Enantioselective synthesis of \(\alpha\)-alkenyl \(\alpha\)-amino acids via N–H insertion reactions†

Jun-Xia Guo,a Ting Zhou,a Bin Xu,a Shou-Fei Zhu*ab and Qi-Lin Zhouab

A new highly enantioselective route to \(\alpha\)-alkenyl \(\alpha\)-amino acid derivatives, which are important naturally occurring compounds with attractive bioactivity and synthetic utility, was developed using a N–H insertion reaction of vinyldiazoacetates and tert-butyl carbamate cooperatively catalyzed by achiral dirhodium(II) carboxylates and chiral spiro phosphoric acids under mild, neutral conditions. This reaction has a broad substrate scope, a fast reaction rate (turnover frequency > 6000 h\(^{-1}\)), a high yield (61–99%), and excellent enantioselectivity (83–98% ee). The chiral spiro phosphoric acid, which is proposed to realize the enantioselectivity of the insertion reaction by promoting the proton transfer of a ylide intermediate by acting as a chiral proton shuttle catalyst, can suppress several usual side reactions of vinyldiazoacetates and broaden the applications of these versatile carbene precursors in organic synthesis. To our knowledge, it is the first highly enantioselective carbene insertion reaction of vinyldiazoacetates with heteroatom–hydrogen bonds in which the heteroatom has lone-pair electrons.

\(\alpha\)-Amino acids are vital building blocks of peptides, proteins, and many other bioactive compounds, and the development of highly efficient and enantioselective methods for the synthesis of diverse \(\alpha\)-amino acids has been a long-standing goal of synthetic chemists. Over the past several decades, many catalytic methods have been established for the synthesis of \(\alpha\)-alkyl and \(\alpha\)-aryl substituted \(\alpha\)-amino acids.\(^1\) However, even though chiral \(\alpha\)-alkenyl \(\alpha\)-amino acids are important naturally occurring compounds\(^2\) with attractive bioactivity\(^4\) and synthetic utility (Fig. 1 and Scheme 1),\(^4\) few enantioselective catalytic methods for their synthesis have been reported.\(^3\) Moreover, only two types of chiral \(\alpha\)-alkenyl \(\alpha\)-amino acids (\(\gamma\)-mono-substituted vinylglycines\(^5\)\(a,b\) and \(\beta\)-carbonyl vinylglycines\(^5\)\(c,d\)) can be prepared via these reported methods. Therefore, general enantioselective catalytic methods for preparing optically active \(\alpha\)-alkenyl \(\alpha\)-amino acids and their derivatives are highly desired. The challenge in the enantioselective synthesis of chiral \(\alpha\)-alkenyl \(\alpha\)-amino acids lies in the lability of the products toward racemization and undesirable isomerization of the double bond.

Fig. 1 Selected naturally occurring \(\alpha\)-alkenyl \(\alpha\)-amino acids.

\(\gamma\) Lys, \(\gamma\) Thr, \(\gamma\) Asp, \(\gamma\) Glu, \(\gamma\) Thr, \(\gamma\) Met, \(\gamma\) Val, \(\gamma\) Ile, \(\gamma\) Leu, \(\gamma\) Pro, \(\gamma\) Ser, \(\gamma\) Asn, \(\gamma\) Gln, \(\gamma\) His, \(\gamma\) Arg, \(\gamma\) His, \(\gamma\) Arg, \(\gamma\) His, \(\gamma\) Arg

