Umpolung Synthesis of Vicinal Diamines: Diastereoselective Addition of 2-Azaallyl Anions to Davis–Ellman’s Imines

Leleti Rajender Reddy,* Sharadsrikar Kotturi, Rajesh Shenoy, Kumara Swamy Nalivela, Chirag Patel, Poojabahen Raval, and Vinkal Zalavadiya

Piramal Discovery Solutions, Pharmaceutical Special Economic Zone, Sarkhej Bavla Highway, Ahmedabad, Gujarat 382213, India

Supporting Information

**ABSTRACT:** A highly regioselective and diastereoselective addition of 2-azaallyl anions to N-tert-butanesulfonylimines is reported. This methodology affords the preparation of enantiomerically and diastereomerically pure vicinal diamines bearing two adjacent stereocenters. Reactions proceed efficiently (yield up to 94%), diastereoselectively (dr values up to 98:2:0:0), and site-selectively to deliver products with differentiated amino groups.
Scheme 1. umpolung Approach of 2-Azaallyl Anions Addition to Davis−Ellman’s Imines

(a) Organometallic reagents addition to chiral bisimine

(b) Reductive Homocoupling

(c) Viscinal diamino acids from glycone enolates

This work

Scheme 2. Azaallyl Anion Addition to Various N-tert-Butanesulfonyl Aldimine

Table 1. Evaluation of Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>SM</th>
<th>base</th>
<th>temperature (°C)</th>
<th>yield (%)</th>
<th>diastereomeric ratio, dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>NaHMDS</td>
<td>−78</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>NaHMDS</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>KHMDS</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>LiHMDS</td>
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<td>90</td>
<td>52:48:0:0</td>
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<tr>
<td>5</td>
<td>1a</td>
<td>LiHMDS</td>
<td>−78</td>
<td>93</td>
<td>98:2:0:0</td>
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<tr>
<td>6</td>
<td>1a</td>
<td>LiHMDS</td>
<td>−78</td>
<td>92</td>
<td>98:2:0:0</td>
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<tr>
<td>7</td>
<td>1a</td>
<td>LDA</td>
<td>−78</td>
<td>55</td>
<td>98:2:0:0</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>LiTMP</td>
<td>−78</td>
<td>39</td>
<td>98:2:0:0</td>
</tr>
</tbody>
</table>

All of the reactions were performed with 2.0 equiv of 1 or 2, 1.8 equiv of base and 1.0 equiv of 4 at −78 °C for 3 h. Isolated yield. The diastereoselectivity was determined by 1H NMR analysis of crude product. DMPU (1.8 equiv) used.

(4e and 4f) derivatives afforded corresponding vicinal diamine 5f−5j (Scheme 2, entries 6−10) in high yields (85%−94%) and with excellent diastereomeric ratios (dr = 90:10:0:0−98:2:0:0). The vicinal diamine 5g was obtained as a colorless crystalline solid (melting point (mp) = 110−112 °C). The structure and absolute stereochemistry of (R,S,S)-5g were confirmed by single-crystal X-ray diffraction analysis (see Figure 1). The high diastereoselectivity in the formation of compound 5 can be explained if the reaction passes through a chelation transition state during the addition step of 2-azaallyl anion 3 to imine 4 (see Figure 2).
In the similar way, the reaction of the o-chlorophenyl-substituted azaallyl anion 3c smoothly reacted with several substituted N-tert-butanesulfonyl aldimines such as aromatic (4a and 4b), heteroaromatic (4c and 4d), and aliphatic (4e and 4f) derivatives afforded corresponding vicinal diamines 5k−5p (Scheme 2, entries 11−16), in excellent yields (85%−94%) and with excellent diastereomeric ratios (dr = 90:10:0:0−98:2:0:0). Similarly, the p-bromophenyl-substituted azaallyl anion 3d reacted with 4c, 4d, and 4e, affording the corresponding vicinal diamines 5q, 5r, and 5s in 90%, 91%, and 84% yields (dr = 98:2:0:0, 98:2:0:0, and 90:10:0:0), respectively (see Scheme 2, entries 17−19). The p-fluorophenyl-substituted azaallyl anion 3e also reacted with 4e to form vicinal amine 5t in 85% yield with dr = 92:8:0:0 (see Scheme 2).

To illustrate the synthetic potential of our reaction and also multigram requirement of 5g for an ongoing program within our research group, we checked the scalability of this reaction in gram scale. The reaction of 4c (5.0 g, 25.0 mmol) with 3b in THF (50 mL) at −78 °C for 3 h afforded 5g with 93.5% yield (11.8 g) and with dr = 98:2:0:0 (see Scheme 3).

An advantage of this method is the differentiation of the two masked amines within the products, with the benzophenone imine serving as a double protecting group for one N atom while the sulfinamide allows for monofunctionalization of the other N atom. Conversely, selective deprotection will provide more versatile synthetic potential in the industrial application. Fortunately, selective deprotection of benzophenone of 5g proceeds under mildly acidic conditions (1 N H2SO4 in 1,4-dioxane/water at room temperature for 6 h) to reveal the nucleophilic primary amine within 6 with 92% yield, under these conditions the sulfinamide protecting group is not hydrolyzing (see Scheme 2). Subsequent HCl-mediated removal of the sulfinamide group delivers amine. On the other hand, treatment of 5g with 4 M HCl in 1,4-dioxane at room temperature for 16 h affords the di-deprotected amine 7 with 96% yield.

In summary, we have described an efficient, highly regioselective, and diastereoselective addition of 2-azaallyl anions to Davis−Ellman's imines with broad substrate scope. This method is found to be very efficient for the preparation of enantiomerically and diastereomerically pure vicinal diamines bearing two adjacent stereocenters. The differentially protected amines within the products and selective deprotection will facilitate versatile synthetic potential in the industrial application. The development of other stereoselective methods with azallyl reagents is underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b02331.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1856617 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author
*E-mail: rajender.leleti@piramal.com

ORCID

Leleti Rajender Reddy: 0000-0001-9182-2277

Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. E. J. Corey (Sheldon Emory Professor Emeritus, Harvard University, USA) on the occasion of his 90th birthday.

REFERENCES


