 mL) were successively added at r.t. and the mixture was heated at 100 °C for 24 h. Then EtOAc (15 mL) was added and the mixture was extracted with H\textsubscript{2}O (10 mL). The organic layer was dried and concentrated in vacuo. Flash chromatography (silica gel, EtOAc–petroleum ether, 15:85) furnished 7g–i.

(R)-Ethyl 4-[(Benzyloxyl]carbonyl]amino)-3-(4-chlorophenyl)butanoate (7d)
Colorless crystals; yield: 68%; mp 79–81 °C.
HPLC: DAICEL Chiralpak AD-H column; length: 25 cm + 1 cm precolumn; flow: 0.5 mL/min; eluent: n-hexane–i-ProH (90:10); \(t\text{R}(S)\) 37.7 min, \(t\text{R}(R)\) 45.0 min.

1H NMR (CDCl\textsubscript{3}): \(\delta = 1.15 \text{ (t, } J = 7.2 \text{ Hz, 3 H)}, 2.63 \text{ (m, 2 H)}, 3.33 \text{ (m, 2 H)}, 3.53 \text{ (m, 1 H)}, 4.06 \text{ (q, } J = 7.2 \text{ Hz, 2 H)}, 5.07 \text{ (s, 1 H)}, 7.13 \text{ (d, } J = 8.2 \text{ Hz, 2 H)}, 7.26 \text{ (m, 7 H)}.

13C NMR (CDCl\textsubscript{3}): \(\delta = 14.1, 38.4, 41.8, 46.0, 60.6, 66.8, 128.1, 128.7, 128.9, 129.0, 133.0, 136.4, 139.5, 156.2, 171.5.

HRMS: m/z calcd for C\textsubscript{20}H\textsubscript{18}ClNO\textsubscript{4} (M\textsuperscript{+})*: 375.1237; found: 375.1216.

(S)-Ethyl 4-[(Benzyloxyl]carbonyl]amino)-3-(4-fluorophenyl)butanoate (7f)
Colorless crystals; yield: 70%; mp 74–76 °C.
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(E)-4-[(Benzyloxy)carbonyl]amino]-3-phenylbutanoate (7i)
Colorless crystals; yield: 74%; mp 52–53 °C.

A solution of [Rh(acac)(C2H4)2] (1.00 mg, 3.87 μmol, 0.01 equiv) was mixed with NaIO3 (4.03 g, 18.8 mmol, 3 equiv), and H2O (0.2 mL) were successively added at rt. Successive additions of TFA (70.0 mg, 0.17 mmol, 1 equiv) and H2O (0.2 mL) was stirred for 90 min at rt. After cooling to rt., the resultant solution heated at 110 °C for 20 h. After cooling to rt., the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc); yield: 36.7 mg (78%); colorless crystals. NMR data were in accordance with those reported.3

Acknowledgment
This work was supported by EC RTN HPRN-CT-2001-00172 and the Fonds der Chemischen Industrie; we thank Degussa AG and OMG AG for rhodium salts.

References
(6) For a preliminary report on part of the work described here, see: Meyer, O.; Becht, J.-M.; Helmchen, G. Synlett 2003, 1539.


(17) Note added in proof: Using a hydroxorhodium catalyst, generated in situ, recently developed (compound 8 in: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasaawaii, M. J. Am. Chem. Soc. 2002, 124, 5052), the reaction of 3a with 6a proceeded at 70 °C (other conditions as in entry 3 of Table 1) within 1 h to give (S)-7a in 70% isolated yield with 95% ee. Accordingly, use of the new catalyst would likely allow an improvement for all reactions described here.