Scheme 1 Synthetic utilities of vinylglycines.
Transition-metal-catalyzed carbenoid insertion into N–H bonds is one of the most efficient methods for constructing C–N bonds, and remarkable progress in asymmetric N–H insertion reactions has been achieved in recent years. However, asymmetric N–H insertion reactions of vinyldiazoacetates, which could be used to produce chiral α-alkenyl α-amino acid derivatives, remain an unresolved problem. Such reactions can be expected to be challenging because the highly reactive olefin moiety of the vinyldiazoacetates might undergo migration, rearrangement, or cyclopropanation in the presence of traditional metal-complex catalysts. For instance, Doyle and co-workers prepared the reaction of 3-(trialkylsiloxy)-2-diazo-3-buten-2-one with aldehyde-derived hydrazones using chiral dirhodium catalysts but found that the reaction occurred at the vinyl terminus (referred to as vinylogous N–H insertion), instead of at the α position, to generate α,β-unsaturated γ-amino acid derivatives. Fu and co-workers described an asymmetric N–H insertion of 2-diazo-4-phenylbut-3-enoate with good enantioselectivity (87% ee) but very low yield (25%) in a footnote (experimental data not given). Herein we report that vinyldiazoacetates and tert-butyl carbamate undergo a highly enantioselective N–H insertion reaction cooperatively catalyzed by chiral dirhodium(n) carbamates and chiral spiro phosphoric acids (SPAs) under mild, neutral conditions. This reaction, which constitutes a new route to α-alkenyl α-amino acid derivatives, has a broad substrate scope, a fast reaction rate (turnover frequency > 6000 h⁻¹), a high yield (61–99% yields), and excellent enantioselectivity (83–98% ee). The SPA is proposed to promote the proton transfer of a ylide intermediate by acting as a chiral proton shuttle catalyst, consequently achieving the enantioselectivity of the insertion reaction. Moreover, the SPA suppresses several usual side reactions of vinyldiazoacetates and broadens the applications of these versatile carbene precursors in organic synthesis. To our knowledge, this is the first highly enantioselective carbene insertion reaction of vinyldiazoacetates with heteroatom–hydrogen bonds in which the heteroatom has lone-pair electrons.

To evaluate various chiral catalysts, we carried out the insertion reaction of (E)-benzyl 2-diazo-3-enolate 1a with tert-butyl carbamate in CHCl₃ at 25 °C (Table 1). The traditional chiral metal-complex catalysts for carbene insertion reactions, including copper and palladium complexes with chiral spirobixazoline ligand 3,¹¹ Rh₂(R-DOSP)₄,¹² and Rh₂(S-PTAD)₄,¹³ exhibited only modest yields and low enantioselectivities (entries 1–4). We next turned to cooperative catalysts composed of achiral dirhodium complexes and SPAs 4, which may accelerate the proton shift step of the insertion reaction by acting as chiral proton shuttles (entries 5–13).¹⁴ The use of the SPAs significantly increased the yields of the desired N–H insertion products and suppressed double bond rearrangement and carbene dimerization. The SPA (R)-4g, which bears 6,6'-di[2,4,6-(Me)₃C₆H₂] substituents, exhibited the best performance (78% yield, 61% ee; entry 11). The investigation of various achiral dirhodium complexes revealed that the steric characteristics of the complexes strongly affected the enantioselectivity of the N–H insertion reaction (entries 14–16). With dirhodium complex Rh₂(TPA)₄, which has bulky carboxylate ligands, the reaction was complete in <1 min and afforded a high yield (74%) of the desired product with excellent enantioselectivity (96% ee) (entry 16). Considering their significant effects on the enantioselectivity of the reaction, the rhodium catalysts are most likely involved in the proton transfer step. Chlorinated solvents dichloromethane and dichloroethane were suitable for the N–H insertion reaction, whereas the use of THF or toluene dramatically lowered the enantioselectivity (to 3% ee and 6% ee, respectively; Table S1, ESIF). Increasing the reaction temperature increased the yield of the reaction (entries 17–19). The unexpected high enantioselectivity at 80 °C (entry 19) implies

