Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines**

Baoqiang Wan and Shengming Ma*

Naturally occurring biomolecules that display chirality are enantiomerically enriched and different enantiomers show different biological activities. Thus, the development of new enantioselective approaches for chiral compounds is of great interest. Allenes are now an important class of compounds and versatile intermediates in organic synthesis.[1] Thus, efficient methodologies for synthesizing allenes is of current interest for organic chemists.[2] The synthesis of axially chiral allenmes are particularly important because of their efficient chirality transfer.[3] and the chirality transfer of chiral propargyl alcohols[6] or propargyl amine derivatives.[7] However, most of these procedures require stoichiometric amounts of enantiomerically enriched chiral compounds, and are thus inefficient. Recently, asymmetric catalysis for the synthesis of chiral allenmes has attracted much attention.[8–10] Trost et al.[9] and Imada et al.[10] have independently reported the asymmetric synthesis of allenyl amines with 76–91% ee by using intermolecular reactions. Interestingly, in two reported examples, 95 or 97% of ee has been realized (Scheme 1, top). Herein, we disclose a different approach for the synthesis of axially chiral allenmes relies on the decarboxylative amination reaction of the N-tosylcarbamates[11] of alkenyl, allenyl, and alkynyl, were tolerated in the reaction; 3) when \( \text{R}_2 \) is an aromatic group, the reaction afforded the monoallenylation product \( \text{2n} \) in 73% and 8% yields, respectively, upon isolation.

With this approach in hand, we envisioned that such a decarboxylative amination reaction could afford the axially chiral allenmes if a chiral catalyst was used. The N-tosylcarbamate \( \text{1a} \) was chosen as a model substrate to optimize the reaction conditions. Firstly a variety of chiral phosphine ligands were examined in the decarboxylative amination of N-tosylcarbamates for the synthesis of racemic allenyl amines. After screening the reaction conditions, it was observed that the reaction of \( \text{1} \) could proceed smoothly to afford the allenyl amine \( \text{2} \) by utilizing 5 mol% of \( \text{Pd(PPh}_3\text{)}_4 \) in \( \text{CH}_2\text{Cl}_2 \) at \( 40^\circ\text{C} \). The scope of decarboxylative reaction of the N-tosylcarbamates \( \text{1} \) was investigated and the results are listed in Table 1. Some issues should be noted: 1) the yields of these reactions are good to excellent; 2) functional groups such as alkynyl, allenyl, and alkynyl, were tolerated in the reaction; 3) when \( \text{R}_2 = \text{H} \), the reaction afforded the monoallenylation product \( \text{2a} \) and the diallenylation product \( \text{2n} \) in 73% and 8% yields, respectively, upon isolation.

Next, the effect of solvent (1,4-dioxane, DME, \( \text{CH}_2\text{Cl}_2 \), toluene, and DMF) was studied, and DMF resulted in the complete consumption of \( \text{1a} \) and highest enantioselectivity (Table 2, entries 1–6). By conducting the reaction at \( 25^\circ\text{C} \), the enantioselectivity was improved to 91% ee (entry 7). Finally,

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** Financial support from the National Natural Science Foundation of China (21232006) and the Major State Basic Research and Development Program (2011CB808700) is greatly appreciated. We thank Minyan Wang from our research group for reproducing the results for compounds \( \text{21} \), \( \text{5}-\text{2d} \), and \( \text{5}-\text{2v} \).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204796.

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[*] B. Wan, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (P.R. China)
E-mail: masm@sioc.ac.cn
Prof. Dr. S. Ma
Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University
3663 North Zhongshan Lu, Shanghai 200062 (P.R. China)

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it was observed that a combination of DMF and DME led to a higher yield and enantioselectivity (entry 8).

Substituents on the phenyl ring have a limited influence on the yields and enantioselectivities (Scheme 3). The 4-Cl and 2-Cl substituents on the phenyl ring were also suitable in this reaction, thus providing an opportunity for elaboration of the product.

