Bismuth- and Iron-Catalyzed Three-Component Synthesis of \( \alpha \)-Amino Acid Derivatives: A Simple and Convenient Route to \( \alpha \)-Arylglycines

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Abstract Efficient bismuth- and iron-catalyzed three-component syntheses of \( \alpha \)-arylglycines have been developed. These methods provide a general, atom-economic route to various N-protected \( \alpha \)-arylglycines starting from readily available amides (or carbamates), glyoxalates, and (hetero)arenes with water as the only by-product. Scope and limitations of bismuth- and iron-catalyzed reactions are discussed and compared. In addition, mechanistic investigations as well as initial forays into stereoselective three-component reactions are presented.

Key words multicomponent reactions, iron, bismuth, aza-Friedel–Crafts reaction, amino acids, homogeneous catalysis

\( \alpha \)-Amino acids are of fundamental importance for biology, biochemistry, and chemistry. They form the backbone of proteins, an essential part of every living organism, and are used as common feedstock for the production of biodegradable plastics, fertilizers, nutritional supplements, or drugs. Many proteinogenic and nonproteinogenic \( \alpha \)-amino acids have important biological, nonprotein-related functions, such as glutamate, an important neurotransmitter or glycine, the starting material for the biosynthesis of porphyrin-type cofactors. With the expansion of the genetic code and the discovery of protein-based drugs, nonproteinogenic (or unnatural) \( \alpha \)-amino acids have gained increasing attention. Among these nonproteinogenic \( \alpha \)-amino acids, \( \alpha \)-arylglycines are of particular importance, as they are building blocks for various drugs, such as cardiovascular agents and \( \beta \)-lactam antibiotics like amoxicillin and norcardicin A (Figure 1). The \( \alpha \)-arylglycine moiety is also part of numerous natural products, such as vancomycin or chloropeptin (Figure 1). Expanding the organic chemist’s tool box with novel efficient, modular and practical methods for the synthesis of the \( \alpha \)-arylglycine structure is therefore of great interest.

Common procedures for the preparation of these compounds are based on the addition of a nucleophile to an imine species, such as the Mannich reaction, the Strecker reaction, the Petasis–(Borono–Mannich) reaction, or asa-Friedel–Crafts-type reactions (Scheme 1).

![Image of biologically active substances](image-url)

Figure 1 \( \alpha \)-Arylglycine moiety in biologically active substances
synthetic routes to α-arylglycines. They utilize readily available reactants and offer a promising opportunity for the sustainable and atom-economic synthesis of this important compound class. However, reported aza-Friedel–Crafts-type reactions are often limited to very reactive (hetero)arenes or require stoichiometric amounts of strong Brønsted or Lewis acids. These restrictions lead to a rather small substrate scope and the formation of considerable amounts of waste and by-products.

In the course of our research on imine-based multicomponent reactions, we were able to develop three-component reactions for the synthesis of α-arylglycines using inexpensive and nontoxic bismuth and iron catalysts. These reactions provide straightforward access to a broad scope of α-(hetero)arylglycines. They utilize readily available starting materials and water is generated as the only by-product. Herein we report the full scope and limitations of both methods, together with comparison of the specific advantages and disadvantages as well as detailed mechanistic investigations.

**Optimization and Scope**

At the onset of our studies, we hypothesized that an ideal catalyst should be able to catalyze both the formation of a reactive N-acylimine via condensation of an amide with a glyoxylic acid derivative and the addition of an unreactive arene to the in situ formed N-acylimine. Small quantities of water formed in the condensation step should not lead to a significant catalyst deactivation. For the sake of practicality the glyoxalate was used in its more stable polymeric or hydrated form.

To identify a suitable catalyst system, the reaction of benzamide (1a) with commercially available ethyl glyoxalate (2a) and the moderately reactive m-xylene (3a) was chosen using only 1 mol% of the catalyst (Table 1). Preliminary results revealed that several Lewis and Brønsted acids are able to catalyze this reaction, albeit with various degrees of efficiency (Table 1). Water-sensitive Lewis acids, such as BF3·OEt2 and AlCl3, or weak Brønsted acids, for example, TFA or (PhO)2P(O)OH, did not catalyze the reaction at all (yields <10%, results not shown).

The stronger Brønsted acids TFOH and TsOH provided the desired product in >20% yield (Table 1, entries 6 and 8). A higher loading of TFOH did not lead to a greatly improved yield (entry 7). Most promising results were obtained with Bi(OTf)3, In(OTf)3, and Yb(OTf)3 (entries 2–4). Other metal triflates such as Sc(OTf)3, Mg(OTf)2, or Zn(OTf)2 did not show a similar catalytic activity. Surprisingly, 1 mol% Fe(CIO4)3 furnished the α-arylglycine 4a in 91% yield (entry 1).

From an ecological and economic point of view, readily available, cheap, and nontoxic iron salts would be an ideal catalyst system for this three-component reaction. Therefore, iron-based catalysts were investigated in more detail. During our previous research on amidooalkylation reactions, Bi(OTf)3 was identified as a very active, nontoxic, and relatively cheap catalyst. Thus, we decided to take

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**Table 1** Initial Screening of Different Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe(ClO4)3·xH2O</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Bi(OTf)3</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)3</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)3</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)3</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>TFOH</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>TFOH (5 mol%)</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>TsOH</td>
<td>12</td>
</tr>
</tbody>
</table>

*a Yields are given for the isolated product. The product was obtained as a 98:2 mixture of regioisomers. Only the major regioisomer is shown.*

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focus on bismuth-catalyzed reactions as well. Although In(OTf)_3 and Yb(OTf)_3 showed promising catalytic activity (Table 1, entries 3 and 4), In- and Yb-based catalysts were not examined due to the toxicity and teratogenic potential of In(III) and Yb(III) salts.\textsuperscript{24}

To optimize the reaction conditions for both bismuth- and iron-based conversions, the initial model reaction between benzamide (1a), ethyl glyoxalate (2a), and m-xylene (3a) was chosen. The results for the optimization of the iron catalyst are depicted in Table 2. Both, iron chloride either in its anhydrous form or as hexahydrate, as well as iron perchlorate displayed high catalytic activities. Despite the fact that both Fe(ClO_4)_3 and FeCl_3·6H_2O gave similar yields during the initial optimization reactions (Table 2, entries 1 and 7), Fe(ClO_4)_3 led to higher yields in general. Additionally, for Fe(ClO_4)_3 the catalyst loading can be decreased without significant loss of efficiency (entry 9). Whereas 1 mol% FeCl_3 led to the desired product in 91% yield (entry 8), the yield with 1 mol% FeCl_3 dropped to 18% (entry 5). The corresponding Fe^{2+} salts could catalyze the model reaction only 0.5 mol% of Bi(OTf)_3 the product could be isolated in 77%. As shown in Table 1, TfOH, a possible by-product from the hydrolysis of Bi(OTf)_3, did not display a similar catalytic activity. In the case of the Bi-catalyzed reaction, nitromethane also proved to be the optimal solvent (Table 3, entry 7). Again no significant decrease in the catalytic activity was observed, indicating a Bi(III)-species as the active catalyst. In the case of the Bi-catalyzed reaction, nitromethane also proved to be

\begin{table}
\centering
\caption{Optimization of the Reaction Parameters for Fe-Catalyzed Three-Component Reaction for the Synthesis of \( \alpha \)-Arylglycine 4a}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Catalyst & Solvent & Yield (%) \tabularnewline
\hline
1 & FeCl_3·6H_2O (5 mol%) & MeNO_2 & 84 \tabularnewline
2 & FeCl_3·6H_2O (2 mol%) & MeNO_2 & 84 \tabularnewline
3 & anhyd FeCl_3 (5 mol%) & MeNO_2 & 86 \tabularnewline
4 & anhyd FeCl_3 (2 mol%) & MeNO_2 & 87 \tabularnewline
5 & anhyd FeCl_3 (1 mol%) & MeNO_2 & 18 \tabularnewline
6 & FeCl_3·4H_2O (2 mol%) & MeNO_2 & 82 \tabularnewline
7 & Fe(OTf)_3·xH_2O (5 mol%) & MeNO_2 & 91 \tabularnewline
8 & Fe(OTf)_3·xH_2O (1 mol%) & MeNO_2 & 91 \tabularnewline
9 & Fe(OTf)_3·xH_2O (0.5 mol%) & MeNO_2 & 75 \tabularnewline
10 & Fe(OTf)_3·xH_2O (0.1 mol%) & MeNO_2 & 37 \tabularnewline
11 & Fe(OTf)_3·xH_2O (2 mol%) & MeNO_2 & 82 \tabularnewline
12 & Fe(OTf)_3·xH_2O (5 mol%) + dbpy (10 mol%) & MeNO_2 & 86 \tabularnewline
13 & FeCl_2·4H_2O (2 mol%) & DCE & 39 \tabularnewline
14 & FeCl_2·4H_2O (2 mol%) & CH_2Cl_2 & 23 \tabularnewline
15 & FeCl_2·6H_2O (2 mol%) & 1,4-dioxane & <10 \tabularnewline
16 & FeCl_2·6H_2O (2 mol%) & MeCN & 10 \tabularnewline
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Optimization of the Reaction Parameters for Bi-Catalyzed Three-Component Reaction for the Synthesis of \( \alpha \)-Arylglycine 4a}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Catalyst & Solvent & Yield (%) \tabularnewline
\hline
1 & Bi(OTf)_3 (5 mol%) & MeNO_2 & 84 \tabularnewline
2 & Bi(OTf)_3 (2 mol%) & MeNO_2 & 89 \tabularnewline
3 & Bi(OTf)_3 (1 mol%) & MeNO_2 & 88 \tabularnewline
4 & Bi(OTf)_3 (0.5 mol%) & MeNO_2 & 77 \tabularnewline
5 & BiCl_3 (5 mol%) & MeNO_2 & 72 \tabularnewline
6 & BiBr_3 (5 mol%) & MeNO_2 & 69 \tabularnewline
7 & Bi(OTf)_3 (5 mol%) + dbpy (10 mol%) & MeNO_2 & 84 \tabularnewline
8 & Bi(OTf)_3 (5 mol%) & DCE & 52 \tabularnewline
\hline
\end{tabular}
\end{table}
the ideal solvent. While yields in 1,2-dichloroethane were still acceptable (entry 8), the use of other solvents led to significant lower yields (results not shown).

### Scope of (Hetero)Arenes, Amides, and Glyoxalates

After identification of the ideal reaction conditions, the scope of our methods was explored. First, reactions of different arenes with benzamide (1a), and ethyl glyoxalate (2a) were investigated. Various electron-rich arenes are suitable substrates for both the Fe- and the Bi-catalyzed aza-Friedel–Crafts reaction (Scheme 2). The combined results are shown in Scheme 2. Both types of catalyst furnished different α-arylglycine derivatives in good to excellent yields. Interestingly, N-pivalolyl-protected aniline 3m reacted chemoselectively and α-arylglycine 4m was isolated in 67% (Bi) and 80% (Fe) yield. The reactions of polycyclic arenes led to the formation of glycine derivatives 4q and 4r, useful building blocks for the synthesis of fluorescence labels, in 49–64% yield. Less reactive arenes, such as benzene, did not react, even under harsh reaction conditions. In most cases only one regioisomer was obtained. However, in some cases, such as in the reaction with anisole, a mixture of regioisomers was isolated. To our surprise, the use of Bi(OTf)₃, supposedly the more active catalyst, always led to higher regioselectivities. In certain cases, such as with anisole, only a small, negligible difference in the regioselectivity was observed (75:25 vs. 71:29). However, for reactions with other arenes, Bi(OTf)₃ furnished the desired products with a significantly higher regioselectivity. This fact is exemplified by the arylglycines 4e (86:14 vs.

