Synthesis of $\alpha,\gamma$-Chiral Trifluoromethylated Amines through the Stereospecific Isomerization of $\alpha$-Chiral Allylic Amines

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ABSTRACT: Chiral $\gamma$-branched aliphatic amines are present in a large number of pharmaceuticals and natural products. However, enantioselective methods to access these compounds are scarce, and rely on the use of designed chiral transition-metal complexes. Herein, we have combined an organocatalytic method for the stereospecific isomerization of chiral allylic amines with a diastereoselective reduction of the chiral imine/enamine intermediates, leading to $\gamma$-trifluoromethylated aliphatic amines with two noncontiguous stereogenic centers, in excellent yields and with high diastereo- and enantioselectivities. This approach has been used with primary amine substrates. Additionally, a gram-scale reaction demonstrates the applicability of this synthetic procedure.

Chiral primary amines are very valuable and versatile building blocks for the synthesis of amine-containing pharmaceuticals and natural products. Furthermore, chiral aliphatic amines bearing at least one stereogenic center are common substructures in natural products and pharmaceuticals, where the amine functional group is crucial for their biological activity (Figure 1).²,³

Figure 1. Relevant examples of chiral aliphatic amines.

There are numerous synthetic methods that allow the stereochemistry of $\alpha$- and $\beta$-chiral amines to be controlled.³,⁴ However, the synthesis of chiral amines with the stereogenic center at a remote position remains challenging.⁵ Buchwald and coworkers developed a copper(I)-catalyzed hydrocupration/$\beta$-alkoxide elimination reaction of allylic esters, followed by an anti-Markovnikov hydroamination of the olefin intermediate (Figure 2a).⁵ This method provides $\gamma$-chiral aliphatic amines with excellent enantioselectivities. However, it requires the use of specific electrophilic aminating reagents, and it is limited to tertiary amines. The Hull group contributed to this area with a Rh-catalyzed enantioselective isomerization/reductive amination of allylic diethyl amines (Figure 2b).⁷ In this case, the product of the redox-neutral isomerization process, a chiral enamine, reacts with amines in the presence of a reducing agent (NaBH₄ or HCO₂H), to give $\gamma$-chiral primary and secondary amine products with high enantioselectivities. To the best of our knowledge, these are the only two methods that have been reported for the synthesis of $\gamma$-chiral substituted aliphatic amines. Furthermore, neither of these methods tolerates further substitution at $\alpha$ and neither works with primary amines.

The transition-metal-catalyzed isomerization of allylic alcohols or amines has been widely used to access $\gamma$-chiral carbonyl compounds and enamines (i.e., as in step 1 in Scheme 1b), respectively.⁷,¹¹ Chirality is introduced by using metal complexes with specially designed chiral ligands. The synthesis of these ligands requires additional work, and the substrate scope of the reaction is dependent on the ligand used.¹² An alternative method for the synthesis of carbonyl compounds with remote stereogenic centers is the stereospecific isomerization of $\alpha$-chiral allylic alcohols, which are easily
accessibility α-chiral starting materials. These isomerization reactions can be mediated by achiral metal catalysts or by achiral bases, and take place through [1,3]-hydrogen shifts. The reaction takes place by a stepwise mechanism, so stereospecific reactions are scarce. Our group has contributed to this field with the stereospecific isomerization of β-trifluoromethylated allylic amines, ethers, and halides mediated by catalytic amounts of the base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD; Figure 2c). Chirality is transferred from Cα to Cβ in a stepwise manner, through the formation of a tight-ion-pair intermediate with induced noncovalent chirality (Figure 2c). When it comes to the base-mediated isomerization of allylic amines yielding enamines, only one protocol has been reported to the best of our knowledge, which in this example is non-stereospecific. A related recent example is the base-mediated of α-chiral allylic amines into axially chiral enamines.

Figure 2. Enantioselective and enantiospecific strategies for the synthesis of chiral γ-branched amines.

In this work, we report a new method for the synthesis of chiral γ-aliphatic amines with two stereogenic centers in noncontiguous positions. The method relies on a stereospecific TBD-mediated isomerization of α-chiral allylic amines. As the reaction tolerates a further substituent at Cα, a subsequent reduction leads to functionalized aliphatic amines with two stereogenic centers, at Cα and Cγ, starting from readily available chiral allylic amines (Figure 2d). Importantly, the reaction works on primary allylic amines, so it represents a direct method for the synthesis of α,γ-chiral primary amines. We started our investigations by designing an enantioselective synthesis of trifluoromethylated allylic amines (Scheme 1). Inspired by Güjarro’s work on the synthesis of N-(tert-butylsulfinyl)amines, we subjected enone 1 to a titanium (IV) mediated, microwave-assisted reaction with (R)-2 to obtain the desired chiral sulfinimine (R)-3 in 70% yield. A diastereoselective reduction with DIBAL-H and a final acidic deprotection gave trifluoromethylated chiral allylic amine (R)-4a with 95% ee and in 42% yield over three steps.