<table>
<thead>
<tr>
<th>Entry</th>
<th>[M]</th>
<th>SPA</th>
<th>Time</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Pd[(PhCN)₂]Cl₂ and 3</td>
<td>None</td>
<td>12 h</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>2a</td>
<td>Cu(PhCN)₄PF₆ and 3</td>
<td>None</td>
<td>12 h</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(R-DOSP)₄</td>
<td>None</td>
<td>3 min</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(S-PTAD)₄</td>
<td>None</td>
<td>1 min</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4a</td>
<td>2 min</td>
<td>66</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Rh₂(OAc)₄</td>
<td>(S)-4b</td>
<td>3 min</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4c</td>
<td>4 min</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4d</td>
<td>2 min</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4e</td>
<td>4 min</td>
<td>76</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4f</td>
<td>2 min</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>11</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4g</td>
<td>2 min</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>Rh₂(OAc)₄</td>
<td>(S)-4h</td>
<td>3 min</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>Rh₂(OAc)₄</td>
<td>(R)-4i</td>
<td>3 min</td>
<td>64</td>
<td>34</td>
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<tr>
<td>14</td>
<td>Rh₂(piv)</td>
<td>(R)-4j</td>
<td>&lt;1 min</td>
<td>37</td>
<td>71</td>
</tr>
<tr>
<td>15</td>
<td>Rh₂(TFA)</td>
<td>(R)-4k</td>
<td>3 h</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>16</td>
<td>Rh₂(TPA)</td>
<td>(R)-4l</td>
<td>&lt;1 min</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>17f</td>
<td>Rh₂(TPA)</td>
<td>(R)-4m</td>
<td>&lt;1 min</td>
<td>66</td>
<td>95</td>
</tr>
<tr>
<td>18f</td>
<td>Rh₂(TPA)</td>
<td>(R)-4n</td>
<td>&lt;1 min</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>19f</td>
<td>Rh₂(TPA)</td>
<td>(R)-4o</td>
<td>&lt;1 min</td>
<td>93</td>
<td>96</td>
</tr>
</tbody>
</table>

a Reaction conditions: [Rh]₄/1a/BocNH₂ = 0.002 : 0.002 : 0.2 : 0.2 (mmol) in 3 mL CHCl₃, 25 °C. b Isolated yield. c Determined using HPLC using a Chiralcel OD-H column. d Using 5 mol% catalyst. e Performed at 0 °C. f Performed at 60 °C. g Performed at 80 °C. h Using 5 mol% catalyst.
that the SPAs can effectively promote the proton shift of the unstable ylide intermediate in this insertion reaction even under harsh conditions.

Using the optimized reaction conditions, we carried out reactions of vinyldiazoacetate substrates \(1\) bearing various substituents on the C\(=\)C bond (Table 2).\(^{15}\) Impressively, all the reactions were complete within 1 min (turnover frequency \(>6000\) \(\text{h}^{-1}\)). The length of the \(\gamma\)-alkyl group \(\left(R^2\right)\) had a negligible effect on the yield and enantioselectivity of the reaction \((1a-1d)\). The reaction of \(\gamma\)-isopropyl-substituted substrate \(1e\) proceeded in a slightly lower yield, and this result may be attributable in part to increased steric hindrance due to the branched alkyl group. \((E)\)-Benzyl 2-diazo-4-phenylbut-3-enoate \((1f)\), which has a \(\gamma\)-phenyl group, also underwent the insertion reaction, but the enantioselectivity was lower than that for vinyldiazoacetates with a \(\gamma\)-alkyl group. The N–H insertion reactions of \(\gamma\)–\(\gamma\)-disubstituted vinyldiazoesters \(1g-1n\) also exhibited excellent enantioselectivities. Substrates with substituted phenyl groups \((1h-1j)\), fused rings \((1k\) and \(1l)\), and a thiophenyl moiety \((1m)\) were tolerated. The reaction of benzyl 2-diazo-4-methylpent-3-enoate \((1n)\), which has \(\gamma\)–\(\gamma\)-dimethyl groups, afforded excellent enantioselectivity (98% ee) albeit with a relatively low yield (66%). Benzyl 2-diazobut-3-enoate \((1o)\), which bears a terminal olefin, was also a suitable substrate for the N–H insertion reaction, which afforded the ester form of vinylglycine in high yield with excellent enantioselectivity. A vinyldiazoacetate with a cyclic olefin moiety \((1p)\) also afforded the desired product (61% yield, 94% ee). The benzoyloxy functional group in the side chain of vinyldiazoacetate \(1q\) was also tolerated. The size of the ester moiety slightly affected the enantioselectivity; bulkier esters gave higher enantioselectivities (compare substrates \(1g, 1r,\) and \(1s)\). The cooperative catalytic system is highly active. The catalyst loading could be reduced to 0.5 mol\% or even 0.3 mol\% catalyst without significantly affecting the outcome of the N–H insertion reaction of diazoester \(1s\). The further reduction in the catalyst loading to 0.2 mol\% and 0.1 mol\%, leads to lower enantioselectivity (83% ee and 77% ee, respectively). The reaction could be easily performed at a gram scale (Scheme 2), which demonstrates its potential for practical applications.