![Scheme 2](image)

Scheme 2: Substrate scope: arene component. Yields are given for isolated products. Unless otherwise mentioned, the corresponding α-arylglycine was observed as one single regioisomer (d.r. >98:2). In the case of regioisomers, only the major one is shown. Bz = benzoyl, Piv = pivalolyl.
Not only arenes but also heteroaromatic compounds are suitable substrates for the three-component reaction (Scheme 4). The corresponding heteroarylglycines 7a–l were obtained in good to excellent yields with both Fe and Bi catalysis. In general, lower reaction temperatures were necessary to avoid direct addition of the heteroarene to the aldehyde (Scheme 5).27 Reaction of benzamide (1a) with ethyl glyoxalate (2a) and a heteroarene 6 as the nucleophilic component furnished different heteroarylglycines in 47 to 88% yield (Scheme 4). Interestingly, reactions with carbamates, such as urethane, as the amide component, led to overall higher yields as well as improved regioselectivities. Improved regioselectivities can be rationalized by the decreased reactivity of the in situ formed N-carbamoylimine compared to the N-acylimine in the benzamide case. The low yields with benzamides are most probably associated with the instability of the formed aminoalkylated products under acidic conditions. We assume that these compounds decompose under acidic conditions via dissociation of the benzamide, thereby forming a stabilized heterobenzylic cation 9, which can react with excess of the heteroarene to the corresponding diarylmethane derivative 10.
Indeed, Bi(OTf)₃-catalyzed reactions of very electron-rich heterocycles, such as benzofuran, N-tosylpyrrole, or N-indole, with benzamide (1a) and ethyl glyoxalate (2a) led to the selective formation of the double addition products of type 10 (Scheme 5). Using the less active iron catalyst, heteroarylglycines 7g, 7i, and 7k could be isolated in 51, 62, and 74% yield, respectively. Both methods are not limited to ethyl glyoxalate as the aldehyde component (Scheme 6). Reactions with different glyoxalates, such as isopropyl glyoxalate (2b) furnished the desired amino acid derivative 11a in 50 and 83% yield. Even free glyoxylic acid, used as aqueous solution, can be employed as aldehyde source, thereby providing the free acid 11b in 71 and 81% yield. Reactions with carbamates, such as urethane or the Fmoc-derivative, afforded the N-protected arylglycines 11c and 11d in 45–92% yield. Especially, the Fmoc-protected acid 11d would be an ideal starting material for solid-phase peptide synthesis with unnatural amino acid derivatives. In the case of the carbamates, iron catalysis proved to be more reliable and furnished the desired products in higher yields and purity.

**Limitations**

In general, similar yields were obtained with bismuth and iron catalysis. In the case of competing regioisomer formation, reactions with Bi(OTf)₃ gave consistently higher regioselectivities. During our studies on the scope of the
arene component, a significant difference was observed in the reactivity for very electron-rich as well as for unreactive aromatics (Scheme 7). These differences in reactivity are most probably associated with the activity of the used catalyst. For very reactive, electron-rich arenes, such as dimethoxybenzenes, anthracene, or anisidine derivatives, the less active iron catalyst proved to be advantageous. The amidoalkylated arenes 12a-j were obtained in 63–89% yield. Reactions of electron-rich arenes in combination with the more active Bi(OTf)3 gave the corresponding products in lower yields or did not afford the product at all. In these cases, the competing formation of diarylmethane derivatives was observed in significant quantities (cf. Scheme 5).

For free phenols, such as 4-bromophenol, bismuth catalysis proved to be advantageous and furnished the glycine derivative 12g in 65% yield (vs 11% with Fe3+). With iron catalysts oxidative coupling reactions of the phenol were observed. In the case of less reactive arenes, such as o-xylene, the more active bismuth catalyst proved to be more efficient and afforded the arylglycine in 89% yield (vs 54% with Fe3+ catalysis). Bi(OTf)3 could even catalyze the reaction of toluene, furnishing product 12j in 50% yield. In the case of iron catalysis no product formation was observed with toluene.

Although the lower catalytic activity of the iron salts might look like a disadvantage at the first glance, it proved to be a major advantage in terms of practicability. Commercially available, technical ethyl glyoxalate, is commonly provided as a solution of the polymer form in toluene. In the case of Bi-catalyzed reactions, toluene has to be removed prior to the reaction to avoid the formation of 12j as side-product. For iron-catalyzed reactions the commercially available solution can be used without further processing, thereby leading to a more straightforward procedure.

Also in the case of less reactive amide components, the higher catalytic activity of Bi(OTf)3 proved to be beneficial (Scheme 8). Bi(OTf)3-catalyzed reactions with cyclic secondary amides or carbamates afforded the desired products 14a and 14b in 63 and 80% yield. No product formation...
with iron catalysts was observed. Acyclic secondary amides or carbamates proved to be unreactive using either bismuth or iron catalysis.

Interestingly, Bi(OTf)₃ was able to catalyze reactions with different sulfonamides as amide component (Scheme 9). The corresponding N-sulfonylated arylglycines 16a–c were obtained in 54–79% yield. Presumably, Bi(OTf)₃ is active enough to catalyze the addition of arenes to in situ less electrophilic N-sulfonylimines.


diagram

Scheme 9 Substrate scope with sulfonamides. Yields are given for the isolated products.

**Investigations into Stereoselective Reactions**

Since most of the natural α-aryl glycines exist in one enantiomeric form, stereoselective synthesis of these compounds would be highly desirable. Therefore, we decided to investigate a possible asymmetric version of our three-component reactions (Scheme 10). The most obvious approach would be the use of chiral ligands in our transformation. Hence various common chiral ligands were tested in combination with different Bi³⁺ or Fe³⁺ salts (Scheme 10). Unfortunately, no asymmetric induction was observed using various metal–ligand combinations, solvents, or temperatures (Scheme 10). In further studies using different ligands and variations of the amide or arene component as well as In³⁺ and Yb³⁺, promising Lewis acids in our initial screening, were studied. Again no asymmetric induction was observed.


diagram

Scheme 10 Unsuccessful enantioselective approaches

Since no enantioselective version of the three-component reaction could be realized with chiral catalysts, we decided to explore diastereoselective reactions with chiral amide components (Schemes 11–13).

For first tests chiral carbamates based on the Evans auxiliary were selected (Scheme 11). However, chiral oxazolidinones, such as 20a and 20b, did not furnish the desired products under our standard reaction conditions. Whereas 20b did not react at all, an interesting reactivity was observed for oxazolidinone 20a. The bismuth-catalyzed reaction of 20a furnished cyclic amino acid derivative 21 in 84% yield as single diastereomer (Scheme 12). Formation of the cyclic product can be rationalized by an intramolecular addition of the phenyl moiety to the formed N-acylimine. Even in the presence of excess of mesitylene no intermolecular addition was observed. Therefore, we next selected chiral primary amides as potential chiral starting materials for our three-component reaction.


diagram

Scheme 11 Unsuccessful diastereoselective approach using Evans-type carbamates

Reaction of phthalimide-protected valine amide 22 with ethyl glyoxalate (2a) and mesitylene (3b) furnished the expected product 23 in 84% with Bi(OTf)₃ and 78% yield with FeCl₃·6H₂O (Scheme 13). Only moderate diastereoselectivities (67:33 and 65:35) were observed. Variation of the temperature, solvent, or catalyst did not improve the stereoselectivity. Replacing the amide protecting group by a carbamate, led to a diminished diastereoselectivity and a drastic decrease in isolated yields. Reactions with amide-protected valine amides did not furnish any desired product at all. In summary, all our approaches to stereoselective reactions did not lead to the expected results. Only in the case of chiral amide components moderate stereoselectivi-
ties could be achieved. Therefore, further studies into the field of asymmetric three-component reactions were not pursued.

**Scheme 13** Reaction of N-protected valine amide 22. Yields are given for the isolated products. Phth = phthaloyl, PG = protecting group.

**Mechanistic Investigations**

In order to gain further insight into the reaction mechanism and the different catalytic activities of Bi(OTf)₃ and Fe³⁺ salts, a series of experiments were performed. First the progress of the reaction between benzamide (1a), ethyl glyoxalate (2a), and mesitylene (3b) in the presence of different catalysts as well as catalyst loadings was monitored by gas chromatographic analysis (Scheme 14, Figures 2 and 3).

**Scheme 14** Model reaction for kinetic experiments

In order to obtain a clearer distinction between the different systems, the reaction was performed at a slightly decreased temperature of 60 °C. Initially we compared the rates for conversion of the limiting starting material, benzamide (1a), and product formation with 5 mol% of Bi(OTf)₃ and 5 mol% Fe(ClO₄)₃. In both cases an interesting observation was made: the rates of benzamide conversion and product formation deviate significantly from each other at the onset of the reaction (Figure 2).

In the case of Fe(ClO₄)₃, a fast conversion of the benzamide (20% conversion after 10 min and 70% after 45 min) was observed. However, the rate of product formation was slower (<1% yield after 10 min and 50% yield after 45 min). Similar observations were made with 5 mol% of Bi(OTf)₃ (20% and 45% conversion vs 2% yield and 30% yield after 10 and 45 min, respectively). Since in both cases the yield of α-arylglucine 4b exceeded 90% after 24 hours reaction time, no unproductive side-reactions of benzamide can account for the fast conversion of the amide component. Therefore, formation of some kind of productive intermediate, most probably by the reaction of two of the three components, has to take place.

As can be seen from Figure 3, Fe(ClO₄)₃ catalyzes the reaction with a higher efficiency than Bi(OTf)₃, both at high (5 mol%) and low (1 mol%) catalyst loading. With 5 mol% Fe(ClO₄)₃, 64% of the amidoalkylated product is observed after 60 minutes, compared to only 28% with 5 mol% Bi(OTf)₃. As expected, reduction of the catalyst loading to 1 mol% leads to a considerable decrease in the reaction rate (Figure 3).

Interestingly, FeCl₃·6H₂O displays the lowest catalytic activity. After 50 minutes at 60 °C, only 5% product formation was observed with 5 mol% FeCl₃·6H₂O. Presumably, a facile dissociation of the noncoordinating counterions to form an active metal catalyst is crucial for a high activity.³¹ We have to emphasize that under our standard reaction conditions (80 °C; 16 h, 24 h, respectively) all three catalysts [Fe(ClO₄)₃, FeCl₃·6H₂O, and Bi(OTf)₃] give similar yields at 5 mol% and even 2 mol% loadings (>90% in all cases). To our surprise, Bi(OTf)₃, the catalyst with the best performance with less reactive arenes, displayed an inferior activity compared to Fe(ClO₄)₃ in the reaction with mesitylene.
(Figure 3). Therefore, Fe(ClO₄)₃ is the catalyst of choice for more reactive arenes, considering the activity and the economic and ecologic aspects of iron(III) salts.

