Asymmetric Synthesis of Both Enantiomers of α-Trifluoromethyl Substituted Homoallylamine

Kazumasa Funabiki,* Masashi Nagamori, Masaki Matsui, Dieter Enders

a Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan
Fax +81(58)2301893; E-mail: kfunabik@apchem.gifu-u.ac.jp

b Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, 52074 Aachen, Germany

Received 2 September 2002

Abstract: An efficient asymmetric synthesis of both enantiomers of α-trifluoromethylated homoallylamine via nucleophilic allylation of trifluoroacetaldehyde SAMP- or RAMP-hydrazone, followed by benzoylation and SmI₂-promoted nitrogen-nitrogen single bond cleavage is described.

Key words: asymmetric synthesis, fluorine, hydrazone, allylation, amines

The asymmetric nucleophilic allylation of imino derivatives has received increasing attention in organic synthesis,¹,² because the resulting enantio-enriched homoallylamines or hydrazines are promising precursors of β-amino substituted aldehydes, ketones, epoxides, and carboxylic acid derivatives. Although some reports recently described the asymmetric synthesis of α-alkyl, aryl or vinyl substituted α-trifluoromethylamines,³ to the best of our knowledge, there is no report on the stereoselective allylation of α-trifluoromethylated imines or hydrazones leading to enantiopure α-trifluoromethylated homoallylamines despite their synthetic utility.⁴,⁵ As a part of our studies directed towards the asymmetric synthesis of organofluorine compounds by means of the SAMP- or RAMP-hydrazone method,⁶ we describe herein the first asymmetric synthesis of both enantiomers of α-trifluoromethylated homoallylamine (R)- or (S)-4a using trifluoroacetaldehyde SAMP- or RAMP-hydrazone (S)- or (R)-1a as a starting substrate (Scheme 1).

Scheme 1

For the screening of the allylation reaction of trifluoroacetaldehyde hydrazones, the reaction between trifluoroacetaldehyde morpholinohydrazone (1b) and tetraallyltin was first examined (Scheme 2). The results are summarized in Table 1.

Scheme 2

Table 1 Screening of the Reaction Conditions for the Allylation of Trifluoroacetaldehyde Morpholinohydrazone (1b)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tetraallyltin (equiv)</th>
<th>PhLi (equiv)</th>
<th>Yield of 2b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7 (38)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td>21 (35)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3</td>
<td>20 (15)</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>0</td>
<td>0 (quant)</td>
</tr>
</tbody>
</table>

*The reaction was performed with hydrazone 1b (1 mmol) in Et₂O (11 mL).

b Yields of isolated products. Values in parentheses stand for the recovered 1b.

c Allyltriphenyltin was used in place of tetraallyltin.

d The reaction was carried out in the presence of 5 mol% of Yb(OTf)₃ in MeCN at r.t.

As shown in Scheme 2, treatment of tetraallyltin (3 equiv) with phenyllithium (12 equiv) at room temperature, followed by addition of trifluoroacetaldehyde morpholinohydrazone (1b) at −78 °C, gave the corresponding trifluoroacetaldehyde morpholinohydrazone 2b in 62% yield (entry 4). The reaction of 1b with three equivalents of tetraallyltin and PhLi, respectively, was extremely sluggish, providing only a trace amount of 2b (entry 1). Employing tetraallyltin (1–2 equiv) and PhLi (4–8 equiv) produced 2b in 21–47% yields along with recovered 1b (entries 2 and 3). The use of allyltriphenyltin (3 equiv) in place of tetraallyltin with PhLi (3 equiv) was also ineffective, giving 2b in 20% yield together with 15% of 1b (entry 5). Yb(OTf)₃-catalyzed (5 mol%) allylation⁷ with 0.3 equivalent of tetraallyltin in acetonitrile at room tempera-
ture did not occur at all, and 1b was recovered in quantitative yield (entry 6). With other allylic nucleophiles e.g., allyl magnesium bromide (3 equiv, −78 °C to r.t., overnight), only trace amount of 2b was formed with 67% recovery of 1b.

Next, in order to synthesize diastereo- and enantiomerically pure hydrazines, the stereoselective allylation of trifluoroacetaldehyde SAMP- or RAMP-hydrazone (S)- or \((R)-1\)a was carried out (Scheme 3).^8

![Scheme 3](image)

Reagents and conditions: (a) tetraallyltin, PhLi, r.t., then −78 °C; (b) catalytic DMAP, Et₃N, PhCOCl, r.t.; (c) SmI₂, THF/DMPU, r.t.

When SAMP-hydrazone (S)-1a was treated with a mixture, obtained by the reaction between 3 equivalents of tetraallyltin and 12 equivalents of PhLi at room temperature, in Et₂O at −78 °C for 4 hours, the allylated hydrazine (2R,2’S)-2a was produced with high diastereoselectivity (93:7), and diastereomerically pure 2a was easily obtained by flash column chromatography in 80% yield. Hydrazine (R)-1a also nicely underwent the allylation reaction to give (2S,2’R)-2a (>98% ee) in 67% yield after column chromatography.

The obtained diastereomerically pure hydrazines 2a were easily converted to the enantiopure homoallylamines. After benzylation of SAMP- or RAMP-hydrazone 2a with an excess amount of triethylamine and benzoyl chloride in anhyd Et₂O solution (10 mL) of tetraallyltin (0.424 g, 1.5 mmol) at r.t. under argon. After the reaction mixture was stirred at r.t. for 1 h and cooled to −78 °C, an allylated homoallylamines (ee >99%).