Table 1. Optimization of the stereospecific isomerization reaction of chiral allylic amines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Yield [%]</th>
<th>c.t. [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>TBD (0.1)</td>
<td>Toluene</td>
<td>120</td>
<td>&gt;99</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>DBU (0.1)</td>
<td>Toluene</td>
<td>120</td>
<td>52</td>
<td>n.d.</td>
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<tr>
<td>3</td>
<td>MTBD (0.1)</td>
<td>Toluene</td>
<td>120</td>
<td>17</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>Py-Bu (0.1)</td>
<td>Toluene</td>
<td>120</td>
<td>7</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>TBD (0.1)</td>
<td>Toluene</td>
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<td>&gt;99</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>TBD (0.1)</td>
<td>Toluene</td>
<td>25</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>TBD (0.1)</td>
<td>HFIP</td>
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<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>TBD (0.1)</td>
<td>CHCl₃</td>
<td>60</td>
<td>11</td>
<td>n.d.</td>
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<tr>
<td>9</td>
<td>TBD (0.1)</td>
<td>Dioxane</td>
<td>60</td>
<td>&gt;99</td>
<td>86</td>
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<tr>
<td>10</td>
<td>TBD (0.1)</td>
<td>EtOAc</td>
<td>60</td>
<td>&gt;99</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
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<td>Toluene</td>
<td>60</td>
<td>&gt;99</td>
<td>95</td>
</tr>
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<td>12</td>
<td>TBD (0.025)</td>
<td>Toluene</td>
<td>60</td>
<td>45</td>
<td>n.d.</td>
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</table>

Reactions carried out using 4a (0.1 mmol) 0.02 M. Yield determined by 19F NMR spectroscopy. c.t. = (ee product/ee SM)×100. 0.8 M solution in hexane.

Scheme 1. Synthesis of chiral trifluoromethylated allylic amines.

Reaction conditions: 1 (4 g, 14.5 mmol), (R)-2 (2.6 g, 21.8 mmol, 1.5 equiv.), Ti(OTf)₃ (6.6 g, 29 mmol, 2 equiv.), MW, 100 °C, 2 h (70%). (R)-3 (3.8 g, 10.2 mmol), DIBAL-H (1 M in THF; 11 mL, 1.1 equiv.), THF (10 mL, 1 M), 0 °C, 2 h. HCl (4 M in H₂O; 10 mL), r.t., 18 h (60% over two steps).

Having developed this enantioselective protocol for the synthesis of chiral trifluoromethylated allylic amines, we went on to examine the base-catalyzed stereospecific isomerization of γ-trifluoromethylated allylic amine 4a. When allylic amine 4a is treated with base, it undergoes isomerization to give a mixture of the primary enamine and the imine, as observed by NMR spectroscopy, which cannot be isolated. We therefore hydrolyzed this mixture by treatment with HCl (2 M) to give the corresponding chiral ketone, from which we could determine the efficiency of the chirality transfer. We found that when 4a was treated with catalytic amounts of TBD, it underwent the isomerization reaction to yield ketone 5a in quantitative yield and with high levels of chirality transfer (c.t.: Table 1, entry 1). The reaction also took place in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene.
(DBU) or MTBD (N-methyl TBD), although the yields were significantly lower (Table 1, entries 2 and 3 vs entry 1). Catalytic amounts of the more basic phosphazene P4-t-Bu did not yield 5a. This result indicates that the reaction relies not only on the basicity of the catalyst, but also on the ability of its conjugate acid to protonate the allylic anion intermediate (Table 1, entry 4). Decreasing the temperature to 60 °C did not show any significant effect on either the conversion or the chirality transfer (Table 1, entry 5), and the reaction did not work at room temperature (Table 1, entry 6). As expected, solvents that can be deprotonated did not give the product (Table 1, entries 7 and 8). In polar aprotic solvents such as 1,4-dioxane and ethyl acetate, the yields were similar to those obtained in toluene, but the chirality transfer was less efficient (Table 1, entries 9 and 10 vs entry 5). Finally, the effect of the catalyst loading was studied, and 5% of TBD was found to be sufficient for the reaction to take place in high yield, and, importantly, with an increased chirality transfer of 95% (Table 1, entry 11). Any further decrease in the catalyst loading was found to be detrimental to the reaction (Table 1, entry 12).