As outlined in the introduction, our first rationale for the development of these three-component reactions was the in situ formation of a reactive N-acylimine species. Initial experiments indicated the formation of a two-component adduct of benzamide with one of the other starting materials (Figure 2). Therefore, we examined the reaction between benzamide (1a) and ethyl glyoxalate (2a) in the presence of 5 mol% Fe(ClO₄)₃ or 5 mol% Bi(OTf)₃ (Scheme 15). At room temperature quantitative formation of N,O-hemiaminal 24a is observed within 24 hours (Scheme 15). Longer reaction times (96 h) or heating to 80 °C led to the formation of bisamide 25a, insoluble in most common organic solvents, in almost quantitative yields. Indeed, the formation and precipitation of bisamide 25 could be observed in some of our three-component reactions. During the reaction the bisamide 25a is consumed completely and at the end the reaction mixture becomes homogenous again. Due to the insolubility of bisamide 25a and the instability of bisamide 25a and hemiaminal 24a, we were not able to quantify the amount of both intermediates during the course of the reaction with the analytical methods available at our department (GC, HPLC, React-IR, or NMR). Neither were we able to detect any reactive N-acylimine species. As expected, the reaction of benzamide (1a) and mesitylene (3b) in the presence of an iron or bismuth catalyst did not furnish any new product at all (Scheme 15). Treatment of either hemiaminal 24a or bisamide 25a, both known precursors for acylimines, with Bi(OTf)₃ or Fe(ClO₄)₃ and mesitylene (3b) led to the expected formation of the aryl glycine derivative 4b in 85 and 83% yield. To elucidate further reaction pathways, the two-component reaction of mesitylene (3b) with ethyl glyoxalate (2a) was investigated next. Both 2 mol% Bi(OTf)₃ and 2 mol% Fe(ClO₄)₃ furnished the double addition product 26 in 70–74% yield. Formation of such diarylmethane products was already observed in the case of more reactive (hetero)arenes (cf. Scheme 5) and is described in the literature. Addition of a ligand, 2,2’-bipyridine (bipy) to the iron-catalyzed reaction, enabled the controlled synthesis of monoaddition product 27 in 66% yield. Alcohol 27 is the presumed intermediate in the synthesis of diarylmethane products of type 26. We next examined alcohol 27 as a possible intermediate in our three-component reaction. Treatment of 27 with 1.0 equivalent of benzamide and 2.0 equivalents of mesitylene under our standard reaction conditions did furnish the expected product 4b and diarylmethane derivative 26 in less than 5% yield, using either Bi(OTf)₃ or Fe(ClO₄)₃. These experiments indicate that alcohol 27 is not involved in the main reaction pathway. On the basis of these results, we assume the following mechanism (Scheme 15). In the first step, the amide adds to the glyoxylic acid derivative 2 to form hemiaminal 24. Elimination of water furnishes a reactive acylimine species 28. Trapping of this highly electrophilic imine with a second molecule of the amide gives bisamide 25, observed intermediate in some of our three-component reactions. The fast addition of a second amide is not surprising, if one considers the higher nucleophilicity of the amide nitrogen. Under the reaction conditions, bisamide 25, favored under kinetic control, can decompose to yield the reactive N-acylimine 28. In the presence of a suitable, nucleophilic arene, the N-acylimine can undergo an aza-Friedel–Crafts type reaction to afford the desired α-arylglycine product 4 containing a thermodynamically more stable C–C bond. The catalytic activity of the used catalyst greatly depends on two factors. On the one hand, the catalyst has to be stable in the presence of significant amounts of water, since up to 100 equivalents of water are generated during the course of the reaction (with respect to the catalyst).

On the other hand the catalyst has to promote the addition of the amide 1 to the glyoxalate 2 over the direct addition of the arene 3 to the aldehyde 2. Only the right combination of both reactivities leads to an efficient catalyst for these three-component reactions. In addition, the Lewis acidic catalyst could further activate the N-acylimine towards the addition of a nucleophile. This might partially explain the higher activity of Bi(OTf)₃, a strong Lewis acid, in reactions with less nucleophilic arenes. Another possible explanation for the high catalytic efficiency of bismuth as well as the observed improved regioselectivities is the activation of the arene component by the bismuth catalyst. Although Bi(III)-arene complexes have been reported in literature, we do not have any solid experimental evidence for an additional activation of the arene component. We assume that two factors contribute to the observed low stereoselectivities in our asymmetric approaches. The high intrin-
**Scheme 15** Mechanistic studies and postulated reaction pathway

**Postulated Mechanism:**

1. $\text{R}^1\text{NH}_2 + \text{R}^2\text{CO}_2\text{R}^3 + \text{L.A.} \rightarrow \text{R}^2\text{CO}_2\text{R}^3$ (fast formation of arylglycine)

2. Fast Lewis acid (L.A.) addition

3. Slow rate-determining step

4. $\text{R}^2\text{CO}_2\text{R}^3 + \text{L.A.} \rightarrow \text{R}^2\text{CO}_2\text{R}^3$ (slow equilibrium)

5. $\text{R}^2\text{CO}_2\text{R}^3 + \text{H}_2\text{O} \rightarrow \text{N-acylimine}$ (fast equilibrium)

6. $\text{N,O-hemiaminal}$

7. $\text{N,O-hemiaminal} + \text{L.A.} \rightarrow \text{bisamide}$

8. $\text{N,O-hemiaminal} + \text{H}_2\text{O} \rightarrow \text{acylimine}$

**Notes:**
- 1.0 equiv of $\text{R}^1\text{NH}_2$ and 1.0 equiv of $\text{R}^2\text{CO}_2\text{R}^3$ with 1.0 equiv of Lewis acid (L.A.) at 80 °C, 24 h in MeNO$_2$.
- 2.0 equiv of $\text{R}^1\text{NH}_2$ and 1.0 equiv of $\text{R}^2\text{CO}_2\text{R}^3$ with 1.0 equiv of Lewis acid (L.A.) at 80 °C, 24 h in MeNO$_2$.
- 2.5 equiv of $\text{R}^1\text{NH}_2$ and 2.0 equiv of $\text{R}^2\text{CO}_2\text{R}^3$ with 1.0 equiv of Lewis acid (L.A.) at 80 °C, 24 h in MeNO$_2$.
sic reactivity of N-acylimines leads to a low selectivity in general, both for the diastereoselective and enantioselective reactions. As reported in the literature, coordination of a Lewis acid to the N-acylimine takes place at the oxygen atom.\textsuperscript{34} This places the catalyst far away from the reactive center, thereby severely hampering any stereoselective induction by the ligand. Based on this assumption, one can rationalize that tailor-made sterically very demanding ligands should offer a solution to this problem. However, the catalytic activity of such encumbered systems might be too low for these types of multicomponent reactions.

**Conclusion and Outlook**

In summary, two general Bi(OTf)\textsubscript{3} and Fe\textsuperscript{3+}-catalyzed three-component reactions between amides, (hetero)arenes, and glyoxylic acid derivatives have been developed. Scope and limitations as well as advantages and disadvantages of both catalyst systems were investigated in detail. These investigations show that very cheap Fe\textsuperscript{3+} salts are the catalysts of choice in most reactions. The lower activity of iron-based catalysts offers an additional advantage in the case of very reactive arene components. On the other hand, the high activity of Bi(OTf)\textsubscript{3} significantly expands the scope of the three-component reaction and allows the utilization of less reactive arenes and sulfonamides. Investigations into potential asymmetric versions of the three-component reaction were unsuccessful. No enantioselective reaction was realized and the diastereoselective induction with chiral amide components was low to moderate. Mechanistic investigations indicate a reaction pathway via formation of a reactive, highly electrophilic acylimine followed by an aza-Friedel–Crafts–type reaction with the arene as nucleophilic component. These practical and operationally simple reactions enable the efficient and straightforward synthesis of N-protected arylglycines from simple commercial available starting materials and nontoxic catalysts. With water as the only generated side-product, these methods constitute a promising approach towards the sustainable synthesis of important α-amino acids.

For reactions and column chromatography, solvents were obtained from different commercial suppliers in >97% purity and used as received.

All reactions were performed without any precautions to exclude ambient air or moisture. TLC was performed on precoated aluminum sheets (silica gel 60 F254). The spots were visualized by using UV radiation, I\textsubscript{2}, or cerium(IV) ammonium molybdate. Flash column chromatography was performed by using Silica 60 (0.04–0.063 mm, 230–400 mesh). All yields refer to isolated yields of compounds estimated to be >95% pure, as determined by \textsuperscript{1}H NMR spectroscopy. Melting points are uncorrected.

N-(m-Tolyl)pivalamide, N-(3-methoxyphenyl)pivalamide, 1-methoxy-3,5-dimethylbenzene, 2-methoxy-naphthalene, 1-tosyl-1H-pyrrole, 1-tosyl-1H-indole, N-(o-tolyl)pivalamide, N-(2-methoxy-phenyl)pivalamide, N-(4-methoxyphenyl)pivalamide, methanesulfonamide, 4-methylbenzenesulfonamide, 4-methoxybenzenesulfonamide, 4-bromomethanesulfonamide, thiophene-2-sulfonamide, and 2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide were synthesized according to literature.\textsuperscript{16} Ethyl glyoxalate was obtained as 50 wt% solution in toluene. Glyoxylic acid was obtained as 50 wt% solution in H\textsubscript{2}O and used as received. All other starting materials were purchased from commercial sources and used without further purification. Fe(ClO\textsubscript{4})\textsubscript{3} was obtained as undefined hydrate (Fe(ClO\textsubscript{4})\textsubscript{3}·xH\textsubscript{2}O, yellow form, reagent grade) from different providers. The exact H\textsubscript{2}O content was determined by elemental analysis. Depending on the provider and storage time (or even the time for weighting out a defined amount for elemental analysis) Fe(ClO\textsubscript{4})\textsubscript{3} contained from one up to ten molecules of H\textsubscript{2}O. Therefore, the amount of Fe(ClO\textsubscript{4})\textsubscript{3} used is always calculated on anhyd Fe(ClO\textsubscript{4})\textsubscript{3}. No changes in catalytic activity were observed for different batches of Fe(ClO\textsubscript{4})\textsubscript{3}, or upon prolonged storage times. No special precautions were taken to avoid exposure of Fe(ClO\textsubscript{4})\textsubscript{3} to moisture. Caution! Perchlorate salts are known to be shock-sensitive and are potential explosives. They should be handled with care and the necessary precautions. Since most of these properties are associated with anhyd perchlorate salts, we strongly advise to use the hydrated form of Fe(ClO\textsubscript{4})\textsubscript{3}. Under no circumstances should Fe(ClO\textsubscript{4})\textsubscript{3} be dried or handled in its anhydrous form. Since similar yields are obtained even with the decahydrate Fe(ClO\textsubscript{4})\textsubscript{3}·10H\textsubscript{2}O, this is not necessary. Special precautions should be taken to avoid accidental drying of the perchlorate, for example, by accidental evaporation of the solvent from the reaction. During our studies we never encountered problems associated with Fe(ClO\textsubscript{4})\textsubscript{3}. Even prolonged heating of Fe(ClO\textsubscript{4})\textsubscript{3} in MeNO\textsubscript{2} up to 120 °C did not lead to any decomposition. (In fact it is known the anhydrous LiClO\textsubscript{4} is stable in Et\textsubscript{2}O at temperatures up to 140–150 °C. For further information on perchlorate safety and stability, we recommend the article of Long.\textsuperscript{35})

Anhyd Bi(OTf)\textsubscript{3} was obtained from different providers and used directly. No special precautions were taken to avoid exposure of Bi(OTf)\textsubscript{3} to moisture. Therefore, we cannot rule out the formation of Bi(OTf)\textsubscript{3}·H\textsubscript{2}O during storage. Indeed, depending on the provider and storage time (or even the time for weighting out a defined amount for elemental analysis) Bi(OTf)\textsubscript{3} contained up to six molecules of water. However, no changes in catalytic activity and yield even upon prolonged storage (>1 year) were observed. Therefore, the amount of Bi(OTf)\textsubscript{3} used is always calculated on anhyd Bi(OTf)\textsubscript{3}. The actual catalyst loading for particular reactions might be slightly lower, depending on the batch quality and storage time.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded at 300, 400, or 500 MHz and 75, 101, or 126 MHz, respectively. Chemical shifts are reported as δ-values relative to the residual CDCl\textsubscript{3} or DMSO-d\textsubscript{6} peak (δ = 7.26 for \textsuperscript{1}H and δ = 77.16 for \textsuperscript{13}C; δ = 2.50 for \textsuperscript{1}H and δ = 39.52 for \textsuperscript{13}C). Coupling constants (J) are given in Hz and standard abbreviations are used for signal multiplicities.