Notably, the R group on the nitrogen atom greatly influences the enantioselectivity, and an isopropyl group gave the best result with a 97% ee (Table 3). The absolute configuration was assigned by analogy to that of (S)-2t, the configuration of which was determined by a single-crystal X-ray diffraction study (Figure 1).[14]

Interestingly, with the synthetically attractive tertiary alcohol group as R, the decarboxylative reaction proceeded smoothly to afford the axially chiral allenyl amines in 93–97% ee (Table 4). To our delight, the en-allene (S)-2m was obtained, and can be used for additional cyclization.[15]

To emphasize the practicability of the methodology, the reactions of 1u and 1m were conducted on a one-gram scale, thus affording the desired products (S)-2u and (S)-2m, respectively, in 97% ee (Scheme 4). The reaction of 1w afforded 2w in 97% ee. After removal of the TBS group from

**Table 1:** (Pd(PPh3)4)-catalyzed decarboxylation of the N-tosylcarbamates 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>1a (rec.)</th>
<th>2a</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>50</td>
<td>48</td>
<td>52</td>
<td>33</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1,4-dioxane</td>
<td>50</td>
<td>48</td>
<td>12</td>
<td>75</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>50</td>
<td>48</td>
<td>29</td>
<td>40</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CHCl3</td>
<td>50</td>
<td>48</td>
<td>67</td>
<td>20</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>50</td>
<td>48</td>
<td>17</td>
<td>70</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>50</td>
<td>48</td>
<td>0</td>
<td>85</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>DMF/DME</td>
<td>25</td>
<td>96</td>
<td>0</td>
<td>79</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>DMF/DME</td>
<td>25</td>
<td>84</td>
<td>0</td>
<td>88</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

[a] Under argon, a mixture of 1a (0.1 mmol), (Pd(dba)2) (5 μmol), and (S)-DTBM-Segphos (7.5 μmol) was stirred in 1 mL of the indicated solvent. [b] recovered starting compound 1a, determined by 1H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The reaction was carried out on a 0.5 mmol scale in 2 mL of DMF/DME (1:1). DME = dimethoxyethane, DMF = N,N'-dimethylformamide, THF = tetrahydrofuran.

**Scheme 3.** The effect of the substituent of the phenyl ring on the reaction.

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**Scheme 2.** Ligand effect on the enantioselective decarboxylative amination of 1a. dba = dibenzylideneacetone, n.d. = not detected.

**Scheme 3.** The effect of the substituent of the phenyl ring on the reaction.
The preparation of allene derivatives was achieved by the palladium(II)-catalyzed cyclization of allyl bromide, which provided complete chirality transfer. The triene \((\text{S})-\text{C}0\text{-}3c\) with an N-allylic unit could be transformed into the hetero-bicyclic diene product \(4\) in 82% yield and 96% ee using a ring-closing metathesis reaction at 10°C. Furthermore, the reaction of \(1x\), bearing a secondary alcoholic group, afforded a pair of diastereoisomers (d.r. = 1:1) with high ee values [Scheme 5, Eq. (1)]. When the optically active substrates having a central chirality such as \((\text{S})-1x\) and \((\text{R})-1x\) were used, all four isomers \((\text{S})-2x\), \((\text{R})-2x\), \((\text{S})-2x\), and \((\text{R})-2x\) were obtained successfully with this protocol using either \((\text{S})\)-DTBM-Segphos or \((\text{R})\)-DTBM-Segphos as the ligand. It is interesting to observe that there is a case for matched or mismatched pairs between the chiral substrates and the ligand affording different diastereoisomeric excess [Scheme 5, Eqs. (2)–(5)].

