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Divergent and Scalable Synthesis of α-Hydroxy/Keto-β-Amino Acid Analogues by Catalytic Enantioselective Addition of Glyoxylate Cyanohydrin to Imines

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ABSTRACT: The catalytic enantioselective addition of glyoxylate cyanohydrin to imines to afford α-keto-β-amino acid equivalents is reported. Sterically tuned aminobenzothiadiazine catalysts provided high yields and stereoselectivities (up to 100% yield, 99% ee, >99:1 dr) for both aromatic and aliphatic imines and the stereodivergent synthesis of both diastereomers was achieved. The optimal catalytic system was scalable, even with a low catalyst loading. The resulting adducts were converted into various chiral building blocks, including β-amino acid analogues, which are important motifs in medicinal chemistry, while maintaining a high enantiomeric excess.

KEYWORDS: asymmetric synthesis, organocatalysis, β-amino acid, cyanohydrin, diastereodivergent synthesis

β-Amino acids are important non-proteinogenic amino acid motifs that can dramatically change the physical properties and biological activity of peptides. Among them, α-oxygen-functionalized analogues, such as α-hydroxy- and α-keto-β-amino acids, are important substructures found in various bioactive natural products and pharmaceuticals (Scheme 1a). Furthermore, α-keto-β-amino acids can be effectively used for decarboxylative transformations, including ketoadid-hydroxylamine (KAHA) ligation, which enables chemoselective coupling with complex fragments. Owing to the importance of β-amino acids, catalytic and stereoselective transformations for their rapid preparation have recently been explored.

The efficient synthetic approach, in which a C–C bond forms simultaneously with stereoselective introduction of functional groups at the α- and β-positions, can be accomplished by the Mannich-type addition of C2 nucleophiles to imines (Scheme 1b). Terada and coworkers reported the asymmetric addition of an α-diazoester to N-benzoylimine catalyzed by a BINOL-based chiral phosphoric acid. Matsumaga, Kumagai, and Shibasaki have also described Mannich reactions using special α-hydroxyacetamides as nucleophiles. Although these pioneering works have demonstrated that Mannich adducts obtained enantioselectively can be converted into α-oxygen-functionalized β-amino acids, the derivatization need relatively harsh conditions such as strong oxidants, acids, or bases. Therefore, a new efficient approach is needed.

To establish a new method that allows the divergent synthesis of α-oxygen-functionalized β-amino acids, we focused on the cyanohydrin motif, which is regarded as a carbonyl equivalent. Rawal and coworkers recently reported the enantioselective addition of masked acyl cyanide (MAC) to imines, where the adduct was transformed into α-amino acids by subsequent deprotection steps (Scheme 1c). We envisaged that glyoxylate cyanohydrin, a C2 nucleophile which has not previously been used in catalytic enantioselective reactions, could be applied to the Mannich-type addition using chiral bifunctional organocatalysts to afford α-keto-β-amino acid equivalents enantioselectively (Scheme 1d).

Based on the above concept, we initially screened reaction conditions for the asymmetric Mannich-type reaction using glyoxylate cyanohydrin 1 as a nucleophile (Table 1). First, nucleophile 1 and Boc-imine 2a were treated with bifunctional aminothiourea catalyst 4a in CH2Cl2 at −20 °C to afford the desired adduct in 100% yield as a 1:6:1 diastereomeric mixture, with major diastereomer 3a having 57% ee (entry 1). To improve the stereoselectivity, we screened other hydrogen-bond donors in the catalyst structure (entries 2 and 3). Squaramide 4b, also afforded moderate stereoselectivity, while benzothiadiazine 4c, which was recently developed as a powerful hydrogen-bond-donating organocatalyst, provided significantly better enantioselectivity (87% ee, entry 3). By changing the solvent from CH2Cl2 to toluene, the enantioselectivity for the major diastereomer was improved to 95% ee (entry 4). Furthermore, lowering the reaction temperature provided better diastereoselectivity while maintaining the high yield and enantioselectivity (entry 5).

Next, we modified the chiral amine motif in the catalysts to achieve higher diastereoselectivity. Cinchona alkaloid-based catalyst 4d provided lower enantioselectivity, while 1,2-diphenylethenediamine structure 4e did not significantly improve the selectivity (entries 6 and 7). In contrast, replacing one methyl substituent with a benzyl group boosted the diastereoselectivity to 9:4:1 (entry 8). Additional fine tuning of the alkyl substituents showed that secondary alkyl groups (Pr and cyclopentyl) afforded better diastereoselectivity (entries 9 and 10).
Finally, the reaction using catalyst 4h provided desired adduct 3a as almost a single stereoisomer, with 97% ee and 31:1 dr (entry 10). This catalytic system was easily scalable, with compound 3a prepared on a gram-scale using a catalyst loading of only 1 mol% (eq 1). Surprisingly, substituents at the 5-position of the aromatic ring changed the diastereoselectivity in the products (entry 11). In particular, catalyst 4j, bearing an isopropyl group, predominantly generated 3a\textsuperscript{13} with excellent yield and stereoselectivity (entry 12). The reversal of diastereoselectivity through catalyst control remains challenging, while several organocatalytic asymmetric transformations have been previously reported.\textsuperscript{14,15}