Mass spectra (MS) were measured using ESI (electrospray ionization) techniques. High-resolution mass spectra (HRMS) were measured using MALDI (Matrix-assisted Laser Desorption/Ionization) techniques. IR spectra were recorded on an FTIR (Fourier transform infrared spectroscopy) spectrophotometer including a diamond universal ATR sampling technique (attenuated total reflectance) from 4000–400 cm\textsuperscript{-1}. The absorption bands were reported in wave numbers (cm\textsuperscript{-1}).

**Three-Component Synthesis of α-Arylglycines; General Procedure (GP)**

A 10 mL screw cap vial was charged with the respective iron salt (1–5 mol%) or Bi(OTf)\textsubscript{3} (1–5 mol%), the appropriate amide (1.0 equiv), and MeNO\textsubscript{2} (4.0 mL/mmol amide) or DCE wherever applicable. Ethyl glyoxalate (1.2 equiv) and the appropriate aromatic compound...
Ethyl 2-Benzamido-2-(2,4-dimethylphenyl)acetate (4a)

**Bi Catalysis:** Compound 4a was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), m-xylene (0.37 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 1 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (78 mg, 9%; ratio of regioisomers \( r_{\text{r}} = 98:2 \)). Further purification of the major regioisomer could be achieved by precipitation from hexane/CH₂Cl₂ (\( r_{\text{r}} = 78:22 \), as judged by 1H NMR analysis). Analytical data were obtained for this purified regioisomer.

**MS (ESI):** \( [M + H]^{+} \) calcd for C₁₉H₂₁NO₃: 314.1384; found: 314.1387.

**IR (ATR):** 3319 (m), 2980 (w), 1727 (s), 1632 (s), 1597 (w), 1570 (w), 1526 (s), 1490 (w), 1364 (w), 1287 (m), 1259 (s), 1232 (w), 1119 (m), 1053 (s), 929 (w), 872 (s), 810 (w), 774 (w), 722 cm⁻¹ (m).

**1H NMR (400 MHz, CDCl₃):** \( \delta = 7.78–7.68 (d, J = 7.3, 2 H), 7.52–7.40 (m, 3 H), 7.17 (d, J = 7.3 Hz, 2 H), 7.07–6.96 (m, 3 H), 5.93 (d, J = 7.1 Hz, 1 H), 4.31–4.11 (m, 2 H), 2.52 (s, 3 H), 2.30 (s, 3 H), 1.23 (t, \( J = 7.1 \) Hz, 3 H).

**13C NMR (101 MHz, CDCl₃):** \( \delta = 171.8, 166.7, 138.4, 136.9, 133.9, 132.5, 132.0, 128.7, 127.4, 127.3, 126.4, 62.0, 53.5, 21.2, 19.6, 14.2.

**MS (ESI):** \( m/z [M + Na]^+ \) calcd for C₁₉H₂₂NO₄Na: 336.1; found: 336.4.

**HRMS (MALDI):** \( m/z [M + H]^+ \) calcd for C₁₉H₂₂NO₄: 314.1387; found: 314.1384.

**Ethyl 2-Benzamido-2-mesitylacetae (4b)**

**Bi Catalysis:** Compound 4b was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.7 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 1 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (308 mg, 95%).

**Fe Catalysis:** Compound 4b was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl₃·6H₂O (3 mg, 0.010 mmol, 2 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (153 mg, 94%).
Ethyl 2-Benzamido-2-(4-methoxy-2-methylphenyl)acetate (4e)

**Bi Catalysis**: Compound 4e was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), 2-chloroanisole (0.38 mmol, 3.0 equiv) and Fe(ClO₄)₃ (10 mg, 0.02 mmol, 2 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (266 mg, 77%; r.r. = >98:2).

**Fe Catalysis**: Compound 4e was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), 2-chloroanisole (0.38 mmol, 3.0 equiv) and Fe(ClO₄)₃ (18 mg, 0.05 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (205 mg, 63%; r.r. = >98:2).

1H NMR (400 MHz, CDCl₃): δ = 7.27 (d, J = 7.4 Hz, 2 H), 7.18 (d, J = 7.4 Hz, 1 H), 7.32 (d, J = 7.4 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 2.35 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 142.3, 129.1, 128.8, 128.5, 127.7, 118.8, 117.2, 114.0, 56.6, 22.6.


HRMS (MALDI): m/z [M + H]+ calcd for C₁₉H₂₂NO₄: 328.1543; found: 328.1543.

Ethyl 2-Benzamido-2-(2-methoxy-5-methylphenyl)acetate (4f)

**Bi Catalysis**: Compound 4f was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 1-methoxy-4-methylbenzene (0.19 mL, 1.5 mmol, 3.0 equiv) and Bi(Otf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (102 mg, 62%; r.r. = >98:2).

**Fe Catalysis**: Compound 4f was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), 1-methoxy-4-methylbenzene (0.38 mmol, 3.0 equiv) and Fe(ClO₄)₃ (18 mg, 0.05 mmol, 5 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (205 mg, 63%; r.r. = >98:2).

1H NMR (400 MHz, CDCl₃): δ = 7.82–7.77 (m, 2 H), 7.52–7.46 (m, 1 H), 7.42 (t, J = 7.1 Hz, 1 H), 7.25 (d, J = 8.1 Hz, 1 H), 7.10 (d, J = 8.1 Hz, 1 H), 6.80 (d, J = 8.3 Hz, 1 H), 1.68 (s, 3 H), 1.20 (t, J = 7.9 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 171.1, 166.6, 158.1, 134.0, 131.9, 129.7, 128.7, 128.4, 127.5, 127.3, 126.1, 110.3, 62.0, 56.5, 55.5, 16.4, 14.2.

MS (ESI): m/z [M + Na]+ calcd for C₁₉H₂₁NO₄Na: 351.0; found: 350.3.

HRMS (MALDI): m/z [M + H]+ calcd for C₁₉H₂₂NO₄: 328.1543; found: 328.1543.

Ethyl 2-Benzamido-2-(3-chloro-4-methoxyphenyl)acetate (4g)

**Bi Catalysis**: Compound 4g was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), 2-chloroanisole (0.38 mmol, 3.0 equiv) and Fe(ClO₄)₃ (18 mg, 0.05 mmol, 5 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (266 mg, 77%; r.r. = >98:2).

**Fe Catalysis**: Compound 4g was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), 2-chloroanisole (0.38 mmol, 3.0 equiv) and FeCl₃·6H₂O (14 mg, 0.05 mmol, 5 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (235 mg, 68%; r.r. = >98:2).

1H NMR (400 MHz, CDCl₃): δ = 7.37–7.31 (m, 3 H), 7.25–7.15 (m, 1 H), 6.80 (d, J = 6.5 Hz, 1 H), 1.28 (s, 3 H), 1.25 (s, 3 H), 1.27–1.16 (m, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 141.9, 129.4, 128.6, 128.3, 127.7, 127.5, 127.3, 127.1, 121.8, 116.6, 112.2, 111.9, 62.0, 55.7, 55.4, 53.3, 21.8, 19.9, 14.2 (peaks not assigned to regioisomers).
1H NMR (400 MHz, CDCl3): δ = 7.85–7.79 (m, 2 H), 7.55–7.41 (m, 4 H), 7.33 (dd, J = 8.5, 2.2 Hz, 1 H), 7.19 (d, J = 6.6 Hz, 1 H), 6.93–6.89 (m, 1 H), 5.67 (d, J = 6.8 Hz, 1 H), 4.32–4.15 (m, 2 H), 3.89 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 170.8, 166.4, 155.1, 133.5, 131.9, 130.0, 128.9, 128.7, 127.2, 127.0, 123.0, 112.2, 62.3, 56.2, 55.9, 14.03.


Ethyl 2-Benzamido-2-(3-bromo-4-methoxyphenyl)acetate (4h)

Bi Catalysis: Compound 4h was synthesized according to the GP from benzamide (121 mg, 1.0 mmol) ethyl glyoxalate (0.30 mL, 1.5 mmol, 1.5 equiv), 2-bromoanisole (0.37 mL, 3.0 mmol, 3.0 equiv), and Bi(OI)3 (13 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (344 mg, 74%).

IR (ATR): 3390 (w), 2362 (w), 1840 (s), 1655 (s), 1600 (w), 1579 (w), 1518 (m), 1483 (s), 1347 (w), 1286 (m), 1259 (m), 1214 (s), 1180 (s), 1153 (m), 1097 (w), 1048 (m), 1012 (s), 972 (w), 799 (m), 714 cm–1 (s).

1H NMR (400 MHz, CDCl3): δ = 7.86–7.78 (m, 3 H), 7.56–7.38 (m, 4 H), 7.17 (d, J = 6.6 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 1 H), 5.65 (d, J = 6.8 Hz, 1 H), 4.32–4.15 (m, 2 H), 3.87 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 171.0, 166.6, 158.4, 138.2, 133.7, 132.1, 131.1, 129.0, 128.8, 127.3, 111.1, 86.5, 62.4, 56.6, 55.7, 14.1.

MS (ESI): m/z [M + H]+ calcd for C18H19BrNO4: 392.1; found: 392.1.

HRMS (MALDI): m/z [M + H]+ calcd for C18H17BrNO4: 439.0; found: 439.2.

Ethyl 2-Benzamido-2-(5-bromo-2-methoxyphenyl)acetate (4j)

Bi Catalysis: Compound 4j was synthesized according to the GP from benzamide (121 mg, 1.0 mmol) ethyl glyoxalate (0.24 mL, 1.2 mmol), 4-bromoanisole (0.38 mL, 3.0 mmol, 3.0 equiv), and Bi(OI)3 (33 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 16 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (161 mg, 41%).

IR (ATR): 3390 (w), 2362 (w), 1840 (s), 1655 (s), 1600 (w), 1579 (w), 1518 (m), 1483 (s), 1347 (w), 1286 (m), 1259 (m), 1214 (s), 1180 (s), 1153 (m), 1097 (w), 1048 (m), 1012 (s), 972 (w), 799 (m), 714 cm–1 (s).

1H NMR (400 MHz, CDCl3): δ = 7.85–7.79 (m, 2 H), 7.53–7.41 (m, 4 H), 7.28–7.24 (m, 1 H), 6.82–6.75 (m, 1 H), 6.18 (dd, J = 6.6 Hz, 1 H), 5.60 (d, J = 6.7 Hz, 1 H), 4.32–4.16 (m, 2 H), 3.89 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 170.7, 166.6, 156.2, 133.7, 132.1, 130.6, 128.8, 127.9, 127.3, 112.3, 112.2, 62.4, 56.5, 55.9, 14.2.


HRMS (MALDI): m/z [M + H]+ calcd for C18H17BrNO4: 439.0; found: 439.2.

Ethyl 2-Benzamido-2-(5-iodo-2-methoxyphenyl)acetate (4k)

Bi Catalysis: Compound 4k was synthesized according to the GP from benzamide (121 mg, 1.0 mmol) ethyl glyoxalate (0.24 mL, 1.2 mmol), 4-iodoanisole (0.38 mL, 3.0 mmol, 3.0 equiv), and Bi(OI)3 (33 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 16 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (132 mg, 34%).

IR (ATR): 3390 (w), 2362 (w), 1840 (s), 1655 (s), 1600 (w), 1579 (w), 1518 (m), 1483 (s), 1347 (w), 1286 (m), 1259 (m), 1214 (s), 1180 (s), 1153 (m), 1097 (w), 1048 (m), 1012 (s), 972 (w), 799 (m), 714 cm–1 (s).