Optical rotations were measured in Uvasol grade CHCl₃ (Merck) on a HORIZA SEPA-300 instrument. HPLC was carried out using Daicel CHIRALCEL OD (Daicel, 0.46 cm × 25 cm) column on a Shimadzu LC-4A liquid chromatograph. Melting points were obtained on a Yanagimoto MP-S2 micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8100A spectrometer. ^1H NMR spectra were measured with a JEOL α-400 (400 MHz) FT-NMR spectrometer in CDCl₃ with tetramethylsilane as the internal standard. ^13C NMR spectra were obtained on a JOEL α-400 (100 MHz) FT-NMR spectrometer in CDCl₃ with tetramethylsilane as the internal standard. ^19F NMR spectra were recorded on a JEOL α-400 (376 MHz) FT-NMR spectrometer in CDCl₃ solution using trifluoroacetic acid as the external standard. Mass spectra were taken on a Hitachi QP 1000 spectrometer (70 eV). HRMS were measured on a JEOL JMS-700 mass spectrometer. Sml₂ (0.1 M THF solution) and tetraallyltin were purchased from Aldrich Chemical Co.

**Allylation of Trifluoroacetaldehyde SAMP-Hydrazone (S)-1a; (2R,2’S)-2-[2’-(Methoxymethyl)pyrrolidin-1-yl]amino-1,1,1-trifluoropent-4-ene (2R,2’S)-2a; Typical Procedure**

A solution of PhLi (5.7 mL of a 1.06 M cyclohexane–Et₂O solution, 6 mmol) was slowly added to an anhyd Et₂O solution (10 mL) of trifluoroacetaldehyde SAMP-hydrazone (S)-1a (0.105 g, 0.5 mmol) at −78 °C. After stirring at −78 °C for 4 h, the resulting mixture was quenched with a cold sat. aq NaHCO₃ solution (50 mL), and the precipitate formed was removed by suction filtration with hexane (30 mL). The mixture was extracted with Et₂O (2 × 30 mL), dried (Na₂SO₄), and the solvent was removed under reduced pressure. After the isomer ratio of the products was determined by ^19F NMR, the residue was purified by flash chromatography on silica gel (hexane–Et₂O, 10:1) to give hydrazine 2a (80%, 0.102 g); yield: 80%; R₉ 0.28 (hexane–Et₂O, 10:1); [al]₀⁻³⁴.8 (c = 0.97, CHCl₃).

**IR (KBr):** 3293, 2977, 1645, 1458, 1379, 1273, 1173, 1125, 920, 762 cm⁻¹.

**HRMS (Cl):** m/z calcld for C₁₁H₁₉ON₂F₃: (M⁺, 253.1529); found, 253.1529.

1H NMR (400 MHz, CDCl₃): δ = 1.50–1.59 (m, 1 H, CH₂CH₂H₂CH₂), 1.64–1.77 (m, 2 H, CH₂CH₂H₂CH₂), 1.86–2.05 (m, 1 H, CH₂CH₂H₂CH₂), 2.25–2.33 (m, 1 H, CH₂H₂), 2.42–2.49 (m, 1 H, CH₂H₂), 2.45 (q, J = 8.78 Hz, 1 H, NCH₂), 2.63–2.70 (m, 1 H, NCH₂), 2.70 (m, 1 H, CF₃CH), 3.30 (br s, 1 H, NH), 3.35 (s, 3 H, OCH₃), 3.38 (AB quartet, J = 20.92 (s), 26.19 (s), 32.61 (s), 57.45 (s), 58.98 (s), 61.09 (q, Jₓ = 25.91 Hz), 66.58 (s), 75.14 (s), 126.21 (q, Jᵣ = 282.30 Hz), 133.60 (s).

13C NMR (100 MHz, CDCl₃): δ = 19.29 (s), 26.19 (s), 32.61 (s), 57.45 (s), 58.98 (s), 61.09 (q, Jₓ = 25.91 Hz), 66.58 (s), 75.14 (s), 126.21 (q, Jᵣ = 282.30 Hz), 133.60 (s).

MS (EI): m/z (%) = 252.0 (M⁺, 7.9), 207.0 (M⁺ – CH₂OCH₃, 100.0), 129.0 (M⁺ – CF₃CH₂CH₂, 8.1).

HRMS (Cl): m/z calcld for C₁₁H₁₉ON₂F₃: (M⁺, 253.1529); found, 253.1520.
Benzoylation of SAMP-Hydrazide 2a; (2R,2'S)-N-[2-(Methoxymethyl)pyrrolidin-1-yl]-N-(4-amino-1,1,1-trifluoropent-4-yl)benzamide [(2R,2'S)-3a]; Typical Procedure

This compound was prepared starting from (2R,2'S)-2a following the above typical procedure; yield: 61%; Rf 0.16 (hexane-EtO, 5:1); [α]D20 +43.62 (c = 0.96, CHCl3).

Acknowledgments

K.F. is grateful to the Alexander von Humboldt Foundation for a postdoctoral fellowship (2000–2001). This work was supported by the Saijiro Endo Foundation. We thank Professors Hiroki Yamana-ka and Takashi Ishihara as well as Dr. Tsutomu Konno of the Kyoto Institute of Technology for the HRMS measurements of 2a,b.

References

(5) For alkylation of chiral trifluoromethylated aminal, see:
(9) For the SmI₂-induced cleavage of the nitrogen–nitrogen single bond, see Ref. 4.