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Efficient Synthesis of Racemic α-Aryl-α-Amino Acid Esters via Aminoalkylation with in situ Generated Glycine Cation Equivalents


Synthesis of Unnatural Amino Acids from in situ Generated Glycine Cation Equivalents

Significance: Unnatural amino acids, especially α-aryl-α-amino acids, are ubiquitous building blocks found in many natural products and biologically active compounds. The authors developed an efficient method for the synthesis of unnatural amino acid esters by amino alkylation with in situ generated glycine cation equivalents.

Comment: The aminoalkylation of phenols and aromatic N- and O-heteroaromatics with in situ generated glycine cation equivalents proceeded smoothly and offer various unnatural α-aryl-α-amino acid esters in good yields. This method is practically simple and showcases a broad functional group tolerance.

Conditions A

AlCl₃ (1 equiv), 0 °C, THF, 1 h then Ar-H (1 equiv), reflux 4–5 h

Conditions B

TiCl₄ (1 equiv), –78 °C, CH₂Cl₂, 0.5 h then Ar-H (1 equiv), –60 °C, 2 h

Selected examples:

87% yield<sup>a</sup>

83% yield<sup>ab</sup>

86% yield<sup>c</sup>

98% yield<sup>c</sup>

72% yield<sup>d</sup>

85% yield<sup>a</sup>

77% yield<sup>d</sup>

93% yield<sup>d</sup>

96% yield<sup>d</sup>

84% yield<sup>d</sup>

<sup>a</sup>Method A was used. <sup>b</sup>Method B was used.