1H NMR (400 MHz, CDCl3): δ = 7.86–7.78 (m, 2 H), 7.56–7.44 (m, 2 H), 7.17 (d, J = 6.6 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 1 H), 5.65 (d, J = 6.8 Hz, 1 H), 4.32–4.15 (m, 2 H), 3.87 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl3): δ = 170.7, 166.6, 158.4, 138.2, 133.7, 132.1, 131.1, 129.0, 128.8, 127.3, 111.1, 86.5, 62.4, 56.6, 55.7, 14.1.
Ethyl 2-Benzamido-2-(5-dimethylphenyl)acetate (4l)

**Bi Catalysis**: Compound 4l was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), p-xylene (0.19 mL, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 12 h at 100 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a yellow solid (45 mg, 32%).

**Fe Catalysis**: Compound 4l was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), p-xylene (0.19 mL, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless oil (77 mg, 40%).

**IR (ATR)**: 3362 (w), 2981 (w), 2863 (s), 1741 (m), 1711 (s), 1652 (s), 1627 (s), 1593 (s), 1577 (s), 1543 (s), 1484 (m), 1455 (m), 1391 (w), 1368 (m), 1322 (m), 1297 (m), 1265 (s), 1238 (s), 1204 (s), 1188 (s), 1130 (m), 1103 (m), 1023 (s), 913 (m), 862 (m), 831 (m), 801 (m), 771 (m), 713 (s), 692 (m), 647 (m), 630 (m), 589 (m), 541 (m), 473 cm⁻¹ (s).

**HRMS (MALDI)**: m/z [M + H]⁺ calcd for C₁₈H₁₉INO₄: 440.0347; found: 440.0347.

**Ethyl 2-Benzamido-2-(3,4,5-trimethoxyphenyl)acetate (4o)**

**Bi Catalysis**: Compound 4o was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), ethyl 4-methoxybenzoate (360 mg, 2.0 mmol, 4.0 equiv), and Bi(OTf)₃ (16 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 72 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow oil (77 mg, 40%; r.r. = 98:2).

**Fe Catalysis**: Compound 4o was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), ethyl 4-methoxybenzoate (270 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow oil (128 mg, 66%; r.r. = 71:28); R₉ = 0.3 (hexane/EtOAc = 7:3).

**IR (ATR)**: 3342 (w), 2963 (w), 2843 (w), 1741 (m), 1711 (s), 1650 (s), 1608 (s), 1585 (m), 1544 (m), 1484 (m), 1455 (m), 1402 (m), 1391 (w), 1368 (m), 1322 (m), 1297 (m), 1265 (s), 1238 (s), 1204 (s), 1188 (s), 1130 (m), 1103 (m), 1023 (s), 913 (m), 862 (m), 831 (m), 801 (m), 771 (m), 713 (s), 692 (m), 647 (m), 630 (m), 589 (m), 541 (m), 473 cm⁻¹ (s).

**HRMS (MALDI)**: m/z [M + H]⁺ calcd for C₁₈H₁₉INO₄: 397.2122; found: 397.2182.

**Ethyl 3-(1-Benzamido-2-ethoxy-2-oxoethyl)-4-methoxybenzoate (4n)**

**Bi Catalysis**: Compound 4n was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), ethyl 4-methoxybenzoate (360 mg, 2.0 mmol, 4.0 equiv), and Bi(OTf)₃ (16 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 72 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow oil (77 mg, 40%; r.r. = 98:2).

**Fe Catalysis**: Compound 4n was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), ethyl 4-methoxybenzoate (270 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow oil (128 mg, 66%; r.r. = 71:28); R₉ = 0.3 (hexane/EtOAc = 7:3).

**IR (ATR)**: 3342 (w), 2963 (w), 2843 (w), 1741 (m), 1711 (s), 1650 (s), 1608 (s), 1585 (m), 1544 (m), 1484 (m), 1455 (m), 1402 (m), 1391 (w), 1368 (m), 1322 (m), 1297 (m), 1265 (s), 1238 (s), 1204 (s), 1188 (s), 1130 (m), 1103 (m), 1023 (s), 913 (m), 862 (m), 831 (m), 801 (m), 771 (m), 713 (s), 692 (m), 647 (m), 630 (m), 589 (m), 541 (m), 473 cm⁻¹ (s).

**HRMS (MALDI)**: m/z [M + H]⁺ calcd for C₁₈H₁₉INO₄: 397.2122; found: 397.2182.
The product was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 1.2 equiv), 1-dialkylamino-2,2′-bipyridine (0.06 mmol, 6 mol%, 9 mg) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (cyclohexane/MeOAc = 9:1) yielded the product as an orange oil (85 mg, 58%; Rₚ = 0.23 (cyclohexane/MeOAc = 7:3). IR (ATR): 3343 (w), 3286 (w), 2979 (w), 2871 (w), 1737 (s), 1714 (s), 1589 (m), 1500 (m), 1378 (s), 1278 (s), 1240 (s), 1161 (s), 1129 (s), 1105 (s), 881 (m), 710 (s), 627 (s), 616 (s), 590 (m), 546 (m), 526 (m), 502 cm⁻¹ (s).

**Bi Catalysis:** Compound 4p was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-methoxynaphthalene (237 mg, 1.5 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (n-hexane/MeOAc = 4:1) yielded the product as an orange oil (89 mg, 49%). IR (ATR): 3449 (w), 3319 (w), 2979 (w), 2841 (w), 2099 (w), 1739 (s), 1651 (s), 1626 (m), 1598 (m), 1580 (m), 1560 (m), 1512 (s), 1482 (s), 1473 (s), 1445 (m), 1386 (s), 1367 (m), 1319 (s), 1267 (s), 1251 (s), 1204 (s), 1158 (s), 1147 (s), 1086 (s), 1024 (s), 906 (m), 888 (w), 864 (m), 848 (m), 810 (s), 783 (m), 708 (s), 692 (s), 672 (m), 645 (m), 605 (m), 589 (m), 546 (m), 526 (m), 502 cm⁻¹ (s).

1H NMR (400 MHz, CDCl₃): J = 7.3 Hz, 1 H), 4.31–4.15 (m, 2 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 171.5, 166.7, 154.3, 151.8, 142.2, 134.3, 131.8, 128.7, 127.3, 124.6, 123.5, 117.3, 113.6, 110.9, 62.0, 61.4, 55.5, 55.0, 52.5, 50.2, 21.5, 20.8, 19.9, 14.2, 14.1 (peaks not assigned to regions).
Ethyl 2-Mesityl-2-(4-methoxybenzamido)acetate (5a)

**Bi Catalysis:** Compound 5a was synthesized according to the GP from 4-methoxybenzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)3 (7 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3) yielded the product as a colorless solid (166 mg, 94%).

**Fe Catalysis:** Compound 5a was synthesized according to the GP from 4-methoxybenzamide (73 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl3·6H2O (3 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (161 mg, 80%).

Ethyl 2-(4-Bromobenzamido)-2-mesitylacetate (5b)

**Bi Catalysis:** Compound 5b was synthesized according to the GP from 4-bromobenzamide (100 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)3 (7 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (161 mg, 80%).

**Fe Catalysis:** Compound 5b was synthesized according to the GP from 4-bromobenzamide (100 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl3·6H2O (3 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1 → 4:1) yielded the product as a colorless solid (172 mg, 85%).


Ethyl 2-(2-Chloroacetamido)-2-mesitylacetate (5d)

**Bi Catalysis:** Compound 5d was synthesized according to the GP from 2-chloroacetamide (47 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)3 (7 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1 → 7:3) yielded the product as a colorless oil (121 mg, 81%).

**Fe Catalysis:** Compound 5d was synthesized according to the GP from 2-chloroacetamide (47 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl3·6H2O (3 mg, 0.010 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1 → 7:3) yielded the product as a colorless oil (131 mg, 88%); Rf = 0.30 = (cyclohexane/EtOAc = 7:3).
IR (ATR): 3307 (w), 2975 (w), 1733 (s), 1660 (m), 1519 (m), 1463 (w), 1370 (w), 1311 (m), 1195 (s), 1150 (m), 1096 (m), 1017 (s), 925 (w), 853 (m), 769 cm⁻¹ (m).

1H NMR (400 MHz, CDCl₃): δ = 6.83 (s, 2 H), 6.68 (d, J = 6.0 Hz, 1 H), 5.96 (d, J = 6.7 Hz, 1 H), 4.30–4.06 (m, 2 H), 2.40 (s, 6 H), 2.24 (s, 3 H), 1.24–1.16 (m, 12 H).

13C NMR (101 MHz, CDCl₃): δ = 177.7, 172.0, 137.60, 137.0, 131.1, 130.1, 62.0, 52.4, 38.9, 27.7, 21.0, 20.4, 14.2.

MS (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃: 298.2064; found: 298.2064.

**Ethyl 4-Chromyl-2-bromobenzoate (5e)**

**Bi Catalysis:** Compound 5f was synthesized according to the GP from ethyl chromylate (71 mg, 0.10 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv) and Bi(OTf)₃ (7 mg, 0.01 mmol, 1 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (233 mg, 85%).

Ms (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃Br: 306.2064; found: 306.2064.

**Ethyl 4-Chromyl-2-bromobenzoate (5g)**

**Bi Catalysis:** Compound 5g was synthesized according to the GP from ethyl chromylate (71 mg, 0.10 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv) and FeCl₃·6H₂O (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3) yielded the product as a colorless solid (233 mg, 85%).

Ms (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃Br: 306.2064; found: 306.2064.

**Ethyl 4-Chromyl-2-bromobenzoate (5h)**

**Bi Catalysis:** Compound 5h was synthesized according to the GP from ethyl chromylate (71 mg, 0.10 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv) and FeCl₃·6H₂O (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3) yielded the product as a colorless solid (233 mg, 85%).

Ms (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃Br: 306.2064; found: 306.2064.

**Ethyl 2-Acrylamido-2-mesitylacetate (5i)**

**Bi Catalysis:** Compound 5j was synthesized according to the GP from ethyl 2-acrylamido-2-mesitylacetate (5h) (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv) and Bi(OTf)₃ (7 mg, 0.01 mmol, 1 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless oil (233 mg, 85%).

Ms (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃Br: 306.2064; found: 306.2064.

**Ethyl 2-Acrylamido-2-mesitylacetate (5j)**

**Bi Catalysis:** Compound 5j was synthesized according to the GP from ethyl 2-acrylamido-2-mesitylacetate (5h) (0.12 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv) and Bi(OTf)₃ (7 mg, 0.01 mmol, 1 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless oil (233 mg, 85%).

Ms (ESI): m/z [M + H]^+ calcld for C₁₆H₂₂NO₃Br: 306.2064; found: 306.2064.
**Synthesis**

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**Bi Catalysis**

**Ethyl 2-[[Benzyl(oxy)carbonyl]amino]-2-mesitylacetate (5i)**

**Bi Catalysis**: Compound 5i was synthesized according to the GP from benzyl carbamate (76 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OAc)3 (7 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3) yielded the product as a colorless solid (116 mg, 65%).

**IR (ATR)**: 3376 (w), 2981 (w), 1831 (w), 1718 (s), 1649 (w), 1611 (w), 1498 (m), 1369 (m), 1305 (s), 1195 (s), 1093 (s), 932 (m), 852 (m), 775 cm\(^{-1}\) (m).

**1H NMR**: 3.05 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.17–1.12 (m, 6 H), 5.15 (m, 2 H), 4.62–4.31 (m, 2 H), 2.37 (s, 6 H), 2.25 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H).