Having optimized the reaction conditions for the stereospecific isomerization (Table 1, entry 11), we went on to study the reduction of the enamine intermediate to form α,γ-chiral trifluoromethylated aliphatic amine 6a (Table 2). Compound rac-4a was subjected to the isomerization conditions as before, followed by treatment with a reducing agent in a two-step one-pot protocol. When the isomerization was completed, the temperature was adjusted before addition of the reductant. No further manipulations were done. When NaBH4 was used at room temperature, good yields were obtained but the diastereoselectivity was poor (Table 2, entry 1). DIBAL-H showed moderate diastereoselectivity in favor of the reduced product. When NaBH4 was used at room temperature, good yields were obtained but the diastereoselectivity was poor (Table 2, entry 1). DIBAL-H showed moderate diastereoselectivity in favor of.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing agent</th>
<th>Temp [°C]</th>
<th>6a [%]</th>
<th>d.r. (syn:anti)</th>
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<tr>
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<td>NaBH4</td>
<td>25</td>
<td>&gt;99</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>DIBAL-H</td>
<td>25</td>
<td>65^d</td>
<td>58:42</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL-H</td>
<td>0</td>
<td>&gt;99</td>
<td>65:35</td>
</tr>
<tr>
<td>4</td>
<td>DIBAL-H</td>
<td>−78</td>
<td>&gt;99</td>
<td>70:30</td>
</tr>
<tr>
<td>5</td>
<td>DIBAL-H</td>
<td>−90</td>
<td>&gt;99 (75)</td>
<td>75:25</td>
</tr>
</tbody>
</table>

‡Reactions carried out using 4a (0.1 mmol) and reducing agent (2 equiv.), 0.02 M. ¥ Yield and d.r. determined by 19F NMR spectroscopy. Isolated yield in parenthesis. ¥Tolune/MeOH (1:1) used as solvent. ¥Different by-products observed.

**Table 2. Optimization of the one-pot isomerization / diastereoselective synthesis of γ-trifluoromethylated aliphatic amines.**

**Scheme 2. Substrate scope of the base-catalyzed stereospecific isomerization / reduction reaction of allylic amines.**

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<tbody>
<tr>
<td>1‡</td>
<td>NaBH4</td>
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<td>50:50</td>
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<tr>
<td>2</td>
<td>DIBAL-H</td>
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<td>−90</td>
<td>&gt;99 (75)</td>
<td>75:25</td>
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**Scheme 2. Substrate scope of the base-catalyzed stereospecific isomerization / reduction reaction of allylic amines.**
Having optimized the reaction conditions (Table 1, entry 11 for the stereospecific isomerization, and Table 2, entry 5 for the reduction), the scope and limitations were investigated (Scheme 2). The effect of different aryl groups at R1 was evaluated first. Substrates bearing electron-donating or electron-withdrawing groups at the para position of the aryl group reacted smoothly to give the desired products in high yields and with good chirality transfer (6a-6e). The ee of the products (R,R)-6 depends not only on the efficiency of the stereospecific isomerization, but also on the E/Z ratio of the starting materials (4). The bulkier naphthyl derivative gave 6f in good yield with a chirality transfer of 97%. Meta and ortho substitution at R1 were also well tolerated; the diastereoselectivity was not compromised, and yields and chirality transfer levels were maintained (6g-6i). Replacing the aryl group by an alkyl chain resulted in a dramatic decrease in the yield (6j). When 6k was used as a substrate (R1 = 1), 6k was formed in 60% yield.

Variation of R2 was also studied, and aromatic groups with electron-donating groups in the para position gave good yields and good levels of chirality transfer, with moderate diastereoselectivities (6l-6m). Para-trifluoromethyl-substituted allylic amine 4n gave aliphatic amine 6n with a decreased efficiency in terms of yield and chirality transfer, but the diastereoselectivity was enhanced. Meta-methyl-substituted 6o was also obtained in high yield with excellent levels of chirality transfer. Heteroaryl derivative 6p was obtained in excellent yield with high levels of chirality transfer. Replacing the aryl substituent by H had a significant effect on the yield of the reaction, and 6q was obtained in 65% yield.

A gram-scale experiment was carried out on amine 4d (Scheme 3). Aliphatic amine 6d was obtained in 73% yield, with excellent levels of chirality transfer (91%) and good levels of diastereoselectivity (72:28). In addition, the absolute configurations of both aliphatic amine 4d and major diastereomer 6d were determined by X-ray single crystal diffraction analysis (Scheme 3 and Figures S1-S2), and the absolute configuration of the other chiral amines (6a-6r) was assigned by analogy.

In conclusion, we have developed a method for the synthesis of γ-chiral aliphatic amines from easily accessible α-chiral allylic amines using a base catalyst. A subsequent diastereoselective reduction of the chiral imine/enamine intermediate leads to α,γ-chiral γ-trifluoromethylated amines in excellent yields and with high diastereo- and enantioselectivities. We have shown that the reaction has a broad scope, and the reaction has been run on a gram scale. Thus, this represents a straightforward approach to α,γ-chiral trifluoromethylated amines from accessible allylic amines.

ASSOCIATED CONTENT
Supporting Information
Supporting Information containing experimental procedures, characterization of compounds, and spectra is available free of charge on the ACS Publications website (PDF).

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Notes
Authors declare no competing financial interest.

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