At this moment we do not have a working model to predict the absolute configuration of the allene moiety for this reaction. On the basis of the results presented in Scheme 2, we reason that the binaphthyl backbone in the \(L1\) and the biphenyl backbone in \(L4\) and Segphos is responsible for the high catalytic reactivities since the Trost ligands \(L2\) and \(L3\) demonstrated a very slow reaction. The biphenyl backbone in

\(\text{(S)}-2u\), \(\text{(S)}-2w\), and \(\text{(S)}-2m\) to afford the corresponding allenes, the palladium(II)-catalyzed cyclization was performed in the presence of allyl bromide, thus providing the 2,5-dihydrofuran derivatives \((\text{S})-\text{C}0\text{-}3a\), \((\text{S})-\text{C}0\text{-}3b\), and \((\text{S})-\text{C}0\text{-}3c\) with complete chirality transfer. [16] The triene \((\text{S})-\text{C}0\text{-}3c\) with an N-allylic unit could be transformed into the hetero-bicyclic diene product \(4\) in 82% yield and 96% ee using a ring-closing metathesis reaction at 10°C.

Further, the reaction of \(1x\), bearing a secondary alcoholic group, afforded a pair of diastereoisomers (d.r. = 1:1) with high ee values [Scheme 5, Eq. (1)]. When the optically active substrates having a central chirality such as \((\text{S})-1x\) and \((\text{R})-1x\) were used, all four isomers \((\text{S})-2x\), \((\text{R})-2x\), \((\text{S})-2x\), and \((\text{R})-2x\) were obtained successfully with this protocol using either \((\text{S})\)-DTBM-Segphos or \((\text{R})\)-DTBM-Segphos as the ligand. It is interesting to observe that there is a case for matched or mismatched pairs between the chiral substrates and the ligand affording different diastereoisomeric excess [Scheme 5, Eqs. (2)–(5)].

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Experimental Section

(S)-2u (Scheme 4): [Pd(dba)$_2$] (57.8 mg, 0.1 mmol), (S)-DTBM-Segphos (178.0 mg, 0.15 mmol), and a mixed solvent system (6.0 mL; DMF/DMF = 1:1) were added sequentially to a flame-dried Schlenk tube under argon. The mixture was stirred at 25 °C with a preheated oil bath for 30 min. Then 1u (1.0319 g, 2.0 mmol) and the mixed solvent system (2.0 mL; DMF/DMF = 1:1) were added sequentially to the above solution. The resulting mixture was stirred at 25 °C. After completion, as monitored by TLC, the reaction was quenched with Et$_3$O (30 mL), H$_2$O (30 mL), extracted with Et$_3$O (3 × 20 mL), and dried over anhydrous Na$_2$SO$_4$. Filtration, evaporation, and chromatography on silica gel (eluent: petroleum ether/ethyl ether 20:1) afforded (S)-2u (860.8 mg, 91% yield, 97% ee) as a liquid. HPLC conditions: IA column, rate = 0.7 mL min$^{-1}$, hexane/iPrOH 100:1, $t_{R}$(major) = 12.3 min, $t_{R}$(minor) = 13.9 min.

Keywords: allene · amination · chirality · enantioselectivity · synthetic methods

Received: June 19, 2012
Published online:  ■  ■  ■  ■  ■


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[14] Crystal data for compound S-2t: C12H18BrNO2S; MW = 448.41, monoclinic, space group P2(1), final R indices [I > 2σ(I)], R1 = 0.0371, wR2 = 0.0769, R indices (all data) R1 = 0.0619, wR2 = 0.0876, a = 16.1961(8), b = 9.1134(5), c = 16.9321(2) Å, α = 90, β = 118, γ = 90°, V = 2211.1(2) Å3, T = 173(2) K, Z = 4, reflections collected/unique 25939/7746 (Rint = 0.0452), number of observations > 2σ(I) 5779, parameters: 487. CCDC 885180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


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Getting axed: Synthesis of the title amines, bearing functionality (R¹ and R²), involves the enantioselective palladium-catalyzed decarboxylation of allenyl N-tosylcarbamates. The reaction proceeds smoothly using both the chiral ligands (S)- and (R)-DTBM-Segphos (1) to afford the allenyl amines in good yields and with high enantioselectivities.