**13C NMR (126 MHz, CDCl3)**: δ = 171.6, 155.9, 137.5, 136.7, 131.2, 129.8, 61.7, 61.0, 53.7, 20.7, 20.0, 14.4, 14.0.

**MS (ESI):** m/z [M + H]+ calcd for C43H44NO4: 868.3163; found: 868.3170.

**HRMS (MALDI):** m/z [M + H]+ calcd for C43H44NO4: 868.3170; found: 868.3170.


**Bi Catalysis**: Compound 5k was synthesized according to the GP from (9H-fluoren-9-yl)methyl carbamate (239 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and FeCl\(_3\)-6H\(_2\)O (5 mg, 0.020 mmol, 2 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless oil (332 mg, 75%); R\(_f\) = 0.38 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3368 (w), 2956 (w), 1718 (s), 1498 (m), 1448 (m), 1305 (m), 1195 (s), 1050 (s), 852 (m), 739 (s), 621 cm\(^{-1}\) (m).

**1H NMR**: 3.04 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.15–1.06 (m, 6 H), 5.17–4.96 (m, 2 H), 2.37 (s, 6 H), 2.26 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H).

**13C NMR (75 MHz, CDCl3)**: δ = 171.4, 155.7, 144.1, 143.9, 137.9, 137.0, 131.1, 130.2, 127.8, 126.7, 62.0, 53.7, 21.0, 20.3, 14.2.

**MS (ESI):** m/z [M + Na]+ calcd for C28H29NO4Na: 466.2; found: 466.0.


**Bi Catalysis**: Compound 5k was synthesized according to the GP from (9H-fluoren-9-yl)methyl carbamate (239 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and FeCl\(_3\)-6H\(_2\)O (5 mg, 0.020 mmol, 2 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless oil (332 mg, 75%); R\(_f\) = 0.38 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3368 (w), 2956 (w), 1718 (s), 1498 (m), 1448 (m), 1305 (m), 1195 (s), 1050 (s), 852 (m), 739 (s), 621 cm\(^{-1}\) (m).

**1H NMR**: 3.04 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.15–1.06 (m, 6 H), 5.17–4.96 (m, 2 H), 2.37 (s, 6 H), 2.26 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H).

**13C NMR (75 MHz, CDCl3)**: δ = 171.4, 155.7, 144.1, 143.9, 137.9, 137.0, 131.1, 130.2, 127.8, 127.2, 125.2, 120.1, 67.3, 62.1, 53.8, 47.3, 21.0, 20.4, 14.2.

**MS (ESI):** m/z [M + Na]+ calcd for C28H29NO4Na: 466.2; found: 466.0.

Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (1.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a yellow solid (119 mg, 37%; Rᵣ = >98:2).

Fe Catalysis

Ethyl 2-((5-Bromothiophen-2-yl)-2-[(ethoxycarbonyl)amino]acetate (7b)

Bi Catalysis: Compound 7b was synthesized according to the GP from urethane (67 mg, 0.75 mmol, 1.5 equiv), ethyl glyoxalate (51 mg, 0.5 mmol, 1.0 equiv), 2-bromothiophene (0.16 mL, 1.5 mmol), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 60 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3) yielded the product as a yellow solid (161 mg, 50%; [M + Na]⁺ calcd for C₁₁H₁₄BrNO₄SNa: 358.0; found: 358.0).

IR (ATR): 3305 (m), 2983 (w), 2951 (w), 2904 (w), 1741 (s), 1686 (s), 1526 (m), 1499 (w), 1433 (m), 1372 (m), 1312 (m), 1257 (m), 1216 (s), 1107 (s), 1061 (s), 1038 (s), 963 (s), 810 (w), 800 (w), 780 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 6.91 (d, J = 3.7 Hz, 1 H), 6.82 (d, J = 3.7 Hz, 1 H), 5.53 (d, J = 7.4 Hz, 1 H), 4.31–4.20 (m, 2 H), 4.19–4.11 (m, 2 H), 1.31–1.23 (m, 6 H).

¹³C NMR (101 MHz, CDCl₃): δ = 165.9, 155.6, 141.1, 129.9, 126.3, 112.6, 62.6, 61.7, 53.8, 14.6, 14.2.

MS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₁₄BrNO₄SNa: 358.0; found: 358.1.

HRMS (MALDI): m/z [M + Na]⁺ calcd for C₁₁H₁₄BrNO₄SNa: 358.0; found: 358.1.

Bi Catalysis: Compound 7c was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), 2-chlorothiophene (0.28 mL, 3.0 mmol, 3.0 equiv), and Fe(ClO₄)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at rt. Purification by chromatography (cyclohexane/MeOH = 9:1–4:1) yielded the product as a colorless solid (97 mg, 64%; Rᵣ = >98:2).

IR (ATR): 3300 (w), 2978 (w), 2929 (w), 1983 (w), 1983 (w), 1739 (s), 1635 (s), 1579 (w), 1525 (s), 1587 (m), 1443 (m), 1369 (m), 1324 (m), 1290 (s), 1204 (s), 1166 (m), 1125 (m), 1086 (m), 1021 (m), 989 (m), 881 (m), 810 (m), 754 (m), 715 (s), 690 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 7.83 (d, J = 7.6 Hz, 2 H), 7.57–7.42 (m, 3 H), 7.12 (d, J = 6.3 Hz, 1 H), 6.95–6.76 (m, 2 H), 5.99–5.91 (m, 1 H), 4.37–4.23 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ = 169.7, 166.7, 140.7, 137.8, 133.4, 132.3, 130.5, 130.0, 128.9, 127.3, 126.6, 126.2, 125.7, 62.8, 52.6, 14.2 (peaks not assigned to regioisomers).

MS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₁₄ClNO₄SNa: 346.0; found: 346.2.

HRMS (MALDI): m/z [M + H]⁺ calcd for C₁₁H₁₂ClNO₃S: 324.0456; found: 324.0454.

Ethyl 2-((5-Chlorothiophen-2-yl)-2-[(ethoxycarbonyl)amino]acetate (7d)

Bi Catalysis: Compound 7d was synthesized according to the GP from urethane (67 mg, 0.75 mmol, 1.5 equiv), ethyl glyoxalate (51 mg, 0.5 mmol, 1.0 equiv), 2-chlorothiophene (0.16 mL, 1.5 mmol, 1.2 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (1.0 mL). The reaction mixture was stirred for 16 h at 60 °C. Purification by chromatography (cyclohexane/MeOH = 9:1–4:1) yielded the product as a yellow solid (76 mg, 52%; Rᵣ = >98:2).

IR (ATR): 3305 (m), 2983 (w), 2951 (w), 2904 (w), 1741 (s), 1686 (s), 1526 (m), 1499 (w), 1433 (m), 1372 (m), 1312 (m), 1295 (m), 1257 (m), 1216 (s), 1107 (s), 1061 (s), 1038 (s), 963 (s), 810 (w), 800 (w), 780 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 6.91 (d, J = 3.7 Hz, 1 H), 6.82 (d, J = 3.7 Hz, 1 H), 5.53 (d, J = 7.3 Hz, 1 H), 4.31–4.20 (m, 2 H), 4.19–4.11 (m, 2 H), 1.31–1.23 (m, 6 H).

¹³C NMR (101 MHz, CDCl₃): δ = 169.5, 155.6, 141.1, 129.9, 126.3, 112.6, 62.6, 61.7, 53.8, 14.6, 14.2.

MS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₁₄ClNO₄SNa: 358.0; found: 358.1.

HRMS (MALDI): m/z [M + K]⁺ calcd for C₁₁H₁₂ClNO₃SNaK: 373.9463; found: 373.9463.

Ethyl 2-Benzamido-2-(5-chlorothiophen-2-yl)acetate (7e)

Bi Catalysis: Compound 7e was synthesized according to the GP from benzamide (61 mg, 0.55 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-chlorothiophene (0.15 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 16 h at 60 °C. Purification by chromatography (cyclohexane/MeOH = 9:1–4:1) yielded the product as a yellow solid (119 mg, 37%; Rᵣ = >98:2).

Fe Catalysis

Ethyl 2-Benzamido-2-(5-methylthiophen-2-yl)acetate (7e)

Bi Catalysis: Compound 7e was synthesized according to the GP from benzamide (61 mg, 0.55 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-methylthiophene (0.15 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 2 mol%) in MeNO₂ (1.0 mL). The reaction mixture was stirred for 16 h at rt. Purification by chromatography (cyclohexane/MeOH = 4:1) yielded the product as a colorless solid (97 mg, 64%; Rᵣ = >89:11).

Fe Catalysis: Compound 7e was synthesized according to the GP from benzamide (61 mg, 0.55 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), 2-methylthiophene (0.15 mL, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL).
(2.0 mL). The reaction mixture was stirred for 24 h at 60 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a yellow solid (72 mg, 47%; r.r. = 88:12).

Mp 66–68 °C; Rf = 0.3 (cyclohexane/EtOAc = 4:1).

IR (ATR): 3315 (w), 2981 (w), 2917 (w), 1737 (s), 1637 (s), 1603 (m), 1542 (s), 1453 (m), 1369 (m), 1337 (s), 1284 (m), 1244 (m), 1172 (m), 1113 (s), 1063 (m), 982 (m), 892 (m), 833 (m), 783 (w), 753 (m), 733 (s), 693 (s), 626 (m), 601 (s), 579 (s), 557 (s), 537 (s), 522 (s), 505 (m), 480 (m), 472 cm–1 (m).

1H NMR (300 MHz, CDCl3): δ (major regioisomer) = 7.83–7.79 (m, 2 H), 7.54–7.41 (m, 3 H), 7.05 (br d, J = 5.5 Hz, 1 H), 6.92–6.89 (m, 1 H), 6.64–6.60 (m, 1 H), 5.95 (d, J = 7.4 Hz, 1 H), 4.36–4.18 (m, 2 H), 2.44 (s, 3 H), 1.32–1.22 (m, 3 H).

13C NMR (75 MHz, CDCl3): δ (major regioisomer) = 171.21, 170.29, 166.66, 140.68, 136.33, 133.80, 133.68, 132.04, 131.94, 128.73, 127.32, 127.25, 125.81, 125.26, 122.71, 63.39, 62.09, 52.63, 50.95, 15.43, 14.17, 13.25.

MS (ESI): m/z [M + H]+ calcd for C16H18NO3: 303.1; found: 304.3.

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Ethyl 2-(Ethoxycarbonyl)amino-2-(5-methylthiophen-2-yl)acetate (7g)

Fe Catalysis: Compound 7h was synthesized according to the GP from urethane (46 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), benzofuran (0.33 mL, 3.0 mmol, 3.0 equiv), and Fe(ClO4)3 (18 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 24 h at 60 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a yellow solid (128 mg, 88%; r.r. = >98:2).

Fe Catalysis: Compound 7h was synthesized according to the GP from urethane (89 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), 2-methylthiophene (0.15 mL, 1.5 mmol, 1.5 equiv), benzofuran (0.33 mL, 3.0 mmol, 3.0 equiv), and Fe(ClO4)3 (7 mg, 0.01 mmol, 2 mol%) in DCE (4.0 mL). The reaction mixture was stirred for 48 h at 40 °C. Purification by chromatography (cyclohexane/EtOAc = 14:6) yielded the product as a yellow oil (265 mg, 62%; r.r. = >98:2).

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Ethyl 2-[(Ethoxycarbonyl)amino]-2-(1-tosyl-1H-pyrrol-2-yl)acetate (7a)

**Bi Catalysis:** Compound 7a was synthesized according to the GP from urethane (46 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), N-tosylpyrrole (332 mg, 1.5 mmol, 3.0 equiv), and Fe(OTf)3 (17 mg, 0.03 mmol, 1 mol%) in DCE (2.0 mL). The reaction mixture was stirred for 16 h at 60 °C. Purification by chromatography (cyclohexane/MeOH = 9:1) yielded the product as a colorless oil (302 mg, 75%; r.r. = >98:2).