With optimal conditions in hand (Table 1, entries 10 and 12), we next examined the substrate scope of the diastereodivergent, enantioselective addition of glyoxylate cyanohydrin 1 to N-Boc imine (Table 2). As the electron density on the aromatic rings increased, the stereoselectivity of catalyst 4h improved, with corresponding adducts 3a–c obtained in high yields (entries 1–3). In contrast, the enantioselectivity was slightly diminished when electron-rich aromatic imines were applied using catalyst 4j (3a'–c'). This trend was in agreement with the results for electron-deficient aromatic rings, while all adducts were still obtained with excellent stereoselectivity (entries 4 and 5). These results also indicated that the electronic properties of N-Boc-imine did not significantly affect the diastereoselectivity of the diastereodivergent catalytic system using 4h and 4j. A methyl substituent at the meta or ortho positions relative to the imino group also resulted in a high yield and excellent stereoselectivity using both catalysts (entries 6 and 7). The reaction of naphthyl, thiophenyl and furanyl imines proceeded similarly, with corresponding adducts 3h–j and 3h'–j' obtained with excellent stereoselectivity (entries 8–10). Finally, the catalytic system was applied to N-Boc-alkylamines derived from cyclohexanecarboxaldehyde and isovaleraldehyde affording the adducts with good stereoselectivities, albeit only the enantioselectivity of the adduct 3k' considerably diminished (entries 11 and 12).

Subsequently, we demonstrated the derivatization of Mannich adduct 3a to obtain α-oxygen-functionalized β-amino...
### Table 2. Substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst 4h</th>
<th>Catalyst 4j</th>
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<tr>
<td></td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>1</td>
<td>![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
</tr>
<tr>
<td>2</td>
<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
</tr>
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<td>3</td>
<td>![Me₂O]⁺ ![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
</tr>
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<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
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<tr>
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<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
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<td>6</td>
<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
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<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
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<td>![HN Boc]⁻</td>
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</tr>
<tr>
<td>12</td>
<td>![Me₂]⁺ ![NC=CO₂Bu]⁻</td>
<td>![HN Boc]⁻</td>
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*1 (0.1 mmol), 2a–2l (0.15 mmol), and 4h or 4j (0.005 mmol) reacted in toluene (1 mL) at −40 °C for 24 h. †Isolated yield. ‡Estimated by chiral HPLC analysis.
acids, as initially planned (Scheme 2). Compound 3a was a stable, easy-to-handle, and storable solid, and Cbz deprotection followed by treatment with aqueous silver nitrate provided β-aminoo-α-ketoester 6 in 56% yield over two steps. Importantly, the optical purity of the compound was retained during this transformation, with β-aminoo-α-ketoester 6 obtained with 94% ee. This is the first report of the isolation and full characterization of an enantioenriched N-carbamate-protected α-oxo-β-phenylalanine. In addition, the reductive transformation of 5 using L-Selectride afforded anti-α-hydroxy-β-amino acid derivative 7 in 66% yield over two steps. Changing the reductant to sodium borohydride resulted in the reduction of not only the cyanohydrin moiety, but also the ester, to afford aminodiol 8 in 68% yield, which is another useful motif in the pharmaceutical sciences. These reductive transformations also proceeded without any loss of stereochemical information in the β-amino group. Furthermore, we attempted the stereo-divergent synthesis of β-amino acid analogues. The cyano groups of 3a and 3a’, diastereoselectively prepared in Table 1, were hydrolyzed under the palladium-catalyzed hydration conditions reported by Naka and co-workers to provide complex β-amino acids 9 and 9’ as single stereoisomers, respectively.

Scheme 2. Derivatization of adducts 3a and 3a’

Isolated yield. (a) Pd/C, H₂ (1 atm), EtOAc. (b) AgNO₃, MeCN, H₂O, 56% yield, 94% ee. (c) L-Selectride, THF, 0 °C, 66% yield, 95% ee. (d) NaBH₄, EtOH, 68% yield, 92% ee. (e) Pd(NO₃)₂•2H₂O, acetamide, MeCN, H₂O, 50 °C: 9: 83% yield, 98% ee, 39:1 dr. 9’: 87% yield, 90% ee, 18:1 dr.

To gain insight into the reaction mechanism, we conducted the reaction using cyanohydrins 10 and 12 bearing different protective groups as nucleophiles (Scheme 3a). The catalytic addition of O-methyl carbonate 10 divergently provided 11 and 11’ with excellent enantioselectivity using catalysts 4h and 4j, respectively (eq 2). Furthermore, methyl ester 12 also afforded corresponding adducts 13 and 13’ with similar stereoselectivity (eq 3). These results indicated that the bulk of the nucleophile was not significantly important for stereoselectivity.

Considering the configuration of the benzothiadiazine catalyst and obtained adduct 3a, we next conducted the computational studies to determine the transition state of the Mannich-type addition. Preliminary results suggested a transition state in which both the deprotonated nucleophile and the N-Boc-imine are activated by two NH protons of benzothiadiazine and an ammonium unit in the catalyst, respectively (Scheme 3b). However, it remains difficult to explain the inverse diastereoselectivities of catalysts 4h and 4j. Therefore, further mechanistic studies to fully explain this unique catalytic system are currently underway.

Scheme 3. Preliminary mechanistic studies

(a) Steric effects of protective groups in cyanohydrin

(b) Calculated transition states to provide (2S,3R)-adduct

In summary, we applied O-Cbz-protected glyoxylate cyanohydrin as a C2 nucleophile in a catalytic Mannich-type addition to afford chiral α-keto-β-amino acid equivalents. An aminobenzothiadiazine catalyst bearing strong hydrogen-bond donor activity was found to be suitable for the transformation, and steric tuning of the catalyst afforded excellent stereoselectivity. The enantioenriched adducts were also readily converted into a series of chiral motifs, including useful β-amino acids, as initially expected. This approach could be applied to the efficient synthesis of various chiral building blocks, and further improvements and applications of this method are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.

Experimental procedures and analytical data for all new compounds (PDF)
X-ray data file (CIF)
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Notes
The authors declare no competing financial interests.

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