ABSTRACT: A boron-catalyzed α-amination of simple carboxylic acids was developed. Catalytically generated boron enolates of carboxylic acids reacted with an electrophilic aminating reagent, diisopropylazodicarboxylate, to provide amino acid derivatives. The catalysis afforded not only α-mono-substituted glycine derivatives but also α,α-disubstituted derivatives. The resulting α-aminocarboxylic acid was easily converted to carboxylic acid derivatives. Extension to a catalytic asymmetric variant was possible by introducing a chiral ligand on the boron catalyst.

α-Amino acids are attractive synthetic targets due to their versatile applicability as building blocks of biologically active molecules and functional molecules. One of the most efficient and straightforward synthetic methods to construct α-amino acids is the catalytic α-amination of readily available carboxylic acids. However, this method is less developed compared to those with other carbonyl congeners, e.g., aldehydes, ketones, 1,3-dicarbonyl compounds, and oxyindoles. The high pKa value of the α-proton of carboxylic acid derivatives causes the major hurdle to realize the catalytic reaction. Pre-formation of active surrogates, such as ketenesilylacetals or α-bromoesters, is an alternative approach toward the α-amination of carboxylic acid derivatives. However, the direct catalytic α-amination via deprotonation of the α-proton has been limited to α-arylacetic acid derivatives, in which the enolate formation is relatively easy due to anion stabilization by conjugation. Hence the utilization of α-alkylsubstituted acetic acid derivatives has been challenging. Smith reported one entry of a catalytic enantioselective α-amination of 3-phenylpropionic acid through in situ pre-formation of an acid anhydride intermediate (Scheme 1a). The acid anhydride is further activated by a chiral isothiourea catalyst for α-amination via a Cl-ammonium enolate. Yazaki and Ohshima recently reported a copper-catalyzed α-amination of acylpyrazoles (Scheme 1b). Wasa employed a frustrated Lewis pair (FLP) system comprised of B(C6F5)3 and a bulky base (pentamethyl piperidine or Barton’s...
base) for α-amination of simple esters (Scheme 1c).\(^1\) Despite these reports, construction of tetra-
substituted carbon centers α to the carboxylic group remains elusive.

We previously reported the chemoselective enolate for-
mation of carboxylic acids using a boron activator.\(^2\) The reversible covalent bond formation between the carboxylic acid and the Lewis acidic boron activator increases the acidity of the α-proton, thus enabling enolate formation of the carboxylic acid under mild basic conditions. We envis-
aged that this method could be extended to the direct α-
amination of carboxylic acids leading to α,α-disubstituted glycine derivatives (Scheme 1d). Herein, we report a boron-catalyzed direct α-amination of carboxylic acids, which is applicable to the synthesis of α,α-disubstituted glycine derivatives.

To assess the feasibility of the proposed reaction, p-
methoxyphenylacetic acid (1a) was selected as a substrate. Based on the results from previous studies of the boron-
catalyzed Mannich-type reaction, conditions with BH3·SMe2 (20 mol%), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (2 equiv), and toluene as a solvent were applied for the carboxylic acid enolate formation, and diaethylazodi-
(carboxylate (DEAD) was used as the electrophilic aminating reagents to avoid the formation of DEAD-
derived hydrazine as a byproduct.\(^3\) Increasing the steric bulk of the aminating reagent by changing DEAD to di-
propylazodicarboxylate (DIAD) was effective to suppress undesired hydrazine formation, promoting the α-
amination reaction to produce 2a in excellent yield (entry 5, 96% yield). Bulkier di-tert-butylazodicarboxylate did not improve the product yield (entry 6, 86% yield). The catalyst loading could be reduced to 2.5 mol% without significant loss of catalytic activity (entry 7, 91% yield). Nitrosobenzene was not reactive as an electrophile.

The conditions optimized for the reaction of 1a did not give satisfactory results for the reaction of α-
monoalkylacetic acid 1b (Table 2, entry 1). The product 2b was obtained in only 27% yield under the same conditions as Table 1, entry 7. This was likely due to the lower acidity of 1b at the α-methylene group compared to that of 1a. The yield could be improved to 66% by increasing the boron catalyst loading to 10 mol% (entry 2). Since a significant amount of hydrazine was observed as a side product even with DIAD, the amount of DIAD was increased to two equivalents. This resulted in a marked increase in the yield to 84% (entry 3).

![Table 1. Boron-Catalyzed α-Amination of α-Monoarylacetic Acid.\(^6\)](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boron source (x mol%)</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH3·SMe2 (20 mol%)</td>
<td>Et</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>BBr3 (20 mol%)</td>
<td>Et</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>(AcO)4B2O (10 mol%)</td>
<td>Et</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>B(OEt)3 (20 mol%)</td>
<td>Et</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>(AcO)4B2O (10 mol%)</td>
<td>iPr</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>(AcO)4B2O (10 mol%)</td>
<td>tBu</td>
<td>86</td>
</tr>
<tr>
<td>7(^a)</td>
<td>(AcO)4B2O (2.5 mol%)</td>
<td>Pr</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\)1a (0.1 mmol), azodicarboxylate (0.1 mmol), boron catalyst, DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. \(^\dagger\)The reaction was conducted in 0.2 mmol scale.