Ethyl 2-Benzamido-2-(1-tosyl-1H-indol-3-yl)acetate (7k)

**Fe Catalysis:** Compound 7k was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.66 mmol, 1.2 equiv), N-tosylindole (407 mg, 1.5 mmol, 3.0 equiv), and Fe(OTf)3 (9 mg, 0.025 mmol, 5 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 24 h at 60 °C. Purification by chromatography (n-hexane/MeOH = 9:1 = >7:3) yielded the product as a white low-melting foam (177 mg, 74%; r.r. = 82:18).

IR (ATR): 1739 (w), 1644 (w), 1520 (w), 1486 (w), 1447 (w), 1367 (m), 1171 (s), 1120 (m), 1089 (m), 979 (m), 812 (w), 746 (m), 703 (s), 666 (s), 570 (s), 536 cm⁻¹ (s).

H NMR (400 MHz, CDCl3): δ = 8.00–8.09 (m, 5 H), 6.65 (d, J = 7.4 Hz, 1 H), 4.40–4.41 (m, 2 H), 2.33 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H).

C NMR (101 MHz, CDCl3): δ = 176.0, 166.9, 145.4, 135.3, 135.1, 133.6, 132.1, 130.1, 129.9, 128.8, 127.3, 127.1, 125.4, 125.1, 123.8, 120.2, 118.0, 113.9, 62.4, 46.9, 21.7, 14.2.

**HRMS (MALDI):** m/z [M + Na]+ calcld for C26H24N2O5SNa: 467.1; found: 467.2.

HRMS (MALDI): m/z [M + Na]+ calcld for C26H23N2O5SNa: 472.1247; found: 472.1239.
Fe Catalysis: Compound 11a was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), isopropyl 2-oxoacetate (174 mg, 1.5 mmol, 1.5 equiv), mesitylene (0.42 mL, 3.0 mmol, 3.0 equiv), and FeCl(OTf)$_3$ (18 mg, 0.050 mmol, 5 mol%) in MeNO$_2$ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1 → 1:1) yielded the product as a colorless solid (281 mg, 83%).

13C NMR (126 MHz, DMSO-$d_6$): δ = 172.8, 156.1, 144.0, 143.7, 140.7, 136.9, 136.5, 131.9, 129.3, 127.7, 127.5, 125.5, 120.1, 65.9, 53.1, 46.7, 20.4, 20.0.

HRMS (MALDI): m/z [M + Na]$^+$ calcd for C$_{14}$H$_{19}$NO$_4$: 265.1; found: 264.2.

Fe Catalysis: Compound 11c was synthesized according to the GP from urethane (45 mg, 0.5 mmol, 1.0 equiv), glyoxylic acid (0.07 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl$_3$·6H$_2$O (7 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (CH$_2$Cl$_2$/MeOH = 50:1 → 20:1) yielded the product as a colorless oil (66 mg, 50%).

1H NMR (500 MHz, DMSO-$d_6$): δ = 12.84 (s, 1 H), 7.90–7.86 (m, 2 H), 7.86–7.81 (m, 1 H), 7.81–7.70 (m, 2 H), 7.44–7.38 (m, 2 H), 7.35–7.26 (m, 2 H), 6.83 (s, 2 H), 5.52 (d, J = 7.6 Hz, 1 H), 4.32–4.16 (m, 3 H), 2.28 (s, 6 H), 2.19 (s, 3 H).

IR (ATR): 3412 (w), 2920 (m), 2520 (w), 1735 (m), 1658 (m), 1536 (m), 1374 (m), 1295 (s), 1067 (s), 925 (s), 851 (cm$^{-1}$).

Fe Catalysis: Compound 11d was synthesized according to the GP from 9H-fluoren-9-yl carbamate (113 mg, 0.5 mmol, 1.0 equiv), glyoxylic acid (0.07 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)$_3$ (7 mg, 0.01 mmol, 2 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 7:3 → 1:1) yielded the product as a colorless oil (94 mg, 45%).

1H NMR (300 MHz, DMSO-$d_6$): δ = 12.84 (s, 1 H), 7.90–7.86 (m, 2 H), 7.86–7.81 (m, 1 H), 7.81–7.70 (m, 2 H), 7.44–7.38 (m, 2 H), 7.35–7.26 (m, 2 H), 6.83 (s, 2 H), 5.52 (d, J = 7.6 Hz, 1 H), 4.32–4.16 (m, 3 H), 2.28 (s, 6 H), 2.20 (s, 3 H).

IR (ATR): 3412 (w), 2920 (m), 2520 (w), 1735 (m), 1658 (m), 1536 (m), 1374 (m), 1295 (s), 1067 (s), 925 (s), 851 (cm$^{-1}$).

Bi Catalysis: Compound 11d was synthesized according to the GP from 9H-fluoren-9-yl carbamate (113 mg, 0.5 mmol, 1.0 equiv), glyoxylic acid (0.07 mL, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and FeCl$_3$·6H$_2$O (9 mg, 0.025 mmol, 5 mol%) in MeNO$_2$ (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 5:1 → 1:1) yielded the product as a colorless oil (246 mg, 84%).

1H NMR (500 MHz, DMSO-$d_6$): δ = 12.84 (s, 1 H), 7.90–7.86 (m, 2 H), 7.86–7.81 (m, 1 H), 7.81–7.70 (m, 2 H), 7.44–7.38 (m, 2 H), 7.35–7.26 (m, 2 H), 6.83 (s, 2 H), 5.52 (d, J = 7.6 Hz, 1 H), 4.32–4.16 (m, 3 H), 2.28 (s, 6 H), 2.20 (s, 3 H).

IR (ATR): 3412 (w), 2920 (m), 2520 (w), 1735 (m), 1658 (m), 1536 (m), 1374 (m), 1295 (s), 1067 (s), 925 (s), 851 (cm$^{-1}$).

HRMS (MALDI): m/z [M + Na]$^+$ calcd for C$_{14}$H$_{19}$NO$_4$: 288.1208; found: 288.1208.

2-[(Ethoxycarbonyl)amino]-2-mesitylactic Acid (11c)

Bi Catalysis: Compound 11c was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), N-(4-methoxyphenyl)pivalimide

Fe Catalysis: Compound 12a was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.12 mL, 0.6 mmol, 1.2 equiv), N-(4-methoxyphenyl)pivalimide
Ethyl 2-Benzamido-2-(4-methyl-3-pivalamidophenyl)acetate (12c)

**Bi Catalysis**: Compound 12c was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-methylpivalaldehyde (287 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow solid (89 mg, 45%; r.r. = 98:2).

**Fe Catalysis**: Compound 12c was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 2-methylpivalaldehyde (287 mg, 1.5 mmol, 3.0 equiv), and Fe(ClO₄)₃ (9 mg, 0.025 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a yellow solid (152 mg, 77%; r.r. = 91:9).

**Purification by chromatography (cyclohexane/EtOAc = 4:1)** yielded the product as a colorless solid (128 mg, 62%; r.r. = 98:2).

Mp 129 °C; Rf = 0.2 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3443 (w), 3283 (w), 2959 (w), 2361 (w), 1743 (m), 1668 (s), 1581 (w), 1520 (m), 1489 (s), 1446 (m), 1417 (w), 1399 (w), 1367 (m), 1340 (s), 1299 (s), 1265 (s), 1218 (m), 1194 (m), 1170 (s), 1092 (m), 1023 (m), 947 (w), 923 (w), 880 (w), 800 (w), 777 (m), 749 (w), 714 (s), 691 (s), 620 (s), 608 (s), 584 (s), 540 (w) cm⁻¹ (m).

**HRMS (MALDI)**: [M + H]+ calcd for C₂₃H₂₉N₂O₅: 413.2071; found: 413.2071.

**Synthesis**

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Ethyl 2-Benzamido-2-(3,4-dimethoxyphenyl)acetate (12e)

**Fe Catalysis:** Compound 12e was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 ml, 1.2 mmol, 1.2 equiv), veratrole (0.38 ml, 3.0 mmol, 3.0 equiv), and Fe(ClO₄)₂ (18 mg, 0.05 mmol, 5 mol%) in MeNO₂ (4.0 ml). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) yielded the product as a colorless oil (216 mg, 63%; r.r. = 98:2).

R₁ = 0.32 (cyclohexane/ETOAc = 7:3).

IR (ATR): 3355 (w), 3058 (w), 2979 (w), 1721 (s), 1640 (s), 1579 (w), 1120 (m), 1090 (s), 1022 (m), 877 (m), 813 (s), 727 (s), 692 cm⁻¹ (m).

Anal. Calcd for C₁₉H₂₁NO₅: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.31; H, 6.18; N, 3.98.

**Ethyl 2-(Anthracen-9-yl)-2-benzamidoacetate (12f)**

**Bi Catalysis:** Compound 12f was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), 4-bromophenol (260 mg, 1.5 mmol, 3.0 equiv), and Bi(OTf)₃ (3 mg, 0.005 mmol, 1 mol%) in DCE (2.0 ml). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) yielded the product as a low-melting solid (123 mg, 65%; r.r. = 98:2).

R₁ = 0.46 (cyclohexane/ETOAc = 7:3).

IR (ATR): 3368, 3099, 2920, 2852, 1736, 1622, 1576, 1530 (s), 1488 (m), 1430 (m), 1363, 1344 (m), 1310 (m), 1278 (s), 1236 (m), 1198 (m), 1120 (m), 1090 (s), 1022 (m), 877 (m), 813 (s), 727 (s), 692 cm⁻¹ (m).

1H NMR (400 MHz, CDCl₃): δ = 9.47 (s, 1 H), 7.86–7.76 (m, 2 H), 7.25 (d, J = 6.7 Hz, 1 H), 5.78–5.52 (m, 2 H), 7.73–7.35 (m, 1 H), 7.13–7.04 (m, 1 H), 5.73 (d, J = 8.7 Hz, 1 H), 5.83 (d, J = 6.9 Hz, 1 H), 1.39–1.40 (m, 3 H), 1.30 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 171.4, 166.6, 133.3, 132.7, 129.9, 128.8, 127.3, 111.0, 110.3, 62.1, 56.7, 56.1, 14.2.

MS (ESI): m/z [M + Na⁺] calcd for C₁₉H₂₁NO₅Na: 366.1; found: 366.3.

HRMS (MALDI): m/z [M + H⁺] calcd for C₁₉H₂₁NO₅: 344.1493; found: 344.1490.

Anal. Calcd for C₁₉H₂₁NO₅: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.31; H, 6.18; N, 3.98.

**Ethyl 2-Benzamido-2-(5-bromo-2-hydroxyphenyl)acetate (12g)**

**Bi Catalysis:** Compound 12g was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (0.24 ml, 1.2 mmol, 1.2 equiv), 4-bromophenol (216 mg, 3.0 mmol, 3.0 equiv), and FeCl₃ (2 mg, 0.02 mmol, 2 mol%) in MeNO₂ (4.0 ml). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/ETOAc = 9:1 → 4:1) yielded the product as a low-melting solid (39 mg, 11%; r.r. = 98:2).

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Ethyl 2-Benzamidoo-2-(5-chloro-2-methoxyphenyl)acetate (12i)

**Bi Catalysis:** Compound 12i was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), 4-chloroanisole (0.49 mL, 4.0 mmol, 4.0 equiv), and Bi(OTf)3 (32 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 16 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (310 mg, 89%; Rf = 0.98:2).

Fe Catalysis: Compound 12i was synthesized according to the GP from benzamide (121 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.2 equiv), 4-chloroanisole (0.37 mL, 3.0 mmol, 3.0 equiv), and FeCl2·6H2O (18 mg, 0.05 mmol, 5 mol%) in MeNO2 (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 9:1) yielded the product as a colorless solid (116 mg, 34%; Rf = 0.982).