This N–H insertion reaction of vinyldiazoacetates provides a new route to chiral \(\alpha\)-amino acids. For example, \(\alpha\)-vinylglycine was easily prepared in good yield by the hydrolysis of insertion product \((S)-2o\) (Scheme 3, eqn (1)).\(^{16}\) Hydrogenation of \((R)-2b\) over a Pd/C catalyst and subsequent acidic hydrolysis gave \(\alpha\)-alkyl-\(\alpha\)-amino acid \(6\) (94% yield, eqn (2)).\(^{16}\) The olefin moieties in the products can be expected to undergo transformations such as dihydroxylation, cyclopropanation, and epoxidation,\(^{11,16}\) making this reaction potentially useful for synthesizing various optically active \(\alpha\)-amino acid derivatives.

In summary, a highly efficient asymmetric synthesis of \(\alpha\)-alkenyl \(\alpha\)-amino acids was realized by means of the N–H

\[\text{Me} \quad \text{COOH} + \text{BocNH}_2 \quad \xrightarrow{1 \text{ mol\% Rh}(TPA)_2} \quad \text{Me} \quad \text{NHBOC} \]

\[\text{Me} \quad \text{COOH} \quad \xrightarrow{6 \text{ N HCl, reflux, 2 h}} \quad \text{Me} \quad \text{NH}_2 \quad \text{COOH} \quad \text{(eq 1)}\]

\[\text{(S)-5} \quad \text{85% yield} \quad \left[\alpha\right]_{D}^{20} +63.4 (c 2.0, \text{H}_2\text{O})\]

\[\text{Me} \quad \text{NHBOC} \quad \xrightarrow{1) H_2 (1 atm), Pd/C (2.5 mol\%)} \quad \text{MeOH, rt, 2 h} \quad \text{Me} \quad \text{NH}_2 \quad \text{COOH} \quad \text{(eq 2)}\]

\[\text{(R)-6} \quad \text{94% yield} \quad \left[\alpha\right]_{D}^{26} -0.8 (c 0.6, \text{H}_2\text{O})\]

\[\text{Me} \quad \text{NHBOC} \quad \xrightarrow{2) 6 \text{ N HCl, reflux, 3 h}} \quad \text{Me} \quad \text{NH}_2 \quad \text{COOH} \]
insertion reaction of vinyldiazoacetates with tert-butyl carba-
mate cooperatively catalyzed by achiral dirhodium(II) carboxyl-
ates and chiral SPAs. The wide substrate scope, good yield, high
enantioselectivity, fast reaction rate, and mild, neutral condi-
tions make this N–H insertion reaction widely applicable for the
preparation of chiral α-amino acid derivatives. The combina-
tion of SPAs and dirhodium(II) carboxylates exhibits a special
advantage in the transformation of highly functionalized
vinyldiazoacetates by minimizing the side-reactions, and has
potential applications in other enantioselective trans-
formations involving vinyldiazoacetates.

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