The scope of the carboxylic acids was examined using 10 mol% (AcO)4B2O. One equivalent of DIAD was used for the reaction of phenylactic acid derivatives (Scheme 2). Both electron-withdrawing and -donating substituents on the α-
aryl group afforded the corresponding amino acid deriva-
tives in good yields (2a: 96%; 2c: 72%; 2d: 72%; 2e: 77%). 1 mmol scale reaction using 1a afforded 2a in 90% yield. On the other hand, 2 equiv of DIAD were used for hydro-
cinnamic acid derivatives. Although an electron-donating methoxy substituent at the para-position of the aryl group decreased the yield (2f: 58%), the electron-withdrawing p-
chloro substituent did not affect the reactivity (2g: 83%). α-Bromo substitution slightly decreased the yield probably due to increased steric bulk (2h: 70%). α-Monoalkylacetic acids other than hydrocinnamic acid derivatives, propionic
acid (1i) and valeric acid (1j), were also competent to afford 2l (91% yield) and 2p (84% yield).

Next, we attempted to use the catalyst for the synthesis of α,α-disubstituted glycine derivatives. Gratifyingly, α-methylhydrocinnamic acid (1k) was converted to the product 2k in 88% yield with 10 mol% (AcO)B2O and 2 equiv DIAD (Scheme 3). The yield was low with 1 equiv of DIAD (28% yield). Both electron-donating and electron-withdrawing substituents were tolerated on the aryl group of α-methylhydrocinnamic acid was also tolerated albeit with a lower yield (2n: 47%). Since there is a member of non-steroidal anti-inflammatory drugs (NSAIDs)

Scheme 2. Substrate Scope for α-Monosubstituted Acetic Acids.α

![Scheme 2]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cl</td>
<td>2a</td>
<td>96% (90%)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>2b</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>2c</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>2d</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>2e</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td>2f</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>2g</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>2h</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>Pr</td>
<td>2i</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>Pr</td>
<td>2j</td>
<td>84%</td>
</tr>
</tbody>
</table>

α1a (0.1 mmol), DIAD (0.1 mmol), (AcO)B2O (0.01 mmol), DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. αThe reaction was conducted on a 1 mmol scale. The yield is shown in parentheses. α1DIAD (0.2 mmol) was used.

Transformation of the carboxy group was examined next (Scheme 4). After the catalytic amination of 1k, the crude material was purified by silica gel column chromatography and subjected to condensation reactions (Scheme 4a). Condensation with benzylamine using hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) gave amide 4 in 81% yield over two steps. When glycine was used as a coupling partner, dipeptide analogue 5 was obtained in 78% yield. Intramolecular self-condensation provided diazetidinone 6 in 51% yield. Although several attempts to cleave the N-N bond of 2a resulted in failure,14 α-N-tert-butoxy carbonyl analogue 2af was successfully transformed to α-amino acid methyl ester 7 in two steps: TFA-mediated cleavage of tert-butoxy carbonyl groups followed by N-N bond scission by hydrogenolysis using Raney-Ni (Scheme 4b).

Scheme 3. Substrate Scope for α,α-Disubstituted Acetic Acids.α

![Scheme 3]

| α1a (0.1 mmol), DIAD (0.2 mmol), (AcO)B2O (0.01 mmol), DBU (0.2 mmol), toluene (0.15 M), room temperature, 3 h. Crude mixture was treated with TMSCHN2 (0.6 mmol) in MeOH (0.1 M). Isolated yield. αThe reaction was conducted on a 1 mmol scale. The yield is shown in parentheses. α1DIAD (0.2 mmol) was used.
Scheme 4. Transformation of the α,α-Disubstituted Glycine Derivative.

Scheme 5. Catalytic Enantioselective α-Amination of a Carboxylic Acid.

Preliminary results of our investigation on the catalytic enantioselective α-amination of 1o by introducing a chiral ligand on the boron catalyst are shown in Scheme 5. Valine derived L1 and 3,3'-l-BINOL L2, which were effective chiral ligands for the previous study of the boron-catalyzed asymmetric C-C bond forming reactions of carboxylic acids,124,125 were selected for initial investigations. Although L2 did not induce meaningful stereoselectivity, L1 provided 2o in decent enantioselectivity, 45% ee. This result suggests that the boron-catalyzed α-amination of carboxylic acids may provide a useful method for the asymmetric synthesis of α,α-disubstituted glycine derivatives through proper chiral modification of the boron catalyst.

In summary, we have developed the first boron-catalyzed direct α-amination of carboxylic acids. The reaction provided a variety of α-amino acid derivatives including α,α-disubstituted glycine derivatives. Preliminary investigations revealed that the present method can be extended to an asymmetric variant by introducing a chiral ligand on the boron catalyst. Modification of the chiral ligand to improve the enantioselectivity is ongoing in our laboratory.

ASSOCIATED CONTENT

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

Detailed experimental procedures, characterization data, NMR spectra, HPLC chart.

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Notes
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