Mp 88.8 °C; Rf = 0.55 (cyclohexane/EtOAc = 7:3).

IR (ATR): 3257 (w), 2959 (w), 1737 (s), 1638 (s), 1602 (w), 1579 (w), 1523 (m), 1488 (s), 1458 (m), 1365 (w), 1270 (m), 1247 (s), 1190 (s), 1130 (m), 1093 (s), 1026 (s), 979 (w), 804 (m), 719 (m), 658 cm⁻¹ (s).

1H NMR (400 MHz, CDC13): δ = 7.79 (dd, J = 5.2, 3.3 Hz, 2 H), 7.53–7.40 (m, 4 H), 7.30–7.23 (m, 2 H), 6.83 (d, J = 8.8 Hz, 1 H), 5.88 (d, J = 8.0 Hz, 1 H), 4.24–4.17 (m, 2 H), 3.85 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H).

13C NMR (101 MHz, CDC13): δ = 170.6, 166.5, 155.7, 134.0, 131.7, 130.6, 129.4, 126.8, 127.4, 127.2, 125.9, 112.3, 61.9, 56.0, 53.3, 14.1.

MS (ESI): m/z [M + H]+ calcd for C21H21NO4: 348.1; found: 348.2.


Ethyl 2-Benzamidoo-2-(p-tolyl)acetate (12j)

**Bi Catalysis:** Compound 12j was synthesized according to the GP from benzamide (61 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), tolune (0.22 mL, 2.1 mmol, 4.2 equiv), and Bi(OTf)3 (7 mg, 0.005 mmol, 2 mol%) in DCE (2.0 mL). The reaction mixture was stirred for 16 h at 100 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (74 mg, 50%; Rf = 75:25).

Mp 99–101 °C; Rf = 0.4 (n-hexane/EtOAc 4:1).

IR (ATR): 3290 (w), 1743 (s), 1636 (s), 1603 (m), 1581 (m), 1527 (s), 1488 (s), 1447 (m), 1372 (m), 1348 (m), 1330 (m), 1275 (w), 1252 (m), 1206 (s), 1178 (s), 1153 (m), 1096 (m), 1075 (w), 1021 (s), 928 (w), 815 (m), 803 (w), 791 (w), 759 (m), 723 (s), 711 (s), 691 (s), 634 (m), 615 (m), 587 (m), 573 (m), 512 (m), 487 (m), 459 cm⁻¹ (w).

1H NMR (300 MHz, CDC13): δ (major regioisomer) = 7.83–7.80 (m, 2 H), 7.54–7.40 (m, 3 H), 7.35–7.32 (m, J = 8.1 Hz, 2 H), 7.24–7.16 (m, J = 15.2, 5.8 Hz, 2 H), 7.11 (br, d, J = 6.9 Hz, 1 H), 5.73 (d, J = 7.0 Hz, 1 H), 4.33–4.11 (m, 2 H), 2.34 (s, 3 H), 1.29–1.19 (m, 3 H).

13C NMR (75 MHz, CDC13): δ = 171.33, 166.61, 138.51, 137.19, 135.48, 133.94, 131.93, 131.17, 129.81, 128.73, 128.60, 127.34, 127.28, 126.67, 126.45, 62.12, 56.75, 53.71, 21.30, 19.68, 14.18. (peaks are not assigned to regioisomers).

MS (ESI): m/z [M + H]+ calcd for C18H20NO2: 298.5; found: 298.5.

HRMS (MALDI): m/z [M + H]+ calcd for C18H20NO2: 298.1438; found: 298.1439.
The reaction mixture was stirred for 20 h at 80 °C. Purification by chromatography (n-hexane/ETHOAc = 4:1) yielded the product as a colorless solid (118 mg, 54%).

Mp 126–128 °C; Rf = 0.5 (n-hexane/ETHOAc 7:3).

IR (ATR): 3298 (w), 2965 (w), 1732 (s), 1610 (w), 1577 (w), 1473 (w), 1449 (w), 1391 (m), 1370 (m), 1323 (s), 1299 (m), 1278 (s), 1247 (m), 1223 (m), 1200 (m), 1159 (s), 1147 (s), 1090 (s), 1071 (s), 1033 (m), 1012 (m), 975 (w), 925 (m), 852 (m), 818 (s), 764 (w), 740 (s), 724 (m), 703 (m), 615 (s), 593 (m), 562 (s), 533 (s), 532 (m), 475 cm–1 (m).

1H NMR (300 MHz, CDCl3): δ = 7.37–7.30 (m, 4 H), 6.63 (s, 2 H), 5.84 (br d, J = 4.2 Hz, 1 H), 5.57 (d, J = 4.3 Hz, 1 H), 4.23–4.06 (m, 2 H), 2.29 (s, 6 H), 2.19 (s, 3 H), 1.14 (t, J = 7.1 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 170.65, 139.23, 138.40, 137.17, 131.58, 129.83, 128.78, 128.32, 127.12, 62.68, 55.01, 20.88, 20.01, 14.09.

MS (ESI): m/z [M + Na]+ calcld for C20H19NO5SNa: 462.0; found: 462.0.


Ethyl 2-Mesityl-2-(4-methoxyphenylsulfonamido)acetate (16b, R = OMe)

Bi Catalysis: Compound 16b (R = OMe) was synthesized according to the GP from 4-methoxybenzenesulfonamide (196 mg, 0.5 mmol, 1.0 equiv), ethyl glyoxalate (61 mg, 0.6 mmol, 1.2 equiv), mesitylene (0.21 mL, 1.5 mmol, 3.0 equiv), and Bi(OTf)3 (7 mg, 0.01 mmol, 2 mol%) in MeNO2 (2.0 mL). The reaction mixture was stirred for 16 h at 80 °C. Purification by chromatography (n-hexane/ETHOAc = 4:1) yielded the product as a colorless solid (126 mg, 64%).

Mp 173–175 °C; Rf = 0.5 (n-hexane/ETHOAc 4:1).

IR (ATR): 3274 (w), 2929 (w), 1738 (m), 1594 (m), 1496 (m), 1437 (w), 1412 (m), 1329 (m), 1311 (w), 1288 (w), 1263 (s), 1228 (s), 1183 (m), 1157 (m), 1119 (w), 1096 (m), 1063 (m), 1024 (s), 939 (w), 913 (m), 870 (m), 828 (s), 801 (m), 779 (m), 722 (m), 674 (s), 628 (w), 585 (s), 559 cm–1 (s).

1H NMR (300 MHz, CDCl3): δ = 7.50–7.45 (m, 2 H), 6.75–6.70 (m, 2 H), 6.66 (s, 2 H), 5.67 (br d, J = 4.5 Hz, 1 H), 5.51 (d, J = 4.6 Hz, 1 H), 4.20–4.04 (m, 2 H), 3.80 (s, 3 H), 2.21 (s, 6 H), 2.19 (s, 3 H), 1.13 (t, J = 7.1 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 170.95, 162.74, 137.90, 137.17, 131.85, 129.87, 129.42, 129.09, 113.71, 62.55, 55.66, 55.00, 20.92, 20.13, 14.12.

MS (ESI): m/z [M + Na]+ calcld for C20H19NO5SNa: 414.1; found: 414.08.

Ethyl 3,5,10,10a-Tetrahydro-3-oxo-1H-oxazo[3,4-b]isoquinoline-5-carboxylate (21)

Bi Catalysis: Compound 21 was synthesized according to the GP from (R)-4-benzylxazolin-2-one (59 mg, 0.3 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 2.0 equiv), and Bi(OTf)₃ (7 mg, 0.01 mmol, 5 mol%) in MeNO₂ (2.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (cyclohexane/EtOAc = 4:1) yielded the product as a colorless solid (393 mg, 87%).

**Analytical and spectral data** are consistent with those reported in the literature.

Diastereomer a

Mp 63–65 °C; Rf = 0.2 (n-hexane/EtOAc = 4:1).

Ethyl 2-(3-Methyl-(1,3-dioxoisodindolin-2-yl)butanamido)-2-mesitylacetate (23, PG = Phth)

Bi Catalysis: Compound 23 (PG = Phth) was synthesized according to the GP from 3-methyl-2-(1,3-dioxoisodindolin-2-yl)butanamide (246 mg, 1.0 mmol, 1.0 equiv), ethyl glyoxalate (122 mg, 1.2 mmol, 1.2 equiv), mesitylamine (0.41 mL, 3.0 mmol, 3.0 equiv), and Bi(OTf)₃ (13 mg, 0.02 mmol) in MeNO₂ (4.0 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (n-hexane/EtOAc = 4:1) yielded the product as a colorless solid (393 mg, 87%; Rr = 67:33).

**Analytical and spectral data** are consistent with those reported in the literature.

Diastereomer a

Mp 63–65 °C; Rf = 0.2 (n-hexane/EtOAc = 4:1).
Mp 100–106 °C; Rf = 0.72 (n-hexane/EtOAc = 9:1).

$^{1}H$ NMR (400 MHz, CDCl$_3$): $\delta = 6.79$ (s, 4 H), 4.24 (q, $J = 7.1$ Hz, 2 H), 2.24 (s, 6 H), 2.07 (s, 12 H), 1.27 (t, $J = 7.1$ Hz, 3 H).

Analytical and spectral data are consistent with those reported in the literature.$^{38}$

**Ethyl 2-Hydroxy-2-mesitylacetae (27)**

**Fe Catalysis**

Compound 27 was synthesized according to the GP from ethyl glyoxalate (0.24 mL, 1.2 mmol, 1.0 equiv), mesitylene (0.42 mL, 2.2 mmol, 3.0 equiv), 2,2'-bipyridine (5 mg, 0.03 mmol, 3 mol%), and FeCl$_3$ (7 mg, 0.02 mmol, 2 mol%) in MeNO$_2$ (2 mL). The reaction mixture was stirred for 24 h at 80 °C. Purification by chromatography (hexane/EtOAc = 4:1) yielded the product as a colorless oil (176 mg, 66%).

R$_f$ = 0.51 (n-hexane/EtOAc = 7:3).

$^{1}H$ NMR (400 MHz, CDCl$_3$): $\delta = 6.84$ (s, 2 H), 5.52 (d, $J = 2.8$ Hz, 1 H), 4.34–4.11 (m, 2 H), 3.22 (d, $J = 2.8$ Hz, 1 H), 2.33 (s, 6 H), 2.26 (s, 3 H), 1.22 (t, $J = 7.1$ Hz, 3 H).

Analytical data are consistent with those reported in the literature.$^{39}$

**Acknowledgment**


(17) Monomeric glyoxalates are prepared from the corresponding polymers by pyrolysis. The monomers are so reactive that they polymerize easily and react readily with water to generate the hydrated forms. Therefore, they have to be distilled just prior to use, after pyrolysis, and used under nonaqueous conditions.

(18) Ethyl glyoxalate was obtained in the polymer form (50 wt% solution) in toluene. Toluene was removed prior to the initial experiments by applying vacuum (1 mbar) for 2 h.

(19) For an excellent overview of the nucleophility of amines as well as the reactivity of various other molecules, we recommend the database of Prof. H. Mayr (LMU Munich): http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/.


(27) Competitive formation of the bis(heteroaryl)methane derivatives was observed in other reports; compare: ref. 23f and Soueidan, M.; Collin, J.; Gil, R. Tetrahedron Lett. 2006, 47, 5467.

(28) As shown in our previous studies, only Bi(OTf) 3 could catalyze reactions with less reactive aldehydes. Fe salts were completely inactive in these reactions, compare ref. 16b.


(31) In this study, we focused on readily available (i.e., commercially available) salts.

(32) The reactive N-acylimine species might be too short-lived under our reaction conditions to be detected by common NMR or IR methods.


